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Exploring different aspects related to making and implementing deprescribing decisions in primary care settings

PhD Thesis submitted by

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1. Abstract

Background

The high rate of inappropriate polypharmacy (use of ≥5 medications [1]), has been considered a public health problem due to its association with adverse outcomes, including increased risk for falls, adverse drug reactions, declined functional ability and cognitive capacity, and worsened nutritional status [2-6]. Regular medication reviews and deprescribing (the process of stopping or reducing medications [7]) should be carried out to minimise the risk of medication-related problems, especially among older patients with polypharmacy. However, making and implementing deprescribing decisions in clinical practice is challenging for different reasons.

One of the most common inappropriate medication types are proton pump inhibitors (PPI). Nevertheless, the rates of potentially inappropriate PPI prescriptions have been increasing [8-10]. Inappropriate prescribing of PPIs has been associated with adverse health events and unnecessary costs [8, 11, 12]. General practitioners (GPs) usually have a long-term relationship with their patients and are informed about their patients' medications, medical conditions, and preferences. GPs have therefore a crucial role in the optimisation of PPI use and prescribing. To optimise the prescriptions of PPIs in primary care, it is important to understand how GPs manage PPI prescriptions in clinical practice and how these prescriptions evolve over time. Little is known about how effective increasing GPs' awareness of inappropriate PPI prescriptions would be in optimising PPI prescribing. Understanding how GPs manage potentially inappropriate PPI prescriptions among their patients will help the development of interventions to optimise PPI prescriptions in primary care settings.

Furthermore, shared decision-making has a crucial role in deprescribing, and decisions about whether and how to stop or reduce medications should consider patients' views and preferences [13, 14]. In this context, it is important to understand patients' attitudes towards deprescribing. There is a lack of evidence on which specific medications patients would be more willing to have deprescribed and why. Understanding patients' attitudes towards deprescribing specific medications will help to design tailored deprescribing interventions in clinical practice that consider patients' preferences.

Older patients with polypharmacy do not only use prescription medications, but also over-the-counter substances, such as dietary supplements. The use of dietary supplements is

widespread in developed countries, such as Switzerland [15-17]. Nevertheless, dietary supplements are often used inappropriately, for instance, when there is no indication for their use [18, 19]. Patients are often unaware of the potential risks of supplement use, and therefore often they do not disclose this use to their GPs [20, 21]. However, for a successful implementation of medication reviews and deprescribing, GPs should be aware of all the medications used, including dietary supplements. There is still a lack of evidence focusing on GPs' and patients' attitudes towards deprescribing dietary supplements.

Finally, the involvement of pharmacists and their collaboration with GPs may facilitate the conduct of medication reviews and enhance the process of withdrawal or reduction of inappropriate medications [22-28]. However, more research is needed to better understand the factors associated with pharmacists' willingness to make deprescribing recommendations and their preferences for interprofessional collaboration with physicians for optimising medications in the Swiss context.

Aims

Each one of the four projects involved in my PhD targets different aspects related to medication optimisation and deprescribing in primary care settings. The overall aim of this thesis was to investigate patients' and healthcare professionals' attitudes towards optimising medication use in primary care settings, including the use of dietary supplements. My PhD research is guided by the following four aims:

Aim 1: To investigate the prevalence of potentially inappropriate PPI prescribing in a sample of patients in Swiss primary care settings and to evaluate how GPs manage patients with potentially inappropriate PPI prescribing after being aware of this potentially inappropriate prescribing among their patients.

Aim 2: To explore patients' attitudes towards deprescribing specific medications in 14 countries, by investigating which medications patients were most willing to have deprescribed, the reasons why, and patient factors associated with their willingness to deprescribe.

Aim 3: To investigate the attitudes of patients with polypharmacy towards dietary supplement use, and to explore patients' and their GPs' willingness to reduce or stop the intake of these supplements.

Aim 4: To explore pharmacists' perspectives on medication review and deprescribing, as well as their preferences for interprofessional collaboration regarding medication optimisation within Swiss primary care settings.

