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Optimizing Medication Use in Older Adults with Multimorbidity and Polypharmacy

PhD Thesis submitted by

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1. Abstracts

1.1 Abstract (English)

Background

Globally, societies are ageing. In Switzerland, the population group of adults aged ≥ 65 years is projected to increase from around 17% in 2010 to a third of the population by the year 2050. With ageing societies also come increasing numbers of older adults with chronic conditions. This is mainly due to the fact that certain diseases are more prevalent in older age. With multimorbidity often comes the concurrent use of multiple medications, as patients usually use different medications to manage their different chronic conditions. Patients with polypharmacy are at a higher risk of having inappropriate polypharmacy, which can be a result of both over- and under-prescribing. They are at a higher risk of using potentially inappropriate medications (PIMs), which are medications for which the risk of adverse events outweighs the clinical benefit. While appropriate polypharmacy has a positive effect on patients' health status, inappropriate polypharmacy and the use of PIMs may have detrimental effects. Due to this, there is the need to regularly review, and if necessary, to optimize the medication use of older adults with multimorbidity and polypharmacy. For different reasons, however, efforts to perform medication reviews in this patient group have been difficult to implement. First, many research efforts have focused on older adults in general or older adults with specific chronic conditions, which is why systematic evidence on the use of PIMs in older adults with multimorbidity and polypharmacy is scarce. Second, medication optimization, and in particular deprescribing, is challenging due to different types of barriers faced by GPs and patients, which result in medication optimization interventions being difficult to translate into clinical practice. Third, conducting clinical research with older adults with multimorbidity and polypharmacy and general practitioners with the aim of optimizing medication use can be challenging. In general, older and multimorbid patients are commonly underrepresented in clinical research. Additionally, only a small share of clinical research takes place in the primary care setting.

Aims

The overall objective of this thesis was to study different aspects related to the optimization of medication use in older patients with polypharmacy and multimorbidity. More specifically, this thesis had three different aims; *(1)* to investigate the use of PIMs in adults aged ≥ 65 years with multimorbidity and polypharmacy as well as to explore the factors associated with the new

prescribing of PIMs in this patient group; *(2)* to investigate general practitioners' (GPs) willingness to make deprescribing decisions in older patients with polypharmacy and to examine which patient characteristics are associated with a higher likelihood of making deprescribing decisions; and *(3)* to explore the conduct of the 'Optimizing PharmacoTherapy In the Multimorbid Elderly in Primary Care' (OPTICA) trial in more depth. One the one hand, this entailed comparing the baseline characteristics of GPs and patients from the OPTICA trial with reference cohorts from a Swiss real-world cohort to establish the representativeness of the trial participants. On the other hand, this entailed performing a mixed-methods analysis of the use and implementation of the 'Systematic Tool to Reduce Inappropriate Prescribing' (STRIP) assistant, a new electronic clinical decision support system (CDSS) developed in the Netherlands, during the OPTICA trial.

Methods

A series of quantitative and mixed-methods studies were conducted to investigate the different aspects related to the optimization of medication use in older patients with polypharmacy and multimorbidity. To study *Aim I*, I used a dataset with linked Medicare claims and data from electronic health records from seven hospitals and medical centers in the Boston metropolitan area (RPDR-CMS dataset), which covered the period from 2007 to 2014. Using this data I explored the use of PIMs, defined with the 2019 version of the Beers criteria, in adults aged ≥ 65 years, with ≥ 2 chronic conditions, and ≥ 5 long-term medications. I performed cross-sectional analyses and a retrospective cohort study. I analyzed the retrospective cohort study using Cox regression analysis. For *Aim II*, I collected and analyzed cross-sectional data from more than 1700 GPs in 31 countries. In this questionnaire we presented hypothetical case-vignettes to GPs, which differed in terms of patient characteristics, and for each case-vignette we asked GPs if they would deprescribe any of the medications and if so, which ones. For *Aim III*, I performed descriptive analyses to describe the trial participants, including patients' willingness to have medications deprescribed, and to assess the representativeness of participant characteristics in the OPTICA trial and I conducted an explanatory mixed-methods study. In the descriptive analysis, I compared the characteristics of patients and GPs participating in the OPTICA trial to those the 'Family medicine ICPC Research using Electronic medical records' (FIRE) project, which is a database with data from electronic health records from around 700 GPs in the Swiss German part of Switzerland and thus constitutes a real-world cohort. In the mixed-methods study we first collected quantitative data, which we then sought to further explain and understand through qualitative data collection. In the qualitative interviews we explored questions related to the barriers and facilitators linked to using the STRIP assistant during the OPTICA trial.

Results

For *Aim I*, I found that >69% of older patients with multimorbidity and polypharmacy used ≥ 1 PIMs from 2007 to 2014. Central nervous system drugs and gastrointestinal drugs were found to be the most commonly used PIMs. More than 10% of medication costs were spent on potentially inappropriate medications. Furthermore, I found that 2.5% of PIM-naïve[1] older adults with polypharmacy and multimorbidity were prescribed a PIM during the 90-day follow-up period. Male sex (Hazard ratio (HR) = 1.29, 95% confidence interval (CI) 1.06-1.57, reference: female sex), the number of ambulatory visits (18-29 visits: HR = 1.42, 95% CI 1.06-1.92; ≥ 30: HR = 2.12, 95% CI 1.53-2.95, reference: ≤ 9 visits), the number of prescribing orders (HR = 1.02 per unit increase, 95% CI 1.01-1.02), and heart failure (HR = 1.38, 95% CI 1.07-1.78, reference: no heart failure diagnosis) were independently associated with a higher risk of being newly prescribed a PIM. Higher age was independently associated with a lower risk of being newly prescribed a PIM (85 years: HR = 0.75, 95% CI 0.56-0.99, reference: 65-74 years). For *Aim II*, I found that >80% of GPs reported they would deprescribe ≥ 1 medication(s) in patients aged ≥ 80 years with polypharmacy. There was some variation across countries and GP characteristics with regards to the reported deprescribing decisions. The GPs' odds of making deprescribing decisions was higher in patients with a higher level of functional dependency in activities of daily living (ADL) (high functional dependency in ADL: odds ratio (OR) = 1.5, 95% CI 1.25-1.80, medium: OR = 1.29, 95% CI 1.09-1.55, reference category: low functional dependency in ADL) and when cardiovascular disease was absent (OR = 3.04, 95% CI 2.58-3.57, reference: history of cardiovascular disease). For *Aim III*, I found that more than 80% of older multimorbid patients with polypharmacy, who participated in the OPTICA trial, reported being willing to stop ≥ 1 of their medications if their doctor said that this would be possible. The baseline characteristics of GPs participating in the OPTICA trial were similar in terms of sociodemographic characteristics and their work as GPs to those regularly exporting data to the FIRE project database (e.g., age, years of experience as GP, employment status). Patients participating in the OPTICA trial and those from the FIRE database were comparable in terms of age, health services use, and certain clinical characteristics (e.g., systolic blood pressure, body mass index). I also demonstrated that patients recruited based on pre-defined screening lists were similar to those identified by GPs. Finally, we observed an overall good acceptance of the STRIP assistant by general practitioners who used this tool during the OPTICA trial. GPs reported to perceive the STRIP assistant as a useful tool, due to its nature to manage a large amount of data and to generate recommendations. Despite this, some substantial implementation challenges were observed. The qualitative findings showed

[1] PIM-naïve patients were defined as those who did not use nor were prescribed a potentially inappropriate medication during the 180-day baseline period.

that the main reasons for the limited implementation of the STRIP assistant are as follows: incomplete data imports, significant time expenditure for preparing the use of the STRIP assistant, technical problems when running the medication review analysis, and occasional lack of quality and inappropriateness of the generated recommendations.

Conclusions

This thesis provides important information for optimizing medication use in older adults with multimorbidity and polypharmacy. First, I found an overall high utilization of PIMs in older adults with multimorbidity and polypharmacy, which is associated with substantial costs. We as researchers should use the information on the factors associated with new PIM prescribing and the information on the most commonly used PIMs when developing interventions targeted at optimizing the medication use in older adults with multimorbidity and polypharmacy that aim at reducing the use of PIMs in this patient group. Second, GPs overall seem to be willing to deprescribe medication in older patients with polypharmacy. However, GPs' willingness to make deprescribing decisions differed for patients with different levels of functional dependency in activities of daily living and cardiovascular disease. In addition, patients with multimorbidity and polypharmacy also show a high willingness to have medications deprescribed. I conclude that designing deprescribing interventions that build on GPs and patients' willingness to make deprescribing decisions could be a crucial factor for the implementation and long-term efficacy of such interventions. Finally, I conclude that testing new medication optimization interventions in primary care trials with comparable groups of GPs and older multimorbid patients is possible. However, the implementation of new electronic decision support systems may come with substantial challenges, which have to be addressed to facilitate and enable the future rollout of such tools.

1.2 Zusammenfassung (deutsch)

Hintergrund

Die Gesellschaft altert weltweit. In der Schweiz wird erwartet, dass die Bevölkerungsgruppe der Erwachsenen im Alter von ≥ 65 Jahren von rund 17 % im Jahr 2010 auf ein Drittel der Bevölkerung im Jahr 2050 ansteigen wird. Mit der Alterung der Gesellschaft steigt auch die Zahl der älteren Erwachsenen, die an mehreren chronischen Erkrankungen leiden. Dies ist vor allem auf die höhere Lebenserwartung zurückzuführen und darauf, dass bestimmte Krankheiten im höheren Alter häufiger vorkommen. Mit dieser sogenannten Multimorbidität geht oft die gleichzeitige Einnahme mehrerer Medikamente einher (definiert als Polypharmazie), da die Patient*innen in der Regel verschiedene Medikamente zur Behandlung ihrer unterschiedlichen chronischen Erkrankungen einnehmen müssen. Patient*innen mit Polypharmazie haben ein höheres Risiko für unangemessene Verschreibungen, die sowohl eine Folge von Über- als auch von Unterverschreibung sein können. Das bedeutet, dass diese Patient*innen ein höheres Risiko haben, potenziell unangemessene Medikamente («potentially inappropriate medications» im Englischen, abgekürzt «PIMs») zu verwenden. PIMs sind Medikamente, bei denen das Risiko unerwünschter Nebenwirkungen den klinischen Nutzen überwiegt. Während sich eine angemessene Polypharmazie positiv auf den Gesundheitszustand der Patient*innen auswirkt, können eine unangemessene Polypharmazie und die Verwendung von PIMs nachteilige Auswirkungen haben.

Aus diesem Grund besteht die Notwendigkeit, den Medikamenteneinsatz bei älteren Patient*innen mit Multimorbidität und Polypharmazie regelmässig zu prüfen und, falls notwendig, zu optimieren (d.h. überflüssige Medikamente zu stoppen, fehlende Medikamente zu starten, usw.). Aus verschiedenen Gründen sind die Bemühungen, Medikationsüberprüfungen und Medikamentenoptimierung bei dieser Patientengruppe durchzuführen, jedoch oftmals schwierig umzusetzen. Erstens haben sich viele Forschungsbemühungen auf ältere Erwachsene im Allgemeinen oder auf ältere Erwachsene mit spezifischen chronischen Erkrankungen konzentriert, weshalb es kaum systematische Evidenz für den Einsatz von PIMs bei älteren Erwachsenen mit Multimorbidität und Polypharmazie gibt. Zweitens ist die Medikamentenoptimierung und insbesondere das Absetzen von Medikamenten («deprescribing» im Englischen) eine Herausforderung, da Hausärzt*innen und Patient*innen mit unterschiedlichen Schwierigkeiten konfrontiert sind. Diese führen dazu, dass sich Interventionen zur Optimierung der Medikation und zum Absetzen von Medikamenten nur schwer in die klinische Praxis umsetzen lassen. Drittens kann die Durchführung von klinischen Forschungsprojekten mit älteren multimorbiden Patient*innen mit Polypharmazie und Hausärzt*innen eine Herausforderung darstellen. Im Allgemeinen sind ältere und multimorbide Patient*innen in der klinischen

Forschung häufig unterrepräsentiert. Ausserdem findet nur ein kleiner Teil der klinischen Forschung im Umfeld der Hausarztmedizin statt.

Ziele

Das Hauptziel dieser Arbeit war es, verschiedene Aspekte im Zusammenhang mit der Optimierung des Medikamentengebrauchs bei älteren multimorbiden Patient*innen mit Polypharmazie zu untersuchen. Genauer gesagt hatte diese Arbeit drei verschiedene Ziele; *(1)* die Verwendung von PIMs bei Erwachsenen im Alter von ≥ 65 Jahren mit Multimorbidität und Polypharmazie zu untersuchen sowie die Faktoren, die mit der Neuverschreibung von PIMs in dieser Patientengruppe verbunden sind zu analysieren; *(2)* die Bereitschaft von Hausärzt*innen zu untersuchen bei älteren Patient*innen mit Polypharmazie «*Deprescribing*»-Entscheidungen zu treffen, und zu analysieren, welche Patientencharakteristika mit einer höheren Wahrscheinlichkeit von «*Deprescribing*»-Entscheidungen von Hausärzt*innen assoziiert sind; und *(3)* verschiedene Aspekte der Durchführung der «Optimizing PharmacoTherapy In the Multimorbid Elderly in Primary Care»-Studie (OPTICA) zu untersuchen. Dies beinhaltete zum einen den Vergleich der Merkmale von Hausärzt*innen und Patient*innen aus der OPTICA-Studie mit Referenzkohorten aus einer Schweizer Real-World-Kohorte, um die externe Validität der Studienteilnehmer*innen evaluieren zu können. Zum anderen wurde eine Mixed-Methods-Studie, mit qualitativen und quantitativen Studienelementen, durchgeführt, um die Implementierung des sogenannten «Systematic Tool to Reduce Inappropriate Prescribing» (STRIP) Assistenten während der OPTICA-Studie zu analysieren. Der STRIP Assistent ist eine neue elektronische Entscheidungshilfe für Hausärzt*innen, die in den Niederlanden entwickelt wurde.

Methoden

Im Rahmen dieser Doktorarbeit wurden eine Reihe von quantitativen Studien und eine Mixed-Methods-Studie durchgeführt, um die verschiedenen Aspekte im Zusammenhang mit der Optimierung des Medikamenteneinsatzes bei älteren multimorbiden Patient*innen mit Polypharmazie zu untersuchen. Zur Untersuchung von *Ziel I* verwendete ich einen verknüpften Datensatz mit Medicare-Versicherungs-Daten und Daten aus elektronischen Patientenakten von sieben Krankenhäusern und medizinischen Zentren im Grossraum Boston (RPDR-CMS-Datensatz), der den Zeitraum von 2007 bis 2014 abdeckt. Mit diesen Daten untersuchte ich die Verwendung von PIMs, bei Erwachsenen im Alter von ≥ 65 Jahren, mit ≥ 2 chronischen Erkrankungen und ≥ 5 Langzeitmedikationen. Zur Definition von PIMs verwendeten wir die 2019 Beers-Kriterien der Amerikanischen Geriatrie-Gesellschaft. Ich führte Querschnittsanalysen und

eine retrospektive Kohortenstudie durch. Die retrospektive Kohortenstudie analysierte ich mit Hilfe einer Cox-Regressionsanalyse. Für *Ziel II* sammelte und analysierte ich Querschnittsdaten von mehr als 1700 Hausärzt*innen in 31 Ländern. In diesem Fragebogen präsentierten wir den Hausärzt*innen hypothetische Fallvignetten, die sich in Bezug auf die Patientencharakteristika unterschieden, und für jede Fallvignette fragten wir die Hausärzt*innen, ob sie eines der Medikamente absetzen oder dessen Dosis reduzieren würden und wenn ja, welches. Für *Ziel III* führte ich deskriptive Analysen durch, um die Teilnehmercharakteristika zu beschreiben sowie die externe Validität der Teilnehmercharakteristika in der OPTICA-Studie zu bewerten. Ausserdem führte ich eine Mixed-Methods-Studie durch. In der deskriptiven Analyse verglich ich die Charakteristika von Patient*innen und Hausärzt*innen, die an der OPTICA-Studie teilnahmen, mit denen des Projekts «Family medicine ICPC Research using Electronic medical records» (FIRE) Projekt. Das FIRE Projekt der Universität Zürich ist eine Datenbank mit Daten aus elektronischen Patientenakten aus den Praxen von etwa 700 Hausärzt*innen in der Deutschschweiz ist und stellt somit eine Real-World-Kohorte dar. Ausserdem analysierte ich die Bereitschaft der teilnehmenden Patient*innen Medikamente zu stoppen. In der Mixed-Methods-Studie haben wir zunächst quantitative Daten erhoben, die wir dann durch qualitative Datenerhebung weiter zu erklären und zu verstehen versuchten. In den qualitativen Interviews mit Hausärzten untersuchten wir die Nutzung des STRIP-Assistenten während der OPTICA-Studie.

Ergebnisse

Für *Ziel I* fand ich heraus, dass mehr als >69% der älteren Patient*innen mit Multimorbidität und Polypharmazie von 2007 bis 2014 mindestens ein potentiell unangebrachtes Medikament (PIM) verwendeten. Medikamente des zentralen Nervensystems und gastrointestinale Medikamente waren die am häufigsten verwendeten PIMs. Mehr als 10 % der Medikamentenkosten wurden für potenziell unangebrachte Medikamente ausgegeben. Ausserdem zeigte sich, dass 2,5% der älteren Patient*innen mit Polypharmazie und Multimorbidität, die im 180-tägigen Referenzzeitraum noch keinen PIM verwendet hatten, während einer 90-tägigen Nachbeobachtungszeit ein potenziell unangebrachtes Medikament verschrieben bekamen. Männliches Geschlecht (Hazard ratio (HR) = 1.29, 95% CI 1.06-1.57, Referenz: weibliches Geschlecht), die Anzahl der ambulanten Arztbesuche (18-29 Besuche: HR = 1.42, 95% CI 1.06-1.92; ≥ 30: HR = 2.12, 95% CI 1.53-2.95, Referenz: ≤ 9 Besuche), die Anzahl der Medikamentenverschreibungen (HR = 1.02 pro zusätzliche Verschreibung, 95% CI 1.01-1.02) und Herzinsuffizienz (HR = 1.38, 95% CI 1.07-1.78, Referenz: keine Herzinsuffizienz) waren unabhängig voneinander mit einem höheren Risiko assoziiert, neu ein potentiell unangebrachtes

Medikament verschrieben zu kommen. Ein höheres Alter war unabhängig mit einem geringeren Risiko verbunden, neu ein potentiell unangebrachtes Medikament verschrieben zu bekommen (85 Jahre: HR = 0.75, 95% CI 0.56-0.99, Referenz: 65-74 Jahre).

Bezüglich *Ziel II* fand ich heraus, dass >80% der Hausärzt*innen berichteten, dass sie ≥ 1 Medikament(e) bei Patient*innen im Alter von ≥ 80 Jahren mit Polypharmazie absetzen oder dessen Dosis reduzieren würden. Es gab eine gewisse Variation zwischen den teilnehmenden Ländern und den Merkmalen der Hausärzt*innen in Bezug auf die berichteten «*Deprescribing*»-Entscheidungen. Die Wahrscheinlichkeit, dass die Hausärzt*innen «*Deprescribing*»-Entscheidungen trafen, war höher bei Patient*innen mit einem höheren Grad an Abhängigkeit in Aktivitäten des täglichen Lebens (hohe Abhängigkeit: Odds ratio (OR) = 1.,5, 95% CI 1.25-1.80, mittlere Abhängigkeit: OR = 1.29, 95% CI 1.09-1.55, Referenz: geringe Abhängigkeit) und wenn keine kardiovaskuläre Erkrankung vorlag (OR = 3.04, 95% CI 2.58-3.57).

Für *Ziel III* fand ich, dass mehr als 80% der älteren multimorbiden Patient*innen mit Polypharmazie, die an der OPTICA-Studie teilnahmen, angaben, dass sie bereit wären, ≥ 1 ihrer Medikamente abzusetzen, wenn ihr Arzt ihnen sagen würde, dass dies möglich wäre. Die Merkmale der an der OPTICA-Studie teilnehmenden Hausärzt*innen waren in Bezug auf soziodemographische Merkmale und ihre Tätigkeit als Hausarzt/Hausärztin ähnlich denen, die regelmässig Daten in die FIRE-Projektdatenbank exportieren (z. B. Alter, Jahre der Erfahrung als Hausarzt/Hausärztin, Beschäftigungsstatus). Die Patient*innen, die an der OPTICA-Studie teilnahmen, und die aus der FIRE-Datenbank waren vergleichbar in Bezug auf Alter, Inanspruchnahme von Gesundheitsdiensten und bestimmte klinische Merkmale (z. B. systolischer Blutdruck, Body-Mass-Index). Es konnte auch gezeigt werden, dass die Patient*innen, die auf der Basis von vordefinierten Screening-Listen rekrutiert wurden, denen ähnlich waren, die von Hausärzt*innen identifiziert wurden. Schliesslich beobachteten wir eine insgesamt gute Akzeptanz des STRIP-Assistenten bei den Hausärzt*innen, die dieses Instrument während der OPTICA-Studie einsetzten. Die Hausärzte berichteten in den Interviews, dass sie den STRIP-Assistenten als ein nützliches Werkzeug wahrnehmen, da er in der Lage ist, eine grosse Menge an Daten zu verarbeiten und basierend darauf Empfehlungen für die Medikamentenverschreibung zu generieren. Trotzdem wurden einige erhebliche Herausforderungen bei der Implementierung beobachtet. Die qualitativen Ergebnisse zeigten, dass die Hauptgründe für die eingeschränkte Implementierung des STRIP-Assistenten wie folgt sind: Unvollständiger Datenimport, erheblicher Zeitaufwand für die Vorbereitung der Nutzung des STRIP-Assistenten, technische Probleme bei der Durchführung der Medikationsüberprüfungsanalyse und gelegentlich mangelnde Qualität und Unangemessenheit der generierten Empfehlungen.

Schlussfolgerungen

Diese Doktorarbeit liefert wichtige Informationen für die Optimierung der Medikamentennutzung bei älteren Patient*innen mit Multimorbidität und Polypharmazie. Erstens fand ich eine insgesamt hohe Nutzung von PIMs bei älteren Erwachsenen mit Multimorbidität und Polypharmazie. Dies ist mit erheblichen Kosten verbunden. Wir als Forscher sollten die Informationen über die Faktoren, die mit der Neuverschreibung von PIMs assoziiert sind sowie die Informationen über die am häufigsten verwendeten PIMs nutzen, wenn wir beispielsweise Interventionen zur Medikamentenoptimierung und Reduktion von PIMs in dieser Patientengruppe entwickeln.

Zweitens scheinen Hausärzt*innen insgesamt bereit zu sein, Medikamente bei älteren Patient*innen mit Polypharmazie abzusetzen oder deren Dosis zu reduzieren. Allerdings unterschied sich die Bereitschaft der Hausärzt*innen, «Deprescribing»-Entscheidungen bei Patient*innen anhand der Gebrechlichkeit von Patient*innen (e.g. Abhängigkeit von anderen im Alltag) und kardiovaskuläre Vorerkrankungen. Darüber hinaus zeigen Patient*innen mit Multimorbidität und Polypharmazie eine hohe Bereitschaft, Medikamente absetzen zu lassen. Ich schliesse daraus, dass das Design von «Deprescribing»-Interventionen, die auf der Bereitschaft von Hausärzt*innen und Patient*innen aufbauen, «Deprescribing»-Entscheidungen zu treffen, ein entscheidender Faktor für die Implementierung und langfristige Wirksamkeit solcher Interventionen sein könnte.

Abschliessend komme ich zu dem Schluss, dass das Testen neuer Interventionen zur Medikationsoptimierung in Primärversorgungsstudien mit Hausärzt*innen und älteren multimorbiden Patient*innen mit guter externer Validität möglich ist. Die Implementierung neuer elektronischer Entscheidungsunterstützungssysteme kann jedoch mit erheblichen Herausforderungen verbunden sein, die angegangen werden müssen, um die zukünftige Einführung solcher Hilfsmittel zu erleichtern und zu ermöglichen.

2. Abbreviations

ADL	Activities of daily living
AGS	American Geriatrics Society
AHRQ	Agency for Healthcare Research and Quality
AOU	Assessment of Underutilization
ASD	Absolute standardized difference
BMI	Body Mass Index
CCI	Chronic Condition Indicator
CDSS	Clinical decision support system
CHERRIES	Checklist for Reporting Results of Internet E-Surveys
CI	Confidence Interval
CMS	Centers for Medicare and Medicaid Services
CVD	Cardiovascular disease
EGPRN	European General Practice Research Network
EHR	Electronic health records
FDA	Food and Drug Administration
FIRE	Family medicine ICPC Research using Electronic medical records
GCP	Good Clinical Practice
GP	General practitioner
HR	Hazard ratio
ICC	Intraclass correlation coefficient
ICTRP	International Clinical Trials Registry Platform
IQR	Interquartile range
IRR	Incidence rate ratio
LESS	barriers and enabLers to willingnESs to depreScribing in older patients with multimorbidity and polypharmacy and their General Practitioners

MAI	Medication Appropriateness Index
OECD	Organization for Economic Co-operation and Development
OPERAM	OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people
OPTICA	Optimising PharmacoTherapy In the multimorbid elderly in primary Care
OR	Odds ratio
PIM(s)	Potentially inappropriate medication(s)
PPO	Potential prescribing omission
PROM	Patient reported outcomes measures
QALYs	Quality-adjusted life years
rPATD	revised Patients' Attitudes Towards Deprescribing
RPDR	Partners Research Patient Data Registry
RR	Relative risk
START	Screening Tool to Alert doctors to Right Treatment
STOPP	Screening Tool of Older Person’s Prescriptions
STRIP	Systematic Tool to Reduce Inappropriate Prescribing
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
WHO	World Health Organization

3. Figures in the Overall Introduction, Background, and Overall Discussion

4. Tables in the Overall Introduction, Background, and Overall Discussion

5. Overall Background and Introduction

5.1 Global Aging

Medical advancements and improvements in sanitation, housing and education have contributed to reduced mortality and higher life expectancies over the last two centuries [1]. Combined with other factors, such as decreasing birth rates, higher life expectancies have resulted in ageing societies all over the world [2]. The population group of adults aged ≥ 65 years of age is growing at a faster pace than all other age groups combined [3]. While globally one in every 11 persons was ≥ 65 years in the year 2019, predictions say that this population group will increase to one in six persons by the year 2050 [4]. In Switzerland for example, life expectancy increased throughout the twentieth and into the twenty-first century. While in 1999 the life expectancy was 81.7 years for men aged 65 years and 85.6 years for women aged 65 years, by 2019 life expectancies had risen to 85.0 and 87.7, respectively [5]. According to projections made by the United Nations in 2019, life expectancy in Switzerland is expected to increase to 93 years (for both sexes combined) by the year 2100 [6,7].[2]

According to a recent survey of the Organization for Economic Co-operation and Development (OECD), Switzerland's population group of adults aged ≥ 65 years has increased from 10% in 1960 to 17% in 2010 [8]. By the year 2050, the population group of adults aged ≥ 65 years is projected to increase to 30% [8]. These trends are shown in *Figure 1, part A*. Furthermore, it has been observed that Switzerland has a faster rate of ageing than most other OECD countries, which can be seen in *Figure 1, part B* [8].

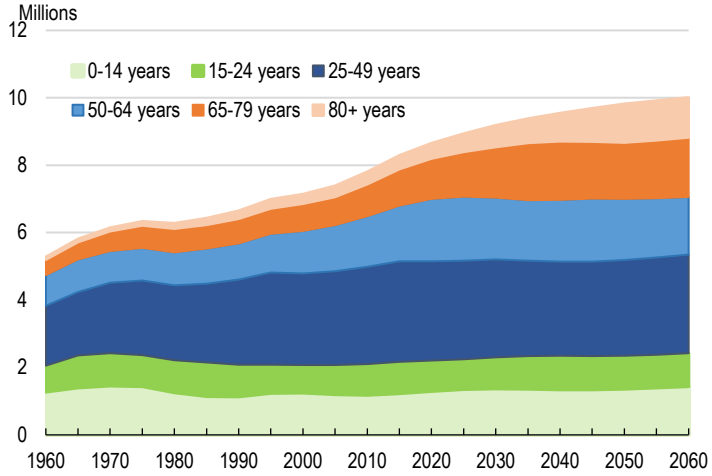
Some other European countries have already seen decreases in life expectancies in recent years (e.g. Wales, England [9]). Some possible explanations for this decline include a slowdown in mortality improvements, increasing socio-economic inequalities, and financial pressures on national health systems, which may have affected quality and coordination of care for older adults in particular [10-12]. At the same time, Switzerland has seen steady increases in life expectancies in recent years. Due to the currently ongoing COVID-19 pandemic, however, life expectancy in Switzerland declined by two years in 2020 [13]. Further, it is expected that the decline will continue in subsequent years. Despite this decline, the overall life expectancy is expected to remain high in Switzerland in the coming decades and the population group of adults aged ≥ 65 years will constitute a growing part of the Swiss society. Consequently, irrespective of the COVID-19

[2] This estimate was published before the global COVID-19 pandemic.

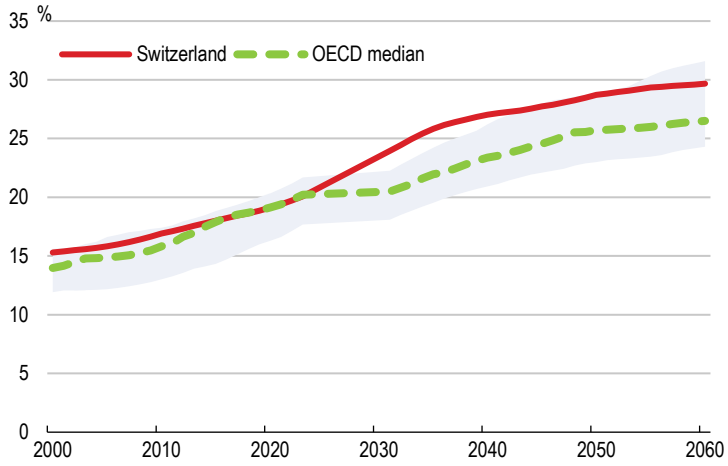
pandemic, social security and health systems globally must adapt in order to take care of the increasing proportion of older adults in the population.

Figure 1. Prediction of the development of the age distribution of the Swiss population

A. Swiss population by age group, from 1960 to 2060



B. Population share of those aged ≥65 years, from 2000 to 2060



Source: United Nations (2019), World Population Prospects: The 2019 Revision, Online Edition; OECD Economics Department Long-term Model (at June 2019).

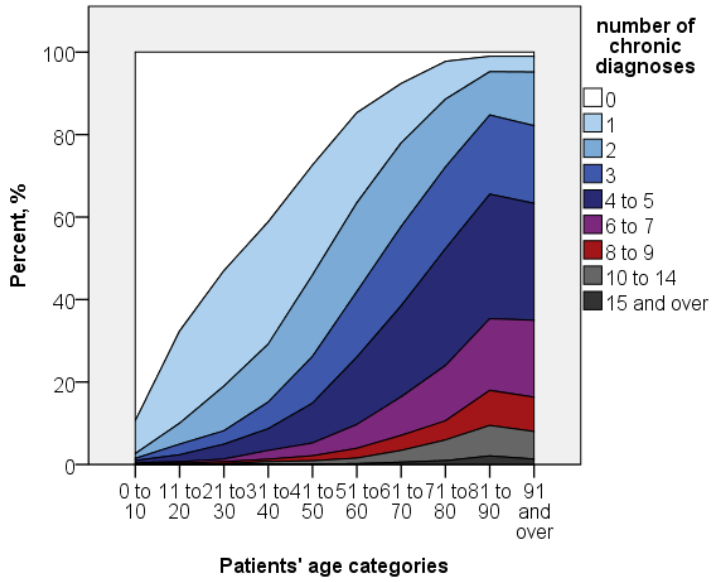
5.2 Multimorbidity

With ageing societies also come growing numbers of older adults with chronic conditions. This is mainly due to increased life expectancies and certain diseases being more prevalent in older age. Age is a strong risk factor for many chronic conditions (e.g., dementia, cardiovascular disease, and cancer) [14]. However, more than half of older adults aged ≥65 years has not only one but several chronic conditions [15]. The coexistence of multiple chronic conditions and diseases is commonly referred to as multimorbidity in the scientific literature. Although there are multiple approaches to defining multimorbidity, the most commonly used approach being a count of chronic conditions [16]. The most frequently used definition for defining multimorbidity is ≥2 chronic conditions [17]. While this approach is the most pragmatic one, it does not consider the severity of the coexisting conditions nor cognitive and functional limitations.

Due to the variety of definitions and thresholds used, systematic reviews have observed a wide range of estimates for the prevalence of multimorbidity across different studies and in different population groups, from 12.9% to 95.1% in the primary care setting to 55% to 98% among older adults [15,18]. A recent meta-analysis found a pooled multimorbidity prevalence of 37.9% in high income countries, but also emphasized the high variability between the results from different studies included in the review [19]. A recent study investigating trends in multimorbidity across Europe in adults aged ≥ 50 years found that the multimorbidity prevalence estimate varies across countries [20]. Further, this study found that while some countries saw stable estimates of multimorbidity prevalence (e.g., Sweden, Denmark) between 2004 to 2017, others, such as Switzerland, France, and Germany observed an increase in multimorbidity in both men and women in the same period [20]. Despite this increase in recent years, this study also found that Switzerland has a lower overall multimorbidity prevalence than other European countries [20].

Despite this lower prevalence estimate, Switzerland has a significant population with multimorbidity and the prevalence of multimorbidity significantly increases with age. For example, as shown by a representative study from the Swiss Sentinel Surveillance Network, the distribution of chronic conditions in the Swiss primary care population increases with age (*Figure 2*). While around 50% of adults aged ≥ 50 years have ≥ 2 chronic conditions, the percentage increases to >80% in adults aged ≥ 60 years [21]. Data from the same study shows that the median number of chronic conditions in primary care patients 61-70 years is 3, 4 for patients aged 71-90, and 5 for patients aged >90 years [21]. Another study analyzed a representative sample of patients from a sample of GPs within the Swiss Sentinel Surveillance Network and found similar results [22]. Despite also finding an increase by age, a study using a large Swiss database with electronic health records from the primary care setting found slightly lower multimorbidity rates for these age groups [23].

Figure 2. Chronic conditions and multimorbidity in the Swiss primary care population by age categories.

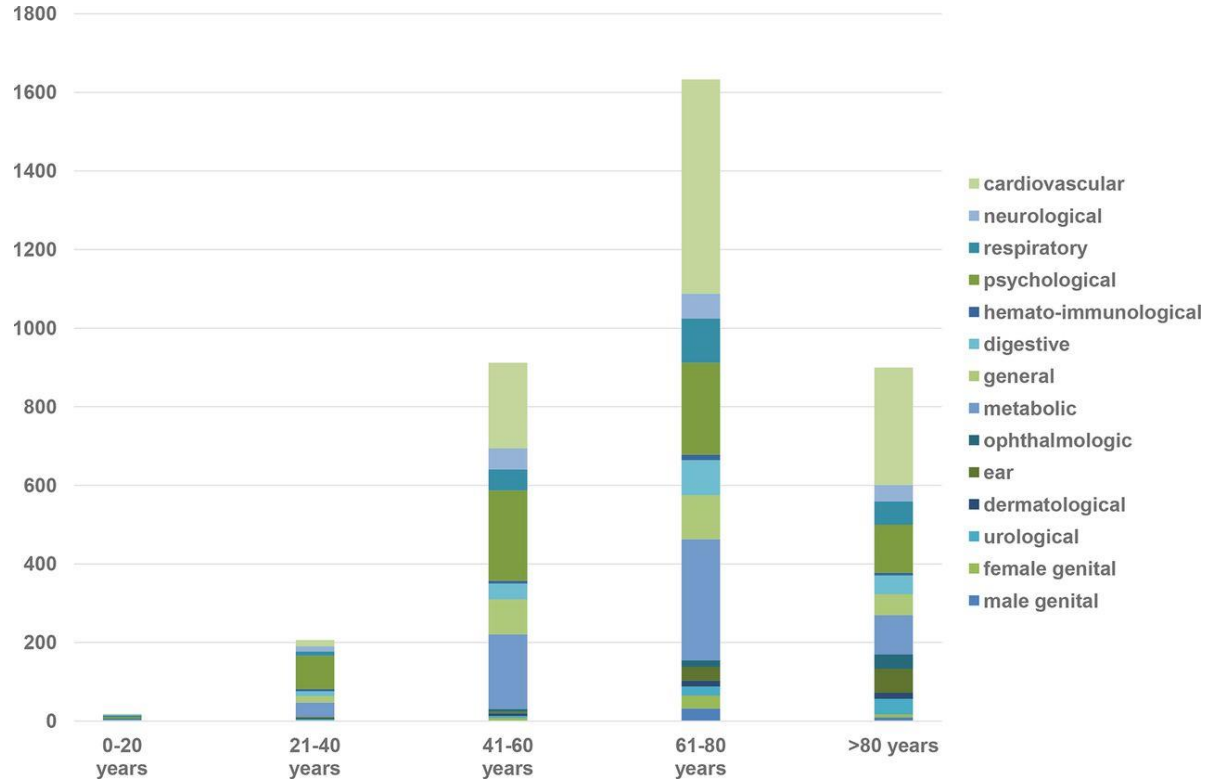


Source: 'Gnädinger, M., Herzig, L., Ceschi, A. et al. Chronic conditions and multimorbidity in a primary care population: a study in the Swiss Sentinel Surveillance Network (Sentinella). Int J Public Health 63, 1017–1026 (2018).' (Figure e2 in the Supplementary Material)

As shown by a cross-sectional study conducted in Switzerland's primary care setting, cardiovascular conditions, age-related and metabolic conditions, tobacco-related and alcohol-related conditions, pain, musculoskeletal as well as psychological conditions were the most frequent chronic conditions [24]. *Figure 3* shows the prevalence estimates of chronic conditions in a representative sample of patients from a sample of GPs who are within the Swiss Sentinel Surveillance Network [22]. This study found that the most common chronic conditions were cardiovascular (43%), psychological (29%), as well as metabolic or endocrine disorders (24%) [22], which is consistent with the other above-mentioned cross-sectional study conducted on this topic.

As shown above, multimorbidity is associated with age. However, age is not the only risk factor for multimorbidity. As shown by a systematic review, female sex and low socioeconomic status are also factors found to be associated with multimorbidity [15]. Multimorbidity poses one of the greatest challenges to health systems, as patients with multimorbidity often have complex healthcare needs and worse health outcomes than healthier, non-multimorbid patients [25,26]. The main consequences of multimorbidity are functional decline and disability, higher mortality, and poor quality of life [15].

Figure 3. Prevalence estimates of chronic conditions in the representative sample of 2904 patients from a sample of GPs within the Swiss Sentinel Surveillance Network.



Source: 'Excoffier S, Herzig L, N'Goran AA, et al. Prevalence of multimorbidity in general practice: a cross-sectional study within the Swiss Sentinel Surveillance System (Sentinella). BMJ Open 2018;8:e019616.'

Multimorbidity is likely to become even more prevalent in the future, due to expected increases in the aging population. The number of conditions in individual patients will increase as well, and is expected to become an increasingly serious problem. For instance, the proportion of patients with ≥ 4 chronic conditions is predicted to double by the year 2035 [27]. This means that there will not only be a larger number of older adults with multimorbidity, but that older adults will live more years being multimorbid and that the cases of older multimorbid adults will be increasingly complex. This in turn is challenging for health systems and will have implications on how care for older adults should be organized in the future in order to be able to provide the best available care.

5.3 Polypharmacy

Patients with multimorbidity often have complex healthcare needs. For instance, with multimorbidity often comes the concurrent use of multiple medications, as patients usually need different medications to manage their chronic conditions. In spite of a lack of consensus in the scientific literature, the concurrent use of ≥ 5 medications is most commonly defined as polypharmacy [28]. However, there exist multiple definitions of polypharmacy in the literature, including counts of medications, therapy durations and care setting [28]. A cut-off of ≥ 5 medications is associated with disability, frailty, mortality, and falls in older adults [29].

As shown by different studies and despite changes across settings, polypharmacy is common in older adults. In the US, 39% of adults aged ≥ 65 years of age used ≥ 5 medications in 2011-2012 [30]. A systematic review found that up to 91% of residents use ≥ 5 medications in long-term care settings [31]. In Switzerland, 17% of all community-dwelling adults and 21% of adults aged ≥ 65 years use ≥ 5 medications as shown by a study using claims data from Swiss health insurers [32]. These results are consistent with findings from a cohort study conducted in the Lausanne area, which showed that 12% of adults in their cohort aged 40 to 81 years have polypharmacy [33]. Another study based on claims data found polypharmacy among 86% of nursing home residents aged ≥ 65 and among only 50% of the community-dwelling adults of the same age [34]. Differences in polypharmacy prevalence estimates can also stem from the use of different definitions.

Table 1 shows that the number of medications used in Swiss primary care patients by sex. The median number of medications increases with age in the general Swiss primary care population [21], suggesting that more complex patients are more likely to have polypharmacy. Indeed, multimorbidity, frailty, obesity, chronic pain, certain chronic conditions (e.g., metabolic syndrome, gastrointestinal conditions) as well as a decreased physical and mental health status are factors associated with polypharmacy in older adults [35-38].

Due to medical advancements, more treatment options (e.g., approved medications available on the market) and regularly updated evidence-based treatment recommendations, polypharmacy is a common characteristic of modern medicine. Despite the fact that polypharmacy is often viewed negatively, it can be a desirable situation when medications are used appropriately. This implies that using “many drugs” is not equivalent to using “too many drugs”. Appropriate polypharmacy denotes a situation in which patients receive the most appropriate combination of available medications based on the best available scientific evidence and their clinical conditions and in which drug-drug and drug-disease interactions have been minimized [39]. Appropriate

polypharmacy improves quality of life, prevents negative consequences of disease and thereby improves health outcomes [39].

Table 1. Number of drugs by age categories in Swiss primary care population.

Age categories	Drugs *Median (IQR)*	
	Men	*Women*
0 - 10	0 (0-1)	0 (0-1)
11 - 20	0 (0-0)	0 (0-0)
21 - 30	0 (0-0)	0 (0-1)
31 - 40	0 (0-1)	0 (0-1)
41 - 50	1 (0-2)	1 (0-2)
51 - 60	2 (0-4)	2 (0-4)
61 - 70	3 (1-5)	3 (1-5)
71 - 80	4 (3-7)	4 (2-6)
81 - 90	5 (3-7)	5 (4-8)
≥ 91	5 (3-7)	5 (3-8)

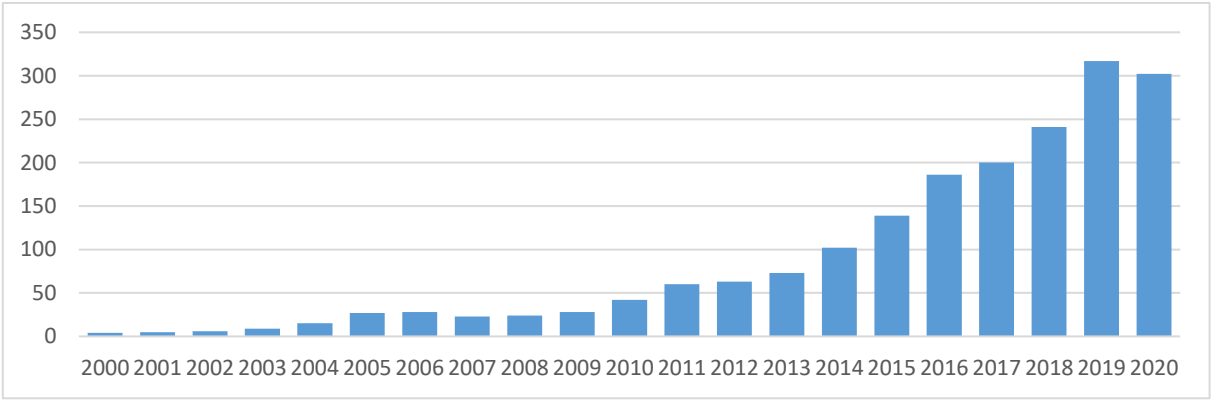
Source: 'Gnädinger, M., Herzig, L., Ceschi, A. et al. Chronic conditions and multimorbidity in a primary care population: a study in the Swiss Sentinel Surveillance Network (Sentinella). Int J Public Health 63, 1017–1026 (2018).' (extract from Table e4 in the Supplementary Material).

On the other hand, inappropriate polypharmacy denotes a situation in which medications are used without clinical indications, doses are inadequate, or there are unacceptable side-effects, drug-drug or drug-disease interactions [40]. Inappropriate polypharmacy can be harmful to patients' health [29], as it is associated with fractures and falls [41], cognitive decline [42,43], a decrease in quality of life [41], adverse drug events, mortality, and hospitalizations [44]. Despite polypharmacy being associated with potentially inappropriate medication use [45], it should not be used as a synonym thereof, as there can indeed be situations of appropriate polypharmacy. The pure numerical count of the number of medications, which is commonly used to define polypharmacy, does not allow for an evaluation of the appropriateness of medication use. In the next sub-chapter, I will describe different ways of identifying and measuring inappropriate polypharmacy.

5.4 Use of Potentially Inappropriate Medication in Older Adults

Patients with polypharmacy are at an increased risk of using potentially inappropriate medications (PIMs) [46-49]. PIMs are medications for which the risk of adverse event outweighs the clinical benefit. They should be avoided specifically when there are safer or more effective alternative medications available that can be used in older adults [50]. In addition to the use of multiple medications (in other words: having polypharmacy), female sex and a higher number of ambulatory healthcare and emergency department visits are associated with the utilization of PIMs [49]. As shown by *Figure 4*, there is an increasing interest in studying the use of PIMs in older adults since the beginning of the 21st century. While there were a handful of scientific papers mentioning "potentially inappropriate medications" at the turn of the last century, the number has risen to around 300 as of 2020.

Figure 4. Search query on *pubmed.gov* for 'Potentially Inappropriate Medications', by year.



Source: https://pubmed.ncbi.nlm.nih.gov/, accessed January 27, 2021

The main consequences associated with the use of PIMs in older adults are an increased risk of adverse drug events, cognitive impairment, and falls [51-55]. A systematic review and meta-analysis found a significant association between PIM use and adverse drug reactions (Odds ratio (OR) = 1.44, 95% confidence interval (CI) 1.33-1.56) [51]. In this study, the authors also observed that the risk of adverse events was higher in patients who used ≥ 2 PIMs [51]. A recent study conducted with hospitalized patients aged ≥ 65 years observed that 66% of patients were prescribed a PIM at hospital discharge (31% were prescribed a new PIM during their hospital stay and 49% continued a PIM, which had been used minimum three months prior to the hospital admission) [56]. Their main study finding was that both chronic PIM use (OR = 1.10, 95% CI 1.01-1.21) and new PIM use (OR = 1.21, 95% CI 1.01-1.45) were positively associated with an increased risk of patients having an adverse event [56].

It follows that the use of PIMs is also associated with increased health services use, emergency department visits and hospitalizations, thereby contributing to healthcare costs [57-60]. The systematic review on the association between the use of PIMs and adverse health outcomes found a significant association between PIM use and hospitalizations (OR = 1.27, 95% CI 1.20-1.35) [51]. Further, a prospective cohort study conducted in community-dwelling adults aged ≥ 65 years observed that older adults with PIM use had a higher rate of GP visits compared to those without PIM use (adjusted incident rate ratio (IRR) =1.15, 95% CI 1.06-1.24) [61]. The current scientific evidence, however, remains inconclusive on whether the use of PIMs is positively associated with mortality [51,62-64]. For example, the above-mentioned systematic review on the association between the use of PIMs and adverse health outcomes found a statistically non-significant association between PIM use and mortality (OR = 1.04, 95% 0.75-1.45) [51].

Different criterion-based (explicit) and judgment-based (implicit) lists to define PIMs exist in the scientific literature. Implicit criteria focus largely on the patient rather than different medications or medical conditions, whereas explicit criteria are specific statements that identify PIMs in specific clinical circumstances [65]. Explicit lists are commonly based on scientific evidence and expert opinions [65]. As shown by a recent systematic review, around 62% of all available tools for the assessment of the appropriateness of medication use are explicit tools [66]. The use of implicit criteria is time-consuming and heavily relies on the knowledge and experience of the prescriber about a particular patient. On the other hand, explicit criteria are much faster to use, but do not take into account patient factors and individual circumstances. Consequently, a medication that is indicated and appropriate to be used in a specific patient (e.g., due to patient preferences, allergy of alternative medication, alternatives did not work, etc.) may still be flagged as potentially inappropriate by an explicit tool. Despite these shortcomings, explicit lists to identify PIMs in older adults are the most commonly used tools in research due to their pragmatic nature.

As shown by *table 2*, there are a variety of lists that can be used for identifying PIMs. A systematic review on validated explicit criteria for identifying PIM use in older adults identified 36 such lists up to the year 2017 [67]. One example is the ‘Screening Tool of Older People's Prescriptions’ (STOPP) criteria, an evidence-based tool to inform prescribing in older adults based on an expert consensus [68,69]. Version 2 of STOPP, published in 2015, has 80 criteria including “Long-term aspirin at doses greater than 160mg per day (increased risk of bleeding)”, “Anticholinergics/ antimuscarinic drugs in patients with delirium or dementia (risk of exacerbation of cognitive impairment)” and “First-generation antihistamines (safer, less toxic antihistamines now widely available)”, among others [68]. Another example is the Beers criteria, which was first published in 1991 and has undergone multiple updates. The 2019 version of the Beers criteria contains different types of criteria: “medications that are potentially inappropriate in most older adults, those that should typically be avoided in older adults with certain conditions, drugs to use with caution,

drug-drug interactions, and drug dose adjustment based on kidney function" (p. 674) [70]. The STOPP and Beers criteria were used in several of my thesis articles.

Contributors to the prescribing of PIMs are multifaceted. For instance, provider and health-system factors leading to PIM prescriptions are thought to include lack of communication between different prescribers, providers' lack of knowledge in geriatric medicine and geriatric pharmacology, and insufficient time allocated to prescribing and performing medication reviews [71]. Previous research on patient factors associated with the prescribing of PIMs for older adults have focused on broad populations of community-dwelling older adults or patients with selected chronic conditions [72-74]. Consequently, we know little about the patient factors associated with the prescribing of PIMs in older adults with polypharmacy and multimorbidity. Furthermore, since most of the previous studies on this topic did not explicitly exclude patients who were prescribed a PIM, previous results have to be interpreted with caution. Future research should study the factors associated with potentially inappropriate prescribing in patients, who are new to using PIMs (hereafter referred to as PIM-naïve patients). Studying the factors associated with PIM prescribing is crucial as these factors should be considered when designing medication optimization interventions. This may increase the success of interventions designed to improve medication optimization, which have shown limited to no effect on clinical outcomes [75].

Table 2. Selection of explicit lists to identify potentially inappropriate medications, including key characteristics.

Author	Year	List name	Country	Population	Validation method	Evidence
Beers et al. [76,77]	1991, (Updated version in 1997)	Beers criteria	United States of America	Nursing home residents aged ≥ 65 years, Persons aged ≥ 65 years in updated version	Delphi method (two-round)	Literature review, previous versions
Laroche et al. [78]	2007	French criteria	France	Persons aged ≥ 75 years	Delphi method (two-round)	Beers criteria 1991 and 1997; Beers–Fick criteria 2003, McLeod criteria 1997; the criteria adapted to French practice (2001) and the guidelines of the French Medicine Agency on medication prescribing in the elderly
Gallagher et al. [69]	2008	STOPP version 1	Ireland	Persons aged ≥ 65 years	Delphi method (two-round)	Literature review
Rognstad et al. [79]	2009	NORGEP	Norway	Persons aged ≥ 70 years in general practice	Delphi method (three-round)	Beers criteria 1991 and 1997, Beers–Fick criteria 2003, and Swedish recommendations, Norwegian studies and literature
American Geriatrics Society [70,80,81]	2012 (Updated versions in 2015, 2019)	Beers criteria	United States of America	Persons aged ≥ 65 years	Modified Delphi method (two-round)	Literature review
Holt et al. [82]	2012	Priscus	Germany	Persons aged ≥ 65 years	Modified Delphi method (two-rounds)	Beers criteria 1997, Beers- Fick criteria 2003, Mcleod criteria 1997; French criteria 2007 and literature review
Renon-Guiteras et al. [83]	2015	EU (7) PIM list	Europe	Persons aged ≥ 65 years	Delphi method (two-round)	Priscus 2010, French criteria 2007, STOPP version 1, Beers 1997 e 2012, Beers–Fick, Mcleod 1997 and Micromedex
Nyborg et al. [84]	2015	NORGEP-NH	Norway	Nursing home residents aged ≥ 70 years	Delphi method (three-round)	NORGEP 2009
O'Mahony et al.	2015	STOPP version 2	Europe	Persons aged ≥ 65	Delphi method (two-round)	Literature review
Pazan et al. [85]	2018	EURO FORTA ('Fit fOR The Aged') list	Germany / Austria	Older people ≥ 65 years; or ≥ 60 years with ≥ 6 medications	Delphi consensus	Literature review

This table was adapted from: 'Motter FR, Fritzen JS, Hilmer SN, Paniz ÉV, Paniz VMV. Potentially inappropriate medication in the elderly: a systematic review of validated explicit criteria. Eur J Clin Pharmacol. 2018 Jun;74(6):679-700. & Curtin D, Gallagher PF, O'Mahony D. Explicit criteria as clinical tools to minimize inappropriate medication use and its consequences. Ther Adv Drug Saf. 2019;10:2042098619829431.'

PIM use, however, is not only about the over-use of medications that are potentially inappropriate, but also about under-use and under-prescribing of medications and potential prescribing omissions (PPOs). Under-prescribing is defined as a missing pharmacological treatment when there is a clinical indication for this medication and no valid reason for not prescribing the missing medication [86]. The probability of under-prescribing increases with the number of different medications used [86]. A study conducted in the primary care setting, showed that 43% percent of the older patients with polypharmacy were undertreated with regards to one or several of their chronic conditions, while two studies conducted in hospitalized older adults found 58% and 67% of study participants having at least one prescribing omission, respectively [86-88]. The most common potential prescribing omissions were associated with under-use of statins, aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, anticoagulants and calcium supplementation [87,88]. Prescribing omissions are not only associated with polypharmacy, but also with increased age, and the number of chronic conditions [87]. Prescribing omissions have been found to be associated with a higher rate of emergency department visits (incidence rate ratio (IRR) = 1.30, 95% CI 1.02-1.66) and GP visits (IRR = 1.14, 95% CI 1.06-1.24) in a prospective cohort study with older community-dwelling adults aged ≥ 65 years conducted in Ireland [61]. Furthermore, the same study showed that prescribing omissions were associated with functional decline in activities of daily living (ADL) (OR = 1.55, 95% CI 1.07-2.25). To identify situations in which there is under-prescribing in older adults, tools such as the 'Systematic Tool to Alert doctors to the Right Treatment' (START) criteria were established. START is an evidence-based screening tool based on an expert consensus, which contains 34 criteria like "start warfarin in the presence of chronic atrial fibrillation", "ACE inhibitor following acute myocardial infarction", "calcium and vitamin D supplement in patient with known osteoporosis" [68,69,87].

Some of the existing lists to identify PIMs have geographical particularities and are specific to certain settings (e.g. geriatrics, primary care, palliative care, etc.). Thus they may not be widely used (e.g., some medications on the Beers list are not available on the European market). The content of the criteria also differ. While some contain information about which medications and/or dosages should be avoided in older adults, others highlight potential drug-drug or drug-disease interactions. The tools have been created for and validated in different settings (e.g., slightly different age groups, community-dwelling vs. nursing home, etc.). These differences imply that different studies may lead to different results. For instance, a systematic review and meta-analysis on the association between health outcomes and PIM use revealed that their results changed when different criteria were used for the analysis [51]. To conclude, when using these lists for research purposes, we as researchers must bear in mind these strengths and limitations in order to accurately interpret our findings.

Aside from context-specific differences, variations in tools and geographic settings may contribute to the observed differences in the prevalence of PIM use and to the variation in the most frequently used PIMs. For example, a study conducted in China among hospitalized patients aged ≥ 65 years found that the most commonly used PIMs were proton-pump inhibitors and benzodiazepine receptor agonists [89]. The most commonly used PIMs in a nationwide cross-sectional study from Portugal were proton-pump inhibitors, benzodiazepines and non-steroidal anti-inflammatory drugs [47]. A population-based study from Canada conducted with data from community-dwelling older adults found proton-pump inhibitors, benzodiazepines, antipsychotics, antidepressants and long-duration sulfonylureas to be the most commonly used PIMs [48]. Irrespective of their differences, the currently available PIM lists also have some commonalities with regards to the most common medication classes reported. In the systematic review by Motter et al. on validated explicit PIM lists, 88% included benzodiazepines, 70% antihistamines, and 57% tricyclic antidepressants [67].

The prevalence in PIM use varies substantially in the existing scientific literature. This can be due to context-related differences in medication use, but also due to the different lists used to define PIMs. For instance, a systematic review of studies on PIM use in older inpatients with and without cognitive impairment found a prevalence of 53% to 90% in patients with cognitive impairment and 30 to 91% in patients without cognitive impairment [90]. A systematic review on the use of PIMs in nursing home residents found a prevalence ranging from 19% to 83% in studies that used the Beers criteria and from 24% to 80% in studies using the STOPP criteria [91]. Although there currently is no systematic review on the utilization of PIMs in older adults in the primary care setting, the findings of individual studies point towards considerable use of PIMs in this setting. For instance, a longitudinal study conducted in Ireland found that 51% of adults aged ≥ 65 years used ≥ 1 PIMs [92]. A nationwide cross-sectional study from Portugal found a PIM prevalence of 69% in primary care patients aged ≥ 65 years [47]. A population-based cohort study from Quebec, Canada found that 44% community-dwelling older adults aged ≥66 years used ≥ 1 PIM. These findings point to a high prevalence of PIMs in older adults irrespective of cognitive impairment.

Research efforts have primarily focused on the use of PIMs in patients with specific diseases or in specific settings (e.g., community dwelling older adults vs. nursing homes residents, hospitalized patients, patients with Alzheimer's disease) or in older adults more generally [51,57,93-95]. Consequently, there is a lack of evidence on the utilization of PIMs in older adults with multimorbidity and polypharmacy, despite the fact that this population may be at an increased risk of adverse health outcomes.

5.6 Deprescribing

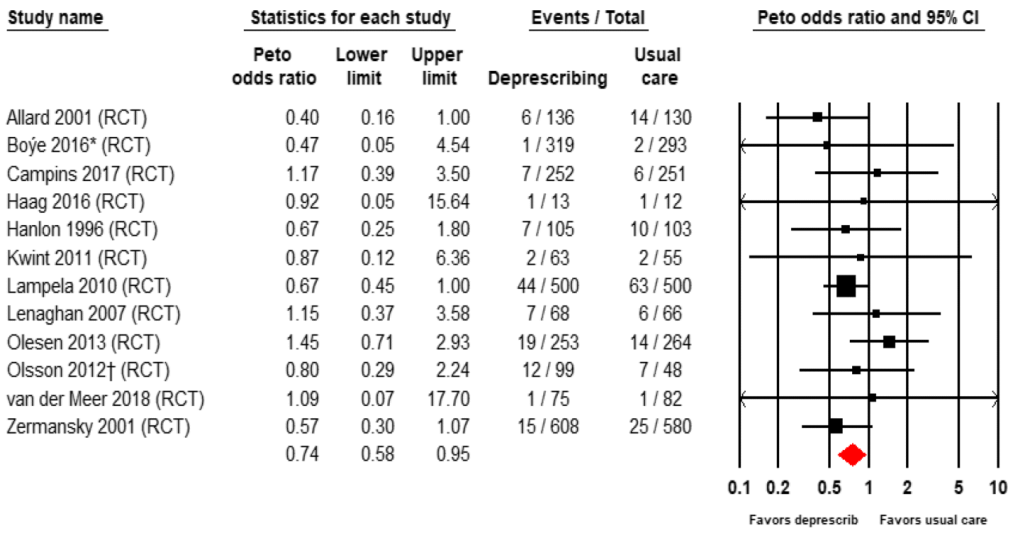
Throughout the previous chapters, I demonstrated that a large share of older adults use multiple medications. However, the risk-benefit profile of older adults changes throughout their ageing process, which in turn puts older adults a greater risk of medication-induced harm. Changes in physiological properties that occur during the ageing process lead to changes in pharmacokinetic and pharmacodynamic properties. This alters the absorption and efficacy of certain medications in older adults and can lead to an increased rate of adverse drug reactions [96,97]. Patients with polypharmacy have a higher risk of using potentially inappropriate medications. In addition, older patients may not have sufficient remaining lifespan to benefit from the use of preventive medications [98,99]. As patients age, their main treatment goals often shift from the prevention of morbidity and mortality to maintaining quality of life and functional independence. Research has shown that self-management and end-of-life care planning are crucial for older patients with multimorbidity [100]. These elements should thus be important factors to be considered when taking prescribing decisions and performing medication reviews in older adults.

Since quality of life, function and independence of older adults are closely linked to the medication use, as demonstrated in the section on PIMs (refer to *Section 5.4* 'Use of Potentially Inappropriate Medication in Older Adults'), stopping or reducing certain medications can have a big impact on patients' health and wellbeing. Patients would benefit from deprescribing interventions especially in situations when the risk of adverse events outweighs the clinical benefits of the medications. Deprescribing is a relatively new concept and has received increasing attention in recent years [101,102]. A systematic review on different definitions of deprescribing proposed the following one: deprescribing is "the process of withdrawal of an inappropriate medication, supervised by a healthcare professional with the goal of managing polypharmacy and improving outcomes" (p. 81) [103]. Rather than just referring to the withdrawal of medications, I would rephrase it to "withdrawal or reduction of" medications to account for the fact that deprescribing is not only the stopping of medications. Further, some of the existing definitions also include the substitution of medications [103].

Main concerns related to deprescribing are whether it is safe for patients and whether it has a positive impact on patients' health outcomes. So far, several randomized and non-randomized studies have evaluated the safety of deprescribing interventions and the impact of clinical outcomes. The results of these studies have been synthesized in multiple systematic reviews and meta-analyses, some of which focus on specific settings. For instance, a systematic review and meta-analysis showed that deprescribing significantly decreased mortality in non-randomized studies (OR = 0.32, 95% C) 0.17-0.60), but this finding was not statistically significant in the

randomized clinical trials (OR = 0.82, 95% CI 0.61-1.11) [104]. Another systematic review and meta-analysis of clinical trials conducted in older community-dwelling adults found that deprescribing as a result of comprehensive medication reviews was associated with a reduction in all-cause mortality (OR = 0.74, 95% 0.58-0.95) (*Figure 5*), but had little to no effect on hospitalization rates (relative risk (RR) = 1.07, 96% 0.92-1.26) and falls (the results from different studies could not reliably be pooled) [105]. The same systematic review and meta-analysis noted that educational deprescribing interventions had little to no effect on hospitalizations and all-cause mortality [105]. Similarly, another systematic review and meta-analysis highlighted that patient-specific deprescribing interventions led to a reduction in mortality (OR = 0.62, 95% CI 0.43-0.88), but that educational programs educating physicians about deprescribing did not (OR = 1.21, 95% CI 0.86, 1.69) [104]. Furthermore, a systematic review on studies conducted in the nursing home setting showed that deprescribing interventions were associated with a decrease in all-cause mortality (OR = 0.74, 95% CI 0.65-0.84) and with a decrease in the number of falls (OR = 0.76, 95% CI 0.62-0.93) [106]. Another trial published in January 2021 found that a 5-step deprescribing intervention involving a multidisciplinary care team consisting of physicians, nurses, and pharmacists was associated with a reduction in hospitalizations (Hazard ratio (HR) = 0.16, 95%CI 0.10-0.26) and a reduction in mortality (HR = 0.16, 95% CI 0.07-0.41) among nursing home residents aged ≥ 65 years of age [107]. Their analysis also showed a reduction in pill burden and in daily cost of around 7 USD. However, their results did not show a significant reduction in the number of falls (OR = 1.41, 95%CI 0.58-3.43) [107].

Figure 5. All-cause mortality for comprehensive medication review randomized controlled trials.

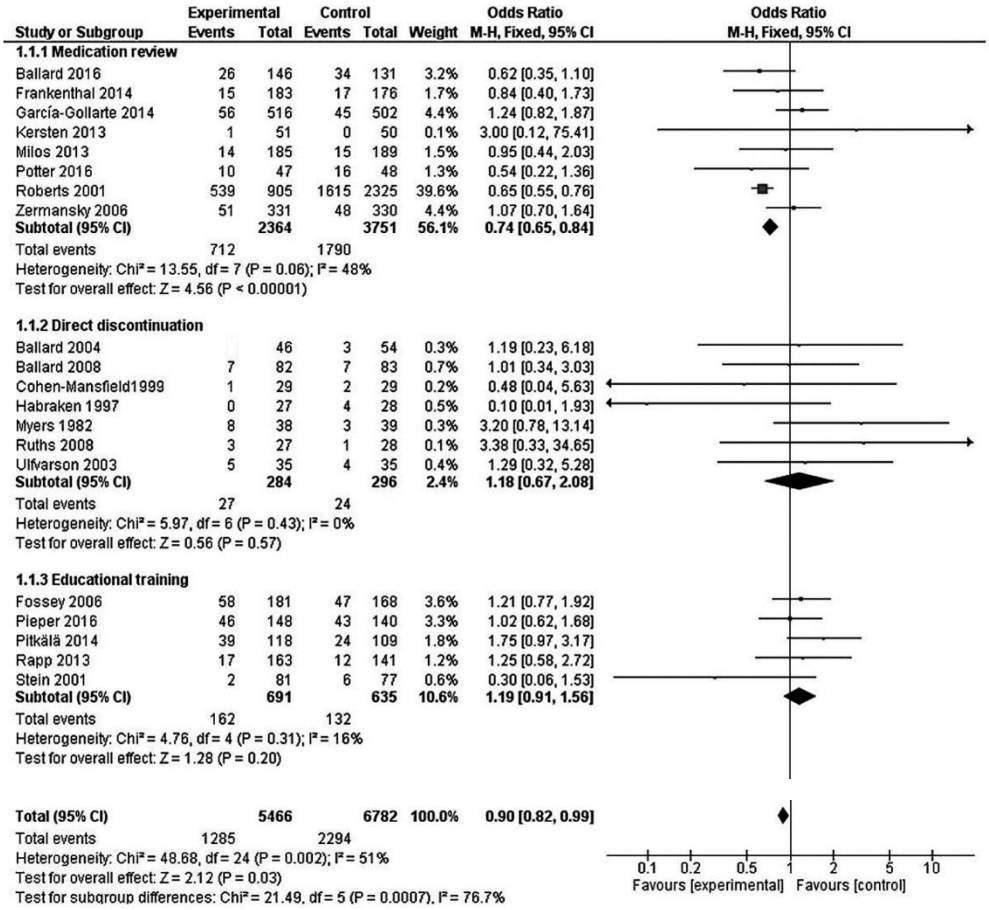


I^2 = 0%; *The authors reported the participants who died in the study flow chart but did not include them in the analyses. † Intervention arms combined.

Source: 'Bloomfield HE, Greer N, Linsky AM, Bolduc J, Naidl T, Vardeny O, et al. Deprescribing for Community-Dwelling Older Adults: a Systematic Review and Meta-analysis. J Gen Intern Med. 2020;35(11):3323-32.'

In the systematic review on different deprescribing interventions in nursing home residents, as shown by *Figure 6*, different types of deprescribing interventions had different effect sizes on mortality in nursing home residents [106]. This is line with the results of the systematic review on medication optimization interventions in community-dwelling older adults, which found different results for different types of deprescribing interventions [105]. Overall, these systematic reviews highlight that deprescribing interventions appear to be safe. One of the systematic reviews emphasized, however, that the included studies varied in terms of quality, primary outcomes (e.g., most focused on the feasibility of deprescribing and may not have been powered to detect safety outcomes), health and age of participants, follow-up duration, and type of deprescribing interventions [104]. This may explain the contradictions and uncertainties in the overall findings.

Figure 6. Effect of deprescribing on mortality in nursing home residents.



Source: 'Kua C-H, Mak VSL, Huey Lee SW. Health Outcomes of Deprescribing Interventions Among Older Residents in Nursing Homes: A Systematic Review and Meta-analysis. Journal of the American Medical Directors Association. 2019;20(3):362-72.e11.' *(extract of original figure presented)*

Deprescribing not only seems to be safe for patients and beneficial for certain clinical outcomes, it also has also been shown to contribute to better health outcomes through resolving adverse

drug reactions, better medication adherence, and direct medical cost reductions [108]. Nonetheless, multiple systematic reviews of deprescribing trials showed that deprescribing did not lead to a difference in quality of life between intervention groups and control groups, in which usual care was provided [105,109]. In the nursing home setting, a systematic review of different deprescribing trials showed that deprescribing led to a decrease in the number of PIMs used (OR = 0.41, 95% CU 0.19-0.89) [106].

Deprescribing may also lead to negative consequences such as worsening health conditions, the return of medical conditions, or withdrawal symptoms. For instance, a systematic review of deprescribing interventions in the primary care setting showed that while deprescribing of long-term medication use was safe with regards to clinical outcomes (e.g., health-related quality of life, Mini Mental State Exam, number of new falls, etc.), there was a risk of symptom relapse [110]. Potential harms resulting from deprescribing can be reduced by informing patients about potential negative consequences, planning, monitoring the patients' health status, and restarting medications if needed [108]. Despite potential risks being associated with deprescribing, overall findings suggest that deprescribing interventions seem to be safe and beneficial for patients in different settings.

However, deprescribing interventions may be difficult to implement. As pointed out by a systematic review, 20-100% of patients agreed to have a medication deprescribed but there was also a relapse of symptoms and medication use in 2%-80% of patients [110]. In a recently published trial from Switzerland that tested a patient-centered deprescribing intervention, only 8% of medications remained stopped at the end of the follow-up period. Certain medications were reported to be restarted and new ones were added [111]. The same trial found that the deprescribing intervention led to an immediate decline in the number of medications used, but six and twelve months after the intervention there no longer was a significant difference between the intervention and control groups with regards to this outcome [111]. This shows that deprescribing is challenging to implement in a sustainable manner in clinical practice and may explain why deprescribing interventions did not show any effect on certain outcomes (e.g., outcomes which may need a longer time to adapt). The reasons for these implementation challenges are multifaceted. In reality, both patients and physicians report barriers to deprescribing.

Knowing the barriers and facilitators to deprescribing decisions in both physicians and patients is key for informing the development of interventions designed to have a sustainable impact. *Table 3* summarizes results from a systematic review on patient barriers and enablers towards deprescribing and shows that barriers to deprescribing are diverse. A qualitative study conducted in Switzerland with multimorbid older patients with polypharmacy found that physician inertia and fragmented care were major barriers to deprescribing [112]. Consequently, the authors write that

patient involvement and coordination of care are crucial factors for deprescribing in this patient group [112]. Despite these barriers, multiple observational studies found that >70% of patients would be willing to stop ≥ 1 medications (e.g., 77% in Switzerland [113], 88% in Australia [114], 92% in the United States [115], and 83% in Singapore [116]). A study from Malaysia of older adults with polypharmacy and ≥ 1 chronic condition found that 83% of participants reported to be willing to stop one or more medications if their physician said that this was possible [117]. While these estimates need to be interpreted with caution (e.g., social desirability bias, hypothetical deprescribing decisions not specific to certain medications), they indicate that older patients seem to be open to optimizing their medication use through deprescribing. Researchers and clinicians can build on this willingness to create sustainable deprescribing interventions.

To create successful deprescribing interventions, not only patient factors, but also factors related to prescribers (e.g. GPs) should be considered. Table 4 shows prescriber barriers and facilitators to deprescribing adapted from the results of two systematic reviews of the literature [118,119]. Previous research has also investigated physicians' willingness to make deprescribing decisions in different groups of patients. A study conducted with geriatricians found that limited life expectancy cognitive impairment were endorsed as important factors in deprescribing decisions among 96% and 84% of respondents, respectively [120]. In this study, as hypothetical case-vignettes described increasing levels of functional dependency and cognitive impairment, geriatricians were more likely to report deprescribing donepezil, aspirin, atorvastatin and antihypertensive medications. However, little is currently known about GPs' willingness to make deprescribing decisions and about which medications they would be most likely to deprescribe in older adults with polypharmacy. In particular, which and how patient characteristics (e.g., history of cardiovascular disease, functional independency in ADL) influence general practitioners' deprescribing decisions should be further studied.

Table 3. Patient barriers and enablers to deprescribing.

Barriers		Enablers	
Theme(s)	*Sub-theme(s)*	*Theme(s)*	*Sub-theme(s)*
Appropriateness	-Medication is currently necessary/beneficial -Hope of future benefits -Psychological benefits of taking the medication -Lack of suitable alternative/unwillingness to try alternatives -Desire for increased dose of medication -Mistrust/scepticism of recommendations to deprescribe -Acceptance of medical conditions and thus need for medications	**Appropriateness**	-Experiencing side effects -Fear of side effects -Medication is not necessary -Lack of efficacy -Fear of addition/dependency -Considering alternative treatment option -Unsure about continued need -Mistrust of prescriber who started the medication
Fear	-Psychological issues related to cessation/non-specific fears -Fear of return of condition -Fear of withdrawal effects	**Process**	-Knowledge that medications could be restarted -Follow-up/Physician support available -Other support available (e.g., friends, family) -External factors relating to ability to deprescribe removed
Process	-Lack of primary care physician support/time -Unknown how to cease/conflicting information -Need for appropriate timing for deprescribing	**Influences**	-Influence of general practitioner -Other advice
Influences	-Previous bad experiences with deprescribing -Influence of general practitioners, family, friends	**Dislike**	-Psychological benefit of deprescribing -Inconvenience (including cost) -General dislike of taking medications -Medications are unnatural -Stigma associated with taking medications
Other	-Pragmatic considerations -Habit -Not wanting to have one's mind occupied with tapering -Guilt related to depriving loved ones of something that might work	**Other**	-Lack of fear of consequences of stopping -Concern about compatibility of drugs

Adapted from: 'Reeve E, To J, Hendrix I, Shakib S, Roberts MS, Wiese MD. Patient barriers to and enablers of deprescribing: a systematic review. Drugs Aging. 2013 Oct;30(10):793-807.'

Table 4. Prescriber barriers and enablers to deprescribing.

Barriers		Enablers	
Theme	*Sub-theme(s)*	*Theme*	*Sub-theme(s)*
Awareness	-Discrepant beliefs & practice. -Prevailing attitudes and assumptions towards older patients. -Poor insight	**Awareness**	-Review, observation, audit & feedback
Inertia	-Prescriber beliefs/attitude: fear of unknown/negative consequences, drugs work, few side effects, prescribing is kind, stopping is difficult/futile/will fail, stopping is a lower priority compared to starting -Prescriber behavior: devolve responsibility	**Inertia**	-Prescriber behavior: devolve responsibility -Prescriber beliefs/attitude: fear of negative consequences of continuation, positive attitude towards deprescribing, stopping brings benefits
Self-efficacy	-Skill and knowledge gaps, "doctor knows best" attitude -Information/influencers: lack of evidence, incomplete clinical picture, single disease focused guidelines, influence by specialists and other health professionals, "professional etiquette" -Lack of deprescribing guidance and tools	**Self-efficacy**	-Information/decision support: data to quantify benefits/harms, dialogue with patients, access to specialists -Skills/attitudes: confidence, work experience, training
Feasibility	-Patient: patent uncertainties, resistance to change, poor acceptance of alternatives, discrepant goals to prescriber -Resources: time and effort, insufficient reimbursement, limited availability of effective alternatives -Work practice: prescribe without review -Medical culture: Prescribers' right to autonomy -Health beliefs and culture: Culture to prescribe more, prescribing validates illness -Regulatory: Quality measure driven care -Fragmented care: Lack of shared IT between primary care, specialist care, hospital care, and pharmacist	**Feasibility**	-Regulatory: raise prescribing threshold, monitoring by authorities -Patient: receptivity/motivation to change, poor prognosis -Resources: adequate reimbursement, access to support services -Work practice: stimulus to review

Adapted from: 'Anderson K, Stowasser D, Freeman C, et al. Prescriber barriers and enablers to minimising potentially inappropriate medications in adults: a systematic review and thematic synthesis. BMJ Open 2014;4:e006544.' & 'Doherty AJ, Boland P, Reed J, Clegg AJ, et al. Barriers and facilitators to deprescribing in primary care: a systematic review. BJGP Open 2020; 4 (3): bjgpopen20X101096.'

5.7 Use of Electronic Clinical Decision Support Systems for Conducting Medication Reviews

Clinical decision support systems (CDSS) are computerized or non-computerized tools that are intended to improve healthcare delivery by supporting healthcare professionals in their decision making [121]. In this section, I focus on electronic, computerized CDSS, which became possible due to the digital revolution and represent a new, promising paradigm in medicine. Electronic CDSS are software-based tools that are capable of managing large amounts of data and are designed to be a direct aid to clinical decision making [122]. In the context of rapidly expanding amounts of clinical data (e.g., electronic health records, disease registries, etc.) the use of such tools helps to use all the available data in order to improve patient care. Electronic CDSS are able to match information such clinical knowledge and evidence-based guidelines to patient information and thereby can generate patient-specific recommendations or assessments [122]. When being presented to healthcare professionals and patients, these recommendations can then be used to enhance and facilitate medical decision-making.

The use of CDSS has multiple advantages. For instance, it helps improve patient care and safety (e.g., by reducing prescribing errors), increase adherence to clinical guidelines, increase physician performance, and contain costs (e.g., by suggesting cheaper alternative medications) [123-125]. On the downside, however, the use of CDSS can lead to fragmented workflows (e.g., when different CDSS are not integrated in the electronic health record systems used), the triggering of inappropriate alerts/recommendations/assessments, alert fatigue, and a need for continuous system and content maintenance [123]. Further, the functionality of electronic CDSS is limited when data flows (e.g., from electronic health record systems to CDSS) do not work appropriately or when the data used in the CDSS is not of high quality. Consequently, while they are promising tools, electronic CDSSs need to be further studied and developed to make the most of their potential.

Electronic CDSSs are particularly valuable and advantageous in situations where large amounts of data need to be handled, such as when performing medication reviews in patients with different pre-existing conditions and those who are using multiple medications. Medication reviews can be defined as a “structured, critical examination of a patient’s medicines with the objective of reaching an agreement with the patient about treatment, optimizing the impact of medicines, minimizing the number of medication-related problems and reducing waste” (p. 12) [126]. In other words, medication reviews should determine: i) whether the patient still needs to be on all of his/her medications, ii) whether the medicines are helpful to the patient, iii) whether the medicines are causing harm or risk to the patient, iv) whether the patient is happy to continue taking the medications, and v) whether the patient should be offered any additional medication for treated

or untreated conditions [127]. On balance, electronic CDSSs should be leveraged to incorporate the best available scientific evidence and consider all relevant information when performing comprehensive medication reviews.

Indeed, the literature shows that the use of CDSS can be beneficial on different medication-related outcomes. For instance, as shown by multiple systematic reviews, the use of CDSS reduces medication errors, improves the prescribing quality of physicians, and thereby improves medication safety [128,129]. Similarly, as shown by a systematic review, the utilization of electronic CDSS is associated with a decrease in the use of PIMs [130]. Despite these promising results, however, the results of recent completed clinical trials showed negative or inconclusive results related to the efficacy of CDSS on other clinical outcomes. For instance, an electronic CDSS for comprehensive drug review of older adults did not show any effect on unplanned hospital admissions or death after a follow-up period of 24 months in primary care patients [131]. However, in this trial, a decrease in the number of drugs was achieved without detriment to patient outcomes. Next, the use of the CDSS called G-MEDSS by clinical pharmacists when conducting home medicines reviews did not reduce patients' drug burden index after a follow-up period of 3 months [132]. Though trials using new electronic CDSS having been completed, evidence on the efficacy of using such tools when reviewing the medication use of older adults with multimorbidity and polypharmacy remains scarce. Evidence from the primary care setting is particularly lacking.

The mixed evidence on the efficacy of electronic CDSS could also stem from problems related to the implementation of these electronic CDSS. For instance, it has been shown there is a low implementation rate of recommendations generated by CDSS. Recommendations are often ignored or overridden [133]. A mixed-methods study on the usefulness and usability of a CDSS for pharmacogenomics clinical decision support reported the negligence of other relevant patient characteristics as a limitation of this CDSS [134]. Further, a qualitative study of the implementation of a CDSS to manage acute kidney in the hospital setting showed three common pitfalls related to the implementation of CDSS: i) when the technology is not fit for the purpose (e.g., when the algorithm/rules used are too simplistic or too complex), ii) when it takes too much work to make the technology fit for practice (e.g., when every recommendation generated needs to be double checked, which is labor-intensive), or iii) when CDSS use has consequences on ongoing planning and resource use, sustainability of CDSS use may be jeopardized [135]. Another mixed-methods evaluation of a CDSS to help general practitioners with cardiovascular disease risk management showed that integration with practice software, minimal data entry, regular updates with revised and new guidelines, and having a self-auditing feature are crucial for successful implementation [136]. These findings demonstrate the importance of not only studying the efficacy of electronic CDSS, but also the implementation of such tools.

5.7.1 'Systematic Tool to Reduce Inappropriate Prescribing' (STRIP) Assistant

The 'Systematic Tool to Reduce Inappropriate Prescribing' (STRIP) assistant represents an example of an electronic CDSS. The STRIP assistant is a web-based CDSS developed by a team from the Utrecht University and the University Medical Centre Utrecht in the Netherlands [137]. The STRIP assistant is based on the algorithms of the 'Screening Tool to Alert doctors to Right Treatment' (START) criteria and the 'Screening Tool of Older Person's Prescriptions' (STOPP) (version 2) [138]. Both the STOPP and START criteria are evidence-based screening tools established based on expert consensus. They inform prescribing in older adults by indicating situations of over-prescribing and inappropriate medication use (STOPP) and situations of prescribing omissions (START) (refer to the *Section 5.4* 'Use of Potentially Inappropriate Medication in Older Adults' for more information) [68,69,87]. Taking into consideration medication use, diagnoses, vital data and laboratory values, the STRIP assistant generates recommendations for prescribers. There are four different types of recommendations: over-prescribing, under-prescribing (prescribing omissions), interactions (drug-drug or drug-disease), and recommendations to adapt the medication dosage [137]. A validation study showed that the use of the STRIP assistant by general practitioners on two hypothetical test cases of older patients with multimorbidity and polypharmacy helped to increase appropriate prescribing decisions and decrease inappropriate prescribing decisions [139]. The STRIP assistant is currently being tested in multiple clinical trials in different settings [140,141]. In Switzerland, for instance there is the 'OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people' (OPERAM) trial[3] in the hospital setting and the 'Optimizing PharmacoTherapy in older multimorbid adults In primary CAre' (OPTICA) trial in the primary care setting (refer to *Section 5.10.1* below for additional information). The results of the OPERAM trial, in which the use of the STRIP assistant was compared to usual care in older multimorbid patients with polypharmacy who were hospitalized, is currently under review. The main outcome of the OPERAM trial was drug-related hospital readmissions. The results of the OPTICA trial, whose main outcome is medication appropriateness, are expected for 2021.

[3] The OPERAM trial is a multicenter trial. Other trial sites were located in Ireland, Belgium, and in the Netherlands. The protocol paper of the OPERAM trial can be found in *Section 15.1.4.*

5.8 Underrepresentation of Older and Multimorbid Adults in Clinical Research and its Implications on the Available Scientific Evidence

To assess whether a medication is safe and effective to be used in older adults requires new medical products and devices to be tested in a sufficiently large sample of older adults. However, older adults are underrepresented in clinical research, despite shouldering a large share of the global multimorbidity burden and using a large part of available medications [142]. This underrepresentation is often due to the exclusion of older adults from clinical trials based on arbitrary age cut-offs and exclusion criteria related to chronic conditions that are highly prevalent in older adults [143]. For instance, a review examining the inclusion and exclusion criteria of 839 trials investigating drug interventions for ischemic heart disease found that 53% of the trials excluded older adults [144]. Another study comparing the inclusion and exclusion criteria of 440 ongoing randomized trials on type 2 diabetes mellitus registered on the International Clinical Trials Registry Platform (ICTRP) of the World Health Organization (WHO) found that 66% used an arbitrary age cut-off [145]. A review of 623 phase 3 trials that studied major causes for hospitalization and/or disability-adjusted life years in older adults showed that 33% of the randomized trials had an arbitrary age limit with approximately 25% of those trials not allowing adults aged ≥ 65 years to participate [146]. Encouragingly, a review of 742 randomized trials on oncological treatments showed that age limits have become less prevalent over time [147]. But despite this progress, the underrepresentation of older adults remains a challenge in clinical research.

The underrepresentation of older adults in clinical research is problematic because it leads to an evidence base that does not include information on pharmacokinetics, pharmacodynamics, safety and efficacy of medications in older adults. Consequently, effectiveness outcomes and safety concerns that are specific to older adults will not be detected and thus cannot be considered in medical decision making [143]. Despite these shortcomings, regulatory authorities around the world commonly approve medication for use in older adults. Between 2010 and 2018, only 75% of the new medications[4] approved by the American Food and Drug Administration (FDA) contained information on pharmacokinetics in older adults [148]. Information on safety and efficacy of new medications specific to older adults was only present in only 45% of FDA medication approvals in the same period. As such, the risk-benefit assessments of newly approved medications may not be externally valid and it remains unknown whether these medications are safe to use for older adults.

[4] The following drug classes were included in the analyses: 10 most frequently used on-label drug classes, drugs with known pharmacokinetic differences in older adults, drugs that are contraindicated in older adults.

The underrepresentation of complex patients with one or multiple chronic conditions is particularly challenging, even as such patients are increasingly becoming the norm and may be at a higher risk of adverse drug events. A systematic review of registration details of ongoing clinical trials showed that three quarters excluded patients with concomitant chronic conditions [149]. In the aforementioned review on clinical trials related to type 2 diabetes, exclusion of patients with comorbidities was present in 77% and exclusion of patients with polypharmacy was present in 30% of the studies [145]. In the review of trials on major causes for hospitalization and/or disability-adjusted life years in older adults, 37% of trials excluded patients with polypharmacy and concomitant medication use for treating multiple chronic conditions [146]. Similarly, another study found that multimorbidity was less common in clinical trials than in a community population with the same conditions; specifically, the prevalence of chronic conditions in trial participants was only half of the prevalence observed among community-based study participants [150]. The exclusion of more complex patients is done to minimize heterogeneity (e.g., reduce the variability in measured outcomes which helps producing a clearer, more easily interpretable result) and reduce drop-outs (e.g., healthier participants are at a lower risk of dying, drug-drug or drug-disease interactions and side effects) [98,151]. Although the results from such trials may be more easily interpretable, they are only generalizable to a select population group.

The underrepresentation of older patients and/or patients with chronic conditions and polypharmacy is not only due to study designs, but also driven by practical challenges related to the recruitment and retention of older and multimorbid adults in clinical trials. For instance, main barriers to recruiting this type of study participants are linked to their limited mobility due to major health issues, doubts about the usefulness of trials for their own clinical situation, and - in the case of cognitive impairment - their inability to provide informed consent without relatives/representatives present [143,151-153]. Replying to questions or filling in questionnaires as demanded by study protocols is often mentally and physically exhausting for older, more frail adults [143]. Further, since research regulations often consider older multimorbid adults to be vulnerable, there is an increased regulatory burden linked to conducting research with this group, which may discourage research efforts. Despite these challenges, it is crucial for older, multimorbid adults to be able to participate in clinical research, as it is the only way to create evidence-based clinical guidelines that suit their needs and ensure their safety.

5.9 Conducting Clinical Research in the Primary Care Setting

Primary care services are the first point of contact for many older patients with multimorbidity and polypharmacy. Clinical research in the primary care setting aims to improve the effectiveness, quality, and cost-effectiveness of primary care services [154]. Despite its importance for strengthening health care service delivery, improving patient safety and quality of care, and tackling the growing disease burden, primary care research is a relatively new field of research compared to other medical disciplines. It remains underfunded and underdeveloped in many countries [155]. A study from the United Kingdom showed that while around 90% of patient-provider contacts take place in the primary care setting [156], the vast majority of clinical trials and other medical research takes place in the hospital or specialist care setting. The reasons for this disparity are multifaceted and described below.

First, the recruitment of general practitioners for clinical trials in the primary care setting can be challenging [157]. Research has shown that time constraints, lack of training, fear of loss of professional autonomy, concerns about patient well-being, and the lack of rewards and recognition are barriers to research participation for physicians in general, and this also applies to general practitioners in the primary care setting [158]. Additional challenges specific to the primary care setting were reported as follows: a lack of infrastructure for research activities, lack of financial acknowledgment of practice staff involvement, misunderstandings on how daily clinical work in general practice could accommodate clinical research, perceived loss of control when patients participate in trials in which the GPs are only marginally involved, lack of standard processes, lack of benefit for the participating GP, and seasonal changes in the workload [159-161]. In addition, depending on the setup of the primary care setting, it may be more challenging to approach independent GPs, who are not affiliated to any health network, institution, or similar. However, research has also shown widespread support for clinical trials among general practitioners [161]. This willingness to participate in clinical research should be built upon while addressing the challenges that arise when recruiting general practitioners for clinical research.

Second, the study designs used in clinical research in the primary care setting may differ from the “traditional clinical trial”, which is commonly conducted in the hospital setting. Trials in the hospital care setting usually take place in one or multiple study centers located at hospital(s), and have trained study personnel on site. Due to these differences, primary care trials may be more difficult to implement in practice. For instance, general practitioners involved in a trial and their patients may be located in different regions/areas, which may be under the jurisdiction of different ethics committees. Next, interventions for older patients with multimorbidity, a key patient group in the primary care setting, likely involve a team of inter-professional healthcare professionals and may be more complex to integrate into the clinical workflow [162]. This requires a solid collaboration

between inter-professional team members and standardized research protocols. Next, the heterogeneity of study participants, which is often a goal in primary care research in order achieve external validity of study results, may also add an additional layer of complexity. In addition, primary care research may require the use of other outcomes, such as function and patient-reported outcomes, which go beyond cost and quality indicators commonly used in clinical trials [162]. Together with the geographic dispersion of study participants (e.g., patients being treated in multiple primary care practices rather than some large hospitals) this affects how data can be collected for such trials. These differences need to be considered when writing study protocols for primary care trials and should be addressed when getting ethical approval for those trials. Current rules and regulations for the conduct of clinical trials were written with the "traditional clinical trial" in mind, and creative solutions may be needed.

Challenges may also arise when general practitioners play an active role in the trial (e.g., recruiting study participants and/or testing an intervention). All general practitioners and other healthcare professionals from the primary care setting involved in primary care trials must receive adequate training, as specified by the Good Clinical Practice (GCP) guidelines. Providing this training to professionals who are geographically dispersed with busy work schedules can be more challenging compared to a situation where all staff members of a trial are located at the same hospital and are more easily accessible[5]. Further, the training needs to be adapted when these professionals are only involved in specific trial tasks and for the sake of the conduct of the trial may not receive unblinded information. For instance, let us imagine a situation in which general practitioners are involved in the conduct of the intervention with patients in a real-life setting. The general practitioners in the control group of this trial should remain blinded until the end of the trial while they provide usual care in order not to influence their usual care provision. This means that general practitioners involved in the trial cannot receive an in-depth, unblinded training at the beginning of the study, but need a training tailored to their tasks. All these challenges imply that primary care trials need sufficient preparation and creative solutions to comply with the existing clinical trial guideline.

Finally, regulators and funding agencies often have "traditional clinical trials" in mind. Funding sources and grants for primary care clinical research is sparser than for trials in other medical disciplines. In many countries the largest and most prestigious funding agencies have fewer calls for primary care research than for other clinical research (e.g., specialty care, hospital care)

[5] "Traditional clinical trials" usually know the following structure: sponsor and principal investigator (or sponsor-investigator) and on-site trial staff (research fellows, study nurses, etc). This team at the trial site then recruits study participants.

[163,164]. While the funding situation is slowly but steadily improving, it remains a barrier to primary care research.

5.10 Relevant Projects and Data Sources

5.10.1 The 'Optimizing PharmacoTherapy in older multimorbid adults In primary CAre' (OPTICA) Trial

The 'Optimizing PharmacoTherapy in older multimorbid adults In primary CAre' (OPTICA) trial is a cluster randomized controlled trial, which is being conducted in primary care in the German-speaking part of Switzerland. The aim of the OPTICA trial is to investigate whether when being used in older multimorbid patients with polypharmacy the utilization of a new electronic CDSS, namely the 'Systematic Tool to Reduce Inappropriate Prescribing' (STRIP) Assistant [165], improves medication appropriateness compared to a standard care sham intervention. The STRIP Assistant (STRIPA) is based on the algorithms of the and 'Screening Tool of Older Person's Prescriptions' (STOPP) and the 'Screening Tool to Alert doctors to Right Treatment' (START) (version 2) [138], which are lists of medications generally considered to be inappropriate and appropriate in older adults, respectively [68]. The standard care sham intervention in the control group consists of a medication discussion between patients and GPs that is in line with usual care. The co-primary outcomes of the OPTICA trial are the 'Medication Appropriateness Index' (MAI) and the 'Assessment of underutilization' (AOU) [166-168]. In the OTPCIA trial, "secondary outcomes include the degree of polypharmacy, degree of overprescribing, degree of under-prescribing, number of falls and fractures, quality of life, the amount of formal and informal care received by patients, survival, patients' quality adjusted life years (QALYs), patients' medical costs, cost-effectiveness of the intervention, percentage of recommendations accepted and rejected by GPs, and patients' willingness to have medications deprescribed" (p. 1) [141]. Patients who participate in the trial were followed-up for one year. The patient follow-up ended in February 2021. At baseline, 6 months and 12 months, data for the OPTICA trial was collected by conducting phone calls (e.g., sociodemographic information, etc.) with patients or relatives (in case of patients with cognitive impairment) and from the FIRE database (e.g., medications, diagnoses, lab values and vital data) (refer to *Section 5.10.3* for more information on the FIRE project).

The protocol of the OPTICA trial is described in more depth in chapter 3, *Article IV.*

5.10.2 The 'Barriers and enabLers to willingnESs to depreScribing in older patients with multimorbidity and polypharmacy and their General Practitioners' (LESS) study

The 'Barriers and enabLers to willingnESs to depreScribing in older patients with multimorbidity and polypharmacy and their General Practitioners' (LESS) study is a cross-sectional study in

older patients with polypharmacy and general practitioners. The patient part of the LESS study consisted of a questionnaire, which contained hypothetical case vignettes of older patients with polypharmacy and different levels of functional dependency in activities of daily living as well as those with and without cardiovascular disease. For each case vignette, we asked participating general practitioners if they would stop or reduce any medications listed in the case vignette and if so, which ones. More details about the questionnaire and how it was administered to GPs in 31 countries has been reported elsewhere [169,170]. The patient questionnaire mainly consisted of the 'revised Patients' Attitudes Towards Deprescribing' (rPATD) questionnaire for older adults. This questionnaire consists of twenty-two 5-point Likert scale questions on attitudes and beliefs about their medications and deprescribing [171]. Two additional open-ended questions were added to the questionnaire to evaluate the reasons why patients would or would not like to have medications deprescribed. The details of the patient questionnaire have been reported elsewhere [113]. The patient questionnaire was used in a sample of Swiss GPs. Data collection in other European countries is planned for the future.

Article III reports the findings from the LESS GP study in 31 countries. The three other articles published based on the results of the LESS study, which I contributed to as a co-author during my PhD, can be found in the supplementary chapters.

5.10.3 The 'Family medicine ICPC Research using Electronic medical records' (FIRE) Project

The FIRE project is the largest Swiss database collecting anonymous routine patient data from the electronic medical records in primary care practices [172]. Data collection on administrative information (patient, year of birth, and sex), diagnosis codes, laboratory and vital signs measurements, and prescribing information has been ongoing since 2009. As of October 2020, the database of the FIRE project contained data from the electronic health record systems of more than 680 GPs and more than 830,000 patients [173], which comprises around 11% of all Swiss GPs [174] and around 10% of the general population. All Swiss GPs, who use an electronic health record (EHR) system that is compatible with exporting anonymized data to the FIRE project, can decide to join the study. Six of the most commonly used EHR systems in the German-speaking part of Switzerland are compatible with the FIRE project. GPs who participate in the FIRE project exported selected, anonymized data from their EHR every two months. In return, the GPs receive feedback reports that they can use for quality assurance.

I used data from the FIRE project in *Article V*, which compares GPs and patients from the OPTICA trial with those from the FIRE project.

5.10.4 The RPDR-CMS Dataset

The RPDR-CMS dataset is a linked dataset of patients who were enrolled in the Partners Research Patient Data Registry (RPDR) [31] and who were beneficiaries of Centers for Medicare and Medicaid Services (CMS). Administrative claims for these patients were available in the CMS database. The linked dataset contains data from 569,969 participants for the period from January 1, 2007 through December 31, 2014. The RPDR contains data from the EHR from seven hospitals and medical centers in the Boston metropolitan area in the United States of America. Records in the RPDR include “demographics, inpatient and outpatient encounters, labs and results, prescribing and dispensing records, and other medical care” (p. 2) [175]. The Medicare claims are from Medicare Parts A (inpatient coverage), B (outpatient coverage), and D (drug coverage) [175]. The data from the CMS database include information about drugs dispensed, medical diagnoses, and start/end dates of insurance coverage [32,33].

I used data from the RPDR-CMS dataset for *Article I* and *Article II.*

6. Hypotheses and Thesis Aims

The overall objective of my thesis was to study different aspects related to the optimization of medication use in older adults with polypharmacy and multimorbidity. The specific hypotheses and aims of my thesis are detailed below. More information on the study designs and data sources used to study these aims can be found in the next section (*Section* 7 'Thesis Outline').

Hypothesis I: I hypothesized that the use of potentially inappropriate medications (PIMs) in older adults with multimorbidity and polypharmacy is high and that patients with complex health problems (e.g. with different chronic conditions) are at higher risk of being newly prescribed a PIM.

Aim I: To study the use of PIMs in adults aged ≥ 65 years with multimorbidity and polypharmacy (*Article I*) and factors associated with new prescribing of PIMs in this patient group (*Article II*).

Hypothesis II: In spite of barriers to deprescribing, I hypothesized that general practitioners (GPs) are open to making deprescribing decisions in older patients with polypharmacy.

Aim II: To investigate GPs' willingness to make deprescribing decisions in older patients with polypharmacy, to examine which patient characteristics are associated with a higher likelihood to deprescribe and to explore which medications were most likely to be reported as deprescribed (*Article III*).

Hypothesis III: Despite challenges linked to conducting clinical research with older adults with multimorbidity and polypharmacy and GPs, I hypothesized that clinical research in the primary care setting with the aim of optimizing medication use can be achieved with external validity. In addition, I hypothesized that while medication optimization interventions based on clinical decision support systems by GPs in older patients with multimorbidity and polypharmacy are feasible, there are challenges to the implementation of these interventions. I hypothesized that this negatively affects the uptake of medication use recommendations generated by such tools.

Aim III: (1) To describe the baseline characteristics of GPs and patients from the OPTICA trial, including patients' willingness to have medications deprescribed, and to compare them with reference cohorts from a Swiss real-world cohort called the 'Family medicine ICPC Research using Electronic medical records' (FIRE) project (*Article V*); and (2) to perform a mixed-methods analysis of the use and implementation of the 'Systematic Tool to Reduce Inappropriate Prescribing' (STRIP) assistant, an electronic clinical decision support system, during the 'Optimizing PharmacoTherapy In the Multimorbid Elderly in Primary Care' (OPTICA) trial (*Article VI*).

7. Thesis Outline

This thesis is a cumulative work consisting of six publications covering the three above-mentioned research aims. The six publications are displayed in three distinct sections:

Section I: Prescribing and Use of Potentially Inappropriate Medications in Older Adults with Multimorbidity and Polypharmacy

This section consists of two thesis papers. The first article (*Article I*) investigates the use and costs of PIMs in older adults with multimorbidity and polypharmacy over time. The second article (*Article II*) investigates measurable patient factors associated with new outpatient prescribing of PIMs in older multimorbid adults already using multiple medications. This retrospective cross-sectional study and the retrospective cohort study used linked Medicare claims and electronic health records from seven hospitals and medical centers in Massachusetts, United States of America (2007-2014).

Section II: General Practitioners' Willingness to Make Deprescribing Decisions in Older Adults with Polypharmacy

This section consists of one thesis paper. This article (*Article III*) is a cross-sectional case vignette study that investigates deprescribing decisions in general practitioners from 31 countries in the oldest-old patients with polypharmacy as well as different levels of cardiovascular disease history and functional dependency in activities of daily living.

Section III: Conducting Interventional Research with Older Adults with Multimorbidity and Polypharmacy with the Aim of Optimizing Medication Use

This section consists of three thesis papers. The first article in this section (*Article IV*) is the protocol paper of the 'Optimizing PharmacoTherapy In the Multimorbid Elderly in Primary Care' (OPTICA) trial, which is a cluster randomized controlled trial conducted in Swiss primary care. The next article (*Article V*) is a cross-sectional analysis describing the baseline characteristics of general practitioners and patients participating in the OPTICA trial and comparing them to reference cohorts from the 'Family medicine ICPC Research using Electronic medical records' (FIRE) project. In addition, this article explores whether patients recruited from random screening lists are comparable to patients identified directly by their GP during the recruitment process. It also investigates patients' willingness to have medications deprescribed. Finally, the last article (*Article VI*) is a mixed-methods study that explores the use of the 'Systematic Tool to Reduce Inappropriate Prescribing' (STRIP) assistant in a real-life clinical setting during the OPTICA trial.

8. Results

8.1 Section I: Prescribing and Use of Potentially Inappropriate Medications in Older Adults with Multimorbidity and Polypharmacy

Article I: Utilization and Spending on Potentially Inappropriate Medications by US Older Adults with Multiple Chronic Conditions using Multiple Medications

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My contributions: Together with Julie C Lauffenburger and Sven Streit, I conceptualized and designed this study. I had full access to all the data used in this research and I had the main responsibility for conducting the data analysis. I created all figures and tables shown in the manuscript and the supplementary material. I wrote the first draft of the manuscript and I made the necessary changes based on comments made by co-authors and reviewers during the peer-review process.

Tables and Figures in Article I

(as displayed in the published article below)

Figure 1. Different types of potentially inappropriate medications used in adults aged ≥ 65 years with multimorbidity and polypharmacy, from 2007 to 2014

Table 1. Demographics and main clinical characteristics of adults aged ≥ 65 years with multimorbidity* and polypharmacy, by year

Table 2. Percentage of adults aged ≥ 65 years with multimorbidity and polypharmacy who filled ≥1 potentially inappropriate medication by year, sex, and age group

Table 3. Multivariable logistic regression analyses of the association between the use of potentially inappropriate medications and sex or age in 2007 and 2014.

Table 4. Average medication costs spent on potentially inappropriate medications versus all medications in adults aged ≥65 years with multimorbidity, polypharmacy and utilization of ≥ 1 potentially inappropriate medication, by year and sex

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Utilization and Spending on Potentially Inappropriate Medications by US Older Adults with Multiple Chronic Conditions using Multiple Medications

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ABSTRACT

Background: The utilization of potentially inappropriate medications (PIMs) in older adults can lead to adverse events and increased healthcare costs. Polypharmacy, the concurrent utilization of multiple medications, is common in older adults with multiple chronic conditions.
Objective: To investigate the utilization and costs of PIMs in multimorbid older adults with polypharmacy over time.
Methods: This retrospective cross-sectional study used linked Medicare claims and electronic health records from seven hospitals/medical centers in Massachusetts (2007-2014). Participants were ≥65 years old, had ≥2 chronic conditions (to define multimorbidity), and used drugs from ≥5 pharmaceutical classes for ≥90 days (to define polypharmacy). Chronic conditions were defined using the Chronic Conditions Indicator from the Agency for Health Research and Quality. PIMs were defined using the American Geriatrics Society 2019 version of the Beers criteria. We calculated the percentage of patients with ≥1 PIMs and the percentages of patients using different types of PIMs. We used logistic regression analyses to test the odds of taking ≥1 PIMs. We calculated mean costs spent on PIMs by dividing the costs spent on PIMs by the total medication cost.
Results: ≥69% of patients used ≥1 PIM. After adjusting for healthcare utilization, chronic conditions, medication intake, and demographic factors, female sex (2014: Odds ratio (OR)=1.27, 95%CI 1.25-1.30), age (2014: OR=0.92, 95%CI 0.90-0.93), and Hispanic ethnicity (2014: OR=1.41, 95%CI 1.27-1.56) were associated with PIM use. Gastrointestinal drugs and central nervous system drugs were the most commonly-used PIMs. In patients using ≥1 PIM, >10% of medication costs were spent on PIMs.
Conclusion: The utilization of PIMs in US older adults with multimorbidity and polypharmacy is high.

1. Introduction

Multimorbidity, often defined as coexistence of two or more chronic conditions (Johnston et al., 2019), is highly prevalent in older adults with 55-98% of adults aged ≥65 years being multimorbid as shown by a systematic review (Marengoni et al., 2011). In the United States, the prevalence of multimorbidity has increased in the past few decades; in one recent study, ≥90% of adults aged ≥65 years were multimorbid (King et al., 2018). Due to expected increases in the aging population, multimorbidity is likely to become even more prevalent in the future. With multimorbidity often comes polypharmacy, which is commonly understood as the concurrent utilization of ≥5 medications (Masnoon et al., 2017). In the United States, as of 2011/2012, 39% of adults aged ≥65 years used ≥5 medications (Kantor et al., 2015).

The more medications older adults regularly use, the more likely they are to also use potentially inappropriate medications (PIMs)

Abbreviations: AGS, American Geriatrics Society; AHRQ, Agency for Healthcare Research and Quality; CCI, Chronic Condition Indicator; CMS, Centers for Medicare and Medicaid Services; OR, Odds ratio; PIMs, Potentially inappropriate medications; RPDR, Partners Research Patient Data Registry; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

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(Bazargan et al., 2018, Simões et al., 2019, Roux et al., 2020). Potentially inappropriate medications are defined as drugs for which the risk of an adverse event outweighs its clinical benefit (Fu et al., 2004). There are numerous judgment-based (implicit) and criterion-based (explicit) lists to define potentially inappropriate medications (e.g., Beers list, FORTA, STOPP criteria) (Motter et al., 2018, Curtin et al., 2019). The Beers list, published and regularly updated by the American Geriatrics Society (AGS) (American Geriatrics Society, 2015, American Geriatrics Society, 2019, American Geriatrics Society, 2012), are commonly-used in the US.

The utilization of potentially inappropriate medications in older adults can be problematic because it may lead to health problems, such as adverse drug reactions, falls, cognitive decline, and functional impairment (Xing et al., 2019, Masumoto et al., 2018, Koyama et al., 2014, Liew et al., 2019, Fabbietti et al., 2018). This in turn results in greater health service use, in particular hospitalizations and emergency department visits, thus contributing to higher health care costs (Hyttinen et al., 2016, Heider et al., 2018, Lau et al., 2005, Weeda et al., 2020). For now however, the evidence on the association between the use of potentially inappropriate medications and mortality is mixed (Paque et al., 2019, do Nascimento et al., 2017, Huang et al., 2019).

Previous research efforts have largely focused on the utilization of potentially inappropriate medications in older adults more broadly, in patients with specific diseases or in specific settings (e.g. aged ≥65 years, community dwelling vs. older adults in nursing homes, hospitalized older adults, patients with Alzheimer's disease) (Xing et al., 2019, Hyttinen et al., 2016, Cho et al., 2019, Fralick et al., 2020, Tao et al., 2020). Conversely, little is known about the use of potentially inappropriate medications in multimorbid older adults with polypharmacy issues, even though this population may be at even greater risk of adverse health outcomes. Therefore, the goal of this study was to investigate the utilization of and spending on potentially inappropriate medications in older multimorbid men and women with polypharmacy in the US from 2007 to 2014. Exploring these factors could inform interventions and policy discussions on how to optimize pharmacotherapy in this population group.

2. Methods

2.1. Data Source

To perform this retrospective cross-sectional study, we used a linked dataset of patients who were enrolled in the Partners Research Patient Data Registry (RPDR) (Partners Healthcare, 2020) and were beneficiaries of Centers for Medicare and Medicaid Services (CMS), which means that administrative claims for these patients were available in the CMS database. The linked dataset contains data from 569,969 participants from January 1, 2007 through December 31, 2014. The RPDR contains electronic health records from two tertiary medical centers, three community hospitals, a rehabilitation center, and a psychiatric hospital in the Boston metropolitan area. Records include demographics, inpatient and outpatient encounters, labs and results, prescribing and dispensing records, and other medical care. The Medicare claims are from Parts A (inpatient coverage), B (outpatient coverage), and D (drug coverage). These data include information about drugs dispensed, medical diagnoses, and start/end dates of insurance coverage (Desai et al., 2018). The use of pharmacy claims is considered the gold standard for measuring medication utilization (West et al., 1994, West et al., 1995). Therefore, the use of linked data allowed for the complete capture of clinical criteria to define potentially inappropriate medications (e.g., creatinine) and medication utilization by patients.

2.2. Patient Population

2.2.1. Multimorbidity

Chronic conditions were defined using the Chronic Condition Indicator (CCI) of the Agency for Healthcare Research and Quality (AHRQ), which categorizes ICD-9 diagnosis codes as chronic and not chronic (HCUP Chronic Condition Indicator (CCI) 2009). First, we extracted the ICD-9 codes classified as chronic. Then we assigned related codes (e.g. 249.0 secondary diabetes mellitus, 249.1 secondary diabetes mellitus with ketoacidosis, 250.0 diabetes mellitus) to ICD-9 code categories to ensure that people with two closely-related diagnoses were not misclassified as having multiple chronic conditions. We excluded chronic conditions from the CCI related to pregnancy and childbirth due to their non-relevance in our study population. We ended up with 77 categories of chronic conditions (eTable1 in the supplementary materials). This approach allowed us to capture patients with different and more types of chronic conditions, compared to commonly-used lists of comorbidities, such as the Elixhauser comorbidity tool with 30 categories (Elixhauser et al., 1998). We required ≥2 diagnosis codes on separate days for the category to count as a chronic condition to increase the specificity of the underlying condition (Franklin et al., 2019). We considered patients as multimorbid when they had diagnoses from two or more categories, since this cut-off is widely used in the literature (Johnston et al., 2019, Smith et al., 2016, Barnett et al., 2012).

2.4. Polypharmacy

To define polypharmacy, we used information provided by the U.S. Food and Drug Administration on the classification of medications available on the US market into different pharmaceutical classes (e.g., HMG-CoA reductase inhibitors/statins) (U.S. Food and Drug Administration, 2019). Because molecularly-related medications are typically considered interchangeable (e.g., within statins), we measured utilization at the class level (eAppendix1 in the supplementary materials). We defined all pharmaceutical classes with ≥90 days' supply as chronic use (Lauffenburger et al., 2018). To define polypharmacy, days' supply from claims was defined conservatively. First, for fills on the same day, we assumed concurrent utilization and if the recorded durations differed, we selected the medication with the longest supply. Second, for non-concurrent fills, we used a limited shift of supply (30 days) for overlapping utilization. We considered patients as receiving polypharmacy when they had ≥5 pharmaceutical classes with ≥90 days' supply each. This ≥5 medication threshold is commonly used in the literature (Masnoon et al., 2017).

2.5. Inclusion and Exclusion Criteria

Patients were excluded if they did not have any claim (medication, procedure or encounter) from 2007 to 2014 (13,726, 2.4% of total). Second, we restricted the study population to individuals who are ≥65 years of age. Third, we excluded patients if there was missing information on their sex (0.5-3.7% depending on the year). Fourth, we excluded patients if they were enrolled in Medicare for <180 days in the year of the respective analysis. Next, we excluded patients without ≥5 medication classes with ≥90 days' supply each (i.e., long-term use). And finally, we excluded patients who did not have chronic conditions from ≥2 categories as defined above. A cohort flow diagram for each year from 2007 to 2014 can be found in the supplementary materials (eFigure 1).

3. Potentially Inappropriate Medication Use

We identified potentially inappropriate medications using the American Geriatrics Society (AGS) 2019 updated version of the Beers criteria for potentially inappropriate medications use in older adults (American Geriatrics Society, 2019). The Beers criteria contain evidence-based recommendations that are formulated through a consensus panel of experts using the Delphi method (American Geriatrics Society, 2019). We chose to use the 2019 Beers list, rather than previous versions, to inform current clinical decision-making. All

medications dispensed that met any of the drug, dosage, and duration requirements specified in table 2 of the 2019 Beers criteria were identified as potentially inappropriate. Some of the drugs listed in the 2019 Beers criteria are considered as potentially inappropriate only when they are used for more than a certain number of days, together with or without a certain diagnosis, or when certain laboratory values are below a certain level (e.g. creatinine clearance <30mL/min and use of nitrofurantoin). For example, non-cyclooxygenase-selective nonsteroidal anti-inflammatory drugs (NSAIDs) are considered potentially inappropriate when used chronically, which we defined as ≥90 days when no other information was provided (Lauffenburger et al., 2018). We chose to focus on dispensed medications and utilization to confirm that patients actually filled the medications as opposed to just being prescribed them.

3.1. Statistical Analyses

The cohorts were created using the Aetion Evidence Platform (Version: r3.5.20180426_1659), which has previously been validated for a range of studies. (Aetion Evidence Platform®, 2020, Wang et al., 2016) Descriptive analyses were performed with STATA 15.1 (StataCorp, College Station, TX, USA).

We described the demographics and main clinical characteristics of the study participants. We presented a selection of chronic conditions using the Coding Algorithms for Elixhauser Comorbidities by Quan et al. (Quan et al., 2005). We calculated the percentage of patients with ≥1 potentially inappropriate medication in different age groups and in subgroups with different levels of chronic conditions and long-term medication use. We used logistic regression analyses, including multivariable analyses adjusting for measurable covariates (age-continuous, sex-binary, Hispanic ethnicity-categorical, race-categorical, number of chronic conditions-continuous, number of medications dispensed-continuous, number of hospital admissions-continuous, number of emergency department visits-continuous, number of ambulatory visits-continuous, types of comorbidities-categorical), to test the odds of taking ≥1 PIM. We calculated the percentages of men and women using different types of potentially inappropriate medications from 2007 to 2014. We counted the number of unique potentially inappropriate medications in different age groups as well as in subgroups of patients with different levels of chronic conditions and medication utilization. Finally, to capture additional consequences of potentially inappropriate medication utilization, we calculated mean costs spent on PIMs by dividing the costs spent on PIMs by the total medication costs (based on allowed amounts covered by Medicare). We also performed analyses with different thresholds of chronic conditions (<2) and long-term medications (<5, ≥10).

3.2. Ethical approval

This study was approved by the Brigham and Women's Hospital Institutional Review Board.

3.3. Additional information

This research follows the requirements of the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) reporting guideline (von Elm et al., 2008).

4. Results

Of all 569,969 patients in the RPDR-CMS database, between 61,500 and 103,153 met criteria and were defined as multimorbid with polypharmacy for the yearly cross-sectional analyses from 2007 to 2014 (eFigure 1). Their demographics and main clinical characteristics are described in Table 1. The average age (range: 77.3-77.8 years), BMI (range: 28.7-29.1), number of long-term medications (mean: 7.2), and distributions by race/ethnicity stayed fairly similar over time. More differences between years were noted for female sex (decrease from 65.2% in 2007 to 59.3% in 2014), mean number of chronic conditions (increase from 7.2 to 8.4) and certain chronic conditions.

As shown in Table 2, ≥69% of multimorbid older men and women with polypharmacy across all ages used ≥1 potentially inappropriate medication from 2007 to 2014. In addition to differences by sex, there also appeared to be age differences. When we excluded PIM recommendations that had a low quality of evidence (as defined by the AGS Beers criteria themselves), the percentage of patients with ≥1 PIM dropped slightly but remained above 63% in both men and women. The same age and sex differences were observed (eTable2 in the supplementary materials).

Table 3 presents the associations of different sociodemographic and other variables (e.g. health services use, medication count, and chronic conditions count) with the utilization of potentially inappropriate medications in the 2007 and 2014 cohort (first and last year of available data). In both 2007 and 2014, female sex (2007: Odds ratio (OR)=1.14, 95%CI 1.11-1.16; 2014: OR=1.27, 95%CI 1.25-1.30), age (2007: OR=0.94, 95%CI 0.92-0.95; 2014: OR=0.92, 95%CI 0.90-0.93), and Hispanic ethnicity (2007: OR=1.19, 95% CI 1.04-1.36; 2014: OR=1.41, 95% CI 1.27-1.56) were associated with the utilization of potentially inappropriate medications. While significant in 2007, most categories of the race variable were no longer statistically significant in 2014.

Central nervous system (e.g. benzodiazepines, antidepressants, antipsychotics, etc.) and gastrointestinal potentially inappropriate medications (e.g., proton-pump inhibitors) were the most common potentially inappropriate medications in both sexes (Figure 1 and eFigure 2). As shown by eFigure 2 in the supplementary materials, we observed sex differences in commonly used types of potentially inappropriate medications. Cardiovascular potentially inappropriate medications were more common in men than in women, while their utilization along with endocrine potentially inappropriate medications decreased in both sexes over time. Potentially inappropriate anticholinergic medications and pain medications were used in around 10% of patients, with slightly lower use in men than in women.

The number of potentially inappropriate medications per patient remained stable over time (median: 1, IQR: 1-2, eTable3). The average number of PIMs and the percentage of patients with ≥1 potentially inappropriate medication increased as the number of pharmaceutical classes increased, in patients with and without multimorbidity (eTable4 and eTable5).

As shown in Table 4, in older multimorbid patients with polypharmacy using ≥1 PIM, between 11.0% and 12.8% of medication costs were spent on potentially inappropriate medications in women and between 11.0% and 12.2% in men throughout the study period. The average amount spent on PIMs ranged from $392 USD to $719 for women and $395 to $759 for men from 2007 to 2014.

5. Discussion

In this study of US older adults with multiple chronic conditions and polypharmacy medication use, ≥69% in this population use ≥1 PIM, with differences that did not change over time. Meaningful gaps by sex were also observed, as women had a higher likelihood of using potentially inappropriate medications than men. Central nervous system and gastrointestinal medications were the most common PIMs in both men and women. The impact of PIM use is substantial, as >10% of all medication expenses by Medicare were spent on potentially inappropriate medications in patients using ≥1 PIM.

To our knowledge, this is the first study to specifically focus on the utilization of potentially inappropriate medications in older multimorbid adults with polypharmacy. Most previous research has investigated the utilization of potentially inappropriate medications in broader groups of older adults, even though they may be at lower risk of complications from PIM use. A recent meta-analysis of 66 studies from 27

Table 1
Demographics and main clinical characteristics of adults aged ≥65 years with multimorbidity* and polypharmacy**, by year

	2007 n = 61,500	2008 n = 67,816	2009 n = 72,394	2010 n = 75,567	2011 n = 82,030	2012 n = 88,114	2013 n = 102,547	2014 n = 103,153
Mean age (SD), years	77.3 (7.4)	77.5 (7.5)	77.6 (7.6)	77.7 (7.7)	77.7 (7.7)	77.8 (7.7)	77.8 (7.8)	77.8 (7.7)
Female sex (%)	40,088 (65.2)	43,390 (64.0)	45,909 (63.4)	47,405 (62.7)	50,344 (61.4)	53,311 (60.5)	61,408 (59.9)	61,143 (59.3)
Hispanic ethnicity (%)	1,161 (1.9)	1,288 (1.9)	1,431 (2.0)	1,519 (2.0)	1,616 (2.0)	1,684 (1.9)	1,688 (1.7)	1,656 (1.6)
Race*								
White (%)	55,207 (89.8)	60,897 (89.8)	64,851 (89.6)	67,596 (89.5)	73,395 (89.5)	78,845 (89.5)	92,525 (90.2)	92,891 (90.1)
African-American (%)	2,921 (4.8)	3,223 (4.8)	3,413 (4.7)	3,540 (4.7)	3,848 (4.7)	4,086 (4.6)	4,430 (4.3)	4,408 (4.3)
Asian (%)	966 (1.6)	1,047 (1.5)	1,094 (1.5)	1,128 (1.5)	1,169 (1.4)	1,188 (1.4)	1,149 (1.1)	1,123 (1.1)
Native American / Native Hawaiian (%)	°°	°°	53 (0.1)	45 (0.1)	48 (0.1)	45 (0.1)	47 (0.1)	49 (0.1)
Other (%)	2,278 (3.7)	2,515 (3.7)	2,847 (3.9)	3,065 (4.1)	3,285 (4.0)	3,526 (4.0)	3,724 (3.6)	3,765 (3.7)
Missing information (%)	°°	°°	130 (0.2)	194 (0.3)	270 (0.33)	400 (0.5)	643 (0.6)	886 (0.9)
Mean BMI (SD)	28.9 (6.1)	28.7 (6.1)	28.9 (6.2)	29.1 (6.3)	29.1 (6.2)	28.9 (6.2)	28.8 (6.1)	28.9 (6.1)
Number of chronic conditions								
Median (IQR)	7 (4)	7 (4)	7 (4)	7 (5)	7 (4)	8 (4)	8 (4)	8 (4)
Mean (SD)	7.2 (3.0)	7.4 (3.2)	7.5 (3.2)	7.7 (3.3)	8.0 (3.5)	8.1 (3.5)	8.2 (3.6)	8.4 (3.6)
Number of drugs dispensed*								
Median (IQR)	11 (6)	11 (6)	11 (6)	11 (6)	11 (6)	11 (6)	12 (6)	12 (6)
Mean (SD)	11.8 (4.7)	12.0 (4.8)	12.1 (4.8)	12.1 (4.8)	12.3 (4.9)	12.2 (4.9)	12.5 (5.0)	12.5 (5.0)
Number of drugs per patient with ≥90-day supply								
Median (IQR)	7 (3)	7 (3)	7 (3)	7 (3)	7 (3)	7 (3)	7 (3)	7 (3)
Mean (SD)	7.2 (2.2)	7.1 (2.2)	7.2 (2.2)	7.2 (2.2)	7.2 (2.2)	7.2 (2.2)	7.3 (2.3)	7.2 (2.3)
Healthcare utilization								
≥1 hospital admission (%)	20,515 (33.4)	24,863 (36.7)	27,137 (37.5)	28,451 (38.7)	30,537 (37.2)	31,541 (35.8)	35,227 (34.4)	34,999 (34)
≥1 ER visit (%)	29,316 (47.7)	32,898 (48.5)	34,713 (48.0)	36,804 (48.7)	40,269 (49.1)	43,591 (49.5)	50,251 (49.0)	50,255 (48.7)
≥1 ambulatory visit (%)	61,159 (99.4)	66,487 (98.0)	70,413 (97.3)	73,317 (97.0)	79,694 (97.2)	85,820 (97.4)	99,920 (97.4)	100,543 (97.5)
Comorbidities***								
Congestive heart failure (%)	12,673 (20.6)	14,613 (21.6)	15,534 (21.5)	16,366 (21.7)	18,402 (22.4)	19,920 (22.6)	23,145 (22.6)	23,793 (23.1)
Cardiac arrhythmias (%)	6,460 (10.5)	7,355 (10.9)	7,483 (10.3)	8,001 (10.6)	8,932 (10.9)	9,550 (10.8)	10,526 (10.3)	10,936 (10.6)
Valvular disease (%)	10,172 (16.5)	11,073 (16.3)	11,689 (16.2)	12,257 (16.2)	14,221 (17.3)	15,439 (17.5)	18,456 (18.0)	19,204 (18.6)
Pulmonary circulation disorders (%)	2,000 (3.3)	2,570 (3.8)	2,900 (4.0)	3,273 (4.3)	4,074 (5.0)	4,559 (5.2)	5,381 (5.3)	5,799 (5.6)
Peripheral vascular disorders (%)	12,601 (20.5)	14,462 (21.3)	15,291 (21.1)	15,828 (21.0)	17,639 (21.5)	19,019 (21.6)	21,684 (21.2)	21,907 (21.2)
Hypertension (%)	49,089 (70.1)	53,845 (79.4)	57,979 (80.1)	60,931 (80.6)	67,096 (81.8)	72,000 (81.7)	84,011 (81.9)	83,992 (81.4)
Other neurological disorders (%)	4,593 (7.5)	5,307 (7.8)	5,833 (8.1)	6,512 (8.6)	7,434 (9.1)	8,380 (9.5)	9,886 (9.6)	10,266 (10.0)
Chronic pulmonary disorders (%)	14,655 (23.8)	16,844 (24.8)	17,966 (24.8)	19,010 (25.2)	21,199 (25.8)	22,956 (26.1)	26,746 (26.1)	27,064 (26.2)
Diabetes (%)	23,205 (37.7)	25,382 (37.4)	27,189 (37.2)	28,650 (37.9)	31,697 (38.6)	33,961 (38.5)	38,305 (38.4)	38,593 (37.4)
Hypothyroidism (%)	12,197 (19.8)	13,783 (20.3)	14,869 (20.5)	16,068 (21.3)	18,404 (22.4)	20,290 (23.0)	24,250 (23.7)	24,892 (24.1)
Renal failure (%)	7,090 (11.5)	8,881 (13.1)	10,257 (14.2)	11,385 (15.1)	14,052 (17.1)	16,254 (18.5)	19,873 (19.4)	21,234 (20.6)
Liver disease (%)	2,218 (3.6)	2,510 (3.7)	2,668 (3.7)	2,879 (3.8)	3,118 (3.8)	3,448 (3.9)	4,201 (4.1)	4,480 (4.4)
Peptic ulcer disease (excluding bleeding) (%)	521 (0.9)	653 (1.0)	658 (0.9)	726 (1.0)	878 (1.1)	970 (1.1)	1,222 (1.1)	1,071 (1.0)
Lymphoma (%)	1,151 (1.9)	1,427 (2.1)	1,589 (2.2)	1,688 (2.2)	1,929 (2.4)	2,297 (2.6)	2,839 (2.8)	3,012 (2.9)
Metastatic cancer (%)	1,425 (2.3)	1,925 (2.8)	2,042 (2.8)	2,305 (3.1)	2,573 (3.1)	2,941 (3.3)	3,573 (3.5)	3,566 (3.5)
Solid tumor without metastasis (%)	9,792 (15.9)	11,213 (16.5)	11,997 (16.6)	12,745 (16.9)	14,195 (17.3)	15,601 (17.7)	18,391 (17.9)	18,862 (18.3)
Rheumatoid arthritis/collagen vascular diseases (%)	4,344 (7.1)	4,849 (7.2)	5,212 (7.2)	5,600 (7.4)	6,341 (7.7)	7,152 (8.1)	8,528 (8.3)	8,848 (8.6)
Coagulopathy (%)	3,059 (5.0)	3,288 (4.9)	3,556 (4.9)	3,822 (5.1)	4,249 (5.2)	4,527 (5.1)	5,331 (5.2)	5,226 (5.1)
Weight loss (%)	2,608 (4.2)	3,264 (4.8)	3,512 (4.9)	3,962 (5.2)	4,555 (5.6)	5,007 (5.7)	6,166 (6.0)	6,201 (6.0)
Fluid and electrolyte disorders (%)	5,045 (8.2)	5,949 (8.9)	6,477 (9.0)	6,888 (9.1)	7,644 (9.3)	8,270 (9.4)	9,422 (9.2)	9,467 (9.2)
Psychoses (%)	2,727 (4.4)	3,301 (4.9)	3,657 (5.1)	3,984 (5.3)	4,293 (5.2)	4,624 (5.3)	5,510 (5.4)	5,571 (5.4)
Depression (%)	19,719 (17.4)	12,542 (18.5)	13,642 (18.8)	15,060 (19.9)	17,345 (21.1)	19,494 (22.1)	23,493 (22.9)	24,275 (23.5)

* multimorbidity defined as chronic conditions from ≥2 chronic condition categories;
** polypharmacy defined as medications with ≥90 days' supply each from ≥5 pharmaceutical classes
*** comorbidities defined with coding algorithms for defining Elixhauser comorbidities in ICD-9 administrative data (Quan et al. 2005), ≥2 ICD-9 codes per category, hypertension categories merged, diabetes categories merged, drug abuse, alcohol abuse, obesity, HIV/AIDS, paralysis, blood loss anemia and deficiency anemia not reported;°° cells with sizes 0-10 suppressed.

Table 2
Percentage of adults aged ≥65 years with multimorbidity* and polypharmacy** who filled ≥1 potentially inappropriate medication*** by year, sex, and age group

	2007	2008	2009	2010	2011	2012	2013	2014
Both sexes (%)								
	n = 61,500	n = 67,816	n = 72,394	n = 75,567	n = 82,030	n = 88,114	n = 102,547	n =103,153
65 – 74	18,353 (75.4)	20,152 (75.9)	21,548 (75.8)	22,378 (74.7)	23,764 (73.5)	25,106 (72.3)	31,761 (78.4)	31,558 (77.6)
75 – 84	18,991 (73.4)	20,395 (73.2)	21,235 (72.5)	21,282 (71.3)	22,622 (70.2)	23,800 (69.0)	29,458 (74.5)	28,996 (73.1)
≥ 85	7,927 (70.3)	9,434 (70.6)	10,286 (70.1)	10,737 (68.1)	11,494 (65.8)	12,443 (65.8)	15,867 (70.5)	15,814 (69.4)
All ages	45,271 (73.6)	49,981 (73.7)	53,069 (73.3)	54,398 (72.0)	57,880 (70.6)	61,349 (69.6)	77,086 (75.2)	76,368 (74.0)
Women (%)								
	n = 40,088	n = 43,390	n = 45,909	n = 47,405	n = 50,344	n = 53,311	n = 61,408	n = 61,143
65 – 74	11,368 (77.3)	12,121 (77.1)	12,905 (77.1)	13,360 (76.5)	13,878 (75.3)	14,747 (74.4)	18,800 (81.6)	18,675 (81.0)
75 – 84	12,599 (74.0)	13,205 (73.6)	13,527 (73.1)	13,405 (72.1)	13,959 (71.1)	14,317 (69.9)	17,677 (76.5)	17,314 (75.6)
≥ 85	5,840 (69.9)	6,808 (70.1)	7,443 (69.8)	7,672 (67.7)	8,044 (65.4)	8,533 (65.6)	10,894 (71.4)	10,690 (70.5)
All ages	29,807 (74.4)	32,134 (74.1)	33,875 (73.8)	34,437 (72.6)	35,881 (71.3)	37,597 (70.5)	47,371 (77.1)	46,679 (76.3)
Men (%)								
	n = 21,411	n = 24,425	n = 26,482	n = 28,155	n = 31,678	n = 34,793	n = 41,128	n = 42,000
65 – 74	6,985 (72.5)	8,030 (74.1)	8,640 (73.8)	9,015 (72.2)	9,880 (71.0)	10,253 (69.5)	12,953 (74.3)	12,878 (73.1)
75 – 84	6,392 (72.3)	7,190 (72.5)	7,708 (71.6)	7,877 (70.1)	8,662 (68.7)	9,482 (67.8)	11,780 (71.6)	11,680 (69.7)
≥ 85	2,087 (71.2)	2,626 (71.7)	2,843 (70.9)	3,065 (69.3)	3,450 (66.8)	3,919 (66.2)	4,973 (68.7)	5,124 (67.1)
All ages	15,464 (72.2)	17,846 (73.1)	19,191 (72.5)	19,957 (70.9)	21,992 (69.4)	23,745 (68.3)	29,706 (72.2)	29,682 (70.7)

* multimorbidity defined as chronic conditions from ≥2 chronic condition categories
** polypharmacy defined as medications with ≥90 days' supply each from ≥5 pharmaceutical classes;
*** Reference: (2019), American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 67: 674-694. doi:10.1111/jgs.15767.

Table 3
Multivariable logistic regression analyses of the association between the use of potentially inappropriate medications and patient characteristics in 2007 and 2014.

	2007 (n=344,331) Multivariable model[1]		**2014 (n=397,146)** Multivariable model[1]	
	Odds ratio	95% CI	Odds ratio	95% CI
Age (10-year increase)	0.94	0.92-0.95***	0.92	0.90-0.93***
Female sex	1.14	1.11-1.16***	1.27	1.25-1.30***
Hispanic ethnicity	1.19	1.04-1.36**	1.41	1.27-1.56***
Race (ref. White)				
African-American	1.23	1.16-1.31***	0.87	0.83-0.91***
Asian	1.53	1.39-1.68***	1.00	0.93-1.08
Other[2]	1.39	1.27-1.51***	1.01	0.95-1.07
Medication count (1-unit increase)	1.58	1.57-1.58***	1.47	1.46-1.47***
Ambulatory visits (1-unit increase)	0.99	0.99-0.99***	1.00	0.99-1.00***
Emergency room visits (1-unit increase)	1.00	0.99-1.00	1.00	0.99-1.00
Inpatient stays (1-unit increase)	0.91	0.89-0.93***	0.87	0.87-0.90***
Number of chronic conditions (1-unit increase)	1.03	1.03-1.04***	1.04	1.03-1.04***

[1] The models are adjusted for the types of comorbidities. Comorbidities were defined with coding algorithms for defining Elixhauser comorbidities in ICD-9 administrative data (Quan et al. 2005), ≥2 ICD-9 codes per category
[2] Native American, native Hawaiian and 'other' combined.
** p<0.05
*** p<0.001

countries found that 33% of adults aged ≥65 years used ≥1 PIM, regardless of criteria for defining potentially inappropriate medications (e.g., Beers, FORTA or STOPP/START criteria) (Liew et al., 2020). Similarly, several studies conducted in community-dwelling adults aged ≥65 years found that around 35-40% of them were using ≥1 PIM (defined by Beers criteria) (Morgan et al., 2016, Fick et al., 2008, Huang et al., 2020). Closer to our study population, two studies found that potentially inappropriate medications were used in about 50% of community-dwelling older adults with hypertension or diabetes (Bazargan et al., 2018, Gagnon et al., 2020). Contrasted with these prior studies, our findings suggest that PIM uses is even higher (e.g., ≥69%) in older adults with multiple chronic conditions and multiple long-term medications.

Our findings concerning the most commonly-used potentially inappropriate medications are in line with prior research in this area, which had also identified proton-pump inhibitors, benzodiazepines and other central nervous system drugs, endocrine medications, such as sulfonylureas, and nonsteroidal anti-inflammatory drugs as commonly used potentially inappropriate medications (Bazargan et al., 2018, Simões et al., 2019, Roux et al., 2020, Fralick et al., 2020, Gagnon et al., 2020). Of note, the spike in potentially inappropriate central nervous system drugs in 2013 and 2014 can be explained by the fact that benzodiazepines and barbiturates were covered by Medicare Part D (drug coverage) as of January 1, 2013 (Centers for Medicare & Medicaid Services, 2012). Future efforts should focus on how the prescribing of the most commonly-used potentially inappropriate medications could be optimized and how these drugs, if applicable, could be sustainably deprescribed.

We found that female sex is associated with an increased PIM use, which is in line with findings from studies in other settings and populations (Simões et al., 2019, Roux et al., 2020, Gagnon et al., 2020, Toepfer et al., 2019, Achterhof et al., 2020). However, the mechanisms behind this association remain unclear. The observed sex difference should be interpreted with caution, since it was likely driven by more chronic use of certain medications in women (i.e. benzodiazepines), the fact that because of a lower creatinine clearance in women some medication may have been flagged as potentially inappropriate in women but not in men, or some potentially inappropriate medications listed in the Beers criteria are exclusively used in women (e.g. estrogens). It is beyond the scope of this paper to analyze the effect of sex differences in comorbidities or to examine potential gender biases in the use of potentially inappropriate medications, but future studies could explore this and potentially determine whether sex-based deprescribing interventions may be necessary.

Our results do not suggest clinically-relevant differences by age. In the current literature, there is contradicting evidence on the association between age and the utilization of potentially inappropriate medications. Some studies found that it increases with age (Roux et al., 2020, Morgan et al., 2016, Gagnon et al., 2020) while another one found that

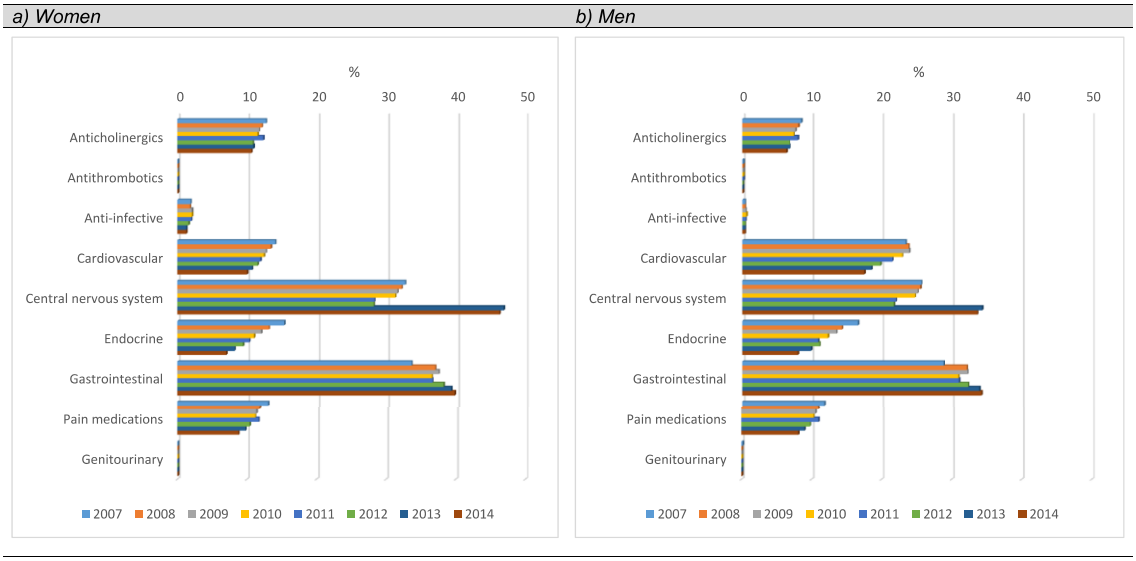

Fig. 1. Different types of potentially inappropriate medications* used in adults aged ≥65 years *with multimorbidity*** *and polypharmacy****, from 2007 to 2014.
Reference: (2019), American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 67: 674-694. doi:10.1111/jgs.15767– table 2.
** multimorbidity defined as chronic conditions from ≥2 chronic condition categories;
*** polypharmacy defines as medications with ≥90 days' supply each from ≥5 pharmaceutical classes.

there is no age effect (Simões et al., 2019). Despite this, the age effect deserves to be further studied, to investigate which age group is most likely to benefit from deprescribing interventions.

Further, we observed an association of the utilization of potentially inappropriate medications with Hispanic ethnicity, but our results concerning the association with race were inconclusive. This is in line with previous research, which found that older Hispanics were more likely than older Whites to use potentially inappropriate psychotropic medications (Lim and Jung, 2019). The question of the association between the utilization of PIMs and race and ethnicity deserves to be further studies, as this information may be crucial for tailoring future interventions to optimize medication use and deprescribe.

The high use of potentially inappropriate medications in older adults is not without other consequences. A recent study from the US estimated that 7.3 billion doses of PIMs were dispensed in 2018 to patients who were enrolled in Medicare Part D and that this PIM use corresponded to a reported spending of US$ 4.4 billion (Fralick et al., 2020). Similarly, another study also conducted in the US context also found PIM use to be associated with higher costs (Clark et al., 2020). The fact that >10% are being spent potentially inappropriate medications in patients who use ≥1 PIM means substantial additional and potentially unnecessary spending by Medicare. To our knowledge, this is the first study to investigate the cost associated with the utilization of potentially inappropriate medications in relation to all medication costs in the United States. Average yearly spending on potentially inappropriate medications in this population was higher than in a previous study conducted in Canada (Morgan et al., 2016), which of course could be explained by different drug prices in the US and Canada (Gooi and Bell, 2008, Quon et al., 2005, Kim et al., 2017). Further, we only measured direct costs associated with potentially inappropriate medications (Xing et al., 2019), and indirect costs are likely to be much higher as higher utilization of potentially inappropriate medications is associated with higher total medical costs (Harrison et al., 2018).

In summary, our findings have important implications for clinical care and intervention development (e.g. tailored to what PIMs are most commonly used, based on what patient group is most likely to use PIMs). Due to the high utilization of potentially inappropriate medications in older multimorbid adults with polypharmacy and the potential negative and financial consequences linked to the PIM use, regular screening for PIMs should be incorporated in standard practice (e.g. screenings by pharmacists or primary care physicians) and deprescribing interventions should be explored.

5.1. Limitations

The findings of this study should be interpreted in light of several limitations. First, since the different tools used to define potentially inappropriate medications include different medications, the results of this study may not be comparable to studies using different tools (e.g. STOPP criteria instead of Beers). Different tools result in different proportions of PIM use (Sakr et al., 2018, Ma et al., 2019). Second, the Beers criteria are criterion rather than judgment-based. Despite using diagnoses and clinical criteria to determine PIM use, some medications defined as potentially inappropriate may have been used as a last resort. In other cases, alternative to PIMs might have been more expensive. Regardless, the Beers criteria are the most commonly-used metric for PIM use in the US and excluding medications with a low-level of evidence did not meaningfully change the results. Third, despite using a broad approach for identifying patients with multiple chronic conditions, we cannot rule out some potential misclassification because of the nature of the data. Fourth, we were not able to capture dispensation over-the-counter medications, which may have led to an underestimation of the utilization potentially inappropriate medications. Fifth, the data are from several years ago (owing to an administrative lag in acquisition and linkage); given that we observed no changes over time, these findings should remain relevant. Sixth, we did not account our cost analyses for inflation. Finally, our results might not be generalizable to commercially insured older adults or beyond the Boston metropolitan region. For example, while the demographic makeup of the metropolitan area compared with other urban US regions is similar (Kaiser Family

Table 4
Average medication costs spent on potentially inappropriate medications* versus all medications in adults aged ≥65 years with multimorbidity**, polypharmacy*** and utilization of ≥1 potentially inappropriate medication, by year and sex

	2007	2008	2009	2010	2011	2012	2013	2014
Women								
	n = 29,807	n = 32,134	n = 33,875	n = 34,437	n = 35,881	n = 37,597	n = 47,371	n = 46,679
PIMs in US$, mean (SD)	719.1 (9,456.9)	418.6 (595.1)	409.3 (461.7)	405.9 (450.7)	400.0 (455.9)	392.1 (434.6)	480.9 (521.1)	472.4 (505.0)
All medications in US$, mean (SD)	6,706.2 (12,9204.6)	3,879.1 (7,109.5)	3,905.5 (3,602.4)	4,003.2 (5,037.0)	4,103.7 (9,123.8)	4,100.7 (5,216.1)	4,186.7 (4,749.7)	4,291.4 (8,564.4)
Average ratio (SD)	12.4 (11.6)	12.2 (11.2)	11.8 (11.1)	11.6 (10.9)	11.2 (10.5)	11.0 (10.4)	12.8 (11.5)	12.6 (11.3)
Men								
	n = 15,464	n = 17,846	n = 19,191	n = 19,957	n = 21,992	n = 23,745	n = 29,706	n = 29,682
PIMs in US$, mean (SD)	758.5 (11,744.1)	423.1 (536.5)	418.8 (461.6)	417.3 (462.1)	403.8 (447.6)	395.9 (430.0)	433.7 (463.2)	423.4 (454.2)
All medications in US$, mean (SD)	7,299.3 (97,622.1)	4,018.5 (6,354.6)	4,033.3 (3,169.1)	4,117.6 (3,545.5)	4,202.3 (5,485.0)	4,191.7 (3,251.8)	4,284.1 (3,926.3)	4,317.6 (5,120.2)
Average ratio (SD)	12.2 (11.1)	12.1 (11.0)	11.8 (10.8)	11.7 (10.7)	11.3 (10.4)	11.0 (10.1)	11.5 (10.5)	11.3 (10.3)

* Reference: (2019), American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 67: 674-694. doi:10.1111/jgs.15767;
** multimorbidity defined as chronic conditions from ≥2 chronic condition categories;
*** polypharmacy defines as medications with ≥90 days' supply each from ≥5 pharmaceutical classes

Foundation, 2020), individuals in urban areas could have more access to healthcare and physicians, which could change the prevalence of prescribing of potentially inappropriate medications

6. Conclusions

Based on the findings of this study, we conclude that the utilization of potentially inappropriate medications in older multimorbid US adults with polypharmacy is high and has not changed over time. After adjusting for health services use and types of chronic conditions, female sex, age and Hispanic ethnicity were associated with potentially inappropriate medication use. The utilization of potentially inappropriate medications contributes to >10% of medication spending. These findings demonstrate the continued need for PIM screening and deprescribing interventions in this population group.

Ethics approval

This study was approved by the Brigham and Women's Hospital Institutional Review Board.

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Availability of data and materials

The data that support the findings of this study are available from the Research Data Assistance Center (ResDAC) from the Centers for Medicare and Medicaid Services and from Mass General Brigham (formerly Partners Healthcare). Restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data may however be available from the authors upon reasonable request and with permission of ResDAC.

Author Contributions

Katharina Tabea Jungo: Conceptualization, Methodology, Formal analysis, Data curation, Writing – Original draft, Project administration, Visualization. **Sven Streit**: Conceptualization, Writing – Review & Editing. **Julie C Lauffenburger**: Conceptualization, Methodology, Formal Analysis, Resources, Writing - Review & Editing, Supervision.

Declarations of Competing Interest

None. The authors have no conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.archger.2020.104326.

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Article II: Patient Factors Associated with New Prescriptions for Potentially Inappropriate Medications in US Older Adults with Multimorbidity Using Multiple Medications

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My contributions: Together with Julie C Lauffenburger and Sven Streit, I conceptualized and designed this study. I had full access to all the data used in this research and I had the main responsibility for conducting the data analysis. I created all figures and tables shown in the manuscript and the supplementary material. I wrote the first draft of the manuscript and I made the necessary changes based on comments made by co-authors and reviewers during the peer-review process.

Tables and Figures in Article II

(as displayed in the published article below)

Figure 1. Flow diagram of cohort definition

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Table 2. Baseline characteristics, by whether the participants had a new prescription of a potentially inappropriate medication (PIM) during the 90-day follow-up period

Table 3. Unadjusted and multivariable associations between demographic and clinical factors and the prescribing of potentially inappropriate medications

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Patient factors associated with new prescribing of potentially inappropriate medications in multimorbid US older adults using multiple medications

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Abstract

Background: The use of potentially inappropriate medications (PIMs) is common in older adults and is associated with potential negative consequences, such as falls and cognitive decline. Our objective was to investigate measurable patient factors associated with new outpatient prescribing of potentially inappropriate medications in older multimorbid adults already using multiple medications.

Methods: In this retrospective US cohort study, we used linked Medicare pharmacy and medical claims and electronic health record data from a large healthcare system in Massachusetts between 2007 and 2014. We identified patients aged ≥65 years with an office visit who had not been prescribed or used a PIM in the prior 180 days. PIMs were defined using 2019 Beers criteria of the American Geriatrics Society. To specifically evaluate factors in patients with polypharmacy and multimorbidity, we selected those who filled medications for ≥90 days (i.e., chronic use) from ≥5 pharmaceutical classes in the prior 180 days and had ≥2 chronic conditions. Multivariable Cox regression analysis was used to estimate the association between baseline demographic and clinical characteristics on the probability of being prescribed a PIM in the 90-day follow-up period.

Results: In total, we identified 17,912 patients aged ≥65 years with multimorbidity and polypharmacy who were naïve to a PIM in the prior 180 days. Of those, 10,497 (58.6%) were female, and mean age was 78 (SD = 7.5). On average, patients had 5.1 (SD = 2.3) chronic conditions and previously filled 6.1 (SD = 1.4) chronic medications. In total, 447 patients (2.5%) were prescribed a PIM during the 90-day follow-up. Male sex (adjusted hazard ratio (HR) = 1.29; 95%CI: 1.06–1.57), age (≥85 years: HR = 0.75, 95%CI: 0.56–0.99, 75–84 years: HR = 0.87, 95%CI: 0.71–1.07; reference: 65–74 years), ambulatory visits (18–29 visits: HR = 1.42, 95%CI: 1.06–1.92; ≥30 visits: HR = 2.12, 95%CI: 1.53–2.95; reference: ≤9 visits), number of prescribing orders (HR = 1.02, 95%CI: 1.01–1.02 per 1-unit increase), and heart failure (HR = 1.38, 95%CI: 1.07–1.78) were independently associated with being newly prescribed a PIM.

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Conclusion: Several demographic and clinical characteristics, including factors suggesting lack of care coordination and increased clinical complexity, were found to be associated with the new prescribing of potentially inappropriate medications. This knowledge could inform the design of interventions and policies to optimize pharmacotherapy for these patients.

Keywords: Multimorbidity, Polypharmacy, Potentially inappropriate prescribing

Introduction

The prevalence of older adults is growing in the United States and many countries globally, in large part because of increasing life expectancy [1]. At the same time, the prevalence of multimorbidity, commonly defined as having ≥2 chronic conditions [2], is also on the rise [3]. Accordingly, due to the association between multimorbidity and age [4], multimorbidity is becoming increasingly common in older adults. Multimorbidity poses one of the greatest challenges to health systems, because multimorbid patients often have complex healthcare needs and worse health outcomes [5, 6], including higher rates of mortality, disability, lower quality of life, and adverse drug events [7, 8]. Another challenge associated with multimorbidity is the increasing number of medications that patients need to take to manage their conditions.

Multimorbid patients often have polypharmacy, i.e., the concurrent use of ≥5 medications [9]. For instance, 39% of community-dwelling US older adults have polypharmacy [10]. Polypharmacy increases the risk of using potentially inappropriate medications (PIMs) [8–10]. PIMs are drugs for which the risk of potential adverse events is greater than the clinical benefits, particularly when there are safer or more effective alternatives that are recommended to be used in older adults [11]. In specific, PIMs are associated with increased risk of adverse drug events, falls, and cognitive impairment [12–15] as well as greater use of healthcare services (e.g., hospitalizations or emergency department visits) and healthcare costs [16–19].

Contributors to the prescribing of PIMs are multifaceted [20]. For example, provider and health-system factors leading to prescribing of PIMs are thought to include lack of communication between different prescribers, providers' lack of knowledge in geriatric medicine and pharmacology, and insufficient time allocated to prescribing. Previous research on patient factors associated with the prescribing of potentially inappropriate medications for older adults have focused on broad populations of community-dwelling older adults or patients with selected chronic conditions [21–23]. Unfortunately, even though PIM use is high among multimorbid older adults using multiple medications, little is known about the patient factors associated with the new prescribing of potentially inappropriate medications in this population group, despite it being at even greater risk of adverse health outcomes than general older adults.

Therefore, the aim of this study was to explore the factors associated with new prescribing of potentially inappropriate medications in older multimorbid men and women with polypharmacy in the US. Investigating these factors could inform the design of interventions and policies aimed at optimizing pharmacotherapy in this patient group.

Methods

Data source

In this retrospective study, we used a dataset containing Medicare claims linked with electronic health records (EHR) of patients enrolled in the Partners Research Patient Data Registry (RPDR) [24]. The Partners Research Patient Data Registry contains EHR data from two tertiary medical centers, three community hospitals, a Rehabilitation center, and a psychiatric hospital that are located in the Boston metropolitan area. The dataset contains data from 569,969 participants from January 1, 2007 through December 31, 2014. Medicare claims include Parts A (inpatient coverage), B (outpatient coverage), and D (drug coverage) containing information on drugs dispensed and start/end dates of insurance coverage [25, 26]. The EHR data contain information on sociodemographic variables, health services use (e.g., ambulatory visits and inpatient care), prescribing records, laboratory tests, and results.

Patient population

This research uses the same approach to define polypharmacy and multimorbidity as our previous research on the use of potentially inappropriate medications in older multimorbid adults with polypharmacy [27]. The key features of this approach are outlined below.

Definition of multimorbidity

We defined the chronic conditions using the Chronic Condition Indicator (CCI) of the Agency for Healthcare Research and Quality (AHRQ). The CCI categorizes ICD-9 diagnosis codes as chronic and not chronic [28]. After extracting the chronic ICD-9 codes, we assigned related codes to ICD-9 code categories. This ensured

that we did not misclassify patients with closely-related diagnoses codes (e.g. different types of cancers) as having multiple chronic conditions. Chronic conditions from the CCI related to pregnancy and childbirth were excluded due to their non-relevance in our study population. In total, there were 77 chronic condition categories. To increase the specificity of underlying chronic conditions, ≥2 diagnosis codes on separate days were required for the condition to count as a chronic condition [29]. Because a definition of two or more chronic diseases is commonly used in the literature to define multimorbidity [2, 30, 31], we used this threshold to define patients as multimorbid.

Definition of polypharmacy

We used information from the U.S. Food and Drug Administration (FDA) on the classification of medications into different pharmaceutical classes (e.g., anticholinergics) [32] to define polypharmacy. We measured medication use at the class level, as medications with structural similarities, such as statins, are generally considered interchangeable. Medication classes with ≥90 days' supply were considered as being used chronically [33]. We measured days' supply from claims conservatively to ascertain long-term polypharmacy. First, we assumed concurrent utilization if there were multiple fills for the same class on the same day, and if the recorded days' supply differed, the medication with the longest duration was selected. Next, a limited shift of supply (30 days) was used for overlapping utilization in the case of non-concurrent fills. We defined patients as having polypharmacy when they filled medications from ≥5 pharmaceutical classes with ≥90 days' supply each, in line with commonly used definitions for polypharmacy and previously used approaches for measuring chronic use [9, 34, 35].

Cohort definition

The cohort was created using the Aetion Evidence Platform (Version: r3.5.20180426_1659), which has previously been validated for a range of studies [25, 36]. An ambulatory visit recorded in the RPDR electronic health records constituted the cohort entry event. From that index ambulatory visit, we excluded patients if they were < 65 years of age, if there was missing information on sex, or if they did not have 180 days Medicare (part D, drug coverage) enrolment prior to the cohort entry to ensure complete data capture. As a result, the effective cohort entry date of patients in our cohort was July 1, 2007 at the earliest. If a patient had multiple possible qualifying ambulatory visits, the patient entered the cohort on the first-occurring qualifying event after exclusions (age, missing sex, and Medicare enrolment) were applied. Patients were only counted once and could not re-enter the cohort at a later stage. Then, we excluded patients who were prescribed or used potentially inappropriate medications during the baseline period, to focus on new PIM prescribing. Next, to ascertain continuity of care and to reduce information bias, we excluded patients who did not have an ambulatory visit during the baseline period of 180 days and for whom there thus was no "data continuity" [37]. Finally, we selected patients with ≥2 chronic conditions and ≥ 5 medication classes with long-term use (i.e., ≥90 days' supply each), as they were the population of interest. A cohort flow diagram can be found in Fig. 1.

Outcome measurement

Prescribing of potentially inappropriate medications

The identification of potentially inappropriate medications can be done using different implicit (judgment-based) or explicit (criterion-based) lists. The Beers list, published by the American Geriatrics Society (AGS) [38–40], is one example of a criterion-based list. We decided to use the 2019 Beers list, rather than previous versions, to identify potentially inappropriate medications with the aim of informing current medical decision-making [39]. We defined all medications prescribed in the EHR that met any of the drug, duration and dosage requirements described in Table 2 of the 2019 Beers criteria as potentially inappropriate. Certain medications on the Beers list are considered potentially inappropriate only when they are used in presence or absence of a certain diagnosis, when a lab value is below/above a certain value, or when they are used for more than a certain number of days (refer to eTable 1 in the Supplement for details). Using this linked claims and EHR dataset, we were able to capture all the clinical criteria necessary to define PIMs (e.g., diagnoses, lab results).

We measured whether patients in our cohort were newly-prescribed a potentially inappropriate medication in the outpatient setting during a 90-day follow-up period, including the index ambulatory visit (any). For reasons related to continuity of care, we limited our analyses to this 90-day follow-up period. Furthermore, this follow-up period seemed reasonable in our study population with a relatively high health services use (i.e., median number of ambulatory visits during the 180-day baseline period = 17).

Covariates

We used peer-reviewed literature to identify patient factors hypothesized to be associated with the prescribing of potentially inappropriate medications and that could also be measured in our EHR-claims dataset [41, 42]. These factors were measured in the 180 days before the index ambulatory visit. The following covariates were included

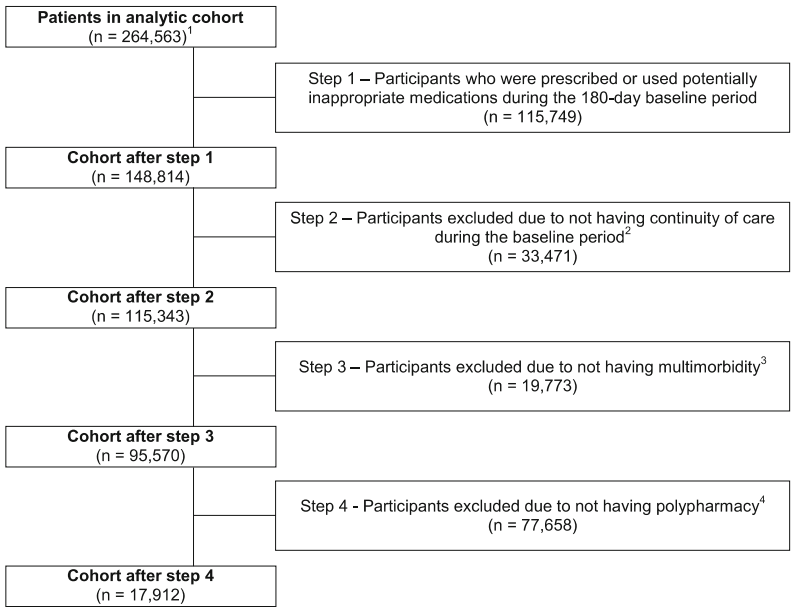

Fig. 1 Flow diagram of cohort definition. [1]cohort entry event = ambulatory visit recorded in RPDR electronic medical records, min. 180 days enrolment in Medicare prior to cohort entry, ≥65 years old, no missing information on sex; [2]as measured by having min. 1 ambulatory care visit recorded in the RPDR electronic health records during this period; [3]multimorbidity defined as chronic conditions from ≥2 chronic condition categories; [4]polypharmacy defined as medications with ≥90 days' supply each from ≥5 pharmaceutical classes

in our models: age, sex, ethnicity, race, number of inpatient stays, emergency department visits, ambulatory visits, non-acute institutional stays, level of polypharmacy (5–9 medications vs ≥10), number of chronic conditions, number of prescribing orders, and selected chronic conditions defined by Elixhauser Comorbidities [43] (shown in Table 2). Sensitivity analyses involved measuring a claims-based frailty index [44].

Statistical analyses

The sociodemographic and clinical characteristics of patients were described for those who were and were not prescribed a potentially inappropriate medication during the 90-day follow-up. To facilitate interpretation, some continuous variables were categorized based on quartiles for ambulatory visits and percentiles for inpatient stays, emergency department visits, and non-acute stays. We provided absolute standardized differences, which are the differences in the mean of a covariate between two groups, to show any differences between groups [45].

Cox regression analysis was conducted to estimate the effect of baseline demographic and clinical characteristics on the probability of being prescribed a new PIM during the 90-day follow-up period. We chose Cox regression analysis in particular as the primary analysis to better model the likelihood of prescribing as a function of time. In specific, we computed hazard ratios (HR) and 95% confidence intervals (CI). First, we tested each variable separately, without adjusting for other covariates, using Cox proportional hazards regression analysis to estimate its association with the new prescribing of potentially inappropriate medications. Next, we used multivariable Cox proportional hazards regression analysis to examine the association between each variable and the prescribing of PIMs, while adjusting for other covariates. In the first multivariable model, we included demographic and healthcare utilization variables. In the second one, we added information on the types of chronic conditions. The first encounter in which a PIM was prescribed was analyzed in the time-to-event analyses. Finally, we analyzed the types of PIMs prescribed in the follow-up period.

We also performed some subgroup (e.g., restricted to patients with ≥1 prescribing order in the baseline period, with ≥2 ambulatory visits in the baseline period) and sensitivity analyses (e.g., exclude Beers criteria with a low level of evidence, adding a claims-based frailty index to the model, extending the baseline period to 365 days, and keeping all continuous variables in their original form). In addition, we performed a multivariable logistic regression with the same outcome and same variables in the model. We performed all analyses using STATA

15.1 (StataCorp, College Station, TX, USA). Statistical significance was determined by using two-sided tests with an α of 0.05.

This study was approved by the Brigham and Women's Hospital Institutional Review Board. We followed the reporting requirements of the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) guidelines [46].

Results

In total, we identified 17,912 older adults with multimorbidity and polypharmacy who were naïve to a potentially inappropriate medication in the prior 180 days and met all other inclusion and exclusion criteria (Fig. 1). Of these, 447 (2.5%) were prescribed a new potentially inappropriate medication during the 90-day follow-up period. Central nervous system drugs, cardiovascular drugs, anticholinergics, and endocrine drugs were the most commonly prescribed PIMs (Table 1). Benzodiazepines were prescribed in 29% of patients who were newly prescribed a central nervous system PIM.

Table 2 shows the baseline characteristics of all patients overall and by whether they were newly-prescribed a PIM. In the entire cohort, the average age was 78 years (SD = 7.5), and 58.6% of patients were female. Patients newly-prescribed a PIM differed from those who were not prescribed a PIM; for example, new PIM prescribing was higher among men and those with greater prior healthcare services use. The types of chronic conditions were relatively comparable between the two groups at baseline, except for congestive heart failure.

Unadjusted and multivariable Cox regression of the association between measured patient factors and the risk of being prescribed a PIM in older multimorbid patients with polypharmacy are shown in Table 3. Of note, there were no violations of the proportional hazards' assumption. In unadjusted analyses, increased age (i.e. ≥85 years), male sex, and some racial groups (e.g. Black) were associated with being newly-prescribed a potentially inappropriate medication (Table 3). Most variables measuring the health services use of patients, such as the number of inpatient stays, number of emergency department visits, number of ambulatory visits, and the number of prescribing orders were associated with an increased risk of PIM prescribing. The number of chronic conditions and some types of chronic conditions (i.e. congestive heart failure, cardiac arrhythmias) were also associated with new PIM prescriptions.

In the multivariable analysis including demographic and healthcare utilization variables, male sex, Black race, ≥85 years of age, number of ambulatory visits (≥18 visits during the baseline period), and number of prescribing orders were associated with new PIM prescribing. In model 2, including chronic conditions, we observed similar results. In this model, male sex (adjusted hazard ratio (HR) = 1.29; 95%CI: 1.06–1.57), age (≥85 years:

Table 1 Potentially inappropriate medications (PIMs) prescribed during the 90-day follow-up period (*N* = 17,912)

Types of potentially inappropriate medications	*Potentially inappropriate medications* *Number of patients (% of total number of patients with PIM prescription)*
All	447 (2.5% of patients in cohort)
Anticholinergics	64 (14.3)
First-generation antihistamines	52 (11.6)
Antiparkinsonian agents	**
Antispasmodics	**
Anti-infective (Nitrofurantoin)	**
Cardiovascular	90 (20.1)
Peripheral alpha-1 blockers	14 (3.1)
Central alpha agonists	**
Disopyramide	**
Digoxin	57 (12.8)
Nifedipine	**
Amiodarone	21 (4.7)
Central nervous system	185 (41.4)
Antidepressants	**
Antipsychotics	35 (7.8)
Barbiturates	**
Benzodiazepines	130 (29.1)
Nonbenzodiazepine	29 (6.5)
Endocrine	77 (17.2)
Androgens	**
Growth hormone	16 (3.6)
Insulin	39 (8.7)
Megestrol	**
Sulfonylureas	16 (3.6)
Gastrointestinal	20 (4.5)
Metoclopramide	12 (2.7)
Mineral oil	**
Proton-pump inhibitors	**
Pain medications	54 (12.1)
Non-cycloocygenase-selective NSAIDs	17 (3.8)
Indomethacin, ketorolac	20 (4.5)
Skeletal muscle relaxants	18 (4.0)

** cells < 11 suppressed for data protection reasons according to Medicare requirements

Not presented due to not having been prescribed during the 90-day follow-up period: Antithrombotics (Dipyridamole), Dronedrone, Meprobamate, Ergoloid mesylates, Desiccated thyroid Estrogens, Meperidine, Genitourinary (Desmopressin)

Table 2 Baseline characteristics, by whether the participants had a new prescription of a potentially inappropriate medication (PIM) during the 90-day follow-up period

	All patients	*Patients with new PIM prescription during follow-up*	*Patients without new PIM prescription during follow-up*	*Absolute standardized differences*[d]
	(n = 17,912)	*(n = 447)*	*(N = 17,465)*	
Demographic characteristics				
Mean age in years (SD)	78.0 (7.5)	77.0 (7.5)	78.0 (7.5)	0.13
Female sex (%)	10,497 (58.6)	225 (50.3)	10,272 (58.8)	0.17
Hispanic ethnicity (%)	161 (0.9)	**	**	0.04
Race (%)				
White	16,593 (92.6)	398 (89.0)	16,195 (92.7)	0.13
Black	653 (3.7)	24 (5.4)	629 (3.6)	
Asian	165 (0.9)	**	**	
Other	417 (2.3)	17 (3.8)	400 (2.3)	
No information	84 (0.5)	**	**	
Medication intake				
Mean (SD) drug items dispensed per patient with min. 90 days' supply	6.1 (1.4)	6.2 (1.4)	6.1 (1.4)	0.07
Mean (SD) drug items dispensed	8.0 (2.4)	8.2 (2.5)	8.0 (2.4)	0.08
Healthcare utilization				
Patients with at least 1 inpatient stay (%)	3001 (16.7)	97 (21.7)	2904 (16.6)	0.13
Patients with at least 1 emergency department visit (%)	4711 (26.3)	143 (32.0)	4568 (26.2)	0.13
Patients with at least 1 non-acute institutional stay (%)	2360 (13.2)	45 (10.1)	2315 (13.3)	0.10
Patients with number of ambulatory visits above the median number of ambulatory visits (median = 17) (%)[b]	9186 (51.3)	293 (65.6)	8893 (50.9)	0.30
Number of chronic conditions				
Mean (SD) number of chronic conditions	5.1 (2.3)	5.4 (2.5)	5.1 (2.3)	0.12
Chronic conditions types[a] (%)				
Congestive heart failure	2931 (16.4)	103 (23.0)	2828 (16.2)	0.17
Cardiac arrhythmias	1061 (5.9)	37 (8.3)	1024 (5.9)	0.10
Valvular disease	2109 (11.8)	56 (12.5)	2053 (11.8)	0.02
Pulmonary circulation disorders	399 (2.2)	83 (18.6)	2748 (15.7)	0.08
Peripheral vascular disorders	2525 (14.1)	70 (16.7)	2455 (14.1)	0.05
Hypertension	11,309 (63.1)	285 (63.8)	11,024 (63.1)	0.01
Chronic pulmonary disorders	2831 (15.8)	83 (18.6)	2748 (15.7)	0.08
Diabetes	5718 (31.9)	161 (36.0)	5557 (31.8)	0.09
Hypothyroidism	2531 (14.1)	59 (13.2)	2472 (14.2)	0.03
Renal failure	1669 (9.3)	46 (10.3)	1623 (9.3)	0.03
Liver disease	274 (1.5)	**	**	0.08
Cancer	2447 (13.7)	67 (15.0)	2380 (13.6)	0.04
Rheumatoid arthritis / collagen vascular diseases	940 (5.3)	20 (4.5)	920 (5.3)	0.04
Coagulopathy	619 (3.5)	19 (4.3)	600 (3.4)	0.04
Fluid and electrolyte disorders	783 (4.4)	25 (5.6)	758 (4.3)	0.06
Psychoses	309 (1.7)	**	**	0.05
Depression	1580 (8.8)	38 (8.5)	1542 (8.8)	0.01

Table 2 Baseline characteristics, by whether the participants had a new prescription of a potentially inappropriate medication (PIM) during the 90-day follow-up period *(Continued)*

	All patients	*Patients with new PIM prescription during follow-up*	*Patients without new PIM prescription during follow-up*	*Absolute standardized differences*[d]
	(n = 17,912)	*(n = 447)*	*(N = 17,465)*	
Other characteristics				
Mean frailty index (SD)[c]	0.16 (0.1)	0.16 (0.1)	0.16 (0.1)	0.04

Missing data < 2% for all variables listed. [a]comorbidities defined with coding algorithms for defining Elixhauser comorbidities in ICD-9 administrative data (Quan et al. 2005), ≥2 ICD-9 codes per category, hypertension categories merged, diabetes categories merged, different cancer categories merged, drug abuse, alcohol abuse, obesity, weight loss, HIV/AIDS, paralysis, other neurological disorders, blood loss anemia and deficiency anemia not presented; [b]due to our cohort definition all patients had min. 1 ambulatory visit during the baseline period; [c]Kim DH, Schneeweiss S, Lipsitz LA, Glynn R, Rockwood K, Avorn J. Measuring Frailty in Medicare Data: Development and Validation of a Claims-Based Frailty Index. J Gerontol A Biol Sci Med Sci. 2018; 73: 980–987. doi: https://doi.org/10.1093/gerona/glx229. PMID: 29244057; PMCID: PMC6001883; [d] A significant difference between the proportions of patients is usually characterized by an absolute standardized difference ≥ ±0.1; **cells < 11 suppressed for data protection reasons according to Medicare requirements

HR = 0.75, 95%CI: 0.56–0.99, 75–84 years: HR = 0.87, 95%CI: 0.71–1.07; reference: 65–74 years), number of ambulatory visits (18–29 visits: HR = 1.42, 95%CI: 1.06–1.92; ≥30 visits: HR = 2.12, 95%CI: 1.53–2.95, reference: ≤9 visits), the number of prescribing orders (HR = 1.02 per 1-unit increase, 95%CI: 1.01–1.02), and a heart failure diagnosis (HR = 1.38, 95%CI: 1.07–1.78) were associated with being newly-prescribed a PIM, but Black race was no longer significantly associated with new PIM prescribing.

Extending the baseline period to 365 days (eTable 2) and analyzing all continuous variables as continuous variables (eTable 3) did not change the results, and there were similar results using multivariable logistic regression (eTable 4). Similar results were also observed when restricting the analyses to Beers criteria with moderate or high level of evidence (eTable 5). When analyzing patients with ≥3 chronic conditions (eTable 6) or those with ≥2 ambulatory visits during the baseline period (eTable 7), we found however that age (≥85 years) and Black race where no longer significantly associated with new PIM prescribing. Age was also no longer significantly associated when adding a claims-based frailty index to the model (eTable 8).

Discussion

This is the first study exploring factors associated with new prescribing of potentially inappropriate medications in older multimorbid adults with polypharmacy in a US sample without prior PIM use. Of the 2.5% of patients who were newly prescribed a PIM within the follow-up period of 90 days, male sex, more ambulatory visits, more prescriptions, and prior diagnosis of heart failure were associated with new receipt of a PIM prescription and being ≥85 years of age was associated with a lower risk of new PIM prescribing. Central nervous system drugs, cardiovascular drugs, anticholinergics, and endocrine drugs were the most commonly prescribed PIMs. The finding that benzodiazepines was the most commonly prescribed PIM is in line with previous research [21, 47].

Of the patient demographic factors found to be associated with new PIM prescribing, male sex, and Black race were found to be associated with an increased risk of a new prescription for a PIM, while advanced age was found to be associated with an decrease risk of a new PIM prescription. Prior literature is inconclusive on whether sex is associated with the prescribing of PIMs. While some studies found an association with female sex and PIM prescribing [22, 48], others did not find any significant association [21, 49, 50]. Most previous studies were cross-sectional, which does not provide evidence about the incidence of new PIM prescribing and factors associated with it.

Our results were mixed on whether there is an association between the new prescribing of PIMs and age. In our main model, we observed that those ≥85 years had a lower risk of new PIM prescribing, but this was no longer significant in some sensitivity analyses. Similarly, while some previous studies did not observe any association, others also found a protective factor of age [48, 51]. Furthermore, when examining Black race we found mixed results, as Black race was no longer significantly associated with PIM prescribing after adjusting for the types of chronic conditions. Prior research in more general populations of older adults has, in fact, found a positive association between white race and greater PIM prescribing [52, 53].

We found that an above median number of ambulatory care visits and the number of prescribing orders were positively associated with PIM prescribing, which could be indicators of clinical complexity. Current literature on PIM prescribing and health services use is mixed: one study found an association between inpatient stays, emergency department visits and outpatient visits [54], while another one did not find an association between PIM prescribing and outpatient visits [50]. There is some evidence that PIM prescribing may be positively associated with the number of prescribers [21].

Table 3 Unadjusted and multivariable associations between demographic and clinical factors and the prescribing of potentially inappropriate medications during the 90-day follow-up period

Demographics and clinical characteristics	*Unadjusted associations*		*Model 1: Demographic and healthcare utilization variables*		*Model 2: Model 1 + chronic conditions*	
	Unadjusted hazard ratio (*N* = 17,912)	*95% CI*	*Adjusted hazard ratio* (*n* = 17,911)	*95% CI*	*Adjusted hazard ratio* (*n* = 17,911)	*95% CI*
Age (reference: 65–74)						
75–84	0.85	0.69–1.04	0.86	0.70–1.06	0.87	0.71–1.07
85 and above	0.67	0.52–0.88**	0.76	0.58–0.99**	0.75	0.56–0.99**
Male sex (reference: female sex)	1.41	1.17-1.79***	1.30	1.08–1.57**	1.29	1.06–1.57**
Hispanic ethnicity (reference: non-hispanic)	1.51	0.67–3.38	0.96	0.35–2.59	0.95	0.35–2.67
Race (reference: White)						
Asian	1.26	0.52–3.03	1.37	0.57–3.31	1.31	0.54–3.17
Black	1.54	1.02–2.33**	1.54	1.02–2.33**	1.50	0.98–2.27
Other	1.71	1.05–1.78**	1.64	0.90–2.99	1.59	0.87–2.90
Number of inpatient stays (reference: 0[b])						
At least 1	1.39	1.11–1.75**	0.98	0.72–1.33	0.94	0.69–1.28
Number of emergency department visits (reference: 0[c])						
At least 1	1.33	1.09–1.62**	1.12	0.86–1.33	1.09	0.84–1.41
Number of ambulatory visits (reference: ≤9[d])						
10–17	0.94	0.70–1.28	0.96	0.70–1.31	0.96	0.70–1.31
18–29	1.39	1.05–1.84**	1.42	1.05–1.91**	1.42	1.06–1.92**
≥ 30	2.12	1.64–2.76***	2.12	1.55–2.93**	2.12	1.53–2.95**
Number of non-acute institutional stays (reference: 0[e])						
At least 1	0.74	0.55–1.01	0.81	0.58–1.13	0.76	0.54–1.08
Level of polypharmacy (reference: 5–9 medications)						
10 and above	1.27	0.77–2.09	1.16	0.70–1.92	1.08	0.65–1.79
Number of chronic conditions (1-unit increase)	1.06	1.02–1.10**	0.96	0.91–1.01	0.94	0.88–1.01
Number of prescribing orders (1-unit increase)	1.02	1.01–1.02***	1.02	1.01–1.02***	1.02	1.01–1.02***
Types of chronic conditions[a]						
Congestive heart failure	1.56	1.25–1.94***	–	–	1.38	1.07–1.78**
Cardiac arrhythmias	1.44	1.03–2.02**	–	–	1.02	0.71–1.46
Valvular disease	1.08	0.82–1.43	–	–	0.85	0.63–1.15
Pulmonary circulation disorders	1.64	0.99–2.71	–	–	1.41	0.84–2.38
Peripheral vascular disorders	1.14	0.88–1.47	–	–	1.09	0.84–1.42
Hypertension	1.03	0.85–1.25	–	–	0.98	0.78–1.22
Chronic pulmonary disorders	1.23	0.97–1.56	–	–	1.10	0.85–1.43
Diabetes	1.20	0.99–1.46	–	–	1.15	0.93–1.43
Hypothyroidism	0.92	0.70–1.21	–	–	1.08	0.81–1.45
Renal failure	1.13	0.83–1.53	–	–	0.90	0.65–1.25
Cancer	1.12	0.86–1.45	–	–	0.88	0.66–1.17
Rheumatoid arthritis/collagen vascular diseases	0.85	0.54–1.33	–	–	0.81	0.51–1.28

Table 3 Unadjusted and multivariable associations between demographic and clinical factors and the prescribing of potentially inappropriate medications during the 90-day follow-up period *(Continued)*

Demographics and clinical characteristics	*Unadjusted associations*		*Model 1: Demographic and healthcare utilization variables*		*Model 2: Model 1 + chronic conditions*	
	Unadjusted hazard ratio	*95% CI*	*Adjusted hazard ratio*	*95% CI*	*Adjusted hazard ratio*	*95% CI*
	(*N* = 17,912)		(*n* = 17,911)		(*n* = 17,911)	
Coagulopathy	1.25	0.79–1.98	–	–	0.95	0.58–1.54
Fluid and electrolyte disorders	1.30	0.87–1.95	–	–	1.11	0.73–1.68
Depression	0.97	0.69–1.35	–	–	1.04	0.73–1.48
Liver disease	1.81	1.02–3.20	–	–	1.54	0.86–2.75

Overall follow-up time in days: 1,575,994; average follow-up time in days: 88. [a] comorbidities defined with coding algorithms for defining Elixhauser comorbidities in ICD-9 administrative data (Quan et al. 2005), ≥2 ICD-9 codes per category, hypertension categories merged, diabetes categories merged, different cancer categories merged, drug abuse, alcohol abuse, obesity, weight loss, HIV/AIDS, paralysis, other neurological disorders, blood loss anemia and deficiency anemia not included, [b] 90th percentile = 1, [c] 75th percentile = 1. [d] categories based on quartiles, [e]85th percentile = 1
** $p < 0.05$; *** $p < 0.001$

Contrasted with patient demographic and health services use factors, the presence of specific chronic comorbidities was generally not found to be associated with new PIM prescribing. This is in line with previous research [22].

Overall, we observed that patients who were newly prescribed a PIM during the follow-up period were slightly sicker, had a higher health services use, and thus were more complex. This increased clinical complexity could lead to less oversight by individual providers on patients' medication regimens, which in turn could make the prevention and reduction of PIM prescribing more difficult. We hypothesize that rather being a question of the individual factors associated with new PIM prescribing, the complexity of individual patients their treatment schedules and medication regimens could be strongly associated with greater PIM prescribing.