Methods

For Aim 1, we recruited 11 GPs working in the canton of Bern in Switzerland, who participated in a specific quality circle ("quality circles" are meetings in which a small group of GPs reflect together to improve their care practice [29]). This quality circle meeting had the aim to raise the GPs' awareness of optimising PPI prescriptions by instructing GPs to flag patients as having a potentially inappropriate PPI prescription in their medical records. We used a convenience retrospective sampling strategy, in which GPs were asked to use their electronic medical records to screen all patients they had seen before the baseline (June 1st, 2021) until they find the first 20 patients who had an active PPI prescription for ≥8 weeks. After identifying these patients, GPs flagged potentially inappropriate PPI prescribing in their medical records. After 12 months, we asked the same GPs whether the potentially inappropriate PPI prescriptions of those flagged patients had changed and, if so, how. We used multilevel logistic regression adjusted for the clustering effect at the GP level to analyse the association between patient and GP characteristics and the frequency of deprescribing.

Aim 2 and Aim 3 are part of the same cross-sectional study. For Aim 2, national coordinators from 14 countries recruited 10 GPs each, and each GP recruited 10 patients (≥65 years old with ≥5 regular medications). Patients then completed an anonymous survey about their attitudes towards deprescribing. We described patient attitudes towards deprescribing, as well as the number and types of medications patients reported that they would like to stop or reduce. We used multilevel logistic regression analysis adjusted for the clustering effect at the country level to investigate the association between patient characteristics and wanting to stop or reduce medications.

For Aim 3, we used the same recruitment strategy, but it involved additional questionnaires only for Switzerland. For Aim 3, older patients with polypharmacy and their GPs were invited to respond to a survey on patients' use of dietary supplements and attitudes towards deprescribing those. We described and compared their responses regarding dietary supplement use and willingness to deprescribe those, and assessed the association of

supplement disclosure with patients' characteristics using multilevel logistic regression analysis.

For Aim 4, a random sample of 1000 pharmacist members of the Swiss pharmacists association pharmaSuisse was invited to respond to an online survey on medication review, deprescribing, and interprofessional collaboration for medication optimisation. The survey had three case vignettes of multimorbid patients aged ≥80 years old with potentially inappropriate polypharmacy, and with different levels of dependency in activities in daily living (ADL) and history of cardiovascular disease (CVD). Pharmacists responded if and which medications they would deprescribe in each case vignette. We calculated the proportions of pharmacists' willingness to deprescribe by case vignette and performed a multilevel logistic regression analysis to assess associations between pharmacist characteristics, patient history of CVD and dependency in ADL, and willingness to deprescribe.

Results

For Aim 1, we found that potentially inappropriate PPI prescribing was common in Swiss primary care settings, with 41% (n=85) out of the 206 patients with a PPI prescription having a potentially inappropriate PPI prescription. After raising GPS' awareness of such potentially inappropriate prescriptions, deprescribing was possible for 35% (n=29) of the patients having a potentially inappropriate PPI prescription. The most frequently mentioned reasons for deprescribing not being possible were a lack of discussion with the patient (no contact or no time), the presence of symptoms requiring the PPI, or the unwillingness of the patient to deprescribe. Aim 1 resulted in the Article 1 of this thesis.

For Aim 2, we recruited 1,340 patients (average 96/country), of which 82% (n=1,089) reported being satisfied with their medications. 81% (n=1,088) of the patients were willing to deprescribe if their doctor said it was possible and 44% (n=589) said they would be willing to have at least one of their medications deprescribed. The three most commonly reported medication types for deprescribing were diuretics (n=111, 11%), lipid modifying agents (n=109, 11%), and agents acting on the renin–angiotensin system (n=83, 8%). The odds of being willing to deprescribe specific medications were higher for patients with less satisfaction with medications (OR=0.31, 95%CI 0.21 to 0.47) and lower trust in their GP (OR=0.96, 95%CI 0.93 to 1.00). Aim 2 resulted in Article 2.1 of this thesis.