These findings have several implications for clinical care. Healthcare professionals, such as pharmacists and physicians, should be aware of key demographic factors that appear to be associated with PIM prescribing when taking prescribing decisions and potentially incorporate these into decision support for prescribers. Relatedly, improvement of care coordination across providers and fragmentation of healthcare prescribing decisions may also be critical ingredients for reducing PIM prescribing in this population, given that more ambulatory visits and unique prescribing orders are also associated with receiving PIMs.

Further, these findings have implications for the design of interventions aimed at reducing the prescribing of PIMs and deprescribing interventions. Prior medication optimization interventions in older adults more broadly have had little or no effect on clinical outcomes, such as mortality or cognitive impairment [55]. Current evidence on interventions in multimorbid older adults using multiple medications remains scarce [56]. Interventions designed to optimize prescribing also may need to be multifaceted, as they should aim at changing behaviors of different stakeholders (e.g. patients, physicians, pharmacists, etc.) and should involve different components (i.e. medication review, education/training, and use different tools/instruments) [57, 58]. Such interventions must not only solve medication-related problems (e.g. PIM prescribing), but they must target the underlying mechanisms that lead to these problems (e.g. complexity). Consequently, while not all of the above-mentioned factors are modifiable, the knowledge of their association with PIM prescribing must be built into medication optimization interventions and may be even more important for this more complex population.

Limitations

While to the best of our knowledge this study was the first to examine patient factors for new prescribing of PIMs in older multimorbid adults with polypharmacy, there are several limitations. First, the data are from several years ago (owing, in part, to an administrative lag in Medicare data and linking with EHR data); however, prescribing rates of PIMs have not changed since 2007-2014 [59]. Consequently, we expect the exploration of risk factors to remain highly relevant. Second, due to the criterion-based rather than judgment-based nature of the Beers list, medications indicated in certain circumstances (e.g. use as last resort, etc.) may have been flagged as potentially inappropriate. Despite this, the Beers criteria are the most commonly used tool for defining PIM use in the US and restricting the analyses to medications with medium and high level of evidence did not change the results. Despite our data covering the period from 2007 to 2014, we used the 2019 Beers list to inform current medical decision making. This comes with a modest limitation that medications that were included in the Beers list were excluded in the meantime and some new ones were added. Overall, however, these

changes only concerned a small number of medications listed in Table 2 of the Beers criteria (e.g., in the 2015 version of the Beers criteria, four medications were removed and three were added; in the 2019 version of the Beers criteria, two medications were removed and three medications were added) [38, 39]. Furthermore, we were not able to adjust our models for the number and types of prescribers, but we specifically focused on patient factors for this reason. Third, we had limited information on dose and route of administration of medications, which may have affected the definition of PIMs; however, this might have led to an underestimation of the prescribing of gastrointestinal PIMs. We also may have underestimated the new prescribing of PIMs because we may not have captured over-the-counter prescribing of medications (e.g. anti-histamines). Fourth, despite the demographic makeup of the Boston metropolitan area being similar to other urban US regions [60], access to healthcare and physicians may be higher in this area compared to other parts of the country. The present study is an observational study, so residual confounding cannot be excluded because of unmeasured or inadequately measured confounders. Finally, there may have been selection bias, since the patients who achieve a high age without being prescribed or using a PIM may differ from those with PIM prescribing or use.

Conclusion

Several demographic and clinical characteristics are associated with the new prescribing of potentially inappropriate medications in older patients who were naïve to PIMs (e.g. age of ≥85 years, male sex, and number of ambulatory visits). This also indicates that patients with more complex health problems may be at a higher risk of new PIM prescribing. Central nervous system drugs, cardiovascular drugs, anticholinergics and endocrine drugs were the most commonly prescribed PIMs during the 90-day follow-up period. Due to the potential negative outcomes associated with the use of PIMs, these study findings should inform the creation of interventions to improve coordination of care and reduce the prescribing of potentially inappropriate medications in older multimorbid adults with polypharmacy.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-021-02089-x.

Additional file 1.

Abbreviations

AGS: American Geriatrics Society; AHRQ: Agency for Healthcare Research and Quality; CCI: Chronic Condition Indicator; CMS: Centers for Medicare and Medicaid Services; EHR: Electronic health records; FDA: Food and Drug Administration; PIMs: Potentially inappropriate medications; RPDR: Partners Research Patient Data Registry; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Authors' contributions

K.T.J. and J.C.L. conceptualized and designed the study. K.T.J. had full access to all of the data in the study. K.T.J. and J.C.L. analyzed the data. All authors worked on the interpretation of the data and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors critically revised the manuscript. J.C.L. and S.S. provided administrative, technical and material support. J.C.L. supervised the project. The authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the Research Data Assistance Center (ResDAC) from the Centers for Medicare and Medicaid Services and from Mass General Brigham (formerly Partners Healthcare). Restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data may however be available from the authors upon reasonable request and with permission of ResDAC.

Ethics approval and consent to participate

This study was approved by the Brigham and Women's Hospital Institutional Review Board. This analysis is a secondary analysis of subjects in the CMS-RPDR dataset. Given the nature of the data previously being collected for routine care, patient consent was waived by the Brigham and Women's Hospital Institutional Review Board. All methods were performed in accordance with the relevant guidelines and regulations (e.g. declaration of Helsinki).

Consent for publication

Not applicable.

Competing interests

The authors have no conflicts of interests to disclose.

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Publisher's Note

8.2 Section II: General Practitioners' Willingness to Make Deprescribing Decisions in Older Adults with Polypharmacy

Article III: General Practitioners' Deprescribing Decisions in Older Adults with Polypharmacy: a Case Vignette Study in 31 Countries

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My contributions: Together with Sophie Mantelli, Zsofia Rozsnyai, Emily Reeve, Rosalinde Poortvliet, Clare Luymes, Nicolas Rodondi, Jacobijn Gussekloo and Sven Streit I designed and conceptualized the study. Together with the national coordinators (from Aristea Missiou to Viktoria Tkachenko on the author list) I collected the data in the participating countries by managing the entire data collection process. I had full access to all the data used in this research and I had the main responsibility for conducting the data analysis. I created all figures and tables shown below. I wrote the first draft of the manuscript and I made the necessary changes based on comments made by co-authors and reviewers during the peer-review process.

Tables and Figures in Article III

(as displayed in the published article below)

Table 1. Baseline characteristics of general practitioners (GPs) from all participating countries (N countries = 31, N GPs = 1706)

Figure 1. Per country average of the percentage of case vignettes in which GPs (N = 1706) reported they would deprescribe at least one (map A) vs. at least two (map B) medications

Figure 2. Factors important to general practitioners (GPs) when making deprescribing decisions1, ordered by importance (N = 1706)

Table 2. Percentage of general practitioners (GPs) deprescribing in case vignettes, sorted by GPs' decisions to deprescribe at least one, two or three medications in the respective case vignette, patients' level of dependency in activities of daily living, and patients' history of cardiovascular disease (CVD) (N = 1706)

Table 3. Multilevel logistic regression model: adjusted effect of patient and general practitioners' (GPs) characteristics on general practitioners' decisions to deprescribe at least one medication in any of the case vignettes (N = 1706)

Table 4. Comparison of crude percentages of general practitioners (GPs) reporting to deprescribe the medications in the case vignettes, sorted by medication type, history of cardiovascular disease (CVD), and dependency level (N = 1706)

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General practitioners' deprescribing decisions in older adults with polypharmacy: a case vignette study in 31 countries

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Abstract

Background: General practitioners (GPs) should regularly review patients' medications and, if necessary, deprescribe, as inappropriate polypharmacy may harm patients' health. However, deprescribing can be challenging for physicians. This study investigates GPs' deprescribing decisions in 31 countries.

Methods: In this case vignette study, GPs were invited to participate in an online survey containing three clinical cases of oldest-old multimorbid patients with potentially inappropriate polypharmacy. Patients differed in terms of dependency in activities of daily living (ADL) and were presented with and without history of cardiovascular disease (CVD). For each case, we asked GPs if they would deprescribe in their usual practice. We calculated proportions of GPs who reported they would deprescribe and performed a multilevel logistic regression to examine the association between history of CVD and level of dependency on GPs' deprescribing decisions.

Results: Of 3,175 invited GPs, 54% responded ($N = 1,706$). The mean age was 50 years and 60% of respondents were female. Despite differences across GP characteristics, such as age (with older GPs being more likely to take deprescribing decisions), and across countries, overall more than 80% of GPs reported they would deprescribe the dosage of at least one medication in oldest-old patients (> 80 years) with polypharmacy irrespective of history of CVD. The odds of deprescribing was higher in patients with a higher level of dependency in ADL (OR =1.5, 95%CI 1.25 to 1.80) and absence of CVD (OR =3.04, 95%CI 2.58 to 3.57).

(Continued on next page)

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Interpretation: The majority of GPs in this study were willing to deprescribe one or more medications in oldest-old multimorbid patients with polypharmacy. Willingness was higher in patients with increased dependency in ADL and lower in patients with CVD.

Keywords: Deprescribing, Polypharmacy, Multimorbidity, Primary health care, Old age,

Background

Polypharmacy, commonly defined as the concurrent use of 5 or more medications, is a growing concern in a context of common overtreatment. More than 40% of older adults aged 65 years and over and an even higher percentage of older nursing home residents have polypharmacy [1, 2]. Polypharmacy can be problematic as it is associated with a higher risk of being prescribed potentially inappropriate medications (PIMs) [3]. One third of adults aged 65 years and over are taking at least one PIM [4]. Polypharmacy and PIMs are linked to an increased risk of adverse drug events [5, 6], drug-drug and drug-disease interactions [7, 8], functional decline [9–11], decline in cognitive function [10, 12], increased risk for falls [13, 14], and increase in direct medical healthcare costs [15].

Older multimorbid adults with cardiovascular diseases (CVD) have been shown to be disproportionately affected by medication-related issues [16]. Due to these potential negative consequences optimizing polypharmacy in older adults including those with CVD is highly relevant.

With increasing age the main treatment goals often shift from the prevention of mortality and morbidity to the maintaining of functional independence and quality of life, especially in less robust older adults with limited levels of independence [17]. In addition, the benefit-risk profile of older dependent and less robust adults is altered as they are at greater risk of medication induced harm and may not have sufficient remaining life span to benefit from preventive medications [18, 19]. Therefore, older adults with limited functional independence might particularly benefit from medication optimization through deprescribing. However, little is currently known about general practitioners' (GPs) attitudes towards deprescribing in patients with and without history of cardiovascular disease or in those with limited functional independence.

In recent years, deprescribing has become a popular "new word to guide medication review" [20]. It is commonly defined as 'the process of withdrawal or [reduction] of an inappropriate medication, supervised by a healthcare professional with the goal of managing polypharmacy and improving outcomes' [21]. Deprescribing has several benefits, such as achieving better health outcomes through resolving adverse drug reactions, better medication adherence, and direct medical healthcare costs reductions [22]. However, deprescribing may also have negative consequences, such as withdrawal reactions and the worsening or return of medical conditions. These potential harms can be minimized with appropriate planning, monitoring, and re-initiation of medications if needed [22]. As evidenced by the high prevalence of inappropriate medication use in older adults, deprescribing is not routinely conducted in practice. Despite its potential benefits, deprescribing is difficult to implement [23]. In practice, both physicians and patients report barriers to deprescribing, such as uncertainty on how to deprescribe due to a lack of evidence-based guidelines. Patients have reported believing that their medications are still necessary or beneficial [24–27]. An understanding of GPs' deprescribing decisions and the potential barriers they face is needed to inform GP education and develop interventions to optimise appropriate medication use in older adults.

In a case vignette study with 157 GPs in Switzerland, we found a high rate of hypothetical deprescribing of certain medications, which was influenced by patients' history of CVD [28]. However, we were not able to establish the generalisability of these results and the influence of other patient characteristics on GPs deprescribing decisions. Therefore, the aim of this study was to examine deprescribing decisions of GPs in oldest-old patients (80 years and over) with polypharmacy across different countries and to examine whether increasing levels of dependency in activities of daily living (ADL) and history of CVD influenced these decisions.

Methods

Setting and study design

This is a cross-sectional case vignette study conducted with GPs from 31 countries (see Fig. 1). It is part of the LESS (barriers and enabLers to willingnESs to depreScribing in older patients with multimorbidity and polypharmacy and their General Practitioners) study.

Participants

Our total sample consisted of 3,175 GPs from 31 countries who were invited to participate by email through national coordinators. Participants had previously

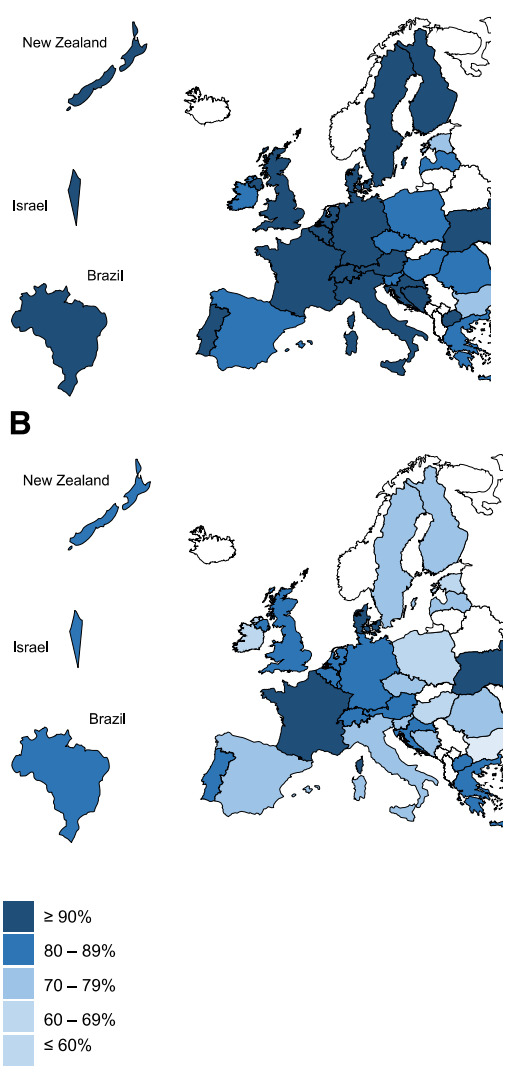

Fig. 1 Per country average of the percentage of case vignettes in which GPs ($N = 1,706$) reported they would deprescribe at least one (map A) vs. at least two (map B) medications. List of participating countries (alphabetical order): Austria, Belgium, Bosnia and Herzegovina, Brazil, Bulgaria, Croatia, Czech Republic, Denmark, United Kingdom, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Latvia, Luxembourg, Macedonia, the Netherlands, New Zealand, Poland, Portugal, Romania, Slovenia, Spain, Sweden, Switzerland, Ukraine. Maps designed by and adapted from PresentationGO.com / © *Copyright* PresentationGO.com

provided consent to be contacted with opportunities to participate in future research [29, 30]. Participants were eligible for inclusion if they were practicing GPs.

Questionnaire

We used the same questionnaire as described in Mantelli et al. (2018), but we included additional case vignettes [28]. We used the *Checklist for Reporting Results of Internet E-Surveys* (CHERRIES) guidelines for reporting results of internet e-surveys [31, 32]. The questionnaire had 3 parts: 1) GP characteristics, 2) 3 case vignettes of oldest-old patients with higher/heightened dependency in activities of daily living (ADL) including increasing cognitive impairment, each presented with and without history of CVD, and 3) Likert-scale questions concerning factors influencing GPs' deprescribing decisions. For the complete questionnaire, refer to Additional file 1: Appendix 1. Where necessary, national coordinators translated and back-translated the survey from English into 22 languages. In Finland and Israel, the survey was distributed in English. In all other countries the survey was distributed in one or several national languages (see Additional file 1: Appendix 2 for more information on survey languages). The online survey was distributed and administered with SurveyMonkey (Palo Alto, CA, USA).

To sample the participating GPs, first, we engaged with national coordinators through the European General Practice Research Network (EGPRN). Second, national coordinators identified relevant networks through which the survey could be distributed. Available networks varied depending on the country. Most national coordinators did a convenience sampling in which they distributed the survey by email to GPs in their personal networks, who had previously consented to be invited to participate in research. Participation was voluntary. In some countries, the survey was sent to lists of GPs available at primary care research institutes or professional societies, which explains the bigger sample size in these countries. Reminders were used when necessary (maximum two reminders where sent). The response rate for each country can be found in Additional file 1: Appendix 2. In Ukraine the survey was administered on paper during a national GP conference due to infrastructure-related reasons. We collected responses from February to December 2018.

Our research team, largely composed of GPs, designed the case vignettes with the aim of creating hypothetical patients aged ≥80 years representing patients typically seen in primary care. Repeated meetings to discuss the case vignettes were held. Collaborators in other countries were consulted by email, with changes made as necessary. Before starting the data collection, the online questionnaire was piloted among five Swiss GPs to test its content validity. Before starting the data collection in each participating country, each national coordinator checked and, if applicable, adapted the layout of the survey based on the local context.

The case vignettes were identical except for CVD status and levels of dependency in ADL. We provided descriptions of dependency related to low, medium and high impairment of ADL and cognitive function. All hypothetical patients were prescribed the same medications. For every case vignette, we asked GPs whether they would stop/reduce the dosage of at least one medication (i.e. deprescribe), and if so which one(s). GPs were instructed to respond as to how they would act in their usual practice.

In part 3 of the questionnaire, GPs were asked to rate the importance of sixteen factors that potentially influenced their deprescribing behaviour using 5-point Likert-scales ranging from "not important" to "very important". The selection of these factors was based on work done by Luymes et al. [33] and Anderson et al. [34] and was completed with factors based on our team's experience.

Completion of the survey took 10–15 minutes. The different parts of the questionnaire were presented on different pages and where necessary the content of one part was distributed over different pages to keep the number of items per page small. Respondents were able to navigate back and forth through the survey. The national coordinators sent a web link to GPs, which was required to access the survey. The selection of one response option was enforced. We did not use cookies nor did we collect IP addresses. We did not perform a timestamp analysis.

Statistical analyses

We described GP characteristics by calculating proportions, means, and confidence intervals (CI). We calculated crude odds ratios (OR) from univariate logistic regressions to determine if GP characteristics were associated with decisions to deprescribe. For each case vignette we described the proportions of GPs who would deprescribe. As a sensitivity analysis, we also performed this analysis in countries with a > 60% response rate. We calculated the average number of medications deprescribed per case vignette. We performed a multilevel logistic regression to examine the association between both history of CVD and level of dependency in ADL and GPs' decisions to deprescribe at least one medication in any of the case vignettes by accounting for the clustering of GPs at country level. We adjusted the model for the following GP characteristics: age, sex, average number of consultations per day, frequency of seeing patients with polypharmacy. Subsequently, we performed a comparison of proportions to determine whether GPs' deprescribing decisions concerning specific medications changed with increased patient dependency. Lastly, for the factors included in the Likert-scales we calculated the percentage of GPs who rated these factors as (very) important. We defined a two-sided p-value of < 0.05 as significant. All analyses were performed with STATA 15.1 (StataCorp, College Station, TX, USA).

Results

GP characteristics

In the participating countries, the median response rate was 50% (range: 11–95%). Of the total of 3,175 invited GPs across countries, 1,706 responded (54%), and 1415 GPs completed the whole questionnaire. The number of participants differed by country (range: 20 in Czech Republic and Ireland; 247 in Hungary).

Table 1 presents characteristics of the participating GPs. 60% were female, mean age was 50 years, and the mean clinical experience as GP was 18 years. As shown in this table, being female reduced the odds of deprescribing in all case vignettes (compared to not deprescribing in one or more case vignettes), whereas the odds of deprescribing increased with increasing age of GPs, with GPs regularly treating patients aged 70 years or more with polypharmacy and with GPs regularly dealing with the topic of deprescribing.

Deprescribing decisions

Table 2 shows the percentage of GPs reporting stopping at least one, two or three medications per case vignette. More than 90% (range: 94–95%) of GPs reported that they would deprescribe at least one medication in all the case vignettes without history of CVD whereas the proportion was slightly lower (range: 82–90%) in the case vignettes with history of CVD. Around 70% of GPs (range: 68–78%) opted for deprescribing at least 3 medications in the case vignettes without CVD history while the percentage again was lower (range: 27–59%) in the case vignettes with CVD history. In CVD cases, the proportion of GPs who reported deprescribing medications increased with increasing dependency levels. The sensitivity analysis performed in countries with a response rate > 60% showed the same trends (Additional file 1: Appendix 3).

The multilevel logistic regression model of GPs' decisions to deprescribe at least one medication in any case vignette, adjusted for GP characteristics, showed that the odds of GPs reporting deprescribing in patients without CVD history were 3 times higher than the odds of GPs reporting to deprescribe in patients with history of CVD (Table 3). The odds of GPs reporting deprescribing in the scenarios with an increased level of dependency were 1.29 to 1.50 times higher than the odds of GPs reporting deprescribing in the scenarios in which patients had lower dependency levels. While GPs' age was associated with taking deprescribing decisions (OR: 1.14 for 10-year increase, 95% CI: 1.06–1.23), female sex was not (OR: 0.89, 95% CI: 0.75–1.05) nor were the average number

Table 1 Baseline characteristics of general practitioners (GPs) from all participating countries (N countries = 31, N GPs = 1,706)

GP characteristics	Overall	GPs' deprescribing decisions[a] (*N* = 1,428, only complete records)			
		Deprescribing in < 6 case vignettes (*n* = 370)	Deprescribing in all 6 case vignettes[b] (*n* = 1,058)	Crude odds ratio of deprescribing in all 6 case vignettes[c] (95% CI)	*P*-value[d]
Sex					
female, n (%)	1,021 (60)	240 (65)	593 (56)	0.74 (0.57 to 0.96)	0.024
male, n (%)	685 (40)	130 (35)	465 (44)	ref.	
Age, in years					
mean (standard deviation)	50 (12)	49 (12)	50 (12)	*per 10 years*: 1.14 (1.02 to 1.28)	0.020
Clinical experience as GP, in years					
mean (standard deviation)	18 (11.4)	17 (11)	18 (11)	*per 10 years:* 1.12 (1.00 to 1.25)	0.055
Average number of consultations per working day, n (%)					
< 15	197 (12)	31 (8)	121 (11)	ref.	–
15–25	567 (33)	123 (33)	356 (34)	0.78 (0.48 to 1.25)	0.30
26–35	468 (27)	93 (25)	300 (28)	0.91 (0.56 to 1.50)	0.72
> 35	474 (28)	123 (33)	281 (27)	0.71 (0.43 to 1.20)	0.21
Frequency of seeing/treating patients aged ≥ 70 years with polypharmacy, n (%)					
frequently / very frequently	1,469 (87)	310 (84)	942 (89)	1.63 (1.15 to 2.32)	0.006
very rarely / rarely / occasionally	218 (13)	60 (16)	116 (11)	ref.	–
Frequency of dealing with the topic of deprescribing medications in daily practice, n (%)					
frequently / very frequently	935 (56)	176 (48)	638 (60)	1.53 (1.18 to 1.97)	0.001
very rarely / rarely / occasionally	729 (44)	194 (52)	420 (40)	ref.	–
Frequency of deprescribing medications during consultations in daily practice, n (%)					
frequently / very frequently	438 (26)	76 (21)	305 (29)	1.46 (1.09 to 1.97)	0.012
very rarely / rarely / occasionally	1,226 (74)	294 (79)	753 (71)	ref.	-

[a]deprescribing defined as stopping or reducing the dosage of at least one medication; [b]median deprescribing behaviour corresponds to deprescribing or reducing the dosage of at least one medication in all of the 6 hypothetical patients; [c]crude odds ratios from multilevel univariate logistic regression; [d]*P*-values from univariate logistic regression

of consultations per day or the frequency of seeing patients with polypharmacy (Table 3).

Geographical variation

Figure 1 maps the differences in the per country averages of case vignettes in which GPs from our convenience sample opted for deprescribing in at least one versus at least two medications. The percentages of deprescribing a minimum of one medication ranged from 77% in Bulgaria to 100% in Ukraine, whereas the percentages of deprescribing a minimum of two medications ranged from 58% in Bulgaria to 92% in Denmark. Both maps show variation across countries.

Deprescribing decisions by medication type

Table 4 shows the proportion of GPs who would deprescribe sorted by medication type, CVD history, and level of dependency in ADL. There was little variation in

Table 2 Percentage of general practitioners (GPs) deprescribing in case vignettes, sorted by GPs' decisions to deprescribe at least one, two or three medications in the respective case vignette, patients' level of dependency in activities of daily living, and patients' history of cardiovascular disease (CVD) ($N = 1,706$)

Case vignette	Patients' dependency level	Deprescribing decision	Without history of CVD (95% CI)	With history of CVD (95% CI)	Difference (95% CI)[a]
1	low				
	(living in own house, no help needed for activities of daily living)	min. 1 medication	95.1% (94.0 to 96.1)	81.6% (79.6 to 83.5)	13.5% (11.3 to 15.7)
		min. 2 medications	88.2% (86.6 to 89.8)	60.1% (57.7 to 62.5)	28.1% (25.2 to 31.0)
		min. 3 medications	69.2% (66.9 to 71.5)	26.5% (24.3 to 28.7)	42.7% (39.6 to 45.9)
2	medium				
	(living in own house, some help needed for activities of daily living)	min. 1 medication	94.3% (93.1 to 95.5)	87.4% (85.7 to 89.1)	6.8% (4.8 to 8.9)
		min. 2 medications	85.8% (84.0 to 87.5)	68.5% (66.1 to 70.9)	17.3% (14.3 to 20.3)
		min. 3 medications	67.6% (65.3 to 70.0)	36.6% (34.1 to 39.1)	31.0% (27.6 to 34.5)
3	high				
	(living in nursing home, help needed for nearly all activities of daily living)	min. 1 medication	94.1% (92.8 to 95.3)	90.4% (88.8 to 91.9)	3.7% (1.7 to 5.7)
		min. 2 medications	88.5% (86.8 to 90.1)	79.2% (77.1 to 81.3)	9.3% (6.6 to 12.0)
		min. 3 medications	78.4% (76.2 to 80.5)	58.6% (56.0 to 61.1)	19.8% (16.5 to 23.1)

[a]Two-sample test of proportions

reported deprescribing for pantoprazole, tramadol, and paracetamol among the different levels of dependency and CVD history. For atorvastatin, aspirin, amlodipine, and enalapril the percentages of GPs reporting to deprescribe generally increased with increasing levels of dependency and was lower when there was a history of CVD. Overall, GPs were most likely to deprescribe proton-pump inhibitors and pain medication.

Factors important for deprescribing decisions

Figure 2 shows the importance given to different factors reported to impact GPs' deprescribing decisions. Risks and benefits of medications, patients' quality of life, patients' life expectancy and patients' fear of potential negative health outcomes were important or very important to more than 90% of GPs. Less than half of GPs rated the time needed for deprescribing as important or very important for making deprescribing decisions.

Discussion

In this study of over 1,700 GPs from 31 countries, we investigated GPs' deprescribing decisions in oldest-old patients with polypharmacy. Despite differences across GP characteristics and across countries, a large proportion of GPs reported that they would deprescribe at least one medication in all scenarios. The odds of GPs reporting decisions to deprescribe was higher in patients with a higher dependency level (OR =1.5, 95%CI, 1.25 to 1.80) and in absence of CVD history (OR =3.04, 95%CI 2.58 to 3.57). The medications GPs were most willing to deprescribe in case vignettes with and without history of CVD were pain medications and proton-pump inhibitors. However, history of CVD appeared to affect deprescribing decisions of certain medications. While GPs were likely to deprescribe cholesterol medication used for primary prevention (no history of CVD), GPs were less likely to deprescribe those medications when used for secondary prevention. Factors GPs rated as important or very important for deprescribing decisions were patients' quality of life, life expectancy, fear of potential negative health outcomes resulting from deprescribing, and the risks and benefits of medications.

This is the first study to examine deprescribing decisions of GPs across a large number of countries. We found variation in deprescribing decisions across countries and based on GP characteristics, such as age with older GPs being more likely to take deprescribing decisions. Bolmsjö et al. (2016) found that deprescribing behaviours were largely dependent on the structure of healthcare systems [35]. This might explain the differences we found between countries. Previous qualitative studies reported that GPs with greater clinical experience were more able to draw on their own clinical knowledge [36–39], which might explain why older and more experienced GPs in our sample were more likely to deprescribe. Further research is needed to explore the association between GP characteristics and deprescribing in more depth.

Our findings show that GPs were willing to deprescribe in patients with high dependency and increasing cognitive impairment. The results built on a first analysis with the Swiss data from the LESS study, in which we had only included the most dependent, least robust oldest-old adults (case vignette 3) and found that GPs reported to be influenced by the risk and benefit of medications, quality of life and life expectancy when taking

Table 3 Multilevel logistic regression model: adjusted effect of patient and general practitioners' (GPs) characteristics on general practitioners' decisions to deprescribe at least one medication in any of the case vignettes (N = 1,706)

	Overall		
	Odds ratio	*95% confidence interval*	*P-value*
Patient's history of cardiovascular disease (CVD)			
History of CVD	ref.	–	–
No history of CVD	3.04	2.58 to 3.57	< 0.001
Patient's level of dependency in activities of daily living			
Low	ref.	-	-
Medium	1.29	1.09 to 1.55	0.004
High	1.50	1.25 to 1.80	< 0.001
Age (GP), 10-year increase	1.14	1.06 to 1.23	< 0.001
Female sex (GP)	0.89	0.75 to 1.05	0.167
Number of consultations per day			
< 15	ref.	–	–
15–25	1.04	0.77 to 1.40	0.79
26–35	1.2	0.88 to 1.65	0.25
> 35	0.94	0.68 to 1.30	0.698
Frequency of seeing patients with polypharmacy			
Never	ref.	–	–
Rarely	0.64	0.18 to 2.28	0.497
Occasionally	0.80	0.25 to 2.53	0.699
Frequently	1.27	0.39 to 3.87	0.728
Very frequently	1.42	0.45 to 4.49	0.554

The multilevel model accounts for clustering of the GPs at country level

deprescribing decisions [28]. Our findings are in line with previous research, which revealed cognitive impairment as an important factor for deprescribing [40]. This also aligns with the basic principles of appropriate medication use which contend that potential benefits of the medication should outweigh potential risks and align with the goals of care of the individual [19]. As mentioned before, the benefit-risk profile of dependent and less robust older adults is altered as they are at greater risk of medication induced harm and may not have sufficient remaining life span to benefit from preventive medications [18, 19]. That GPs seem more willing to deprescribe in older adults with increased dependency levels implies that we need better ways to identify such patients in primary care settings. The routine use of frailty screening tools in primary care is gaining interest. However, it remains unclear which tools are the most useful and feasible and how to best deliver care for those identified as frail and less robust [41, 42]. Furthermore, despite the fact that certain tools exist to conduct deprescribing in older adults with frailty or limited life expectancy, little is known about how such tools can be used in a way that reduces inappropriate medication use and improves clinical outcomes [43].

In line with a qualitative study by Luymes et al., we found that GPs were more likely to deprescribe in patients with a lower CVD risk [33]. A recent national cross-sectional survey of US geriatricians, general internists, and cardiologists found that > 90% of physicians in each specialty reported to deprescribe cardiovascular medications when patients experienced adverse drug reactions [44]. In addition, this study also pointed out potential barriers linked to the communication between physicians when making deprescribing decision. Our finding of the impact of CVD on deprescribing, however, is likely driven by the fact that four out of the seven medications in the case vignette are related to the cardiovascular system. Further research is warranted to find ways to overcome the barriers linked to interprofessional communication, as this is crucial for sustainable deprescribing.

The medications presented in our case vignettes are commonly used in older adults. However, some of them are considered potentially inappropriate to be used in older adults. For instance, according to the 2019 Beers criteria aspirin should not be used for primary prevention of cardiovascular disease, tramadol should be used with caution as it may cause or exacerbate the syndrome

Table 4 Comparison of crude percentages of general practitioners (GPs) reporting to deprescribe the medications in the case vignettes, sorted by medication type, history of cardiovascular disease (CVD), and dependency level (*N* = 1,706)

Medication	Level of dependency in activities of daily living		
	Low (case vignette 1)	*Medium (case vignette 2)*	*High (case vignette 3)*
	Percentage of GPs (95% CI)	**Percentage of GPs (95% CI)**	**Percentage of GPs (95% CI)**
Pain medications			
Tramadol 50 mg, twice daily			
Without history of CVD	63.5% (61.1 to 65.9)	69.4% (67.0 to 71.7)	68.5% (66.0 to 70.9)
With history of CVD	57.3% (55.2 to 60.2)	67.0% (64.5 to 69.4)	67.6% (65.2 to 70.1)
Paracetamol 1 g, three times daily			
Without history of CVD	47.5% (45.0 to 50.0)	41.9% (39.4 to 44.5)	44.9% (42.3 to 47.5)
With history of CVD	43.8% (41.3 to 46.3)	40.8% (38.3 to 43.4)	43.6% (41.0 to 46.2)
Proton-pump inhibitor			
Pantoprazole 20 mg, once daily			
Without history of CVD	64.5% (63.0 to 67.8)	64.4% (61.9 to 66.8)	67.8% (65.3 to 70.2)
With history of CVD	47.1% (44.6 to 49.6)	49.0% (46.4 to 51.6)	55.6% (53.0 to 58.2)
Antihypertensive medications			
Amlodipine 5 mg, once daily			
Without history of CVD	15.2% (13.4 to 17.0)	18.9% (17.0 to 21.0)	33.9% (31.4 to 36.4)
With history of CVD	8.7% (7.3 to 10.2)	15.1% (13.3 to 17.1)	30.3% (27.9 to 32.8)
Enalapril 10 mg, once daily			
Without history of CVD	7.7% (6.4 to 9.1)	9.8% (8.3 to 11.4)	19.4% (17.4 to 21.5)
With history of CVD	2.5% (1.7 to 3.4)	4.6% (3.6 to 5.8)	15.5% (13.6 to 17.5)
Cholesterol-lowering medication			
Atorvastatin 40 mg, once daily			
Without history of CVD	59.1% (56.6 to 61.5)	62.7% (60.2 to 65.2)	76.8% (74.5 to 78.9)
With history of CVD	13.7% (12.0 to 15.5)	26.5% (24.3 to 28.9)	52.5% (49.9 to 55.1)
Antiplatelet medication			
Aspirin 100 mg, once daily			
Without history of CVD	52.1% (49.6 to 54.5)	49.1% (46.5 to 51.7)	60.3% (57.7 to 62.8)
With history of CVD	4.3% (3.4 to 5.5)	7.2% (5.9 to 8.6)	23.9% (21.7 to 26.2)

Acronyms: *CI* Confidence interval; *CVD* Cardiovascular disease; *GP* General practitioner

of inappropriate secretion of antidiuretic hormone, and the use of proton pump inhibitors for more than eight weeks should be avoided in non-high-risk patients [45]. In this study, GPs were most likely to opt for deprescribing proton pump inhibitors and pain medication in case vignettes with and without history of CVD while they were least likely to deprescribe antihypertensive medications. GPs were also likely to deprescribe aspirin and atorvastatin for primary prevention. This shows that GPs in our sample were likely to opt for deprescribing medications that are potentially inappropriate when used in older adults. This awareness needs to be built upon when shifting deprescribing from theory to practice. Generally reported deprescribing was high among the GPs when considering the medications as a whole. However, the results for aspirin show that there remain barriers to deprescribing even in hypothetical scenarios. In 2018 three large studies established that aspirin for primary prevention of CVD has a greater risk of harm and shows relatively modest benefits in relation to cardiovascular outcomes [46–48]. Therefore it would be interesting to see whether our study would yield different results (pertaining to aspirin) if it was repeated.

Further research is needed to create thorough guidance on how to deprescribe in older adults with potentially inappropriate polypharmacy, which includes studying the safety of deprescribing in this population group and to further investigate patient barriers to deprescribing [28]. Over 70% of GPs in our study perceive the existence of deprescribing guidelines and tools that facilitate deprescribing as important or very important. This underscores the need for creating such

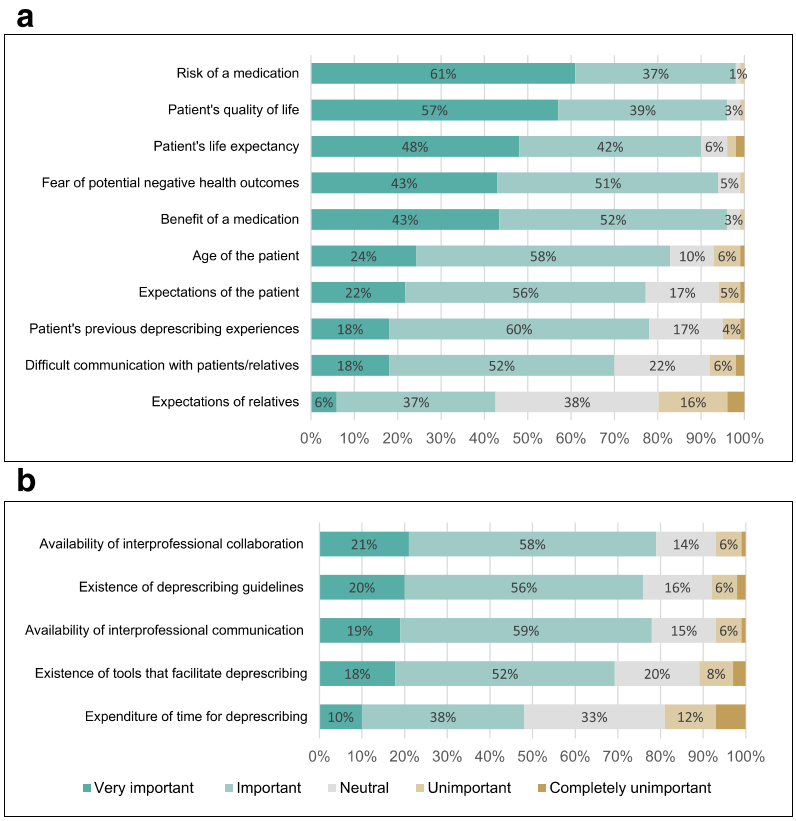

Fig. 2 Factors important to general practitioners (GPs) when making deprescribing decisions[1], ordered by importance (N = 1,706). a) factors related to the patient, and b) factors related to the GP. [1]each GP was asked to rate the importance of each factor

guidelines, not just on when to deprescribe but also how to deprescribe. It also points to a need to raise awareness of currently existing guidelines and potential benefits of translating guidelines to local languages. Currently, evidence-based deprescribing clinical practice guidelines exist for proton pump inhibitors, benzodiazepines and Z-drugs, antihyperglycemics, antipsychotics and cholinesterase inhibitors and memantine [49–53]. Furthermore, an in-depth exploration into the nuanced reasons why GPs do or do not deprescribe specific medications in specific situations and into how deprescribing could be sustainably implemented will be useful for improving deprescribing practices and guidelines.

Our study is strengthened by the inclusion of a large number of GPs from many different countries in Europe and beyond, some of which are rarely included in studies among GPs. Furthermore, the average response rate of 53% is higher than typical response rates of 30–40% in surveys among GPs [54]. The LESS study comes with several limitations. The first one is the hypothetical nature of our case vignettes, which were intended to establish and correspond to GPs' routine clinical practice [28]. However, we were not able to capture the decision-making process, including barriers and facilitators of deprescribing, such as time limitations and patient preferences, values or goals of care, or capture the reasons why GPs selected to deprescribe or not. Therefore, the results of this study may not reflect the complex process of shared decision making. That said, the simple nature of the hypothetical case vignettes is also a strength, as it allowed gathering of a large number of responses from GPs in standardized cases. Second, we do not know how reported deprescribing decisions would transfer to other medications not included in the case vignettes. Third, we did not randomly sample the GPs in each country but performed a convenience sample based on the networks of our national coordinators, which comes with limited generalizability of our study results. Despite this, to

maximise the number of countries involved in order to increase generalisability by reaching a larger number of GPs, we allowed for variations in the types of networks that national co-ordinators used to recruit participants. The variation in the types of networks used was also reflected in the large variation in response rates by country. In addition, GPs self-selecting to complete the survey were likely to be more interested in deprescribing, which may mean that our results could be biased towards overestimating deprescribing decisions. Fourth, we were limited to the self-reported data about GPs' deprescribing decisions, which might have been affected by social desirability bias and the order in which case vignettes were presented. Fifth, we do not know to what extent the reported deprescribing decisions reflect or were influenced by national deprescribing guidelines or other deprescribing initiatives.

Conclusions

Despite international variation, most GPs in our convenience sample reported they would deprescribe at least one medication in hypothetical oldest-old multimorbid patients with polypharmacy. Older GPs were more likely to take deprescribing decisions. GPs were more likely to deprescribe in patients with a higher dependency in activities of daily living and in the absence of a history of cardiovascular disease. Overall, medications most often chosen for deprescribing in the presented case vignettes were proton pump inhibitors and pain medications. Antiplatelet and cholesterol-lowering medication was frequently selected for deprescribing when used for primary prevention.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-020-01953-6.

Additional file 1. Appendix 1-3.

Abbreviations

ADL: Activities of daily living; CHERRIES: Checklist for Reporting Results of Internet E-Surveys; CI: Confidence interval; CVD: Cardiovascular disease; EGPRN: European General Practice Research Network; GPs: General practitioners; LESS: barriers and enabLers to willingnESs to depreScribing in older patients with multimorbidity and polypharmacy and their General Practitioners; OR: Odds ratio; PIM: Potentially inappropriate medication

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Authors' contributions

Study concept and design: KTJ, SM, ZR, ER, CL, RKEP, NR, JG, SS. Acquisition of data: KTJ (Switzerland and all other countries), SM (Switzerland), ZR (Switzerland), AM (Greece), BGK (Macedonia), BW (Germany), CM (England/UK), CC (Ireland), DB (Brazil), DK (Poland), FP (Italy), GD (Romania), HT (Sweden), HL (Germany), KLJ (Denmark), KW (New Zealand), KH (Austria), LPeremans (Belgium), LPiilv (Estonia), MPS (Slovenia), MB (Germany), MS (Luxembourg), MVDP (the Netherlands), PT (Hungary), PBK (Czech Republic), SV (Israel), RA (Bulgaria), RGB (Spain), RPAV (Portugal), RT (France), SKP (Bosnia), SG (Latvia), THK (Finland), VL (Croatia), VT (Ukraine), CL (the Netherlands), SS (Switzerland and support of data collection in all other countries). Statistical analysis: KTJ and SS had full access to all data in the study. All authors (KTJ, SM, ZR, AM, BGK, BW, CM, CC, DB, DK, FP, GD, HT, HL, KLJ, KW, KH, LPeremans, LPiilv, MPS, MB, MS, MVDP, PT, PBK, SV, RA, RGB, RPAV, RS, SKP, SG, THK, VL, VT, ER, CL, RKEP, NR, JG, and SS) take responsibility for the integrity of data and the accuracy of the data analysis. Interpretation of data: All authors (KTJ, SM, ZR, AM, BGK, BW, CM, CC, DB, DK, FP, GD, HT, HL, KLJ, KW, KH, LPeremans, LPiilv, MPS, MB, MS, MVDP, PT, PBK, SV, RA, RGB, RPAV, RS, SKP, SG, THK, VL, VT, ER, CL, RKEP, NR, JG, and SS). Drafting of the manuscript: KTJ created a first draft. Critical revision of the manuscript: All authors (KTJ, SM, ZR, AM, BGK, BW, CM, CC, DB, DK, FP, GD, HT, HL, KLJ, KW, KH, LPeremans, LPiilv, MPS, MB, MS, MVDP, PT, PBK, SV, RA, RGB, RPAV, RS, SKP, SG, THK, VL, VT, ER, CL, RKEP, NR, JG, and SS) have revised multiple drafts of the manuscript and approved of the submission. Obtained funding: SS, NR, RKEP, and JG. Administrative, technical, or material support: SS. Study supervision: SS.

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Availability of data and materials

The dataset used and analysed during the current study is available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Canton of Bern in Switzerland (reference number 2017–02188), the Albert Einstein Ethics Committee in Brazil (reference number: 90812118.3.0000.0071), the University of Auckland Human Participants Ethics Committee in New Zealand (reference number 017502), the RSU Research Ethics Committee (reference number 58 / 28.06.2018) in Latvia, and the Commission of Ethics and Professional Deontology of the Dolj College of Doctors in Romania (reference number: nr.1 din 24102018). The Ethics Committee of the Medical Faculty of the "Rheinische Friedrich-Wilhelms-Universität" in Germany issued a waiver (ref. 117/18). In the remaining countries, no country-specific ethical approval was required. Participating GPs were informed about the aim of the study. They gave their informed consent by clicking to proceed to respond to the online questionnaire after reading the introduction to the survey. Participation was voluntary. This procedure was approved by the above-mentioned ethics committees. All responses were collected anonymously. No incentive was given to participating GPs.

Consent for publication

Not applicable.

Competing interests

The authors declare they have no competing interests.

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Publisher's Note

8.3 Section III: Conducting Interventional Clinical Research with Older Adults with Multimorbidity and Polypharmacy with the Aim of Optimizing Medication Use

Article IV: 'Optimising PharmacoTherapy In the multimorbid elderly in primary CAre' (OPTICA) to improve medication appropriateness: study protocol of a cluster randomised controlled trial

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My contributions: Together with Sven Streit, Sven Trelle, Marco Spruit, Matthias Schwenkglenks, Rahel Meier, Nicolas Rodondi, and Sven Streit, I further designed and conceptualized the conduct of the clinical trial for which the funding had already been received when I joined the team. I prepared the

application to the ethics committee and wrote the first draft of the protocol paper. After receiving feedback from the co-authors, I did the necessary revisions made by the co-authors and the reviewers. I created all figures and tables shown in the manuscript.

Tables and Figures in Article IV

(as displayed in the published article below)

BMJ Open

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ABSTRACT

Introduction Multimorbidity and polypharmacy are major risk factors for potentially inappropriate prescribing (eg, overprescribing and underprescribing), and systematic medication reviews are complex and time consuming. In this trial, the investigators aim to determine if a systematic software-based medication review improves medication appropriateness more than standard care in older, multimorbid patients with polypharmacy.

Methods and analysis Optimising PharmacoTherapy In the multimorbid elderly in primary CAre is a cluster randomised controlled trial that will include outpatients from the Swiss primary care setting, aged ≥65 years with ≥three chronic medical conditions and concurrent use of ≥five chronic medications. Patients treated by the same general practitioner (GP) constitute a cluster, and clusters are randomised 1:1 to either a standard care sham intervention, in which the GP discusses with the patient if the medication list is complete, or a systematic medication review intervention based on the use of the 'Systematic Tool to Reduce Inappropriate Prescribing'-Assistant (STRIPA). STRIPA is a web-based clinical decision support system that helps customise medication reviews. It is based on the validated 'Screening Tool of Older Person's Prescriptions' (STOPP) and 'Screening Tool to Alert doctors to Right Treatment' (START) criteria to detect potentially inappropriate prescribing. The trial's follow-up period is 12 months. Outcomes will be assessed at baseline, 6 and 12 months. The primary endpoint is medication appropriateness, as measured jointly by the change in the Medication Appropriateness Index (MAI) and Assessment of Underutilisation (AOU). Secondary endpoints include the degree of polypharmacy, overprescribing and underprescribing, the number of falls and fractures, quality of life, the amount of formal and informal care received by patients, survival, patients' quality adjusted life years, patients' medical costs, cost-effectiveness of the intervention, percentage of recommendations accepted by GPs, percentage of recommendation rejected by GPs and patients' willingness to have medications deprescribed.

Ethics and dissemination The ethics committee of the canton of Bern in Switzerland approved the trial protocol. The results of this trial will be published in a peer-reviewed journal.

Main funding Swiss National Science Foundation, National Research Programme (NRP 74) 'Smarter Healthcare'.

Strengths and limitations of this study

- The Optimising PharmacoTherapy In the multimorbid elderly in primary CAre (OPTICA) trial is the first randomised controlled trial to examine the effect of the 'Systematic Tool to Reduce Inappropriate Prescribing'-Assistant, a software-assisted clinical decision support tool, on medication appropriateness in older, multimorbid patients with polypharmacy in a primary care setting.
- OPTICA is the first randomised controlled trial to test the use of software-based structured medication reviews in Swiss primary care.
- The OPTICA trial demonstrates how linked and coded data from electronic medical records can be used to evaluate primary care interventions in a randomised controlled trial setting. The investigators limit selection bias by using screening lists with a random sample of potentially eligible patients and randomising general practitioners (GPs) after patient recruitment is complete, but cannot eliminate the risk of selection bias.
- The investigators chose a sham intervention in accordance with usual care in the control group to improve patient blinding but, by design, they could not blind GPs.

Trial registration numbers Clinicaltrials.gov (NCT03724539), KOFAM (Swiss national portal) (SNCTP000003060), Universal Trial Number (U1111-1226-8013).

INTRODUCTION

Globally, there is a high prevalence of multimorbidity and polypharmacy in people more than 65 years old.[1 2] Multimorbidity is commonly defined as the coexistence of three or more chronic diseases,[3] and polypharmacy is commonly defined as the regular intake of five or more medications.[4] Polypharmacy is often caused by multimorbidity and is linked to a high risk of potentially inappropriate prescribing,[5 6] which has three main elements, namely: (1) overuse, (2) underuse and (3) inappropriate use of medications (ie, wrong dose/medication for the indication).[7]

Appropriate polypharmacy denotes a situation in which 'medication use is optimised according to the patients' clinical needs' and in which patients 'receive the most appropriate combinations of medications based on the best available evidence'.[8] While appropriate polypharmacy can improve quality of life and prevent consequences of disease, inappropriate polypharmacy can harm patients' health.[4] For instance, it can increase the risk of falls and fractures,[9] lead to cognitive decline,[10 11] and it can reduce quality of life.[9] Polypharmacy also increases the risk of drug–drug interactions, drug–disease interactions and adverse drug events.[12–15] Treatment of older patients with multimorbidity and polypharmacy is a complex problem in primary care and other medical fields and both conditions are increasingly common as populations age. Due to the relatively small number of randomised controlled trials on different interventions for the management of multimorbid people, there currently remain uncertainties about the effectiveness of these interventions.[16] Medication reviews in older adults with multimorbidity and polypharmacy can be complicated and time-consuming.[17] General practitioners (GPs) have reported that time limitations and lack of user-friendly and reliable tools pose significant barriers to regular medication optimisation activities in practice.[18]

Current evidence is ambiguous on whether review interventions that aim at optimising medication can reduce inappropriate polypharmacy. A systematic review and meta-analysis of short-term medication review interventions published in 2017 showed that such isolated medication reviews have an impact on drug-related outcomes, but only minimally influence clinical outcomes and have no impact on quality of life.[19] A more recent systematic review and meta-analysis on interventions to improve the appropriateness of medication use in older people showed that such interventions may be beneficial for reducing potential prescribing omissions, but that it remains uncertain whether they improve the appropriateness of medication use.[20]

The increasing use of electronic medical records (EMR) and electronic prescribing has opened opportunities to incorporate web-based clinical decision support systems (CDSS) at the point of care. For instance, a complex intervention with an informatics tool and financial incentives has led to a reduction in high-risk prescribing of non-steroidal anti-inflammatory drugs and antiplatelet medications.[21] Medication optimisation studies that use CDSS enabled by electronic medical records have shown that the interventions are feasible and acceptable to clinicians, but evidence that they lead to more appropriate use of medications in general and improve clinical outcomes is still limited.[22]

Objectives

The primary aim of the cluster-randomised 'Optimising PharmacoTherapy In the multimorbid elderly in primary CAre' (OPTICA) trial is to test whether the use of a systematic, software-assisted medication review intervention leads to a more appropriate use of medications than a usual care sham intervention. This primary outcome will be measured by the Medication Appropriateness Index (MAI) and the Assessment of Underutilisation (AOU). Secondary outcomes are the degree of polypharmacy, the degree of overprescribing, the degree of underprescribing, the number of falls and fractures, quality of life, the amount of formal and informal care received by patients, survival, patients' quality adjusted life years (QALYs), patients' medical costs, cost-effectiveness of the intervention, percentage of recommendations accepted and rejected by GPs, and patients' willingness to have medications deprescribed.

METHODS AND ANALYSIS

General study design and setting

The OPTICA trial is a cluster randomised controlled trial (RCT), coordinated at the Institute of Primary Healthcare of the University of Bern (BIHAM). Participating GPs, who will each systematically recruit multimorbid, older patients with polypharmacy, define the clusters. Through randomisation, the GPs will be allocated to the structured medication review or a usual care based sham intervention.

The investigators used the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist when they wrote this protocol.[23] Please refer to figure 1 for the study flow chart and figure 2 for a description of the data flow within the OPTICA trial.

Cluster definition

The trial will be conducted in about 40 primary care offices in the German-speaking regions of Switzerland. Each participating GP, who prescribes the medication of his/her patients, constitutes a cluster. GPs were recruited as subinvestigators from October 2017 until June 2018 from the pool of teaching physicians at the University of Bern and from the group of GPs who attended project presentations hosted by the BIHAM throughout 2017 and 2018. Additional GPs will be recruited throughout 2019

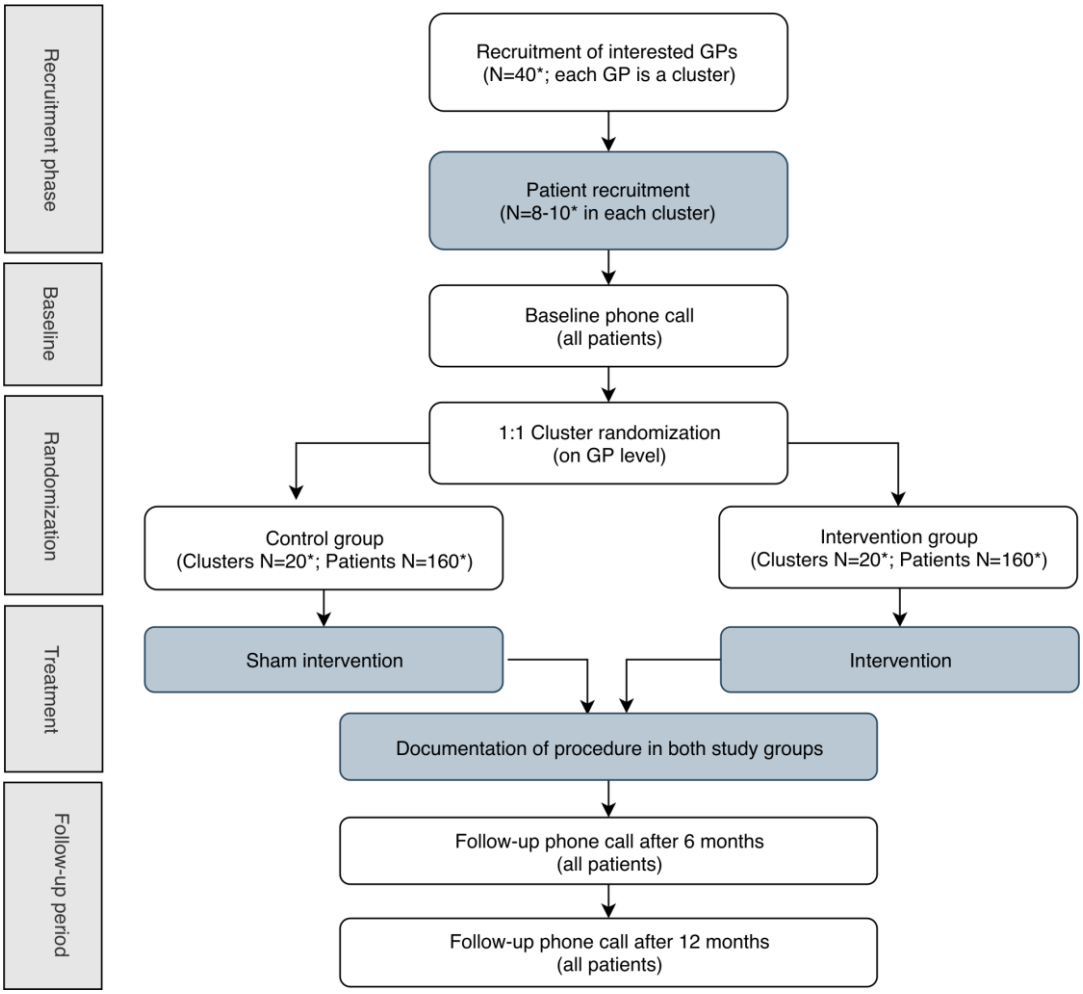

Figure 1 OPTICA trial flow chart. Flow diagram of the progress through the phases of the OPTICA trial. In dark grey: steps done by general practitioners. In white: steps done by study team at BIHAM. *Target number. BIHAM, Institute of Primary Healthcare of the University of Bern; GPs, general practitioners; OPTICA, Optimising PharmacoTherapy In the multimorbid elderly in primary CAre; STRIPA, Systematic Tool to Reduce Inappropriate Prescribing-Assistant.

to replace GPs who had to withdraw from the study, as the data export to the FIRE database did not work in their GP office. Engagement with GPs started early in anticipation of slow recruitment, which has been reported in previous studies.[24 25] All eligible GPs who showed interest in the OPTICA trial were visited by the investigators at their GP office and given a detailed explanation of the trial.[26] As of July 2019, 83% of the participating GPs are male. Eighty per cent of the GPs work in group practice, while 20% work in single practice. Twenty-nine per cent of GPs work in the countryside and 71% work in urban and suburban areas.

Randomisation

Randomisation is done after the cluster has been completed. The randomisation is done centrally in a web-based system (REDCap) by a study team member after all cluster information has been entered. Each participating GP is allocated 1:1 to the intervention group or the control group, using unstratified randomisation with a random sequence of block sizes of two and four. An independent statistician, who is otherwise not involved in the trial, generated the randomisation list. To uphold the concealment of allocation only system administrators who are otherwise not involved in the trial can access the randomisation list.

Eligibility criteria

Inclusion criteria

GP level

To be eligible for participation, GPs must be participating in the 'Family medicine ICPC Research using Electronic

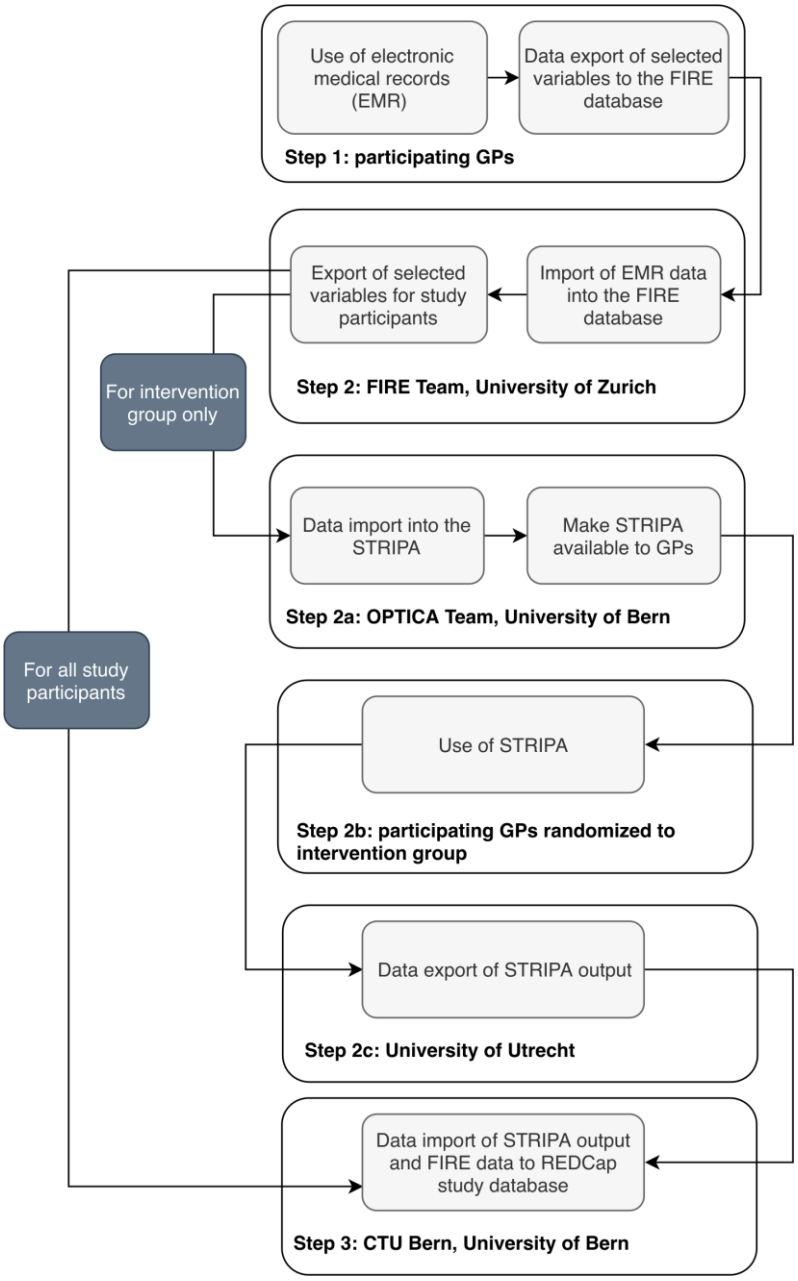

Figure 2 OPTICA data flow chart. Step-by-step explanation of the data flow during the OPTICA trial. EMR, electronic medical record; FIRE, Family medicine ICPC Research using Electronic medical records; GPs, general practitioners; OPTICA, Optimising PharmacoTherapy In the multimorbid elderly in primary CAre; STRIPA, Systematic Tool to Reduce Inappropriate Prescribing-Assistant.

medical records' (FIRE) project led by the Institute of Primary Care of the University of Zurich.[27] The EMR they use in their GP office have to be compatible with the FIRE database, which is a database with anonymous data from the EMR of more than 500 GPs in Switzerland. The database of the FIRE project contains administrative data, vital data, laboratory values, International Classification of Primary Care 2 (ICPC-2) codes for diagnoses and information on medications prescribed. Participating GPs can, only for the purpose of this trial, identify individual

patients in the usually anonymous FIRE database, so that their data can be used in this trial. All participating GPs must complete an online training for Good Clinical Practice (GCP).

Patient level

Patients must be enlisted by one of the participating GPs, so that this GP is their main prescribing physician and they must see their GP regularly. The investigators left the definition of regularity to the judgement of participating physicians. Patients must be ≥65 years of age, have ≥three chronic diseases based on ICPC-2 coding or based on the GP's clinical decision (multimorbidity), and regularly take ≥five medications (polypharmacy). Written informed consent must be sought from patients or, if patients suffer from cognitive impairment, their relative prior to enrolment. This consent includes the right to obtain data from the FIRE project about the study participant.

Exclusion criteria

GP level

In group practices, only one GP can take part in the trial.

Patient level

To maximise the generalisability of the study population, the investigators kept exclusion criteria to a minimum. They excluded patients currently taking part in another interventional study.

Intervention

The intervention, a systematic medication review, includes the use of a web-based CDSS called 'Systematic Tool to Reduce Inappropriate Prescribing'-Assistant (STRIPA), developed by a team from the Utrecht University and the University Medical Centre Utrecht in the Netherlands.[28] STRIPA is based on all algorithms of the 'Screening Tool of Older Person's Prescriptions' (STOPP) and 'Screening Tool to Alert doctors to Right Treatment' (START) criteria V.2,[29] which are expert-consensus lists of inappropriate and appropriate medications for older adults that consider coexisting medical conditions and are thus suited for optimising the prescriptions of multimorbid older patients.[30] STRIPA combines implicit and explicit prescribing tools and takes a stepped approach that actively encourages patient involvement in decision-making.[28 31] Taking into account medications, diagnoses, laboratory values and vital data, the STRIPA generates recommendations for physicians about 'underprescribing, ineffective prescribing, overprescribing, side effects, contraindications, (…) drug–drug and drug–disease interactions, incorrect dosages/dosing frequencies and practical intake issues'.[28] The intervention's recommendations allow patients and GPs to conduct a shared decision-making process about patients' medication intake, so patient preferences play an important role in this trial.

A STRIPA validation study with GPs based on two test cases showed appropriate prescribing decisions increased and inappropriate decisions decreased during a medication review of an older, multimorbid patient with polypharmacy.[31] STRIPA is being tested in the European multicentre clinical trial 'OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people' (the OPERAM trial) in the hospital setting to find out if it can reduce drug-related hospital re-admissions.[32]

This study adapted the intervention from the OPERAM trial so it could be tested in the primary care setting.[33] The intervention comprises six steps:

1. This data will be imported from the FIRE database into the STRIPA: patients' baseline characteristics (eg, sex, age); vital data and laboratory measurements (eg, kidney function, blood pressure), patients' signs and symptoms, different scores (eg, HAS-BLED score for major bleeding risk), ICPC-2 coded diagnoses, and medications entered as Anatomical Therapeutic Chemical codes.
2. GPs log in to STRIPA and see a list with their recruited patients' identifiers. When they click on a patient's ID, the information exported from the EMR to STRIPA via FIRE becomes visible (from Step 1). The GP can add unrecorded values or adjust values (eg, when more recent laboratory values are available). This might be necessary because it might take some time to obtain the FIRE data and to import it to STRIPA and hence the information might change in the meantime.
3. GPs use a drag and drop function to link each medication to a diagnosis.
4. GPs run the analysis in STRIPA and then look at STRIPA's recommendations. After the analysis is finished, STRIPA records the recommendations it generates so that they will be available for later analysis and generates a PDF report that can be saved by GPs.
5. GPs then must decide if they agree with STRIPA's advice given and if they will present it to their patient. They can follow, partly follow, or decline STRIPA's recommendations.
6. At the next appointment with the same patient, GPs will present the recommendations that they consider appropriate. GP and patient will decide together, in a shared decision-making process, which recommendations to implement. GPs will work from a checklist that explains how to conduct the shared decision-making process so that the patients' preferences are met. The shared-decision making process is based on Elwyn *et al*'s model[34] and was adapted from the OPERAM trial. The four key elements of this shared decision-making process are 'choice talk', 'option talk', 'preference talk', and 'decision talk'.[34] Patients may follow, partly follow or decline the recommendations. Because multimorbid patients are likely to have multiple prescribers, GPs and patients can discuss recommendations with other prescribers, for example, specialists. The GP records in the REDCap study database the patient's decisions and the reasons recommendations were accepted, partially accepted, or declined. These records will be analysed later.

Before the intervention, GPs in the intervention group will watch an instruction video and read training material that will guide them through the intervention step-by-step.

Sham intervention

Patients assigned to the control arm receive a sham intervention from their GP—a medication discussion in accordance with usual care. This means that the GP will, as usual in standard care, ask the patient if the current list of medication is complete or needs to be adapted, then share decision making with the patient about possible changes. The GPs who do the sham intervention will receive the same shared decision-making checklist as the GPs in the intervention group. The investigators explicitly ask GPs not to deviate from their usual practice when they review the patients' medication and not to use additional tools. After the sham intervention, GPs record procedures, decisions, and reasons in the REDCap study database for later analysis. This sham intervention ensures that the medication list of control group study participants, which will be used to assess study outcomes, is up-to-date, while also ensuring patients are blinded.

Screening and enrolment

For patient recruitment, the investigators use data from the FIRE project to prepare a screening list for each GP that contains a random selection of eligible patients. On each screening list, there are about 20 patients who were randomly sampled from all enlisted patients after they met the age criteria and were determined to regularly take at least five chronic medications, based on the Pharmacy-based Cost Group model.[35–37] Since ICPC-2 coding is suboptimal in many GP offices, the investigators decided not to include the chronic disease criterion when they prepared the screening lists. From the list, GPs systematically recruit eight to 10 patients who meet the full inclusion criteria, which now include the number of chronic diseases, and do not meet any of the exclusion criteria. GPs will recruit patients starting either at the bottom of the list or the top. If GPs have finished the first screening list without recruiting the minimum amount of participants, the investigators will provide them with a second list.

Since the screening lists are compiled from a random patient sample from each GP office based on FIRE data, patients on the list may have been treated by a different GP who works in the same group practice. It is also possible that patients on the list changed their GP or have died. Since prescriptions frequently change,[38] some patients with polypharmacy might not have qualified for the screening list when data was last exported. For all these reasons, the protocol allows GPs to skip patients on the screening list if they provide an explanation, or to recruit patients who are not on the list but fulfil the inclusion and do not meet the exclusion criteria. After identifying patients on the list and verifying their eligibility, GPs then inform the patient about the study and seek their informed consent. Study-related appointments are added to the patients' regular appointments at no charge.

Data collection

Study participants or their relatives are followed up by phone at baseline and at 6 and 12 months after study enrolment to collect data. At these times, complementary information from the FIRE database, including information about medications and chronic diseases, is imported into the REDCap study database.[27]

Blinding procedures

The OPTICA trial is blinded to the extent the cluster design of this RCT allows. The method of partial blinding, which is similar to that used in the OPERAM trial,[32] is set out in detail in table 1.

Follow-Up

Outcome information is collected at baseline, at 6, and at 12 months via telephone calls with patients or relatives conducted by a blinded study team member, and through FIRE database exports. The study team will make every reasonable effort to keep each patient in the study until all planned treatments and assessments have been performed. But patients may withdraw from the study or be withdrawn when they are lost to follow-up.

Assessment of primary outcome

The primary endpoint is medication appropriateness, measured jointly by the MAI and the AOU, in each study group. While the AOU assesses underprescribing, the MAI is a tool to assess different elements of medication prescribing (eg, overprescribing, drug–drug interactions, etc).[7 39 40]

Blinded study team members assess the MAI for each regular medication study participants take and assess the AOU for each chronic condition study participants have. The investigators will use the weighted 10-item version of the MAI developed by Samsa *et al*.[40] However, due to the rapidly changing drug prices the MAI item on cost-effectiveness will not be included. The criteria of the MAI, including corresponding weights, can be found in table 2. Using clinical data and the predefined operational definitions for each item, the assessor rates each medication on a three-point scale ranging from A=appropriate, B=marginally appropriate, C=inappropriate. Each 'inappropriate' rating will receive the respective weight from table 2, while the weight of ratings 'appropriate' and 'marginally appropriate' will be 0. Thus, the score for each medication ranges from 0 to 17 (as the cost-effectiveness criterion will not be included).[40] A higher score indicates a greater degree of medication inappropriateness. The investigators will calculate the score for each medication and then calculate the summated score for each patient, by summing up the scores for each medication. For the AOU, assessors decide for each chronic condition if there is (i) no omission, (ii) marginal omission, or (iii) omission of indicated medication.[41–43] For each patient,

Table 1 Blinding status and measures to assure blinding

Role	Blinding status	How to achieve blinding
General practitioners	Unblinded	When screening for patients and seeking informed consent, GPs are still blinded, as each cluster (GP) will be only randomised after the cluster is full (8–10 patients). The screening list GPs use for recruitment contains a random sample of potentially eligible patients, which was generated from FIRE data by a blinded study team member. All this is done to prevent selection bias. However, since GPs can recruit patients outside this list, not all study participants are recruited randomly. However, the study design makes it impossible to blind GPs throughout the trial. When GPs do the medication review/discussion, they know what group they are allocated to. Nevertheless, GPs in the control arm do not know the procedures in the intervention arm, which prevents cross-contamination; if they knew the procedure in the intervention arm, they might adapt their usual care.
Data collectors and assessors	Blinded	The randomisation of GPs is kept concealed from the team that makes follow-up calls to avoid interviewer bias. Data collectors and assessors have no access to unblinded study information in the database or to local source data. If a SAE occurs, the study coordinator and project manager will be informed.
Data manager and data analyst	Unblinded	The investigators cannot blind the data managers and analysts because they can see the differences in data structure between the study groups. This is why the investigators will use a new data analyst to prepare a clean data set with truncated data to conduct a blinded analysis of the primary outcome.
Study coordinator and project manager, including principal investigator	Unblinded	The study coordinator, project manager and the principal investigator of the trial know the treatment allocation. They are responsible for collecting information about SAEs and performing safety assessments.
Patients	Partially blinded	Patients stay partially blinded. They are only given a 'high-level description' of the study question so they know that their GP has been allocated to one of two study groups, but they do not know which one. To uphold patient blinding, patients in the control group will meet their GP for a medication discussion and a shared decision-making about their prescriptions. This means patients in each study arm see GPs the same number of times during the trial and cannot guess their allocation status based on the number of consultations.

The OPTICA trial's approach to blinding resembles the approach used in the OPERAM trial.[32]
GP, General Practitioner; OPERAM, OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older peopl; OPTICA, Optimising PharmacoTherapy In the multimorbid elderly in primary CAre; SAE, serious adverse event.

the investigators will calculate how many omissions there are.

The MAI and the AOU will be assessed and calculated for baseline, the follow-up one at 6 months and the follow-up two at 12 months. For at least 32 cases (10% of the targeted sample size), two blinded investigators will conduct a blinded independent double assessment of the MAI and the AOU to check inter-rater reliability. The investigators will use information about diagnoses (coded in ICPC-2) and medication intake from the FIRE database for these assessments.

Assessment of secondary outcomes

The following secondary outcomes are assessed at baseline, 6 and 12 months (data source in brackets)

- Degree of polypharmacy; that is, the number of regular long-term medications patients take (FIRE database).
- Degree of overprescribing, measured by the MAI (assessment of FIRE data done by study team).
- Degree of underprescribing, measured by the AOU (assessment of FIRE data done by study team).
- Number of falls and fractures in the last six months (patient/relative phone call).
- Quality of life, based on the five-level version of the European Quality of Life-5 Dimensions questionnaire, including pain/discomfort[44 45] (patient/relative phone call).
- Amount of formal care received in the last six months: number and length of stay of planned and unplanned hospitalisations; visits to the emergency room without inpatient hospitalisation; GP visits; medical specialist visits (differentiated by specialty); hospital outpatient visits; inpatient stays; length of stay at rehabilitation facilities; physiotherapist and other allied therapist visits; nursing home admissions (in patients who were living in the community at baseline); length of stay in nursing homes; and, number of home nursing visits (patient/relative phone call, except for number of GP visits which comes from FIRE database).
- Amount of informal care received in the last six months: unpaid care by, for example, family members, relatives, friends (patient/relative phone call).

Table 2 Criteria of the Medication Appropriateness Index including weights

	Item	Weight
1	Is there an indication for the drug?	3
2	Is the medication effective for the condition?	3
3	Is the dosage correct?	2
4	Are the directions correct?	2
5	Are the directions practical?	1
6	Are there clinically significant drug–drug interactions?	2
7	Are there clinically significant drug–disease/condition interactions?	2
8	Is there unnecessary duplication with other drug(s)?	1
9	Is the duration of therapy acceptable?	1

Item 10 'Is this drug the least expensive alternative compared to others of equal utility?' has been excluded.[40]

- Survival (patient/relative phone call or reported by GP).
- QALYs accrued in one year,[46] measured as a function of the length and the quality of life (calculated based on data from patient/relative phone call).
- Direct medical costs accrued in one year, measured by combining formal and informal healthcare resource use observed in the trial (patient/relative phone call), including the time GPs spend on the intervention (reported by GP) and software costs (literature search), and Swiss unit costs from sources external to the trial (literature search).
- Cost-effectiveness of the intervention, calculated by combining clinical data (FIRE database), quality of life data (patient/relative phone call) and healthcare use data collected in the trial (patient/relative phone call).

The following outcome will be assessed after the intervention

- Percentage of STRIPA recommendations accepted and rejected by GPs (reported by GPs, cross-verified with STRIPA reports).

The following secondary outcome is assessed at baseline only:

- Patients' willingness to have medications deprescribed, measured with the validated 'revised Patient Attitudes Towards Deprescribing' questionnaire[47 48] (patient/relative phone call).

Safety outcomes include adverse events, serious adverse events and device deficiencies.

Study duration

GPs can recruit the patients over a period of at least six months, so they can integrate recruitment into their daily practice. Recruited patients are followed up for one year.

Sample size

Sample size calculation is based on testing the two co-primary outcomes for superiority and uses the Bonferroni-approach to account for multiple testing. Based on trial results published by Gallagher *et al* in 2011, the investigators assumed that 35% of patients in the control group and 60% of patients in the intervention group will improve their total MAI score (at least one less point) and that 10% of patients in the control group and 30% of patients in the intervention group will have a better AOU score (at least one fewer prescribing omission).[49] Intracluster correlations (ICC) of 0.01–0.05 are typically found for binary outcomes in elderly individuals.[50] The investigators conservatively assumed an ICC of 0.05 to calculate the sample size. The investigators fixed the type I error at a Bonferroni-corrected two-sided alpha level of 0.025.

Based on a two-sample comparison of proportions and a prespecified number of clusters of about 40 (about 20 per arm), seven patients per cluster are required to detect a difference of 25% between the two groups in the proportion of improvement in the MAI, with a power of 90%. The number of 40 GPs was selected arbitrarily for feasibility reasons. Using the same assumption for the AOU, the investigators found they also need seven patients per cluster to detect a difference of 20%. The investigators thus need a sample of 280 patients (140 per arm) to provide 81% power to detect a significant improvement in both the MAI score and the AOU. To account for attrition from dropout or death (15% estimated), the number of patients per cluster was increased to eight (max. ten), so the final sample size should be about 320 patients (160 per arm). The investigators will closely support GPs to help them reach the target sample size.

Statistical analysis

In case data on outcomes are incomplete, the investigators will use multiple imputation to replace missing values, taking data clustering into account. No interim analyses are planned.

There are two co-primary outcomes: improvement in the MAI at 12 months, defined as decrease of at least one point, and improvement in the AOU at 12 months, defined as at least one less prescribing omission. Both outcomes will be tested separately; success is indicated by the significance of at least one of the two tests.

For the co-primary outcomes, the investigators will present and compare the proportion of patients whose MAI and AOU score improved in the control and intervention group. The relative difference between groups will be determined in a mixed-effects logistic model with a random intercept at the GP level to account for clustering. The effect measure for the primary outcomes will be odds ratios (OR). The relative difference will be presented as OR with a 95% CI. The primary analysis will be an intention-to-treat analysis. In a per-protocol

analysis, the investigators will only evaluate patients who adhered to the protocol and exclude patients who violate any inclusion or exclusion criteria.

Secondary binary outcomes will be evaluated like the primary outcomes. Secondary continuous outcomes will be analysed using random-effects linear regression with a random intercept at the GP level. Models will also be adjusted for the baseline value as a covariate. Secondary count outcomes will be analysed using random-effects Poisson regression with a random intercept at the GP level.

Health economic analyses will assess (i) resource use and cost differences between the trial arms, (ii) differences in quality-adjusted lifetime between the trial arms, expressed as QALYs, and (iii) a comparison of cost-effectiveness between intervention and standard care.

Because cluster-randomisation may not balance characteristics between groups to match individual-level randomisation, the investigators will adjust each model for patient-level and physician-level variables to account for case-mix differences between groups and potential recruitment bias in a sensitivity analysis. They will also account for the correlated nature of data among GPs by using multilevel mixed-effects models. Unadjusted models will be provided for information only.

Patient and public involvement

Multimorbid, older patients with polypharmacy are represented in the independent Safety and Data Monitoring Board of the OPTICA trial. Throughout the trial, the Safety and Data Monitoring Board, which will consist of one GP, one statistician and one multimorbid, older layperson with polypharmacy, will meet regularly to discuss safety and data management issues. Patients are not actively involved in recruiting study participants, but play a key role in shared decision-making during the intervention and sham intervention. The investigators have created a priority list of questionnaire components to reduce the burden of the intervention on very old and sick study participants by reducing the duration of the follow-up calls where necessary. At the end of the study, the investigators will disseminate the results to study participants in a letter.

DISCUSSION

This protocol paper highlights the features of the OPTICA trial, the first RCT in primary care to test an intervention based on the STRIPA clinical decision support tool, which helps GPs customise medication reviews and optimise polypharmacy in older multimorbid patients.

This clinical trial compares the effect of a structured medication review on medication appropriateness in a Swiss primary care setting to a sham intervention. Systematic medication review may facilitate shared decision-making and improve medication appropriateness, especially for GPs who treat complex multimorbid patients with polypharmacy. It may also improve patients' quality of life and health economic outcomes. This trial will add to the literature, as it examines in a real life setting a software-based intervention, which implements the STOPP/START criteria, based on data from electronic medical records. If successful, this study will demonstrate the usefulness of an electronic database, with coded data collected routinely in primary care, to be used in a clinical decision support tool. Additionally, it focuses on multimorbid patients who are often excluded from trials.

OPTICA is subject to the following limitations

- Despite taking precautions to avoid and reduce selection bias (cluster randomisation to avoid learning effect, screening lists for patient recruitment, randomisation of GPs after patient recruitment), selection bias is still possible because of the study design. Since GPs can recruit patients outside of the screening list for practical reasons, not all patients are recruited randomly. Patients who are more engaged and/or more likely to adhere to advice may be more likely to be enrolled in the trial, which might decrease the representativeness of the study population and the generalisability of the results. The investigators will use data from FIRE to compare the characteristics of study participants with those of non-participants.
- The investigators chose a usual care sham intervention in the control group to improve patient blinding, but this design does not eliminate the risk GPs in the control group will be contaminated by the thematic of the trial (risk of deviating from their previous routine prescribing practices). In addition, this sham intervention might lead GPs to suggest medication changes that could improve the appropriateness of patients' medications.
- Outcome assessment is based on self-reported data from patients and relatives and on data from FIRE, so some events may be missed. To ensure FIRE data is as complete as possible, GPs must code their patient's medication intake and their diagnoses correctly. Diagnoses require ICPC-2 codes. GPs were instructed, in face-to-face meetings, about how to code and update data in their EMR for patients in this trial.[26]
- Like all interventions that take an eHealth approach (STRIPA intervention in this case), people have different perceptions of what is user-friendly. New procedures may seem complicated in comparison to usual care. The investigators tried to simplify the process by (i) using EMR data so that GPs do not have to enter all the data themselves, but only update them if needed; and (ii) giving detailed instructions for using STRIPA in writing and in an online video training.
- Unrestricted randomisation designs, such as the block randomisation used in this trial, are more likely to result in imbalance of factors by chance.[51]
- Another limitation of the study is the restriction to self-control during the intervention, as it is a mono-professional intervention, and that the scope

of the intervention is limited to the use of the software-based CDSS. However, due to the structure of the Swiss primary healthcare setting this design is feasible in a real life setting, whereas multiprofessional interventions would be difficult to organise.
- The primary outcome of this trial is not directly patient-relevant. However, directly patient-relevant outcomes, such as quality of life, figure among the secondary outcomes of this trial.

It may be difficult to follow-up multimorbid, older patients, who are often excluded from trials.[52] The investigators believe that the task is worth the effort because trial results need to be generalisable to exactly this population. To reduce the duration of the phone calls with particularly weak study participants only the core elements of the study questionnaire will be used, if necessary, based on a predefined priority list.

The OPTICA trial has the following strengths:
- The OPTICA trial is the first RCT to examine the effect of STRIPA on medication appropriateness in older, multimorbid patients with polypharmacy in a primary care setting.
- OPTICA is the first RCT to test the use of software-based structured medication reviews in Swiss primary care.
- OPTICA demonstrates the usefulness of coding and linking data from EMR, and re-using this data to evaluate primary care interventions in a randomised controlled trial setting.
- In the OPTICA trial, the investigators do not exclude patients with cognitive impairment if a relative gives their informed consent, because patients with cognitive impairment are especially prone to polypharmacy, yet they have been excluded from many other trials.

CONCLUSION

The OPTICA trial will compare the effect of the systematic medication review that uses STRIPA, including shared decision-making, to usual care (sham intervention) with the goal of improving medication appropriateness. The investigators expect the intervention to improve the quality of life and health status of a rapidly ageing population with increasing multimorbidity and polypharmacy. The study results will inform other studies and interventions designed to optimise medication use by integrating a CDSS with electronic medical records.

Current status of the OPTICA trial

The patient recruitment in the OPTICA trial began in December 2018. By early July 2019, 278 patients (about 85% of the target sample size) have been recruited. The investigators have randomised 31 out of about 40 GPs. Last patient out is expected in the second half of 2020.

Ethics

All participant data will be handled according to the principles of the Declaration of Helsinki.[53] The OPTICA trial complies with all applicable standards of the guideline for Good Clinical Practice of the International Conference on Harmonisation (ICH-GCP).[54]

Data management, monitoring, safety reporting and audits meet the requirements of the Swiss law. The investigators uphold the principle of patients' right to privacy and comply with applicable privacy laws. Confidentiality and anonymity of the patients shall be guaranteed when the data is presented at scientific meetings or published in scientific journals. Only selected study team members will have access to the final trial dataset.

Risks, including human failure and software malfunction, cannot be excluded. But STRIPA only makes prescription recommendations to GPs in the intervention group. Participating GPs are experienced (mean age of experience as GP: 16 years), and will take the final decision about whether to accept the recommendations and to present them to the patient. Patients thus are not exposed to more risk than they would be in standard care. This clinical trial entails minimal risk for participants and the benefit-risk ratio is positive. *Basler Versicherungen* will provide insurance and cover eventual damages.

Participating GPs have signed a non-disclosure agreement.

Dissemination

OPTICA embraces an open access policy and will vigorously disseminate all resulting data, study results and publications. The investigators closely collaborate with the National Research Programme 74 (NRP74) 'Smarter Health Care' to optimise dissemination of the study results to the public.

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Article V: Baseline characteristics and representativeness of older multimorbid patients with polypharmacy and general practitioners participating in a randomized controlled primary care trial

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My contributions: Together with Rahel Meier and Sven Streit, I conceptualized and designed this study. Rahel Meier and I did the data analysis. I created all figures and tables shown in the manuscript and the supplementary material. I wrote the first draft of the manuscript and I made the necessary changes based on comments made by co-authors.

Tables and Figures in Article V

Abstract

Objectives: Recruiting general practitioners (GPs) and their multimorbid older patients for trials is challenging for multiple reasons (e.g., high workload, limited mobility). Representativeness of study participants is important for interpreting study findings. This manuscript describes the baseline characteristics of GPs and patients participating in the 'Optimizing PharmacoTherapy in older multimorbid adults In primary CAre' (OPTICA) trial, a study of optimization of pharmacotherapy for multimorbid older adults. The overall aim of this study was to determine if the GPs and patients participating in the OPTICA trial are representative of the real world population in Swiss primary care.

Design: Analysis of baseline data from GPs and patients in the OPTICA trial and a reference cohort from the FIRE ('Family medicine ICPC Research using Electronic medical records') project

Setting: Primary care, Switzerland.

Participants: 323 multimorbid (≥ 3 chronic conditions) patients with polypharmacy (≥ 5 regular medications) aged ≥ 65 years and 43 GPs recruited for the OPTICA trial were compared to 22,907 older multimorbid patients with polypharmacy and 227 GPs from the FIRE database.

Methods*:* We compared the characteristics of GPs and patients participating in the OPTICA trial with other GPs and other older multimorbid adults with polypharmacy in the FIRE database. We described the baseline willingness to have medications deprescribed of the patients participating in the OPTICA trial using the revised Patients' Attitudes Towards Deprescribing (rPATD) questionnaire.

Results*:* The GPs in the FIRE project and OPTICA were similar in terms of sociodemographic characteristics and their work as a GP (e.g. aged in their fifties, ≥ 10 years of experience, ≥ 60% are self-employed, ≥ 80% work in a group practice). The median age of patients in the OPTICA trial was 77 years and 45% of trial participants were women. Patients participating in the OPTICA trial and patients in the FIRE database were comparable in terms of age, certain clinical characteristics (e.g. systolic blood pressure, body mass index) and health services use (e.g. selected lab and vital data measurements). More than 80% of older multimorbid patients reported to be willing to stop ≥ 1 of their medications if their doctor said that this would be possible.

Conclusion: The characteristics of patients and GPs recruited into the OPTICA trial are relatively comparable to characteristics of a real world Swiss population, which indicates that

recruiting a generalizable patient sample is possible in the primary care setting. Multimorbid patients in the OPTICA trial reported a high willingness to have medications deprescribed.

Ethics and dissemination: The ethics committee of the canton of Bern in Switzerland approved the protocol of the OPTICA trial. The Ethics Committee of the Canton of Zurich approved studies within the FIRE project.

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Trial registration numbers: Clinicaltrials.gov (NCT03724539), KOFAM (Swiss national portal) (SNCTP000003060), Universal Trial Number (U1111-1226-8013)

Introduction

Globally, the population group of adults aged ≥ 65 years is growing faster than all other age groups combined. In 2019 one in every 11 persons was 65 years and over, this has been predicted to increase to one in six persons by the year 2050 [4]. With ageing societies, also come growing numbers of older adults with multiple chronic conditions. Multimorbid patients often use multiple medications and with polypharmacy comes a higher risk of using potentially inappropriate medications (PIMs). PIMs are medications for which the risk of potential adverse events outweighs the clinical benefits, such as when there are more effective and safer alternatives available for use in older adults [50]. The use of PIMs is associated with increased risk of adverse drug events, falls and cognitive impairment [51-54]. Patients with multimorbidity and polypharmacy often have complex healthcare needs, which in turn lead to substantial health services use and associated costs [176]. The use of potentially inappropriate medications is high in this patient group [175]. In this context, the 'Optimizing PharmacoTherapy in older multimorbid adults In primary CAre' (OPTICA) trial was launched with the aim of investigating whether an electronic clinical decision support tool can help GPs to optimise medication use of older multimorbid patients with polypharmacy.

Lack of external validity of clinical trials, the extent to which results can be generalised to the wider population, has been cited as a reason that interventions do not get adopted after publication of the study. One factor that can influence external validity is the characteristics of the participants recruited into the trial; that is, whether they are representative (have similar characteristics) to those found in the real-world population [177].

Despite societal ageing and widespread multimorbidity, patients with chronic conditions and older adults in general are often underrepresented in clinical research [178,179]. Evidence from studies of younger and healthier participants may not be generalizable to the broader older multimorbid population [180]. The reasons for the exclusion and general underrepresentation of complex older adults in research are multifaceted. On the one hand, studies often have inclusion and exclusion criteria to maximise participant retention and minimise variability among participants. [98,149,151]. On the other hand, even if older multimorbid adults are not explicitly excluded, major barriers to recruiting this type of study participants include limited mobility (e.g. not being able to attend multiple appointments or complete certain tests), and in the case of cognitive impairment, inability to provide informed consent [151-153]. Additionally, the person identifying and selecting patients for recruitment (e.g. member of the research team or through healthcare professionals with established relationships) can impact the representativeness of participants [181]. Use of routinely collected patient information to identify participants for clinical trials is a promising method to

reduce the labour of recruitment. However, concerns exist about the error rate of using electronic medical records for this [182].

Not only can the recruitment of older multimorbid patients be challenging, so can the recruitment of GPs [157]. Previous studies found that time constraints, lack of training, fear of loss of professional autonomy as well as lack of rewards and recognition are barriers to research participation for physicians in general [158]. Conducting clinical research in the primary care setting comes with additional challenges. For instance, a lack of infrastructure, lack of financial remuneration of practice staff involvement, misunderstandings on how daily clinical work in general practice could accommodate the clinical research, and seasonal changes in workload [159,160]. There is the concern that GPs with specific characteristics or attitudes can be motivated more easily to participate in clinical research. If true, it would mean that the results of an interventional study (such as our OPTICA trial) would not be generalizable to even the local context outside of those who participated in the trial. Overall, little is known about whether it is possible to recruit an externally comparable sample of older multimorbid patients and GPs for research in primary care.

Further, past medication optimization interventions in patients with polypharmacy have shown limited effect in changing medication use [132,183] and/or clinical outcomes (e.g. mortality, cognitive decline) [184]. This may be due to patient resistance to medication changes and their unawareness of potentially inappropriate medication use [185]. It is therefore important to consider not only the characteristics of participants, but their attitudes as well.

The ‘Family medicine ICPC Research using Electronic medical records’ (FIRE) database is the largest Swiss electronic database containing anonymized routine patient data from the electronic medical records in >10% of Swiss primary care practices. It also contains information about the GPs who regularly export data from their electronic medical records. The FIRE database therefore provides a unique opportunity to examine the external validity of the OPTICA study results with regards to the wider Swiss general population in primary care.

The overall aim of this study was to determine if the GPs and patients participating in the OPTICA trial are representative of the real world population in Swiss primary care. We hypothesised that our broad inclusion criteria and support provided to participating GPs would result in recruitment of representative participants. This information is not only important for interpreting the forthcoming results of the OPTICA trial (i.e. the likely external validity of the study findings), but can also inform the ability to recruit complex older adults for clinical trials in primary care.

Specifically, the aims of this manuscript were to:

1. Describe the baseline characteristics of participants (GPs and older patients with multimorbidity and polypharmacy) recruited to the OPTICA trial.
2. Compare the characteristics of GPs and patients participating in the OPTICA trial with those in the FIRE database.
3. Compare the characteristics of the patients recruited for OPTICA from random screening lists generated from electronic medical records with patients recruited through GP identification of eligible patients.
4. Describe the patients' willingness to have medications deprescribed.

Methods

Study Design and Setting

For this analysis we used baseline data from the ongoing cluster-randomized controlled trial (cRCT) 'Optimizing PharmacoTherapy in older multimorbid patients In primary CAre' (OPTICA). We were able to compate the OPTICA study participants to reference cohorts from the 'Family medicine ICPC Research using Electronic medical records' (FIRE) project database, as all GPs who participated in the OPTICA trial regularly export data to the FIRE project. Details about these two research projects have been reported elsewhere [141,172].

The FIRE project is the largest Swiss database collecting anonymized routine patient data from the electronic medical records in primary care practices since 2009 [172]. The following information is available in the FIRE database: administrative information (patient, age, and sex), diagnosis codes, laboratory and vital signs measurements, and prescribing information. As of October 2020, the database of the FIRE project contains data from the electronic medical records of more than 680 GPs (about 11% of all Swiss GPs [174]) and more than 830,000 patients (about 10% of the Swiss population) [173]. All Swiss GPs are invited to join the FIRE project if they use an electronic health record (EHR) program that is compatible with exporting anonymized data to the FIRE project.

The OPTICA trial is a cluster randomized controlled trial, being conducted in primary care in the German speaking part of Switzerland. The aim of the OPTICA trial is to investigate whether the use of an electronic clinical decision support system, namely the 'Systematic Tool to Reduce Inappropriate Prescribing' (STRIP) Assistant [165], improves medication appropriateness compared to a standard care sham intervention in older multimorbid patients with polypharmacy. The STRIP Assistant (STRIPA) is based on the algorithms of the 'Screening Tool to Alert doctors to Right Treatment' (START) and 'Screening Tool of Older Person's Prescriptions' (STOPP) version 2 [138] which are lists of medications generally considered to be inappropriate and appropriate in older adults, respectively [68]. The standard care sham intervention in the control group consists of a medication discussion between GPs and patients in accordance with usual care. The co-primary outcomes of the OPTICA trial are the 'Medication Appropriateness Index' (MAI) and the 'Assessment of underutilization' (AOU) [166-168]. More detailed background information about the OPTICA trial, the study intervention, and the FIRE project is reported in eAppendix 1 in the supplement.

Participants

OPTICA Trial

We present the inclusion and exclusion criteria for GPs and patients in the OPTICA trial in Table 1. To maximise the generalizability of the study population, we kept the exclusion criteria to a minimum. Patients were recruited through their GPs. GPs were instructed to use a random screening list generated from the data they exported to the FIRE project, but also had the flexibility to recruit other eligible patients after exhausting the screening lists. The calculated sample size of the OPTICA trial was 320 patients (details reported in the OPTICA protocol paper [141]).

Table 1. Inclusion and exclusion criteria for general practitioners and patients in the OPTICA trial[1]

General practitioners		**Patients**	
Inclusion criteria	Exclusion criteria	Inclusion criteria	Exclusion criteria
- Be a practicing GP in Switzerland - Complete online GCP training - Work with electronic medical records that are compatible with FIRE project[2]	- Not participating in the FIRE project -Other GP from same practice already participating in the trial	- Be a patient of one of the participating GPs - Regularly see his/her GP, who is the main prescriber - ≥ 65 years or older - ≥ 3 chronic conditions - ≥ 5 chronic medications	-Participation in other clinical trial -No written informed consent obtained from patient or from relative in case of cognitive impairment of the patient

[1]As specified in: 'Jungo KT, Rozsnyai Z, Mantelli S, et al. 'Optimising PharmacoTherapy In the multimorbid elderly in primary CAre' (OPTICA) to improve medication appropriateness: study protocol of a cluster randomised controlled trial. BMJ Open 2019;9:e031080.'

[2]The FIRE project is a Swiss database with anonymized data from electronic health records of participating GPs. For the purpose of the OPTICA trial, we collect some relevant information for the trial through the FIRE project database, which is why the participation to the FIRE project has to be possible throughout the trial.

Abbreviations: GCP = Good Clinical Practice; FIRE = 'Family medicine ICPC Research using Electronic medical records', OPTICA = Optimising PharmacoTherapy In the multimorbid elderly in primary CAre, GP = general practitioner

FIRE Project

As of May 2019, around 520 GPs participated in the FIRE project. To define the target population of patients, we identified patients in the FIRE database who were at least 65 years and were prescribed at least 5 different medications at the time point of May 1st, 2019. The selection of reference GPs for the analyses took place as follows: GPs participating in the FIRE project, who were the GP of one of the patients included in the patient reference population (as described above) were included in the GP reference cohort (n=227). GPs who participated in FIRE, but did not have any older multimorbid patients with polypharmacy (e.g. because they had only recently joined the project and did not yet export data) and those who took place in the OPTICA trial (n=43) were excluded from the GP reference cohort. eFigure 1 in the supplement visualizes the creation of the reference cohorts.

Data Query and Variables

From the FIRE database we extracted patients and GP characteristics. For GPs we extracted sociodemographic information and variables describing their work as GP (as shown in table 2). For patients we extracted sociodemographic information, clinical parameters and variables describing their health services use (table 3). All variables measuring health services use or reporting vital data and lab values were reported for the period of the last 12 months before May 2019.

The information on patients' willingness to have medications deprescribed was collected in the baseline phone call conducted with participants in the OPTICA trial using the German translation of the revised Patients' Attitudes Towards Deprescribing (rPATD) questionnaire. The original questionnaire was developed by Reeve et al. [171,186]. The German translation was validated and used in a Swiss study on patients' attitudes towards having medication deprescribed [113]. The rPATD questionnaire for both caregivers and patients contains two global questions as well as questions grouped into four factors: medication burden, mediation appropriateness, concerns about stopping, and involvement. There are four to five questions per factor, which can be used to calculate a factor score. Each factor score ranges from 1 to 5 [171].

Statistical Analysis

First, we compared the characteristics of GPs participating in the OPTICA trial with those of the reference GPs in the FIRE database. Second, we compared the characteristics of the OPTICA study participants with those of other older, multimorbid patients in the FIRE

database. Third, we compared the characteristics of the patients recruited for OPTICA from the random screening lists with the OPTICA patients recruited directly by GP identification of eligible participants (i.e. not from the screening lists). Finally, we described patients' willingness to have medications deprescribed. We also performed a sensitivity analysis, by comparing the characteristics of the OPTICA study participants with all other older patients of the same GP only.

Categorical data are presented as frequencies and percentages, and continuous variables as median and interquartile range (IQR), as the variables were non-normally distributed. For categorical variables we performed a Fisher's exact text and for continuous variables a Kruskal-Wallis test was performed, as defined in the R package "tableone" [187]. For this study, if the p-value was <0.05 we concluded that there was sufficient evidence to say that the groups were statistically different. We also calculated standardized differences, which can be used to compare balances in measured variables [188]. While p-values were used for the statistical hypothesis testing, absolute standardized difference (ASD) values helped quantify the differences between groups. An ASD value >0.2 has previously been defined as representing an imbalance between two groups [189]. Hence for the purpose of this study we considered a maximum threshold of 0.2 for ASD value as being acceptable in terms of comparability of the two groups. The group comparisons were performed using the statistical software package R (Version 3.6.3) [190].

The analyses on patients' willingness to deprescribe were performed using the statistical software Stata 15.1 (StataCorp, College Station, TX, USA). We calculated the four factor scores (involvement, burden, appropriateness, and concerns about stopping) as described previously [171]. Each score is calculated based on responses to the 5 items within each factor of the rPATD questionnaire and ranges from 1-5. In addition, we present the responses to the two stand-alone statements from the rPATD ("Overall, I am satisfied with my current medicines" and "If my doctor said it was possible I would be willing to stop one or more of my regular medicines").

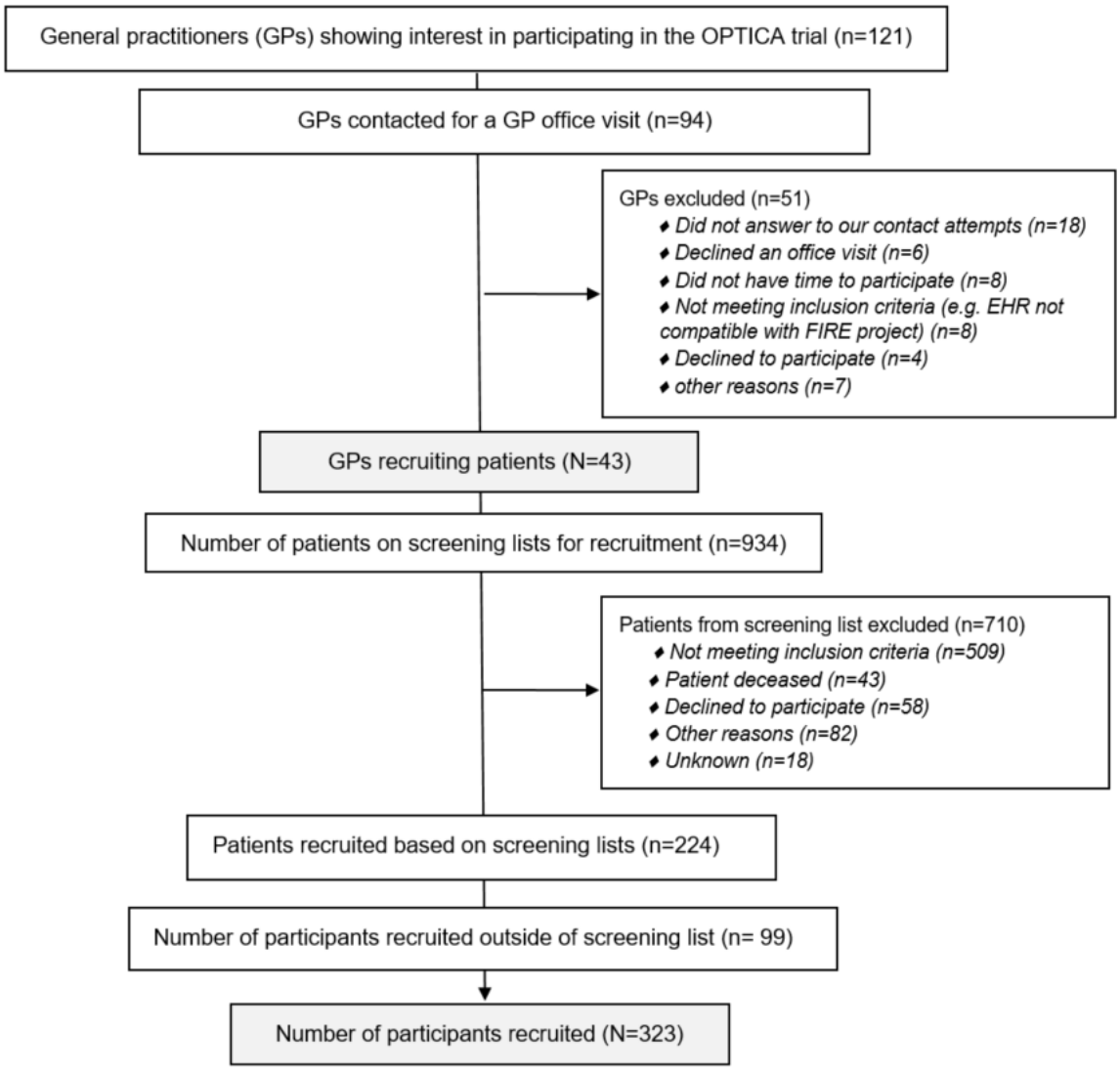
Patient and Public Involvement

As described in the OPTICA protocol paper [141], GPs and older patients with multimorbidity and polypharmacy are represented in the independent Safety and Data Monitoring Board of the OPTICA trial. GPs participating in the OPTICA trial receive regular newsletters. At the end of the study, study participants are informed about their study allocation and the results of the study.

Results

The process of the recruitment of GPs and patients in the OPTICA trial is shown in the trial flow chart (Figure 1). Out of 121 GPs showing interest in the OPTICA trial, 94 were contacted for a recruitment visit in their GP office (explanation of study design, tasks for participating GPs, and if needed, installation of FIRE data export tools), and 43 were recruited. Out of 934 patients on the screening lists, 224 were recruited. Additionally, 99 patients (30.6% of the total patients recruited) were recruited through GP identification of eligible patients (outside of the screening list).

Figure 1. Flow chart of recruitment of general practitioners and patients in the OPTICA trial[1].



[1] cluster-randomized controlled trial in Swiss primary care

Abbreviations: OPTICA = Optimizing PharmacoTherapy in older multimorbid adults In primary CAre

What types of GPs participated in the OPTICA trial, and how did they compare to the non-participating GPs from FIRE?

As shown in Table 2, GPs who participated in OPTICA and those from the FIRE reference cohort were in their fifties on average (OPTICA median=54, FIRE median=51), had several years of experience working as a GPs (OPTICA median=15, FIRE median=10), and the majority were self-employed (OPTICA self-employed=70%, FIRE self-employed=63%). The GPs in the FIRE reference cohort and OPTICA were similar in terms of age, median years since starting to work as a GP, employment status, GP practice type, and participation in integrated care models (p-values>0.05 and absolute standardized differences (ASD)<0.2). We found differences between OPTICA and GPs from the FIRE reference cohort with regards to sex (lower proportion of female GPs in the OPTICA trial), location (greater proportion of OPTICA GPs in non-urban areas), and self-dispensing of medications in GP office (lower proportion of OPTICA GPs than FIRE GPs). The median work percentage was 80% in both groups (4-day week), but p-value and ASD showed that the distribution of the work percentages was different between groups.

What types of patients consented to participate in the OPTICA trial, and how did they compare to non-participants?

As shown in Table 3, patients participating in the OPTICA trial were relatively comparable to other older patients with multimorbidity in the FIRE reference cohort with regards to their clinical characteristics and health services use. On average, patients were in their late seventies (OPTICA median=77, FIRE median=78), and regularly saw their GP (OPTICA median consultation counts in the last 6 months=16, FIRE median=13). We did not find evidence for a difference between the groups with regards to age, the median number of Body Mass Index (BMI) measurements, the median number of lipid profile measurements, median systolic blood pressure, median BMI and median number of glomerular filtration rate (GFR) measurements (p-values>0.05 and ASD<0.1 for all these variables). Median diastolic blood pressure and median HbA1c values were found to be statistically significant between groups, but the ASD was close or equal to 0.1. For most of the remaining variables, we found statistically significant differences and standardized differences of around 20% (e.g. sex, median number of consultations, median number of medications, etc.). On average, patients in the OPTICA trial had more chronic conditions (OPTICA median=4, FIRE median=3, ASD=0.422), but less medications (OPTICA median=6, FIRE median=7, ASD=0.23). Within patients of the same GP, patients participating in OPTICA were comparable to patients not participating in OPTICA (eTable 1 in the supplement).

How did patients recruited from random screening lists and other patients compare?

Two hundred and twenty-four patients were recruited from the random screening lists and 99 patients were recruited outside of these lists. The comparison of these two group (Table 4) found that they were comparable. We only found a statistically significant difference concerning median number of consultations (p=0.031) and number of BMI measurements (p=0.022).

What was study participants' willingness to have medications deprescribed?

As shown in Table 5, at baseline of the OPTICA trial, the majority of patients in the OPTICA trial (>90%) reported to be satisfied with their current medications. Furthermore, most of the study participants (>80%) reported to be willing to stop one or more of their medications if their doctor said that it was possible. The OPTICA study participants reported to be involved in their medication use (median involvement score=4.8 (IQR=4.2-5.0); score can range from 1 to 5, with 5 representing a high reported involvement). The median medication burden score was 2.2 (IQR=1.6-2.8) and the concerns about stopping score was 1.6 (IQR=1.0-2.4). Results of caregivers who completed the caregiver rPATD (where the patient was unable to complete the questionnaire due to cognitive impairment, n=16) are shown in table 5.

Table 2. Baseline characteristics of general practitioners in the OPTICA trial compared to the general practitioners in the FIRE database.

Characteristics	OPTICA GPs (N = 43)	FIRE GPs (N = 227)[1]	p-value[5]	Absolute standardized difference[6]
Median age (IQR)	54 (45-60)	51 (44-58)	0.572	0.073
Median years since starting to work as GP (IQR)	15 (6-23)	10 (5-21)	0.302	0.159
Sex				
Women (%)	8 (19)	80 (35)	0.034	0.385
Men (%)	35 (81)	146 (65)		
Employment status				
Self-employed (%)	28 (70)	131 (63)	0.474	0.143
Employed (%)	12 (30)	76 (37)		
GP practice type				
Group practice (%)	36 (84)	200 (88)	0.452	0.126
Single practice (%)	7 (16)	27 (12)		
Location				
Non-urban (%)	17 (40)	51 (23)	0.022	0.375
Urban (%)	26 (60)	176 (78)		
Self-dispensation of medications in GP office[2]				
Yes (%)	25 (60)	175 (77)	0.046	0.386
No (%)	13 (31)	41 (18)		
Limited[3] (%)	4 (10)	11 (5)		
Median work percentage (IQR)	80 (80-100)	80 (60-100)	0.020	0.401
Participation in integrated care model				
Yes	39 (93)	202 (95)	0.456	0.103
No	3 (7)	10 (5)		
Median percentage of eligible patients based on OPTICA inclusion criteria (IQR)[2]	6 (3-14)	7 (4-11)	0.614	0.287

[1] as of spring May 2019, excludes GPs who were part of the OPTICA trial and who did not have any eligible patients for the OPTICA trial; [2] depending on the area/region they work in, Swiss GPs may be able to sell and dispense medications to their patients; [3] only for selected medications; [4] ≥ 5 medications from different ATC groups and age ≥ 65 years. The other inclusion and exclusion criteria were not implemented, as they had to be double checked by the GPs; [5] For categorical variables we performed a Fisher's exact text and for continuous variables a Kruskal-Wallis test was performed; P-values of <0.05 represent that there is evidence for a statistically significant difference between the two groups. [6] An imbalance between the two groups was previously defined as an absolute standardize difference value >0.2. Abbreviations: GP = general practitioner, IQR = interquartile range, OPTICA = Optimizing PharmacoTherapy in older multimorbid adults In primary CAre, FIRE = Family medicine ICPC Research using Electronic medical records

Table 3. Baseline characteristics of patients in the OPTICA trial compared to other multimorbid patients with polypharmacy in the FIRE database.

Characteristics	OPTICA study participants[1] (N = 323)	Patients in the FIRE database[2] (N = 22'907)	p-value[3]	Absolute standardized difference[4]
Median age (IQR)	77 (73-83)	78 (72-84)	0.630	0.053
Sex				
Women (%)	146 (45)	12'699 (55)	0.001	0.206
Men (%)	177 (55)	10'207 (45)		
Median number of chronic conditions (IQR)[5]	4 (3-6)	3 (3-5)	<0.001	0.422
Median number of medications in the last 12 months (IQR)[6]	6 (5-9)	7 (5-8)	<0.001	0.23
Health services use (in the last 12 months)				
Median number of consultations (IQR)	16 (10-25)	13 (7-22)	<0.001	0.216
Median number of blood pressure measurements (IQR)	3 (2-5)	2 (1-4)	<0.001	0.276
Median number of Body Mass Index measurements (IQR)	2 (1-3)	1 (1-3)	0.501	0.03
Median number of HbA1c measurements (IQR)	2 (1-4)	2 (1-3)	0.001	0.24
Median number of glomerular filtration rate (GFR) measurements (IQR)	2 (1-3)	1 (1-3)	<0.001	0.208
Median number of lipid profile measurements (IQR)	1 (1-2)	1 (1-1)	0.166	0.093
Lab values & vital signs (in the last 12 months)				
Median systolic blood pressure (IQR)	138 (126-148)	138 (127-149)	0.541	0.023
Median diastolic blood pressure (IQR)	76 (70-83)	79 (72-85)	0.005	0.154
Median Body Mass Index (IQR)	29 (25-32)	28 (24-31)	0.235	0.101
Median HbA1c (IQR)	6.3 (5.7-7)	6.1 (5.6-6.9)	0.023	0.1
Median GFR (IQR)	66.2 (51.4-79.7)	68.3 (52.3-82.5)	0.314	0.041

1 patients who participated in the OPTICA trial, **2** patients eligible to participate in the OPTICA trial based on the inclusion and exclusion criteria, excludes patients who participated in the OPTICA trial; **3** For categorical variables we performed a Fisher's exact text and for continuous variables a Kruskal-Wallis test was performed. P-values of <0.05 represent that there is evidence for a statistically significant difference between the two groups **4** An imbalance between the two groups was previously defined as an absolute standardize difference value >0.2. [5] chronic conditions were defined according to Lamers et al. and O'Halloran et al. [39,40]. [6] number of medications belonging to different groups defined by the Anatomical Therapeutic Chemical (ATC) classification system.

Abbreviations: BMI = Body Mass Index; IQR = Interquartile range; GFR=Glomerular filtration rate; HbA1c = Hemoglobin A1C; OPTICA = Optimizing PharmacoTherapy in older multimorbid adults In primary CAre; FIRE = Family medicine ICPC Research using Electronic medical records

Table 4. Baseline characteristics of patients in the OPTICA trial who were recruited from the screening list and those who were recruited outside of the screening list.

Characteristics	OPTICA study participants from screening list (n = 224)	OPTICA study participants not from screening list (n = 99)	p-value[1]	Absolute standardized difference[2]
Median age (IQR)	77 (72-82)	79 (74-84)	0.088	0.183
Sex				
Women (%)	106 (47)	40 (40)	0.276	0.14
Men (%)	118 (53)	59 (60)		
Median number of chronic conditions (IQR)	4 (3-6)	4 (3-6)	0.774	0.086
Median number of medications in the last 12 months (IQR)	6 (5-9)	7 (3-9)	0.464	0.16
Health services use (in the last 12 months)				
Median number of consultations (IQR)	17 (10-26)	14 (9-21)	0.031	0.303
Median number of blood pressure measurements (IQR)	3 (2-6)	3 (1-5)	0.197	0.034
Median number of Body Mass Index measurements (IQR)	1 (1-2)	2 (1-3)	0.255	0.329
Median number of HbA1c measurements (IQR)	2 (1-3)	2 (1-4)	0.332	0.147
Median number of glomerular filtration rate (GFR) measurements (IQR)	2 (1-3)	2 (1-3)	0.901	0.045
Median number of lipid profile measurements (IQR)	1 (1-2)	1 (1-2)	0.667	0.101
Lab values & vital signs (in the last 12 months)				
Median systolic blood pressure (IQR)	137 (125-147)	139 (130-150)	0.397	0.102
Median diastolic blood pressure (IQR)	76 (70-83)	76 (71-83)	0.801	0.078
Median Body Mass Index (IQR)	29 (25-32)	29 (25-33)	0.902	0.015
Median HbA1c (IQR)	6.3 (5.8-7.0)	6.4 (5.6-7.0)	0.991	0.02
Median GFR (IQR)	66.5 (53.4-80.1)	62.7 (48-6-78.9)	0.264	0.167

[1] For categorical variables we performed a Fisher's exact text and for continuous variables a Kruskal-Wallis test was performed. P-values of <0.05 represent that there is evidence for a statistically significant difference between the two groups. [2] An imbalance between the two groups was previously defined as an absolute standardize difference value >0.2. Abbreviations: BMI = Body Mass Index; IQR = Interquartile range; GFR = Glomerular filtration rate; HbA1c = Hemoglobin A1C; OPTICA = Optimizing PharmacoTherapy in older multimorbid adults In primary CAre

Table 5. Patients' and caregivers' willingness to have medications deprescribed assessed with 'revised Patients' Attitudes Towards Deprescribing' (rPATD) questionnaire[1]

	OPTICA patients (n = 298)	Caregivers of OPTICA participants with cognitive impairment (n = 16)
"Overall, I am satisfied with my current medicines" (%) and respectively "Overall, I am satisfied with my care recipient's current medicines"		
strongly agree	215 (72.2)	11 (68.7)
agree	64 (21.5)	5 (31.3)
unsure	4 (1.3)	-
disagree	11 (3.7)	-
strongly disagree	4 (1.3)	-
"If my doctor said it was possible I would be willing to stop one or more of my regular medicines" (%) and respectively "If their doctor said it was possible I would be willing to stop one or more of my care recipient's medicines"		
strongly agree	224 (75.2)	10 (62.5)
agree	38 (12.8)	3 (18.8)
unsure	9 (3.0)	1 (6.3)
disagree	14 (4.7)	1 (6.3)
strongly disagree	13 (4.4)	1 (6.3)
Factor scores		
Involvement: Median involvement in medication management score (IQR)	4.8 (4.2-5.0)	4 (3.4-5.0)
[range: 1-5, the higher the score the more 'involved' patients are with their medications and caregivers with the medications of the person they care for]		
Burden: Median perceived burden of medications score (IQR)	2.2 (1.6-2.8)	2.3 (1.3-3.8)
[range: 1-5, the higher the score the more burdensome patients and caregivers perceive/view/experience the medications to be]		
Appropriateness: Median belief in appropriateness of medications score (IQR)	3.8 (3.4-4.2)	3.8 (3.4-4.2)
[range: 1-5, the higher the score the more appropriate patients respectively caregivers perceive/view/experience the medications]		
Concerns about stopping: Median concerns about stopping medications score (IQR)	1.6 (1.0-2.4)	1.2 (0.8-1.6)
[range: 1-5, the higher the score the potential concerns patients respective caregivers have about stopping one or more of the medications]		

[1] Reeve, E., Low, L. F., Shakib, S., & Hilmer, S. N. (2016). Development and Validation of the Revised Patients' Attitudes Towards Deprescribing (rPATD) Questionnaire: Versions for Older Adults and Caregivers. Drugs & Aging, 33(12), 913-928. Since the scores were not normally distributed we decided to present the medians. Abbreviations: OPTICA = Optimizing PharmacoTherapy in older multimorbid adults In primary CAre; rPATD = Revised Patients' Attitudes Towards Deprescribing

Discussion

To inform the likely external validity of the results of the OPTICA trial, we compared the characteristics of our participating GPs and patients to a Swiss real world reference cohort. We also examined the characteristics of patients recruited based on random screening lists (created from electronic medical records) and those recruited outside of these lists by their GP to see whether a selection bias may exist. Finally we explored the willingness of patients in OPTICA to have medications deprescribed which allows us to reflect on the possible impact that this may have on the outcomes of the trial and compare them to previously studied populations. From our analyses we have some confidence that the findings of the OPTICA study will be generalizable to the broad Swiss population of GPs and patients. We found that the GPs in the FIRE project and OPTICA were similar in terms of sociodemographic characteristics and their work as a GP (e.g. age, experience as GP, employment status, and GP practice type). We also found that patients participating in the OPTICA trial and patients in the FIRE database were comparable in terms of age, median number of certain lab and vital data measurements (e.g. BMI, lipid profile, GFR measurements) and certain clinical characteristics (e.g. systolic blood pressure, BMI). For the variables that differed between the two groups according to the statistical tests, the absolute standardized differences were generally around 0.2 (or 20%), with an imbalance of the two groups having previously been defined as >0.2. Patients who participated in the OPTICA trial reported a high level of willingness to stop one or more of their medications.

Overall, our study results showed that GPs who participated in the OPTICA trial and those who participated in the FIRE project were comparable in most of the variables examined. Previous research showed that high performing physicians are more likely to participate in research [191]. When looking at the patient data, we observed that OPTICA patients had more chronic conditions, but less medications. The absolute standardized differences indicate some imbalances between the groups on these variables. While one can argue about whether the differences are clinically relevant, this observation could indicate that GPs in the OPTICA trial may have been more proactive in reviewing the medications of their patients than other GPs. If the latter was the case, this would mean that the intervention of the OPTICA trial may be limited in its effect (i.e. if the patients had little room for further optimisation of their medications). We also found differences in sex, location and self-dispensing between GPs in both groups. These differences may have stemmed from the recruitment strategy used in the OPTICA trial, which in the context of difficulties of recruiting Swiss GPs for clinical research focused (and therefore needing to optimise GP recruitment) did not specifically recruit based on their baseline characteristics. The sex composition of the OPTICA GPs could affect the

final results, since female physicians have been found to be less likely to make deprescribing decisions [169].

We found that the multimorbid older patients who participated in the OPTICA trial were comparable to those in the FIRE database in terms of sociodemographic variables, health services use and clinical characteristics. For the variables were there was a statistically significant difference between the groups, most had standardized differences close but not passing the ASD threshold of 0.2 for meaningful differences between the groups (e.g. number of medications: OPTICA median=6, FIRE median=7, ASD=0.23, number of consultations OPTICA median=16, FIRE median=13, ASD=0.216). There is a lower proportion of female participants in the OPTICA trial than in the reference FIRE cohort. However, since no difference in willingness to deprescribe according to sex has been identified [113,114], we do not anticipate that this sex imbalance will affect the results of the OPTICA trial.

We found that the trial participants recruited from the random screening lists (around two thirds of patients) and those who were recruited outside of these lists (around one third of patients) were comparable. While systematic differences in recruitment behaviour (i.e. differential recruitment [192]) has been reported previously in the context of a cluster-randomized controlled trial in primary care (UK BEAM trial) [193], we did not find evidence for selection bias in the OPTICA trial. The UK BEAM trial reported, for example, that patients in participating practices were experiencing milder back pain (which the intervention targeted) than those in the control group and thus highlighted the potential for the recruitment process to bias study results[193]. The use of random screening lists helped to standardize patient recruitment but, in light of the imperfect nature of the screening lists, we also allowed GPs to recruit patients who were not on these lists. We assumed that giving participating GPs some flexibility in the recruitment process would allow them to better integrate recruitment into their regular practice and would therefore optimise recruitment.

Concerning patients' willingness to deprescribe, we found that the OPTICA study participants had a high involvement in their medication use and >80% were willing to stop one or more of their regular medications if their doctor told them this was possible. These findings are in line with previous research. Another study conducted in Switzerland found that 77% of older adults would be willing to stop one or more of their medications [113] and similar proportions were found in studies in other countries (88% in Australia [114], 92% in the United States [115], 83% in Singapore [116]). While these numbers have to be interpreted with caution (e.g. social desirability bias, not medication specific, hypothetical nature of the question), it shows that older patients may be open to optimizing their medication use through deprescribing. We also found the factor scores to be comparable to the results from a study in Australian older adults [114]. This information is crucial for implementing medication optimization interventions, and

in the context of the OPTICA trial, it shows that patients' attitudes towards deprescribing may not be a barrier to implementation of deprescribing.

While the results presented in this manuscript are primarily Swiss-specific, we can draw a more broadly applicable conclusion; it appears to be possible to recruit a sample of study participants in primary care trials that is comparable to real life cohorts.

Strengths & Limitations

The OPTICA trial had a low number of exclusion criteria, which facilitated broad recruitment of study participants. However, the analyses in this manuscript have several limitations. First, in Switzerland there are no complete GP or patient registries. The FIRE project maintains the only primary care database in Switzerland of this size, but it does not include all Swiss GPs, and in turn, does not include all Swiss patients. In Switzerland, not all GPs use electronic health record programs. The use of electronic health records in Switzerland increased from around 40% to >70% from 2012 to 2020 [17,34], but remains lower than in other high income countries. Furthermore, not all GPs who fulfil the eligibility criteria self-select to participate in the FIRE project. This raises the question of the representativeness of the GPs in the FIRE database. However, two recent assessments of the Swiss GP workforce showed that the GPs in the FIRE project are comparable to the entire GP workforce in terms of age, sex, experience as GP and work percentage (eTable 2 in the supplement). These similarities between OPTICA, FIRE and all Swiss GPs signify that the recruitment of an externally comparable sample of GPs is possible in randomized clinical trials in the Swiss primary care setting. This confirms previous evidence from the UK, which showed that achieving good levels of external validity was possible in clinical trials in primary care [194]. However, due to the lack of patient registries, we cannot comment on the comparability of patients in the FIRE project and Swiss patients in general. While the analyses presented in this manuscript do not confirm external validity of the forthcoming OPTICA trial results, they do facilitate future interpretation of our findings.

Next, inherent to routine medical databases, like the FIRE database, is a certain risk of information bias and missing data as information is only collected when it is clinically relevant [195]. Since we used data from before the OPTICA study intervention started, we assume that both our groups would have been affected by the same potential sources of bias. Despite the similarities found between the FIRE and Swiss GP workforce in terms of sociodemographic and work-related characteristics, we were unable to compare other important characteristics between the two groups (e.g. quality of care, relationship and trust between doctor and patient). Our finding that the patients included in the OPTICA trial had less medication but

more chronic conditions than the reference cohort could reflect the selection of “good performers” which may bias the findings of the OPTICA trial. Our analysis of patients’ willingness to deprescribe was limited to patients in the OPTICA trial and could not be compared directly to the reference cohort and this questionnaire is not used in regular clinical care. Other limitations related to the rPATD are that it asks hypothetical questions, it is not specific to certain medications, and it might be subject to social desirability bias. Furthermore, for the purpose of the OPTICA trial the rPATD was translated from English to German; back-translation and piloting was conducted to increase the validity of the translation, but other measures of validation and reliability of the translation in the local context were not conducted (e.g. test-retest reliability). Finally, due to the uncertainties surrounding the absolute standardized differences, we decided to present both p-values and ASD. While there may be debate of the cut off to use for ASD, we used >0.2 as this has been recommended by Yang et Dalton [188,189]. If we considered a smaller threshold, such as >0.1, it would not have changed our conclusions about the groups being comparable.

Conclusion

In the OPTICA trial, it was possible to recruit GPs and their older patients with multimorbidity and polypharmacy that are generally comparable to a real world reference cohort of GPs and older patients with multimorbidity and polypharmacy in Switzerland. The observed similarities between OPTICA, FIRE and all Swiss GPs signify that the recruitment of an externally valid sample of GPs is possible in randomized clinical trials in the Swiss primary care setting. The findings from this manuscript about the baseline characteristics of study participants will be crucial for interpreting the wider applicability of the OPTICA study intervention and its findings. Ensuring that clinical trials recruit representative populations is crucial for improving the care of older multimorbid patients, which have previously been underrepresented in clinical research.

Abbreviations

ASD	Absolute standardized difference
FIRE	Family medicine ICPC Research using Electronic medical records
GCP	Good Clinical Practice
GP	General practitioner
OPTICA	Optimising PharmacoTherapy In the multimorbid elderly in primary CAre
rPATD	Revised Patients' Attitudes Towards Deprescribing

Declarations

Ethical Approval

The ethics committee of the canton of Bern (Switzerland) and the Swiss regulatory authority (Swissmedic) approved the study protocol of the OPTCIA trial and other documentation on study conduct (BASEC ID: 2018–00914). The ethics committee and Swissmedic receive annual safety reports and information about study stops/end and protocol amendments, as per local requirements. The local Ethics Committee of the Canton of Zurich approved studies within the FIRE project database (BASEC-Nr. Req-2017-00797).

The OPTICA trial was performed in accordance with relevant guidelines and regulations. Written informed consent was obtained from all study participants participating in the OPTICA trial.

Consent for Publication

Not applicable.

Availability of Data and Materials

OPTICA embraces an open access policy and will vigorously disseminate all resulting data, study results and publications. The FIRE database can be accessed at any time by the scientific team of the institute. For external requests, access has to be requested from the head of the institute.

Competing Interests

The authors do not have any conflicts of interest to declare.

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Authors' Contributions

Study concept and design: All authors (KTJ, RM, FV, NS, CS, ER, MSp, MSch, NR, SS). Statistical analysis: KTJ, RM. Drafting of the manuscript: KTJ, RM, SS. Critical revision of the manuscript for important intellectual content: all authors (KTJ, RM, FV, NS, CS, ER, MSp, MSch, NR, SS). Obtained funding: NR, SS. Administrative, technical, or material support: NS, SS. Supervision: SS.

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Article VI: A Mixed-Methods Analysis of the Use of the 'Systematic Tool to Reduce Inappropriate Prescribing' in Swiss Primary Care Practices

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**** CONFIDENTIAL, UNPUBLISHED MANUSCRIPT DRAFT ****
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Notes: This is an unpublished article. It can only be submitted for publication after the OPTICA main trial results have been published.

My contributions: Together with Michael Deml and Sven Streit, I conceptualized and designed this study. I collected the quantitative data and contributed to planning the qualitative data collection. I analyzed the quantitative data and contributed to the qualitative data analysis. I created all figures and tables shown in the manuscript. I wrote the first draft of the manuscript and adapted it based on the comments made by the co-authors.

Tables and Figures in Article VI

Abstract

Background: With an increasing number of older multimorbid adults (≥ 65 years) with potentially inappropriate polypharmacy, evidence-based clinical decision support systems (CDSS), such as the 'Systematic Tool to Reduce Inappropriate Prescribing' (STRIP) assistant, have become promising tools for assisting general practitioners (GPs) with medication reviews and optimizing pharmacotherapy. Little is known about how GPs perceive the STRIP assistant. The aim of this study was therefore to investigate the use of the STRIP assistant during the 'Optimising PharmacoTherapy In the multimorbid elderly in primary CAre' (OPTICA) trial.

Methods: We used an explanatory mixed-methods design, meaning that we first collected quantitative data, which we sought to subsequently further explain and understand through qualitative methods. First, we collected quantitative data about the acceptance and implementation of recommendations generated by the STRIP assistant from GPs in the OPTICA intervention group (N = 21) about their patients who participated in the trial (N = 160). The mean number of recommendations generated, accepted and implemented by GPs were calculated by recommendation type (stop, start, adapt dosage, interaction). Then, semi-structured qualitative interviews (n = 8) were conducted with GPs from the OPTICA intervention group. We performed a thematic analysis.

Results: Overall, GPs found the STRIP assistant useful, in particular the fact that it was able to generate recommendations based on a large number of data. Our quantitative findings show, however, that the expenditure of GPs' time for the preparation and use of the STRIP assistant and for the discussion of the recommendations generated by the clinical decision support system was consequential, which may have limited their implementation of the intervention. During qualitative interviews, GPs discussed how the main reasons for the limited implementation of the STRIP assistant are related to problems with: the data source (e.g. incomplete data imports), preparation of the CDSS (e.g. time expenditure for updating and adapting the information) and its functionality (e.g. technical problems when downloading PDF reports containing recommendations), as well as the appropriateness of recommendations.

Conclusions: The qualitative findings help explain the low implementation rate of the recommendations demonstrated by the quantitative findings, but also show the overall acceptance of the tool by GPs. GPs were using the STRIP assistant for their first time in 8-10 patients each and time expenditure might improve from gaining routine. Our results provide crucial insights for adapting the STRIP assistant to make it more suitable for a regular use in primary care settings in the future.

Trial registration: The ethics committee of the canton of Bern in Switzerland approved the protocol of the OPTICA trial. Trial registration numbers: Clinicaltrials.gov (NCT03724539), KOFAM (Swiss national portal) (SNCTP000003060), Universal Trial Number (U1111-1226-8013).

Key words: Multimorbidity, polypharmacy, general practitioners, clinical decision support system, mixed-methods

Background

Globally the number of older adults with multimorbidity is growing. In Switzerland, for instance, the proportion of adults with multimorbidity has increased in the past decades [196]. The causes for this involve increased life expectancies and the fact that chronic conditions are more prevalent in older age [14]. More than 50% of older adults aged ≥ 65 years have not only one chronic condition but several [15]. The coexistence of ≥ 2 chronic conditions is commonly referred to as multimorbidity [17]. Multimorbidity is usually accompanied by polypharmacy, which can be defined as the concurrent, regular intake of ≥ 5 medications [28]. The higher the number of medications used, the more likely older adults are to have inappropriate polypharmacy, which not only consists of the use of potentially inappropriate medications (PIMs), but also prescribing omissions [46-49,86]. A prospective cohort study conducted with Irish community-dwelling adults aged ≥ 65 years found a potentially inappropriate medication in 57% and potential prescribing omissions in 42% of participants [61]. The utilization of PIMs is associated with an increased risk of adverse drug events, falls, and cognitive decline [51-55]. This in turn is associated with a greater health services use, such as hospitalizations or emergency department visits, and higher healthcare costs [49-52]. Prescribing omissions were also shown to lead to a higher rate of emergency department and GP visits [61]. Due to this, optimizing the medication use of older adults with multimorbidity and polypharmacy should be a central task of general practitioners (GPs), who often are the key coordinator of care of their older multimorbid patients.

However, performing medication reviews are time-consuming and can be challenging especially in a context in which the time allocated to treating individual patients is short and large amounts of data need to be processed (e.g. medications, diagnoses, lab values, patient preferences, etc.). In light of the new possibilities available through the digital revolution, electronic, computerized clinical decision support systems (CDSS) can be a useful tool, supporting healthcare professionals, when performing medication reviews. Electronic CDSS are software-based tools, which are able of managing large amounts of data and are designed to be a direct aid to clinical decision making [122]. They are capable of matching information, such as evidence-based clinical knowledge, with patient information (e.g. lab values, medications, diagnoses, etc.) and can thereby generate patient-specific recommendations. One such electronic CDSS is the ‘Systematic Tool to Reduce Inappropriate Prescribing’ (STRIP). It is based on the algorithms of the and ‘Screening Tool of Older Person’s Prescriptions’ (STOPP) and the ‘Screening Tool to Alert doctors to Right Treatment’ (START) (both version 2) [138]. Both the STOPP and the START criteria were established through an expert-consensus process [68]. While the STOPP criteria highlight situation of potentially

inappropriate medication use (e.g. overprescribing, drug-drug interactions, drug-disease interactions, incorrect dosages, etc.), the START criteria indicate potential prescribing omissions. The STRIP assistant generates patient-specific recommendations, based on the START and STOPP criteria, by taking into account medication lists, diagnoses, selected lab values and vital data [137]. It is thus a promising tool for optimizing pharmacotherapy in older adults and is currently being tested in several clinical trials to determine whether its use can improve clinical outcomes (e.g. European multicenter OPERAM trial in Switzerland, the Netherlands, Belgium and Ireland [140], OPTICA trial in Switzerland [141]).

The use of CDSS has been shown to be beneficial for certain medication-related outcomes, such as a reduction of medication errors, an improvement in prescribing quality and a decrease in the use of potentially inappropriate medications, which in turn leads to increased medication safety [128-130]. However, the evidence supporting the use of electronic CDSS is largely focused on the hospital setting (e.g. reduction of use of potentially inappropriate medications) and results are mixed for nursing homes and the primary care setting [197]. Further, while the use of CDSS has led to reductions in healthcare costs in some settings, it has led to an increase in other settings [198]. In addition, the current evidence shows a lot of variability in the effectiveness and implementation of such tools in the primary care setting and reports implementation challenges (e.g. time-consuming data entry, alert fatigue) [133,199-201]. The documented problems related to the implementation of such tools, can be hypothesized to have influenced the results of the use of such tools. Consequently, studying the implementation of electronic CDSS is crucial, as this will influence the future development of effective implementation strategies of such tools. In this context, the aim of this study was to explore the use of the STRIP assistant in a real-life clinical setting during the ‘Optimising PharmacoTherapy In the multimorbid elderly in primary CAre’ (OPTICA) trial by using an explanatory mixed-methods approach.

Methods

This research was embedded in the OPTICA trial, which is cluster randomized controlled trial that took place in Swiss primary care practices. The main goal of this trial was to investigate whether the use of the STRIP assistant helps to improve the medication appropriateness in older multimorbid adults with polypharmacy. The participating GPs formed one cluster each and were randomly assigned 1:1 to the study arms. In the intervention arm GPs used STRIP to perform a medication review and engage in shared-decision making with patients. Figure 1 provides an overview of the different steps of the intervention. In the control arm, GPs performed a sham intervention, which consisted of a medication review in accordance with usual care. Study participants were ≥ 65 years or older, had ≥ 3 chronic conditions regularly used ≥ 5 medications, and were treated by one of the participating GPs. Patients were followed-up for 12 months. One part of the trial data was collected through the 'Family medicine ICPC Research using Electronic medical records' (FIRE) project, which is a database collecting anonymized patient and routine data, such as medications, diagnoses, selected lab values, and vital data, from the electronic medical records in primary care practices [172]. Only for the purpose of this trial and with the informed consent of participating patients, we were able to identify their information in the FIRE database. For each participating patient the FIRE team prepared an XML data file for the central trial team. Author 1 at the central trial team then prepared STRIP assistant accounts for the GPs in the intervention group and performed the semi-automated import of the patient data. The details of the trial protocol and the baseline characteristics of study participants have previously been reported [141,202].

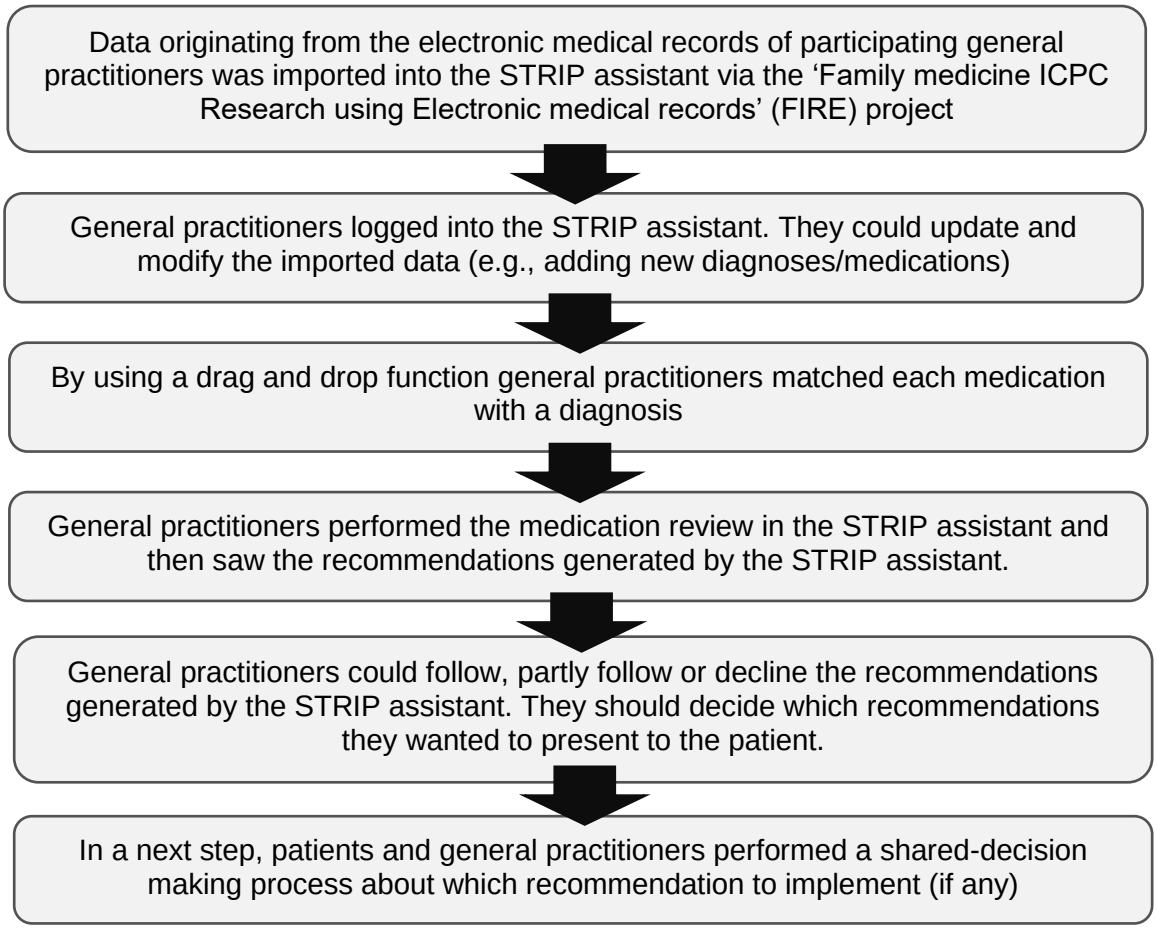
Study Design

We used a mixed-methods design in which we combined information collected from participating GPs on the recommendations generated, discussed and implemented during the intervention and semi-structured interviews with GPs from the OPTICA intervention group. It was an explanatory design, as defined by Creswell & Clark, in which we first collected quantitative data, which we sought to subsequently further explain and understand through qualitative methods [203]. In this design, the qualitative and quantitative components of the project are analyzed independently and interpreted together.

Participants

In both the quantitative and qualitative part of the research project, the study participants were the general practitioners GPs who were randomly assigned to the intervention arm of the OPTICA trial. In total, there were 21 GPs in the intervention group.

Figure 1. Schema of the six steps of the OPTICA study intervention using the 'Systematic Tool to Reduce Inappropriate Prescribing' (STRIP) assistant



As described in: 'Jungo KT, Rozsnyai Z, Mantelli S, et al. 'Optimising PharmacoTherapy In the multimorbid elderly in primary CAre' (OPTICA) to improve medication appropriateness: study protocol of a cluster randomised controlled trial. BMJ Open 2019;9:e031080.'

Data Collection

Quantitative Component

After the GPs from the OPTICA intervention group (N = 21) performed the structured medication review using the STRIP assistant, they were asked to directly enter the information about the recommendations generated, discussed with patients and implemented in the REDCap study database. Author 1 verified the entries in REDCap and completed them from information available in the STRIP assistant. The following variables were collected for each

recommendation generated: name of the recommendation, code of the recommendation, type of the recommendation, whether the recommendation was presented to the patient, and (if applicable) whether the recommendation was or will shortly be implemented. Furthermore, GPs directly reported the time used to prepare the STRIP assistant, the time used to conduct the medication review, and the time spent on the shared decision-making with the patient. Quantitative data were collected between May 2019 and February 2020.

Qualitative Component

We performed semi-structured interviews with GPs from the OPTICA intervention group. To arrange these interviews the GPs were contacted by Author 1 and invited to participate. Overall, there were 8 interviews semi-structured interviews conducted by Author 3, a medical student trained in qualitative interviews. The interview guide included questions related to GPs' attitudes towards treating older adults with multimorbidity and polypharmacy, the use of the STRIP assistant intervention during the OPTICA trial, and GPs' attitudes towards the use of using electronic clinical decision support systems. The interviews were recorded and transcribed to prepare them for the analysis. Qualitative data were collected between January and March 2020.

Data Analysis

Quantitative Component

We performed descriptive analyses. First, we calculated the median number of recommendations generated. Next, we calculated the total number of recommendations generated by recommendation type and per study participant in the OPTICA intervention arm. We then calculated the number of recommendations reported to have been presented to and discussed with patients and implemented after a shared decision-making by patients and GPs (by recommendation type). In addition, we calculated the average time spent on preparing and conducting the medication review and the average time used to conduct the shared decision-making. Since these variables were non-normally distributed, we present median and interquartile ranges. We performed all analyses with STATA 15.1 (StataCorp, College Station, TX, USA).

Qualitative Component

We analyzed qualitative data through the use of *thematic analysis*, which is a commonly used tool to identify and analyze patterns in qualitative data. We followed the six phases defined by Braun and Clarke to conduct the thematic analysis: 1) getting familiar with the data, 2) generating initial codes, 3) searching for themes, 4) reviewing themes, 5) defining and naming themes, and 6) producing the report [204]. Three of the investigators (Author 1, Author 2, Author 3) contributed to the identification of themes. In addition, we used the Framework Method by Gale et al. to structure our analysis [205]. We used TamsAnalyzer to code and organize the qualitative data into meaningful themes.

Ethical Approval

The ethics committee of the canton of Bern (Switzerland) and the Swiss regulatory authority (Swissmedic) approved the study protocol of the OPTICA trial and other documentation on study conduct (BASEC ID: 2018–00914).

Results

Baseline Characteristics

Table 1 provides baseline characteristics of the GPs in the OPTICA intervention group. For 155 out of 160 study participants in the intervention group we received the information that they received the study intervention.

Table 1. Baseline characteristics of general practitioners in the intervention group of the OPTICA trial (N = 21)

Sex	
Male (%)	18 (85.7)
Female (%)	3 (14.3)
Mean age, in years (SD)	50.2 (8.9)
Mean experience working as a general practitioner, in years (SD)	13.9 (8.5)
GP practice type	
Single practice (%)	2 (9.5)
Group practice (%)	19 (90.5)
Location	
Rural (%)	9 (42.9)
Urban or Sub-urban (%)	12 (57.1)
Self-dispensation in GP office	
Yes (%)	7 (33.3)
No (%)	14 (66.7)
Use of interaction checker in electronic health records	
Yes (%)	1 (4.8)
No (%)	20 (95.2)

Quantitative Findings

All the patients in the intervention group, for whom we were able to collect information on the generated recommendations, minimum one recommendation was generated. The median number of recommendations generated was 5 (interquartile range = 3 - 7). Table 2 shows the expenditure of time for the preparation and use of the STRIP assistant as well as the discussion with the patient. For the 160 patients in the intervention group, 699 recommendations were generated. On average this corresponds to 4.4 recommendations per patient. Figure 2 displays the information on the number of recommendations generated by the STRIP assistant, discussed with patients, and finally implemented from the seven GPs who provided information on this. We present the recommendations by type: stop medication, start medication, dosage (adaptation of dosage recommended), and interaction (drug-drug or

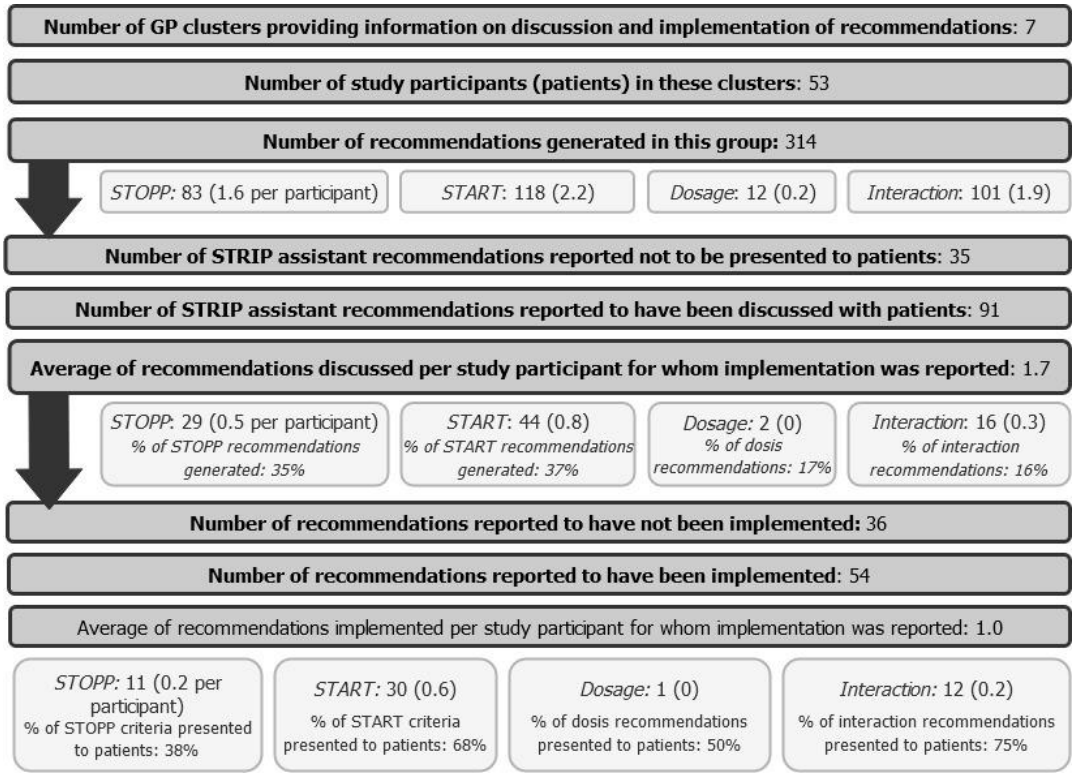
drug-disease interaction flagged). We observe that only a small number of the recommendations that were generated by the STRIP assistant were implemented in the shared decision-making process with patients. The reasons mentioned for this were that patients did not want any change, that the condition of the patient was stable which did not warrant any medication change, the perception that the medication in question had a health benefit, negative experiences with deprescribing in the past, the treatment having been prescribed by other specialist, and the senselessness of a medication change in view of the current health status of the patient (e.g. palliative situation).

Table 2. Information about expenditure of time for preparation and use of the STRIP assistant and the discussion of recommendations with the patients

GPs: n = 10 / Patients: n = 76	*Median (IQR), in minutes*
Preparation time	12.5 (25)
Use of the STRIP assistant	10 (10)
Discussion with patient	5 (5)

Information reported by 10 GPs from the intervention group about 76 patients. Information missing from 11 GPs and 84 patients from the OPTICA intervention group.

Figure 2. Overview of generated, discussed, and implemented recommendations



GP = General practitioner, STRIP assistant = 'Systematic tool to reduce inappropriate prescribing' assistant

Qualitative Findings

Overall, GPs appreciate the fact that the STRIP assistant was able to manage a large amount of data and to generate different types of prescribing recommendations (e.g. stop medication, start medication, etc.). The following themes were identified as being problematic barriers for GPs during the semi-structured interviews: length of time for the preparation of the STRIP assistant, problems with the data source and poor quality of the entered data, less than ideal functionality of the STRIP assistant, sub-optimal quality and practicability of the recommendations, and problems related to the implementation of the recommendations.

Preparation of the STRIP Assistant

Different subthemes related to the preparation of the STRIP assistant came up during the interviews. Before starting the intervention, we had provided information material (written and video) to GPs in the intervention group to explain how the STRIP assistant works. In general, GPs were satisfied with the quality of the information material and found it self-explanatory. One of the GPs, however, emphasized that the information provided should not be patronizing. Further, one GP mentioned the time-sensitiveness of the training provided: "*The problem is, that if you do not use [the tool] right away and become active, you'll forget how the tool works*" (GP, male, 45 years).

Most GPs mentioned that the coding of diagnoses (to ICPC-2) was a time-consuming and cumbersome task, mostly because most of them were not yet familiar with it at the beginning of the trial. GPs found the expenditure of time to prepare the STRIP assistant, including the coding of diagnoses, too long and time-consuming. For instance, one GP (male, 57 years) stated "*I was a little overwhelmed by the administrative burden*". It also became clear that the long expenditure of time would be a limiting factor to the future use of the tool: *"if the expenditure of time remains that high, the STRIP assistant has no chance of being used*" (GP, male, 44 years). It was also stated that this long preparation time would not have made it possible for GPs to use the tool during the consultations with patients present.

Data entry

Another major theme was the sub-optimal completeness of data imported from electronic health records to the web-based STRIP assistant, which created additional work for GPs in the intervention group. Problems with the data import were multifaceted. First, not all the information needed for the use of the STRIP assistant was systematically captured in the electronic health records or able to be exported to the FIRE project database. For instance,

this concerned unstructured information in text fields and lab values for which the FIRE team did not yet standardize the import into their database. Some GPs criticized the "missing information" in the exported data from their electronic health records, which we had imported into the STRIP assistant. Second, the time lag, which is inherently linked to the data structure of the FIRE project, between the data export from electronic health records to the FIRE project and then to the STRIP assistant caused the need for data to be updated and verified once they were in the STRIP assistant. Overall, GPs expressed that this time-consuming data entry, was a limiting factor to the future use of the STRIP assistant: *"I had to capture quite a lot of information by hand, and that is of course terribly tedious and time-consuming and thus not suitable for daily practice*" (GP, male, 44 years). Some GPs mentioned that they would have appreciated an automated data transfer from the electronic health records program used in their GP office to the STRIP assistant, as this would have facilitated their use of the tool. However, GPs also noted that there seemed to be a learning effect (e.g. after getting to know the tool, GPs were able to perform the subsequent reviews faster).

Functions and features of the STRIP assistant

Overall, GPs reported to be satisfied with the functions and features of the STRIP assistant. For instance, GPs appreciated that the STRIP assistant is capable of incorporating many different values into the analyses (i.e. different lab values, medication lists, diagnoses, vital data), which they would not have been able to do in the same way manually. Further, GPs reported to appreciate the different types of recommendations (recommendation to stop medication, start medication, adapt dosage, and highlight drug-drug or drug-disease interaction), since this highlighted different types of prescribing problems. However, not all GPs reported the tool as being intuitive to use. Further, some GPs reported technical problems when using the tool (e.g., long buffering when loading a new page or the next step of the analyses, problems with the download of the PDF report).

GPs' perceptions of the suitability and practicability of recommendations

Several sub-themes related to the quality and practicability of recommendations generated by the STRIP assistant came up during the interviews. Overall, GPs reported being satisfied with the overall quality of the recommendations. However, GPs emphasized that the recommendations were not always suitable/practicable. First, due to the above-mentioned problems with the data import, the recommendations were sometimes not applicable to the patients (e.g. there may have been valid reasons for why a certain medication was prescribed

in a certain dose, which was not captured in the STRIP assistant). Second, sometimes the recommendations were not suitable because of the seasonality of recommendation (i.e., influenza vaccine: most GPs used the STRIP assistant in spring 2019, which did not correspond to the influenza vaccination season). Furthermore, GPs usually did not add the influenza vaccine to the regular medications used by their patients, which is why the recommendation to vaccinate appeared, irrespective of whether the patient had been vaccinated in the past fall. Third, in some cases the STRIP assistant was not able to use the full information provided (e.g. it did not capture that some medications had several active ingredients). In some instances, GPs reported not to implement certain recommendations as they did not believe that these recommendations would change the patients' health-status and well-being.

Further, some recommendations were perceived as too basic and thus not useful for experienced GPs. One GP put it like this: "*Some of the information provided is not necessary for an experienced general practitioner*" (GP, male, 44 years). In some instances, the STRIP assistant generated recommendations that were already known to the GPs (e.g. dosage recommendation, or interaction), but had deliberately not been implemented for specific reasons (e.g. patient preferences). Another GP explicitly stated that he had wished for more "courageous" recommendations, which would have gone beyond the "evident" recommendations and would have challenged his previous prescribing decisions. GPs, however, also emphasized that the fact that few recommendations were generated for some of his patients confirmed his prescribing decisions and his work as a physician: "I *was happy, that the medication was not questioned in general. Otherwise I would had to doubt the quality of my work*" (GP, male, 44 years). The recommendations, or rather the lack thereof, was thus perceived as a confirmation of their work by some GPs.

Implementation of recommendations

The implementation of the recommendations generated by the STRIP assistant also was one of the themes that was discussed during the interviews. In general, GPs confirmed the low implementation rate with only around 10-20% of the recommendations being implemented, which is in line with our first step quantitative findings. Because the STRIP assistant sometimes did not capture all nuances of a patients' health status (e.g. due to missing information, problems with data import, etc.), the GPs often had valid reasons to reject the recommendations generated. As a consequence, only a small percentage of recommendations was presented to and discussed with patient. One GP, however, also told us that while he was not able to implement many of the recommendations directly, seeing the

recommendations helped him to become aware of potential prescribing problems. With regards to the implementation of recommendations that they deemed practicable, some GPs reported challenges when having to present the generated recommendations to their patients. One GP expressed it like this: *"You have to be careful not to make yourself "lower" than you are as a doctor. You should radiate a certain competence and not give the impression 'I need a computer to help me treat you, otherwise it'll be too complicated'*" (male, 44 years).

Finally, the overall impressions expressed by GPs were that the STRIP assistant was a potentially useful tool, but that its functionality was not ideal for regular use in clinical practice. For instance, a GP (male, 57 years) said "*The STRIP assistant is actually very useful, even in the way in which it works right now, but it is too complex for everyday use.*" Another GP (male, 44 years) echoed this sentiment, "*If the STRIP assistant wants to get a chance, it has to run a lot smarter*," meaning that data entry has to be fully automated and technical problems have to be solved. Overall, while some GPs stated that their expectations were met, others stated that they were disappointed by the tool due to its many technical problems. Despite this, the interviewed GPs reported to be willing to use electronic clinical decision support systems in the future if the above-mentioned challenges were addressed so that the use of CDSS could be better integrated into their clinical practice.

Discussion

This mixed-methods study set out to explore the use of the STRIP assistant in a real-life clinical setting during the OPTICA trial, a cluster-randomized controlled trial conducted in the Swiss primary care setting with patients aged ≥ 65 years with multimorbidity and polypharmacy, in which GPs used the tool for 8-10 patients. Our quantitative findings show that the expenditure of time for the preparation and use of the STRIP assistant as well as for the discussion of the recommendations generated was consequential, which may have limited the overall implementation of the intervention. Further, despite having a significant amount of missing data on the implementation of recommendations, our quantitative findings point towards the fact that a relatively low number of recommendations generated was presented to and implemented in a shared decision-making process with patients. The qualitative part of the study helped to explain the quantitative findings and showed that the main reasons for the limited implementation of the STRIP assistant are related to problems with the data source (e.g. incomplete data imports from the FIRE database), preparation of the CDSS (e.g. time expenditure for updating and adapting/entering information) and its functionality (e.g. technical problems when downloading the PDF report containing the recommendations, buffering), as well as the quality and practicability of recommendations (e.g. recurring influenza vaccine recommendation in spring). Overall, however, GPs perceived the STRIP assistant as a useful tool, in particular because it was able to manage a large amount of data.

Both our quantitative and qualitative findings showed a consequential expenditure of time needed to prepare the STRIP assistant, to run the analysis and to discuss the recommendation in a shared decision-making procedure together with the patient. The qualitative findings had the advantage of explaining the quantitative findings from the GPs' perspective. This finding is in line with the results from a process evaluation of a deprescribing intervention based on an electronic CDSS, in which GPs mainly reported retrieving additional information for the use of the tool to be time-consuming and inconvenient [200]. A previous study on the efficiency of medication reviews performed with the STRIP assistant showed that the time expenditure declined as the reviewers gained more experience (e.g., from ca. 20 to ca. 10 minutes per review) [206]. We are unable to compare the time needed for the medication review based on the STRIP assistant to other medication reviews performed by the same GPs. While the preparation of the CDSS may have taken more time, the quick generation of recommendations may have overall saved time.

Another major implementation challenge that we observed in our study involved problems with the data import and the cumbersome nature of the manual data entry, which may have been needed to add or updated missing or incorrect information. In the OPTICA trial, the purpose

of using data from electronic health records (via an export from the FIRE project database) was to facilitate the data entry for GPs. Despite this well-planned export, we faced similar challenges as in the above-mentioned deprescribing CDSS intervention, in which data for the tool was collected by GPs during routine appointments [200]. In our study, despite the import of data from their EHR, most GPs reported that they had to spend a relatively large amount of time to manually update and add information (e.g. code diagnoses, update medication lists due to frequent changes in older multimorbid patients). In most cases this was due to the fact that there was a time lag between the last exports to the FIRE project database, which may have rendered an update necessary, and that not all information from electronic health record programs can be exported to FIRE (e.g. unstructured text information or certain lab values, who are collected with different units in different reference laboratories). Some GPs criticized the “missing information” in the data that had been imported into the STRIP assistant from their electronic health records programs via the FIRE project database. This could have stemmed from the fact that GPs may not have known how the data exported to the FIRE project was structured (i.e. that it was limited to selected values, that data had to figure in the EHR for a certain amount of time before an export, which is why last-minute updates before an export may not have been captured).

A direct, fully automated import from the electronic health records (EHR) into the STRIP assistant would not have been technically feasible due to the multiple different EHR software providers used in the Swiss German part of Switzerland. It thus made sense to collaborate with the FIRE project, as this was the best available option operationalizing EHR data for a clinical trial with an electronic CDSS in the Swiss context. This mixed-methods study, however, shows the limitations of this approach. This should be a wake-up call for Swiss software developers to implement industrial standards that make different EHR software programs compatible with one another (e.g. feed data from one software into another, combine data from different software). In the future, this would allow for an easier use of electronic CDSS, such as the STRIP assistant. In addition, an effort should be made to make the coding of ICPC-2 diagnoses more common in the Swiss primary care setting. At the moment, the coding of diagnoses is not commonly done in routine care, which affects the feasibility of implementing tools like the STRIP assistant.

Another main barrier to the use of the STRIP assistant, which was shown by the quantitative findings and explained by the qualitative findings, was the low implementation rate of the recommendations generated by the tool. While we know that the STRIP assistant analysis was performed for 155 out of the 160 patients in our intervention group, we have a lot of missing information on the implementation of recommendations. In light of the qualitative findings, which in line with previous research showed that some recommendations were

perceived as less appropriate or practicable [201], we assume that only a small share of generated recommendations was implemented. The previously mentioned process evaluation on the use of the deprescribing CDSS found that 32% of GPs reported not to have implemented any recommendation [201], which we believe to be lower than in our study. Previous research showed that more experienced healthcare professionals were more likely to overlook and reject recommendations [123]. Hence the fact that more experienced GPs participated in the OPTICA trial (mean experience of working as a GP = 14 years), could have contributed to the lower implementation rate. In the previous study on the use of the deprescribing CDSS, there seemed to be a discrepancy related to how many recommendations were implemented by different GPs. For instance, it found that while some GPs implemented nearly all of the recommendations, others implemented few or any [200]. While we do not have quantitative data to prove this in our study, our qualitative findings provide support for this argument. In addition, we would like to emphasize that a low implementation rate is not necessarily bad, as GPs may have had valid reasons for not implementing recommendations (e.g. recommendation not being appropriate for the patient based on past experience, etc.). Finally, our main trial results, will reveal whether the low implementation rate of prescribing recommendations stems from a high medication appropriateness.

The reasons for implementation problems reported in the above-mentioned trial with a deprescribing intervention based on an electronic CDSS were similar to what we found in our qualitative analysis [200,201]. First, the CDSS did not capture all relevant patient-specific information, which is why some recommendations were not appropriate or practicable. The fact that recommendations may not appear to be applicable to individual patients had been reported previously in the literature [207]. Second, there can be difficulties in implementing recommendations when prescribing decisions had been taken by other medical specialists. Third, GPs' or patients' hesitancy toward medication changes can be a major barrier to implementing recommendations. These challenges need to be considered when further developing CDSS, such as the STRIP assistant. Despite the potentially low immediate implementation of recommendations, research shows that the use of electronic CDSS can a useful tool to start reflections and discussions about the medication use [38]. Hence, CDSS-based interventions can positively influence GPs' prescribing behaviors, as GPs have reported an increased awareness of prescribing problems after using a CDSS [29].

Even though GPs reported a learning effect when performing the medication review using the STRIP assistant, we retrospectively assume that 8-10 medication reviews may not have been enough to benefit from this learning effect. Performing such a small number of medication reviews using the STRIP assistant may not have allowed GPs to incorporate the use of their

tool in their workflow in an efficient manner. Fragmented workflows are a commonly reported problem linked to the use of CDSS, as these tools are often designed without considering the human information processing and behaviors [123]. While providing assistance to the participating GPs during the study intervention, our study team had also noticed that the computer literacy differed between participating GPs. We assume that this influenced the STRIP assistant use during the trial. Consequently, working on better integrating the use of the STRIP assistant into the routine clinical practice of GPs and adapting it to the computer literacy of individual GPs is crucial for a successful implementation of electronic CDSS in the primary care setting.

Our findings showed that overall GPs would be willing to use electronic CDSS, such as the STRIP assistant, for medication review if the above-mentioned issues were to be addressed. This openness to using CDSS is in line with previous research [200]. In one study, 65% of respondents mentioned that they would be willing to use CDSS in routine practice if the CDSS was integrated into their EHR program [201]. In addition to this, there would have to be minimal data entry so that the additional expenditure of time for using such tools would be as short as possible. Further, it must not be forgotten that the algorithms behind CDSS have to regularly be updated (e.g. with latest guidelines) [136]. And finally, what our research clearly showed is that providing a new CDSS is not enough. GPs need to be supported with communication strategies on how to conduct shared decision making with patients and strategies on how to overcome their own barriers to deprescribing.

Overall, qualitative findings suggest that GPs were dissatisfied with reoccurring problems when using the STRIP assistant (e.g. problems with data entry, generation of recommendations that the GPs did not deem useful, etc.). Consequently, apart from solving technical problems and improving data imports, it will be crucial to work on presenting recommendations in a way that is perceived as useful by GPs. This is crucial, because instead of GPs focusing their energy on discarding non-useful recommendations, they should be able to focus on the other recommendations that are potentially useful for their prescribing decisions in older adults with multimorbidity and polypharmacy.

Strengths & Limitations

The combined analyses of both quantitative and qualitative data strengthen our findings and allow for better data triangulation and thus is a strength of this project. However, this mixed-methods study also comes with several limitations. First, since there were problems when generating the PDF report at the end of the STRIP assistant use, it proved more difficult than initially planned to collect the information on generated recommendations. We retrospectively

collected the information about the recommendations by manually exporting them from the STRIP assistant. This came with the downside that we could only see which recommendations were generated based on the available information, but we could not see which ones had been accepted by GPs. Second, despite sending multiple reminders to GPs, we have a significant amount of missing information in the quantitative data, as only 7 out of 21 GPs reported information about the discussion and implementation of the recommendations generated. Third, the GPs willing to be interviewed were all male. Fourth, we did not collect the information which would have allowed us to quantify the learning effect over time.

Conclusion

Overall, GPs found the STRIP assistant useful, in particular the fact that it was able to generate recommendations based on a large number of data. During the OPTICA trial, however, general practitioners only discussed and implemented a small number of the recommendations generated by the STRIP assistant. In particular, technical problems related to the STRIP assistant's usability, general practitioners' high expectations about the tool's functionalities, the data intersection and the time expenditure to prepare the STRIP assistant for the analysis were important findings from our semi-structured interviews. The qualitative findings help explain the low acceptance and implementation rate of the recommendations. Due to a learning effect, a decline in the expenditure of time needed to perform medication reviews with the STRIP assistant would be expected if GPs would use this tool more regularly and for a larger number of patients. In its current form, it is unlikely that the STRIP assistant will be implemented more broadly. Our results, however, are crucial for adapting the STRIP assistant, or other CDSS, in a meaningful way to make it more suitable for a regular use in primary care settings on a larger scale.

Abbreviations

CDSS	Clinical decision support system
EHR	Electronic health records
FIRE	Family medicine ICPC Research using Electronic medical records
GP	General practitioner
OPTICA	Optimizing PharmacoTherapy In older multimorbid adults in primary CAre: a cluster randomized controlled trial
START	Screening Tool to Alert doctors to Right Treatment
STOPP	Screening Tool of Older Person's Prescriptions
STRIP	Systematic Tool to Reduce Inappropriate Prescribing

Declarations

Ethical Approval and Consent to Participate

The ethics committee of the canton of Bern (Switzerland) and the Swiss regulatory authority (Swissmedic) approved the study protocol and other documentation on study conduct (BASEC ID: 2018–00914). The ethics committee and Swissmedic receive annual safety reports and information about study stops/end and protocol amendments, as per local requirements. All study participants (GPs and patients) provided informed consent to participate in the trial.

Consent for Publication

Not required.

Availability of Data and Materials

The datasets and interview transcripts used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The author do not have any conflicts of interests to declare.

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Author Contributions

All authors designed the OPTICA trial. KTJ, MJD, and SS designed the mixed-methods study. KTJ and FS acquired the data. KTJ, FS, and MJD analyzed the data. KTJ drafted the manuscript with help from MJD. All authors reviewed and edited the manuscript and approved the final version.

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9. Overall Discussion

This thesis examined different aspects related to the optimization of medication use in older adults with multimorbidity and polypharmacy by presenting the results of both quantitative and mixed-methods research projects. This body of work presents new knowledge about the use of potentially inappropriate medications (PIMs) in older patients with multimorbidity and polypharmacy, GPs' attitudes towards deprescribing medications in this patient group, the representativeness of participants (both GPs and patients) in a primary care clinical trial, and the implementation of a new electronic clinical decision support system during this trial. This discussion also provides some information on the current status of the 'Optimizing PharmacoTherapy In older multimorbid adults with polypharmacy in primary CAre' (OPTICA) trial. At the end of the discussion, I discuss the strengths and limitations of the work presented, before ending it by addressing avenues for future research.

In this thesis I presented six thesis papers, three of which are published manuscripts as of February 2021. I grouped the six thesis papers into three sections. *Section I* of this thesis explored the utilization of and spending on PIMs in older adults with multimorbidity and polypharmacy *(Article I*) and the patient factors associated with the new prescribing of PIMs in older adults with multimorbidity and polypharmacy (*Article II*). *Section I* can thus be considered as the part of this thesis providing more information about the problematic of PIM use in older adults with polypharmacy and multimorbidity.

For their part, *Section II* and *Section III* of this thesis provide information about potential solutions to optimizing medication use in older adults with multimorbidity and polypharmacy. *Section II* provides an exploration of GPs' willingness to make deprescribing decisions in older patients with polypharmacy. *Article III* described the findings of our case-vignette study on GPs' attitudes towards making deprescribing decisions in patients with different levels of dependency in ADL as well as with or without cardiovascular disease. *Section III* was dedicated to the conduct of interventional, clinical research with older adults with multimorbidity and polypharmacy with the aim of optimizing medication use. *Article IV* presented the protocol of the 'Optimising PharmacoTherapy In the multimorbid elderly in primary CAre' (OPTICA) trial, which is a cluster-randomized controlled trial with Swiss GPs and older multimorbid adults with polypharmacy. *Article V* presented the baseline characteristics of GPs and patients participating in the OPTICA trial, including patients' willingness to have medications deprescribed, and discussed the external validity of the trial. Lastly, *Article VI* provided a mixed-methods exploration of the implementation of the 'Systematic Tool to Reduce Inappropriate Prescribing', an electronic clinical decision support system, during the OPTICA trial.

9.1 Summary of Principal Findings

High utilization of potentially inappropriate medications in older adults with multimorbidity and polypharmacy associated with non-negligible spending on potentially inappropriate medications

In *Article I*, I found that >69% of older patients with multimorbidity and polypharmacy used ≥ 1 PIM(s). The high use remained constant between 2007 and 2014. After adjusting for covariates (e.g., chronic conditions, demographic factors, medication intake, and healthcare utilization), female sex (OR = 1.20, 95% CI 1.17-1.22) and Hispanic ethnicity (OR = 1.41, 95% CI 1.27-1.56) were associated with higher odds of using PIM(s). Higher age was associated with lower odds of PIM use (OR = 0.92, 95% CI 0.90-0.93). In this patient group, central nervous system drugs and gastrointestinal drugs were found to be the most commonly used PIMs. More than 10% of medication costs were spent on PIMs in this patient group per year. This corresponds to an average of ≥390 USD spent on PIMs per year per patient.

Several demographic and clinical characteristics were found to be associated with new prescribing of potentially inappropriate medications in older adults with multimorbidity and polypharmacy

In PIM-naïve older adults with polypharmacy and multimorbidity, 2.5% were prescribed a PIM during the 90-day follow-up period *(Article II)*. The following patient factors were independently associated with a higher risk of being newly prescribed a PIM. First, male sex (HR = 1.29, 95% CI 1.06-1.57, reference: female sex). Second, an increased number of ambulatory visits (18-29 visits: HR = 1.42, 95% CI 1.06-1.92; ≥30: HR = 2.12, 95% CI 1.53-2.95, reference: ≤ 9 ambulatory visits). Third, a higher number of prescribing orders (HR = 1.02 per unit increase, 95% CI 1.01-1.02). Fourth, heart failure diagnosis (HR = 1.38, 95% CI 1.07-1.78, reference: no heart failure). Higher age was associated with a lower risk of new PIM prescribing (85 years: HR = 0.75, 95% CI 0.56-0.99, reference: 65-74 years). Central nervous system drugs, cardiovascular drugs, anticholinergics and endocrine drugs were the most commonly prescribed new PIMs.

GPs' willingness to make deprescribing decisions is higher in patients with increased functional dependency in activities of daily living and lower in patients with cardiovascular disease

In *Article III*, I showed that despite differences across 31 countries and GP characteristics, more than 80% of GPs reported they would make a deprescribing decision for ≥1 medication(s) in the presented oldest-old patients (aged ≥80) years with polypharmacy. The GPs' odds of reporting to make deprescribing decisions was higher in patients without history

of cardiovascular disease (OR = 3.04, 95% CI 2.58-3.57, reference: history of cardiovascular disease) and in patients with an increased level of functional dependency in ADL (high: OR = 1.5, 95% CI 1.25-1.80, medium: OR = 1.29, 95% CI 1.09-1.55, reference: low level of functional dependency in ADL). Increased age of GPs was also increased with higher odds of deprescribing decisions (OR = 1.14 per 10-year increase, 95% CI 1.06-1.23). Female sex (OR = 0.89, 95% CI 0.75-1.05, reference: male sex), the frequency of seeing patients with polypharmacy, and the number of patients consultations per day were not found to be significantly associated with making deprescribing decisions.

High willingness to have medications deprescribed in older adults with multimorbidity and polypharmacy

More than 80% of older multimorbid patients with polypharmacy, who participated in the OPTICA trial, reported to be willing to stop ≥ 1 of their medications if their doctor indicated that this was be possible (*Article V*). More than 90% of the patients reported to be satisfied with their current medication intake. Further, patients reported to have a high involvement in their medication use (average involvement score = 4.8, inter quartile range (IQR) = 4.2-5, range = 0-5[6]) and low concerns about stopping medications (average stopping score = 1.6, IQR = 1-2.4[7]).

Good external validity of clinical trial with GPs and older patients with multimorbidity and polypharmacy in the Swiss primary care setting is possible

As shown in *Article V*, the baseline characteristics of GPs participating in the OPTICA trial were similar in terms of sociodemographic characteristics and their work as GPs to those regularly exporting data to the FIRE project database (e.g., age, years of experience as GP, employment status). Patients participating in the OPTICA trial and those from the FIRE database were comparable in terms of age, health services use, and certain clinical characteristics (e.g., systolic blood pressure, body mass index). This shows that the OPTICA trial achieved a good external validity, which will be crucial for the further applicability of its study results.

No differential recruitment observed in the recruitment of older patients with multimorbidity and polypharmacy by their GPs

In *Article V*, I also demonstrated that patients recruited based on pre-defined screening lists (n = 224) were similar to those identified by GPs (n = 99). Patients who were recruited outside

[6] A score of 5 represents a high involvement.
[7] A score of 1 represents low concerns about deprescribing.

of the screening lists (i.e., identified by their GP) on average had a higher number of consultations with their GP, which may explain why the GPs identified and recruited them for the trial. Overall, this provides some evidence against differential recruitment.

Challenges observed related to the implementation of an electronic clinical decision support system, called STRIP assistant, in the Swiss primary care setting

Overall GPs reported a good acceptance of the STRIP assistant and perceived it as a useful tool due to its ability to manage a large amount of data. Despite this, we observed some implementation challenges in our mixed-methods study, which I described in *Article VI.* As shown by the quantitative findings, the expenditure of GPs' time for the preparation and use of the STRIP assistant as well as for the discussion of the recommendations generated by the STRIP assistant was consequential, which may have affected the implementation of the tool. During the semi-structured interviews, GPs explained how the main reasons for the limited implementation of the STRIP assistant are related to the following problems: incomplete data imports, significant time expenditure for preparing the use of the STRIP assistant, technical problems when running the medication review analysis in the STRIP assistant, and the quality and appropriateness of the generated recommendations.

9.2 Implications and Interpretation of the Findings

In the sub-sections that follow, I discuss the results of my thesis papers and their implications on research and clinical practice along the lines of three main themes: (1) the use of PIMs in older adults with multimorbidity and polypharmacy; (2) general practitioners' and patients' willingness to make deprescribing decisions respectively to have medications deprescribed; and (3) the conduct and the representativeness of the OPTICA trial, including challenges related to the implementation of its study intervention, the STRIP assistant, a CDSS with the aim of optimizing medication use in older adults.

9.2.1 Interpretation and Implications of the Use and Prescribing of Potentially Inappropriate Medications in Older Adults with Multimorbidity and Polypharmacy

In *Section I* of this thesis, I presented evidence related to the use and prescribing of PIMs specifically in older adults with multimorbidity and polypharmacy. This evidence is crucial for designing interventions with the aim of optimizing medication use in this patient group.

In *Article I*, we showed that the use of PIMs in older adults with multimorbidity and polypharmacy is high. Contrasted with previous research, which mostly focused on PIM use in older adults more broadly, in specific settings, or older adults with specific chronic conditions [46,208-212], the results presented in *Article I* suggest that the use of PIMs is even higher in in older adults with multimorbidity and polypharmacy. These results demonstrate the continued need for screening for PIMs and medication optimization interventions, including deprescribing, in this patient group. This is particularly relevant in light of the association between PIM use and different adverse outcomes in older adults.

Further, in *Article II* we showed that there are significant direct costs associated with the use of PIMs. Hence, if these PIMs were deprescribed there could be a double cost reduction, as not only the costs related to the adverse events caused by the use of PIMs could be prevented, but also the direct medication costs associated with PIM use could be saved. In the context of the globally rising number of older adults with multimorbidity and polypharmacy together with the clinical consequences of PIM use this is an important argument to consider. Finally, *Article I* also showed that in this patient group nonsteroidal anti-inflammatory drugs, endocrine medications, benzodiazepines and other central nervous system drugs, and proton-pump inhibitors were the most commonly used PIMs in this patient group. This is in line with previous research [46-48,94,212]. These findings on the most commonly used PIMs should be used to direct the focus of medication optimization and deprescribing interventions in older adults with

multimorbidity and polypharmacy. Regular screenings for PIMs, such as screenings by GPs or pharmacists, should be integrated into usual care.

In *Article II*, we found that several patient factors were associated with the new prescribing of PIMs in PIM-naïve older adults with multimorbidity and polypharmacy (i.e., male sex, ambulatory visits, number of prescribing orders, heart failure, age). We noted that patients who were prescribed a new PIM during the follow-up period were slightly sicker and had a higher health services use. These patients can thus be considered as being more complex patients from a clinical perspective. Further, *Article II* also showed that central nervous system drugs, cardiovascular drugs, anticholinergics, and endocrine drugs were the medications that were most often prescribed as a new PIM during the follow-up period. These patient factors and types of new PIMs should be considered when designing policies and interventions designed for healthcare professionals to prevent the new prescribing of PIMs in this patient group.