For Aim 3, we collected data from 10 GPs (3 (30%) female, average age 52 years (SD=8)) and 65 of their patients (29 (45%) female, average 7 patients per GP). We found that 70% of the patients were taking ≥1 supplement (n=45). On average patients reported to be using 3 supplements (SD=2). For 60% (n=39) of the patients, GPs were unaware of ≥1 supplement used. 8% (n=5) of patients and 60% (n=6) of GPs reported ≥1 supplement they would be willing to stop or reduce, and none of the supplements reported by GPs and patients to deprescribe matched. Aim 3 resulted in Article 3 of this thesis.

For Aim 4, we collected data from 138 pharmacists: 113 (82%) were female, their mean age was 44 years (SD=11), 66% (n=77) reported having never received any specific training on how to conduct structured medication reviews, 83 (72%) reported to be confident in identifying deprescribing opportunities, and 88 (81%) wished to be more involved in the process of medication review and deprescribing. All pharmacists were willing to deprescribe ≥1 medication in all vignettes. Patients with CVD were at lower odds of having medications deprescribed (OR=0.27, 95%CI 0.21 to 0.36). Willingness to deprescribe was lower with higher dependency in ADL (medium versus low dependency: OR=0.68, 95%CI 0.54 to 0.87, high versus low dependency: OR=0.72, 95%CI 0.56 to 0.91). However, the joint presence of medium/high dependency in activities of daily living and a history of CVD increased the odds of making a deprescribing suggestion (CVD x medium dependency: OR=1.61 95%CI 1.11 to 2.33, CVD x high dependency: OR= 1.75 95%CI 1.21 to 2.52). In sensitivity analysis, higher levels of dependency in ADL had lower odds of willingness to recommend deprescribing only in cases without history of CVD (medium versus low dependency: OR=0.69, 95%CI 0.54 to 0.87, high versus low dependency: OR=0.72, 95%CI 0.57 to 0.91), but it was different in cases with history of CVD (medium versus low dependency: OR=1.10, 95%CI 0.83 to 1.47, high versus low dependency: OR=1.26, 95%CI 0.95 to 1.67). The odds of recommending deprescribing were also higher for pharmacists who had received training in medication review (OR=2.48, 95%CI 1.38 to 4.44). Aim 4 resulted in Article 4 of this thesis.

Conclusions

This thesis sheds light on different aspects related to patients' and healthcare professionals' attitudes towards medication optimisation and deprescribing. First, the finding that raising GPs' awareness of potentially inappropriate PPI prescribing resulted in deprescribing potentially inappropriate PPIs in only 35% of the patients suggests that more personalised and targeted interventions are necessary to successfully implement deprescribing of potentially

inappropriate PPIs. Second, our findings show that patients' willingness to have medications deprescribed is lower when patients are asked about specific medications compared to the literature asking non-specific questions. This could be one of the reasons why willingness to deprescribe has not yet been found to translate to real-world medication changes and highlights the need for measures that reflect more accurately the patients' deprescribing attitudes in real-life clinical situations. A better understanding of which types of medications patients are more willing to have deprescribed can inform the scope of future deprescribing interventions that consider patients' preferences. Third, Swiss GPs were unaware of many dietary supplements used by their older patients with polypharmacy, which may affect medication optimisation efforts. Older adults with polypharmacy seemed to be unsure about the benefits, necessity, and possible risks of dietary supplements and were not willing to have those deprescribed. This highlights the need to involve and educate patients in these regards. Fourth, Swiss pharmacists were willing to make deprescribing suggestions for older patients with polypharmacy, but most reported having received no specific training on how to perform structured medication reviews. Pharmacists would like to be more involved in the process of medication review and deprescribing, which should be leveraged in the context of Swiss primary care settings. Our findings help to better understand patients', GPs', and pharmacists' attitudes towards deprescribing. This in turn will inform future interventions that aim to successfully implement deprescribing and medication optimisation in primary care settings.