In *Article II,* the relatively low percentage of patients being newly prescribed a PIM (2.5%) could be because older patients with polypharmacy and multimorbidity, who did not use nor were prescribed a PIM in the 180-day baseline period, are a very specific, selected group of patients and may differ from those who were already using PIM(s). To the best of our knowledge, previous research projects on factors associated with the prescribing of PIMs did not restrict their analyses to PIM-naïve older adults. Further, most of the previous studies had a cross-sectional study design, whereas we performed a time-to-event analysis. In addition, when reviewing the existing literature, I noticed that the terms “prescribing of potentially inappropriate medications” and “use of potentially inappropriate medications” are used inconsistently. The differences in study design and inconsistency in definitions use comes with challenges and limitations related to the interpretation and comparisons of study results. To give an example: while we found female sex to be associated with PIM use in our cross-sectional analyses (*Article I*), we found male sex to be associated with new PIM prescribing in our time-to-event analysis (*Article II*). At first glance, these results may seem contradictory. When considering the differences in study design and definitions (PIM use vs. PIM prescribing, in PIM-naïve population vs. in all older patients with polypharmacy and multimorbidity), however, these differences could be explained and plausible. Consequently, despite the need for the factors associated with PIM prescribing to be studied further, these factors merit to be considered when designing medication optimization interventions. Helping healthcare professionals to target patients at highest risk of being prescribed a PIM could help reducing PIM use and avoid the associated adverse events and costs.

As an implication of the findings from this section, there is a need for developing interventions targeted at reducing PIM prescribing and PIM use in older adults with multimorbidity and polypharmacy. To do so, there is an opportunity of using factors associated with the prescribing and utilization of PIMs in this patient group when designing such interventions. Targeting medication optimization interventions to the patients at highest risk of using PIMs and based on the most commonly used PIM, could be a crucial factor for the implementation and long-term efficacy of such interventions.

9.2.2 Interpretation and Implications of the Willingness to Make Deprescribing Decisions in Both General Practitioners and Older Patients with Polypharmacy

In *Section II* of this thesis, I presented evidence related to the willingness of GPs to make deprescribing decisions in older patients with polypharmacy and different levels of functional dependency in ADL as well as with and without history of cardiovascular disease. This information is crucial as we can use this information when designing interventions designed to help healthcare professionals to optimize medication use and perform deprescribing in older adults with polypharmacy. Below, I discuss the findings from my thesis articles and the other articles that I contributed to as a co-author during my PhD (refer to *Section 15* 'Supplementary Chapters').

In *Article III*, we showed that GPs' willingness to make deprescribing decisions in older adults with polypharmacy is high. In our cross-sectional case vignette study, >80% of GPs from 31 countries reported that they would deprescribe ≥ 1 medication in patients aged ≥ 80 years of age with polypharmacy. Their willingness to make deprescribing decision was high irrespective of whether the patient had a history of cardiovascular disease. Hence, despite some variation across countries, the overall reported willingness to make deprescribing decisions was consequential. We found that the odds of GPs making deprescribing decisions were higher in patients with an increased level of functional dependency in ADL (e.g. more dependent patients) and lower when a history of cardiovascular disease was present. While we had some evidence that not only patient characteristics, but also some GP characteristics (e.g., age) were associated with making deprescribing decisions, we did not find any evidence for other GP characteristics being associated with deprescribing decisions (e.g., number of consultations, sex).

The medications that GPs were most willing to deprescribe in the presented case vignettes (both with and without cardiovascular disease) were pain medications and proton-pump inhibitors. We observed that while GPs were most likely to deprescribe cholesterol medication used in absence of cardiovascular diseases (primary prevention), they reported to be less like to make deprescribing decisions related to cholesterol medication in patients with history of cardiovascular disease (secondary prevention). These findings are in line with the results of a different sub-study of the LESS project, in which we investigated GPs' willingness to make deprescribing decisions in oldest-old (>80 years), frail patients with polypharmacy (refer to *Section 15.1.1*). In this study, we found that GPs reported to be willing to make deprescribing decisions for preventive cardiovascular medications in cases in which patients did not have a history of cardiovascular disease. Most GPs, however, reported that they would not

deprescribe any of the pain medications [170]. In *Article III*, GPs also reported that the following factors important or very important for making deprescribing decisions: “patients’ quality of life, patients’ life expectancy, fear of potential negative health outcomes resulting from deprescribing, and the risks and benefits of medications” (p. 6) [169]. This is in line with previous research [118,119].

To the best of our knowledge, the study reported in *Article III* was the first study investigating deprescribing decisions in such a large number of different countries. Due to the social desirability bias, our findings however likely over-estimate the overall willingness to make deprescribing decisions. Further, since this study was about hypothetical deprescribing decisions, GPs may not have been faced by the same barriers as in real clinical practice. This may also have contributed to an over-estimation of the overall willingness to make deprescribing decisions. Nevertheless, the information that the findings provided on what type of patients GPs are willing to deprescribe in (e.g., patients with higher level of functional dependency in ADL and patients without history of cardiovascular disease) is crucial for designing successful deprescribing interventions that utilize and build on GPs pre-existing willingness to make deprescribing decisions. As GPs’ hesitancy and uncertainty is often a major barrier to making deprescribing decisions, identifying patients who have specific characteristics (e.g., no history of cardiovascular disease) or who take certain medications (e.g., proton pump inhibitors) may be helpful for GPs to identify patients in which they would be confident to make deprescribing decisions.

A systematic review of studies related to GPs’ willingness to make deprescribing decisions in patients with multimorbidity and polypharmacy found that the barriers and enablers to deprescribing faced by GPs concern different levels: individual level, interpersonal level, organizational level, and cultural level [119]. To give an example of the interconnectedness of the different levels: while we have growing evidence that deprescribing seems to be safe, most guidelines do not address deprescribing, which makes it challenging for GPs adhering to guidelines to perform deprescribing. In addition to this, work processes commonly do not provide a support system for physicians that allows them to talk about deprescribing with other healthcare professionals [213]. Consequently, when designing future deprescribing interventions we have to make sure that barriers and enablers on all these four levels are addressed in a way that acknowledges their interconnectedness.

There are, however, not only major challenges to deprescribing on the GP side, but also on the patient side. In *Article IV*, we report the willingness of patients aged ≥ 65 years and over with multimorbidity and polypharmacy who took part in the OPTICA trial. More than 80% of patients reported that they were willing to deprescribe ≥ 1 medication(s) if their GP said this

was possible. More than 90% of the patients reported to be satisfied with their current medication intake. Overall, we observed a high involvement in medication use in the OPTICA study participants and relatively low concerns about stopping their medications. These findings are very similar to the results from the cross-sectional LESS study, in which we investigated the willingness to have medications deprescribed in a Swiss sample of older patients (aged ≥ 70 years) with polypharmacy (≥ 5 long-term medications) [113,185]. Please refer to the supplementary chapters of this thesis for the manuscripts on the patient-related part of the LESS study (*Section 15.1.2* and *Section 15.1.3*). Further, these findings are in line with previous studies conducted in other countries, such as Australia, Singapore, and the United States [114-116]. Overall, this shows that there seems to be a high willingness to have medications deprescribed older patients with polypharmacy[8], which does not seem to differ from older adults more broadly. However, it remains crucial to study further the patient group of older adults with multimorbidity and polypharmacy, as they may be at the highest risk of PIM use and the associated adverse events.

Qualitative findings can help explain the quantitative findings. As shown by the literature, a systematic reviews has synthesized the results from qualitative studies on patients' attitudes towards deprescribing [214]. The evidence on the willingness of specifically older adults with multimorbidity and polypharmacy, however, remains scarce. Nevertheless, some qualitative studies have already explored the willingness to have medications deprescribed in this specific patient group. For instance, there was one qualitative study with older adults who rejected a deprescribing suggestion during their participation in a clinical trial [112], a focus group study with older adults with polypharmacy on deprescribing cardiometabolic medications [215], and a focus group study with community-dwelling adults aged ≥ 65 with polypharmacy [216]. These studies also found patients to be generally open to making deprescribing decisions, but at the same time revealed major barriers to deprescribing (e.g., inertia, fear of stopping, etc). Information about patients' willingness to have medications deprescribed and the knowledge gained on concerns about deprescribing, medication burden, and involvement in medication use are crucial elements for designing and implementing deprescribing interventions that fit patients' needs. In particular, combining qualitative and quantitative evidence on patients' attitudes towards deprescribing will be crucial for the future development and implementation of deprescribing interventions.

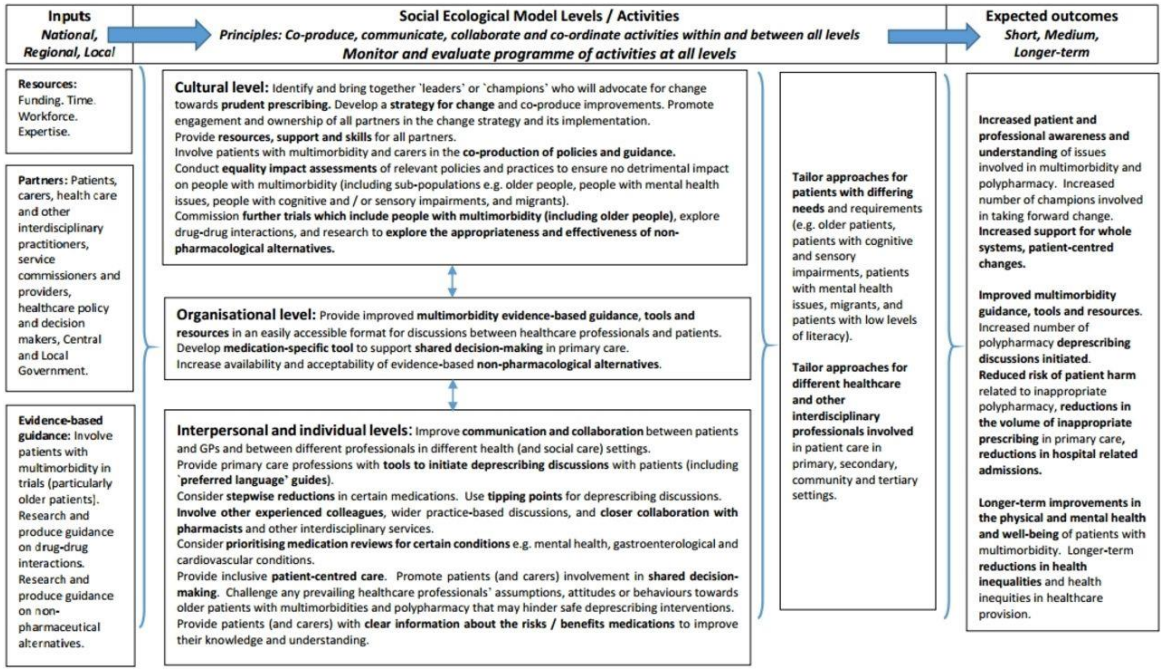
In their systematic review, Doherty et al. propose a 'Logic Model' which illustrates the types of inputs and activities, which are required within the four levels (*cultural, organizational,*

[8] The term "to deprescribe" speaks more to the prescriber side, as it refers to the act of prescribing, which is done by healthcare providers rather than the patient himself/herself. When talking about the patient side of deprescribing, it is preferable to use the terms "to have medications deprescribed".

*interpersonal, and individua*l) to “bring about whole systems change and desired outcomes for safe deprescribing in primary care” (p. 9) (*Figure 7*) [119]. This Logic Model shows that substantial change is needed on the different levels so that deprescribing interventions can be successfully and efficiently implemented in the future. Further, it demonstrates that patient and GP factors are closely intertwined, as patients must be partners in all activities related to deprescribing. Further, we know that multiple barriers faced by GPs are also faced by patients (e.g., fear of negative consequences, difficulties to start “deprescribing discussions”, etc.). This shows that designing deprescribing interventions in older patients with multimorbidity and polypharmacy requires integrating both inputs from GPs and patients. Especially in light of the difficulties arising when trying to implement deprescribing practices in routine clinical care, the simultaneous work on both patient and GP barriers and enablers to deprescribing could be the missing key to success. To put it differently, the lack of integrating both patient and physician preferences and priorities related to deprescribing may be one of the reasons why past deprescribing often were difficult to implement in a sustainable way.

As an implication of all these findings, designing deprescribing interventions that build on and combine GPs’ and patients’ attitudes towards deprescribing, could be a crucial factor for the implementation and long-term efficacy of such interventions. In the context of the difficult translation of deprescribing from research to routine clinical practice, exploring new approaches, which may give patients’ attitudes and preferences a more prominent role in making deprescribing decisions, is warranted.

Figure 7. Logic model showing the types of inputs, activities, and interconnectivities needed for system change and safe deprescribing in primary care



Source: 'Doherty AJ, Boland P, Reed J, Clegg AJ, et al. Barriers and facilitators to deprescribing in primary care: a systematic review. BJGP Open 2020; 4 (3): bjgpopen20X101096.'

9.2.3 Interpretation and Implications of the Findings Related to the Conduct of the 'Optimizing PharmacoTherapy In older multimorbid adults with polypharmacy in primary CAre' (OPTICA) Trial

In this section, I will first discuss three aspects related to the conduct of the 'Optimizing PharmacoTherapy In older multimorbid adults with polypharmacy in primary CAre' (OPTICA) trial, a cluster randomized controlled trial conducted in the Swiss primary care setting. First, the external validity of the OPTICA trial and the representativeness of study participants. Second, the recruitment of patients for the trial. Third, the implementation and use of the 'Systematic Tool to Reduce Inappropriate Prescribing' (STRIP) assistant during the OPTICA trial. Subsequently, I will provide an update on the current status of the OPTICA trial (as of February 2021).

9.2.3.1 Representativeness

Article V in this thesis showed that achieving a good external validity was possible in a Swiss primary care trial with participating GPs and older adults with multimorbidity and polypharmacy. Despite our initial concerns, this shows that we did not seem to have recruited a highly specific sub-group of GPs and patients for this trial. This information is not only crucial for the future interpretation of the OPTICA trial results and the wider applicability of the study intervention in Swiss primary care, but also for future clinical primary care research in Switzerland. For the variables that differed between FIRE and OPTICA participants, the absolute standardized differences were generally around 0.2 (or 20%). Despite an imbalance of the two groups having previously been defined as >0.2 [189], I would like to argue that a difference of 20% was acceptable was based on an assumption we made as a study team. Using a lower threshold (e.g., 0.1 or 10%), however, would not have changed our overall conclusions related to the external validity of the trial and the representativeness of study participants.

A major advantage of the OPTICA trial was our close collaboration with the FIRE project, which allowed us to compare the characteristics of GPs and patients to a real-life cohort. Despite this, I would like to discuss the implications of having compared OPTICA trial participants to GPs and patients from the FIRE project. First, despite the FIRE project database being the largest and continuously growing database with EHR data in Switzerland, it comes with certain limitations. The participation in the FIRE project is not mandatory nor possible for all Swiss GPs. It requires the use of certain EHR systems in the GP office. Further, GPs who work with compatible EHR systems have to self-select to participate in the FIRE

project. Consequently, the FIRE database contains data from a selection of Swiss GPs only. Despite this, based on two recent studies on the Swiss GP workforce we were able to show that GPs participating in the FIRE project are similar to the entire Swiss GP workforce (e.g., age, sex, work experience as GP) [174,217]. These comparisons allowed us to make our claims about the good external validity of the OPTICA trial with regards to the GPs participating in our trial.

Our results also showed a good representativeness of the patients enrolled into the trial. However, our comparisons were limited to the administrative EHR data available in the FIRE database. Consequently, since for instance information about cognition is not included in the FIRE database unless GPs code the diagnoses using the ICPC-2 tool, which is only done by a minority of participating GPs, we were not able to compare whether the number of OPTICA study participants with cognitive impairment compares to the number in the FIRE database. In the context of the underrepresentation of this patient group in clinical research, this would have been an interesting and relevant comparison. Further, due to nature of the data in the FIRE database, we were not able to compare the quality of care provided by all GPs and the GPs participating in the OPTICA trial. Despite the shortcomings of the FIRE project database, we are confident about the conclusions we drew in *Article V* about the overall external validity of the OPTICA trial and the representativeness of study participants.

However, in spite of the promising results related to the representativeness of the OPTICA trial participants, challenges related to the recruitment and retention of GPs persist. During my PhD, we have published a non-peer-reviewed article in a journal commonly read by Swiss GPs, in which we summarized a couple of recommendations for the recruitment of GPs for research, based on the existing evidence (refer to *Section 15.2* 'Non-Peer-Reviewed Publications') [218]. *Table 5* summarizes our recommendations. Next, concerns raised in the literature are that GPs participating in research often do not get any feedback about the different steps of the research project they are involved in nor are they provided with all the relevant information after their active participation is over [161]. It is thus recommended to inform GPs about their patient selection and enrolment (e.g., did they pick the right patients?), to share the results of clinical trials once they are available, and to give GPs professional recognition for their involvement in clinical research. Providing the necessary assistance to GPs and acknowledging their effort is crucial for keeping GPs motivated to participate in clinical research.

Not only GP recruitment, but also the recruitment of older adults with multimorbidity and polypharmacy for research projects remains challenging. Based on the existing literature, I propose the following approaches to facilitate the participation of older adults with

multimorbidity in clinical research, while of course protecting the rights and needs of older patients, in particular the most vulnerable ones (e.g., older adults with cognitive impairment):

i) to develop best practices and standardize research protocols to facilitate the inclusion of older, multimorbid adults,

ii) to establish and reinforce guidelines that require age-related and/or disease-related pharmacokinetic and safety disclosures on all approved medical products, which requires clinical research to be conducted in this patient group.

iii) to employ age-friendly methods of communication in research (e.g., age-appropriate information and consent forms, which are adjusted to literacy levels),

iv) to support geriatric education and training for researchers conducting clinical research with older adults,

v) to improve monitoring by regulatory authorities and accountability with regards to the use of new medical products in older, multimorbid adults

vi) to use different outcomes that are relevant for older, multimorbid adults (e.g., measures of functional independence may be more relevant than using outcomes like survival or time-to-event)

vii) to make extra funding available to account for challenges in the recruitment and the retention of older, multimorbid adults

(list based on and adapted from Herrera et al, 2010 [142], Habicht et al, 2008 [219], and van Marum, 2020 [143])

Table 5. Tips for the recruitment of general practitioners for research projects.

- to have GPs as part of the study team [159,220]
- to invest enough time and resources into the recruitment process [221]
- to reach out to GPs early in the recruitment process to let them express interest [159], first by written communication and then follow-up by phone, if needed
- to organize in person meetings between GPs and researchers [159,160,220]
- to provide detailed information about the conduct of the study and the feasibility of the study participation [221]
- to provide detailed information about the tasks that would have to be done by participating GPs, if they participated in the research, and how these tasks could be integrated into daily practice [159,160]
- to provide information about financial reimbursement of GPs [157,222]
- to provide information material [159,221]
- to answer to specific questions and issues raised by GPs, find solutions for potential barriers to a study participation [158]
- to give GPs time to think about the study participation [159]
- to implement suggestions for improvement made by GPs

Translated and adapted from: 'KT Jungo, A Löwe, S Mantelli, R Meier, N Rodondi, S Streit. Klinische Studie zur Medikamentenoptimierung bei älteren Patient/-innen mit Polypharmazie: Die OPTICA-Studie. Prim Hosp Care Allg Inn Med. 2018;18(06):100-102.'

9.2.3.2 Differential Recruitment

In *Article V*, we were able to show that patients recruited from the screening lists and those identified by GPs were similar, which provides some evidence against differential recruitment. In the OPTICA trial, roughly two thirds of patients were recruited based on the screening lists that we provided to GPs and around one third of patients was identified by their GP.

We had provided the screening lists to GPs in an attempt to standardize recruitment. However, for the following reasons we had also given GPs the option to identify other patients, who fulfilled all the inclusion and exclusion criteria. First, the screening lists based on FIRE data were imperfect and may not have included all potentially eligible patients (e.g., due to lag between time of export and sending to screening list to GPs: some patients newly having polypharmacy, patients recently turning 65 years old, patients deceased). Second, in some GP offices, who had recently switched to electronic health records or who had only recently started to export data to the FIRE project), had very short screening lists of potentially eligible patients. Third, some patients on the list may have been absent or generally see their GP only a couple of times a year. Due to this, after (if possible) sending two screening lists to GPs, we allowed them to identify eligible patients themselves in order to meet their recruitment target.

Due to the selection bias/differential recruitment concerns stated in the OPTICA protocol paper, we were relieved to see in our analyses that the two types of recruited patients (from screening lists vs. identified by GPs) were comparable in terms of sociodemographic and clinical characteristics. However, I also have to acknowledge that we were not able to compare the two groups in terms of patient-provider relationship and other unmeasured patient characteristics, which may have been important determinants of patient recruitment, but which were not measured in the OPTICA trial nor the FIRE project database.

9.2.3.3 Implementation of the 'Systematic Tool to Reduce Inappropriate Prescribing' (STRIP) Assistant during the OPTICA Trial

Our mixed-methods study on the implementation of the 'Systematic Tool to Reduce Inappropriate Prescribing' (STRIP) assistant during the OPTICA trial showed that GPs generally showed a good acceptance of this tool. Overall, they reported that they appreciated that the tool was able to help them manage a large amount of data. However, this study also revealed major implementation challenges ranging from the significant expenditure of time to technical problems and challenges related to the implementation of the recommendations generated by the STRIP assistant. The qualitative part of the study allowed us to explain and further explore the reported low implementation rate of the recommendations, which we found in the quantitative part of the study. Overall, the implementation barriers we found were in line with previous research [200,201,207] and thus seem to be inherent to the use of electronic CDSS. From the results of our study, it became clear that in the form it is now, the STRIP assistant would not be suitable for a broader implementation. Consequently, the implementation challenges put forward in the OPTICA protocol paper were confirmed by the results of our mixed-methods study. However, it remains to be analyzed how the limited implementation of the study intervention has affected our main study results. Further, the use of the STRIP assistant during the OPTICA trial will have to be compared to process evaluations conducted in other trials testing the STRIP assistant (e.g., OPERAM trial). However, these research findings have not yet been published.[9]

Despite revealing significant implementation challenges related to the use of the STRIP assistant during the OPTICA trial, our findings provide important insights for adapting this electronic CDSS in the future in an attempt to make it more suitable for use in routine clinical care in the primary care setting. Based on our findings and insights from the literature, I would like to put forward the following suggestions:

i) to work on the intersection between the data source and the electronic CDSS. Developers of the EHR systems used in Switzerland should work on implementing industrial standards that would make different EHR systems compatible with one another and electronic CDSS, as this would allow the future use of such tools.

ii) to the extent possible, and maybe by using artificial intelligence, tailor the electronic CDSS to the needs of GPs (e.g., how often alerts are shown to counteract alert fatigue, what medication types they would like to focus on)

[9] This is based on personal communication, which I received due to my role as the administrator of the OPERAM trial publications committee.

iii) to provide more information and specific training sessions on how to conduct a shared-decision making process with patients based on the recommendations generated by an electronic CDSS to give patients a more central role in the medication optimization process

9.2.3.4 Current Status of the 'Optimizing PharmacoTherapy In older multimorbid adults with polypharmacy in primary CAre' (OPTICA) Trial

In *Article IV* of this thesis, I presented the protocol of the 'Optimizing PharmacoTherapy In older multimorbid adults with polypharmacy in primary CAre' (OPTICA) Trial, which is a cluster-randomized controlled trial with Swiss GPs and older patients with multimorbidity and polypharmacy. The recruitment of GPs for this trial started in autumn 2017 by conducting GP office visits. The regulatory authorities approved the trial in August 2018. In November 2018, the trial was approved by the competent ethics committee in the Canton of Bern, Switzerland. Patient recruitment started in December 2018 and ended in February 2020. In total, 43 GPs were randomized: 21 to the intervention group and 22 to the control group. On average, participating GPs recruited 7.5 of patients for the trial. Overall, 160 patients were in the intervention group and 163 were in the control group. The 1-year follow-up of patients ended in February 2021. The study assessment of our co-primary outcomes, Medication Appropriateness Index (MAI) and Assessment of Underutilization (AOU), are currently ongoing. We expect the analysis of our trial results for 2021. The health economic analyses embedded in the OPTICA trial, which will investigate the cost-effectiveness of the use of the STRIP assistant, are also planned for the year 2021.

The following limitations were addressed in the protocol paper: differential recruitment/selection bias, contamination of GPs in the control group who are supposed to provide usual care, outcome assessments based on data from the FIRE project database, implementation of the STRIP assistant intervention, and potential imbalances between study groups due to cluster randomization. Further, we had discussed the mono-professional nature of the intervention and the fact that the co-primary outcomes (MAI and AOU) were not directly patient relevant, but there are patient-relevant outcomes among the secondary outcomes, which can be analyzed later. Our analyses will allow us to investigate how the usual care took place in the intervention group. In other words, since we asked GPs to document what was done during the sham intervention, we will be able to explore how many medication changes were done and how the medication appropriateness changed in control group patients. Similarly, our data analysis will show whether we achieved balanced study groups despite the cluster randomization and whether our study intervention had an effect on patient-relevant outcomes (e.g., quality of life).

Despite several issues that remain uncertain before the completion of the data analysis, we were already able to get an insight into several questions. First, despite some challenges with the EHR data from the FIRE project database for our MAI and AOU study assessments (e.g., missing ICPC-2 diagnosis codes), we found in a first inter-rater reliability assessment based

on baseline data, that the MAI and AOU assessments were usable. This assessment found an agreement of MAI ratings of 67% (Intraclass correlation coefficient (ICC) = 0.52, 95% CI 0.39-0.63) and an agreement of AOU ratings of 80% (Irincheeva et al., 2020, internal communication). The inter-rater reliability assessment at the time point of follow-up 1 (6 months after patient enrolment into the trial), found am agreement of MAI ratings of 66% (ICC = 0.73, 95% CI 0.64-0.81) (Stalder et al., 2021, internal communication). No AOU inter-rater reliability assessment for the follow-up 1 was done as of February 2021. An ICC between 0.5 and 0.75 has previously been reported as moderate reliability, whereas an ICC between 0.75 and 0.9 is considered as a good reliability [223]. The second ICC assessment shows an improvement related to the agreement among reviewers. We interpret this improvement as a consequence of the weekly assessment meetings, which are held by the OPTICA study assessment team. Further, in *Article V*, we were able to investigate whether there was any differential recruitment in the recruitment phase of the OPTICA trial (refer to *Section 9.2.3.2*). Finally, *Article VI* explored the implementation of the STRIP assistant intervention (refer to *Section 9.2.3.3*).

An additional challenge that came up in the OPTICA trial was related to the approval of this trial. To provide some context, in the OPTICA trial, the trial structure was different to “traditional clinical trials” with GPs performing the patient recruitment and informed consent procedure, but also acting as a study participant testing the intervention on their own patients. This special “dual” role of general practitioners within the trial did pose some challenges during the approval process of the trial. For instance, in order to be able to perform these tasks during the trial, all GPs participating in the trial needed to perform a Good Clinical Practice (GCP) course. In Switzerland, such GCP courses are offered by clinical trial units, which are located in Swiss universities. The participating GPs in the OPTICA trial were located in multiple Swiss cantons, which is why it would not have been possible for them to attend a GCP course at the university of Bern in due time. In order to facilitate their conduct of the GCP course and in discussion with the competent ethics committees, we negotiated the right to create an online GCP course for participating general practitioners. This online course was tailored to the needs of the participating general practitioners (e.g., recruitment and informed consent, safety reporting, etc.) and with regards to these items covered all aspects required by GCP and the competent ethics committee [164]. The process of creating this online GCP training was time-consuming, but the advantage is that other study teams planning and conducting primary care trials in Switzerland are now also able to use this course.

Since I wrote the protocol paper, some additional challenges came up. First, the time needed for the outcome assessments is significant. This is important for planning the timeline of the end of the study. Second, the global COVID-19 pandemic may have affected certain aspects

of the OPTICA trial conduct. While it did not affect the recruitment of the trial (with recruitment being terminated right at the onset of the global COVID-19 pandemic), it may have affected the conduct of the study intervention in the last clusters randomized to the intervention arm. This, however, would have only concerned one single GP and his patients. Luckily, there were no in-person data collection visits in the OPTICA trial, which is why the data collection continued by phone during the COVID-19 pandemic. However, since for several patients the follow-up period took place during the COVID-19 pandemic, the pandemic may have affected their health services use, which we may see in our analyses. Both study groups would be affected by this equally though.

Despite all these challenges, the OPTICA trial remains the first randomized controlled trial with the aim of investigating the effect of the STRIP assistant intervention on medication use in older patients with multimorbidity and polypharmacy in the primary care setting. Its results will be important for guiding the future implementation and use of electronic CDSS in Switzerland's primary care. Further, since the OPTICA trial is the first trial testing a software-based structured medication review based on data from electronic medical records in Swiss primary care, it has the potential to prove the usefulness of coding and linking data from electronic health records and their use for the conduct of pragmatic trials.

9.3 Strengths and Limitations of the Work Presented

There are both strengths and limitations connected to each of the thesis articles presented in this thesis. In this section, I discuss these strengths and limitations, by addressing not only the strengths and limitations of the individual thesis articles, but also by describing the overall strengths and limitations of my thesis.

9.3.1 Strengths

In my thesis work, I used multiple study designs and research methods. I worked with different types of data, both qualitative and quantitative, data from different countries, and addressed different research questions related to the medication use of older adults with multimorbidity and polypharmacy. Hence, the main overall strength of this thesis is that it provides insights into different aspects related to optimizing medication use in older adults with polypharmacy and multimorbidity from different methodological standpoints.

Related to *Section I* of my thesis (*Article I and Article II*), I would like to emphasize that we were able to use data collected throughout a period of eight years from an entire health network in the Boston metropolitan area. The fact that we were able to restrict our analyses to patients with a certain level of data completeness in the electronic health records helped to reduce information bias. Further, the data we used for the articles presented in this section have the limitations like any other EHR data. For instance, there is the informed presence bias, which means that patients in EHR are inherently different from those who are not in it, as they may have presented due to receiving particular medical services or having certain conditions [224]. In our case, however, since we focus on patients with multimorbidity and polypharmacy this bias is assumed to be less problematic than in a case in which we would also have healthier patients in our sample, who commonly have less contacts with the healthcare system. Next, despite our ability to compare eight years, *Article I* comes with the limitations of any cross-sectional study (e.g., since exposure and outcome were collected simultaneously there is no evidence of a temporal relationship between outcome and exposure). The retrospective cohort study design used in *Article II* has the advantage that information on covariates and the exposure was collected before the outcome, which allowed to consider the temporal relationship between outcome, exposure and covariates in our analyses. Further, restricting our analyses to patients who were not prescribed nor used a PIM during the baseline period, allowed to analyze the new prescribing of PIMs.

Article III, which presented the results of the cross-sectional case vignette study on GPs' deprescribing decisions, had the advantage of including 31 different countries. To the best of

our knowledge, this is the largest number of countries compared in a deprescribing study. In addition, the study was strengthened by its high response rate. Overall, the LESS study had the advantage of not only collection information on GPs' deprescribing decision, but also to collect information on patients' willingness to have medications deprescribed. Combining information from both GP and patient perspectives on deprescribing is crucial for the future development and implementation of successful deprescribing interventions.

Concerning the conduct of the OPTICA trial, presented in *Article IV to Article VI*, I would like to emphasize the following strengths. Thanks to the OPTICA sub-studies, which I conducted during my PhD work, we were able to investigate important aspects related to the implementation of the trial intervention and the external validity of the trial further. The mixed-methods approach used to study the use of the STRIP assistant during the OPTICA trial and the triangulation of quantitative and qualitative findings allowed for gaining a better, in-depth understanding of the implementation challenges faced by GPs. We were able to show that conducting a clinical trial in the primary care setting with commonly underrepresented patient groups is possible in Switzerland. The interpretation of the results of the OPTICA trial will be strengthened by the fact that we found a good external validity of the trial. Finally, I would like to emphasize the close collaboration between the OPTICA trial and the FIRE project as a strength of this primary care trial. This collaboration not only allowed for a more pragmatic approach to data collection and study assessments, but it also allowed comparing the trial participants with GPs and patients from a in Switzerland unique real-world cohort.

9.3.2 Limitations

The main overall limitation of this thesis is that for feasibility and time-related reasons it does not include the main results of the OPTICA trial nor the results of the cost-effectiveness analyses that will be conducted. In my early postdoctoral research, however, I will continue working on these analyses. Further, multimorbidity was defined as a count of chronic conditions in my thesis papers. This approach, however, comes with the limitation that it does not consider the severity of the individual conditions nor other cognitive or functional limitations that they patients may have.

There are a couple of limitations related to *Article I and Article II*, which I would like to discuss. Both studies were observational in nature, so residual confounding cannot be excluded, as there are unmeasured or inadequately measured confounders in the administrative data (e.g., claims data and data from electronic health records used) that we used for our analyses. The data used for these two articles is from a couple of years ago, which, however, is partly due

to due to a lag in data acquisition and linkage. Next, due to missing data on certain patients (e.g., who left the healthcare network) there may have been selection bias. Indeed, patients who stay in the network over a longer period may be different from those outside of it. In addition, access to healthcare may be higher in the Boston metropolitan area compared to other part of the United States, despite the demographic makeup of this area having been shown to be similar to other regions in the United States [225]. In both articles there were some limitations related to the definition of the outcome and other variables. First, due to the explicit, criterion-based nature of the Beers criteria some medications may have been identified as potentially inappropriate even though they were appropriate based on physicians' judgments. Second, our approach used to identify patients with multimorbidity and polypharmacy may have misclassified some patients. Third, having information on prescribers was not available in the CMS-RPDR dataset, which we worked with on the Aetion platform. This information would have been helpful, especially in *Article II*. Further, we were not able to take over-the-counter medication into account. This limitation may have affected the identification of PIMs and the definition of PIM-naïve patients. Next, we decided to use the 2019 version of the Beers criteria, rather than previous versions, to inform current medical decisions making. Since our data, however, was from 2007 to 2014 this selection certainly has to be mentioned as a limitation. Finally, this is rather an acknowledgment than a limitation, but I would like to emphasize that the two articles in *Section I* of this thesis were conducted based on data from the United States, whereas the other articles presented in this thesis were conducted in Europe or Switzerland specifically.

The studies on deprescribing presented in this thesis (*Article III* and the manuscripts in the supplementary chapters, *Section 15.1.1*, *Section 15.1.2*, and *Section 15.1.3*) all come with the limitation of cross-sectional studies, in which we collected all the information at one moment in time. Next, due to the simple nature of questionnaires administered to GPs and older patients, we were only able to measure a number of potential confounders. Because of how we recruited participants we cannot exclude selection bias. In the GP study, GPs were recruited from the networks of our national coordinators and not from random lists of GPs. This comes with limitations related to the generalizability of our findings. GPs self-selected to complete the online GPs, and GPs deciding not to participate may have been inherently different from those who decided to participate. In the patient study, GPs were instructed to consecutively screen and recruit potentially eligible patients. Despite this, selection bias cannot be excluded. Social desirability bias may also have played a role in both the patient and GP parts of the LESS study. Finally, due to the hypothetical nature of the deprescribing questions the LESS study may have overestimated GPs' and patients' willingness to make deprescribing decisions.

Overall challenges related to the conduct of the OPTICA trial is that during the study intervention there were significant implementation challenges, which may have affected the overall result of the trial. Further, the STRIP assistant intervention was designed as a single time-point intervention, which may also have affected its overall efficacy. Second, in the OPTICA trial we could have put more emphasis on training GPs how to conduct the shared decision making process, which could have gone beyond providing written instructions to GPs. This may have given patients a more central role in their medication use and this may have facilitated the implementation of the recommendations generated by the STRIP assistant. Next, as already mentioned above, there were limitations that were inherent due the FIRE database in *Article V*, despite the FIRE database being the best available option in Switzerland. Finally, the mixed-methods study on the implementation of the STRIP assistant during the OPTICA trial came with two main limitations. First, the qualitative data we collected is very context-specific and not generalizable. Next, we had a significant amount of missing data in the quantitative part of the mixed-methods study, as not all GPs provided the necessary information to us.

9.4 Future Research and Intervention Efforts

Several follow-up questions for future research emerged as a result of the articles presented in this thesis. For instance, future research on the use and prescribing of PIMs in older adults with polypharmacy and multimorbidity should make a clear distinction between PIM prescribing and PIM use. This distinction is crucial for the interpretation of study findings, since there lay steps in between being prescribed a medication and using this medication. Similar to the analyses presented in *Article II,* it would be interesting to explore what factors are associated with the use of PIMs in PIM-naïve older adults with multimorbidity and polypharmacy as compared to the prescribing of PIMs. In addition, it would be interesting to explore if and how the prescribing of the first PIM is associated with subsequent PIM prescribing.

Next, in light of the difficulties observed when translating deprescribing from research to routine clinical practice, it may be worth exploring how patient and GP characteristics found to be associated with making deprescribing decisions could be used and built on when designing deprescribing interventions. Patient and prescriber preferences and priorities related to deprescribing should be investigated, as they may differ, which in turn could be one of the reasons for the difficult implementation of deprescribing in routine care. Next, patients' willingness to have their medications deprescribed using electronic CDSS should be explored, which is why we are planning to explore this as an OPTICA sub-study. In addition, it may be interesting to explore patient-driven deprescribing in the Swiss primary care setting. Furthermore, I noticed that while many of the previous studies focused on challenges related to implementing, it might be worth exploring the factors associated with successful deprescribing decisions.

The main results of the OPTICA trial and the results of the cost-effectiveness analysis are expected for 2021. The end of the 1-year follow-up will end in February 2021 and we are currently working on the study assessments. Over the next couple of months, we will work on several additional OPTICA sub-studies. For instance, we will collaborate with the FIRE project to analyze the prescribing of PIMs in the OPTICA control and intervention groups and we will investigate whether the use of the STRIP assistant had a spill-over effect on the other patients treated by the GPs in the OPTICA intervention group who used the STRIP assistant during the trial. In addition, we will analyze whether the medication appropriateness changed in the control group due to the Hawthorne effect (e.g. their knowledge of participating in a trial related to medication use may have changed their prescribing behaviors).

Finally, I would like to emphasize the following avenues for future primary care trials with the aim of optimizing medication use in older adults. First, patient should receive a more prominent

role and patient-driven approaches to medication reviews and deprescribing should be explored. Patient reported outcomes measures (PROMs) should be used, if possible as primary outcomes. If feasible, inter-professional interventions should be designed, as this may increase the success rate of interventions (e.g., avoid that if one healthcare professional stops a medication, another restarts the prescription). The latter, however, may be limited by the structure of national/regional health systems. Finally, rather than proposing interventions that optimize all medication categories at the same time, it may be worth exploring interventions that explore step-by-step approaches to medication optimization in older adults with multimorbidity and polypharmacy.

9.5 Conclusions

In *Section I* if this thesis, I found high use and costs of PIMs in older adults with multimorbidity and polypharmacy. We found several patient factors to be associated with new prescribing of PIMs in older adults with multimorbidity and polypharmacy who did not use PIMs during the baseline period. As an implication of the findings in *Section I* of this thesis, I conclude that there is a need for developing interventions targeted at optimizing medication use in this population. Intervention design should leverage factors associated with the prescribing of PIMs in this group. Targeting medication optimization interventions to patients at highest risk of using PIMs and based on the most commonly used PIMs will be crucial for the implementation and long-term efficacy of such interventions.

In *Section II* of this thesis, I found a high willingness of GPs to make deprescribing decisions in older patients with polypharmacy. GPs were more likely to report hypothetical deprescribing decisions in patients with higher functional dependency in ADL and patients without a history of cardiovascular disease. As an implication of the findings presented in *Section II* of this thesis, I conclude that GPs as well as patients open to deprescribing, providing further evidence for the need to design and implement sustainable, effective deprescribing interventions. Particularly in the context of the reported difficulties to implement deprescribing decisions in clinical practice, developing interventions that give patients a more central role in the process may be a promising way forward.

In *Section III* of this thesis, I found that the patients and GPs participating in the OPTICA trial were comparable to those from a real-life cohort. I described the attitudes of GPs towards the use of the STRIP assistant and the implementation challenges they faced when they used this electronic CDSS during the OPTICA trial. As an implication of the findings presented in *Section III* of this thesis, I conclude that testing new medication optimization interventions in primary care trials with a good external validity is possible. However, the implementation of new electronic decision support systems may come with substantial challenges that must be addressed in order to facilitate future rollout of such tools. Conducting clinical research in the primary care setting with older adults with multimorbidity and polypharmacy requires the necessary resources to overcome the challenges that often render research in this setting difficult. More research and funding are needed to make the STRIP assistant more user-friendly, which will facilitate its future implementation.

In conclusion, the findings from this thesis add to the literature by providing insights on different aspects related to optimizing medication use in older adults with multimorbidity and polypharmacy. The research presented may provide some guidance for further studying

interventions to optimize medication use in this patient group, and thus ultimately for improving medication use in this patient group in clinical practice. In the context in which societies are ageing globally, multimorbidity and polypharmacy are becoming increasingly prevalent, and PIMs being a serious problem in older adults, these findings are particularly relevant.

10. Curriculum Vitae

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11. List of Publications

PUBLISHED PEER-REVIEWED ORIGINAL RESEARCH

i. **KT Jungo,** S Streit, J Lauffenburger. *Factors associated with the prescribing of potentially inappropriate medications in multimorbid older adults with polypharmacy: retrospective cohort study.* BMC Geriatrics. 2021: 21, 163.

ii. **KT Jungo,** S Streit, J Lauffenburger. Utilization and Spending on Potentially Inappropriate Medications by US Older Adults with Multiple Chronic Conditions using Multiple Medications. Archives of Gerontology and Geriatrics. 2021: 93.

iii. **KT Jungo,** S Mantelli, Z Rozsnyai, et al. *General Practitioners' Deprescribing Decisions in Older Adults with Polypharmacy: a Cross-Sectional Case Vignette Study in 31 Countries*. BMC Geriatrics. 2021: 21, 19.

iv. Z Rozsnyai, **KT Jungo**, E Reeve et al. *What do older adults with multimorbidity and polypharmacy think about deprescribing? The LESS study - a primary care-based survey*. BMC Geriatrics. 2020: 20, 435.

v. A Achterhof, Z Rozsnyai, E Reeve, **KT Jungo** et al. *Potentially inappropriate medication use and attitudes of older adults towards deprescribing*. PloS One. 2020: 15(10), e0240463.

vi. A Bhadhuri, P Kind, P Salari, **KT Jungo**, et al. *Measurement properties of EQ-5D-3L and EQ-5D-5L in recording self-reported health status in older patients with substantial multimorbidity and polypharmacy*. Health and Quality of Life Outcomes. 2020: 18, 317.

vii. C Roulet, Z Rozsnyai, **KT Jungo**, et al. *Managing hypertension in frail oldest-old – the role of guideline use by general practitioners from 29 countries*. PLOS ONE. 2020.

viii. **KT Jungo**, Z Rozsnyai, S Mantelli, C Floriani, A Löwe, F Lindemann, N Schwab, R Meier, L Elloumi, L Huibers, B Sallevelt, M Meulendijk, E Reeve, M Feller, C Schneider, H Bhend, P Bürki, S Trelle, M Spruit, M Schwenkglenks, N Rodondi, S Streit. *Design of 'Optimizing PharmacoTherapy In the Multimorbid Elderly in Primary Care' (OPTICA) to improve medication appropriateness: a cluster randomised controlled trial*. BMJ Open. 2019;9:e031080

ix. L Grummer-Strawn, F Holliday, **KT Jungo**, N Rollins. *Evidence of Sponsorship by Companies that Make Breast-milk Substitutes on the Websites of National and Regional Paediatric Associations*. BMJ Open. 2019: 10;9(8):e029035.

x. L Adam, E Moutzouri, A Loewe, M Feller, K M'Rabet-Bensalah, N Schwab, S Hossmann, C Schneider, S Jegerlehner, C Floriani, A Limacher, **KT Jungo**, L Huibers, S Streit, M Schwenkglenks, M Spruit, A van Dorland, J Donzé, P Kearney, P Jüni, D Aujesky, P Jansen, B Boland, O Dalleur, S Byrne, W Knol, A Spinewine, D O'Mahony, S Trelle, N Rodondi. *Rationale and design of OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people (OPERAM): a cluster randomised controlled trial.* BMJ Open 2019;9:e026769

xi. S Mantelli, **KT Jungo**, Z Rozsnyai, E Reeve, CH Luymes, RKE Poortvliet, A Chiolero, N Rodondi, J Gussekloo, S Streit. *How general practitioners would deprescribe in frail oldest-old with polypharmacy - the LESS study*. BMC Family Practice. 2018; 19:169

ORIGINAL RESEARCH PUBLICATIONS IN PEER-REVIEW

i. Y Rachamin, O Senn, S Streit, J Dubois, M Deml, **KT Jungo**. *Impact of the COVID-19 pandemic on the intensity of health services use in general practice: a retrospective cohort study (accepted for publication in the International Journal of Public Health on April 1, 2021)*

ii. **KT Jungo**, R Meier, F Valeri, et al. Baseline characteristics and representativeness of older multimorbid patients with polypharmacy and general practitioners participating in a randomized controlled primary care trial *(currently under review).*

iii. M Blum, W Knol, A Spinewine, D O'Mahony, … **KTJ Jungo** … S Trelle, N Rodondi. *Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Patients: the OPERAM Cluster Randomized Clinical Trial (currently under review)*

iv. **KT Jungo,** B Cheval, S Sieber, et al. *Life-course Socioeconomic Conditions, Multimorbidity and Polypharmacy in Older Adults: a Multi-country, Observational Cohort Study (currently under review)*

ORIGINAL RESEARCH PUBLICATIONS IN PROGRESS

i. **KT Jungo**, MJ Deml, F Schalbetter. et al. *A Mixed-Methods Analysis of the Use of the 'Systematic Tool to Reduce Inappropriate Prescribing' in Swiss Primary Care Practices (in preparation[10])*

ii. P Salari, C O'Mahony, S Henrard, (…), **KTJ Jungo,** (…), N Rodondi, M Schwenkglenks. *Cost-effectiveness of a software-assisted, structured medication review approach for multimorbid older people: within-trial analysis of the OPERAM study (in preparation)*

iii. C Liu, **KTJ Jungo**, et al. *Racial and ethnic differences in social support and social network among older adults in the United States: a systematic review and meta-analysis (in preparation)*

OTHER PUBLICATIONS

i. **KT Jungo,** D Anker, L Wildisen. *Astana declaration: a new pathway for primary health care*. Int J Public Health (2020).

ii. **KT Jungo**, F Lindemann, S Schwab, S Streit. Klinische Forschung in der Hausarztmedizin - welche Hürden gibt es vor dem Studienstart zu meistern? Prim Hosp Care Allg Inn Med. 2019;19(11):342-344.

iii. **KT Jungo**, A Löwe, S Mantelli, R Meier, N Rodondi, S Streit. *Klinische Studie zur Medikamentenoptimierung bei älteren Patient/-innen mit Polypharmazie: Die OPTICA-Studie*. Prim Hosp Care Allg Inn Med. 2018;18(06):100-102.

[10] This manuscript can only be submitted for publication after the main results of the OPTICA trial have been published.

12. List of Conference Presentations

ORAL PRESENTATIONS*

i. ‘Life Course Socioeconomic Conditions, Multimorbidity and Polypharmacy in Older Adults’, presentation at 16th World Congress on Public Health, Rome, Italy, 12-16 October, 2020, conference held virtually due to COVID19 pandemic, co-authors: **KT Jungo*,** B Cheval, S Sieber, Rose van der Linden, A Ilhe, C Carmeli, A Chiolero, S Streit, S Cullati.

ii. ‘Life Course Socioeconomic Conditions, Multimorbidity and Polypharmacy in Older Adults’, presentation at Swiss Public Health Conference, September 2-3, 2020, conference held virtually due to COVID19 pandemic, co-authors: **KT Jungo*,** B Cheval, S Sieber, Rose van der Linden, A Ilhe, C Carmeli, A Chiolero, S Streit, S Cullati.

iii. ‘Bringing together older multimorbid patients with polypharmacy, general practitioners, and eHealth: protocol of a cluster randomized controlled trial in Swiss primary care’, presented at the European General Practice Research Network (EGPRN) Meeting, Tampere, Finland, May 9-12, 2019, co-authors: **KT Jungo***, Z Rozsnyai, C Florniani, S Streit on behalf of the entire OPTICA Team.

iv. ‘An international case-vignette study to assess general practitioners’ willingness to deprescribe (LESS)’, presented at the European General Practice Research Network (EGPRN) Meeting, Sarajevo, October 4-7, 2018, **KT Jungo*** on behalf of the LESS Study Group.

v. ‘A Primary Care-Based Survey to Assess the Willingness to Deprescribe in Older Patients with Multimorbidity and Polypharmacy and their General Practitioners’: The LESS Study, presented at the Wennberg International Collaborative Spring Policy Meeting, Zurich, April 12-13, 2018, co-authors: **KT Jungo***, S Mantelli, Z Rozsnyai, E Reeve, R Poortvliet, A Chiolero, N Rodondi, J Gussekloo, S Streit.

POSTER PRESENTATIONS*

i. ‘A Mixed-Methods Analysis Of The Use Of The Systematic Tool To Reduce Inappropriate Prescribing In Swiss Primary Care Practices’, presented at the 36th annual meeting of the International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Berlin, Germany, initially planned for August 26-30, 2020, meeting held virtually September 16-17, 2020 due to COVID19 pandemic, co-authors: **KT Jungo***, F Schalbetter, M Deml, S Streit on behalf of the OPTICA team.

ii. ‘Would you stop or reduce medication in this oldest-old patient? A case vignette study in 31 countries to explore general practitioners deprescribing decisions in oldest-old patients with polypharmacy (the LESS study), presented at the 12th European Public Health Conference, Marseille, France, November 21-23, 2019: co-authors: **KT Jungo***, Z. Rozsnyai, S. Streit, on behalf of the LESS study group.

iii. ‘Would You Stop or Reduce Medication in This Older Patient? A Case Vignette Study in 31 Countries to Explore General Practitioners’ Willingness to Deprescribe in Old Patients with Polypharmacy (the LESS study)’, presented at the SSPH+ Lugano Summer School in Public Health Policy, Economics and Management, Lugano, Switzerland, August 29-31, 2019: co-authors: **KT Jungo***, Z. Rozsnyai, S. Streit, on behalf of the LESS study group.

iv. ‘Barriers and Enablers to Deprescribing in Older Patients with Multimorbidity and Polypharmacy: The LESS Study’, presented at the Spring Meeting of the Swiss Society of General Internal Medicine 2019, Basel, Switzerland, June 5-7, 2019, co-authors: Z Rozsnyai*, **KT Jungo**, E Reeve, A Chiolero, RKE Poortvliet, N Rodondi, J Gussekloo, S Streit.

v. ‘Barriers and Enablers to Deprescribing in Older Patients with Multimorbidity and Polypharmacy: The LESS Study’, presented at the International Association of Gerontology and Geriatrics European Region Congress 2019 (IAGG-ER), Gothenburg, Sweden, May 23-25, 2019, co-authors: Z Rozsnyai, **KT Jungo**, E Reeve, A Chiolero, RKE Poortvliet, N Rodondi, J Gussekloo, S Streit*.

vi. ‘The LESS Study: An International Case-Vignette Study to Assess General Practitioners’ Willingness to Deprescribe’, presented at the GHS Symposium, University of Bern, Bern Switzerland, November 22-23, 2018, by **KT Jungo*** & S Streit on behalf of the LESS Study Group.

vii. ‘The LESS Study: An international primary care-based survey to assess general practitioners’ willingness to deprescribe in multimorbid oldest-old patients with polypharmacy’, presented at the Swiss Public Health Conference, Neuchâtel, November 7-8, 2018, by **KT Jungo*** & S Streit on behalf of the LESS Study Group.

viii. ‘Food Waste, Climate Change and Health: The implementation of the “Stop Food Waste - Save the Climate’, presented at the Geneva Health Forum, Geneva, April 19-21, 2016, co-authors: **KT Jungo***, L Favez, LD Geneviève, Y Petros.

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13. Acknowledgements

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15. Supplementary Chapters

In these supplementary chapters, I show the publications to which I have contributed as a co-author during my PhD and that provide additional context to the work presented in this thesis. In addition, I list the two non-peer-reviewed articles about primary care research, which we published in a Swiss journal commonly read by GPs.

15.1 Other Relevant Peer-reviewed Publications

15.1.1 How general practitioners would deprescribe in frail oldest-old with polypharmacy — The LESS Study

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BMC Family Practice

RESEARCH ARTICLE Open Access

How general practitioners would deprescribe in frail oldest-old with polypharmacy — the LESS study

Sophie Mantelli[1], Katharina Tabea Jungo[1], Zsofia Rozsnyai[1], Emily Reeve[2,3,4], Clare H. Luymes[5], Rosalinde K. E. Poortvliet[5], Arnaud Chiolero[1,6], Nicolas Rodondi[1,7], Jacobijn Gussekloo[5,8] and Sven Streit[1*]

Abstract

Background: Many oldest-old (> 80-years) with multimorbidity and polypharmacy are at high risk of inappropriate use of medication, but we know little about whether and how GPs would deprescribe, especially in the frail oldest-old. We aimed to determine whether, how, and why Swiss GPs deprescribe for this population.

Methods: GPs took an online survey that presented case-vignettes of a frail oldest-old patient with and without history of cardiovascular disease (CVD) and asked if they would deprescribe any of seven medications. We calculated percentages of GPs willing to deprescribe at least one medication in the case with CVD and compared these with the case without CVD using paired t-tests. We also included open-ended questions to capture reasons for deprescribing and asked which factors could influence their decision to deprescribe by asking for their agreement on a 5-point-Likert-scale.

Results: Of the 282 GPs we invited, 157 (56%) responded: 73% were men; mean age was 56. In the case-vignette without CVD, 98% of GPs deprescribed at least one medication (usually cardiovascular preventive medications) stating it had no indication nor benefit. They would lower the dose or prescribe pain medication as needed to reduce side effects. Their response was much the same when the patient had a history of CVD. GPs reported they were influenced by 'risk' and 'benefit' of medications, 'quality of life', and 'life expectancy', and prioritized the patient's wishes and priorities when deprescribing.

Conclusion: Swiss GPs were willing to deprescribe cardiovascular preventive medication when it lacked indication but tended to retain pain medication. Developing tools for GPs to assist them in balancing the risks and benefits of medication in the context of patient values may improve deprescribing activities in practice.

Keywords: Deprescribing, Polypharmacy, Multimorbidity, Old age, Frailty, Complexity

Background

General practitioners (GPs) often see oldest-old (> 80 years) and multimorbid patients [1, 2]. Multimorbidity (> 3 chronic conditions) is strongly associated with age and use of multiple medications [3]. In a random sample of Swiss patients [4], 37% of those over 70 took 5 or more medications each day, meeting the common definition of polypharmacy [5]; 44% of patients with polypharmacy took at least one potentially inappropriate medication [4]. Both polypharmacy and inappropriate medication use can increase risk of adverse events in older individuals, including adverse drug events (ADE) [6, 7], medical errors [8], non-compliance, falls [9], impaired physical and cognitive function, hospitalization [10], higher costs of care [11] and mortality [12].

Though these harms are well-established in cross-sectional and longitudinal studies, health care professionals do not have as much clear evidence about either the benefits or safety of stopping or reducing inappropriate medications (deprescribing) [13, 14]. Deprescribing is *'the process of withdrawal of an inappropriate medication, supervised by a health care professional with the*

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goal of managing polypharmacy and improving outcomes' [15]. Deprescribing can reduce ADEs and improve patient quality of life and should be integrated into clinical care [16, 17].

Recent reviews show that appropriately planned and monitored deprescribing is feasible and safe [13, 18, 19] but clinicians may be uncomfortable deprescribing for a variety of reasons including fear of unknown negative consequences of change, the existence of other prescribers, and perceived patient/family expectations [20]. GPs also report that the lack of evidence-based clinical practice guidelines can pose a barrier to deprescribing [20–23]. Treatment guidelines rarely discuss when and how medications should be deprescribed or clearly describe appropriate treatment of older adults with multimorbidity and polypharmacy [24–26]. The lack of specific recommendations may be explained by a scarcity of evidence, since older adults with multimorbidity and polypharmacy are often excluded from the randomized controlled trials (RCTs) [27] that inform guideline development.

GPs do have access to various tools that help them identify inappropriate medications or those suitable for deprescribing, such as lists of medications that may be inappropriate for older adults (e.g., the Beers criteria [28] and the STOPPFrail tool [26]), to implicit guides, and overall processes for deprescribing. However, the usefulness (such as the relevance of PIMs lists to complex individuals) and feasibility (e.g. time taken to complete complex review) of these in regular practice has not yet been established [29]. Complex medical, social and ethical situations also make this group harder to treat [30, 31]. Thus, deprescribing in frail oldest-old and multimorbid patients with polypharmacy poses a challenge to GPs that few studies have explored [32].

We used a survey with case-vignettes to determine whether, how and why GPs deprescribe in frail oldest-old patients with multimorbidity and polypharmacy, and to identify factors that influenced their decision to deprescribe.

Methods

Design

In the LESS Study (*"Barriers and enab**L**ers to willingn**ESS** to depre**S**cribing in older patients with multimorbidity and polypharmacy and their General Practitioners")* we report the findings of a cross-sectional survey in Swiss GPs.

Participants

We set out to sample a group of GPs ($N = 282$) from all regions of Switzerland who had taken part in earlier case-vignette studies and were open to invitations to participate in future research projects [33, 34]. We included all respondents who were currently practicing GPs in Switzerland.

Survey

We used the same method we employed previously to describe GP decisions about antihypertensive treatment in oldest-old patients [33, 34], and developed an online survey with three sections (A-C): A) GP characteristics and self-reported frequency of deprescribing in oldest-old; B) two case-vignettes of frail oldest-old patients with contrasting histories of CVD; and, C) questions designed to identify factors that may have affected GPs' decisions to deprescribe. (See Additional file 1 for the complete questionnaire).

For the case-vignettes in part B, our research team, composed mostly of GPs, came to consensus on a scenario that represented a typical patient seen in primary care, and medications frequently prescribed to patients ≥70 years. We generated two fictitious case-vignettes featuring an 82-year-old patient who presented to the GP for a consultation. His frailty was indicated by severely impaired physical and cognitive functions, a last-recorded MMSE of 12/30, his residence in a nursing home, and his complete dependency in activities of daily living [35]. He was being treated with aspirin 100 mg (once daily [od]), atorvastatin 40 mg (od), enalapril 10 mg (od), amlodipine 5 mg (od), paracetamol 1 g (three times daily [tid]), tramadol 50 mg (twice daily [bid]), and pantoprazole 20 mg (od). The survey asked GPs which medications (if any) they would cease or reduce (both covered by the term 'deprescribing'). The vignettes presented the same patient, but the second added a positive history of CVD. We included an open-ended question where we invited GPs to explain why they chose to deprescribe that medication.

In Part C, we asked GPs to rate the importance of sixteen factors that might influence their decision to deprescribe (5-Point Likert-scales, ranging from "not important" to "very important"). The factors were drawn from the analyses of Anderson et al. [20], and Luymes et al. [36]. An open-ended final question invited participants to name other factors and make additional comments.

To test for clarity and feasibility, we piloted the survey among five experienced GPs. Then sent invitations via email to GPs and asked them to complete the anonymous online survey. Non-responders were sent up to three email reminders. The study was conducted in Switzerland at the Institute of Primary Health Care of the University of Bern (BIHAM) between September 2017 and April 2018. It was approved by the Ethics Committee of the Canton of Bern (reference number 2017–02188).

Statistical analyses

First, we described GP characteristics by calculating proportions, means and standard deviations (SD). Next, we described the proportions of GPs deprescribing per case-vignette and per medication by calculating crude percentages and 95% confidence intervals (CI). We used McNemar's test to compare cases with positive and negative history of CVD and calculated the mean number of medications GPs deprescribed. Then one author (SM) analysed the content of the GPs' free text explanations for deprescribing medications. A senior author (SS) reviewed her codes and themes and helped finalize categories. Finally, we dichotomized Likert-scale responses to the questions in Part C into very important/important and reported as percentages. We analysed the content and coded responses to the final open-ended question. We defined a two-sided p-value of < 0.05 as significant. All analyses were performed with STATA 15.1 (StataCorp, College Station, TX, USA).

Results

GP characteristics

Of 282 GPs invited, 157 (56%) responded: 73% were men; mean age was 56 (SD 8); and, half the participants had > 25 years of experience in practice (Table 1). Most GPs (88%) estimated that they "frequently" or "very frequently" saw patients ≥70 years in their practice; 84% reported they "frequently" or "very frequently" considered deprescribing in their daily practice, but only 30% deprescribed "frequently" or "very frequently".

Table 1 Baseline characteristics of participating GPs (n = 157)

Baseline characteristics	
Female, n (%)	42 (27)
Age, years (SD)	56 (8)
Experience as GP, years (SD)	20 (9)
Number of consultations on average per working day, n (%)	
< 15	12 (7)
15–25	67 (43)
26–35	61 (39)
> 35	17 (11)
How often do you see/treat patients > 70 with multimorbidity and polypharmacy? n (%)	
very rarely	1 (1)
rarely	3 (2)
occasionally	17 (11)
frequently	89 (57)
very frequently	46 (29)
How often do you deal with the topic of deprescribing medications in your daily practice? n (%)	
very rarely	0 (0)
rarely	0 (0)
occasionally	25 (16)
frequently	95 (61)
very frequently	36 (23)
How often do you deprescribe medications during consultations with your patients in your daily practice? n (%)	
very rarely	0 (0)
rarely	8 (5)
occasionally	101 (65)
frequently	39 (25)
very frequently	8 (5)

Case-vignette analyses

In the case-vignette without CVD history, 153 GPs (98%) reported they would deprescribe at least one medication. On average, they would deprescribe 4.2 (95%CI 4.0–4.4) of the possible seven medications. In the case-vignette with CVD history, a similar proportion of GPs (97%) would deprescribe at least one medication; on average, they would deprescribe 3.3 (95%CI 3.1–3.6) medications (Table 2).

In the case-vignette without history of CVD, reported willingness of participants to deprescribe was high for cardiovascular preventive medications like atorvastatin (100%) and aspirin (74%). Many GPs also reported that they would deprescribe at least one of the antihypertensive medications (44% selected amlodipine; 24% selected enalapril), and 88% would deprescribe pantoprazole. Far fewer GPs (29%) reported that they would deprescribe paracetamol.

When we compared the case-vignette with CVD history to the vignette without CVD, we found that 29% of GPs would deprescribe paracetamol in both cases ($p = 0.56$) and an almost equal percentage (70% vs. 71%, $p = 0.71$) would deprescribe tramadol. For patients with CVD history, a smaller percentage of GPs would deprescribe cardiovascular preventive medications like aspirin (32% vs. 74%, $p < 0.001$), atorvastatin (76% vs. 100%, $p < 0.001$), enalapril (19% vs. 24%, $p = 0.033$), amlodipine (36% vs. 44%, $p = 0.011$), and pantoprazole (81% vs. 88% $p = 0.002$).

Reasons to deprescribe

When we categorized the reasons GPs gave for deprescribing in the frail oldest-old without CVD history we found they most frequently deprescribed aspirin for 'no indication' (36% of those who would deprescribe at least one medication), enalapril (10%), amlodipine (14%), and pantoprazole (73%). GPs gave 'lack of benefit' as the main reason for deprescribing atorvastatin (37%). 'Side effects' were the most common reason they would deprescribe tramadol (50%). They were less likely to deprescribe pain medication, especially paracetamol, than cardiovascular medication and explained that they

Table 2 Comparison of percentages of GPs reporting to deprescribe medication in the case of a frail 82-year-old patient without and with history of cardiovascular disease (CVD) and most frequently mentioned reasons to deprescribe for the case

	History of CVD				p-value[1]
	No		Yes		
Medication	Percentage of GPs (95% CI)	Reasons to deprescribe (frequency)	Percentage of GPs (95% CI)	Reasons to deprescribe (frequency)	
Atorvastatin 40 mg	100%	- *Not enough benefit (56)* - *No indication (35)* - *No evidence (16)* - *Short estimated life expectancy (16)*	76% (69–83%)	- *Not enough benefit (30)* - *Other (25)* - *Short estimated life expectancy (19)*	< 0.001
Pantoprazole 20 mg	88% (83–93%)	- *No indication (111)* - *In reserve, no long-term therapy (6)* - *Not enough benefit (5)*	81% (75–87%)	- *No indication (90)* - *Not enough benefit (7)*	0.002
Aspirin 100 mg	74% (67–81%)	- *No indication (55)* - *Not enough benefit (19)* - *Side effects (15)*	32% (25–40%)	- *Other (13)* - *Side effects (9)* - *Short life expectancy (8)*	< 0.001
Tramadol 50 mg	71% (63–78%)	- *Side effects (76)* - *Lower drug dose (8)* - *In reserve, no long-term therapy (8)*	70% (63–77%)	- *Side effects (69)* - *Lower drug dose (9)* - *In reserve, no long-term therapy (8)*	0.71
Amlodipine 5 mg	44% (36–52%)	- *No indication (22)* - *Side effects (22)* - *Not enough benefit (7)* - *Deprescribe the drug and evaluate the effect (7)*	36% (28–44%)	- *No indication (21)* - *Side effects (9)* - *Other (7)*	0.011
Paracetamol 1 g	29% (22–37%)	- *Lower drug dose (13)* - *In reserve, no long-term therapy (13)* - *Deprescribe the drug and evaluate the effect (6)*	29% (22–36%)	- *Lower drug dose (14)* - *In reserve, no long-term therapy (10)* - *Deprescribe the drug and evaluate the effect (6)*	0.56
Enalapril 10 mg	24% (17–31%)	- *No indication (15)* - *Side effects (5)* - *Lower drug dose (4)*	19% (13–25%)	- *No indication (13)* - *Lower drug dose (3)* - *Other (3)*	0.033

[1]P-value from McNemar's test comparing percentages of GPs deprescribing each medication by CVD

would either reduce the dose (8%) or prescribe it as needed (8%).

GPs reasons for deprescribing for the frail oldest-old with CVD history were similar, except for atorvastatin and aspirin. For these drugs, GPs mentioned other reasons, including 'no priority', 'not in >80 years', and 'not appropriate prevention'.

Factors influencing deprescribing among GPs

GPs most commonly rated four factors as "important" or "very important" in their decisions about deprescribing: 'risk of a medication' (99%); 'benefit of a medication' (98%); 'quality of life' (98%); and, 'life expectancy of the patient' (96%) (Table 3). GPs considered the factors 'expenditure of time for deprescribing' (19%) and 'self-dispensation of medication in GP office' (which means in Switzerland drug delivery by GPs in their own office) (7%) to be much less important.

In their response to the open-ended question, many GPs mentioned the importance of patients' wishes and priorities, and that their own 'assessment of cost/benefit of a medication' and 'drug interactions' could influence their decision to deprescribe.

Discussion

Summary

In a hypothetical frail oldest-old patient on 7 long-term medications, GPs would deprescribe (cease or reduce the dose of) an average of 4 medications for patients with no CVD history and 3 medications for patients with CVD history. In either case, they would usually deprescribe cardiovascular preventive medication (statin, aspirin, blood pressure lowering medication) because they thought it lacked indication or benefit. They would retain pain medication, but might reduce it or prescribe it "as needed" if they expected side effects. Positive CVD history was associated with less deprescription of atorvastatin and aspirin, which may reflect the belief that potential risks like side effects outweighed potential benefits of cardiovascular preventive medication in patients with low CVD risk. This accords with the European guidelines on preventing cardiovascular disease, which recommend that patients with low CVD risk be given lifestyle advice and not necessarily treated with antihypertensives and/or lipid-lowering drugs [36, 37]. When they decided which medication to deprescribe, GPs considered the risk/benefit of the medication, and the patient's quality of life and life expectancy to be important.

Table 3 Factors important to GPs (n = 157) when deprescribing (per GP more than one answer was possible)

Factors	Rated as very important or important, %
Risk of a medication	99%
Benefit of a medication	98%
Quality of life of the patient	98%
Life expectancy of the patient	96%
Potential negative health outcomes of medication's change	76%
Interprofessional communication (between GPs and other prescribing physicians)	73%
Interprofessional collaboration (between GPs and other prescribing physicians)	72%
Age of the patient	73%
Existence of deprescribing guidelines	64%
Expectations of the patient	63%
Difficult communication (between GP and patient, e.g. due to cognitive impairment)	56%
Expectation of relatives	49%
Existence of tools that facilitate deprescribing	48%
Expenditure of time for thinking about and deprescribing in the older multimorbid patient with polypharmacy	19%
Self-dispensation of medication in GP office[1]	7%

[1]Self-dispensation means 'drug delivery by general practitioners in their office'

They also took the views and priorities of their patient into account.

Strengths and limitations

Our study had a higher-than-usual survey response rate (56% vs. the typical rate of 30–40%) [38] and our sample closely matches the general Swiss population of GPs in age, gender, and years in practice, but our results might not be generalizable to GPs in other countries where prescribing practices differ. The GPs we surveyed may have been more interested in deprescribing than GPs in the general population since our sample was taken from those who had already consented to participate in research studies. Our study was also limited by the deliberate simplicity of the case-vignettes we chose, since we were forced to omit potentially interesting patient and GP characteristics. For instance, the patient in the case-vignette has no chronic health problems and takes no medicines associated with adverse drug events or that pose a risk when deprescribed. But we deliberately chose this case-vignette for the following reasons: 1) to standardize the case; 2) to avoid overloading respondents with information, 3) to make participation more feasible for GPs, and 4) to ensure responders had a common understanding of the case. Our analysis relied on claims GPs made about their intentions (that they would deprescribe selected medications) but these may not reflect their true practice. To mitigate this problem, we used standardized case-vignettes to exemplify a complex problem frequently encountered by GPs who treat frail oldest-old patients with polypharmacy. A GP who intends to describe may find that they cannot follow through on the intention in clinical practice because they are faced with barriers and factors outside their control. Social desirability bias may also have affected our results; for example, only 19% of respondents reported that time was an important factor in deprescribing, though the qualitative literature regularly reports time as a significant barrier to deprescribing [20, 39]. But the anonymous nature of the survey may have minimised this bias. Our case-vignette may also have encouraged the GP to opt to deprescribe, since the patient has impaired physical function and is likely to have limited life expectancy. In the vignette, the patient's MMSE was 12 and he depended on others for activities of daily living. Since dementia does not progress predictably, and varies between individuals, we could describe a patient with limited life expectancy, but not be any more specific. If we told the GP the patient was expected to live less than 12 months or needed palliative care, it might have changed our results [40, 41].

Comparison with existing literature

Our quantitative research complements qualitative findings by *Sinnige* et al. [42], who assessed GPs' medication management strategy and factors that influenced the deprescribing process in a similar setting. They also used case-vignettes for hypothetical patients to understand how GPs would deprescribe, identified patient- and medication-related factors that influenced medication management and highlighted the importance of taking a patient-centred approach, considering the patient's age and life expectancy, and weighing patient's preferences and perspectives into the decision.

Our study accords with previous research that showed CVD history influences GP prescribing decisions [33, 36]. We found higher rates of deprescribing statins than did previous studies [43], perhaps because the patient in our case-vignette was a nursing home resident. Deprescribing patterns might have been different in patients with no or mild cognitive impairment [44]. Our case-vignette also provided sparse information about family and caregiver involvement and advanced directives might have facilitated deprescribing.

Ní Chróinín et al. [45] also used case-vignettes in a similar study of deprescription among geriatricians (N = 930, response rate 14,4%). Like Ní Chróinín et al., we found considerable willingness to deprescribe cardiovascular preventive medication in the scenario of cognitive impairment and dependency. Ní Chróinín et al.'s sample included a higher percentage of women and younger geriatricians

than are present in the general population of GPs. Our study population more closely matches the GP population in age, gender, and years in practice, so our results suggest these observations are more generally applicable.

Patients with dementia may be undertreated for pain [46, 47], possibly because members of this group express pain differently than those without dementia (particularly if patients with dementia are non-verbal) [48]. Pain symptoms like agitation or aggression may be attributed to dementia (labelled behavioural and psychological symptoms of dementia) and not treated appropriately [49]. It is thus unsurprising that GPs were less likely to deprescribe pain medications, particularly paracetamol, than cardiovascular medications. Since under-treatment of pain is a concern in people with dementia, the proportion of GPs who would deprescribe paracetamol (29%) when an individual has chronic back pain may be higher than ideal, but 13/19 of the GPs we surveyed would prescribe paracetamol as a reserve medication instead of eliminating it entirely. A high proportion of GPs reported they would deprescribe tramadol, perhaps because of the risks the medication poses. Our study was not designed to determine which medications GPs would prescribe to best manage the patient's pain (for example, starting oxycodone instead of tramadol or initiating non-pharmacological management). GP's deprescribing patterns may also have been influenced by the results of recent studies that found paracetamol and opioids might not be effect for treating chronic pain [50, 51].

We found GPs heavily weighted the patient's quality of life and life expectancy, wishes and priorities, in their decisions about deprescribing, perhaps because the patient in the case vignette had advanced dementia. A focus on quality of life is a key part of modern medical care for people with dementia [52]. Our findings complement those of recently published reviews of patient barriers to and enablers of deprescribing [53, 54] which emphasize the importance of centring the deprescribing process on the patient [55]. Elements of patient-centred care include shared decision making, viewing the person as a whole, and maintaining a positive doctor-patient relationship [56]. But our study was not designed to determine whether GPs felt able to share decision-making about deprescribing, or how they approached the discussion with patients. Other studies found that GPs would appreciate guidelines or tools that made it easier for them to deprescribe [14, 22, 39, 57]. The Swiss GPs we included in our studies would welcome this but did not prioritise it. Our findings also dovetail with results from qualitative studies that assessed why GPs decide to deprescribe [20]. Our research suggests that Swiss GPs would try to reduce medication burden in frail individuals with multimorbidity and polypharmacy through deprescribing. However, while most responded that they regularly dealt with the topic of deprescribing in practice, only 30% reported that they frequently deprescribed.

Implications for research and practice

We did not assess barriers to deprescribing (like fear of negative consequences) in our case-vignette. Further clinical trials are needed to measure the safety, benefits, and best practices for deprescribing, especially in oldest-old multimorbid patients. We also suggest researchers explore more complex cases in the future by adding details to case-vignettes. They may also wish to ask GPs about deprescribing in a stable patient without current problems, to see if it changes the results. We hope others will explore the reasons GPs prioritise or do not prioritise reviewing medicines with an eye to deprescribing. Since medication and patient characteristics are important factors in deprescribing, researchers should also study patient and family beliefs and attitudes. If we knew more about how, why, and when GPs decide to deprescribe, it should be possible to develop tools that assist them in balancing these (sometime competing) interests.

Conclusion

In case-vignettes, Swiss GPs were most likely to deprescribe cardiovascular preventive medication, citing lack of indication and benefit, and less likely to deprescribe pain medications. Overall, Swiss GPs expressed willingness to deprescribe for frail oldest-old patients and were guided in their decisions by the risks and benefits of a medication, quality of life and life expectancy of patients, and patient priorities.

Additional file

Additional file 1: The survey used in the LESS Study. (DOCX 21 kb)

Abbreviations

ADE: Adverse drug event; Bid: Twice daily; CI: Confidence interval; CVD: Cardiovascular disease; GP: General practitioner; Od: Once daily; OR: Odds ratio; PPI: Proton-pump inhibitor; SD: Standard deviation; Tid: Three times daily; Vs: Versus

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Availability of data and materials

The dataset used and analysed during the current study is available from the corresponding author on reasonable request.

Authors' contributions

SM and SS had full access to all data in the study and SM, KTJ, ZR, ER, CL, RKEP, AC, NR, JG and SS take responsibility for the integrity of data and the accuracy of the data analysis. Study concept and design: SM, KTJ, ZR, ER, CL,

RKEP, AC, NR, JG and SS. Acquisition, analysis, or interpretation of data: SM, KTJ, ZR, ER, CL, RKEP, AC, NR, JG and SS. Drafting of the manuscript: SM, SS made a first draft. Critical revision of the manuscript for important intellectual content: KTJ, ZR, ER, CL, RKEP, AC, NR, and JG. Statistical analysis: SS. Obtained funding: SS, AC, NR, RKEP, JG. Administrative, technical, or material support: SS. Study supervision: SS. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study has been approved by the Ethics Committee of the Canton of Bern (reference number 2017–02188). GPs were informed in writing about the goals of the study and that data would be anonymized. GPs were informed that they were granting consent by clicking to access the survey. The Ethics Committee reviewed and approved this process, which accords with the Swiss Human Research Act (Humanforschungsgesetz, HFG).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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15.1.2 What do older adults with multimorbidity and polypharmacy think about deprescribing? The LESS study - a primary care-based survey

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What do older adults with multimorbidity and polypharmacy think about deprescribing? The LESS study - a primary care-based survey

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Abstract

Background: Multimorbidity and polypharmacy are very common in older adults in primary care. Ideally, general practitioners (GPs), should regularly review medication lists to identify inappropriate medication(s) and, where appropriate, deprescribe. However, it remains challenging to deprescribe given time constraints and few recommendations from guidelines. Further, patient related barriers and enablers to deprescribing have to be accounted for. The aim of this study was to identify barriers and enablers to deprescribing as reported by older adults with polypharmacy and multimorbidity.

Methods: We conducted a survey among participants aged ≥70 years, with multimorbidity (≥3 chronic conditions) and polypharmacy (≥5 chronic medications). We invited Swiss GPs, to recruit eligible patients who then completed a paper-based survey on demographics, medications and chronic conditions. We used the revised Patients' Attitudes Towards Deprescribing (rPATD) questionnaire and added twelve additional Likert scale questions and two open-ended questions to assess barriers and enablers towards deprescribing, which we coded and categorized into meaningful themes.

(Continued on next page)

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(Continued from previous page)
Result: Sixty four Swiss GPs consented to recruit 5–6 patients each and returned 300 participant responses. Participants were 79.1 years (SD 5.7), 47% female, 34% lived alone, and 86% managed their medications themselves. Sixty-seven percent of participants took 5–9 regular medicines and 24% took ≥10 medicines. The majority of participants (77%) were willing to deprescribe one or more of their medicines if their doctor said it was possible. There was no association with sex, age or the number of medicines and willingness to deprescribe. After adjustment for baseline characteristics, there was a strong positive association between willingness to deprescribe and saying that because they have a good relationship with their GP, they would feel that deprescribing was safe OR 11.3 (95% CI: 4.64–27.3) and agreeing that they would be willing to deprescribe if new studies showed an avoidable risk OR 8.0 (95% CI 3.79–16.9). From the open questions, the most mentioned barriers towards deprescribing were patients feeling well on their current medicines and being convinced that they need all their medicines.

Conclusions: Most older adults with polypharmacy are willing to deprescribe. GPs may be able to increase deprescribing by building trust with their patients and communicating evidence about the risks of medication use.

Keywords: Deprescribing, Polypharmacy, Multimorbidity, Patient attitudes, Older adults, General practice

Background

Managing patients with multimorbidity (≥3 chronic conditions) has become the norm for general practitioners (GPs). In the UK for example, three quarters of consultations involve patients with multimorbidity [1]. Multimorbidity is strongly associated with age and with polypharmacy (often defined as ≥5 chronic medicines [2]). Currently, treatment guidelines are mainly based on the management of single diseases and on evidence from trials that often exclude older patients with multimorbidity [3] Therefore, recommendations for individual medical conditions often fail to consider competing factors, such as drug-disease interactions and risks due to polypharmacy [4]. As a result, the prevalence of polypharmacy is on the rise, especially in patients with multimorbidity. With this comes an increased risk for potentially inappropriate medications (PIMs); these are medications where the potential risk outweighs the potential benefit in the individual. The possible consequences of polypharmacy and PIMs use include increased risk of adverse drug events [5], medicine errors [6], adverse drug reactions [7], poor adherence [8], and impaired quality of life [9], especially in older multimorbid patients [10].

Deprescribing is the withdrawal of PIMs with the goal of managing polypharmacy and improving outcomes [11]. Deprescribing is relevant and should be considered for all patients who may be taking an inappropriate medicine [12]. However, certain medications are often targeted, such as high risk medicines in frail older adults, preventive medicines in patients with limited life expectancy [13] including people with cancer under palliative care [14, 15].

While the rationale to deprescribe is clear, the implementation is less clear and in practice, important barriers exist for physicians and patients [16]. Physicians have reported that patient resistance or unwillingness to deprescribe is a major barrier to deprescribing in practice [17]. Studies with patients have found that [18] fear, lack of knowledge on how to deprescribe and belief that their medicines are appropriate are barriers to their willingness to have a medication deprescribed. Despite these barriers, older adults have reported willingness towards deprescribing when their health care professional is supportive [19]. Barriers and enablers for deprescribing might differ by countries, cultures and local health care systems. Patient willingness to deprescribe has been previously studied in several countries, however, not all participants had polypharmacy and multimorbidity and were often not recruited from primary care [20–22] leaving a gap in understanding the perspective of older patients with multimorbidity and polypharmacy in general practice.

This study aims to determine the willingness towards deprescribing in older adults with polypharmacy in Switzerland, who are at high risk for potentially inappropriate medication and would therefore likely benefit from deprescribing. We further wanted to learn which potential barriers and enablers are most prevalent in this population and to explore their association with the reported willingness to deprescribe.

Methods

Design

Cross-sectional survey among patients in general practice using anonymous paper based questionnaires distributed by their GPs from May 2018 to February 2019.

Study population and processes

Inclusion criteria for patients were age 70 years or older, multimorbidity (three or more chronic conditions), and polypharmacy (regular intake of five or more chronic

medicines). Furthermore, patients had to be able to read and write in German language. There were no exclusion criteria.

Patients were recruited by GPs. We invited Swiss GPs to each recruit five to six eligible patients. Switzerland has no registry of GPs which made it impossible to select a random sample. We therefore asked GPs who participated in a former study using an online questionnaire on attitudes of GPs towards deprescribing [23] if they would assist in recruitment of patients. We also allowed other GPs interested to participate through advertising the study at Primary Care institutes and in GP quality circles. All participating practices were paid 100 Swiss Francs (about 100 Euros) to compensate for time required for screening, obtaining informed consent and other recruitment related activities. The Ethics committee of the Canton of Bern approved the study. (Nr: 2017–02188).

Participating GPs were instructed to *consecutively* screen for eligible patients during their regular consultation program to limit selection bias. GPs recorded the number of screened patients, number of eligible patients and number of those not willing to participate.

All patients gave written informed consent to participate before receiving the paper-based study questionnaire. Patients were invited to answer the questionnaire in the waiting room or at home anonymously and return the survey to the medical assistant of their practices (who then returned them as a batch to the study team).

Questionnaire

- We used the revised Patients' Attitudes Towards Deprescribing (rPATD) questionnaire for older adults which contains twenty-two 5-point Likert scale questions on attitudes and beliefs about their medications and deprescribing. The rPATD was developed and validated in Australia [24] and has been employed in various countries and settings [20, 21, 24]. The rPATD contains four factors with five questions per factor (involvement, burden, appropriateness, and concerns about stopping) as well as two global questions. We translated the original questions from the rPATD from English into German. This then underwent independent back-translation from German to English by an individual who had not seen the original English version. The translation and back-translations were then reviewed by the research team (including the primary author of the original English rPATD, ER) with discussion and editing of the German version to resolve any concerns about the translation. As one of the aims of the study was to quantify the barriers to and enablers of deprescribing, 12 questions were added to the questionnaire to cover topics important to patients in a primary care setting identified in previous qualitative research [18]. These additional questions were developed by members of the research team (SS, NR, RKEP) and chosen for inclusion in the study due to their perceived relevance to the local context of primary care in the German speaking part of Switzerland. The questions were not chosen according to themes that were not represented in the rPATD (as the factors of the rPATD are closely aligned with the themes from this systematic review), and instead were to broaden capturing of attitudes within the themes. Where possible, the wording of the question was kept as close to the quotes from older adults in the original research studies included in the systematic review, however, wording was developed and refined by the research team. The possible answers for all questions were: strongly agree - agree – unsure – disagree – strongly disagree.
- Two additional open-ended questions on other barriers and enablers towards the willingness to deprescribing were also added to capture potential barriers and enablers not included in the rPATD or additional quantitative questions ("Do you think there are other reasons why you wouldn't reduce or stop medicines?" and "Do you think there are other reasons why you would like to reduce or stop medicines?"). We then piloted the translated questionnaire and additional questions with four eligible patients for comprehensibility (no changes were required).

We also collected self-reported data:

- demographic data: age, sex, living status and involvement in medication management.
- full list of current chronic medicines (intake of > 6 months). If participants had trouble self-completing this list, they could seek help from their GP
- chronic conditions. We provided participants a list of most prevalent chronic conditions in patient-friendly language [25]. Participants could tick boxes, if they were diagnosed with those diseases.

We used the STROBE statement checklist to report our study findings [26].

Preliminary results of this project were presented at the annual meeting of the European General Practice Research Network in Tampere in May 2019 [27].

Statistical analysis

Our main outcome was willingness towards deprescribing, which was measured with the question from the

rPATD: *'If my doctor said it was possible, I would be willing to stop one or more of my regular medicines'*. If participants answered, "strongly agree or agree" they were considered to be willing to deprescribe.

We used descriptive statistics to report baseline characteristics of our sample stratified by willingness to deprescribe. To compare participants who were willing to deprescribe versus not willing to deprescribe, we used t-test and Chi2 test where appropriate. Likert-scale answers from rPATD and the additional questions about deprescribing were dichotomized from the 5-point Likert scale responses into "strongly agree/agree" versus "unsure/disagree/strongly disagree" for analysis. Different members of the study team then separately categorized them as enablers, barriers or involvement-related and then discussed potential disagreement until agreement was reached. These categories were formed for the case if the question was answered with "strongly agree/agree" (e.g. "I don't like to take medicines", if answered with "strongly agree/agree" the statement qualifies as an enabler towards deprescribing, but if answered with "unsure/disagree/strongly disagree" it is not necessarily a barrier).

To adjust for baseline characteristics, we used a multivariable mixed-effects logistic regression model that also accounted for possible clustering within each GP as a random-effect. The same model was used to assess the associations of items from the questionnaire and willingness to deprescribe. In the model we adjusted a priori for sex and age and for baseline characteristics if there was a significant difference (p-value< 0.05) between those willing and those not willing to deprescribe.

The first and last author analyzed the responses to the open-ended questions. They coded and categorized answers to the open questions (*"Do you think there are other reasons why you wouldn't reduce or stop medicines?" and "Do you think there are other reasons why you would like to reduce or stop medicines?)* into meaningful themes. Disagreements were resolved by consensus. After creating the list of themes, it was counted how often the topics were mentioned by participants. Multiple answers were possible per participant.

A p-value < 0.05 was considered significant. Data management was done using EpiData Manager and EpiData Entry Client v.4.4.1.0 (EpiData Association, Denmark). Statistics were computed using Stata 15.02 (StataCorp, College Station, TX, USA) for all analyses.

Results

We invited 830 Swiss GPs from all over the German part of Switzerland to participate. Out of these, 64 (7.7%) GPs recruited participants. Reasons why GPs did not participate included lack of time, health issues or personnel shortage in their practice. Participating GPs and therefore their patients came from all over the German speaking part of Switzerland.

Target recruitment was 5 to 6 patients per GP. During the screening period, the 64 GPs screened 2537 consecutive patients for eligibility, of those 531 (21%) met the inclusion criteria. Ultimately 300 participants were included in this analysis. Reasons for non-participation and a study flow chart is provided in Fig. 1.

Participant characteristics

Table 1 describes the baseline characteristics of our participants: 47% were female, with a mean age of 79.1 years (SD, 5.7). Thirty-four percent were living alone and 86% managed their own medications. Twenty-nine percent had no further or vocational education after obligatory school; 49% had done an apprenticeship (vocational education) and another 22% had higher education.

Participants had a mean number of 3.3 (SD 1.3) chronic conditions from our list of common chronic conditions in ambulatory care. The mean number of medicines was 8.0 (SD 2.8) with the largest number of medicines taken by a single participant being 22 medicines. Twenty-four percent had excessive polypharmacy [28], defined as taking 10 or more regular medicines. The majority of our sample were willing to deprescribe (77%). There was no significant differences in willingness to deprescribe based on participant characteristics, except for educational level. A greater proportion of participants who were willing to deprescribe had higher education compared to those who were not willing to deprescribe (26% vs. 12%, $p = 0.006$).

Barriers and enablers towards deprescribing

Figure 2 describes results of the enablers, barriers and other questions related to deprescribing. Among the enablers, most participants reported that they had a good relationship with their GP and therefore felt that deprescribing was safe (86%) and agreed that if new studies found harm from taking too many medicines, they would want to deprescribe (81%). Out of the 14 questions categorized as barriers, the majority agreed to 5 of them. There was high satisfaction with current medications (97%) and most participants noticed an improvement when taking their medicines (92%). Only 13% had a previous bad experience with deprescribing. Participants showed a high involvement with their medicines: 97% wanted to know as much as possible about their medicines; 95% stated to understand the reasons why they were taking each of their medicines; 94% wanted to be involved in decision making about their medicines; 89% always asked a healthcare professional if they had a question about their medicines and 88% like to know as much as possible about their medicines *(*Fig. 2*)*.

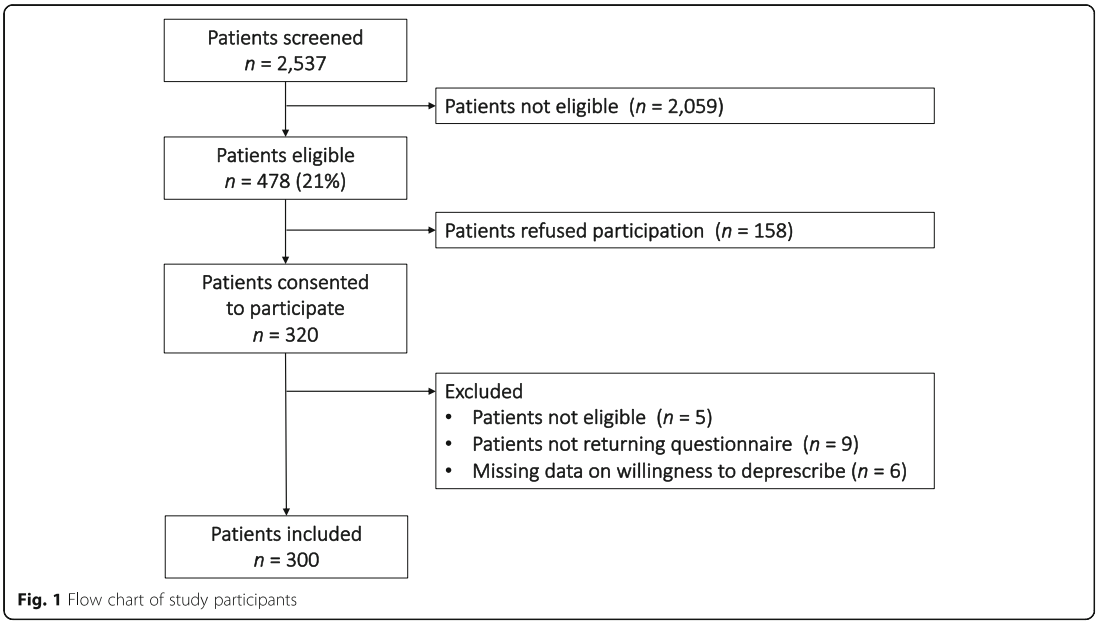

Fig. 1 Flow chart of study participants

Associations with willingness to deprescribe

In Table 2, we show the associations between baseline characteristics and willingness to deprescribe with an adjusted multilevel mixed-effects model. There was no significant association between age, sex, number of medicines, medication-self management, and living status with the willingness to deprescribe. Participants with higher education were more likely to be willing to deprescribe, compared to those with basic education ($p = 0.006$).

Among our participants, 83 (28%) reported themselves that they had less than three chronic conditions, despite this being an inclusion criterion. As this likely indicates a problem with how this data was collected (self-report according to a pre-defined list), we did not use this variable for analysis as intended a priori.

Figure 3 shows all the questions that had a statistically significant association with willingness to deprescribe, sorted by their strength of association. There was a

Table 1 Baseline characteristics of study participants stratified by willingness to deprescribe

Baseline characteristics	Overall $n = 300$	Willing to deprescribe[a] $n = 231$ (77%)	Not willing to deprescribe[a] $n = 69$ (23%)	*p*-value
Female, n (%) ($n = 300$)[b]	141 (47)	104 (45)	37 (54)	0.21
Age, mean (SD) ($n = 292$)	79.1 (5.7)	78.9 (5.7)	79.8 (5.8)	0.24
Living alone, n (%) ($n = 298$)	100 (34)	76 (33)	24 (35)	0.81
Self-management of medication, n (%) (n = 298)	256 (86)	196 (86)	60 (87)	0.78
Education level, n (%) ($n = 299$)				0.006
obligatory education	86 (29)	57 (25)	29 (42)	
Apprenticeship	146 (49)	114 (49)	32 (46)	
Higher education	67 (22)	59 (26)	8 (12)	
Number of medicines, mean (SD) ($n = 294$)	8.0 (2.8)	8.0 (2.7)	8.1 (2.9)	0.89
5–9 medicines	228 (76)	176 (76)	52 (75)	
≥ 10 medicines	72 (24)	52 (24)	13 (25)	0.89

SD standard deviation

[a]Willing to deprescribe, when answering true/rather true and not willing to deprescribe, when answering don't know/rather not true/not true to the question: "*If my doctor said, it was possible I would be willing to stop one or more of my regular medicines*' "

[b]numbers report the number of patients with no missing information on the respective variable

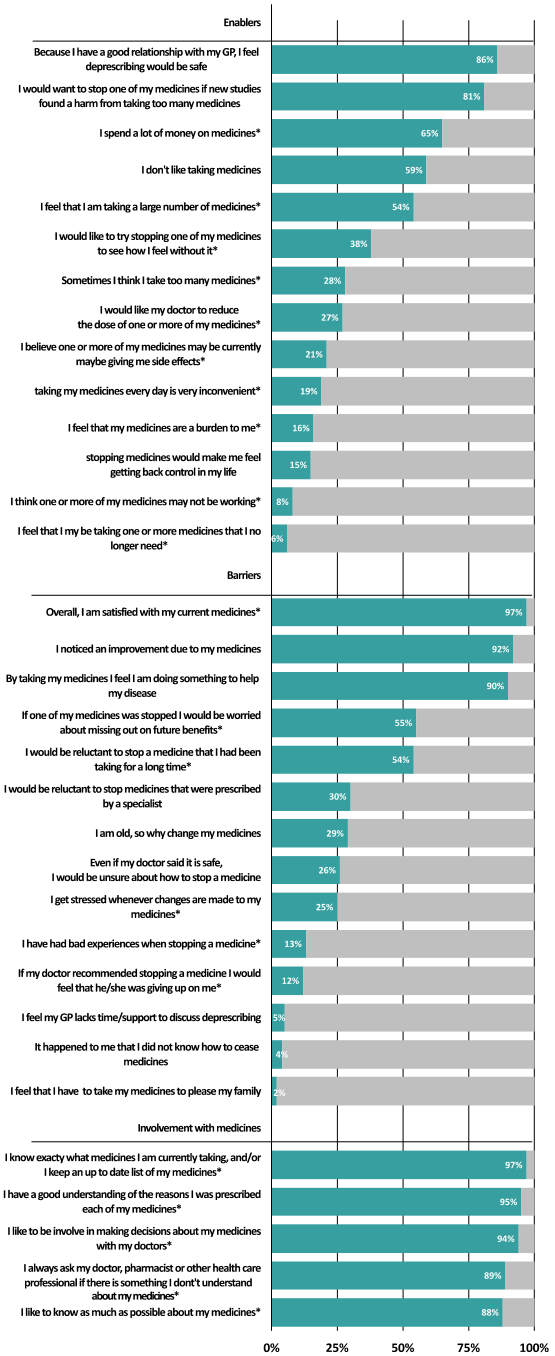

Fig. 2 (See legend on next page.)

(See figure on previous page.)
Fig. 2 Enabler, barrier and involvement items, sorted by proportion of patients agreeing with questions per domain; Legend: Enabler, barrier and involvement items from questionnaire, agreed or strongly agreed on (coloured part of the bar) versus unsure, disagreed, strongly disagreed on (grey part of the bar) by patients with multimorbidity and polypharmacy. Items are sorted by proportion of patients agreeing with questions per domain. * from rPATD

strong positive association with participants belief that they have a good relationship with their GP and so feel safe about deprescribing (OR 11.3, 95%CI 4.6–27.0) and that they would like to deprescribe if new studies found harm from taking too many medicines (OR 8.0, 95%CI 3.8–16.9). Other enablers were, wanting their GP to reduce the dose of their medicines (OR 2.64, 95%CI 1.2–5.8) and believing that they take too many medicines (OR 2.5, 95%CI 1.2–5.5). Important barriers with a negative association to willingness to deprescribe were being unsure about how to stop a medicine, even if their doctor said that it is safe (OR 0.33, 95%CI 0.2–0.6) and previously having had a bad experience with deprescribing (OR 0.4, 95%CI 0.2–0.8) *(*Fig. 3*)*.

Open-ended questions

The highly mentioned barriers from the open questions were participants feeling well with their current medicines and being convinced that they need all of their medicines. Other barriers were fear of recurrent symptoms or worsening of health. The most commonly mentioned enablers were experiencing a side effect or no effect from the medicines, drug-drug interactions, trust in doctors to only prescribe what is necessary and cost reduction (Table 3).

Discussion

Summary

In a consecutive sample of Swiss primary care patients, 21% were older than 70 years and had multimorbidity and polypharmacy and were therefore eligible for inclusion in our study. In our participants, who had a mean age of 79.4 years and took an average of 8 regular medications, we found that most (77%) are willing to have a medicine deprescribed if their doctor said it was possible. Individuals with a higher level of education were more likely to be willing to deprescribe. Based on our results, the strongest enablers for patient willingness to deprescribe are having a good relationship with their GP and if new studies found harm from taking too many medicines. Barriers were previously having a bad experience with deprescribing and uncertainties about how to stop a medicine. Via our open questions, additional reported barriers were being convinced that they need all of their medicines and fear of recurrent symptoms. While noticing side effects or no effects from their medicines were reported enablers.

Comparison to existing literature

Our most important finding, that the majority of participants were willing to deprescribe, is consistent with findings from other studies using the rPATD internationally [19, 21, 22, 29, 30]. Our population was unique in

Table 2 Willingness to deprescribe, adjusted for patient characteristics and GP-clusters ($n = 284$)

Baseline characteristics	Adjusted[1] OR (95%CI) of participants willingness to deprescribe	*p*-value[1]
Sex		
Female	0.94 (0.49–1.79)	0.84
Male	ref.	
Age, per year increase	0.97 (0.92–1.02)	0.29
Living alone		
Yes	1.27 (0.66–2.44)	0.47
No	ref.	
Self-management of medication		
Yes	0.79 (0.33–1.92)	0.61
No	ref.	
Education level		
Obligatory education	ref.	
Apprenticeship	1.63 (0.84–3.16)	0.15
Higher education	3.28 (1.26–8.55)	0.015
Number of medicines, per unit increase	1.01 (0.91–1.12)	0.92

1 Multivariable mixed-effects logistic regression model adjusting for all covariates in the table and for GP-cluster as a random-effect

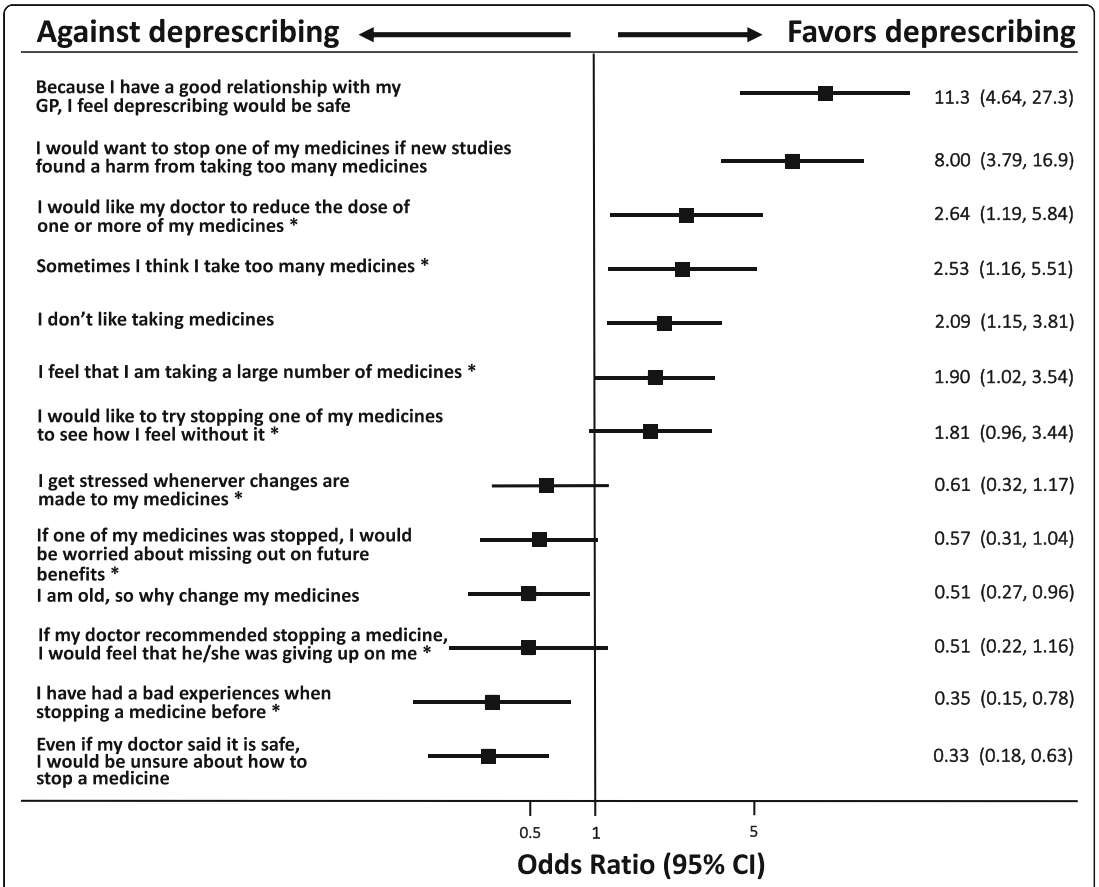

Fig. 3 Significant enablers and barriers towards the willingness to deprescribe in a forest plot; Legend: Significant barriers and enablers towards the willingness to deprescribe. Odds ratios from a multivariable mixed-effects logistic regression model adjusted for age, sex, education level, number of medicines, living status, medication self management and GP as random-effect. OR sorted by point estimate (top-down); * from rPATD

Table 3 Answers to open questions on other enablers and barriers towards deprescribing[a]

Enablers	Number of participants[a]
side effects, interactions or no effect of medicines, feeling bad with medicine	37
trust in doctor to deprescribe when necessary	16
cost reduction	16
Barriers	
feel well with current medicine, convinced that all are needed	56
fear of recurrent symptoms or worsening of health	45
trust in doctors to only prescribe what is necessary	25

[a] *179 participants replied to both open-ended questions*
[b] *More than one answer per patient possible*

comparison to many of the earlier studies in that we only included participants with polypharmacy and multimorbidity. For example, the Australian study recruited older adults taking one or more medicines and less than half of their sample were taking 6 or more medicines [30]. Eliciting the attitudes and beliefs of older adults with polypharmacy is important because this is the population that is most likely to benefit from deprescribing and it is possible that the views of this population will differ. Older adults with polypharmacy may feel a strong dependency towards their medicines, and also might have established habits. It was interesting that in the open-ended questions a commonly reported barrier was the belief that all their medicines were necessary. While we chose to only include participants with polypharmacy, there have been inconsistent results in previous studies about the relationship between polypharmacy and patient willingness to deprescribe. In a Japanese study, a lower willingness to deprescribing in a healthier and younger population was found, with a higher willingness in older participants with more medicines [22]. Similarly, in a US study having 2 or more chronic medical conditions was found to be associated with higher willingness to deprescribe, however age was not associated [21].

Previous studies internationally have found contradictory results as to whether or not number of medicines is associated with willingness to deprescribing [19–22, 30]. We did not find an association between number of medicines and willingness to deprescribe in our population, however, as we only included participants with polypharmacy, we are not able to determine if those on less medicines had different attitudes. Willingness to deprescribe might be influenced by the individual's perception of the number of medicines that they take. Despite all our participants having polypharmacy, only 54% felt that they took a large number of medicines. Participants who agreed that they take a large number or too many medicines were more likely to be willing to deprescribe. This is in line with a recent study in Switzerland, where patient perception of treatment burden differed significantly from the doctor's perception. For practice, it is therefore important to find out the patient's perceived burden, so that discussion about deprescribing can be accordingly targeted [31].

The only participant characteristic that we found to be associated with willingness to deprescribe was higher education. It may be that people who are more educated are more open to change and critical of doctors' advice. Other baseline characteristics showed no association with willingness to deprescribe similarly to studies in Japan, Australia and USA [21, 22, 32].

The most important barriers from participant responses to our open questions were being convinced that all their medicines are necessary and fear of recurrent symptoms. This is similar to the findings of a qualitative study in Switzerland among patients who did not pursue deprescribing offers from their GP [33].

Implications

For the future, a good knowledge of barriers and enablers from the patient view is important for developing deprescribing interventions, guidelines, and patient and clinician educational materials. Another important finding of this study was that 81% would like to deprescribe if new studies found harm from taking too many medicines. This supports the need for further research into the benefits and harms of deprescribing of different medicines and in different populations. For guidelines and patient and clinician educational materials, our results can be used to inform their content; older adults with polypharmacy and multimorbidity want to be informed about their medicines and to understand the reasons for taking them. Talking about former bad experiences and how potential negative outcomes of deprescribing will be managed is important as this was associated with reduced willingness to deprescribe. Furthermore, asking about the subjective burden of medicine intake in every patient, rather than looking at the number of medicines taken regularly, could lead to more success in deprescribing, since it was more associated with the willingness to deprescribe while number of medicines was not.

Clear instructions for participants how to cease certain medicines will also be helpful. Overall, discussing the beliefs and attitudes of patients and determining if there are any barriers towards deprescribing in the individual will enhance shared decision making and support deprescribing.

Limitations and strengths

In this study, the screening and recruitment was done by GPs. Simple random sampling was not possible (many Swiss GPs still have paper documentation) and so we instructed the GPs to conduct consecutive sampling to identify and recruit participants to reduce selection bias. However, as this was external to the research team, we cannot completely rule out the possibility of selection bias by the GPs. Screening records from the GPs show that 21% of participants were eligible during the screening period. This number is comparable to other Swiss studies in ambulatory care on number of multimorbid participants with polypharmacy [34]. Overall, men were slightly overrepresented in our sample, but female participants were significantly older with mean age of 79.8 years (SD 6) for women, compared to Swiss census data [35]. It is also possible that patients who chose to participate may have had more favorable views about

deprescribing than those who refused (33% refusal rate). Among our participants, 83 (28%) of participants reported that they had less than three chronic conditions, despite this being an inclusion criterion for screening through GPs. As this likely indicates a problem with how this data was collected (self-report according to a pre-defined list), we were not able to use this variable for analysis as intended a priori. Specifically, the under-reporting of co-morbidities is likely due to our method of checkboxes listing most prevalent chronic conditions in patient-friendly language; participants might have had conditions, which were not listed or might have known their conditions by a different name. However, this likely had little impact on our findings in regard to the results representing the attitudes of those with multimorbidity as it was the participants GP that determined their eligibility based on this criteria. Another limitation is the hypothetical and non-medicine specific nature of the rPATD and additional questions used in this study. Additionally, due to the cross-sectional nature of this study we are not able to confirm directionality (i.e. cause and effect) of the associations we identified between barriers and enablers and willingness to deprescribe. Another important limitation is that the non-rPATD additional questions did not undergo any formal validation. The two questions that were found to have the strongest associations with willingness to deprescribe (saying that because they have a good relationship with their GP, they would feel that deprescribing was safe and agreeing that they would be willing to deprescribe if new studies showed an avoidable risk) are both questions that were created just for this study (not rPATD questions). As they have not undergone validation (other than piloting in four participants), these finding should be interpreted with caution.

To our knowledge, this was the first study to use the rPATD and other questions about barriers and enablers towards deprescribing in a population most likely to have potentially inappropriate medicines in Switzerland, namely older adults with polypharmacy and multimorbidity. However, we do not know if our results are generalizable to populations outside the German speaking part of Switzerland, as we only used the German translation of the rPATD (for pragmatic reasons). By instructing GPs to recruit 5–6 eligible patients each we aimed to maximize the distribution of participants from across the German speaking part of Switzerland and prevent bias that could have been created by a small number of GPs recruiting a large proportion of the participants.

Conclusion

Most German speaking Swiss older adults with polypharmacy are willing to deprescribe. GPs may be able to increase deprescribing by building trust with their patients and communicating evidence about the risks of medication use. Future research should explore how to best engage patients in conversations about deprescribing.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-020-01843-x.

Additional file 1.

Abbreviations

GP: General practitioner; PIMs: Potentially inappropriate medications; rPATD: Revised patients' attitudes towards deprescribing

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Authors' contributions

ZR, KTJ, ER, RKE, NR, JG, SS came up with the study concept. All authors developed the study design and the protocol. ZR, KTJ and SS collected the study data. ZR and SS had full access to all data in the study. All authors contributed to the analysis and interpretation of data. All authors take responsibility for the integrity of data and the accuracy of the data analysis. ZR, ER and SS drafted the first version of the manuscript. All authors critically revised the manuscript. SS obtained funding for the project, provided administrative, technical and material support, and supervised the project. The final version of the manuscript was approved by all authors.

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Availability of data and materials

The dataset used and analyzed during the current study is available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The Ethics committee of the Canton of Bern approved the study. (Nr: 2017–02188). All patients gave their written consent to participate.

Consent for publication

Not applicable.

Competing interests

The authors declare to have no conflict of interest.

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15.1.3 Potentially inappropriate medication and attitudes of older adults towards deprescribing

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RESEARCH ARTICLE

Potentially inappropriate medication and attitudes of older adults towards deprescribing

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Abstract

Introduction

Multimorbidity and polypharmacy are current challenges when caring for the older population. Both have led to an increase of potentially inappropriate medication (PIM), illustrating the need to assess patients' attitudes towards deprescribing. We aimed to assess the prevalence of PIM use and whether this was associated with patient factors and willingness to deprescribe.

Method

We analysed data from the LESS Study, a cross-sectional study on self-reported medication and on barriers and enablers towards the willingness to deprescribe (rPATD questionnaire). The survey was conducted among multimorbid (≥3 chronic conditions) participants ≥70 years with polypharmacy (≥5 long-term medications). A subset of the Beers 2019 criteria was applied for the assessment of medication appropriateness.

Results

Data from 300 patients were analysed. The mean age was 79.1 years (SD 5.7). 53% had at least one PIM (men: 47.8%%, women: 60.4%%; p = 0.007). A higher number of medications was associated with PIM use (p = 0.002). We found high willingness to deprescribe in both participants with and without PIM. Willingness to deprescribe was not associated with PIM use (p = 0.25), nor number of PIMs (p = 0.81).

Conclusion

The willingness of older adults with polypharmacy towards deprescribing was not associated with PIM use in this study. These results suggest that patients may not be aware if they

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are taking PIMs. This implies the need for raising patients' awareness about PIMs through education, especially in females, in order to implement deprescribing in daily practice.

Background

An ageing population with multimorbidity (≥3 chronic conditions) and polypharmacy (≥5 long-term medications) poses a worldwide challenge to healthcare organisations, particularly in primary healthcare. As the prevalence of polypharmacy has increased due to high multimorbidity in especially the older population, potentially inappropriate medication (PIM) use has increased as well [1–3]. The single most important risk factor for PIM use is the number of prescribed medications [4]. Medications are considered 'potentially inappropriate' when its potential risk outweighs its clinical benefit in an individual [5]. Previous studies have reported a prevalence of PIMs between 40–80% [6–9]. Due to associated negative health consequences (e.g. reduced adherence and quality of life and increased risk of adverse drug reactions and hospitalizations), PIMs are an unnecessary burden to the older population [10–12].

Appropriate prescribing in the older population is challenging. First, older individuals have an increased risk of medication-related harm due to an age-related change in pharmacokinetics and -dynamics, a lower physiological reserve and drug-drug or drug-disease interactions [13–15]. Additionally, they are more susceptible to PIMs due to a lack of evidence regarding the benefits and harms of medications in multimorbid older adults and the frequently observed "prescribing cascade" where new medication is prescribed to treat a side effect of another medication [16]. Lastly, the application of single disease evidence-based guidelines to an individual with multimorbidity results in complex polypharmacy as they do not take into account potential drug- and disease-drug interactions [17,18].

The high prevalence and negative impact of PIMs, as well as the need to individualise therapy illustrates the importance of deprescribing in older individuals. Deprescribing is the process of withdrawal or dose reduction of inappropriate medications, supervised by a healthcare professional. This is endorsed by more recent guidelines, such as the NICE guidelines on multimorbidity and medication optimisation, that were developed to reduce polypharmacy and PIMs by recommending approaches on how to best manage and optimise pharmaceutical treatment in complex older adults [19,20].

Currently, deprescribing tools that assist physicians in detecting PIMs are increasingly being applied in daily practice. An example is the AGS Beers criteria, which is a globally used tool that lists PIMs that should be avoided in most older adults due to increased risk of harm or low/no benefit. Deprescribing can have a considerable positive impact on the health status and treatment burden of the older multimorbid population [21]. It may reduce adverse drug reactions, improve patients' quality of life and promote medication adherence [22–24]. Understanding patients' attitudes towards their medications and deprescribing can inform patient-centered care which is a key part of all clinical care [18].

Patients beliefs and attitudes towards deprescribing have increasingly been investigated [1,25–30], but whether these are correlated with appropriateness of their medications has not yet been determined. So far, quantitative research has mostly reported patients' and clinicians' attitudes towards deprescribing and investigated its relationship with patient-related factors (such as age). To date, the only medication-related factor that the revised Patients' Attitudes Towards Deprescribing questionnaire (rPATD) has been related with is the number of prescribed medications, with studies finding inconsistent results. It is not yet known how attitudes towards deprescribing may be related to the suitability of that individual for deprescribing (i.e.

whether they are taking a PIM). We hypothesized that patients who use PIMs experience more side effects than patients who do not use any PIMs, which in turn might affect their willingness to deprescribe.

In this study, we investigated whether there is an association of PIM use and willingness to deprescribe in older individuals and which factors influence patients' attitudes towards deprescribing. Second, we were interested to see how prevalent PIM was in a population of older patients with polypharmacy and which types of PIMs were most commonly used in men and women.

Methods

Design

The current study was nested in the LESS Study [31], which is a cross-sectional anonymous survey-study that evaluates the overall willingness to deprescribe and the barriers and enablers towards the willingness to deprescribe in older Swiss individuals with multimorbidity and polypharmacy. This manuscript reports the results of patients' attitudes towards deprescribing related to PIMs.

Study population

Sixty-four general practitioners (GPs) from the German-speaking part of Switzerland recruited primary care patients for involvement in this study. All of them were located in different GP offices. Eligible patients were ≥70 years old with multimorbidity and polypharmacy. Multimorbidity was defined as the presence of ≥3 chronic diseases, with chronic diseases being present for at least six consecutive months [32]. Polypharmacy was defined as the concurrent use of ≥5 long-term medications [33,34]. GPs were instructed to consecutively screen eligible patients and recruit 5 participants, reporting the number of patients screened, to reduce the risk of selection bias. The questionnaire was completed by a total of 306 patients, 6 of whom were excluded based on missing information about prescribed medication. Patients anonymously filled in the survey and handed it back to the practice nurse to limit the chance of social desirability bias.

Questionnaire

For this study, we used data from 300 questionnaires on demographic status like age, gender, living situation, help with medication intake, involvement in medication self-management and education level. As for willingness to deprescribe, we used data from the revised Patients' Attitudes Towards Deprescribing questionnaire (rPATD). This is a validated and reliable tool that has been applied in multiple studies [1,35–38]. It contains 22 questions on a 5-point Likert scale, ranging from "strongly agree" to "strongly disagree" which relate to beliefs and attitudes about their medications and deprescribing [37]. The rPATD was translated into German as previously described [31].

Medication appropriateness

In the present study, we used the self-reported list of prescribed medications and medication dosages for the assessment of PIMs. Self-reported medication is proven accurate and valid for long-term medication in the general population [39,40] and was chosen in this case to specifically focus on which medications patients report they take. The self-reported medication list was checked for inconsistencies (e.g. spelling errors) before analysis of PIMs was performed. In case of uncertainty regarding self-reported medication (e.g. due to poor or unreadable handwriting), in consultation with a GP researcher, the best applicable option was chosen

[41]. Next, each medication was coded according to the WHO ATC-coding system. For the assessment of medication appropriateness, a selection of the AGS Beers 2019 criteria was used [42]. The AGS Beers list is the most commonly used tool for assessment of PIMs worldwide [43]. Since data on medical conditions was limited in this study, we used only the criteria that were applicable without clinical information (52 of 97 criteria). A list of the included criteria is added in S1 Appendix. Criteria were excluded based on weak strength of evidence as defined in the AGS Beers list (n = 8) or lack of information (n = 37). Application of a subset of the Beers 2019 criteria is in line with previous studies that used subsets of the Beers criteria for assessing medication appropriateness [29,44–46].

Willingness to deprescribe

Our main outcome was the willingness to deprescribe in relation to medication appropriateness. We therefore analysed data from the rPATD where patients were asked if they are satisfied with their current medications and if they are willing to deprescribe if their doctor said it was possible, along with 20 other questions grouped into four factors: involvement, burden, appropriateness and concerns about stopping, as described elsewhere [1].

Ethics

Ethical approval for this study was obtained from the Ethics Committee of the Canton of Bern, Switzerland (Ref. 2017–02188). All patients provided written informed consent before participating in the study.

Statistical analysis

Before the analysis, consistency checks were performed on the complete data set including the AGS Beers criteria and uncertainties were resolved by consensus of two researchers. Descriptive results were presented in frequencies, proportions, means and standard deviations (SD), and 95% confidence intervals (CI) were appropriate. Hypothesis testing for categorical variables was done using Chi-squared tests and simple linear regression for continuous variables when normally distributed. Patients with at least one PIM in their medication list where grouped to 'PIM yes', all others to 'PIM no' (exposure).

The individual scores (n = 22) of the rPATD showed a non-normal distribution. For the multivariate model we therefore dichotomized each of the 5-point Likert questions as well as factor scores according to the median as done previously [1]. Individual scores equal to or higher than the median were placed in the "high score" group, whereas scores below the median were placed in the "low score" group. In a multivariate model with different components of the rPATD as the outcome (satisfaction, willingness to stop, involvement, burden, appropriateness, concerns about stopping) [1], we calculated odds ratios (OR) and adjusted for age, gender and number of medications. To account for possible clustering of answers from patients from the same GP, we chose a mixed-effects model with the individual GP as random-effects. In a sensitivity analysis, we repeated the same models but with number of PIMs as the exposure instead of PIM yes vs. no. Significance level was set at <0.05. Data analyses were performed using STATA version 15.2 (Stata Corp, College Station, TX, USA).

Results

For the overall analysis of polypharmacy levels and PIM, 300 participants were included, collectively taking approximately 2700 medications. Seventy-eight percent of all participants used 5–9 regular medications, with the remaining 22% using $\geq$10 medications (excessive

polypharmacy). Participants received on average 8 medications (SD 2.7). More than half of our sample (54%) received at least 1 PIM. The majority received 1 PIM (31.3%), 12.7% received 2 PIMs and 9.7% received ≥3 PIMs up to 7 PIMs. Gender distribution was approximately even, and participants had a mean age of 79.1 years (SD 5.7). The baseline characteristics of participants in each group (no PIM, 1 PIM and >1 PIM) are presented in Table 1. Age, living situation, medication self-management and education level did not significantly differ between participants receiving appropriate medication or PIM. We did, however, find an association of females having more PIM (p = 0.007) than men. Additionally, an association was found between a higher number of prescribed medications and PIMs (p = 0.002). Thus, patients receiving 10 or more medications (i.e. excessive polypharmacy) showed a significantly higher risk of taking PIMs (Table 1).

Fig 1 illustrates the proportion of participants who agreed to the individual questions about satisfaction with treatment and willingness to deprescribe and the proportion of participants with high factor scores stratified by PIM. The majority of participants were satisfied with their current medications (97.1% without PIM vs. 96.9% with PIM; p = 0.90) and were willing to have one or more of their medications deprescribed (74.3% without PIM, 79.9% with PIM; p = 0.25). From the four factor scores, we found more participants with PIM had high burden scores (61% vs. 49%; p = 0.029) and less had high concerns about stopping scores (53% vs. 65%; p = 0.034). The table in S2 Appendix provides more detail about the rPATD factors as shown in Fig 1. However, in the adjusted model the only association remaining was concerns about stopping which was significantly lower in patients with PIM compared to those without PIM (OR 0.55; 95%CI 0.33–0.92; p = 0.023). Moreover, this association disappeared in the sensitivity analysis where number of PIMs was the exposure instead of PIM yes vs. no (OR 0.86; 95%CI 0.69–1.09; p = 0.21).

The level of agreement to all individual rPATD questions for participants with PIM as compared to participants without PIM is presented in Table 2. There was a statistically significant difference in the proportion of participants who agreed with the question, "If my doctor recommended stopping a medicine I would feel that he/she was giving up on me" in participants taking ≥1 PIM compared to those without PIM (OR 0.49; 95%CI 0.29–0.82); p = 0.006). In the sensitivity analysis with number of PIMs as the exposure, the association became weaker (OR 0.80; 95%CI 0.62–1.02; p = 0.07).

Table 1. Baseline characteristics of participants stratified by medication appropriateness.

Baseline characteristics	Overall n = 300	No PIM n = 139 (46%)	1 PIM n = 94 (31%)	>1 PIM n = 67 (22%)	p-value[a]
Female, n %	139 (46)	55 (40)	42 (45)	42 (63)	0.007
Age, mean (SD)	79.1 (5.7)	79.0 (5.5)	78.9 (6.0)	79.5 (6.0)	0.61
Living alone, n %	100 (34)	49 (36)	27 (29)	24 (36)	0.48
Self-management of medication, n %	257 (86)	120 (87)	83 (88)	54 (82)	0.48
Education level, n %					0.33
Basic education	86 (29)	34 (24)	28 (30)	24 (36)	
Apprenticeship	146 (49)	68 (49)	49 (52)	29 (43)	
Higher education	68 (23)	37 (27)	17 (18)	14 (21)	
Number of medicines, mean (SD)	8.0 (2.7)	7.4 (2.3)	7.8 (2.4)	9.4 (3.5)	<0.001
5–9 medicines	233 (78)	117 (84)	74 (79)	42 (63)	
≥10 medicines	67 (22)	22 (16)	20 (21)	25 (37)	0.002

Abbreviations: SD, standard deviation; PIM, potentially inappropriate medication.

[a]p-value is significant at <0.05.

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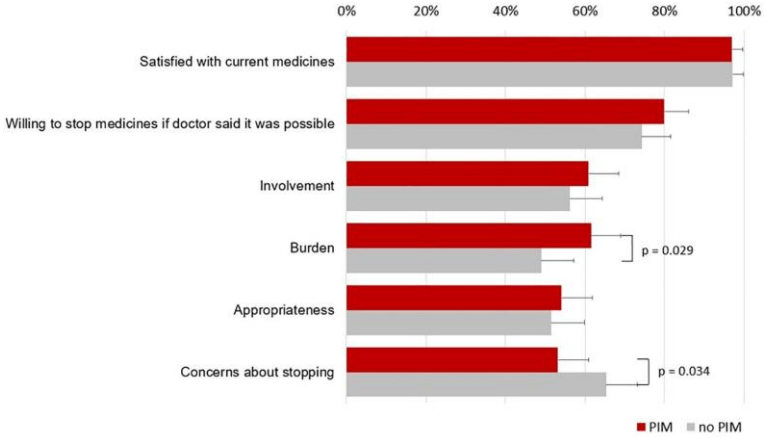

Fig 1. Proportion of participants who agreed to the individual questions about satisfaction with treatment and willingness to deprescribe and the proportion of participants with high factor scores stratified by PIM. Involvement, burden, appropriateness and concerns about stopping are factor scores from the rPATD questionnaire [25]. Each of the four factors consisted of 5 questions of which the possible score ranged from 1–5. We grouped the answers of each patient to either 'yes' (if the factor score was higher than the median) or 'no' (if the factor score was lower than the median). We then calculate the proportion of patients answering "yes". Abbreviations: PIM, potentially inappropriate medication; rPATD, revised patients' attitudes towards deprescribing. p-value is significant at <0.05.

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Fig 2 lists types of PIMs according to the 2019 AGS Beers criteria and their frequency by gender. We found proton pump inhibitors and benzodiazepines to be among the most frequent PIMs in our sample. Additionally, we found that certain PIMs differed by gender. Benzodiazepines ($p<0.001$), nonbenzodiazepines ($p = 0.003$), combinations of ≥ 3 CNS-active drugs ($p = 0.001$) and opioids in combination with benzodiazepines ($p = 0.004$) were significantly more frequent in females compared to males. Other drugs differed by gender as well including (peripheral alpha-1 blockers and estrogens).

Discussion

Summary

In this study, we found PIM to be prevalent (54%) in a consecutive sample of older patients with multimorbidity and polypharmacy in a primary care setting. PIM use was found to be higher in patients with more prescribed medications compared to less. Interestingly, females were more frequently prescribed a PIM, mostly benzodiazepines or other CNS-active drugs, than males. We observed no difference in patients' attitudes and willingness to deprescribe in patients with or without PIM. Our findings suggest that willingness to deprescribe is equally high in patients with and without PIM. There was also no difference in the adjusted analysis in burden, appropriateness or involvement factor scores, but participants taking PIM had lower concerns about stopping. This may therefore indicate that older adults with polypharmacy are not aware of whether they are taking potentially inappropriate medications or not. Therefore, efforts to increase awareness of the concept of PIM may be beneficial to shared-decision making about deprescribing in regular practice. Our study has also highlighted some areas that could be targeted, such as long term use of benzodiazepines in females.

Table 2. Level of agreement to deprescribing in patients with PIM compared to patients without PIM.

rPATD questions[a]	Odds ratio[b] for PIM vs no PIM	95% CI	p-value[c]
"Overall, I am satisfied with my current medicines"	1.06	0.25–4.45	0.93
"I like to be involved in making decisions about my medicines with my doctors"	1.22	0.68–2.21	0.51
"I have a good understanding of the reasons I was prescribed each of my medicines"	1.34	0.79–2.29	0.28
"I like to know as much as possible about my medicines"	1.01	0.61–1.65	0.98
"I always ask my doctor, pharmacist or other health care professional if there is something I don't understand about my medicine"	1.13	0.68–1.89	0.63
"I know exactly what medicines I am currently taking, and/or I keep an up to date list of my medicines"	1.10	0.55–2.18	0.79
"If my doctor said it was possible I would be willing to stop one or more of my regular medicines"	1.60	0.87–2.94	0.13
"I feel that I am taking a large number of medicines"	1.37	0.81–2.30	0.24
"Taking my medicines every day is very inconvenient"	0.89	0.51–1.54	0.67
"I spend a lot of money on my medicines"	0.91	0.54–1.53	0.72
"Sometimes I think I take too many medicines"	1.21	0.73–2.01	0.46
"I feel that my medicines are a burden to me"	0.86	0.53–1.41	0.56
"I would like to try stopping one of my medicines to see how I feel without it"	0.85	0.51–1.40	0.51
"I would like my doctor to reduce the dose of one or more of my medicines"	1.18	0.72–1.92	0.52
"I feel that I may be taking one or more medicines that I no longer need"	1.47	0.91–2.38	0.12
"I believe one or more of my medicines may be currently giving me side effects"	1.14	0.68–1.92	0.61
"I think one or more of my medicines may not be working	0.94	0.13–7.08	0.95
"I have had a bad experience when stopping a medicine before"	0.60	0.35–1.03	0.06
"I would be reluctant to stop a medicine that I had been taking for a long time"	0.71	0.43–1.15	0.16
"If one of my medicines was stopped I would be worried about missing out on future benefits"	0.77	0.48–1.25	0.30
"I get stressed whenever changes are made to my medicines"	0.82	0.50–1.36	0.45
"If my doctor recommended stopping a medicine I would feel that he/she was giving up on me"	0.49	0.29–0.82	0.006

Abbreviations: rPATD, revised patients' attitudes towards deprescribing; PIM, potentially inappropriate medication; CI, confidence interval.

[a] from [25].

[b] Odds ratio is adjusted for age, sex, number of medicines and general practitioners.

[c] p-value is significat at <0.05.

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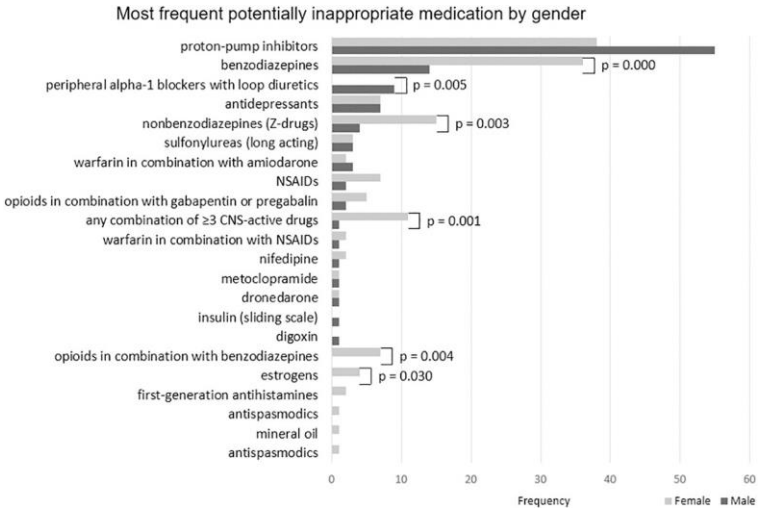

Fig 2. Potentially inappropriate medication stratified by gender. Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; CNS, central nervous system. p-value is significant at <0.05.

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Comparison with existing literature

The proportion of participants receiving at least one PIM matches previous studies from several countries worldwide, which generally report prevalence's between 40 and 80% [6–9,47]. We demonstrated that patients receiving 10 or more medications show a significantly higher risk of PIMs. This confirms findings from previous studies that the number of medications is the most important risk factor for PIMs [4,8,48]. Furthermore, we detected a correlation between gender and prevalence of PIMs. It has been previously reported that females receive a higher number of PIMs on average than males [7,47–50]. It has been suggested that this might be due to females being at a higher risk for developing multiple chronic conditions compared to males. This would imply that they are more susceptible to drug-drug and drug-disease interactions, which challenges appropriate prescribing [47]. Yet, the actual reason for this gender-difference is unknown. Similar to previous studies internationally [29,51], proton-pump inhibitors and benzodiazepines were the most common PIMs identified in our study population.

Interestingly, we found that patients' reported willingness to deprescribe is not related to PIM use according to the 2019 AGS Beers criteria. As investigated in a recent study on PIM and deprescribing interventions that explored factors associated with deprescribing refusal, likewise, PIM use was not associated with acceptance or refusal of deprescribing [29]. Previous qualitative studies on deprescribing, have reported that patients generally lack knowledge of the potential harms of medications and rely on the GP as a central and prominent figure in decision-making [52,53]. These findings suggest that older adults are not aware of whether their medications are appropriate or not. Reported willingness to deprescribe was equally high in our participants with and without PIM. Furthermore, very few of the individual factors had evidence to support a relationship with the use of PIMs, which stems from the fact that the study might not have been sufficiently powered to detect such differences. The factors 'burden' and 'concerns about stopping' were associated in the unadjusted analyses, but the burden

association was lost in the adjusted analyses (likely because of the confounding nature of PIMs being associated with number of medications). Therefore, it is still unclear if and how use of inappropriate medications influences attitudes and beliefs or vice versa. The overall high willingness of older adults with polypharmacy to deprescribe is promising for further implementation of deprescribing in primary healthcare and is in line with prior studies investigating patients' attitudes towards deprescribing [1,25–30].

Limitations and strengths

We acknowledge several limitations in our study. First, we gathered information on prescribed medications through self-reported medication lists, which might have affected the completeness of the medication lists. The accuracy of self-reported medication data can vary with medication type and duration; with self-reporting generally being more accurate for long-term medications [39,40]. Specifically, certain medication categories (e.g. psychoanaleptics and analgesics) were previously found to be less reliably self-reported [40]. Therefore, by using self-reported medication lists in this study, our results may be an underestimation of the use of PIMs. Second, the prevalence of PIMs in our sample might be underestimated due to the limited generalizability of the Beers criteria, published by the American Geriatrics Society, as they are based on medications commonly prescribed in the United States. Additionally, the Beers criteria capture 'potentially' inappropriate medications and so the assessment of appropriateness is not individualised. Third, the recruitment of study participants by GPs could have introduced selection bias. However, since consecutive sampling was used for participant inclusion–as it was not possible to recruit a random sample–the risk of selection bias was minimised. Lastly, since our sample consisted of Swiss older patients, we do not know if our findings are generalizable to other populations. However, as other countries reported similar attitudes towards deprescribing (e.g. 88% willingness to deprescribe in Australia [1], 89% in Italy [25] and 92% in the USA [27]) this increases the confidence in our findings.

To the best of our knowledge, we were the first to investigate the relation between medication appropriateness and patients' willingness to deprescribe using validated tools. The Beers criteria is the most widely used tool for medication appropriateness and has proven to be accurate in the assessment of PIM [42,43]. The Beers 2019 version is updated according to the latest evidence and includes drug-drug interactions when assessing PIMs. Lastly, we used the rPATD questionnaire, which is validated and has been used internationally to assess willingness to deprescribe [37,54]. We followed international standards with independent forward and back translation to translate the rPATD into German.

Implications for future practice and research

Although we did not detect an association of PIM and willingness to deprescribe, we did see positive trends of patients on PIM towards, for instance, the perception of having more side effects (14%) and taking medication they no longer need (47%). However, since willingness to deprescribe is equal, this implies that patients' willingness does not seem to be driven by knowledge that they are on a PIM. This again indicates the need to raise awareness about PIMs in older patients with polypharmacy, especially in females. Clinicians should be encouraged to regularly discuss deprescribing and the fact that the risks and benefits of medication use can change over time. Currently, patient education materials are increasingly being developed that will likely add to patients understanding of PIMs [55]. However, the group most at risk for PIM are vulnerable (oldest-) old patients [13–15] that demonstrate highly varying care wishes and needs, thereby challenging clinicians to provide appropriate care. Hence, in addition to our main finding–medication appropriateness being independent of patients'

willingness to have medication deprescribed–this pleads for an even bigger role of shared decision-making in the deprescribing process.

Future studies should further investigate the relationship between enabling factors of deprescribing and medication appropriateness and whether patients' attitudes and beliefs about medications may change with education [56]. Furthermore, they should focus on what patients consider inappropriate medication and which medications they would be willing to stop. Specific questions about patients' awareness about PIMs should be included in future research. As we found PIMs to be more prevalent in females compared to males, gender specific causes of PIM should be assessed in future studies. We also suggest focusing on specific classes and/or categories of medications in future research into PIM and willingness to deprescribe as this has not yet been explored and could be informative for translating into practice. Lastly, future studies should apply multiple PIM assessment tools, as well as comprehensive medication reviews determining actual appropriateness.

Conclusion

We found PIM to be prevalent in the older population and patients to be generally willing to deprescribe. Patients' willingness to deprescribe was found to be irrespective of whether they were taking one or more PIMs. Female gender and increasing number of prescribed medications were positively associated with PIM use. Our results imply that it is necessary to raise awareness among older patients on PIMs, especially in females.

Supporting information

S1 File.
(XLS)

S1 Appendix. List of included Beers 2019 criteria.
(TIF)

S2 Appendix. Results of the rPATD factor scores.
(TIF)

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15.1.4 Rationale and design of Optimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people (OPERAM): a cluster randomised controlled trial

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Rationale and design of OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people (OPERAM): a cluster randomised controlled trial

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ABSTRACT

Introduction Multimorbidity and polypharmacy are important risk factors for drug-related hospital admissions (DRAs). DRAs are often linked to prescribing problems (overprescribing and underprescribing), as well as non-adherence with drug regimens for different reasons. In this trial, we aim to assess whether a structured medication review compared with standard care can reduce DRAs in multimorbid older patients with polypharmacy.

Methods and analysis OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people is a European multicentre, cluster randomised, controlled trial. Hospitalised patients ≥70 years with ≥3 chronic medical conditions and concurrent use of ≥5 chronic medications are included in the four participating study centres of Bern (Switzerland), Utrecht (The Netherlands), Brussels (Belgium) and Cork (Ireland). Patients treated by the same prescribing physician constitute a cluster, and clusters are randomised 1:1 to either standard care or Systematic Tool to Reduce Inappropriate Prescribing (STRIP) intervention with the help of a clinical decision support system, the STRIP Assistant. STRIP is a structured method performing customised medication reviews, based on Screening Tool of Older People's Prescriptions/Screening Tool to Alert to Right Treatment criteria to detect potentially inappropriate prescribing. The primary endpoint is any DRA where the main reason or a contributory reason for the patient's admission is caused by overtreatment or undertreatment, and/or inappropriate treatment. Secondary endpoints include number of any hospitalisations, all-cause mortality, number of falls, quality of life, degree of polypharmacy, activities of daily living, patient's drug compliance, the number of significant drug–drug interactions, drug overuse and underuse and potentially inappropriate medication.

Ethics and dissemination The local Ethics Committees in Switzerland, Ireland, The Netherlands and Belgium approved this trial protocol. We will publish the results of this trial in a peer-reviewed journal.

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Trial registration number NCT02986425, SNCTP000002183, NTR6012, U1111-1181-9400.

Strengths and limitations of this study

- This is the first multicentre randomised trial that examines the impact of a structured approach to optimise pharmacotherapy in multimorbid older people on drug-related hospital admissions.
- This is one of the largest trials undertaken in the growing population of multimorbid older adults; a population, that is, to date poorly investigated and often excluded from large scale trials.
- We chose a cluster randomisation design in order to limit potential contamination from a learning effect among the prescribing physicians; however, the cluster design of this trial entails some potential for selection bias.
- A blinded adjudication committee (pharmacist and senior physician) for each site will judge whether a hospital admission during follow-up should be considered a drug-related hospital admission.

INTRODUCTION

Patients with multimorbidity have been excluded in >60% of the randomised controlled trials (RCTs) published in high-impact journals during the last 15 years due to

their complexity and frailty.[1] This finding is in contrast to the rapidly growing numbers of patients with coexisting chronic diseases, with associated increased mortality,[2] decreased health-related quality of life (QoL), increased healthcare utilisation, increased hospital admissions[3 4] and higher rates of drug prescriptions with subsequent polypharmacy.[5] Polypharmacy refers to the concurrent use of multiple drugs, often defined as taking ≥5 long-term medications.[6] Appropriate polypharmacy can improve health-related QoL and prevent consequences of diseases, whereas inappropriate polypharmacy is often harmful, particularly in multimorbid older people.[6] Polypharmacy increases the risk of inappropriate prescribing, defined as misuse of medication or overtreatment and drug–drug interactions.[7–9] With polypharmacy, there is also an increased risk of non-compliance, adverse drug reactions (ADRs), drug–drug and drug–disease interactions.[10] Inappropriate prescribing can lead to a drug-related hospital admission (DRA),[11] lower QoL and a higher number of falls.[12 13] The incidence of DRAs in older people may be as high as 30% of all hospital admissions,[13–15] and about half of DRAs are considered potentially preventable.[13 16]

Literature reviews recently suggested that interventions optimising polypharmacy could reduce inappropriate prescribing[17 18] and the risk of ADRs.[19] The Screening Tool of Older People's Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) criteria[20] have been developed by geriatric medicine and pharmacotherapy experts based on review of up-to-date evidence and consensus validation to screen for inappropriate prescribing; they have also been shown to significantly improve medication appropriateness.[21] This property of STOPP/START criteria therefore, has the potential to reduce DRAs.[22] The Systematic Tool to Reduce Inappropriate Prescribing (STRIP) is a tool that combines STOPP/START criteria to increase appropriate prescribing for older people.[23] However, until now, only a few RCTs have examined the impact of reducing inappropriate medications on clinical outcomes and they had several limitations, such as missing adjudication of DRAs by an independent adjudication committee, no cluster randomisation (contamination bias) or small sample size, young population and/or short follow-up time, leaving currently considerable uncertainty on the best ways to improve the appropriate use of polypharmacy.[14 24 25]

The OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people (OPERAM) trial will examine the effect of a structured medication review (STRIP) supported by the STRIP Assistant (STRIPA) clinical decision support software on DRAs (main endpoint) compared with usual care. Secondary endpoints include number of any hospitalisations, all-cause mortality, number of falls, QoL, degree of polypharmacy, activities of daily living (ADL), patient's drug compliance, as well as the number of significant drug–drug interactions, drug overuse and underuse and potentially inappropriate medication.

METHODS AND ANALYSIS

General study design and setting

OPERAM is a European multicentre cluster RCT. A prescribing physician will define a cluster. Older hospitalised patients with multimorbidity and polypharmacy will receive either a structured drug review or usual care, according to the allocation of their prescribing physician. Clusters will be randomised 1:1 to either the intervention arm (drug review) or usual care. Patients will be followed-up by phone at 2, 6 and 12 months after inclusion; information may be provided by proxy persons (table 1).

Table 1 Study population, intervention, control and outcomes

Population	Consecutive **older adults** (≥70 years) with **multimorbidity** (≥3 chronic medical problems) and **polypharmacy** (≥5 regular drugs for >30 days).
Intervention	**Pharmacotherapy optimisation** based on the Systematic Tool to Reduce Inappropriate Prescribing through (1) systematic medication review by a physician and a pharmacist, with support of the STRIP Assistant, a software-based tool taking into account the predictable adverse medication effects, advising safe and appropriate therapy using established STOPP/START criteria, monitoring clinically relevant interactions and dosing appropriately in accordance with renal function, (2) drug discussion and adaptation with the prescribing physician, (3) shared decision-making with the patient and (4) generation of a report with specific recommendations for the patient's general practitioner.
Control	**Usual practice** and a sham intervention using a questionnaire (Medication Adherence Measure Questionnaire, ©MMAS[30–32]*) by a team member (the physician or the pharmacist) to mimic the intervention and improve blinding of the patient and other blinded team members.
Outcomes	*Primary*: **drug-related hospital admission** within 1 year after enrolment *Secondary*: number of any hospitalisations, mortality, number of falls, quality of life, degree of polypharmacy, activities of daily living, patient's drug compliance, as well as the number of significant drug–drug interactions, drug overuse and underuse and potentially inappropriate medication.

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START/STOPP, Screening Tool of Older People's Prescriptions/Screening Tool to Alert to Right Treatment.

This study protocol follows the Standard Protocol Items: Recommendations for Interventional Trials guidelines.[26]

Objective

This study aims to compare the effect of a structured medication review (supported by the STRIPA software) versus usual care on DRAs. Secondary endpoints include number of any hospitalisations, mortality, number of falls, QoL, degree of polypharmacy, ADL, all-cause mortality, patient's drug compliance, as well as the number of significant drug–drug interactions, drug overuse and any rehospitalisation occurring within 1 year after the index-hospitalisation, underuse and potentially inappropriate medication.

Cluster definition

The trial is conducted in four University Hospital Centres in Europe (Bern, Switzerland; Utrecht, The Netherlands; Brussels, Belgium; Cork, Ireland). Clusters are defined by the prescribing physician, that is, the single physician who has the final responsibility for the pharmacotherapy and treatment of patients in the department/ward and also decides on the implementation of potential treatment suggestions made by involved specialists. Clusters are possible in any department/ward at each site with a relevant proportion of the appropriate patient population (multimorbid older people with polypharmacy, see above), where patients are not included in another trial aiming at optimising drug therapy. Recruitment of potential physicians follows a multilevel approach: first, eligible departments/wards are identified by the local principal investigator and then prescribing physicians are enrolled in order to each form a cluster within the trial. Enrolment and opening of clusters is distributed over the complete recruitment period to ensure an approximately similar number of open clusters in each site at any time. The recruitment target ranges from a minimum of 12 to a maximum of 38 patients per cluster in order to achieve recruitment of 2000 patients.

Inclusion criteria

Consecutive patients are screened for eligibility and recruited from the clusters at each site. Inclusion criteria are age 70 years or older, multimorbidity (defined as three or more chronic medical conditions) and polypharmacy (defined as use of five or more regular drugs for >30 days). Written informed consent by patients themselves or, in the case of cognitive impairment by a legal representative, is required before enrolment.

Exclusion criteria

Exclusion criteria are reduced to a minimum to allow for maximum generalisability. Only patients planned for direct admission to palliative care (<24 hours after admission), or patients undergoing a structured drug review other than the trial intervention, or who have passed a structured drug review within the last 2 months are deemed ineligible.

Randomisation

In this study design, each prescribing hospital physician defines a cluster. Physicians are allocated 1:1 to either the intervention arm or the control arm, using a probabilistic minimisation method implemented by a web-based clinical trial management system (WebSpirit hosted by the Clinical Trials Unit (CTU) Bern). Minimisation is done according to country in order to ensure a balanced distribution of hospitals. The minimisation algorithm is implemented using randomisation lists generated by an independent statistician in Stata (StataCorp., Stata Statistical Software Version 14). Only system administrators who are otherwise not involved in the conduct of the trial have access to the randomisation lists, to ensure concealment of allocation.

Blinding procedures

This study is partially blinded, with blinding implemented at each site as follows (table 2):

- *Screening and enrolment.* A person blinded to the allocation of recruiting clusters screens and enrols patients in order to avoid selection bias. Coded information (gender, age, multimorbidity, degree of polypharmacy and so on) from all screened patients is collected and regularly monitored centrally to assess the risk of selection bias. The blinded person works separately from the rest of the trial team at that site and all team members signed a non-disclosure form to limit unblinding of this person.
- *Patients.* A tailored informed consent procedure is implemented in which patients are given a 'high-level description' of the study objectives with only superficial information on the study intervention, as accepted by the ethics committees. They are informed that their prescribing physician is allocated to one of the study groups without revealing which study group it is in order to minimise performance and other reporting biases during follow-up. Patients randomised to the control arm undergo an attention sham intervention (figure 1).
- *Prescribing physician.* Similarly, the cluster-defining physician is not informed about his/her study arm allocation, receiving only a minimum amount of required information regarding the study objectives, as described above. Furthermore, each cluster-defining physician signs a non-disclosure contract to limit unblinding.

To communicate study inclusion and results of the medication review to the patients' general practitioner (GP), all GPs receive the same standardised high-level information about the study goals and a document indicating that one of their patients has been included. For those patients in the intervention arm, the GPs additionally receive a report about the recommendations from the intervention (STRIPA report).

- *Follow-up.* A blinded trial team member assesses the trigger events for the primary outcome and all secondary outcomes by telephone interview. In case

Table 2 Blinding status and measures to assure blinding

	Blinding status	How to achieve blinding
Recruitment team (study nurse/ research physician)	Blinded	Randomisation status will be kept concealed from the recruiting team, no access is given to unblinded study information in the database or locally to the source data.
Intervention team (physician, pharmacist)	Unblinded	In order to perform a safe intervention, including a shared decision-making with the patient, blinding is impossible.
Follow-up team (study nurse)	Blinded	Randomisation status will be kept concealed from the team conducting follow-up calls, no access is given to unblinded study information in the database or locally to the source data. In case an event or serious adverse event has occurred, the unblinded study team will be informed.
	Unblinded	This team is informed about the treatment allocation. They collect the necessary information about events and anonymise revealing information about allocation on the documents for the adjudications. Make safety assessments.
Adjudication (pharmacist/ physician)	Blinded, work independently from study team	Receives only blinded information on hospital admission and deaths after study inclusion.
Patients	Partially blinded	Will be seen by the study team in case of intervention or control allocation. Control patients undergo a sham intervention using the ©MMAS-8.[30–32]
Prescribing physician	Partially blinded	Will receive only high-level information about the trial. Every prescribing physician who defines a cluster will sign a disclosure form in order not to share information about the approach of the study team with their colleagues.
General practitioner	Partially blinded	Will receive only high-level information about the trial using an information flyer that does not inform about the two different study arms. The GP will receive a form about study inclusion for each patient (regardless of study allocation), and in the case of the intervention group, the GP will also receive the STRIPA report.

©MMAS, Medication Adherence Measure Questionnaire; GP, general practitioner; STRIPA, STRIP Assistant.

of hospital readmission, an unblinded team member is informed by the blinded follow-up interviewer. The unblinded team member then collects the necessary documentation and information about the hospitalisation and ensures any clue about the treatment allocation is concealed before giving the documents to the adjudication board.

- *Adjudicators.* Blinded independent adjudication boards composed of an experienced pharmacist and physician at each study site adjudicate the primary outcome (DRA) using a standardised chart review method.[27]

Intervention

An unblinded, independent trial team composed of a research physician and pharmacist conducts the intervention during the hospital stay of the study participant. All team members conducting the intervention underwent training prior to the beginning of the study. The study intervention is a structured method to perform pharmacotherapy optimisation called STRIP. The STRIP intervention consists of nine steps and is administered early during the index hospitalisation. In order to enable healthcare providers to incorporate STRIP into daily practice the so-called STRIPA has been developed, a stand-alone web application of the STRIP. It is a software-based tool for the support of the pharmaceutical analysis (step 2 of STRIP) by means of (1) taking into account the predictable adverse medication effects, (2) advising safe and appropriate therapy using established STOPP/START criteria,[20] (3) monitoring clinically relevant interactions and (4) dosing appropriately in accordance with renal function. With STRIPA, the number of correct medical decisions during a medication review was significantly increased, whereas the number of inappropriate medication decisions was reduced.[28] The nine steps of STRIP are as follows.

1. Structured history taking of medication using a questionnaire for taking the medication history based on the medication taken at home: Structured History taking of Medication use questionnaire.[29]
2. Recording of medications and diagnoses in the decision-support software with implemented STOPP/START criteria (STRIPA).
3. Structured medication review, including evaluation of STRIPA recommendations, by a qualified physician and pharmacist.
4. Generation of a report with specific recommendations for the prescribing hospital physician.
5. Communication and discussion of the structured drug review report with the prescribing physician, with possible adaptation of recommendations. The prescribing physician remains responsible for final decisions on drug therapy.
6. Shared decision-making with the patient to take into account patient preferences, again with possible adaptation of recommendations.

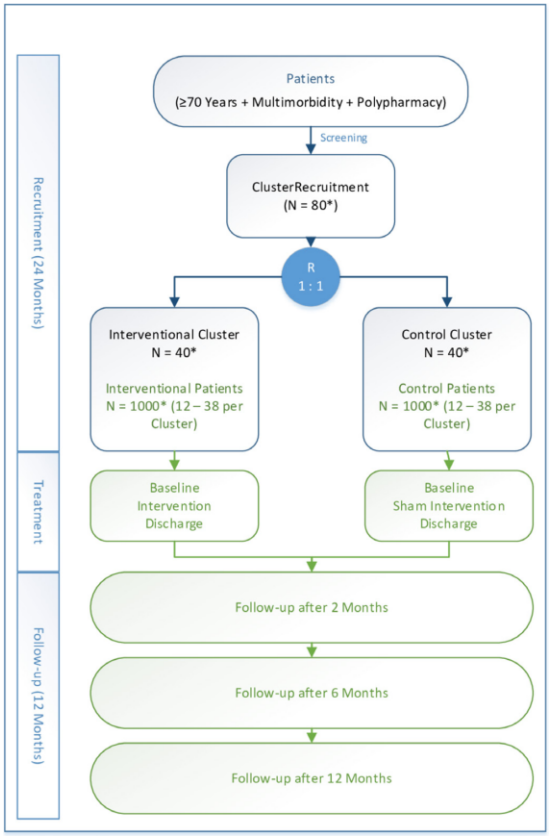

Figure 1 Study flowchart (*planned numbers).

7. Revision based on new data acquired during hospitalisation (eg, new diagnoses, occurrence of ADRs).
8. Generation of a report with specific recommendations for the patient's GP (STRIPA report).
9. Mail delivery of the report to the GP with optional, additional direct communication.

Control intervention (standard/routine/comparator)

Participants in the control group receive medication review by their prescribing physicians in accordance with usual practice at each site. A sham intervention is conducted using the Medication Adherence Measure Questionnaire (©MMAS-8).[30–32] The ©MMAS-8 sham intervention is administered by the team members who are also conducting the intervention, to mimic the intervention. This helps to maintain the blinding status of the patients and blinded team members.

Follow-up

Follow-up and outcome data will be gathered via telephone interviews at 2, 6 and 12 months after the index hospitalisation. Included patients or their proxy persons will be interviewed by a blinded trial team member to assess the trigger events for the primary outcome and all secondary outcomes. If necessary, the treating physician of the included participant will also be contacted to complete the missing data.

Assessment of primary outcome

The primary patient-level outcome of this trial is the first DRA, that is, rehospitalisation within 1 year after enrolment. Rehospitalisations are detected during the follow-up telephone interviews by asking the patient or proxy person directly about any hospital stays since discharge from the index hospitalisation. For all patient-reported rehospitalisations occurring after the initial discharge, detailed documentation will be requested from the respective hospital.

An independent and blinded adjudication committee (per site) composed of one physician and one pharmacist adjudicates the drug relatedness of each hospital admission using a standardised adjudication guideline.[27] For each patient, reported hospitalisations are adjudicated consecutively until the first DRA is confirmed by the adjudication committee. We only consider hospitalisations for adjudication that are preceded by discharge from the hospital where the patient was enrolled in the trial and where the patient is managed in hospital for longer than 24 hours (but not hospitalisations for a diagnostic or elective procedure for a pre-existing condition). The hospital admission is assessed for its relationship with the medication taken by the study participant prior to rehospitalisation. To assess the inter-rater reliability of our standardised adjudication guideline to identify DRA, a certain amount of common cases will be evaluated by adjudicators from all study sites.

Assessment of secondary outcomes

We assess secondary outcomes after enrolment (to generate a baseline) and during the follow-up telephone calls.

Secondary endpoints include number of any hospitalisations, all-cause mortality, number of falls, QoL, degree of polypharmacy, ADL, patient's drug compliance, as well as the number of significant drug–drug interactions, drug overuse and underuse and potentially inappropriate medication.

All follow-up information is assessed via telephone call by a blinded trial team member at 2, 6 and 12 months of follow-up. In case the patient cannot be reached, the team member conducting the telephone interviews attempts to identify the patient's survival status and collect the required information at any of the follow-up calls by contacting family members/proxies, responsible person from a nursing home (if applicable) or the patient's GP.

The team member asks specifically about recent hospitalisations and healthcare utilisation (including unscheduled physician consultations and visits to the emergency department without hospital admission). Furthermore, the medication currently taken by the patient is recorded, as are adverse medical events including adverse drug events and ADRs as well as falls. If necessary (eg, if the

patient does not remember his/her current medication), this information is obtained by contacting patients' GPs, pharmacists, proxies or responsible persons from a nursing home. The degree of polypharmacy is defined as the number of regular chronic medications (<10 vs ≥10). QoL is assessed using the five dimensional EuroQOL (EQ-5D) instrument.[33] ADL are assessed using the Barthel Index basic ADL questionnaire.[34]

Drug compliance is measured using the ©MMAS-8.[30–32] The numbers of drug–drug interactions, drug overuse and underuse, as well as potentially inappropriate medication are assessed for the intervention group at 2 months, based on STRIPA information including the medical diagnoses from the index hospitalisation and the updated medication list from the 2-month telephone follow-up. Assessment of safety outcome will be based serious adverse events. In addition, all recorded device deficiencies will be described.

Data management

All data will be entered electronically using a dedicated electronic data capturing system (WebSpirit) hosted by CTU Bern. Original study forms will be entered and kept on file at each participating study site. Only system administrators will have direct access to the server. For quality control of the study conduct and data retrieval, all study sites will be visited on-site by appropriately trained and qualified monitors of CTU Bern. Data management and monitoring works independently from study investigators. All principal investigators will be given access to the cleaned datasets.

Study duration

We plan to recruit participants over a period of about 2 years. Once recruited, participants will be followed-up for 1 year.

Sample size

Sample size calculation was done using Stata Statistical Software and the *clustersampsi* command V.st0286 2.[35] We estimated that the event rate of experiencing at least one DRA over a 12-month follow-up (primary endpoint) is ~20% in the control group.[15 36] We assumed that patient deaths and drop-outs would be increasing during the follow-up phase and that the DRA event rate would slightly decrease over time. Combining these assumptions with an overall mortality of 20%[37] and a drop-out rate of 6% both at 1 year, we estimated the event rate in the control group at 19.5%. We aimed to detect a 30% relative risk reduction by the intervention at a two-sided alpha of 5%, assuming an intracluster correlation of 0.02 as typically found for binary outcomes in elderly individuals.[38]

This translates into an expected DRA event rate of 13.7% in the intervention group. We also performed a survey at all trial sites to realistically estimate the number of available clusters. All sites responded and the overall number of clusters available for the trial was estimated at ~80. The same survey revealed that a cluster size of 25 participants would be realistic but that this might vary from cluster to cluster. We therefore allowed for variable cluster size with a coefficient of variation of 0.25 (effectively allowing for a cluster size ranging from 12 to 38 participants). Based on these assumptions, 2000 patients, 1000 patients in each arm, need to be recruited over 24 months in order to have 80% power in order to show a statistically significant difference for the primary endpoint.

Statistical analysis

All statistical analyses including a description of all relevant derivations of variables will be described in a statistical analysis plan before the end of recruitment and without inspection of the data. A statistician at CTU Bern will perform the statistical analyses using R Statistical Software.[39]

In the primary analysis, all patients will be analysed using the FAS (full analysis set) according to the intention-to-treat principle. The primary outcome, first confirmed DRA after discharge, will be analysed by using a mixed-effects survival model with a fixed effect for the intervention group and random-effects for centre and treating physician to account for clustering. To deal with competing risks (ie, death as competing risk for DRA), we will use extensions of the Fine-Gray proportional hazards model that account for clustering in competing risk settings.

Secondary time-to-event outcomes will be analysed using Kaplan-Meier curves and a mixed-effects Cox proportional hazards model with a fixed effect for the intervention group and random effects for centre and treating physician. Binary outcomes will be analysed using a mixed-effects logistic regression model using a fixed effect for the intervention group and random effects for centre and treating physician. Continuous outcomes will be analysed using mixed-effects linear model with a fixed effect for the intervention group and random effects for centre and treating physician, adjusted for the baseline value as a covariate if available.

To deal with dropouts and losses to follow-up (expected to be mainly caused by death), we will employ two different strategies: in the first approach, we will impute missing data. In the second approach, we will explore whether data allow for joint modelling of repeated measures and survival data.

In a secondary per-protocol (PP) analysis, all outcomes will be evaluated as described above based on the PP analysis set. Since cluster randomisation may lack the excellent balancing in characteristics between groups seen in individual-level randomisation, we will also adjust each model for additional patient-level, physician-level and hospital-level variables in a sensitivity analysis.

Ethics and dissemination

The local ethics committee at each site has approved the study protocol and other documentation concerning the study conduct. Where needed, approval by a regulatory authority has been obtained before enrolment of the first patient. All participants and their data are handled

according to the ethical principles of the Declaration of Helsinki.[40] This study complies with all applicable standards of the International Conference on Harmonisation E6 Guideline for Good Clinical Practice (ICH-GCP 1996) guideline.[41] The ethics committees and regulatory authorities receive annual safety reports and will be informed about study stop/end in agreement with local requirements. OPERAM embraces an open access policy and strives for complete dissemination of all resulting data, clinical results and publications.

Patient and public involvement

A patient organisation was involved in the trial design and the development of the research question and the choice and measure of the outcomes (WHO Patients for Patient Safety Advocate Group; http://www.who.int/patientsafety/patients_for_patient/en/), as well as in the conduct of the study by being member of the scientific advisory board. Patients were actively involved in several steps of the process of developing the core outcome sets. Specifically, semistructured interviews with older patients and caregivers were undertaken in order to identify the most relevant outcomes for older individuals and stakeholders.[42] To limit the burden of the intervention, special adaptations were planned for very old and sick patients (printable versions of the questionnaires, filling the questionnaire with an interviewer, priority lists to reduce the burden of the intervention) based on pilot patients and first patients enrolled, as well as specific processes for patients with of cognitive impairment, with the support of their relatives. Patients have no role in the recruitment of study participants, but are actively involved in the study intervention through shared decision-making. The results of this study will be disseminated to the patients through newsletters and through the above-mentioned patient organisation.

DISCUSSION

This is the first large multicentre randomised trial that examines the impact of a structured approach to optimising pharmacotherapy in hospitalised multimorbid older individuals on clinical outcomes, including DRAs, inappropriate medication use and QoL. It will also be one of the largest trials in the growing population of multimorbid older adults that are currently understudied, as they are often excluded from trials due to their age and multimorbidity[1]; as a result, clinical guidelines are based on evidence that might not relate to patients with multimorbidity, underlining the need of this trial among elderly patients with multimorbidity.

The above described trial has several important strengths: it is a multicentre, large trial with broad inclusion criteria and very few exclusion criteria in order to provide good external validity. Patients with cognitive impairment will not be excluded, as this population is particularly prone to polypharmacy and its negative consequences and may particularly benefit from medication optimisation.[43] The studied intervention is well defined with clear steps. The primary outcome (DRA) is adjudicated according to well defined standard operating procedures by an adjudication committee consisting of experienced physicians and pharmacists.

Limitations to this trial are the cluster randomised design, which was chosen to avoid a learning effect of the prescribing physicians allocated to the control group. However, this design is susceptible to selection bias, which we will try to avoid through measures summarised below. Finally, the outcome assessment at follow-up is based on the patient's or proxy's self-report and might therefore miss some events. In this cohort of multimorbid older patients, the death rate is expected to be high and we will have to account for death in our analyses.

Potential problems and solutions

To avoid possible selection bias, we aim to keep the study personnel as blinded as possible. Due to the nature of the intervention, complete blinding of all the study staff (eg, the staff conducting the intervention) is not possible. However, recruiting study staff and outcome assessors are kept blinded as to the randomisation status of patients, at all times. Study source data with unblinding potential are stored in a secure place without investigator access. Patients are kept partially blinded from the allocation of their prescribing physician (table 2). All patients included in the study control arm undergo a sham intervention in order to mimic the procedure of the intervention arm.

Outcome assessors are blinded concerning the patient's study group allocation. Adjudication is carried out based on completely anonymised information about deaths and rehospitalisations acquired by the unblinded study personnel. Due to legal regulations and language issues (hospital reports and follow-up notes during hospitalisations are in the local language), a central data adjudication is not possible. However, we cross-reference a limited number of events in a central manner in order to avoid site-specific bias.

In order to avoid bias from cluster contamination, clusters are temporarily closed in case of absence of the prescribing physician. There is the potential of contamination at the level of a patient's GP; however, we used partial blinding of GPs who receive only standardised high-level information about the study goals. Also, the number of GPs with patients in both the intervention and control group is expected to be small, given that the number of GPs referring patients to the enrolling leading university leading centres is very large.

To assess the potential for selection of a specific subpopulation into the trial and better understand generalisability of the study results, we will compare differences in selected characteristics such as age and gender of consenting and non-consenting patients.

CONCLUSION

The cluster-randomised OPERAM trial aims to add to provide direct evidence of best care for the growing

population of older and multimorbid persons among the wider European population. The trial exclusively includes patients aged ≥70 years with multimorbidity for whom few direct comparisons of pharmacotherapy strategies exist. In the long term, we hope to contribute to an improved health status for the rapidly growing older population with multimorbidity and polypharmacy.

Current status of the OPERAM trial

The OPERAM trial started recruitment in December 2016. The trial follow-up will be completed in the 2nd semester of 2019.

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Author note The trial protocol has been peer-reviewed for ethical and funding approval prior to submission.

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15.2 Non-Peer-Reviewed Publications

15.2.1 Klinische Studie zur Medikamentenoptimierung bei älteren Patient/-innen mit Polypharmazie: die OPTICA Studie

Katharina Jungo, Axel Löwe, Sophie Mantelli, Rahel Meier, Sven Streit

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My contributions: I created all figures and tables shown below. I wrote the first draft of the article and I made the necessary changes during the review process.

Klinische Studie zur Medikamentenoptimierung bei älteren Patient/-innen mit Polypharmazie

Die OPTICA-Studie

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Für die Umsetzung der OPTICA-Studie zur Optimierung von Medikamenten bei älteren Menschen mit Polypharmazie ist unser Studienteam auf die Mithilfe von Hausarztkolleg/-innen angewiesen. Bei vergleichbaren Studien im In- und Ausland war dabei meist die Rekrutierung wegen der tiefen Teilnehmerzahlen von Hausärzt/-innen ein Hauptproblem. Deswegen fuhren wir persönlich in allen Hausarztpraxen vorbei, die wir für eine Teilnahme gewinnen wollten. Das hat sich bewährt. An dieser Stelle wollen wir von unserer Erfahrung berichten und Mut machen, der Rekrutierung von Hausärztinnen/-ärzten genügend Zeit, Ressourcen und Freude zu widmen, um erfolgreiche Forschung aus der Praxis für die Praxis zu erreichen.

Die Digitalisierung der Medizin schreitet stetig voran. Häufig wird die Technisierung der Arbeitsprozesse skeptisch betrachtet, hat sich doch der bürokratische Aufwand im gleichen Zeitrahmen nicht verringern lassen. Gerade in der Hausarztmedizin, in der eine vertrauensvolle Arzt-Patienten-Beziehung von besonderer Wichtigkeit ist, ist dies eine ernüchternde Erkenntnis. Andererseits trägt die Digitalisierung unbestreitbar auch grosses Potenzial in sich, mit der Hoffnung auf zeiteffiziente Erleichterung der Arbeitsprozesse, einen Mehrwert für Patient/-innen und sinkende Kosten durch intelligente Nutzung immer grösser werdender Datenmengen in den elektronischen Krankenakten. Die Frage, wie diese sinnvolle Nutzung aussehen soll und realisierbar ist, betrifft uns alle.

Ein aktuell intensiv beforschter Wissenschaftszweig mit hohem erwartetem Anwendungsnutzen ist die softwareunterstützte Medikamentenüberprüfung. Dabei deuten bisherige Forschungsergebnisse einerseits einen klinischen Nutzen für Patient/-innen mit zahlreichen Medikamenten an, bei denen das Risiko ungeeigneter Verschreibungen erhöht ist [1]. Andererseits erhoffen sich die öffentliche Hand und die Krankenkassen finanzielle Entlastungen durch Vermeidung von Mehrkosten durch unerwünschte Arzneimittelwirkungen und Krankenhauseinweisungen, die erwiesenermassen häufig aus schlecht eingestellten Medikationen resultieren [2, 3]. Mit der Fragestellung, ob softwareunterstützte Medikamentenüberprüfungen bei älteren, multimorbiden Patient/-innen mit Polypharmazie eine Verbesserung der bisherigen Verschreibung herbeiführen können, führt unser Forschungsteam am Berner Institut für Hausarztmedizin (BIHAM) aktuell die OPTICA-Studie (Kasten 1) durch. Dabei sollen alle Schritte der Medikamen-

Kasten 1: Hintergrundinformationen zur OPTICA-Studie

Die OPTICA-Studie ist eine vom Schweizerischen Nationalfonds finanzierte klinische Studie, die zum Ziel hat, die bestehende Medikation bei älteren, multimorbiden Patient/-innen mit Polypharmazie zu optimieren. Auch wird untersucht, welche Auswirkungen die Medikamentenoptimierung bei dieser Bevölkerungsgruppe auf ihren Gesundheitszustand, ihre Lebensqualität sowie die Inanspruchnahme von Leistungen im Gesundheitssystem hat. Dazu wird die Anwendung eines softwarebasierten Hilfsmittels durch Hausärzt/-innen mit der gewöhnlichen Behandlung ohne zusätzliche Medikamentenüberprüfung verglichen. Das Programm generiert Empfehlungen zur medikamentösen Optimierung, welche die Ärztin oder der Arzt gemeinsam mit ihren Patient/-innen im Sinne einer gemeinsamen Entscheidungsfindung diskutiert.

Insgesamt werden 40 Hausärzt/-innen für die OPTICA-Studie rekrutiert, die jeweils acht ihrer Patient/-innen in die Studie einschliessen. Geeignete Patient/-innen für eine Studienteilnahme sind ≥65 Jahre alt, haben ≥3 chronische Erkrankungen («Multimorbidität») und nehmen regelmässig ≥5 verschriebene Medikamente («Polypharmazie») ein. Die Rekrutierung der Hausärzt/-innen hat bereits begonnen und wird im Frühjahr 2018 abgeschlossen. Die Patientenrekrutierung durch die teilnehmenden Ärztinnen und Ärzte ist ab Mai 2018 geplant. OPTICA wird am BIHAM von Dr. med. Sven Streit geleitet, in Zusammenarbeit mit den Kollegen des Instituts für Hausarztmedizin in Zürich (IHAMZ), des Instituts für Praxisinformatik (IPI), der Clinical Trials Unit (CTU) Bern, der Universität Basel und der Universität Utrecht in den Niederlanden.

tenoptimierung eigenständig durch Hausärzt/-innen durchgeführt werden, um eine möglichst alltagsgetreue Abbildung der Anwendung des Programms zu gewährleisten.

Gründe für persönliche Hausarztbesuche

Um für die OPTICA-Studie eine erfolgreiche Zusammenarbeit mit den Hausärzt/-innen in die Wege zu leiten, haben wir uns dafür entschieden, interessierte Ärztinnen und Ärzte persönlich in ihrer Praxis zu besuchen anstatt lediglich per Telefon, Post und Email mit Ihnen in Kontakt zu treten. In der Anfangsphase der OPTICA-Studie waren bereits um die 700 Hausärzt/-innen kontaktiert worden, wovon 10% Interesse an einer Studienteilnahme gezeigt haben. Letztere haben wir dann für die Organisation eines Praxisbesuchs erneut angeschrieben. Der erste solche Besuch von fünf Hausarztpraxen fand Mitte Oktober 2017 im Kanton Bern statt (Abb. 1). In den Folgemonaten besuchten wir weitere Hausärzt/-innen in den Kantonen Bern, Luzern, Wallis und Solothurn. Weitere Besuche sind im Raum Freiburg und Zürich geplant.

Die Hausärzt/-innen empfingen das OPTICA-Studienteam, teilweise zusammen mit einer Medizinischen Praxisassistentin (MPA), jeweils in ihrer Praxis. Die Treffen, bei denen zuerst die OPTICA-Studie und dann das FIRE Projekt vorgestellt wurden (Kasten 2), dauerten jeweils um die 40 Minuten. Während dieser Praxisbesuche war es unserem Studienteam möglich, die OPTICA-Studie detailliert zu präsentieren und direkt auf allfällige Fragen einzugehen. Bei der Präsentation der OPTICA-Studie verwendeten wir graphische Hilfsmittel, die das Verständnis der gesamten Studiendurchführung erleichtern sollten. Zusätzlich wurde den Hausärzt/-innen am Ende unseres Besuches eine schriftliche Zusammenfassung der wichtigsten Informationen betreffend der OPTICA-Studie und FIRE übergeben.

Ein weiterer Vorteil der Praxisbesuche ist die Möglichkeit, direkt vor Ort die praktischen Voraussetzungen für eine eventuelle OPTCIA Studienteilnahme vorzubereiten, was vor allem die Bereitstellung des «FIRE Exporters» beinhaltet. Da wir den Arbeitsaufwand der teilnehmenden Hausärzt/-innen so gering wie möglich halten wollen, bietet es sich für uns an, diese Vorbereitungsarbeiten mit dem Aufklärungsgespräch zu kombinieren.

Die Aufklärung interessierter Ärztinnen und Ärzte über das FIRE Projekt und die Bereitstellung des Exporters wurde während der ersten Praxisbesuche von einer Vertreterin des IHAMZ bewerkstelligt.

Diese Aufgaben kann das OPTICA-Studienteam mittlerweile selbst ausführen. Die intuitive Anwendung

Abbildung 1: Sprechstunde einmal anders: Das Team von OPTICA und FIRE beim Erklären und Rekrutieren der ersten Hausärztin.

Kasten 2: Hintergrundinformationen zum FIRE Projekt

Das FIRE *(Family Medicine ICPC Research using Electronic Medical Records)* Projekt beschreibt ein Forschungsnetzwerk von Hausärzt/-innen unter der Leitung des IHAMZ. Die teilnehmenden Hausärztinnen und Hausärzte exportieren regelmässig anonymisierte medizinische Routinedaten (Alter und Geschlecht, Vitaldaten, Labordaten, Diagnosen und Medikationsdaten der Patient/-innen) direkt aus den elektronischen Krankenakten. Anhand einer Software-Applikation, dem «FIRE Exporter», werden die Daten zur wissenschaftlichen Auswertung an die FIRE-Datenbank transferiert. Aktuell unterstützen sieben Praxissoftware-Lösungen das FIRE-Projekt: Aeskulap, E-General, MEDICOwin, triaMED, Vitomed, Winmed und Elexis. Mit weiteren Unternehmen sind Vertreter vom FIRE-Projekt in Kontakt.

Einerseits dienen diese Daten als Grundlage für regelmässige Feedback-Reports an die teilnehmenden Hausärzte, welche durch Statistiken die klinische Arbeit der Hausärzt/-innen widerspiegeln und ins Verhältnis zur Gesamtheit der teilnehmenden Kolleg/-innen setzen. Dies kann eine wertvolle Datengrundlage für Qualitätszirkel und praxisinternes Qualitätsmanagement sein. Andererseits kann dieser kontinuierlich wachsende Datenpool für Forschungsprojekte im Bereich der Hausarztmedizin genutzt werden. Somit leisten die an FIRE teilnehmenden Hausärzt/-innen einen wertvollen Beitrag zur Forschung aus der Praxis für die Praxis [4].

Die Zusammenarbeit zwischen dem FIRE Projekt und OPTICA erlaubt, die für OPTICA notwendigen Daten direkt aus FIRE ins Programm zur Medikationsüberprüfung zu laden, anstatt sie auf zeitraubendem, manuellem Weg einzeln einzugeben. Aus diesem Grund ist die Teilnahme am FIRE Projekt eine Voraussetzung für die Teilnahme an der OPTICA-Studie. Während der Praxisbesuche wird deshalb nicht nur für die OPTICA-Studie, sondern auch für das FIRE Projekt rekrutiert.

des benutzerfreundlichen Exporters wird während des Besuchs von den teilnehmenden Ärztinnen und Ärzten oder gegebenenfalls von den MPA geprobt, und der erste Datenexport erstellt. Generell ist es uns vom OPTICA-Studienteam äusserst wichtig, das Studiendesign so einfach wie möglich für teilnehmende Hausärzt/-innen zu gestalten und diese zu entlasten, wo immer es möglich ist.

Neben den praktischen Vorteilen erlaubt ein persönlicher Praxisbesuch den interessierten Hausärzt/-innen auch, das OPTICA-Studienteam persönlich zu treffen und sich ein genaues Bild von ihnen zu verschaffen. Ein persönlicher Kontakt zwischen Studienteilnehmern und dem Studienteam ist erfahrungsgemäss ein wichtiger Punkt für eine erfolgreiche zukünftige Studiendurchführung. Beim Gestalten des Rekrutierungsprozesses für Hausärzt/-innen haben wir versucht, wissenschaftliche, häufig aus dem Ausland stammende Erkenntnisse bezüglich der Hausarztrekrutierung bei uns umzusetzen (Kasten 3).

Fazit der ersten Hausarztbesuche

Die ersten Praxisbesuchstage waren ein voller Erfolg und ein wichtiger Schritt für uns vom OPTICA-Studienteam, da wir im Vornherein nicht wussten, welche Reaktionen uns in den einzelnen Praxen erwarten würden. Wir haben uns sehr gefreut, dass wir die meisten der bisher besuchten Praxen erfolgreich für FIRE/OPTICA gewinnen konnten. Diese positive Resonanz motiviert uns für die Rekrutierung der verbleibenden Praxen. Ausserdem haben uns diese ersten Hausarztbesuche dabei geholfen, die kommenden Besuche noch besser auf die Bedürfnisse der Hausärzt/-innen anzupassen. Die erhaltenen Rückmeldungen und Anregungen konnten wir laufend umsetzen.

Für die OPTICA-Studie sowie für zukünftige Forschungsprojekte im Bereich der Hausarztmedizin ist ein reger Kontakt zwischen Hausärzt/-innen und Forscher/-innen unentbehrlich. Nur durch diesen Austausch können erfolgreiche Forschungsprojekte entstehen, die sich erfolgreich in den Praxisalltag integrieren lassen.

Gleichzeitig sind wir uns – in Zeiten des Hausärztemangels – über die zusätzlichen Herausforderungen für Hausärzt/-innen bewusst, wenn sie bei Forschungsprojekten mitmachen. Wir versuchen dem Rechnung zu tragen, indem wir unsere Anfragen zeitlich gut verteilen und eng mit den Kollegen der anderen Institute und Partnerorganisationen zusammenarbeiten. Wir sind aber allen Kolleginnen und Kollegen in der Praxis dankbar, dass sie sich Zeit dafür nehmen, die Forschung im Bereich der Hausarztmedizin zu unterstützen, so dass uns in der Schweiz eine erfolgreiche Forschung aus der Praxis mit der Praxis für die Praxis gelingt.

Kasten 3: Tipps zur Rekrutierung von Hausärzt/-innen für Forschungsprojekte

- Hausärzt/-innen als Teil des Forschungsteams [5, 6].
- Investition von genügend Zeit und Ressourcen in den Rekrutierungsprozess durch das Forschungsteam [8].
- Frühzeitige, schriftliche Kontaktaufnahme mit Hausärzt/-innen, inklusive weiterer telefonischer Nachfrage falls notwendig [5].
- Organisation von persönlichen Treffen zwischen Hausärzt/-innen und Forscher/-innen [5,6,7].
- Detaillierte Erklärungen bezüglich der Studiendurchführung, der Machbarkeit der Studie sowie der Vertraulichkeit [8].
- Genaue Erläuterungen der Aufgaben, die teilnehmende Hausärzt/-innen erledigen müssten, und wie sich diese Aufgaben in den Praxisalltag integrieren liessen [5,7].
- Gegenüberstellung von Aufwand und Ertrag einer Studienteilnahme aus der Perspektive von Hausärzt/-innen [5].
- Information über finanzielle Entschädigungen für teilnehmende Hausärzt/-innen [10,11].
- Verteilen von Informationsmaterial über die Studiendurchführung [5,8].
- Eingehen auf spezifische Fragen, Unsicherheiten und Klärung von potenziellen Hindernissen für eine Studienteilnahme von Hausärzt/-innen [9].
- Gabe von Bedenkzeit bezüglich der Studienteilnahme [5].
- Integration von Verbesserungsvorschlägen seitens interessierter Hausärzt/-innen.