2. Abbreviations

ADL	Activities in Daily Living
CVD	Cardiovascular Diseases
EGPRN	European General Practice Research Network
GP	General Practitioner
PPI	Proton pump Inhibitor
rPATD	revised Patients' Attitudes Towards Deprescribing

3. Overall introduction

3.1 Ageing and Polypharmacy

The increasing life expectancy over the last decades and the decreasing fertility rates are leading to changes in the demographic structure of the world's population [30]. As a result, according to the World Health Organization (WHO), the proportion of older adults over 60 years of age will increase from 12% to 22% between 2015 and 2050, with one in six persons ageing 60 years or older by 2030 [31]. This worldwide ageing population has been leading to new challenges in the healthcare of older adults.

With ageing, older adults become more susceptible to having multiple diseases, including neurodegenerative, immunological and cardiovascular diseases, cancer, and musculoskeletal disorders [32]. The occurrence of multiple diseases in the same person is known as multimorbidity, and the prevalence of multimorbidity is particularly high among the older population [33]. The high prevalence of multimorbidity has been leading to an increasing interest and research on the development of new strategies and new treatments to promote healthy ageing [34]. However, research is still needed to understand and develop the best strategies to manage and optimise the complex care of older adults with multimorbidity.

To manage their multiple diseases, older adults with multimorbidity usually take multiple medications, often leading to polypharmacy, which is commonly known as the regular use of ≥5 medications [1, 35, 36]. In Europe, the prevalence of polypharmacy ranges from 26% to 40% [15, 36-38]. When polypharmacy involves medications combined in an appropriate way considering patients' health conditions, it is considered appropriate polypharmacy. On the other hand, when polypharmacy involves potentially inappropriate medications, it is considered as potentially inappropriate polypharmacy [39-41]. Potentially inappropriate medications are medications of which the potential risks outweigh the potential benefits, medications that are being used or prescribed without a clear indication, and those being used or prescribed at doses higher than the necessary dose [39-41]. The prevalence of potentially inappropriate polypharmacy is high worldwide, and it has been considered a public health problem [42, 43]. For instance, among patients with polypharmacy in Switzerland, 21% have a potentially inappropriate medication [44]. To create interventions aiming to tackle inappropriate polypharmacy, more information on patients' and healthcare professionals' attitudes towards inappropriate medications is still needed.

The prevalence of potentially inappropriate medications ranges from 37% to 59% and seems to vary depending on which tool or definition was used to assess medication inappropriateness, and on clinical and geographic settings [45-47]. For instance, the use and prescribing of proton pump inhibitors (PPIs) are often considered inappropriate when used for a long term without a clear indication, or when used in too high doses [10, 48-52]. PPIs, dietary supplements, and benzodiazepines are among the most commonly reported potentially inappropriate medications [53, 54]. Nevertheless, research is still needed to understand and identify the best approaches to help prescribers to deal with these inappropriate medications, once their awareness of potentially inappropriate medications has been raised.

Potentially inappropriate polypharmacy has been associated with several health-related problems, such as adverse drug events, increased risk of drug-drug and drug-nutrient interactions, declined cognitive ability, increased risk for falls, and consequently increased hospital admissions and healthcare costs [4, 5, 35, 37, 55-59]. Physiological and metabolic changes that occur with ageing significantly affect drug pharmacokinetics and pharmacodynamics in older adults, making older adults especially susceptible to possible adverse effects due to inappropriate polypharmacy [39]. Besides adverse health effects, inappropriate polypharmacy is also a burden for healthcare systems and may lead to unnecessary costs. Therefore, preventing and managing inappropriate polypharmacy is crucial for optimising not only older adults' medication use, but also healthcare costs.