Hinweis

Für weitere Fragen und Anregungen bezüglich der Hausarztrekrutierung für die OPTICA-Studie sowie der Studie generell stehen wir Ihnen gerne unter optica[at]biham.unibe.ch zur Verfügung. Weitere Infos zum FIRE-Projekt finden sie unter: www.fireproject.ch

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Verdankung

Wir möchten allen Hausärzt/-innen danken, die uns bereits in ihrer Praxis empfangen haben. Wir schätzen es sehr, dass Sie sich Zeit genommen haben und freuen uns auf die gemeinsame Studiendurchführung. Ebenso danken wir unseren Partnern in der Schweiz und Holland für die Unterstützung.

Literatur

Die vollständige Literaturliste finden Sie in der Online-Version des Artikels unter www.primary-hospital-care.ch.

15.2.2 Hürden und Chancen der klinischen Forschung in der Hausarztmedizin

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My contributions: I created all figures and tables shown below. I wrote the first draft of the article and I made the necessary changes during the review process.

Mögliche Lösungen für auftretende Schwierigkeiten

Hürden und Chancen der klinischen Forschung in der Hausarztmedizin

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Die hausarztmedizinische Forschung in der Schweiz befindet sich im Aufwind. Es gibt immer mehr hausarztmedizinische Institute an den Universitäten, und es werden zunehmend mehr Forschungsprojekte finanziert. Forschung im Bereich der Hausarztmedizin kann jedoch unter Umständen mit gewissen Schwierigkeiten verbunden sein. Auch in unserer aktuellen OPTICA-Studie konnten wir selbst erleben, welche Hürden es vor dem Studienstart zu meistern gibt. In diesem Bericht möchten wir Ihnen einige dieser Hürden nennen und mögliche Lösungsansätze präsentieren.

Projektfinanzierung

Bis man den ersten Studienteilnehmer in ein Forschungsprojekt einschliessen kann, vergehen in der Regel mehrere Jahre. Auch im Falle der OPTICA-Studie (s. Kasten) hat dieser Prozess drei Jahre gedauert. Ein wichtiger Grund hierfür ist die Suche nach adäquater Forschungsfinanzierung, denn während einem mehrjährigen Projekt fallen verschiedenste Kosten wie zum Beispiel Lohnkosten an.

Doch welche Möglichkeiten stehen einem Forschenden hierfür zur Verfügung? Im Gegensatz zur Grundlagenforschung stehen in der Hausarztmedizin noch immer wenig Mittel zur Verfügung. Zwar besteht die Möglichkeit, Anträge bei Stiftungen und Organisationen einzureichen (z.B. SGAIM Foundation oder KHM), doch lassen sich damit nur kurze und weniger aufwändige Projekte finanzieren. Im Fall von OPTICA beantragten wir Fördergelder beim Schweizerischen Nationalfonds (SNF), der die Grundlagenforschung sowie auch den wissenschaftlichen Nachwuchs in der Schweiz mit öffentlichen Mitteln fördert. Dazu mussten wir nicht nur Nachweisen, welche Bedeutung das Projekt hat und dass es unter den gegebenen Umständen machbar ist [1], sondern auch, weshalb dieses Projekt und nicht eines der vielen anderen Beantragten unterstützt werden soll. Wichtig war uns dabei, spezifisch zu schauen, welches Ziel der SNF mit diesem Förderinstrument (NFP 74) verfolgt und darauf zugespitzt unsere Studie zu planen, damit wir diese Ziele gemeinsam erreichen können.

OPTICA-Studie

Die OPTICA (*Optimizing PharmacoTherapy In the multimorbid elderly in primary CAre*)-Studie ist eine nationale, randomisierte einfachverblindete kontrollierte klinische Studie. Es handelt sich um ein vierjähriges Projekt, das durch den Schweizerischen Nationalfonds im Rahmen eines Nationalen Forschungsprogrammes (NFP) unterstützt wird. Ziel ist, durch die Anwendung eines softwarebasierten Hilfsmittels in der Hausarztpraxis, die Medikation multimorbider ≥65-jähriger Patient/-innen mit Polypharmazie zu optimieren. Insgesamt nehmen ca. 40 Hausärzt/-innen mit je acht bis zehn Patient/-innen teil. Die Patientenrekrutierung hat im Dezember 2018 begonnen.

Wird das Projekt vom SNF gutgeheissen und ein Beitrag zugesprochen, so muss die forschende Person innerhalb eines Jahres mit dem Projekt beginnen. Die Beiträge werden höchstens für vier Jahre gewährt, was für den Gesuchsteller einen gewissen Zeitdruck bedeutet. Während der Projektdauer muss die forschende Person regelmässig einen Bericht über den Status des Forschungsprojektes einreichen [2].

Rechtliche und ethische Voraussetzungen

In der Schweiz regeln das Humanforschungsgesetz (HFG) [3] sowie die Verordnung zur Durchführung klinischer Studien (KlinV) [4] alle klinischen Studien, weshalb alle Studienprotokolle diesen Gesetzesvorgaben entsprechen müssen. Dies beinhaltet beispielsweise, dass während der gesamten Studiendurchführung die international anerkannten Richtlinien der sogenannten *Good Clinical Practice* (GCP) [5] umzusetzen sind.

Das HFG und die KlinV beruhen auf einem risikoadaptierten Grundkonzept, das dazu dient, die Studien zu kategorisieren. Für jede Interventionsstudie muss eine Bewilligung der kantonalen Ethikkommission eingeholt werden. Bei der OPTICA-Studie handelt es sich per Definition um eine klinische Studie der Kategorie C mit Medizinprodukten, da die im Rahmen der Studie getestete Software noch kein Konformitätszeichen trägt. Und wird in einer klinischen Studie, wie im Falle von OPTICA, ein Medizinprodukt getestet, das noch kein Konformitätszeichen trägt, braucht es hierfür eine zusätzliche Bewilligung der Schweizerischen Arzneimittelbehörde Swissmedic. Während der Studiendurchführung muss die Sicherheit von Studienteilnehmer/-innen dokumentiert und rapportiert werden, was die Erstellung von regelmässigen Berichten für die Ethikkommission und gegebenenfalls auch Swissmedic beinhaltet, um die Sicherheit von Studienteilnehmenden zu gewährleisten und die Qualität der Studienergebnisse sicherzustellen.

Bei der Planung einer klinischen Studie im Bereich der Hausarztmedizin gibt es einige Besonderheiten zu beachten: Bei der Überprüfung eines Studienprotokolls gilt der Grundsatz der kantonalen Zuständigkeit. Insgesamt gibt es in der Schweiz sieben Ethikkommissionen, die jeweils für mehrere Kantone zuständig sind. Das Studienzentrum der OPTICA-Studie befindet sich am Berner Institut für Hausarztmedizin der Universität Bern (BIHAM), weshalb die Ethikkommission des Kantons Bern (KEK BE) für die Überprüfung und Bewilligung dieser monozentrischen Studie zuständig ist. Dennoch musste sich die KEK BE mit allen anderen betroffenen Ethikkommissionen absprechen, da sich einige der teilnehmenden Hausarztpraxen in den Zuständigkeitsbereichen anderer Ethikkommissionen befinden.

Das Gesetz besagt, dass alle in einer klinischen Studie involvierten Personen ein adäquates Training absolvieren müssen. In der Praxis bedeutet dies, dass ein GCP-Kurs besucht werden muss. Solche Kurse finden an verschiedenen akkreditierten Zentren wie beispielsweise an der universitären CTU *(Clinical Trials Unit)* Bern statt. Da es sich jedoch zeitlich und geografisch als schwierig erwiesen hätte, alle 40 Hausärztinnen und Hausärzte für einen solchen Kurs einzuladen, mussten wir eine Lösung finden, welche die geografischen Umstände der OPTICA-Studie berücksichtigt. Aus diesem Grund haben wir von der Ethikkommission die Erlaubnis erhalten, ein auf die Hausärzt/-innen zugeschnittenes Onlinetraining zu erstellen, das die für die OPTICA-Studie wichtigsten Bereiche der GCP-Richtlinien abdeckt. Dieses Training haben alle teilnehmenden Hausärztinnen und Hausärzte im Vorfeld der OPTICA-Studie von ihrem jeweiligen Standort aus absolviert. Um dieses Problem für zukünftige Forschungsprojekte zu eliminieren, sind wir zudem in Zusammenarbeit mit der *Swiss Academy of Family Medicine* (SAFMED), der Dachorganisation der Schweizeri-

Auszug aus dem GCP-Onlinetraining der OPTICA-Studie.

Praxis-Tipps für die Planung einer Studie

- Das Forschungsthema muss begeistern, denn die Dauer von der Planung bis hin zu den finalen Resultaten kann einige Jahre betragen und braucht Durchhaltevermögen.
- Sorgfältige und umsichtige Budgetplanung.
- Frühzeitige Vorbereitung der Einreichungsunterlagen an Ethikkommission/Swissmedic.
- Frühzeitiger Miteinbezug von den an einer Teilnahme interessierten Hausärzten und Hausärztinnen.

schen Institute für Hausarztmedizin, daran, einen eigenen online GCP-Kurs für Hausärzt/-innen zu entwickeln.

In der Vorbereitungsphase der OPTICA-Studie haben wir stets versucht, einen akzeptablen Kompromiss zu finden, der die Richtlinien zur Durchführung klinischer Studien befolgt aber auch die Durchführbarkeit der Studie im Kontext der Hausarztmedizin gewährleistet. Obwohl dies mit erheblichem zeitlichem Aufwand verbunden war, haben wir nun die Bewilligung zur Durchführung der OPTICA-Studie erhalten und mit der Patientenrekrutierung begonnen.

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Nachwuchsforscher im Bereich der Hausarztmedizin

Um im Bereich der Hausarztmedizin zu forschen, braucht es natürlich auch ausreichend Personal. So gibt es in der OPTICA-Studie neben dem Studienleiter und den Partnern eine Projektkoordinatorin, eine PhD-Studentin sowie einen klinischen wissenschaftlichen Mitarbeiter. Bei Letzterem handelt es sich meistens um junge Ärztinnen oder Ärzte, die eine mehrmonatige Forschungsrotation am BIHAM absolvieren, um ihre Dissertation zu erlangen. Bei diesen Forschungsrotationen geht es darum, mehr über die hausärztliche Forschung zu erfahren, da sich die meisten nur wenig unter dem Begriff vorstellen können, und im Laufe ihrer Ausbildung herausfinden möchten, wie Forschung praktisch umgesetzt wird. Aus Sicht des BIHAM ist es wichtig, interessierte Bewerber für diese Positionen zu finden. Langfristig werden es die Nachwuchsforscherinnen und -forscher im Bereich der Hausarztmedizin sein, die diesen Bereich weiterentwickeln werden. In einem Projekt wie OPTICA können Dissertant/-innen ihr klinisches Wissen einbringen und das Projekt hierdurch vorantreiben.

Da heutzutage fast alle medizinischen Entscheidungen auf «evidenzbasierter» Basis getroffen werden sollen, ist es für alle zukünftigen Hausärztinnen und Hausärzte von Bedeutung, den Bereich, in dem Forschung tatsächlich stattfindet, kennenzulernen, und nicht nur im Praxisalltag Forschungsresultate kritisch zu hinterfragen.

Schlussfolgerung

Trotz den Hürden, die es zu meistern gibt, sind wir sehr froh, Forschungsprojekte wie die OPTICA-Studie, durchführen zu dürfen. Mit viel Motivation arbeiten wir stets daran, die besten Lösungen für die verschiedenen Probleme zu finden und wir hoffen, dass unsere Vorgehensweise (insbesondere das Online-GCP-Training für Hausärztinnen und Hausärzte) dazu beigetragen hat, den Weg für die klinische Versorgungsforschung in der Schweizerischen Hausarztmedizin zu ebnen.

Verdankung
An dieser Stelle möchten wir uns herzlich bei allen teilnehmenden Hausärztinnen und Hausärzten für ihr Engagement und ihre Geduld während der Planungsphase bedanken. Wir schätzen es sehr, weiterhin mit Ihnen zusammenarbeiten zu dürfen.

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16. Supplementary Material

16.1 Supplementary Material Article I: Utilization and Spending on Potentially Inappropriate Medications by US Older Adults with Multiple Chronic Conditions using Multiple Medications

This supplementary material is available from: https://ars.els-cdn.com/content/image/1-s2.0-S0167494320303174-mmc1.docx, accessed February 11, 2021

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eTable 1. Definition of chronic conditions

ICD-9 Category [first digits of ICD-9 codes in these categories]	Chronic ICD-9 Codes [ICD-9 codes defined as chronic by Chronic Conditions Indicator (CCI)]
Human immunodeficiency virus (HIV) infection (042–044)	042, 042.0, 042.1, 042.2, 042.9, 043.0, 043.1, 043.2, 043.3, 043.9, 044.0, 044.9
Poliomyelitis and other non-arthropod-borne viral diseases of central nervous system (045–049)	046.0, 046.1, 046.11, 046.19, 046.2, 046.3, 046.71, 046.72, 046.79, 046.8, 046.9
Viral diseases accompanied by exanthem (050–059)	054.10, 054.11, 054.12, 054.13, 054.19
Other diseases due to viruses and chlamydiae (070–079)	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 076.0, 076.1, 076.9
Syphilis and other venereal diseases (090–099)	093.20, 093.21, 093.22, 093.23, 093.24, 094.0, 094.1, 094.2, 095.8, 095.9, 097.0
Mycoses (110–118)	114.4
Other infectious and parasitic diseases (130–136)	135
Late effects of infectious and parasitic diseases (137–139)	137.0, 137.1, 137.2, 137.3, 137.4, 138, 139, 139.1, 139.8
Malignant neoplasm of lip, oral cavity, and pharynx (140–149)	140.0, 140.1, 140.3, 140.4, 140.5, 140.6, 140.8, 140.9, 141.0, 141.1, 141.2, 141.3, 141.4, 141.5, 141.6, 141.8, 141.9, 142.0, 142.1, 142.2, 142.8, 142.9, 143, 143.1, 143.8, 143.9, 144, 144.1, 144.8, 144.9, 145.0, 145.1, 145.2, 145.3, 145.4, 145.5, 145.6, 145.8, 145.9, 146.0, 146.1, 146.2, 146.3, 146.4, 146.5, 146.6, 146.7, 146.8, 146.9, 147.0, 147.1, 147.2, 147.3, 147.8, 147.9, 148.0, 148.1, 148.2, 148.3, 148.8, 148.9, 149.0, 149.1, 149.8, 149.9
Malignant neoplasm of digestive organs and peritoneum (150–159)	150.0, 150.1, 150.2, 150.3, 150.4, 150.5, 150.8, 150.9, 151.0, 151.1, 151.2, 151.3, 151.4, 151.5, 151.6, 151.8, 151.9, 152.0, 152.1, 152.2, 152.3, 152.8, 152.9, 153.0, 153.1, 153.2, 153.3, 153.4, 153.5, 153.6, 153.7, 153.8, 153.9, 154.0, 154.1, 154.2, 154.3, 154.8, 155.0, 155.1, 155.2, 156.0, 156.1, 156.2, 156.8, 156.9, 157.0, 157.1, 157.2, 157.3, 157.4, 157.8, 157.9, 158.0, 158.8, 158.9, 159.0, 159.1, 159.8, 159.9
Malignant neoplasm of respiratory and intrathoracic organs (160–165)	160.0, 160.1, 160.2, 160.3, 160.4, 160.5, 160.8, 160.9, 161.0, 161.1, 161.2, 161.3, 161.8, 161.9, 162.0, 162.2, 162.3, 162.4, 162.5, 162.8, 162.9, 163.0, 163.1, 163.8, 163.9, 164.0, 164.1, 164.2, 164.3, 164.8, 164.9, 165.0, 165.8, 165.9
Malignant neoplasm of bone, connective tissue, skin, and breast (170–175)	170.0, 170.1, 170.2, 170.3, 170.4, 170.5, 170.6, 170.7, 170.8, 170.9, 171.0, 1s71.2, 171.3, 171.4, 171.5, 171.6, 171.7, 171.8, 171.9, 172.0, 172.1, 172.2, 172.3, 172.4, 172.5, 172.6, 172.7, 172.8, 172.9, 174.0, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.8, 174.9, 175.0, 175.9
Kaposi's sarcoma (176–176)	176.0, 176.1, 176.2, 176.3, 176.4, 176.5, 176.8, 176.9
Malignant neoplasm of genitourinary organs (179–189)	179, 180.0, 180.1, 180.8, 180.9, 181, 182.0, 182.1, 182.8, 183.0, 183.2, 183.3, 183.4, 183.5, 183.8, 183.9, 184.0, 184.1, 184.2, 184.3, 184.4, 184.8, 184.9, 185, 186.0, 186.9, 187.1, 187.2, 187.3, 187.4, 187.5, 187.6, 187.7, 187.8, 187.9, 188.0, 188.1, 188.2, 188.3, 188.4, 188.5, 188.6, 188.7, 188.8, 188.9, 189.0, 189.1, 189.2, 189.3, 189.4, 189.8, 189.9
Malignant neoplasm of other and unspecified sites (190–199)	190.0, 190.1, 190.2, 190.3, 190.4, 190.5, 190.6, 190.7, 190.8, 190.9, 191.0, 191.1, 191.2, 191.3, 191.4, 191.5, 191.6, 191.7, 191.8, 191.9, 192.0, 192.1, 192.2, 192.3, 192.8, 192.9, 193, 194.0, 194.1, 194.3, 194.4, 194.5, 194.6, 194.8, 194.9, 195.0, 195.1, 195.2, 195.3, 195.4, 195.5, 195.8, 196.0,196.1, 196.2, 196.3, 196.5, 196.6, 196.8, 196.9, 197.0, 197.1, 197.2, 197.3, 197.4, 197.5, 197.6, 197.7, 197.8, 198.0, 198.1, 198.2, 198.3, 198.4, 198.5, 198.6, 198.7, 198.81, 198.82, 198.89, 199.0, 199.1, 199.2
Malignant neoplasm of lymphatic and hematopoietic tissue (200–208)	200.00, 200.01, 200.02, 200.03, 200.04, 200.05, 200.06, 200.07, 200.08, 200.10, 200.11, 200.12, 200.13, 200.14, 200.15, 200.16, 200.17, 200.18, 200.20, 200.21, 200.22, 200.23, 200.24, 200.25, 200.26, 200.27, 200.28, 200.30, 200.31, 200.32, 200.33, 200.34, 200.35, 200.36, 200.37, 200.38, 200.40, 200.41, 200.42, 200.43, 200.44, 200.45, 200.46, 200.47, 200.48, 200.50, 200.51, 200.52, 200.53, 200.54, 200.55, 200.56, 200.57, 200.58, 200.60, 200.61, 200.62, 200.63, 200.64, 200.65, 200.66, 200.67, 200.68, 200.70, 200.71, 200.72, 200.73, 200.74, 200.75, 200.76, 200.77, 200.78, 200.80, 200.81, 200.82, 200.83, 200.84, 200.85, 200.86, 200.87, 200.88, 201.00, 201.01, 201.02, 201.03, 201.04, 201.05, 201.06, 201.07, 201.08, 201.10, 201.11, 201.12, 201.13, 201.14, 201.15, 201.16, 201.17, 201.18, 201.20, 201.21, 201.22, 201.23, 201.24, 201.25, 201.26, 201.27, 201.28, 201.40, 201.41, 201.42, 201.43, 201.44 201.45, 201.46, 201.47, 201.48, 201.50, 201.51, 201.52, 201.53, 201.54, 201.55, 201.56, 201.57, 201.58, 201.60, 201.61, 201.62, 201.63, 201.64, 201.65, 201.66, 201.67, 201.68, 201.70, 201.71, 201.72, 201.73, 201.74, 201.75, 201.76, 201.77, 201.78, 201.90, 201.91, 201.92, 201.93, 201.94, 201.95, 201.96, 201.97, 201.98, 202.00, 202.01, 202.02, 202.03, 202.04, 202.05, 202.06, 202.07, 202.08, 202.10, 202.11, 202.12, 202.13, 202.14, 202.15, 202.16, 202.17, 202.18, 202.20, 202.21, 202.22, 202.23, 202.24, 202.25, 202.26, 202.27, 202.28, 202.30, 202.31, 202.32, 202.33, 202.34, 202.35, 202.36, 202.37, 202.38, 202.40, 202.41, 202.42, 202.43, 202.44, 202.45, 202.46, 202.47, 202.48, 202.50, 202.51, 202.52, 202.53, 202.54, 202.55, 202.56, 202.57, 202.58, 202.60, 202.61, 202.62, 202.63, 202.64, 202.65, 202.66, 202.67, 202.68, 202.70, 202.71, 202.72, 202.73, 202.74, 202.75, 202.76, 202.77, 202.78, 202.80, 202.81, 202.82, 202.83, 202.84 202.85, 202.86 202.87, 202.88, 202.90, 202.91, 202.92, 202.93, 202.94, 202.95, 202.96, 202.97, 202.98, 203.0, 203.00, 203.01, 203.02, 203.1, 203.10, 203.11, 203.12, 203.8, 203.80, 203.81, 203.82, 204.0, 204.00, 204.01, 204.02, 204.1, 204.10, 204.11, 204.12, 204.2, 204.20, 204.21, 204.22, 204.8, 204.80, 204.81, 204.82, 204.9, 204.90, 204.9, 204.92, 205.0, 205.00, 205.01, 205.02, 205.1, 205.10, 205.11, 205.12, 205.2, 205.20, 205.21, 205.22, 205.3, 205.30, 205.31, 205.32, 205.8, 205.80, 205.81, 205.82, 205.9, 205.90, 205.91, 205.92, 206.0, 206.00, 206.01, 206.02, 206.1, 206.10, 206.11, 206.12, 206.2, 206.20, 206.21, 206.22, 206.8, 206.80, 206.81, 206.82, 206.9, 206.90, 206.91, 206.92, 207.0, 207.00, 207.01, 207.02, 207.1, 207.10, 207.11, 207.12, 207.2, 207.20, 207.21, 207.22, 207.8, 207.80, 207.81, 207.82, 208.0, 208.00, 208.01, 208.02, 208.1, 208.10, 208.11, 208.12, 208.2, 208.20, 208.21, 208.22, 208.8, 208.80, 208.81, 208.82, 208.9, 208.90, 208.91, 208.92

Neuroendocrine tumors (209–209)	209.00, 209.01, 209.02, 209.03, 209.10, 209.11, 209.12, 209.13, 209.14, 209.15, 209.16, 209.17, 209.20, 209.21, 209.22, 209.23, 209.24, 209.25, 209.26, 209.27, 209.29, 209.30, 209.31, 209.32, 209.33, 209.34, 209.35, 209.36, 209.70, 209.71, 209.72, 209.73, 209.74, 209.75, 209.79
Benign neoplasms (210–229)	225.0, 225.1, 225.2
Carcinoma in situ (230–234)	230.0, 230.1, 230.2, 230.3, 230.4, 230.5, 230.6, 230.7, 230.8, 230.9, 231.0, 231.1, 231.2, 231.8, 231.9, 233.0, 233.2, 233.3, 233.30, 233.31, 233.32, 233.39, 233.4, 233.5, 233.6, 233.7, 233.9, 234.0, 234.8, 234.9
Neoplasms of uncertain behavior (235–238)	237.5, 237.7, 237.70, 237.71, 237.72, 237.73, 237.79, 237.9, 238.77
Neoplasms of unspecified nature (239–239)	239.6
Disorders of thyroid gland (240–246)	240.0, 240.9, 241.0, 241.1, 241.9, 242.00, 242.01, 242.10, 242.11, 242.20, 242.21, 242.30, 242.31, 242.40, 242.41, 242.80, 242.81, 242.90, 242.91, 243, 244.0, 244.1, 244.2, 244.3, 244.8, 244.9, 245.0, 245.1, 245.2, 245.3, 245.4, 245.8, 245.9, 246.1
Diseases of other endocrine glands (249–259)	249.00, 249.01, 249.10, 249.11, 249.20, 249.21, 249.30, 249.31, 249.40, 249.41, 249.50, 249.51, 249.60, 249.61, 249.70, 249.71, 249.80, 249.81, 249.90, 249.91, 250.00, 250.01, 250.02, 250.03, 250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73, 250.80, 250.81, 250.82, 250.83, 250.90, 250.91,250.92, 250.93, 251.0, 251.1, 251.2, 251.3, 251.4, 251.5, 251.8, 251.9, 252.0, 252.00, 252.01, 252.02, 252.08, 252.1, 252.8, 252.9, 253.0, 253.1, 253.2, 253.3, 253.4, 253.5, 253.6, 253.7, 253.8, 253.9, 254.0, 255.0, 255.1, 255.10, 255.11, 255.12, 255.13, 255.14, 255.2, 255.3, 255.4, 255.41, 255.42, 255.5, 255.6, 255.8, 255.9, 256.0, 256.1, 256.2, 256.3, 256.31, 256.39, 256.4, 256.8, 256.9, 257.0, 257.1, 257.2, 257.8, 257.9, 258.0, 258.01, 258.02, 258.03, 258.1, 258.8, 258.9, 259, 259.1, 259.2, 259.3, 259.4, 259.5, 259.50, 259.51, 259.52
Nutritional deficiencies (260–269)	260, 261, 262, 263.0, 263.1, 263.2, 263.8, 263.9, 264.5, 268.0, 268.1, 268.2, 268.9
Other metabolic and immunity disorders (270–279)	270.0, 270.1, 270.2, 270.3, 270.4, 270.5, 270.6, 270.7, 270.8, 270.9, 271.0, 271.1, 271.2, 271.3, 271.4, 271.8, 271.9, 272.0, 272.1, 272.2, 272.3, 272.4, 272.5, 272.6, 272.7, 272.8, 272.9, 273.0, 273.1, 273.2, 273.3, 273.4, 273.8, 273.9, 274.0, 274.00, 274.01, 274.02, 274.03, 274.10, 274.11, 274.19, 274.81, 274.82, 274.89, 274.9, 275.0, 275.01, 275.02, 275.03, 275.09, 275.1, 275.2, 275.3, 275.4, 275.40, 275.41, 275.42, 275.49, 275.5, 275.8, 275.9, 277.00, 277.01, 277.02, 277.03, 277.09, 277.1, 277.2, 277.3, 277.30, 277.31, 277.39, 277.4, 277.5, 277.6, 277.7, 277.8, 277.81, 277.82, 277.83, 277.84, 277.85, 277.86, 277.87, 277.88, 277.89, 277.9, 278.0, 278.00, 278.01, 278.03, 278.1, 278.2, 278.3, 278.4, 278.8, 279.00, 279.01, 279.02, 279.03, 279.04, 279.05, 279.06, 279.09, 279.10, 279.11, 279.12, 279.13, 279.19, 279.2, 279.3, 279.4, 279.41, 279.49, 279.50, 279.51, 279.52, 279.53, 279.8, 279.9
Anemia (280–285)	280.0, 282.0, 282.1, 282.2, 282.3, 282.4, 282.40, 282.41, 282.42, 282.43, 282.44, 282.45, 282.46, 282.47, 282.49, 282.5, 282.60, 282.61, 282.62, 282.63, 282.64, 282.68, 282.69, 282.7, 282.8, 282.9, 283.0, 283.1, 283.10, 283.11, 283.19, 283.2, 283.9, 284.0, 284.01, 284.09, 284.1, 284.11, 284.12, 284.19, 284.2, 284.8, 284.81, 284.89, 284.9, 285.0, 285.21, 285.22, 285.29, 285.3
Coagulation/hemorrhagic (286–287)	286.0, 286.1, 286.2, 286.3, 286.4, 286.5, 286.52, 286.53, 286.59, 286.6, 286.7, 286.9, 287.1, 287.3, 287.30, 287.31, 287.32, 287.33, 287.39, 287.4, 287.5
Other diseases of the blood and blood-forming organs (288–289)	288.0,288.00, 288.01, 288.02, 288.03, 288.04, 288.09, 288.1, 288.2, 288.3, 288.4, 288.50, 288.51, 288.59, 288.60, 288.61, 288.62, 288.63, 288.64, 288.65, 288.66, 288.69, 288.8, 288.9, 289.1, 289.51, 289.52, 289.53, 289.81, 289.82, 289.83, 289.84, 289.89
Organic psychotic conditions (290–294)	290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 290.8, 290.9, 291.0, 291.1, 291.2, 291.3, 291.5, 291.8, 291.81, 291.82, 291.89, 291.9, 292.0, 292.82, 292.83, 292.84, 292.85, 292.89, 292.9, 294.0, 294.1, 294.10, 294.11, 294.20, 294.21, 294.8, 294.9
Other psychoses (295–299)	295.00, 295.01, 295.02, 295.03, 295.04, 295.05, 295.10, 295.11, 295.12, 295.13, 295.14, 295.15, 295.20, 295.21, 295.22, 295.23, 295.24, 295.25, 295.30, 295.31, 295.32, 295.33, 295.34, 295.35, 295.40, 295.41, 295.42, 295.43, 295.44, 295.45, 295.50, 295.51, 295.52, 295.53, 295.54, 295.55, 295.60, 295.61, 295.62, 295.63, 295.64, 295.65, 295.70, 295.71, 295.72, 295.73, 295.74, 295.75, 295.80, 295.81, 95.82, 295.83, 295.84, 295.85, 295.90, 295.91, 295.92, 295.93, 295.94, 295.95, 296.00, 296.01, 296.02, 296.03, 296.04, 296.05, 296.06, 296.10, 296.11, 296.12, 296.13, 296.14, 296.15, 296.16, 296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 296.40, 296.41, 296.42, 296.43, 296.44, 296.45, 296.46, 296.50, 296.51,296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63,296.64, 296.65, 296.66, 296.7, 296.80, 296.81, 296.82, 296.89, 296.90, 296.99, 297.0, 297.1, 297.2, 297.3, 297.8, 297.9, 298.0, 298.1, 298.4, 298.8, 298.9, 299.00, 299.01, 299.10, 299.11, 299.80, 299.81, 299.90, 299.91
Neurotic disorders, personality disorders, and other nonpsychotic mental disorders (300–316)	300.00, 300.01, 300.02, 300.09, 300.10, 300.11, 300.12, 300.13, 300.14, 300.15, 300.16, 300.19, 300.20, 300.21, 300.22, 300.23, 300.29, 300.3, 300.4, 300.5, 300.6, 300.7, 300.81, 300.82, 300.89, 300.9, 301.0, 301.10, 301.11, 301.12, 301.13, 301.20, 301.21, 301.22, 301.3, 301.4, 301.50, 301.51, 301.59, 301.6, 301.7, 301.81, 301.82, 301.83, 301.84, 301.89, 301.9, 302.0, 302.1, 302.2, 302.3, 302.4, 302.50, 302.51, 302.52, 302.53, 302.6, 302.70, 302.71, 302.72, 302.73, 302.74, 302.75, 302.76, 302.79, 302.81, 302.82, 302.83, 302.84, 302.85, 302.89, 302.9, 303.00, 303.01, 303.02, 303.03, 303.90, 303.91, 303.92, 303.93, 304.00, 304.01, 304.02, 304.03, 304.10, 304.11, 304.12, 304.13, 304.20, 304.21, 304.22, 304.23, 304.30, 304.31, 304.32, 304.33, 304.40, 304.41, 304.42, 304.43, 304.50, 304.51, 304.52, 304.53, 304.60, 304.61, 304.62, 304.63, 304.70, 304.71, 304.72, 304.73, 304.80, 304.81, 304.82, 304.83, 304.90, 304.91, 304.92, 304.93, 305.00, 305.01, 305.02, 305.03, 305.1, 305.10, 305.11, 305.12, 305.13, 305.20, 305.21, 305.22, 305.23, 305.30, 305.31, 305.32, 305.33, 305.40, 305.41, 305.42, 305.43, 305.50, 305.51, 305.52, 305.53, 305.60, 305.61, 305.62, 305.63, 305.70, 305.71, 305.72, 305.73, 305.80, 305.81, 305.82, 305.83, 305.90, 305.91, 305.92, 305.93, 306.0, 306.1, 306.2, 306.3, 306.4, 306.50, 306.51, 306.52, 306.53, 306.59, 306.6, 306.7, 306.8, 306.9, 307.0, 307.1, 307.20, 307.21, 307.22, 307.23, 307.3, 307.40, 307.42, 307.44, 307.45, 307.46, 307.47, 307.48, 307.49, 307.50, 307.51, 307.52, 307.53, 307.54, 307.59, 307.6, 307.7, 307.80, 307.81, 307.89, 307.9, 308.0, 308.1, 308.2, 308.3, 308.4, 308.9, 309.0, 309.1, 309.21, 309.22, 309.23, 309.24, 309.28, 309.29, 309.3, 309.4, 309.81,

	309.82, 309.83, 309.89, 309.9, 310.0, 310.1, 310.2, 310.8, 310.81, 310.89, 310.9, 311, 312.00, 312.01, 312.02, 312.03, 312.10, 312.11, 312.12, 312.13, 312.20, 312.21, 312.22, 312.23, 312.30, 312.31, 312.32, 312.33, 312.34, 312.35, 312.39, 312.4, 312.8, 312.81, 312.82, 312.89, 312.9, 313.0, 313.1, 313.21, 313.22, 313.23, 313.3, 313.81, 313.82, 313.83, 313.89, 313.9, 314.00, 314.01, 314.1, 314.2, 314.8, 314.9, 315.00, 315.01, 315.02, 315.09, 315.1, 315.2, 315.31, 315.32, 315.34, 315.35, 315.39, 315.4, 315.5, 315.8, 315.9, 316
Mental retardation (317–319)	317, 318.0, 318.1, 318.2, 319
Organic sleep disorders (327-329)	327.00, 327.01, 327.02, 327.09, 327.10, 327.11, 327.12, 327.13, 327.14, 327.15, 327.19, 327.20, 327.21, 327.23, 327.24, 327.25, 327.26, 327.27, 327.29, 327.30, 327.31, 327.32, 327.33, 327.34, 327.36, 327.37, 327.39, 327.40, 327.41, 327.42, 327.43, 327.44, 327.49, 327.51, 327.52, 327.53, 327.59, 327.8
Hereditary and Degenerative diseases of the central nervous system (330–337)	330.0, 330.1, 330.2, 330.3, 330.8, 330.9, 331.0, 331.1, 331.11, 331.19, 331.2, 331.3, 331.4, 331.5, 331.6, 331.7, 331.81, 331.82, 331.83, 331.89, 331.9, 332.0, 332.1, 333.0, 333.1, 333.2, 333.3, 333.4, 333.5, 333.6, 333.7, 333.71, 333.79, 333.81, 333.82, 333.83, 333.84, 333.89, 333.90, 333.91, 333.92, 333.93, 333.94, 333.99, 334.0, 334.1, 334.2, 334.3, 334.4, 334.8, 334.9, 335.0, 335.10, 335.11, 335.19, 335.20, 335.21, 335.22, 335.23, 335.24, 335.29, 335.8, 335.9, 336.0, 336.1, 336.2, 336.3, 336.8, 336.9, 337.0, 337.00, 337.01, 337.09, 337.1, 337.20, 337.21, 337.22, 337.29, 337.3, 337.9
Pain (338-339)	338.0, 338.21, 338.22, 338.28, 338.29, 338.3, 338.4, 339.00 339.01, 339.02, 339.03, 339.04, 339.11, 339.12, 339.22, 339.41, 339.42
Other disorders of the central nervous system (340–349)	340, 341.0, 341.1, 341.8, 341.9, 342.0, 342.00, 342.01, 342.02, 342.1, 342.10, 342.11, 342.12, 342.80, 342.81, 342.82, 342.9, 342.90, 342.91, 342.92, 343.0, 343.1, 343.2, 343.3, 343.4, 343.8, 343.9, 344.0, 344.00, 344.01, 344.02, 344.03, 344.04, 344.09, 344.1, 344.2, 344.3, 344.30, 344.31, 344.32, 344.4, 344.40, 344.41, 344.42, 344.5, 344.60, 344.61, 344.8, 344.81, 344.89, 344.9, 345.0, 345.00, 345.01, 345.1, 345.10, 345.11, 345.2, 345.3, 345.4, 345.40, 345.41, 345.5, 345.50, 345.51, 345.6, 345.60, 345.61, 345.7, 345.70, 345.71, 345.8, 345.80, 345.81, 345.9, 345.90, 345.91, 346.0, 346.00, 346.01, 346.02, 346.03, 346.1, 346.10, 346.11, 346.12, 346.13, 346.2, 346.20, 346.21, 346.22, 346.23, 346.30, 346.31, 346.32, 346.33, 346.40, 346.41, 346.42, 346.43, 346.50, 346.51, 346.52, 346.53, 346.60, 346.61, 346.62, 346.63, 346.70, 346.71, 346.72, 346.73, 346.8, 346.80, 346.81, 346.82, 346.83, 346.9, 346.90, 346.91, 346.92, 346.93, 347, 347.00, 347.01, 347.10, 347.11, 348.0, 348.1, 348.2, 348.3, 348.30, 348.31, 348.39, 348.4, 348.5, 348.8, 348.81, 348.89, 348.9
Disorders of the peripheral nervous system (350–359)	353.0, 353.1, 353.2, 353.3, 353.4, 353.5, 353.6, 353.8, 353.9, 354.0, 354.1, 354.2, 354.3, 354.4, 354.5, 354.8, 354.9, 355.0, 355.1, 355.2, 355.3, 355.4, 355.5, 355.6, 355.7, 355.71, 355.79, 355.8, 355.9, 356.0, 356.1, 356.2, 356.3, 356.4, 356.8, 356.9, 357.0, 357.1, 357.2, 357.3, 357.4, 357.5, 357.6, 357.7, 357.8, 357.81, 357.82, 357.89, 357.9, 358.0, 358.00, 358.01, 358.30, 358.31, 358.39, 359.0, 359.1, 359.2, 359.21, 359.22, 359.23, 359.24, 359.29, 359.3, 359.5, 359.6, 359.71, 359.79, 359.8, 359.81, 359.89, 359.9
Disorders of the eye and adnexa (360–379)	360.00, 360.01, 360.02, 360.03, 360.04, 360.11, 360.12, 360.13, 360.14, 360.19, 360.20, 360.21, 360.23, 360.24, 360.29, 360.30, 360.31, 360.32, 360.33, 360.34, 360.40, 360.41, 360.42, 360.43, 360.44, 360.50, 360.51, 360.52, 360.53, 360.54, 360.55, 360.59, 360.60, 360.61, 360.62, 360.63, 360.64, 360.65, 360.69, 360.81, 360.89, 360.9, 361.10, 361.11, 361.12, 361.13, 361.14, 361.19, 362.01, 362.02, 362.03, 362.04, 362.05, 362.06, 362.07, 362.10, 362.11, 362.12, 362.13, 362.14, 362.15, 362.16, 362.17, 362.18, 362.20, 362.21, 362.22, 362.23, 362.24, 362.25, 362.26, 362.27, 362.29, 362.30, 362.31, 362.32, 362.33, 362.34, 362.35, 362.36, 362.37, 362.40, 362.41, 362.42, 362.43, 362.50, 362.51, 362.52, 362.53, 362.54, 362.55, 362.56, 362.57, 362.60, 362.61, 362.62, 362.63, 362.64, 362.65, 362.66, 362.70, 362.71, 362.72, 362.73, 362.74, 362.75, 362.76, 362.77, 362.81, 362.82, 362.83, 362.84, 362.85, 362.89, 362.9, 363.00, 363.01, 363.03, 363.04, 363.05, 363.06, 363.07, 363.08, 363.10, 363.11, 363.12, 363.13, 363.14, 363.15, 363.20, 363.21, 363.22, 363.30, 363.31, 363.32, 363.33, 363.34, 363.35, 363.40, 363.41, 363.42, 363.43, 363.50, 363.51, 363.52, 363.53, 363.54, 363.55, 363.56, 363.57, 363.61, 363.62, 363.63, 363.70, 363.71, 363.72, 363.8, 363.9, 364.10, 364.11, 364.42, 364.82, 365.00, 365.01, 365.02, 365.03, 365.04, 365.05, 365.06, 365.10, 365.11, 365.12, 365.13, 365.14, 365.15, 365.20, 365.21, 365.22, 365.23, 365.24, 365.31, 365.32, 365.41, 365.42, 365.43, 365.44, 365.51, 365.52, 365.59, 365.60, 365.61, 365.62, 365.63, 365.64, 365.65, 365.70, 365.71, 365.72, 365.73, 365.74, 365.81, 365.82, 365.83, 365.89, 365.9, 366.00, 366.01, 366.02, 366.03, 366.04, 366.09, 366.10, 366.11, 366.12, 366.13, 366.14, 366.15, 366.16, 366.17, 366.18, 366.19, 366.20, 366.21, 366.22, 366.23, 366.30, 366.31, 366.32, 366.33, 366.34, 366.41, 366.42, 366.43, 366.44, 366.45, 366.46, 366.50, 366.51, 366.52, 366.53 366.8, 366.9, 369.00, 369.01, 369.02, 369.03, 369.04, 369.05, 369.06, 369.07, 369.08, 369.10, 369.11, 369.12, 369.13, 369.14, 369.15, 369.16, 369.17, 369.18, 369.20, 369.21, 369.22, 369.23, 369.24, 369.25, 369.3, 369.4, 369.60, 369.61, 369.62, 369.63, 369.64, 369.65, 369.66, 369.67, 369.68, 369.69, 369.70, 369.71, 369.72, 369.73, 369.74, 369.75, 369.76, 369.8, 369.9, 370.07, 370.21, 370.22, 370.23, 370.33, 370.34, 370.35, 370.44, 370.50, 370.52, 370.54, 370.55, 370.59, 370.60, 370.61, 370.62, 370.63, 370.64, 371.23, 372.10, 372.11, 372.12, 372.13, 372.14, 372.15, 376.10, 376.11, 376.12, 376.13, 376.21, 376.22, 376.30, 376.31, 376.32, 376.33, 376.34, 376.35, 376.36, 376.40, 376.41, 376.42, 376.43, 376.44, 376.45, 376.46, 376.47, 376.50, 376.51, 376.52, 376.6, 376.81, 376.82, 377.00, 377.01, 377.02, 377.03, 377.04, 377.10, 377.11, 377.12, 377.13, 377.14, 377.15, 377.16, 377.21, 377.22, 377.23, 377.24, 377.30, 377.31, 377.32, 377.33, 377.34, 377.39, 377.41, 377.42, 377.43, 377.49, 377.51, 377.52, 377.53, 377.54, 377.61, 377.62, 377.63, 377.71, 377.72, 377.73, 377.75, 377.9, 379.02, 379.03, 379.04, 379.05, 379.06, 379.07, 379.11, 379.12, 379.13, 379.14, 379.15, 379.16, 379.21, 379.22, 379.23, 379.24, 379.25, 379.26, 379.27, 379.29, 379.31, 379.32, 379.33, 379.34, 379.39, 379.40, 379.41, 379.42, 379.43, 379.45, 379.46, 379.49, 379.50, 379.51, 379.52, 379.53, 379.54, 379.55, 379.56, 379.57, 379.58, 379.59
Diseases of the ear and mastoid process (380–389)	380.02, 380.14, 380.15, 380.16, 380.23, 381.10, 381.19, 381.20, 381.29, 381.3, 381.52, 382.1, 382.2, 382.3, 383.1, 383.22, 384.1, 386.00, 386.01, 386.02, 386.03, 386.04, 389.00, 389.01, 389.02, 389.03, 389.04, 389.05, 389.06, 389.08, 389.10, 389.11, 389.12, 389.13, 389.14, 389.17, 389.18, 389.2, 389.20, 389.21, 389.22, 389.7, 389.8, 389.9
Chronic rheumatic heart disease (393–398)	393, 394.0, 394.1, 394.2, 394.9, 395.0, 395.1, 395.2, 395.9, 396.0, 396.1, 396.2, 396.3, 396.8, 396.9, 397.0, 397.1, 397.9, 398.0, 398.90, 398.91, 398.99

Hypertensive disease (401–405)	401.0, 401.1, 401.9, 402.00, 402.01, 402.10, 402.11, 402.90, 402.91, 403.0, 403.00, 403.01, 403.1, 403.10, 403.11, 403.9, 403.90, 403.91, 404.0, 404.00, 404.01, 404.02, 404.03, 404.1, 404.10, 404.11, 404.12, 404.13, 404.9, 404.90, 404.91, 404.92, 404.93, 405.01, 405.09, 405.11, 405.19, 405.91, 405.99
Ischemic heart disease (410–414)	410.0, 410.00, 410.01, 410.02, 410.1, 410.10, 410.11, 410.12, 410.2, 410.20, 410.21, 410.22, 410.3, 410.30, 410.31, 410.32, 410.4, 410.40, 410.41, 410.42, 410.5, 410.50, 410.51, 410.52, 410.6, 410.60, 410.61, 410.62, 410.7, 410.70, 410.71, 410.72, 410.8, 410.80, 410.81, 410.82, 410.9, 410.90, 410.91, 410.92, 411.0, 411.1, 411.8, 411.81, 411.89, 412, 413.0, 413.1, 413.9, 414.0, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.10, 414.11, 414.12, 414.19, 414.2, 414.3, 414.4, 414.8, 414.9
Diseases of pulmonary circulation (415–417)	415.0, 415.13, 416.0, 416.1, 416.2, 416.8, 416.9, 417.0
Other forms of heart disease (420–429)	423.1, 423.2, 424.0, 424.1, 424.2, 424.3, 424.90, 424.91, 424.99, 425.0, 425.1, 425.11, 425.18, 425.2, 425.3, 425.4, 425.5, 425.7, 425.8, 425.9, 426.0, 426.10, 426.11, 426.12, 426.13, 426.2, 426.3, 426.4, 426.50, 426.51, 426.52, 426.53, 426.54, 426.6, 426.7, 426.81, 426.82, 426.89, 426.9, 427.0, 427.1, 427.2, 427.31, 427.32, 427.41, 427.42, 427.5, 427.60, 427.61, 427.69, 427.81, 427.89, 427.9, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9, 429.0, 429.1, 429.2, 429.3, 429.4, 429.5, 429.6 429.71, 429.79, 429.81, 429.82, 429.83, 429.89, 429.9
Cerebrovascular disease (430–438)	430, 431, 432.0,432.1, 432.9, 433.0, 433.00, 433.01, 433.1, 433.10, 433.11, 433.2, 433.20, 433.21, 433.3, 433.30, 433.31, 433.8, 433.80, 433.81, 433.9, 433.90, 433.91, 434.0, 434.00, 434.01, 434.1, 434.10, 434.11, 434.9, 434.90, 434.91, 435.0, 435.1, 435.2, 435.3, 435.8, 435.9, 436, 437.0, 437.1, 437.2, 437.3, 437.4, 437.5, 437.6, 437.7, 437.8, 437.9, 438, 438.0, 438.10, 438.11, 438.12, 438.13, 438.14, 438.19, 438.20, 438.21, 438.22, 438.30, 438.31, 438.32, 438.40, 438.41, 438.42, 438.50, 438.51, 438.52, 438.53, 438.6, 438.7, 438.81, 438.82, 438.83, 438.84, 438.85, 438.89, 438.9
Diseases of arteries, arterioles, and capillaries (440–449)	440.0, 440.1, 440.2, 440.20, 440.21, 440.22, 440.23, 440.24, 440.29, 440.30, 440.31, 440.32, 440.4, 440.8, 440.9, 441.0, 441.00, 441.01, 441.02, 441.03, 441.1, 441.2, 441.3, 441.4, 441.5, 441.6, 441.7, 441.9, 442.0, 442.1, 442.2, 442.3, 442.81, 442.82, 442.83, 442.84, 442.89, 442.9, 443.0, 443.1, 443.21, 443.22, 443.23, 443.24, 443.29, 443.81, 443.82, 443.89, 443.9, 444.0, 444.01, 444.09, 444.1, 444.21, 444.22, 444.81, 444.89, 444.9, 445.01, 445.02, 445.81, 445.89, 446.0, 446.1, 446.2, 446.20, 446.21, 446.29, 446.3, 446.4, 446.5, 446.6, 446.7, 447.0, 447.1, 447.2, 447.3, 447.4, 447.5, 447.6, 447.70, 447.71, 447.72, 447.73, 447.8, 447.9, 448.0
Diseases of veins and lymphatics, and other diseases of circulatory system (451–459)	453.0, 453.1, 453.2, 453.3, 453.50, 453.51, 453.52, 453.71, 453.72, 453.73, 453.74, 453.75, 453.76, 453.77, 453.79, 456.0, 456.1, 456.20, 456.21, 457.0, 457.1, 457.2, 457.8, 457.9, 458.21, 459.1, 459.10, 459.11, 459.12, 459.13, 459.19, 459.30, 459.31, 459.32, 459.33, 459.39
Other diseases of the upper respiratory tract (470–478)	472.0, 472.1, 472.2, 473.0, 473.1, 473.2, 473.3, 473.8, 473.9, 474.0, 474.00, 474.01, 474.02, 474.10, 474.11, 474.12, 474.2, 474.8, 474.9, 476.0, 476.1, 477.0, 477.1, 477.2, 477.8, 477.9, 478.11, 478.30, 478.31, 478.32, 478.33, 478.34
Chronic obstructive pulmonary disease and allied conditions (490–496)	491.0, 491.1, 491.2, 491.20, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 493.00, 493.01, 493.02, 493.10, 493.11, 493.12, 493.20, 493.21, 493.22, 493.81, 493.82, 493.90, 493.91, 493.92, 494, 494.0, 494.1, 495.0, 495.1, 495.2, 495.3, 495.4, 495.5, 495.6, 495.7, 495.8 495.9, 496
Pneumoconioses and other lung diseases due to external agents (500–508)	500, 501, 502, 503, 504, 505, 506.4, 508.1
Other diseases of respiratory system (510–519)	511.81, 512.83, 514, 515, 516.0, 516.1, 516.2, 516.3, 516.30, 516.31, 516.32, 516.33, 516.34, 516.35, 516.36, 516.37, 516.4, 516.5, 516.61, 516.62, 516.63, 516.64, 516.69, 516.8, 516.9, 517.1, 517.2, 517.8, 518.53, 518.6, 518.83, 518.84
Diseases of oral cavity, salivary glands, and jaws (520–529)	523.10, 523.11, 523.40, 523.41, 523.42, 525.40, 525.41, 525.42, 525.43, 525.44
Diseases of esophagus, stomach, and duodenum (530–539)	530.11, 530.13, 530.2, 530.20, 530.21, 530.3, 530.5, 530.81, 530.84, 530.85, 530.86, 530.87, 531.41, 531.50, 531.51, 531.60, 531.61, 531.70, 531.71, 531.90, 531.91, 532.41, 532.50, 532.51, 532.60, 532.61, 532.70, 532.71, 532.90, 532.91, 533.40, 533.41, 533.50, 533.51, 533.60, 533.61, 533.70, 533.71, 533.90, 533.91, 534.40, 534.41, 534.50, 534.51, 534.60, 534.61, 534.70, 534.71, 534.90, 534.91, 535.1, 535.10, 535.11, 535.3, 535.30, 535.31, 535.70, 535.71, 537.2
Noninfectious enteritis and colitis (555–558)	555.0, 555.1, 555.2, 555.9, 556, 556.0, 556.1, 556.2, 556.3, 556.4, 556.5, 556.6, 556.8, 556.9, 557.1, 557.9, 558.41, 558.42
Other diseases of intestines and peritoneum (560–569)	562.00, 562.01, 562.02, 562.03, 562.10, 562.11, 562.12, 562.13, 564.1, 564.81, 569.6, 569.60, 569.61, 569.62, 569.69
Other diseases of digestive system (570–579)	571.0, 571.1, 571.2, 571.3, 571.40, 571.41, 571.42, 571.49, 571.5, 571.6, 571.8, 571.9, 572.3, 572.4, 572.8, 573.0, 573.1, 573.2, 573.3, 573.4, 573.5, 573.8, 573.9, 575.5, 576.1, 576.2, 576.3, 576.4, 576.5, 576.6, 576.7, 577.1, 579, 579.2, 579.3, 579.4, 579.8, 579.9
Nephritis, nephrotic syndrome, and nephrosis (580–589)	581.0, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9, 582.0, 582.1, 582.2, 582.4, 582.81, 582.89, 582.9, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9, 585, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9, 586, 587, 588.0, 588.1, 588.8, 588.81, 588.89, 588.9
Other diseases of urinary system (590–599)	590.00, 590.01, 593.82, 595.1, 595.2, 596.0, 596.1, 596.2, 596.3, 596.4, 596.5, 596.51, 596.52, 596.53, 596.54, 596.55, 596.59, 596.6, 596.7, 596.8, 596.9, 599.1
Diseases of male genital organs (600–608)	600, 600.0, 600.00, 600.01, 600.1, 600.10, 600.11, 600.2, 600.20, 600.21, 600.3, 600.9, 600.90, 600.91, 601.1, 607.0, 607.1, 607.2, 607.3, 607.81, 607.82, 607.83, 607.84, 607.85, 607.89, 607.9
Disorders of Breast (610–612)	610.1, 610.2, 610.3, 610.4
Inflammatory Disease of Female Pelvic Organs (614–616)	614.1, 614.4, 614.7, 615.1
*Other disorders of female genital tract (617–629)**	617.0, 617.1, 617.2, 617.3, 617.4, 617.5, 617.6, 617.8, 617.9, 618.0, 618.00, 618.01, 618.02, 618.03, 618.04, 618.05, 618.09, 618.1, 618.2, 618.3, 618.4, 618.5, 618.6, 618.7, 618.8, 618.81, 618.82, 618.83, 618.84, 618.89, 618.9, 619.0, 619.1, 619.2, 619.8, 619.9, 621.3, 621.30, 621.31, 621.32, 621.33, 621.34, 621.35, 625.0, 625.2, 625.3, 625.4, 625.6, 625.70, 625.71, 625.79, 626.0,
*(*ICD-9 codes related to infertility excluded)*	

	626.1, 626.2, 626.3, 626.4, 626.5, 626.6, 626.7, 626.8, 626.9, 627.0,c627.1, 627.2, 627.3, 627.4, 627.8, 627.9, 629.20, 629.21, 629.22, 629.23, 629.29
Complications mainly related to pregnancy (640–649)	chronic ICD-9 excluded in this category
Other inflammatory conditions of skin and subcutaneous tissue (690–698)	691.8, 694.0, 694.1, 694.2, 694.4, 694.5, 694.60, 694.61, 694.8, 694.9, 695.3, 695.4, 696.0, 696.1, 696.2, 696.3, 696.4, 696.5, 696.8
Other diseases of skin and subcutaneous tissue (700–709)	701.0, 705.0, 705.82, 707.0, 707.00, 707.01, 707.02, 707.03, 707.04, 707.05, 707.06, 707.07, 707.09, 707.1, 707.10, 707.11, 707.12, 707.13, 707.14, 707.15, 707.19, 707.20, 707.21, 707.22, 707.23, 707.24, 707.25, 707.8, 707.9
Arthropathies and related disorders (710–719)	710.0, 710.1, 710.2, 710.3, 710.4, 710.5, 710.8, 710.9, 712.10, 712.11, 712.12, 712.13, 712.14, 712.15, 712.16, 712.17, 712.18, 712.19, 712.20, 712.21, 712.22, 712.23, 712.24, 712.25, 712.26, 712.27, 712.28, 712.29, 712.30, 712.31, 712.32, 712.33, 712.34, 712.35, 712.36, 712.37, 712.38, 712.39, 712.80, 712.81, 712.82, 712.83, 712.84, 712.85, 712.86, 712.87, 712.88, 712.89, 712.90, 712.91, 712.92, 712.93, 712.94, 712.95, 712.96, 712.97, 712.98, 712.99, 713.0, 713.1, 713.2, 713.3, 713.4, 713.5, 713.6, 713.7, 713.8, 714.0, 714.1, 714.2, 714.30, 714.31, 714.32, 714.33, 714.4, 714.81, 714.89, 714.9, 715.00, 715.04, 715.09, 715.10, 715.11, 715.12, 715.13, 715.14, 715.15, 715.16, 715.17, 715.18, 715.20, 715.21, 715.22, 715.23, 715.24, 715.25, 715.26, 715.27, 715.28, 715.30, 715.31, 715.32, 715.33, 715.34, 715.35, 715.36, 715.37, 715.38, 715.80, 715.89, 715.90, 715.91, 715.92, 715.93, 715.94, 715.95, 715.96, 715.97, 715.98, 716.00, 716.01, 716.02, 716.03, 716.04, 716.05, 716.06, 716.07, 716.08, 716.09, 716.10, 716.11, 716.12, 716.13, 716.14, 716.15, 716.16, 716.17, 716.18, 716.19, 716.20, 716.21, 716.22, 716.23, 716.24, 716.25, 716.26, 716.27, 716.28, 716.29, 716.30, 716.31, 716.32, 716.33, 716.34, 716.35, 716.36, 716.37, 716.38, 716.39, 716.40, 716.41, 716.42, 716.43, 716.44, 716.45, 716.46, 716.47, 716.48, 716.49, 716.50, 716.51, 716.52, 716.53, 716.54, 716.55, 716.56, 716.57, 716.58, 716.59, 716.60, 716.61, 716.62, 716.63, 716.64, 716.65, 716.66, 716.67, 716.68, 716.80, 716.81, 716.82, 716.83, 716.84, 716.85, 716.86, 716.87, 716.88, 716.89, 716.90, 716.91, 716.92, 716.93, 716.94, 716.95, 716.96, 716.97, 716.98, 716.99, 717.0, 717.1, 717.2, 717.3, 717.40, 717.41, 717.42, 717.43, 717.49, 717.5, 717.6, 717.7, 717.81, 717.82, 717.83, 717.84, 717.85, 717.89, 717.9, 718.00, 718.01, 718.02, 718.03, 718.04, 718.05, 718.07, 718.08, 718.09, 718.10, 718.11, 718.12, 718.13, 718.14, 718.15, 718.17, 718.18, 718.19, 718.40, 718.41, 718.42, 718.43, 718.44, 718.45, 718.46, 718.47, 718.48, 718.49, 718.50, 718.51, 718.52, 718.53, 718.54, 718.55, 718.56, 718.57, 718.58, 718.59, 718.60, 718.65, 718.70, 718.71, 718.72, 718.73, 718.74, 718.75, 718.76, 718.77, 718.78, 718.79, 719.30, 719.31, 719.32, 719.33, 719.34, 719.35, 719.36, 719.37, 719.38, 719.39, 719.7
Dorsopathies (720–724)	720.0, 720.1, 720.2, 720.81, 720.89, 720.9, 721.0, 721.1, 721.2, 721.3, 721.41, 721.42, 721.5, 721.6, 721.7, 721.8, 721.90, 721.91, 722.0, 722.1, 722.2, 722.3, 722.4, 722.5, 722.6, 722.7, 722.8, 722.9, 722.10, 722.11, 722.12, 722.13, 722.14, 722.15, 722.16, 722.17, 722.18, 722.19, 722.20, 722.21, 722.22, 722.23, 724.03
Rheumatism, excluding the back (725–729)	725
Maternal causes of perinatal morbidity and mortality (760–763)	chronic ICD-9 excluded in this category
Other conditions originating in the perinatal period (764–779)	chronic ICD-9 excluded in this category
Symptoms (780–789)	780.03, 780.51, 780.53, 780.57, 780.71, 780.72, 784.3, 784.61, 787.6, 788.3, 788.30, 788.31, 788.32, 788.33, 788.34, 788.35, 788.36, 788.37, 788.38, 788.39, 788.91, 789.51
Nonspecific abnormal findings (790–796)	795.16, 796.76
Ill-defined and unknown causes of morbidity and mortality (797–799)	797, 799.51, 799.52, 799.53, 799.54, 799.55
Open wound of upper limb (880–887)	885.0, 885.1, 886.0, 886.1, 887.0, 887.1, 887.2, 887.3, 887.4, 887.5, 887.6, 887.7
Open wound of lower limb (890–897)	895.0, 895.1, 896.0, 896.1, 896.3, 897.0, 897.1, 897.2, 897.3, 897.4, 897.5, 897.6, 897.7
Late effects of injuries, poisonings, toxic effects, and other external causes (905–909)	905.9
Injury to nerves and spinal cord (950–957)	952.00, 952.01, 952.02, 952.03, 952.04, 952.05, 952.06, 952.07, 952.08, 952.09, 952.10, 952.11, 952.12, 952.13, 952.14, 952.15, 952.16, 952.17, 952.18, 952.19, 952.2, 952.3, 952.4, 952.8, 952.9

Anomalies: Several cateogories grouped *[Osteopathies, chondropathies, and acquired musculoskeletal deformities (730–739); Nervous system (740–742); Eye, ear, face and neck (743–744); Circulatory system (745–747); Respiratory system (748–748); Digestive system (749–751); Genital organs (752); Urinary system (753); Musculoskeletal system (754–756); Integument (757); Chromosomal anomalies (758); Other anomalies (759)]*	730.00, 730.01, 730.02, 730.03, 730.04, 730.05, 730.06, 730.07, 730.08, 730.09, 730.10, 730.11, 730.12, 730.13, 730.14, 730.15, 730.16, 730.17, 730.18, 730.19, 730.20, 730.21, 730.22, 730.23, 730.24, 730.25, 730.26, 730.27, 730.28, 730.29, 730.30, 730.31, 730.32, 730.33, 730.34, 730.35, 730.36, 730.37, 730.38, 730.39, 730.70, 730.71, 730.72, 730.73, 730.74, 730.75, 730.76, 730.77, 730.78, 730.79, 730.80. 730.81. 730.82. 730.83. 730.84. 730.85, 730.86. 730.87. 730.88. 730.89, 730.90. 730.91, 730.92, 730.93. 730.94. 730.95. 730.96. 730.97. 730.98. 730.99, 731.0, 731.1, 731.2, 731.8, 732.0, 732.1, 732.2, 732.3, 732.4, 732.5, 732.6, 732.7, 732.8, 732.9, 733.00 , 733.01, 733.02, 733.03, 733.09, 733.40, 733.41, 733.42, 733.43, 733.44, 733.45, 733.49, 735.0, 735.1, 735.2, 735.3, 735.4, 737.0, 737.10, 737.11, 737.12, 737.19, 737.20, 737.21, 737.22, 737.29, 737.30, 737.31, 737.32, 737.33, 737.34, 737.39, 737.40, 737.41, 737.42, 737.43; 740.0, 740.1, 740.2, 741.00, 741.01, 741.02, 741.03, 741.90, 741.91, 741.92, 741.93, 742.0, 742.1, 742.2, 742.3, 742.4, 742.51, 742.53, 742.59, 742.8, 742.9; 743.00, 743.03, 743.06, 743.10, 743.11, 743.12, 743.20, 743.21, 743.22, 743.30, 743.31, 743.32, 743.33, 743.34, 743.35, 743.36, 743.37, 743.39, 743.41, 743.42, 743.43, 743.44, 743.45, 743.46, 743.47, 743.48, 743.49, 743.51, 743.52, 743.53, 743.54, 743.55, 743.56, 743.57, 743.58, 743.59, 743.61, 743.62, 743.63, 743.64, 743.65, 743.66, 743.69, 743.8, 743.9, 744.00, 744.01, 744.02, 744.03, 744.04, 744.05, 744.09, 744.1, 744.21, 744.22, 744.23, 744.24, 744.29, 744.3, 744.41, 744.42, 744.43, 744.46, 744.47, 744.49, 744.5, 744.81, 744.82, 744.83, 744.84, 744.89, 744.9; 745.0, 745.10, 745.11, 745.12, 745.19, 745.2, 745.3, 745.4, 745.5, 745.60, 745.61, 745.69, 745.7, 745.8, 745.9, 746.01, 746.02, 746.09, 746.1, 746.2, 746.3, 746.4, 746.5, 746.6, 746.7, 746.81, 746.82, 746.83, 746.84, 746.85, 746.86, 746.87, 746.89, 746.9, 747.0, 747.10, 747.11, 747.20, 747.21, 747.22, 747.29, 747.3, 747.31, 747.32, 747.39, 747.40, 747.41, 747.42, 747.49, 747.5, 747.6, 747.60, 747.61, 747.62, 747.63, 747.64, 747.69, 747.81, 747.82, 747.83, 747.89, 747.9; 748.0, 748.1, 748.2, 748.3, 748.4, 748.5, 748.60, 748.61, 748.69, 748.8, 748.9; 749.00, 749.01, 749.02, 749.03, 749.04, 749.10, 749.11, 749.12, 749.13, 749.14, 749.20, 749.21, 749.22, 749.23, 749.24, 749.25, 750.0, 750.10, 750.11, 750.12, 750.13, 750.15, 750.16, 750.19, 750.21, 750.22, 750.23, 750.24, 750.25, 750.26, 750.27, 750.29, 750.3, 750.4, 750.5, 750.6, 750.7, 750.8, 750.9, 751.0, 751.1, 751.2, 751.3, 751.4, 751.5, 751.60, 751.61, 751.62, 751.69, 751.7, 751.8, 751.9; 752.0, 752.10, 752.11, 752.19, 752.2, 752.3, 752.31, 752.32, 752.33, 752.34, 752.35, 752.36, 752.39, 752.40, 752.41, 752.42, 752.43, 752.44, 752.45, 752.46, 752.47, 752.49, 752.5, 752.51, 752.52, 752.6, 752.61, 752.62, 752.63, 752.64, 752.65, 752.69, 752.7, 752.8, 752.81, 752.89, 752.9; 753.0, 753.1, 753.10, 753.11, 753.12, 753.13, 753.14, 753.15, 753.16, 753.17, 753.19, 753.2, 753.20, 753.21, 753.22, 753.23, 753.29, 753.3, 753.4, 753.5, 753.6, 753.7, 753.8, 753.9; 754.0, 754.1, 754.2, 754.30, 754.31, 754.32, 754.33, 754.35, 754.40, 754.41, 754.42, 754.43, 754.44, 754.50, 754.51, 754.52, 754.53, 754.59, 754.60, 754.61, 754.62, 754.69, 754.70, 754.71, 754.79, 754.81, 754.82, 754.89, 755.00, 755.01, 755.02, 755.10, 755.11, 755.12, 755.13, 755.14, 755.20, 755.21, 755.22, 755.23, 755.24, 755.25, 755.26, 755.27, 755.28, 755.29, 755.30, 755.31, 755.32, 755.33, 755.34, 755.35, 755.36, 755.37, 755.38, 755.39, 755.4, 755.50, 755.51, 755.52, 755.53, 755.54, 755.55, 755.56, 755.57, 755.58, 755.59, 755.60, 755.61, 755.62, 755.63, 755.64, 755.65, 755.66, 755.67, 755.69, 755.8, 755.9, 756.0, 756.1, 756.2, 756.3, 756.4, 756.5, 756.6, 756.7, 756.8, 756.9, 756.10, 756.11, 756.12, 756.13, 756.14, 756.15, 756.16, 756.17, 756.18, 756.19, 756.20, 756.21, 756.22, 756.23, 756.24, 756.25, 756.26, 756.27, 756.28, 756.29, 756.30, 756.31, 756.32; 757.0, 757.1, 757.2, 757.31, 757.32, 757.33, 757.39, 757.4, 757.5, 757.6, 757.8, 757.9; 758.0, 758.1, 758.2, 758.3, 758.31, 758.32, 758.33, 758.39, 758.4, 758.5, 758.6, 758.7, 758.8, 758.81, 758.89, 758.9; 759.0, 759.1, 759.2, 759.3, 759.4, 759.5, 759.6, 759.7, 759.8, 759.81, 759.82, 759.83, 759.89, 759.9
Toxic effects of substances chiefly nonmedicinal as to source (980–989)	984.0, 984.1, 984.8, 984.9, 985.0, 985.1, 985.2, 985.3, 985.4, 985.5, 985.6, 985.8, 985.9,
Complications of surgical and medical care, not elsewhere classified (996–999)	996.73, 996.81, 996.88, 999.81

Reference full Chronic Condition Indicator (CCI): HCUP Chronic Condition Indicator (CCI). Healthcare Cost and Utilization Project (HCUP). 2009; http://www.hcup-us.ahrq.gov/toolssoftware/chronic/chronic.jsp. Accessed March 26, 2020.

eAppendix 1. List of pharmaceutical drug classes available in US

[MoA – mechanism of action; PE – physiologic effect; CS – chemical structure]

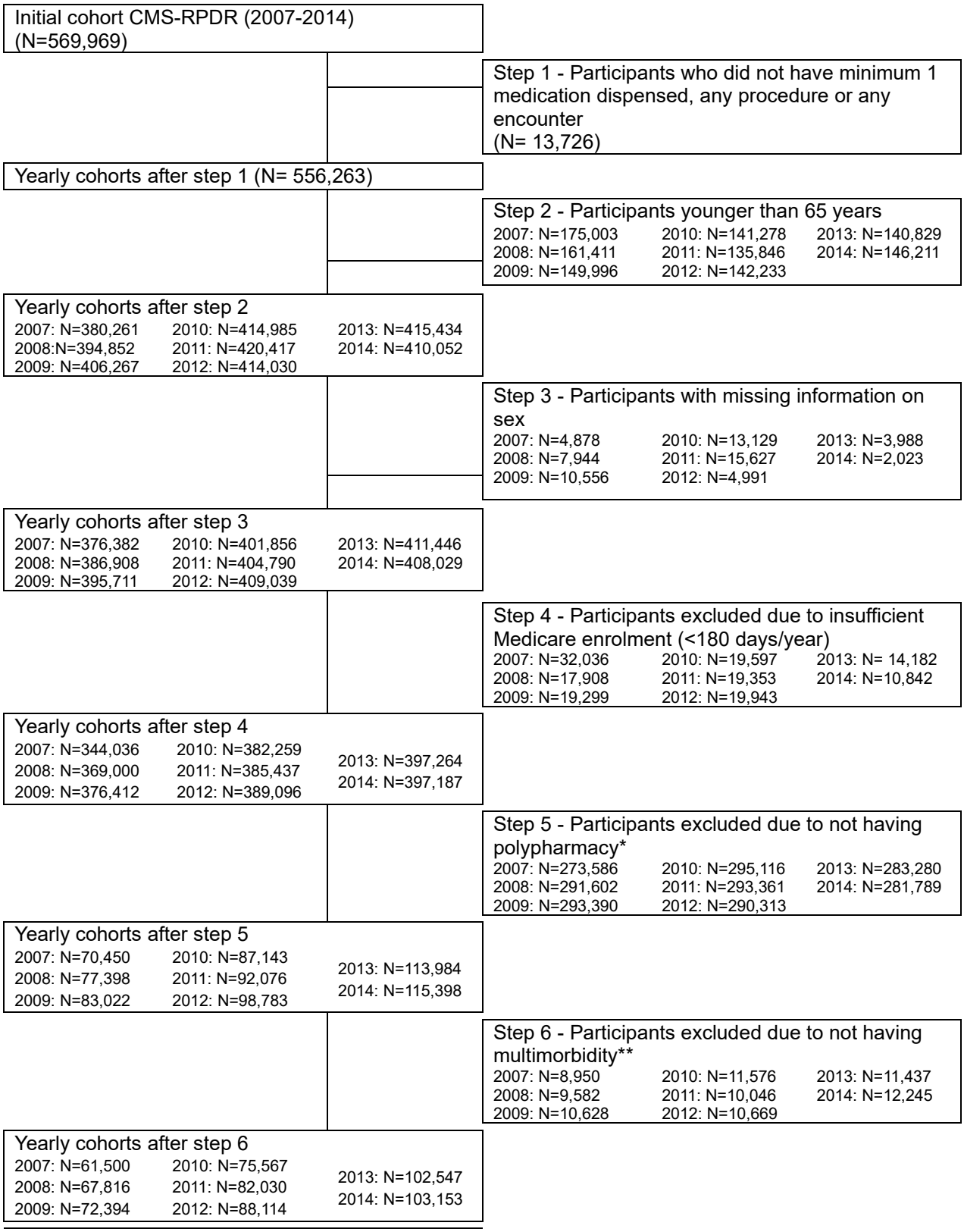
DS - 001) 5-alpha Reductase Inhibitor [EPC]
DS - 002) 5-Lipoxygenase Inhibitors [MoA]
DS - 003) Acetyl Aldehyde Dehydrogenase Inhibitors [MoA]
DS - 004) Acetylcholine Release Inhibitor [EPC]
DS - 005) Acidifying Activity [MoA]
DS - 006) Adrenergic Agonists [MoA]
DS - 007) Adrenergic alpha2-Agonists [MoA]
DS - 008) Adrenergic alpha-Agonists [MoA]
DS - 009) Adrenergic alpha-Antagonists [MoA]
DS - 010) Adrenergic beta2-Agonists [MoA]
DS - 011) Adrenergic beta-Agonists [MoA]
DS - 012) Adrenergic beta-Antagonists [MoA]
DS - 013) Adrenocorticotropic Hormone [CS]
DS - 014) Aldosterone Antagonist [EPC]
DS - 015) Alkylating Activity [MoA]
DS - 016) Allylamine [CS]
DS - 017) alpha Glucosidase Inhibitors [MoA]
DS - 018) alpha-Adrenergic Agonist [EPC]
DS - 019) Aluminum Complex [EPC]
DS - 020) Amino Acid [EPC]
DS - 021) Aminoglycoside Antibacterial [EPC]
DS - 022) Aminoketone [EPC]
DS - 023) Aminosalicylate [EPC]
DS - 024) Ammonium Ion Binding Activity [MoA]
DS - 025) Amphenicol-class Antibacterial [EPC]
DS - 026) Amphetamine Anorectic [EPC]
DS - 027) Amylin Agonists [MoA]
DS - 028) Androgen [EPC]
DS - 029) Androgen Receptor Agonists [MoA]
DS- 030) Androgen Receptor Antagonists [MoA]
DS - 031) Androgen Receptor Inhibitor [EPC]
DS - 032) Angiotensin 2 Type 1 Receptor Antagonists [MoA]
DS - 033) Angiotensin Converting Enzyme Inhibitor [EPC]
DS - 034) Anthelmintic [EPC]
DS - 035) Anthracycline Topoisomerase Inhibitor [EPC]
DS - 036) Anti-anginal [EPC]
DS - 037) Antiarrhythmic [EPC]
DS - 038) Anticholinergic [EPC]
DS - 039) Anti-coagulant [EPC]
DS - 040) Antidiarrheal [EPC]
DS - 041) Antiemetic [EPC]
DS - Anti-epileptic Agent [EPC]
DS - 043) Antifibrinolytic Agent [EPC]
DS - 044) Antihistamine [EPC]
DS - 045) Antihypoglycemic Agent [EPC]
DS - 046) Anti-IgE [EPC]
DS - 047) Antimalarial [EPC]
DS - Event 048) Antimetabolite [EPC]
DS - 049) Antimetabolite Immunosuppressant [EPC]
DS - 050) Antimycobacterial [EPC]
DS - 051) Antiparasitic [EPC]
DS - 052) Antiprotozoal [EPC]
DS - 053) Antirheumatic Agent [EPC]
DS - 054) Appetite Suppression [PE]
DS - 055) Aromatase Inhibitor [EPC]
DS - 056) Aromatic Amino Acid [EPC
DS - 057) Arteriolar Vasodilation [PE]
DS - 058) Atypical Antipsychotic [EPC]
DS - 059) Azole Antifungal [EPC]
DS - 060) Barbiturate [EPC]
DS - 061) Benzodiazepine [EPC]
DS - 062) Benzodiazepine Antagonist [EPC]
DS - 063) Benzothiazole [EPC]
DS - 064) beta3-Adrenergic Agonist [EPC]
DS - 065) Biguanide [EPC]
DS - 066) Bile Acid [EPC]
DS - 067) Bile Acid Sequestrant [EPC]
DS - 068) Bismuth [CS]
DS - 069) Bisphosphonate [EPC]
DS - 070) Blood Coagulation Factor [EPC]
DS - 071) Blood Viscosity Reducer [EPC]
DS - 072) Blood Viscosity Reducer [EPC]
DS - 073) Calcineurin Inhibitor Immunosuppressant [EPC]
DS - 074) Calcitonin [CS]
DS - 075) Calcium Channel Antagonists [MoA]
DS - 076) Calcium-sensing Receptor Agonist [EPC]
DS - 077) Calculi Dissolution Agent [EPC]
DS - 078) Cannabinoid [EPC]
DS - 079) Carbapenems [CS]
DS - 080) Carbonic Anhydrase Inhibitor [EPC]
DS - 081) Carboxypeptidase [EPC]
DS - 082) Carnitine [CS]
DS - 083) Catechol O-Methyltransferase Inhibitors [MoA]
DS - 084) Catecholamine [EPC]
DS - 085) Catecholamine Synthesis Inhibitor [EPC]
DS - 086) CCR5 Co-receptor Antagonist [EPC]
DS - 087) CD123 Interaction [EPC]
DS - 088) CD52-directed Antibody Interactions [MoA]
DS - 089) Cell Death Inducer [EPC
DS - 090) Central alpha-2 Adrenergic Agonist [EPC]
DS - 091) Central Nervous System Stimulant [EPC]
DS - 092) Centrally-mediated Muscle Relaxation [PE]
DS - 093) Cephalosporin Antibacterial [EPC]
DS - 094) Chloride Channel Activator [EPC]
DS - 095) Cholecalciferol [CS]
DS - 096) Cholinergic Agonists [MoA]
DS - 097) Cholinergic Muscarinic Agonist [EPC]
DS - 098) Cholinergic Muscarinic Agonists [MoA]
DS - 099) Cholinergic Muscarinic Antagonist [EPC]
DS - 100) Cholinergic Nicotinic Agonist [EPC]
DS - 101) Cholinesterase Inhibitor [EPC]
DS - 102) Cholinesterase Inhibitors [MoA]
DS - 103) Collagenases [Chemical/Ingredient]
DS - 104) Competitive Opioid Antagonists [MoA]
DS - 105) Copper Absorption Inhibitor [EPC]
DS - 106) Corticosteroid [EPC]
DS - 107) Cyclooxygenase Inhibitors [MoA]
DS - 108) Cystine Disulfide Reduction [MoA]
DS - 109) Cytochrome Inhibitors [MoA]
DS - 110) Cytomegalovirus Nucleoside Analog DNA Polymerase Inhibitor [EPC]
DS - 111) Cytoprotective Agent [EPC]

DS - 112) Decreased Cell Wall Integrity [PE]
DS - 113) Decreased Cell Wall Synthesis & Repair [PE]
DS - 114) Decreased Central Nervous System Disorganized Electrical Activity [PE]
DS - 115) Decreased Cholesterol Absorption [PE]
DS - 116) Decreased Cytokine Activity [PE]
DS - 117) Decreased DNA Replication [PE]
DS - 118) Decreased Histamine Release [PE]
DS - 119) Decreased Immunologic Activity [PE]
DS - 120) Decreased Immunologically Active Molecule Activity [PE]
DS - 121) Decreased Mitosis [PE]
DS - 122) Decreased Platelet Aggregation [PE]
DS - 123) Decreased Platelet Production [PE]
DS - 124) Decreased Protein Synthesis [PE]
DS - 125) Decreased Renal K+ Excretion [PE]
DS - 126) Decreased Respiratory Secretion Viscosity [PE]
DS - 127) Decreased Sebaceous Gland Activity [PE]
DS - 128) Decreased Striated Muscle Contraction [PE]
DS - 129) Decreased Tracheobronchial Stretch Receptor Activity [PE]
DS - 130) Demulcent [EPC]
DS - 131) Depolarizing Neuromuscular Blocker [EPC]
DS - 132) Dihydrofolate Reductase Inhibitor Antibacterial [EPC]
DS - 133) Dihydrofolate Reductase Inhibitor Antimalarial [EPC]
DS - 134) Dihydropyridine Calcium Channel Blocker [EPC]
DS - 135) Dipeptidyl Peptidase 4 Inhibitor(s)
DS - 136) Diphosphonates [CS]
DS - 137) Diterpenes [CS]
DS - 138) DNA Polymerase Inhibitors [MoA]
DS - 139) Dopamine Agonists [MoA]
DS - 140) Dopamine D2 Antagonists [MoA]
DS - 141) Echinocandin Antifungal [EPC]
DS - 142) Endothelin Receptor Antagonist [EPC]
DS - 143) Epidermal Growth Factor Receptor Antagonist [EPC]
DS - 145) Ergocalciferols [CS]
DS - 146) Ergolines [CS]
DS - 147) Ergot Derivative [EPC]
DS - 148) Ergotamine Derivative [EPC]
DS - 149) Ergotamines [CS]
DS - 150) Erythropoiesis-stimulating Agent [EPC]
DS - 151) Estradiol Congeners [CS]
DS - 152) Estrogen Agonist/Antagonist [EPC]
DS - 153) Estrogen Receptor Agonists [MoA]
DS - 154) Estrogen Receptor Antagonist [EPC]
DS - 155) Factor VIII Activator [EPC]
DS - 156) Factor Xa Inhibitor [EPC]
DS - 157) Fatty Acids
DS - 158) Folate Analog [EPC]
DS - 159) Folate Analog Metabolic Inhibitor [EPC]
DS - 160) Full Opioid Agonists [MoA
DS - 161) GABA A Agonists [MoA]
DS - 162) gamma-Aminobutyric Acid A Receptor Agonist [EPC]
DS - 163) gamma-Aminobutyric Acid-ergic Agonist [EPC]
DS - 164) Genitourinary Arterial Vasodilation [PE]
DS - 165) Glinide [EPC]
DS - 166) GLP-1 Receptor Agonist [EPC]
DS - 167) GLP-2 Analog [EPC]
DS - 168) Glucagon-like Peptide-1 (GLP-1) Agonists [MoA]
DS - 169) Glucosylceramidase [CS]
DS - 170) Glycopeptide Antibacterial [EPC]
DS - 171) Glycosaminoglycan [EPC]
DS - 172) Gonadotropin Releasing Hormone Receptor Agonist [EPC]
DS - 173) Granulocyte Colony-Stimulating Factor [CS]
DS - 174) Guanylate Cyclase Stimulators [MoA]
DS - 175) Guanylate Cyclase-C Agonist [EPC]
DS - 176) Hedgehog Pathway Inhibitor [EPC]
DS - 177) Hematopoietic Stem Cell Mobilizer [EPC]
DS - 178) Heparin
DS - 179) Hepatitis B Virus Nucleoside Analog Reverse Transcriptase Inhibitor [EPC]
DS - 180) Hepatitis C Virus NS5A Inhibitor [EPC]
DS - 181) Hepatitis C Virus Nucleotide Analog NS5B Polymerase Inhibitor [EPC]
DS - 182) HER1 Antagonists [MoA]
DS - 183) HER2/neu Receptor Antagonist [EPC]
DS - 184) Histamine H1 Receptor Antagonists [MoA]
DS - 185) Histamine-1 Receptor Antagonist [EPC]
DS- 186) Histone Deacetylase Inhibitor [EPC]
DS - 187) HIV Integrase Inhibitors [MoA]
DS - 188) HIV Protease Inhibitors [MoA]
DS - 189) HMG-CoA Reductase Inhibitor [EPC]
DS - 190) Human alpha-1 Proteinase Inhibitor [EPC]
DS - 191) Human Immunodeficiency Virus 1 Non-Nucleoside Analog Reverse Transcriptase Inhibitor [EPC]
DS - 192) Human Immunodeficiency Virus Nucleoside Analog Reverse Transcriptase Inhibitor [EPC]
DS - 193) Human Platelet-derived Growth Factor [EPC]
DS - 194) Human Serum Albumin [EPC]
DS - 195) Hydroxymethylglutaryl-CoA Reductase Inhibitors [MoA]
DS - 196) Increased Cytokine Activity [PE]
DS - 197) Increased Diuresis [PE]
DS - 198) Increased Diuresis at Loop of Henle [PE]
DS - 199) Increased Megakaryocyte Maturation [PE]
DS - 200) Increased Prothrombin Activity [PE]
DS - 201) Influenza A M2 Protein Inhibitor [EPC]
DS - 202) Inhibit Ovum Fertilization [PE]
DS - 203) Insulin [Chemical/Ingredient]
DS - 204) Integrin Receptor Antagonist [EPC]
DS - 205) Interferon alpha [EPC]
DS - 206) Interleukin receptor antagonists
DS - 207) Intestinal Lipase Inhibitor [EPC]
DS - 208) Iron [CS]
DS - 209) Iron Chelating Activity [MoA]
DS - 210) Janus Kinase Inhibitor [EPC]
DS - 211) Kinase Inhibitor [EPC]
DS - 212) Lead Chelating Activity [MoA]
DS - 213) Leukotriene Receptor Antagonist [EPC]
DS - 214) Lipid-based Polyene Antifungal [EPC]
DS - 215) Lipoglycopeptide Antibacterial [EPC]
DS - 216) Lipopeptide Antibacterial [EPC]
DS - 217) Lipopeptides [CS]
DS - 218) Loop Diuretic [EPC]
DS - 219) l-Thyroxine [EPC]
DS - 220) l-Triiodothyronine [EPC]
DS - 221) Lymphocyte Function-Associated Antigen-1 Antagonist [EPC]
DS - 222) Macrolides [CS]

DS - 223) Melanin Synthesis Inhibitor [EPC]
DS - 224) Melatonin Receptor Agonist [EPC]
DS - 225) Metal Chelating Activity [MoA]
DS - 226) Methylated Sulfonamide Antibacterial [EPC]
DS - 227) Methylating Activity [MoA
DS - 228) Microsomal Triglyceride Transfer Protein Inhibitor [EPC]
DS - 229) Microtubule Inhibition [PE]
DS - 230) Monoamine Oxidase Inhibitor [EPC]
DS - 231) Monobactam Antibacterial [EPC]
DS - 232) Mood Stabilizer [EPC]
DS - 233) Neuraminidase Inhibitor [EPC]
DS - 234) Neurokinin 1 Antagonists [MoA]
DS - 235) Neuromuscular Nondepolarizing Blockade [PE]
DS - 236) Nicotinic Acid [EPC]
DS - 237) Nitrate Vasodilator [EPC]
DS - 238) Nitrofurans [CS]
DS - 239) Nitroimidazole Antimicrobial [EPC]
DS - 240) NMDA Receptor Antagonists [MoA]
DS - 241) Noncompetitive AMPA Glutamate Receptor Antagonist [EPC]
DS - 242) Norepinephrine Reuptake Inhibitor [EPC]
DS - 243) Norepinephrine Uptake Inhibitors [MoA]
DS - 244) Nucleic Acid Synthesis Inhibitors [MoA]
DS - 245) Nucleoside Analog [EXT]
DS - 246) Opioid Agonist [EPC]
DS - 247) Opioid Antagonist [EPC]
DS - 248) Organic Anion Transporting Polypeptide 1B1 Inhibitors [MoA]
DS - 249) Osmotic Activity [MoA]
DS - 250) Osmotic Laxative [EPC]
DS - 251) Oxazolidinone Antibacterial [EPC]
DS - 252) Oxidation-Reduction Activity [MoA]
DS - 253) Parathyroid Hormone [CS]
DS - 254) Partial Cholinergic Nicotinic Agonist [EPC]
DS - 255) PCSK9 Inhibitor [EPC]
DS - 256) Penicillin-class Antibacterial [EPC]
DS - 257) Peroxisome Proliferator Receptor alpha Agonist [EPC]
DS - 258) Peroxisome Proliferator Receptor gamma Agonist [EPC]
DS - 259) Peroxisome Proliferator-activated Receptor Activity [MoA]
DS - 260) Peroxisome Proliferator-activated Receptor alpha Agonists [MoA]
DS- 261) P-Glycoprotein Inhibitors [MoA]
DS - 262) Phenothiazine [EPC]
DS - 263) Phenylalanine Hydroxylase Activator [EPC]
DS - 264) Phosphodiesterase 3 Inhibitor [EPC]
DS - 265) Plasma Kallikrein Inhibitor [EPC]
DS - 266) Plasma Volume Expander [EPC]
DS - 267) Platelet Aggregation Inhibitor [EPC]
DS - 268) Platinum-based Drug [EPC]
DS - 269) Platinum-containing Compounds [EXT]
DS - 270) Polyene Antifungal [EPC]
DS - 271) Polyene Antimicrobial [EPC]
DS - 272) Polymyxin-class Antibacterial [EPC]
DS - 273) Porphyrinogens [CS]
DS - 274) Potassium Channel Blocker [EPC]
DS - 275) Progestational Hormone Receptor Antagonists [MoA]
DS - 276) Progesterone [CS]
DS - 277) Progesterone Congeners [CS]
DS - 278) Prostacycline Vasodilator [EPC]
DS - 279) Prostaglandin Analog [EPC]
DS - 280) Protease Inhibitor [EPC]
DS - 281) Proteasome Inhibitor [EPC]
DS - 282) Protein Kinase Inhibitors [MoA]
DS - 283) Proton Pump Inhibitor [EPC]
DS - 284) Psoralen [EPC]
DS - 285) Pyridone [EPC]
DS - 286) Pyrimidine Synthesis Inhibitor [EPC]
DS - 287) Quinolone Antimicrobial [EPC]
DS - 288) RANK Ligand Inhibitor [EPC]
DS - 289) Recombinant Human Growth Hormone [EPC]
DS - 290) Renin Inhibitor [EPC]
DS - 291) Retinoid [EPC]
DS - 292) Rho Kinase Inhibitor [EPC]
DS - 293) Rifamycin Antimycobacterial [EPC]
DS - 294) RNA Synthetase Inhibitor Antibacterial [EPC]
DS - 295) Selective Estrogen Receptor Modulators [MoA]
DS - 296) Serotonin 1b Receptor Agonists [MoA]
DS - 297) Serotonin 3 Receptor Antagonists [MoA]
DS - 298) Serotonin 4 Receptor Antagonists [MoA]
DS - 299) Serotonin Reuptake Inhibitor [EPC]
DS - 300) Serotonin-2c Receptor Agonist [EPC]
DS - 301) Sodium-Glucose Cotransporter 2 Inhibitor [EPC]
DS - 302) Somatostatin Analog [EPC]
DS - 303) Sphingosine 1-Phosphate Receptor Modulators [MoA]
DS - 304) Streptogramin Antibacterial [EPC]
DS - 305) Sulfonamide Antibacterial [EPC]
DS - 306) Sulfone [EPC]
DS - 307) Sulfonylurea [EPC]
DS - 308) Tetracycline-class Antibacterial [EPC]
DS - 309) Tetracycline-class Drug [EPC]
DS - 310) Thalidomide Analog [EPC]
DS - 311) Thiazide-like Diuretic [EPC]
DS - 312) Thyroid Hormone Synthesis Inhibitor [EPC]
DS - 313) Topoisomerase Inhibitor [EPC]
DS - 314) Tricyclic Antidepressant [EPC]
DS - 315) Tumor Necrosis Factor Blocker [EPC]
DS - 316) Typical Antipsychotic [EPC]
DS -317) Vascular Endothelial Growth Factor Inhibitor [EPC]
DS - 318) Vascular Endothelial Growth Factor Inhibitors [MoA]
DS - 319) Vascular Endothelial Growth Factor Receptor 2 Antagonist [EPC]
DS - 320) Vasoconstrictor [EPC]
DS - 321) Vasopressin Receptor Antagonists [MoA]
DS - 322) Vesicular Monoamine Transporter 2 Inhibitor [EPC]
DS - 323) Vinca Alkaloid [EPC]
DS - 324) Vitamins
DS - 325) Xanthine oxidase inhibitor

Reference full list of pharmaceutical classes available on US market: U.S. Food and Drug Administration. National Drug Code Directory. 2019; https://www.fda.gov/drugs/drug-approvals-and-databases/national-drug-code-directory. Accessed May 19, 2020.

eFigure 1. Flow diagram of cohort definitions



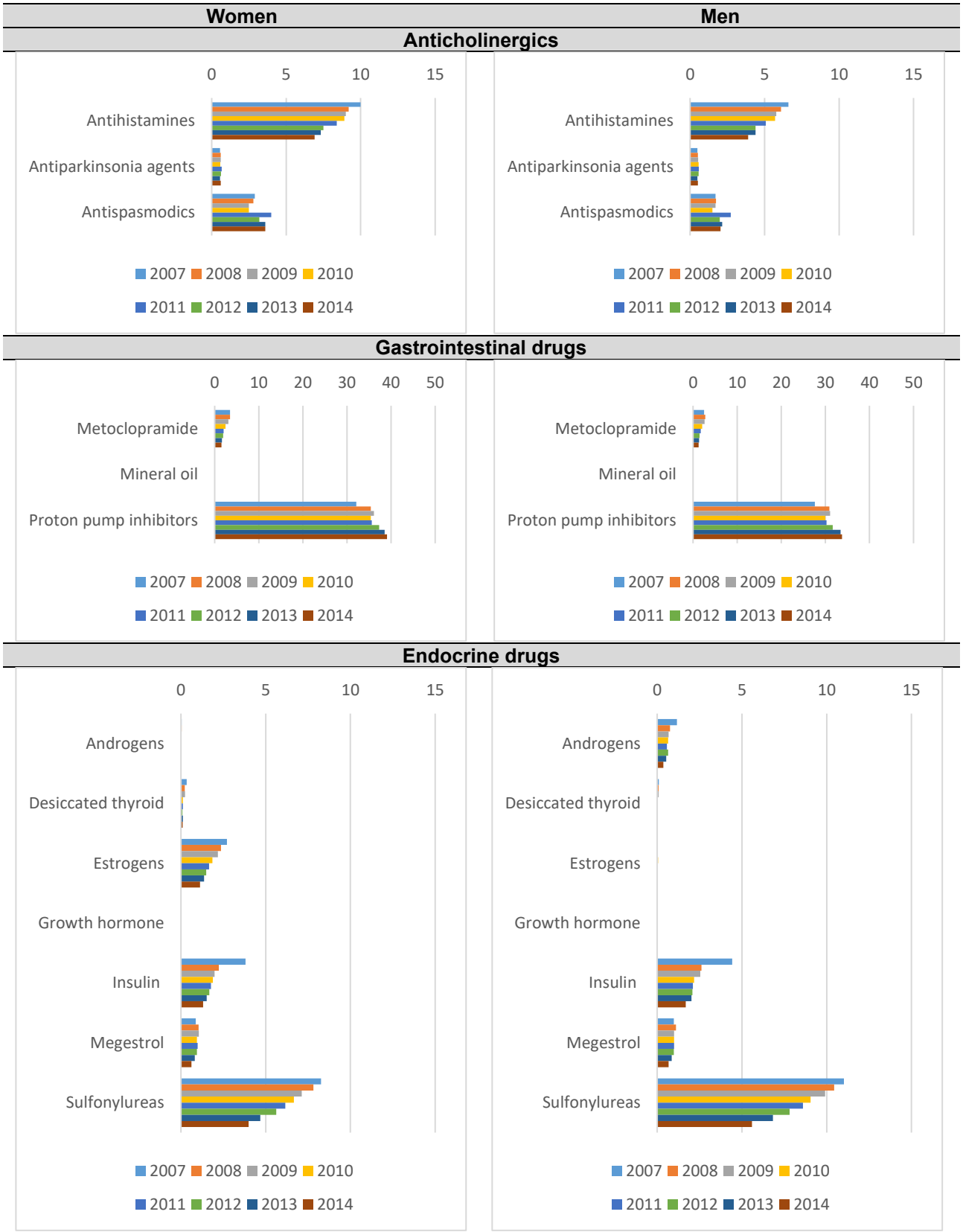
*polypharmacy defines as medications with ≥ 90 days' supply each from ≥ 5 pharmaceutical classes; **multimorbidity defined as chronic conditions from ≥ 2 chronic condition categories

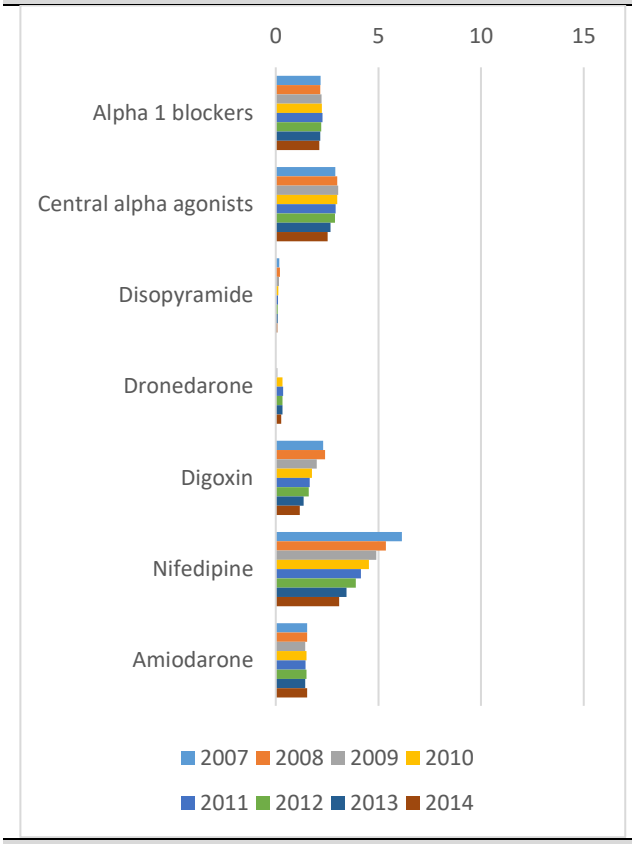
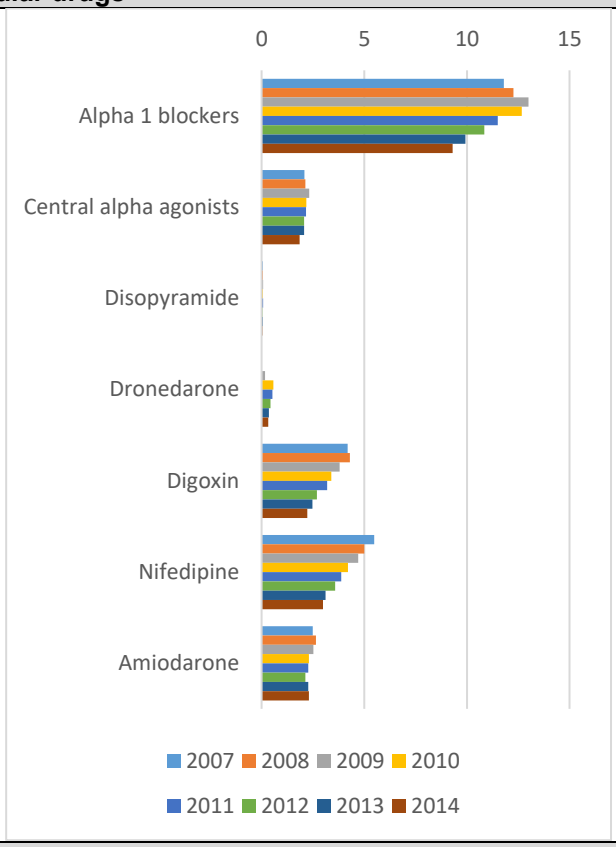
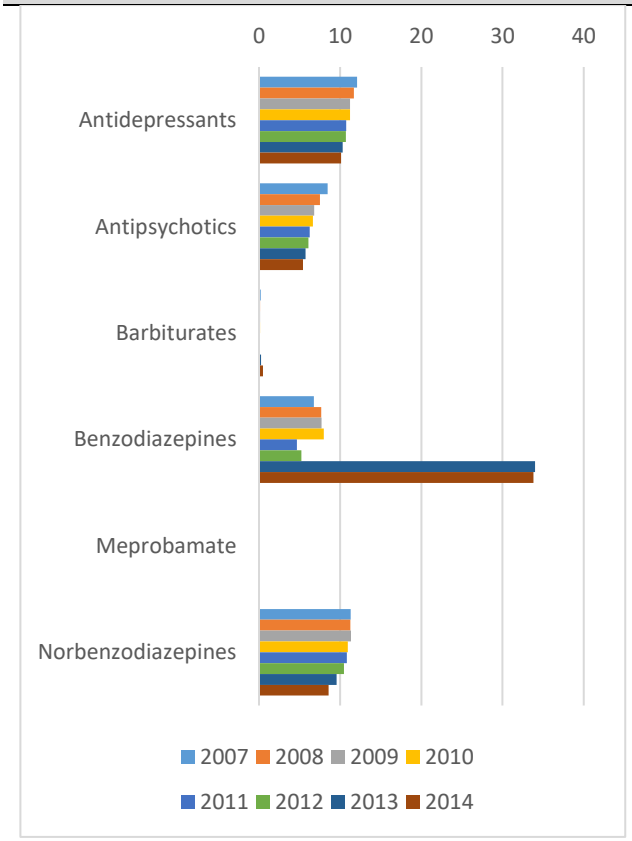
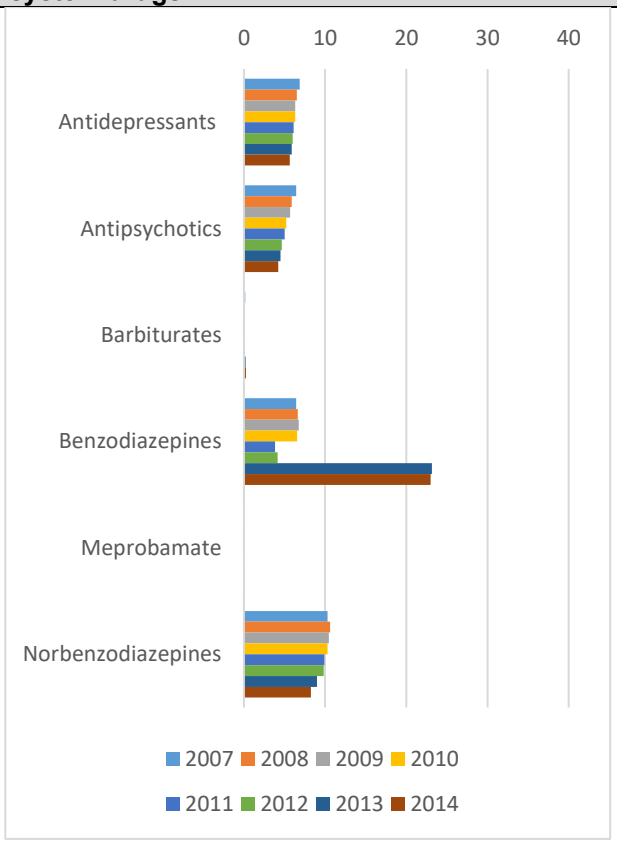
eTable 2. Percentage of adults aged ≥ 65 years with multimorbidity* and polypharmacy who filled ≥ 1 potentially inappropriate medication*** by year, sex, and age group. Recommendations with low level of evidence excluded.**

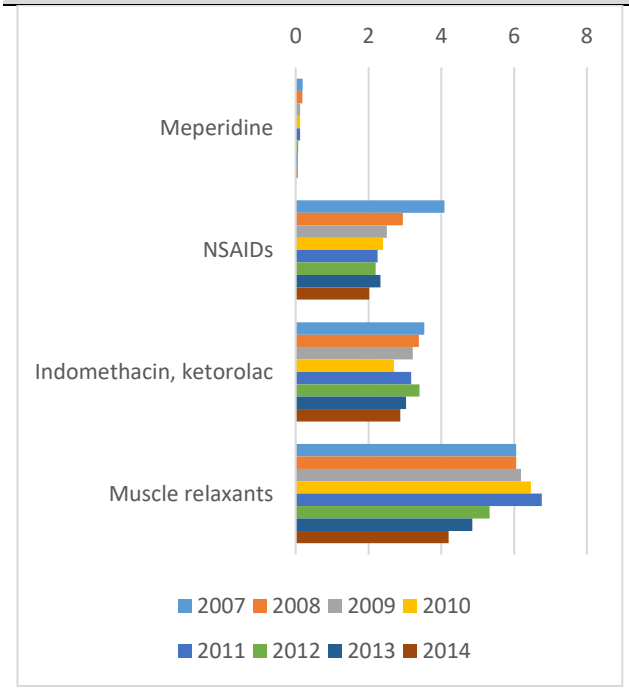
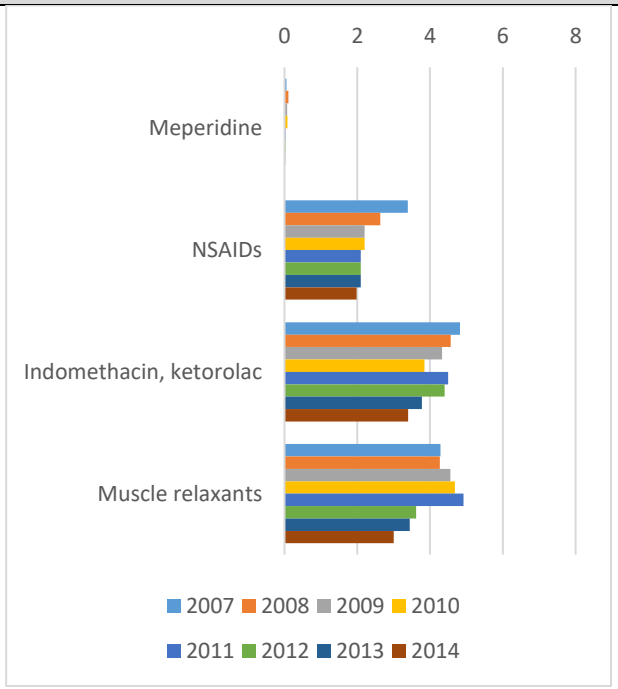
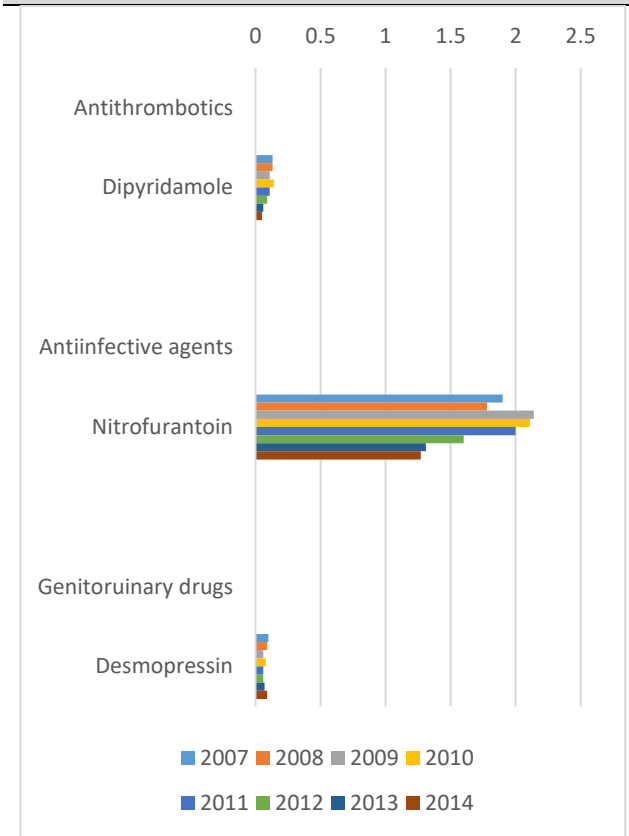
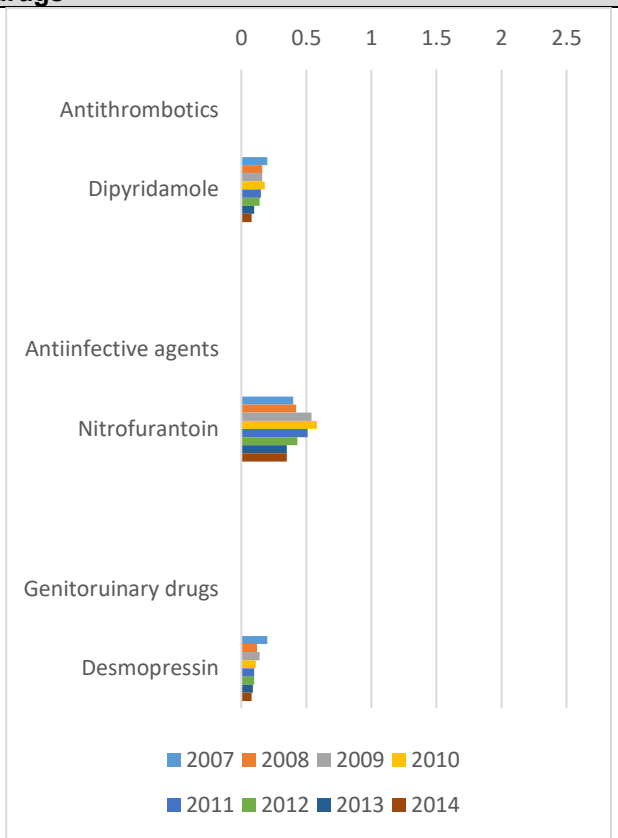
	2007	2008	2009	2010	2011	2012	2013	2014
Both sexes (%)								
	n = 61,500	n = 67,816	n = 72,394	n = 75,567	n = 82,030	n = 88,114	n = 102,547	n =103,153
65 – 74	17,921 (73.6)	19,659 (74.0)	21,037 (74.0)	21,851 (72.9)	23,226 (71.8)	24,592 (70.8)	31,300 (77.3)	31,090 (76.4)
75 – 84	18,382 (71.0)	19,783 (71.0)	20,557 (70.2)	20,614 (69.1)	21,901 (67.9)	23,105 (67.0)	28,871 (73.0)	28,452 (71.7)
≥ 85	7,653 (67.8)	9,123 (68.2)	9,934 (67.7)	10,406 (66.0)	11,098 (63.6)	12,050 (63.7)	15,561 (69.2)	15,508 (68.0)
All ages	43,956 (71.5)	48,565 (71.6)	51,528 (71.2)	52,871 (70.0)	56,225 (68.5)	59,747 (67.8)	75,732 (73.9)	75,050 (72.8)
Women (%)								
	n = 40,088	n = 43,390	n = 45,909	n = 47,405	n = 50,344	n = 53,311	n = 61,408	n = 61,143
65 – 74	11,135 (75.7)	11,857 (75.4)	12,632 (75.5)	13,073 (74.9)	13,606 (73.9)	14,488 (73.1)	18,583 (80.6)	18,465 (80.1)
75 – 84	12,212 (71.7)	12,830 (71.5)	13,106 (70.8)	12,973 (69.7)	13,515 (68.9)	13,893 (67.8)	17,351 (75.1)	17,023 (74.3)
≥ 85	5,634 (67.5)	6,561 (67.6)	7,182 (67.3)	7,418 (65.4)	7,739 (62.9)	8,227 (63.3)	10,666 (69.9)	10,473 (69.1)
All ages	28,981 (72.3)	31,248 (72.0)	32,920 (71.7)	33,464 (70.6)	34,861 (69.3)	36,608 (68.7)	46,600 (75.9)	45,961 (75.2)
Men (%)								
	n = 21,411	n = 24,425	n = 26,482	n = 28,155	n = 31,678	n = 34,793	n = 41,128	n = 42,000
65 – 74	6,786 (70.4)	7,801 (72.0)	8,402 (71.8)	8,775 (70.2)	9,614 (69.1)	10,098 (67.8)	12,710 (72.9)	12,620 (71.6)
75 – 84	6,170 (69.8)	6,953 (70.1)	7,451 (69.2)	7,640 (68.0)	8,384 (66.5)	9,211 (65.9)	11,519 (70.0)	11,427 (68.2)
≥ 85	2,019 (68.9)	3,664 (69.9)	2,752 (68.7)	2,988 (67.5)	3,359 (65.1)	3,823 (64.7)	4,895 (67.6)	5,035 (65.9)
All ages	14,975 (70.0)	17,316 (70.9)	18,605 (70.3)	19,403 (68.9)	21,357 (67.4)	23,132 (66.5)	29,124 (70.8)	29,082 (69.2)

*multimorbidity defined as chronic conditions from ≥ 2 chronic condition categories; **polypharmacy defined as medications with ≥ 90 days' supply each from ≥ 5 pharmaceutical classes; ***Reference: (2019), American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 67: 674-694. doi:10.1111/jgs.15767 – table 2

eFigure 2. Different types of potentially inappropriate medications* used in adults aged ≥ 65 years with multimorbidity and polypharmacy*** (from 2007 to 2014)**



Women	Men
Cardiovascular drugs	
	
Central nervous system drugs	
	

Women	Men
Pain medications	
	
Other drugs	
	

*Reference: (2019), American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 67: 674-694. doi:10.1111/jgs.15767 – table 2; **multimorbidity defined as chronic conditions from ≥ 2 chronic condition categories; ***polypharmacy defines as medications with ≥ 90 days' supply each from ≥ 5 pharmaceutical classes

eTable 3. Number of potentially inappropriate medications* dispensed to adults aged ≥ 65 years with multimorbidity and polypharmacy*** by year, sex, and age group**

	2007 n = 61,500	2008 n = 67,816	2009 n = 72,394	2010 n = 75,567	2011 n = 82,030	2012 n = 88,114	2013 n = 102,547	2014 n =103,153
Both sexes, mean (SD) – median (IQR)								
65 – 74	1.5 (1.3) – 1 (1)	1.5 (1.3) – 1 (1)	1.4 (1.3) – 1 (1)	1.4 (1.2) – 1 (2)	1.3 (1.2) – 1 (2)	1.2 (1.2) – 1 (2)	1.5 (1.3) – 1 (1)	1.5 (1.3) – 1 (1)
75 – 84	1.4 (1.2) – 1 (2)	1.3 (1.2) – 1 (2)	1.3 (1.2) – 1 (2)	1.3 (1.2) – 1 (2)	1.2 (1.1) – 1 (2)	1.2 (1.1) – 1 (2)	1.4 (1.2) – 1 (2)	1.3 (1.2) – 1 (2)
≥ 85	1.2 (1.2) – 1 (2)	1.2 (1.1) – 1 (2)	1.2 (1.1) – 1 (2)	1.1 (1.1) – 1 (2)	1.1 (1.1) – 1 (2)	1.1 (1.0) – 1 (2)	1.2 (1.1) – 1 (2)	1.2 (1.1) – 1 (2)
All ages	1.4 (1.3) – 1 (2)	1.4 (1.2) – 1 (2)	1.3 (1.2) – 1 (2)	1.3 (1.2) – 1 (2)	1.2 (1.2) – 1 (2)	1.2 (1.1) – 1 (2)	1.4 (1.3) – 1 (1)	1.4 (1.2) – 1 (2)
Women, mean (SD) – median (IQR)								
	n = 40,088	n = 43,390	n = 45,909	n = 47,405	n = 50,344	n = 53,311	n = 61,408	n = 61,143
65 – 74	1.6 (1.3) – 1 (1)	1.5 (1.3) – 1 (1)	1.5 (1.3) – 1 (1)	1.5 (1.3) – 1 (1)	1.4 (1.3) – 1 (1)	1.4 (1.2) – 1 (2)	1.7 (1.4) – 2 (1)	1.7 (1.3) – 2 (1)
75 – 84	1.4 (1.3) – 1 (2)	1.4 (1.2) – 1 (2)	1.3 (1.2) – 1 (2)	1.3 (1.2) – 1 (2)	1.2 (1.2) – 1 (2)	1.2 (1.1) – 1 (2)	1.5 (1.3) – 1 (1)	1.4 (1.2) – 1 (1)
≥ 85	1.2 (1.2) – 1 (2)	1.2 (1.1) – 1 (2)	1.2 (1.1) – 1 (2)	1.1 (1.1) – 1 (2)	1.1 (1.1) – 1 (2)	1.0 (1.0) – 1 (2)	1.3 (1.2) – 1 (2)	1.2 (1.1) – 1 (2)
All ages	1.4 (1.3) – 1 (2)	1.4 (1.3) – 1 (2)	1.4 (1.2) – 1 (2)	1.3 (1.2) – 1 (2)	1.3 (1.2) – 1 (2)	1.2 (1.1) – 1 (2)	1.5 (1.3) – 1 (2)	1.5 (1.3) – 1 (1)
Men, mean (SD) – median (IQR)								
	n = 21,411	n = 24,425	n = 26,482	n = 28,155	n = 31,678	n = 34,793	n = 41,128	n = 42,000
65 – 74	1.4 (1.3) – 1 (2)	1.5 (1.2) – 1 (2)	1.4 (1.2) – 1 (2)	1.3 (1.2) – 1 (2)	1.2 (1.2) – 1 (2)	1.2 (1.1) – 1 (2)	1.4 (1.3) – 1 (2)	1.3 (1.2) – 1 (2)
75 – 84	1.3 (1.2) – 1 (2)	1.3 (1.2) – 1 (2)	1.2 (1.1) – 1 (2)	1.2 (1.1) – 1 (2)	1.1 (1.1) – 1 (2)	1.1 (1.1) – 1 (2)	1.3 (1.2) – 1 (2)	1.2 (1.1) – 1 (2)
≥ 85	1.3 (1.2) – 1 (2)	1.2 (1.1) – 1 (2)	1.2 (1.1) – 1 (2)	1.2 (1.1) – 1 (2)	1.1 (1.1) – 1 (2)	1.1 (1.0) – 1 (2)	1.2 (1.1) – 1 (2)	1.1 (1.1) – 1 (2)
All ages	1.3 (1.2) – 1 (2)	1.3 (1.2) – 1 (2)	1.3 (1.2) – 1(2)	1.2 (1.1) – 1 (2)	1.2 (1.1) – 1 (2)	1.1 (1.1) – 1 (2)	1.3 (1.2) – 1 (2)	1.2 (1.2) – 1 (2)

*Reference: (2019), American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 67: 674-694. doi:10.1111/jgs.15767 – table 2; *multimorbidity defined as chronic conditions from ≥ 2 chronic condition categories; **polypharmacy defines as medications with ≥ 90 days' supply each from ≥ 5 pharmaceutical classes

eTable 4. Count of potentially inappropriate medication* in adults aged ≥ 65 years by year, sex, number of chronic conditions, and number of chronic medications*****

	2007	2008	2009	2010	2011	2012	2013	2014
Women	n = 198,473	n = 211,672	n = 215,978	n = 219,421	n = 221,334	n = 224,142	n = 228,871	n = 229,313
< 2 chronic conditions, mean (sd) - median (IQR)								
medications from <5 pharmaceutical classes***	0.2 (0.6) – 0 (0)	0.3 (0.6) – 0 (0)	0.3 (0.6) – 0 (0)	0.3 (0.6) – 0 (0)	0.3 (0.6) – 0 (0)	0.3 (0.6) – 0 (0)	0.3 (0.7) – 0 (9)	0.3 (0.7) – 0 (1)
5 – 9 pharmaceutical classes	1.1 (1.1) – 1 (2)	1.1 (1.1) – 1 (2)	1.2 (1.1) – 1 (2)	1.1 (1.1) – 1 (2)	1.1 (1.1) – 1 (2)	1.1 (1.1) – 1 (2)	1.2 (1.1) – 1 (2)	1.2 (1.1) – 1 (2)
≥ 10 pharmaceutical classes	2.1 (1.5) – 1 (2)	2.0 (1.4) – 2 (2)	2.1 (1.5) – 2 (2)	2.0 (1.4) – 2 (2)	2.0 (1.4) – 2 (2)	1.9 (1.4) – 2 (2)	2.2 (1.5) – 2 (2)	2.1 (1.3) – 2 (2)
≥ 2 chronic conditions, mean (sd) - median (IQR)								
medications from <5 pharmaceutical classes***	0.2 (0.5) – 0 (0)	0.2 (0.6) – 0 (0)	0.2 (0.6) – 0 (0)	0.2 (0.6) – 0 (0)	0.2 (0.6) – 0 (0)	0.2 (0.5) – 0 (0)	0.3 (0.7) – 0 (0)	0.3 (0.7) – 0 (0)
5 – 9 pharmaceutical classes	1.3 (1.2) – 1 (2)	1.3 (1.2) – 1 (2)	1.2 (1.1) – 1 (2)	1.2 (1.1) – 1 (2)	1.1 (1.1) – 1 (2)	1.1 (1.1) – 1 (2)	1.4 (1.1) – 1 (2)	1.3 (1.2) – 1 (2)
≥ 10 pharmaceutical classes	2.3 (1.5) – 2 (2)	2.2 (1.5) – 2 (2)	2.2 (1.4) – 2 (2)	2.1 (1.4) – 2 (2)	2.0 (1.4) – 2 (2)	2.0 (1.4) – 2 (2)	2.4 (1.5) – 2 (2)	2.3 (1.5) –2 (2)
Men	n = 145,859	n = 157,311	n = 160,414	n = 162,811	n = 163,869	n = 164,915	n = 168,354	n = 167,835
< 2 chronic conditions, mean (sd) - median (IQR)								
medications from <5 pharmaceutical classes***	0.2 (0.5) – 0 (0)	0.2 (0.5) – 0 (0)	0.2 (0.5) – 0 (0)	0.2 (0.5) – 0 (0)	0.2 (0.5) – 0 (0)	0.2 (0.5) – 0 (0)	0.2 (0.5) – 0 (0)	0.2 (0.6) – 0 (0)
5 – 9 pharmaceutical classes	0.9 (1.0) – 1 (1)	1.0 (1.0) – 1 (1)	1.0 (1.0) – 1 (1)	0.9 (1.9) – 1 (1)	1.0 (1.0) – 1 (1)	1.0 (1.0) – 1 (1)	1.1 (1.0) – 1 (2)	1.0 (1.0) – 1 (2)
≥ 10 pharmaceutical classes	1.9 (1.4) – 2 (2)	1.7 (1.3) – 2 (1)	1.8 (1.3) – 2 (1)	1.7 (1.2) – 2 (1)	1.7 (1.2) – 2 (1)	1.7 (1.2) – 2 (1)	1.9 (1.4) – 1 (2)	1.8 (1.3) – 2 (2)
≥ 2 chronic conditions, mean (sd) / median (IQR)								
medications from <5 pharmaceutical classes***	0.1 (0.4) – 0 (0)	0.2 (0.5) – 0 (0)	0.2 (0.5) – 0 (0)	0.2 (0.5) – 0 (0)	0.2 (0.5) – 0 (0)	0.2 (0.5) – 0 (0)	0.2 (0.6) – 0 (0)	0.2 (0.6) – 0 (0)
5 – 9 pharmaceutical classes	1.2 (1.1) – 1 (2)	1.2 (1.1) – 1 (2)	1.2 (1.1) – 1 (2)	1.1 (1.1) – 1 (2)	1.1 (1.0) – 1 (2)	1.0 (1.0) – 1 (2)	1.2 (1.1) – 1 (2)	1.1 (1.1) – 1 (2)
≥ 10 pharmaceutical classes	2.2 (1.5) – 2 (2)	2.1 (1.4) – 2 (2)	2.1 (1.4) – 2 (2)	1.9 (1.3) – 2 (2)	1.9 (1.3) – 2 (2)	1.8 (1.3) – 2 (1)	2.1 (1.4) – 2 (2)	2.0 (1.4) – 2 (2)

*Reference: (2019), American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 67: 674-694. doi:10.1111/jgs.15767 – table 2; **multimorbidity defined as chronic conditions from ≥ 2 chronic condition categories; ***polypharmacy defines as medications with ≥ 90 days' supply each from ≥ 5 pharmaceutical classes

eTable 5. Percentage of adults aged ≥ 65 years who filled ≥ 1 potentially inappropriate medication* by year, sex, number of chronic condition categories, and number of long-term medications*****

	2007	2008	2009	2010	2011	2012	2013	2014
Women	n = 198,473	n = 211,672	n = 215,978	n = 219,421	n = 221,534	n = 224,142	n = 228,871	n = 229,313
<2 chronic condition categories, count (%)								
medications from <5 pharmaceutical classes***	3,144 (18.1)	3,849 (20.3)	4,157 (20.7)	4,309 (21.7)	3,683 (21.0)	3,679 (21.2)	4,178 (24.0)	4,436 (25.7)
5 – 9 pharmaceutical classes	3,296 (66.1)	3,546 (67.4)	3,954 (68.5)	4,134 (66.8)	3,709 (69.0)	3,852 (69.3)	4,260 (71.6)	4,592 (71.8)
≥ 10 pharmaceutical classes	626 (89.6)	582 (90.2)	597 (89.4)	686 (89.4)	612 (87.9)	720 (87.8)	881 (91.7)	937 (91.0)
≥ 2 chronic condition categories, count (%)								
medications from <5 pharmaceutical classes***	18,348 (13.6)	21,687 (15.1)	21,989 (15.3)	22,147 (15.3)	23,138 (15.7)	23,972 (16.3)	31,567 (22.1)	33,434 (23.3)
5 – 9 pharmaceutical classes	24,428 (71.3)	26,592 (71.2)	27,807 (70.9)	28,316 (69.7)	29,352 (68.3)	30,874 (67.5)	38,445 (74.3)	38,486 (73.7)
≥ 10 pharmaceutical classes	5,379 (92.0)	5,542 (91.5)	6,068 (91.0)	6,121 (90.0)	6,529 (89.0)	6,723 (88.6)	8,926 (92.5)	8,193 (91.8)
Men	n = 145,859	n = 157,311	n = 160,414	n = 162,811	n = 163,869	n = 164,915	n = 168,354	n = 167,835
<2 chronic condition categories, count (%)								
medications from <5 pharmaceutical classes***	1,876 (12.4)	2,374 (14.3)	2,649 (15.31)	2,755 (16.2)	2,273 (15.2)	2,256 (15.7)	2,499 (17.8)	2,543 (18.6)
5 – 9 pharmaceutical classes	1,697 (58.2)	2,070 (62.1)	2,369 (62.2)	2,558 (61.2)	2,260 (63.6)	2,457 (64.22)	2,644 (66.5)	2,726 (65.8)
≥ 10 pharmaceutical classes	300 (86.5)	286 (84.6)	328 (86.8)	369 (83.7)	365 (86.5)	464 (86.0)	479 (86.8)	590 (87.4)
≥ 2 chronic condition categories, count (%)								
medications from <5 pharmaceutical classes***	10,197 (9.6)	12,564 (11.2)	13,169 (11.7)	13,326 (11.8)	13,778 (12.2)	14,364 (12.9)	17,740 (16.3)	18,791 (17.5)
5 – 9 pharmaceutical classes	12,750 (69.4)	14,762 (70.2)	15,841 (69.6)	16,451 (68.1)	18,132 (66.6)	19,397 (65.2)	23,971 (69.0)	24,234 (67.7)
≥ 10 pharmaceutical classes	2,714 (89.5)	3,084 (90.7)	3,350 (90.2)	3,506 (88.0)	3,869 (86.5)	4,348 (86.0)	5,735 (89.6)	5,448 (88.2)

*Reference: (2019), American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 67: 674-694. doi:10.1111/jgs.15767 – table 2; **multimorbidity defined as chronic conditions from ≥ 2 chronic condition categories; ***polypharmacy defined as medications with ≥ 90 days' supply each from ≥ 5 pharmaceutical classes

16.2 Supplementary Material Article II: Patient factors associated with new prescriptions for potentially inappropriate medications in US older adults with multimorbidity using multiple medications

Unpublished supplementary material as of February 11, 2021.

Table of Content

eTable 1. Beers criteria included in the analyses

Medications	Comments
Anticholinergics	
First-generation antihistamines	medications flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria
Antiparkinsoinian agents	medications flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria
Antispasmodics	medications flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria
Antithrombotics	
Dipyridamole	medications flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria
Anti-infective	
Nitrofurantoin	flagged as potentially inappropriate when Nitrofurantoin used for ≥ 90 days or with min. 2 refills or in individuals with creatinine clearance <30mL/min
Cardiovascular	
Peripheral alpha-1 blockers for treatment of hypertension	flagged as potentially inappropriate when preceded by hypertension diagnosis
Central alpha agonists, other CNS alpha-agonists	Clonidine flagged as potentially inappropriate when preceded by hypertension diagnosis, other CNS alpha-agonists as listed in table 2 flagged as potentially inappropriate
Disopyramide	medication flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria
Dronedarone	Flagged as potentially
Digoxin	Flagged as potentially inappropriate medication when used after previous hypertension diagnosis, when used after heart failure diagnosis
Nifedipine	Medication flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria
Amiodarone	Flagged as potentially inappropriate medication when used after atrial fibrillation therapy, unless patient has heart failure or substantial left ventricular hypertrophy

continued

Medications	Comments
Central nervous system	
Antidepressants, alone or in combination	Medication flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria
Antipsychotics, first and second generation	Flag as potentially inappropriate, unless patient has schizophrenia, bipolar disorder, or for short-term use as antiemetic during chemotherapy
Barbiturates	Medications flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria
Benzodiazepines	Medications flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria
Meprobamate	Medication flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria
Z-drugs	Medications flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria
Ergoloid mesylates	Medication flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria
Endocrine	
Androgens	Flagged as potentially inappropriate unless there is a hypogonadism diagnosis
Desiccated thyroid	Medication flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria
Estrogens	Flagged as potentially inappropriate when oral or topical patch, vaginal cream and vaginal tablets not flagged as potentially inappropriate
Growth hormone	Flagged as potentially inappropriate
Insulin	Flagged as potentially inappropriate when only short- or rapid-acting insulins without combination with long-acting insulins
Megesterol	Medication flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria
Sulfonylureas	Medications flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria
Gastrointestinal	
Metoclopramide	Flagged as potentially inappropriate unless there is a diagnosis of gastroparesis and not used for longer than 84 days or min. 2 refills

continued

Medications	Comments
Gastrointestinal (continued)	
Mineral oil	Flagged as potentially inappropriate when given orally
Proton-pumps inhibitors	Flagged as potentially inappropriate when used for ≥ 56 days or min. 2 refills without any of the mentioned diagnoses (e.g., esophagitis, hypersecretory condition), or when used for ≥ 56 days or min. 2 refills not preceded by chronic corticosteroid or NSAID use (≥ 90 days or min. 2 refills)
Pain medications	
Meperidine	Medication flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria
non-cyclooxygenase-selective NSAIDs	Medications flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria. Flagged as potentially inappropriate when used for ≥ 90 days or min. 2 refills and when there is no overlapping PPI or misoprostol use
Indomethacin, Ketorolac	Medications flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria
Skeletal muscle relaxants	Medications flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria
Genitourinary	
Desmopressin	Medications flagged as potentially inappropriate as listed in table 2 of the 2019 Beers criteria

Reference: (2019), American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 67: 674-694. doi:10.1111/jgs.15767 – table 2.

eTable 2. Cohort with 365 days baseline period (N = 22,072): Multivariable associations between demographic and clinical factors and the prescribing of potentially inappropriate medications (PIMs)

Demographics and clinical characteristics	Model 1: Demographic and healthcare utilization variables		Model 2: Model 1 + chronic conditions	
	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI
	(n = 22,071)		(n = 22,071)	
Age (reference: 65-74)				
75-84	0.85	0.70-1.05	0.88	0.72-1.07
85 and above	0.80	0.62-1.03	0.83	0.64-1.07
Male sex (reference: female sex)	1.29	1.08-1.55**	1.28	1.06-1.53**
Hispanic ethnicity (reference: non-hispanic)	1.23	0.51-3.00	1.23	0.51-2.99
Race (reference: White)				
Asian	2.02	1.00-4.06**	1.88	0.93-3.80
Black	1.52	1.02-2.27**	1.42	0.95-2.11
Other	1.52	0.87-2.65	1.43	0.82-2.51
Number of inpatient stays (reference: 0)				
1 or above	1.08	0.83-1.42	1.07	0.81-1.42
Number of emergency department visits (reference: 0)				
1 or above	1.06	0.83-1.34	1.04	0.82-1.32
Number of ambulatory visits (reference: ≤ 11)				
12-20	1.00	0.75-1.33	1.01	0.75-1.34
21-36	1.47	1.12-1.92””	1.50	1.14-1.97**
≥ 37	1.81	1.33-2.47***	1.86	1.36-2.55***
Number of non-acute institutional stays (reference: 0)				
1 or above	0.89	0.65-1.21	0.87	0.64-1.20
Level of polypharmacy (reference: 5-9 medications)				
10 and above	1.53	1.01-2.31	1.43	0.94-2.17
Number of chronic conditions (1-unit increase)	0.95	0.91-0.99**	0.94	0.89-0.99**
Number of prescribing orders (1-unit increase)	1.01	1.01-1.02***	1.01	1.01-1.02***

continued

Demographics and clinical characteristics	Model 1: Demographic and healthcare utilization variables		Model 2: Model 1 + chronic conditions	
	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI
Types of comorbidities[1]				
Congestive heart failure	-	-	1.05	0.81-1.35
Cardiac arrhythmias	-	-	1.06	0.76-1.46
Valvular disease	-	-	0.97	0.74-1.27
Pulmonary circulation disorders	-	-	1.63	1.04-2.56
Peripheral vascular disorders	-	-	0.99	0.78-1.27
Hypertension	-	-	0.97	9,,78-1.21
Chronic pulmonary disorders	-	-	1.08	0.85-1.38
Diabetes	-	-	1.28	1.05-1.55**
Hypothyroidism	-	-	0.89	0.67-1.16
Renal failure	-	-	1.01	0.75-1.37
Cancer	-	-	0.85	0.64-1.10
Rheumatoid arthritis/collagen vascular diseases	-	-	0.98	0.66-1.45
Coagulopathy	-	-	0.95	0.60-1.52
Fluid and electrolyte disorders	-	-	0.97	0.75-1.45
Depression	-	-	1.08	0.79-1.49
Liver disease	-	-	1.25	0.70-2.23

[1] comorbidities defined with coding algorithms for defining Elixhauser comorbidities in ICD-9 administrative data (Quan et al. 2005), ≥ 2 ICD-9 codes per category, hypertension categories merged, diabetes categories merged, different cancer categories merged, drug abuse, alcohol abuse, obesity, weight loss, HIV/AIDS, paralysis, other neurological disorders, blood loss anemia and deficiency anemia not included;

*PIMs with low level of evidence excluded.

** $p<0.05$; *** $p<0.001$

eTable 3. Multivariable associations between demographic and clinical factors (continuous variables) and the prescribing of potentially inappropriate medications (PIMs)

Demographics and clinical characteristics	Model 1: Demographic and healthcare utilization variables		Model 2: Model 1 + chronic conditions	
	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI
	(n = 17,911)		(n = 17,911)	
Age (per 10-year increase)	0.89	0.78-1.02	0.88	0.77-1.01
Male sex (reference: female sex)	1.31	1.08-1.58**	1.29	1.06-1.57**
Hispanic ethnicity (reference: non-hispanic)	1.00	0.37-2.72	0.98	0.362.67
Race (reference: White)				
Asian	1.34	0.56-3.25	1.29	0.53-3.13
Black	1.58	1.04-2.39**	1.53	1.01-2.33**
Other	1.54	0.84-2.82	1.52	0.83-2.79
Number of inpatient stays (1-unit increase)	0.87	0.76-1.00	0.86	0.74-0.99**
Number of emergency department visits (1-unit increase)	0.99	0.98-1.02	0.99	0.97-1.02
Number of ambulatory visits (10-unit increase)	1.01	1.00-1.02***	1.01	1.00-1.02
Number of non-acute institutional stays (1-unit increase)	0.99	0.98-1.01	0.99	0.97-1.01
Number of chronic medications (1-unit increase)	1.04	0.97-1.11	1.01	0.94-1.09
Number of chronic conditions (1-unit increase)	0.99	0.94-1.04	0.97	0.90-1.04
Number of prescribing orders (1-unit increase)	1.02	1.01-1.02***	1.02	1.01-1.02***

continued

Demographics and clinical characteristics	Model 1: Demographic and healthcare utilization variables		Model 2: Model 1 + chronic conditions	
	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI
Types of comorbidities[1]				
Congestive heart failure	-	-	1.42	1.10-1.83**
Cardiac arrhythmias	-	-	1.09	0.76-1.56
Valvular disease	-	-	0.87	0.64-1.17
Pulmonary circulation disorders	-	-	1.45	0.86-2.44
Peripheral vascular disorders	-	-	1.12	0.86-1.46
Hypertension	-	-	0.99	0.79-1.23
Chronic pulmonary disorders	-	-	1.12	0.86-1.46
Diabetes	-	-	1.13	0.91-1.40
Hypothyroidism	-	-	1.07	0.80-1.43
Renal failure	-	-	0.92	0.66-1.28
Cancer	-	-	0.88	0.66-1.17
Rheumatoid arthritis/collagen vascular diseases	-	-	0.81	0.51-1.29
Coagulopathy	-	-	0.99	0.61-1.62
Fluid and electrolyte disorders	-	-	1.14	0.75-1.73
Depression	-	-	1.03	0.72-1.47
Liver disease	-	-	1.59	0.89-2.86

[1] comorbidities defined with coding algorithms for defining Elixhauser comorbidities in ICD-9 administrative data (Quan et al. 2005), ≥ 2 ICD-9 codes per category, hypertension categories merged, diabetes categories merged, different cancer categories merged, drug abuse, alcohol abuse, obesity, weight loss, HIV/AIDS, paralysis, other neurological disorders, blood loss anemia and deficiency anemia not included;

*PIMs with low level of evidence excluded.

** $p<0.05$; *** $p<0.001$

eTable 4. Unadjusted and multivariable associations between demographic and clinical factors and the prescribing of potentially inappropriate medications (logistic regression)

Demographics and clinical characteristics	*Unadjusted associations*		*Model 1: Demographic and healthcare utilization variables*		*Model 2: Model 1 + chronic conditions*	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
	(N = 17,912)		(n = 17,911)		(n = 17,911)	
Age (reference: 65-74)						
75-84	0.85	0.69-.1.04	0.87	0.70-1.07	0.88	0.71-1.08
85 and above	0.66	0.51-0.78**	0.75	0.57-0.99**	0.74	0.56-0.98**
Male sex (reference: female sex)	1.41	1.17-1.70***	1.30	0.08-1.58**	1.29	1.06-1.58**
Hispanic ethnicity (reference: non-hispanic)	1.52	9,67-3.45	0.99	0.35-2.78	0.96	0.34-2.72
Race (reference: White)						
Asian	1.27	9,52-3.11	1.41	0.57-3.46	1.34	0.55-3.32
Black	1.56	1.02-2.36**	1.55	1.02-2.37	1.51	0.98-2.32
Other	1.72	1.05-2.84**	1.52	0.80-2.89	1.49	0.78-2.84
Number of inpatient stays (reference: 0)						
At least 1	1.39	1.11-1.75	0.94	0.70-1.29	0.91	0.66-1.25
Number of emergency department visits (reference: 0)						
At least 1	1.33	1.09-1.62	1.10	0.85-1.43	1.08	0.82-1.40
Number of ambulatory visits (reference: ≤ 9; categories based on quartiles)						
10-17	0.94	0.69-1.28	0.95	0.69-1.29	0.95	0.69-1.30
18-29	1.39	1.05-1.85**	1.37	1.02-1.86**	1.38	1.02-1.88**
≥ 30	2.14	1.64-2.79***	2.01	1.45-2.78***	2.02	1.44-2.82***
Number of non-acute institutional stays (reference: 0)						
1 or above	0.73	0.54-0.99**	0.78	0.55-1.10	0.74	0.52-1.05
Level of polypharmacy (reference: 5-9 medications)						
10 and above	1.26	0.76-2.10	1.15	0.68-1.92	1.06	0.63-1.79
Number of chronic conditions (1-unit increase)	1.05	1.01-1.02**	0.96	0.91-1.02	0.95	0.88-1.02
Number of prescribing orders (1-unit increase)	1.03	1.02-1.04***	1.03	1.02-1.03***	1.03	1.02-1.03

continued

Demographics and clinical characteristics	*Unadjusted associations*		*Model 1: Demographic and healthcare utilization variables*		*Model 2: Model 1 + chronic conditions*	
	Un-adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI
Types of comorbidities[1]						
Congestive heart failure	1.55	1.24-1.94***	-	-	1.37	1.06-1.78**
Cardiac arrhythmias	1.45	1.03-2.04**	-	-	1.02	0.70-1.47
Valvular disease	1.08	0.81-1.43	-	-	0.83	0.61-1.12
Pulmonary circulation disorders	1.66	0.99-2.75	-	-	1.42	0.83-2.43
Peripheral vascular disorders	1.14	0.88-1.47	-	-	1.42	0.83-1.43
Hypertension	1.03	0.85-1.25	-	-	0.98	0.78-1.23
Chronic pulmonary disorders	1.22	0.96-1.56	-	-	1.12	0.86-1.46
Diabetes	1.21	0.99-1.47	-	-	1.16	0.93-1.44
Hypothyroidism	0.92	0.70-1.22	-	-	1.09	0.81-1.46
Renal failure	1.12	0.82-1.53	-	-	0.87	0.62-1.22
Cancer	1.12	0.86-1.45	-	-	0.80	0.68-1.20
Rheumatoid arthritis/collagen vascular diseases	0.84	0.54-1.33	-	-	0.78	0.49-1.25
Coagulopathy	1.25	0.78-1.99	-	-	0.99	0.60-1.63
Fluid and electrolyte disorders	1.31	0.87-1.97	-	-	1.11	0.72-1.70
Depression	0.96	0.69-1.34	-	-	1.00	0.70-1.44
Liver disease	1.81	1.01-3.26**	-	-	1.53	0.84-2.79

[1] comorbidities defined with coding algorithms for defining Elixhauser comorbidities in ICD-9 administrative data (Quan et al. 2005), ≥ 2 ICD-9 codes per category, hypertension categories merged, diabetes categories merged, different cancer categories merged, drug abuse, alcohol abuse, obesity, weight loss, HIV/AIDS, paralysis, other neurological disorders, blood loss anemia and deficiency anemia not included;

** p<0.05; *** p<0.001

eTable 5. Multivariable associations between demographic and clinical factors and the prescribing of potentially inappropriate medications (PIMs) with moderate or high levels of evidence*

Demographics and clinical characteristics	Model 1: Demographic and healthcare utilization variables		Model 2: Model 1 + chronic conditions	
	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI
	(n = 17,911)		(n = 17,911)	
Age (reference: 65-74)				
75-84	0.79	0.64-0.98**	0.81	0.65-1.01
85 and above	0.70	0.52-0.93**	0.72	0.53-0.96**
Male sex (reference: female sex)	1.32	1.08-1.61**	1.34	1.09-1.65**
Hispanic ethnicity (reference: non-hispanic)	1.21	0.43-3.41	1.20	0.43-3.39
Race (reference: White)				
Asian	1.53	0.63-3.69	1.43	0.59-3.48
Black	1.66	1.09-2.54**	1.59	1.04-2.44**
Other	1.47	0.76-2.85	1.39	0.71-2.71
Number of inpatient stays (reference: 0)				
1 or above	0.91	0.65-1.26	0.93	0.66-1.30
Number of emergency department visits (reference: 0)				
1 or above	1.14	0.87-1.50	1.12	0.85-1.48
Number of ambulatory visits (reference: ≤ 9; categories based on quartiles)				
10-17	0.99	0.72-1.36	0.99	0.73-1.37
18-29	1.32	0.97-1.80	1.35	0.99-1.85
≥ 30	1.91	1.36-2.67***	1.99	1.41-2.81***
Number of non-acute institutional stays (reference: 0)				
1 or above	0.89	0.63-1.27	0.83	0.58-1.20
Level of polypharmacy (reference: 5-9 medications)				
10 and above	0.82	0.44-1.55	0.78	0.41-1.47
Number of chronic conditions (1-unit increase)	0.96	0.90-1.01	0.93	0.87-1.00
Number of prescribing orders (1-unit increase)	1.02	1.01-1.02***	1.02	1.01-1.02***

continued

Demographics and clinical characteristics	Model 1: Demographic and healthcare utilization variables		Model 2: Model 1 + chronic conditions	
	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI
Types of comorbidities[1]				
Congestive heart failure	-	-	1.11	0.83-1.48
Cardiac arrhythmias	-	-	0.92	0.61-1.40
Valvular disease	-	-	0.76	0.54-1.08
Pulmonary circulation disorders	-	-	1.08	0.57-2.07
Peripheral vascular disorders	-	-	1.13	0.85-1.50
Hypertension	-	-	1.03	0.82-1.31
Chronic pulmonary disorders	-	-	1.12	0.85-1.49
Diabetes	-	-	1.17	0.93-1.46
Hypothyroidism	-	-	1.11	0.81-1.52
Renal failure	-	-	1.00	0.71-1.41
Cancer	-	-	0.87	0.64-1.18
Rheumatoid arthritis/collagen vascular diseases	-	-	0.80	0.49-1.32
Coagulopathy	-	-	1.00	0.56-1.65
Fluid and electrolyte disorders	-	-	1.24	0.81-1.91
Depression	-	-	1.17	0.81-1.68
Liver disease	-	-	1.61	0.87-2.96

[1] comorbidities defined with coding algorithms for defining Elixhauser comorbidities in ICD-9 administrative data (Quan et al. 2005), ≥ 2 ICD-9 codes per category, hypertension categories merged, diabetes categories merged, different cancer categories merged, drug abuse, alcohol abuse, obesity, weight loss, HIV/AIDS, paralysis, other neurological disorders, blood loss anemia and deficiency anemia not included;

*PIMs with low level of evidence excluded.

** $p<0.05$; *** $p<0.001$

eTable 6. Multivariable associations between demographic and clinical factors and the prescribing of potentially inappropriate medications in patients with ≥ 3 chronic conditions

Demographics and clinical characteristics	Model 1: Demographic and healthcare utilization variables		Model 2: Model 1 + chronic conditions	
	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI
	(n = 16,134)		(n = 16,134)	
Age (reference: 65-74)				
75-84	0.89	0.71-1.11	0.91	0.72-1.13
85 and above	0.79	0.59-1.05	0.78	0.58-1.05
Male sex (reference: female sex)	1.32	1.09-1.62**	1.32	1.07-1.62**
Hispanic ethnicity (reference: non-hispanic)	1.16	0.41-3.26	1.13	0.40-3.18
Race (reference: White)				
Asian	1.54	0.63-3.72	1.45	0.60-3.53
Black	1.57	1.02-2.42**	1.50	0.97-2.33
Other	1.54	0.79-3.00	1.50	0.77-2.92
Number of inpatient stays (reference: 0)				
1 or above	0.99	0.72-1.35	0.94	0.69-1.30
Number of emergency department visits (reference: 0)				
1 or above	1,06	0.81-1.39	1.03	0.79-1.35
Number of ambulatory visits (reference: ≤ 9; categories based on quartiles)				
10-17	1.03	0.73-1.45	1.04	0.74-1.46
18-29	1.32	0.95-1.84	1.35	0.96-1.88
≥ 30	2.09	1.48-2.95***	2.12	1.48-3.02***
Number of non-acute institutional stays (reference: 0)				
1 or above	0.78	0.55-1.10	0.74	0.52-1.05
Level of polypharmacy (reference: 5-9 medications)				
10 and above	1.19	0.72-1.98	1.09	0.65-1.81
Number of chronic conditions (1-unit increase)	0.98	0.93-1.04	0.96	0.89-1.03
Number of prescribing orders (1-unit increase)	1.02	1.01-1.02***	1.02	1.01-1.02***

continued

Demographics and clinical characteristics	Model 1: Demographic and healthcare utilization variables		Model 2: Model 1 + chronic conditions	
	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI
Types of comorbidities[1]				
Congestive heart failure	-	-	1.43	1.10-1.86**
Cardiac arrhythmias	-	-	1.01	0.70-1.46
Valvular disease	-	-	0.86	0.63-1.16
Pulmonary circulation disorders	-	-	1.41	0.83-2.38
Peripheral vascular disorders	-	-	1.10	0.84-1.44
Hypertension	-	-	1.02	0.81-1.29
Chronic pulmonary disorders	-	-	1.14	0.88-1.49
Diabetes	-	-	1.22	0.98-1.51
Hypothyroidism	-	-	1.11	0.82-1.48
Renal failure	-	-	0.91	0.65-1.27
Cancer	-	-	0.88	0.66-1.18
Rheumatoid arthritis/collagen vascular diseases	-	-	0.86	0.54-1.36
Coagulopathy	-	-	0.94	0.57-1.54
Fluid and electrolyte disorders	-	-	0.94	0.61-1.48
Depression	-	-	1.05	0.73-1.50
Liver disease	-	-	1.57	0.88-2.83

[1] comorbidities defined with coding algorithms for defining Elixhauser comorbidities in ICD-9 administrative data (Quan et al. 2005), ≥ 2 ICD-9 codes per category, hypertension categories merged, diabetes categories merged, different cancer categories merged, drug abuse, alcohol abuse, obesity, weight loss, HIV/AIDS, paralysis, other neurological disorders, blood loss anemia and deficiency anemia not included;

** p<0.05; *** p<0.001

eTable 7. Multivariable associations between demographic and clinical factors and the prescribing of potentially inappropriate medications in patients with min. 2 ambulatory visits recorded in the electronic medical records during the baseline period

Demographics and clinical characteristics	Model 1: Demographic and healthcare utilization variables		Model 2: Model 1 + chronic conditions	
	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI
	(n = 17,466)		(n = 17,466)	
Age (reference: 65-74)				
75-84	0.87	0.70-1.07	0.88	0.71-1.09
85 and above	0.77	0.58-1.01	0.76	0.57-1.01
Male sex (reference: female sex)	1.24	1.03-1.50**	1.23	1.01-1.50**
Hispanic ethnicity (reference: non-hispanic)	0.93	0.34-2.51	0.92	0.34-2.49
Race (reference: White)				
Asian	1.43	0.59-3.46	1.36	0.56-3.29
Black	1.47	0.95-2.26	1.42	0.92-2.19
Other	1.73	0.95-3.15	1.67	0.91-3.06
Number of inpatient stays (reference: 0)				
1 or above	0.98	0.73-1.33	0.94	0.69-1.29
Number of emergency department visits (reference: 0)				
1 or above	1.13	0.69-1.46	1.10	0.85-1.43
Number of ambulatory visits (reference: ≤ 9; categories based on quartiles)				
10-17	1.04	0.75-1.43	1.04	0.75-1.43
18-29	1.53	1.12-2.08**	1.53	1.12-2.10**
≥ 30	2.29	1.64-3.19***	2.27	1.62-3.20***
Number of non-acute institutional stays (reference: 0)				
1 or above	0.78	0.55-1.11	0.73	0.52-1.05
Level of polypharmacy (reference: 5-9 medications)				
10 and above	1.18	0.71-1.95	1.08	0.65-1.79
Number of chronic conditions (1-unit increase)	0.96	0.91-1.01	0.95	0.88-1.01
Number of prescribing orders (1-unit increase)	1.02	1.02-1.02***	1.02	1.01-1.02***

continued

Demographics and clinical characteristics	Model 1: Demographic and healthcare utilization variables		Model 2: Model 1 + chronic conditions	
	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI
Types of comorbidities[1]				
Congestive heart failure	-	-	1.40	1.09-1.81**
Cardiac arrhythmias	-	-	1.03	0.71-1.47
Valvular disease	-	-	0.85	0.63-1.15
Pulmonary circulation disorders	-	-	1.41	0.84-2.38
Peripheral vascular disorders	-	-	1.10	0.84-1.43
Hypertension	-	-	0.96	0.77-1.20
Chronic pulmonary disorders	-	-	1.10	0.84-1.43
Diabetes	-	-	1.18	0.95-1.47
Hypothyroidism	-	-	1.07	0.80-1.44
Renal failure	-	-	0.91	0.65-1.26
Cancer	-	-	0.88	0.66-1.17
Rheumatoid arthritis/collagen vascular diseases	-	-	0.81	0.51-1.28
Coagulopathy	-	-	0.95	9,58-1.56
Fluid and electrolyte disorders	-	-	1.10	0.73-1.67
Depression	-	-	1.06	0.74-1.52
Liver disease	-	-	1.55	0.86-2.77

[1] comorbidities defined with coding algorithms for defining Elixhauser comorbidities in ICD-9 administrative data (Quan et al. 2005), ≥ 2 ICD-9 codes per category, hypertension categories merged, diabetes categories merged, different cancer categories merged, drug abuse, alcohol abuse, obesity, weight loss, HIV/AIDS, paralysis, other neurological disorders, blood loss anemia and deficiency anemia not included;

** p<0.05; *** p<0.001

eTable 8. Multivariable associations between demographic and clinical factors and the prescribing of potentially inappropriate medications in patients: Sensitivity analysis with claims-based frailty index

Demographics and clinical characteristics	Full model plus frailty index[1]	
	Adjusted hazard ratio	95% CI
	(n = 17,911)	
Age (reference: 65-74)		
75-84	0.89	0.73-1.10
85 and above	0.78	0.58-1.02
Male sex (reference: female sex)	1.31	1.08-1.59**
Hispanic ethnicity (reference: non-hispanic)	0.94	0.34-2.54
Race (reference: White)		
Asian	1.28	0.53-3.11
Black	1.47	0.97-2.24
Other	1.58	0.86-2.89
Number of inpatient stays (reference: 0)		
1 or above	1.03	0.75-1.42
Number of emergency department visits (reference: 0)		
1 or above	1.19	0.91-1.55
Number of ambulatory visits (reference: ≤ 9; categories based on quartiles)		
10-17	0.99	0.72-1.34
18-29	1.48	1.09-1.99**
≥ 30	2.22	1.60-3.09***
Number of non-acute institutional stays (reference: 0)		
1 or above	0.93	0.64-1.34
Level of chronic polypharmacy (reference: 5-9 medications)		
10 and above	1.11	0.66-1.84
Number of chronic conditions (1-unit increase)	0.98	0.91-1.05
Number of prescribing orders (1-unit increase)	1.02	1.01-1.02***

continued

Demographics and clinical characteristics		Full model plus frailty index[1]	
		95% CI	95% CI
Types of comorbidities[2]			
Congestive heart failure	1.44	1.11-1.86**	
Cardiac arrhythmias	1.03	0.72-1.48	
Valvular disease	0.86	0.64-1.16	
Pulmonary circulation disorders	1.39	0.82-2.33	
Peripheral vascular disorders	1.12	0.86-1.46	
Hypertension	1.00	0.80-1.24	
Chronic pulmonary disorders	1.18	0.91-1.54	
Diabetes	1.21	0.98-1.50	
Hypothyroidism	1.05	0.78-1.40	
Renal failure	0.96	0.69-1.33	
Cancer	0.84	0.64-1.12	
Rheumatoid arthritis/collagen vascular diseases	0.80	0.51-1.27	
Coagulopathy	0.96	0.59-1.57	
Fluid and electrolyte disorders	1.11	0.73-1.68	
Depression	1.13	0.791.62	
Liver disease	1.47	0.82-2.64	
Frailty index (per unit increase)	0.08	0.01-0.48**	

[1]Kim DH, Schneeweiss S, Lipsitz LA, Glynn R, Rockwood K, Avorn J. Measuring Frailty in Medicare Data: Development and Validation of a Claims-Based Frailty Index. J Gerontol A Biol Sci Med Sci. 2018; 73: 980-987. doi: 10.1093/gerona/glx229. PMID: 29244057; PMCID: PMC6001883; [2]comorbidities defined with coding algorithms for defining Elixhauser comorbidities in ICD-9 administrative data (Quan et al. 2005), ≥ 2 ICD-9 codes per category, hypertension categories merged, diabetes categories merged, different cancer categories merged, drug abuse, alcohol abuse, obesity, weight loss, HIV/AIDS, paralysis, other neurological disorders, blood loss anemia and deficiency anemia not included; ** p<0.05; *** p<0.001

16.3 Supplementary Material Article III: General Practitioners' Deprescribing Decisions in Older Adults with Polypharmacy: a Case Vignette Study in 31 Countries

This supplementary material is available from: https://ndownloader.figstatic.com/files/25992664, accessed February 11, 2021

Table of Content

Appendix 1. GP Questionnaire used in the "barriers and enabLers to willingnESs to depreScribing in older patients with multimorbidity and polypharmacy and their General Practitioners" (LESS) study

A) GP background information

1. Please indicate your age (in number of years).

2. Please indicate your sex. (male/female)

3. How many years have you been working as GP? (in number of years)

4. How many clinical consultations do you have on average per working day? (An average working day is a full day/2 sessions in the practice). (<15, 15-25, 26-35, >35)

5. How often do you see/treat patients who fulfil the following criteria:

- aged ≥ 70 years
- ≥ 3 chronic conditions
- ≥ 5 regular medications

(never, rarely, occasionally, frequently, very frequently)

Thinking of the patients who fulfil these three criteria. How would you answer the following questions?

- aged ≥ 70 years
- ≥ 3 chronic conditions
- ≥ 5 regular medications

6. How often do you deal with the topic of deprescribing medications in your daily practice with these patients? (never, rarely, occasionally, frequently, very frequently)

7. How often do you deprescribe medications during consultations with your patients in your daily practice in respect of these patients? (never, rarely, occasionally, frequently, very frequently)

B) Case vignettes

Case vignette 1

Patient 1, 82 years of age:

Social history: retired carpenter, *lives with his wife in a single-family home. Patient 1 prepares his medication independently, goes grocery shopping and does other work around the house and garden. The couple do not require any help from third parties.*

General health: *in a good physical and cognitive condition. MMSE 28/30.*

Other diagnoses: chronic back pain, hypertension, non-smoker, no past history of cardiovascular events, no family history of cardiovascular events

Laboratory values: dyslipidemia (3.8mmol/l), liver and kidney function are normal (taking into account the age of the patient), normal blood count. Last systolic blood pressure measurements ranged from 130 to 140mmHg.

Daily medication intake:
Aspirin 100 mg once daily
Atorvastatin 40 mg once daily
Enalapril 10 mg once daily
Amlodipine 5 mg once daily
Paracetamol 1 g three times a day
Tramadol 50 mg twice daily
Pantoprazole 20mg once daily

In this case vignette, you consider the patient:

- to have a good physical functioning and somatic condition
- to be totally independent
- to be cognitive not impaired
- to have a low risk of cardiovascular events

8. Would you deprescribe or decrease the dosage of one/several medication/s? (yes/no)

9. Which medication/s would you deprescribe or decrease?
- Aspirin 100 mg once daily
- Atorvastatin 40 mg once daily
- Enalapril 10 mg once daily
- Amlodipine 5 mg once daily
- Paracetamol 1g three times a day
- Tramadol 50 mg twice daily
- Pantoprazole 20 mg once daily

10. Consider that Patient 1 now had a cardiovascular event in the past (e.g., myocardial infarction three years ago). Would you deprescribe or decrease the dosage of one/several medication/s? (yes/no)

11. Which medication/s would you deprescribe or decrease taking into account that Patient 1 has already had a cardiovascular event in the past (e.g., myocardial infarction three years ago)?
- Aspirin 100 mg once daily
- Atorvastatin 40 mg once daily
- Enalapril 10 mg once daily
- Amlodipine 5 mg twice daily
- Paracetamol 1g three times a day
- Tramadol 50 mg twice daily
- Pantoprazole 20 mg once daily

Case vignette 2

Patient 2, 82 years of age:

Social history: retired carpenter, *lives with his wife who is in a good physical and cognitive state. Patient 2 is becoming more and more dependent; household tasks are done by his wife. Patient 2 needs help from third parties for personal hygiene, getting dressed/undressed and preparing medication.*

General state: walking pace significantly decreased over the past year, unsteady on his legs. Increasing forgetfulness and attention deficiency in the past couple of months. MMSE 22/30.

Other diagnoses: Chronic back pain, hypertension, non-smoker, no past history of cardiovascular events, no family history of cardiovascular events

Laboratory values: Dyslipidemia (LDL 3,8mmol/l), liver and kidney function are normal (taking into account the age of the patient), normal blood count. Last systolic blood pressure measurements ranged from 130 to 140mmHG.

Daily medication intake:
Aspirin 100 mg once daily
Atorvastatin 40 mg once daily
Enalapril 10 mg once daily
Amlodipine 5 mg once daily
Paracetamol 1 g three times a day
Tramadol 50 mg twice daily
Pantoprazole 20mg once daily

In this case vignette, you consider the patient:
- to have reduced physical functioning
- to be increasingly dependent in his daily routine
- to be cognitively moderately impaired

- to have a low risk of cardiovascular events

12. Would you deprescribe or decrease the dosage of one/several medication/s? (yes/no)

13. Which medication/s would you deprescribe or decrease?
- Aspirin 100 mg once daily
- Atorvastatin 40 mg once daily
- Enalapril 10 mg once daily
- Amlodipine 5 mg once daily
- Paracetamol 1g three times a day
- Tramadol 50 mg twice daily
- Pantoprazole 20 mg once daily

14. Consider that Patient 2 now had a cardiovascular event in the past (e.g., myocardial infarction three years ago). Would you deprescribe or decrease the dosage of one/several medication/s? (yes/no)

15. Which medication/s would you deprescribe or decrease taking into account that Patient 2 had a cardiovascular event in the past (e.g., myocardial infarction three years ago)?
- Aspirin 100 mg once daily
- Atorvastatin 40 mg once daily
- Enalapril 10 mg once daily
- Amlodipine 5 mg twice daily
- Paracetamol 1g three times a day
- Tramadol 50 mg twice daily
- Pantoprazole 20 mg once daily

Case vignette 3

In the following, there will be a case vignette.

After the case vignette, there will be a few questions asking you which medications you would deprescribe.

Patient X, 82 years of age:

Social history: retired carpenter*, lives together with his wife in a nursing home*

General health: *Patient X walks very little using a walker. Needs daily support for personal hygiene and getting dressed/undressed. Lack of spatial or temporal orientation. Unintended weight loss of 8kg in the past two months. MMSE 12/30.*

Other diagnoses: Chronic back pain, hypertension (last blood pressure measurements ranged from 130 to 140mmHG, systolic), non-smoker, no family history of cardiovascular events

Laboratory values: Dyslipidemia (LDL 3,8mmol/l), liver and kidney function are normal (taking into account the age of the patient), normal blood count

Daily medication intake:
Aspirin 100 mg once daily
Atorvastatin 40 mg once daily
Enalapril 10 mg once daily
Amlodipine 5 mg once daily
Paracetamol 1 g three times a day
Tramadol 50 mg twice daily
Pantoprazole 20mg once daily

In this case vignette, you consider the patient:
- to have strongly impaired physical functioning
- to be strongly dependent in his daily routine
- to be cognitively strongly impaired
- to have a low risk of cardiovascular events

16. Would you deprescribe or decrease the dosage of one/several medication/s? (yes/no)

17. Which medication/s would you deprescribe or decrease?

- Aspirin 100 mg once daily
- Atorvastatin 40 mg once daily
- Enalapril 10 mg once daily
- Amlodipine 5 mg twice daily
- Paracetamol 1g three times a day
- Tramadol 50 mg twice daily
- Pantoprazole 20 mg once daily

18. Consider that this Patient had a cardiovascular event in the past (e.g., myocardial infarction three years ago). Would you deprescribe or decrease the dosage of one/several medication/s? (yes/no)

19. Which medication/s would you deprescribe or decrease taking into account that Patient X had a cardiovascular event in the past (e.g., myocardial infarction three years ago)?

- Aspirin 100 mg once daily
- Atorvastatin 40 mg once daily
- Enalapril 10 mg once daily
- Amlodipine 5 mg twice daily
- Paracetamol 1g three times a day
- Tramadol 50 mg twice daily
- Pantoprazole 20 mg once daily

C) Barriers and enablers to the willingness to deprescribe

20. How important are the following ***patient characteristics*** for you when you deprescribe medications?

	Not important	Slightly important	Neutral	Important	Very important
Age					
Life expectancy					
Quality of life					
Previous experiences with deprescribing					
Expectations of the patient					
Fear of potential negative health outcomes					
Difficult communication					
Expectation of relatives					

21. How important are the following criteria for you when you deprescribe medications?

	Not important	Slightly important	Neutral	Important	Very important
Existence of deprescribing guidelines					
Existence of tools that facilitate deprescribing					
Inter-professional communication (between GPs and other prescribing physicians)					
Inter-professional collaboration (between GPs and other prescribing physicians)					
Expenditure of time					
Self-dispensation of medication in GP office					
Benefit of a medication					
Risk of a medication					

22. Are there any other factors that influence deprescribing from your point of view? (yes/no)
In your opinion, which other factors influence deprescribing?

Remarks and comments

23. Do you have any additional comments or remarks regarding deprescribing?

Appendix 2. Table 1. Response rate by country.

Country	Survey language(s)	Number of GPs in sample	Number of replies receive	Response rate
Slovenia	Slovenian	352	38	10.80%
Latvia	Latvian	1002	122	12.18%
Belgium	French, Dutch	919	134	14.58%
Ireland	English	113	20	17.70%
Luxembourg	French, Dutch, German	100	21	21.00%
Netherlands	Dutch	128	41	32.03%
Israel	English	350	129	36.86%
Germany	German	128	51	39.84%
Macedonia	Macedonian	74	31	41.89%
Hungary	Hungarian	587	248	42.25%
Austria	German	80	36	45.00%
Estonia	Estonian	52	24	46.15%
Sweden	Swedish	113	53	46.90%
Spain	Spanish	51	24	47.06%
France	French	43	21	48.84%
Denmark	Danish	58	29	50.00%
New Zealand	English	78	42	53.85%
Switzerland	German, French	288	157	54.51%
Czech Republic	Czech	35	20	57.14%
Portugal	Portuguese	72	43	59.72%
Romania	Romanian	48	29	60.42%
Poland	Polish	56	38	67.86%
Brazil	Portuguese	87	62	71.26%
Greece	Greek	70	50	71.43%
Italy	Italian	43	31	72.09%
Finland	English	31	23	74.19%
Ukraine	Ukrainian	36	28	77.78%
United Kingdom	English	30	25	83.33%
Bulgaria	Bulgarian	41	36	87.80%
Bosnia and Herzegovina	Bosnian	70	62	88.57%
Croatia	Croatian	40	38	95.00%
Average response rate		**5175**	**1706**	**52.52%**

Appendix 3. Results of sensitivity analysis.

Table 2 Analysis restricted to countries with a response rate >60% (number of countries in the analysis: 11): Percentage of general practitioners (GPs) deprescribing in case vignettes, sorted by GPs' decisions to deprescribe at least one, two or three medications in the respective case vignette, patients' level of dependency in activities of daily living, and patients' history of cardiovascular disease (CVD) (n=361)

Case vignette	Patients' dependency level	Deprescribing decision	**Without** history of CVD (95% CI)	**With** history of CVD (95% CI)	Difference (95% CI)[1]
1	low				
	(living in own house, no help needed for activities of daily living)	min. 1 medication	96.7 (94.8 – 98.6)	84.4 (80.5 – 88.3)	12.3 (8.0 – 16.7)
		min. 2 medications	91.1 (88.0 – 94.1)	67.9 (62.8 – 73.0)	23.0 (17.3 – 29.1)
		min. 3 medications	73.6 (68.9 – 78.3)	33.0 (27.9 – 38.1)	40.6 (33.6 – 47.5)
2	medium				
	(living in own house, some help needed for activities of daily living)	min. 1 medication	94.5 (92.4 – 97.3)	88.6 (85.0 – 92.1)	6.3 (1.9 – 10.6)
		min. 2 medications	88.5 (84.9 – 66.2)	71.2 (66.2 – 76.3)	17.2 (11.0 – 23.4)
		min. 3 medications	67.6 (62.4 – 72.8)	37.9 (32.5 – 43.4)	29.7 (22.2 – 37.2)
3	high				
	(living in nursing home, help needed for nearly all activities of daily living)	min. 1 medication	91.5 (88.3 – 94.7)	88.6 (82.7 – 90.5)	4.9 (0.0 - 9.9)
		min. 2 medications	86.8 (82.9 – 90.6)	76.4 (71.5 – 81.2)	10.4 (4.2 – 16.6)
		min. 3 medications	74.9 (70.0 – 79.9)	51.0 (45.3 – 56.8)	23.9 (16.3 – 31.5)

[1]Two-sample test of proportions using variables

16.4 Supplementary Material Article V: Baseline characteristics and representativeness of older multimorbid patients with polypharmacy and general practitioners participating in a randomized controlled primary care trial

Unpublished supplementary material as of February 11, 2021.

Table of Content

eAppendix 1. Information about the OPTICA trial and the FIRE project.

FIRE project

The FIRE project is the largest Swiss database collecting anonymized routine patient data from the electronic medical records in primary care practices since 2009 [172]. The following information is available in the FIRE database: administrative information (patient, age, and sex), diagnosis codes, laboratory and vital signs measurements, and prescribing information. As of October 2020, the database of the FIRE project contains data from the electronic medical records of more than 680 GPs (about 11% of all Swiss GPs [174]) and more than 830'000 patients (about 10% of the general population) [173]. All Swiss GPs are invited to join the FIRE project if they use an electronic health record (EHR) program that is compatible with exporting anonymized data to the FIRE project. Six of the most commonly used EHR programs in the German speaking part of Switzerland are compatible with FIRE. GPs who participate in the FIRE project export selected, anonymized data from their EHR every two months. In return, the GPs receive feedback reports, which they can use for quality assurance purposes.

OPTICA trial

The protocol for the OPTICA trial is described elsewhere in detail [141]. Briefly, the OPTICA trial is a cluster randomized controlled trial, being conducted in primary care in the German speaking part of Switzerland. The aim of the OPTICA trial is to investigate whether the use of an electronic clinical decision support system (CDSS), namely the 'Systematic Tool to Reduce Inappropriate Prescribing' (STRIP) Assistant [165], improves medication appropriateness compared to a standard care sham intervention in older multimorbid patients with polypharmacy. The STRIP Assistant (STRIPA) is based on the algorithms of the 'Screening Tool to Alert doctors to Right Treatment' (START) and 'Screening Tool of Older Person's Prescriptions' (STOPP) version 2 [138] which are lists of medications generally considered to be inappropriate and appropriate in older adults, respectively [68]. The standard care sham intervention in the control group consists of a medication discussion between GPs and patients in accordance with usual care. The co-primary outcomes of the OPTICA trial are the 'Medication Appropriateness Index' (MAI) and the 'Assessment of underutilization' (AOU) [166-168]. Secondary outcomes include: degree of polypharmacy, degree of overprescribing, degree of under-prescribing, number of falls and fractures, quality of life, the amount of formal and informal care received by patients, survival, patients' quality adjusted life years (QALYs), patients' medical costs, cost-effectiveness of the intervention, percentage of recommendations accepted and rejected by GPs, and patients' willingness to have

medications deprescribed. The latter is assessed using a validated questionnaire: the ‘revised Patient Attitudes Towards Deprescribing” questionnaire, which provides insights into patients' willingness for deprescribing and potential barriers to deprescribing [171,186]. Patients are followed-up for one year. At baseline, 6 months and 12 months, data for the OPTICA trial was collected by conducting phone calls (e.g., sociodemographic information, etc.) and from the FIRE database (e.g., medications, diagnoses, lab values and vital data).

In the OPTICA trial, we tried early on to establish recruitment and retention strategies designed to overcome challenges linked to GP recruitment (e.g., personal visits to explain the study, provide rapid response to questions and problems faced by participating GPs) [218].The recruitment of GPs for the OPTICA trial began in autumn 2018 and ended in late 2019. Clustering occurred on the level of the GP. The participating GPs each formed a cluster. The patient recruitment took place from December 2018 to February 2020 and was done directly by the participating GPs. To standardize the selection of eligible patients, GPs received screening lists with potentially eligible patients. These screening lists were created based on data previously exported to the FIRE database and included random sample of their own patients who were potentially eligible (based on age and polypharmacy). However, due to the nature of the routine data collected in the FIRE project, the provided screening list were not 100% accurate (e.g., inclusion of dead patients, patients who had changed their GP). Due to this, GPs were allowed to recruit other patients that they directly identified who fulfilled the inclusion and exclusion criteria.

eTable 1. Baseline characteristics of patients in the OPTICA trial compared to other multimorbid patients with polypharmacy in the FIRE database who also were patients of the general practitioners participating in the OPTICA trial.

Characteristics	OPTICA study participants (N=323)	Other patients of same general practitioners (N=3'549)	p-value[1]	Absolute standardized difference[2]
Median age (IQR)	78 (72-85)	77 (73-83)	0.31	0.089
Sex				
Women (%)	1858 (52)	146 (45)	0.015	0.143
Men (%)	1691 (48)	177 (55)		
Median number of chronic conditions (IQR)	4 (3-5)	4 (3-6)	<0.001	0.164
Median number of medications in the last 12 months (IQR)	7 (5-9)	6 (5-9)	<0.001	0.268
Health services use (in the last 12 months)				
Median number of consultations (IQR)	14 (7-23)	16 (10-25)	<0.001	0.173
Median number of blood pressure measurements (IQR)	2 (1-4)	3 (2-5)	<0.001	0.293
Median number of Body Mass Index measurements (IQR)	1 (1-2)	1.5 (1-3)	0.186	0.069
Median number of HbA1c measurements (IQR)	2 (1-3)	2 (1-4)	0.005	0.214
Median number of glomerular filtration rate (GFR) measurements (IQR)	1 (1-2)	2 (1-3)	<0.001	0.286
Median number of lipid profile measurements (IQR)	1 (1-1)	1 (1-2)	0.006	0.235
Lab values & vital signs (in the last 12 months)				
Median systolic blood pressure (IQR)	138 (128-149)	138 (126-148)	0.533	0.008
Median diastolic blood pressure (IQR)	78 (71-84)	76 (70-83)	0.124	0.077
Median Body Mass Index (IQR)	28 (24-31)	29 (25-32)	0.146	0.146
Median HbA1c (IQR)	6.1 (5.6-6.9)	6.3 (5.7-7.0)	0.036	0.082
Median GFR (IQR)	69.0 (53.1-82.7)	66.2 (51.4-79.7)	0.223	0.052

[1] For categorical variables we performed a Fisher's exact text and for continuous variables a Kruskal-Wallis test was performed. [2] An imbalance between the two groups was previously defined as an absolute standardized difference value >0.2. Abbreviations: BMI=Body Mass Index; IQR= Interquartile range; GFR=Glomerular filtration rate; HbA1c=Hemoglobin A1C; OPTICA = Optimizing PharmacoTherapy in older multimorbid adults In primary CAre; FIRE = Family medicine ICPC Research using Electronic medical records

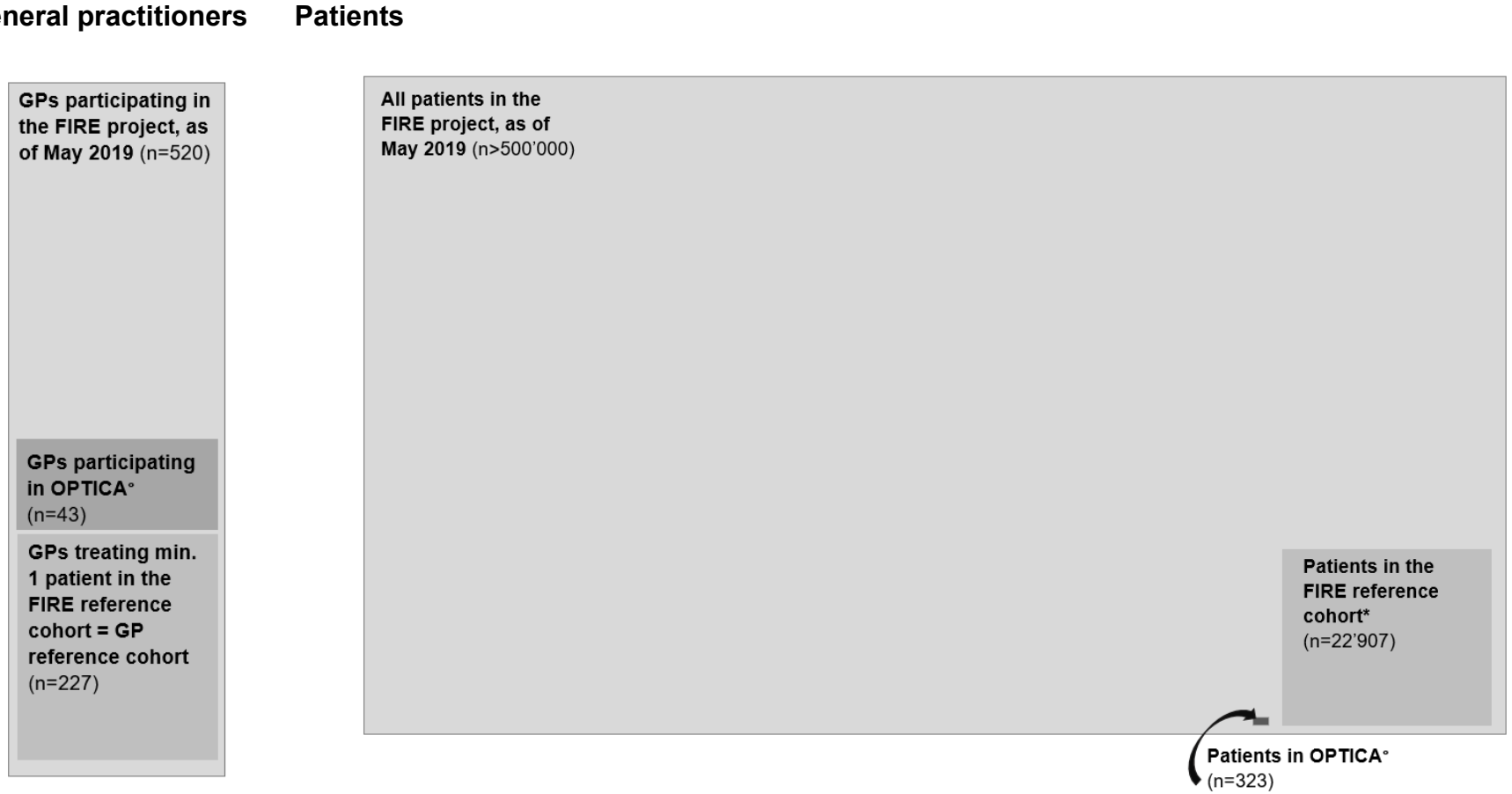
eTable 2. Baseline characteristics of Swiss general practitioners who participated in the Workforce-Study.

Characteristics	General practitioners (N=2'037)
Median age (IQR)	56 (48-63)
Median years since starting to work as general practitioner (IQR)	18 (8-27)
Sex	
Women (%)	737 (36)
Men (%)	1292 (64)
Employment status	
Independent (%)	1467 (72)
Employed (%)	564 (28)
GP practice type	
Group practice (%)	1288 (66)
Single practice (%)	675 (34)
Location	
Non-urban (%)	642 (35)
Urban (%)	1219 (65)
Self-dispensation of medications in GP office[2]	
Yes (%)	1090 (57)
No (%)	832 (43)
Median work percentage (IQR)	80 (60-100)
Type of health records used	
Electronic health records (%)	430 (72)
Paper records (%)	59 (9)
Both (%)	112 (18)

More information about the Workforce-Study: https://www.mfe-standpunkte.ch/de/ausgabe/ausgabe-22020--43/artikel/hausaerztemangel-aber-mit-licht-am-horizont--76, accessed November 24, 2020

Abbreviations: GP=general practitioner, IQR=interquartile range

eFigure 1. FIRE database, FIRE reference cohorts and OPTICA trial participants.



*aged 65 years and over, prescribed at least 5 different medications; °general practitioners who participated in the OPTICA trial also participate in the FIRE project, thus there is information on themselves and their patients in the FIRE database

Declaration of Originality

Declaration of Originality

Last name, first name: Jungo, Katharina

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I hereby declare that this thesis represents my original work and that I have used no other sources except as noted by citations.
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Place, date Fribourg, 15.02.2021

Signature K. Jungo