Different tools can be used to recognise potentially inappropriate medications. For instance, the Beers Criteria provides a list of potentially inappropriate medications for adults aged 65 years old and older [60]. Another tool used to identify potentially inappropriate medications is the STOPP/START criteria, which is a set of guidelines designed to help identify potentially inappropriate prescribing in older adults [41, 61]. The STOPP/START criteria focus not only on identifying potentially inappropriate medications, but also potentially prescribing omissions in older adults [61]. Furthermore, the STOPPFrail is tailored to address inappropriate medications specifically in frail older adults with limited life expectancy [62]. The 'S-I-R-E' is another tool that can be used to assess medication appropriateness, which involves four questions to assess the medication appropriateness: *S = symptoms ('Have symptoms resolved?'), I = indication ('Is there a valid indication?'), R = risks ('Do risks outweigh benefits?') and E = end of life ('Is there short life expectancy limiting clinical benefit?')* [53].

The use of electronic decision support tools based on the available guidelines and other supporting tools has been increasing. Such electronic decision support tools have been shown to efficiently aid physicians and other healthcare professionals in identifying inappropriate medications, but barriers associated with their use, such as time consumption, still need to be overcome [63-66]. Of note, there are many tools and guidelines available to guide prescribers on the management of inappropriate medications. Nevertheless, none of the guidelines or tools aims to completely replace the judgement of prescribers, their purpose is rather to guide the management of inappropriate medications to optimise medications in older adults. Therefore, it is important to understand and consider healthcare professionals' and patients' attitudes towards medications when developing and implementing medication optimisation efforts.

3.2 Raising General Practitioners' Awareness of Inappropriate Medications

General practitioners (GPs) are in constant and close contact with patients and usually have a long-term relationship with them. In this long-term relationship, GPs are usually well-informed about their patients' medications, medical conditions, and overall preferences. Therefore, GPs have a crucial role in identifying and managing patients' medications in a tailored way. Despite academic and media reports aiming to raise GPs' and other healthcare professionals' awareness of potentially inappropriate medications, the use and prescribing of these potentially inappropriate medications are still common [10, 47, 67, 68]. This high rate of potentially inappropriate medications highlights the need to understand and design new approaches to raise GPs' awareness of potentially inappropriate medications.

Barriers such as time constraints, limited access to updated and evidence-based information, and different interpretations of medication optimisation-related tools and guidelines contribute to the low awareness and consequently to the high prevalence of potentially inappropriate medications [69]. In addition, GPs sometimes prescribe medications to meet their patients' expectations, not properly considering the negative consequences [70-72]. Such barriers may affect patient care and pose a risk of adverse events related to inappropriate medications, indicating a need to increase awareness of the implications of inappropriate prescribing.

There are several ways to raise GPs' awareness of inappropriate medications. Training and educational programs have been shown to increase the GPs' awareness and knowledge of

inappropriate prescribing, highlighting the importance of continuous education and awareness campaigns to improve medication management [73]. For instance, multifaceted educational interventions combining patient education and education for healthcare professionals have been the most frequently effective, with 73% of these interventions showing a significant reduction in inappropriate prescribing [74, 75]. On the other hand, education only for healthcare professionals alone has been the least frequently effective intervention type, but still with 50% showing a significant reduction of inappropriate prescribing [75]. Understanding patients' and healthcare professionals' views and preferences in the management of potentially inappropriate medications is important to design future education interventions tailored for patients, GPs, and other healthcare professionals.

The effectiveness of educational interventions also varies across clinical settings, with interventions in hospital settings reported to be more effective compared to outpatient settings and long-term care facilities [75]. Although many educational initiatives have been shown to enhance patients' and healthcare professionals' awareness of inappropriate polypharmacy, more research is still needed to understand whether only raising awareness is enough to tackle the use and prescribing of potentially inappropriate medications [48, 73, 74, 76]. Nevertheless, training, education, and continued professional development have an important role in supporting the management of potentially inappropriate medications.

Strategies involving guidelines and decision support tools also improve the management of medications by GPs and other healthcare professionals [64, 65, 77, 78]. Furthermore, interprofessional collaboration between GPs and other healthcare professionals, such as pharmacists and nurses, can leverage their complementary skills and perspectives to identify and address inappropriate medications [22-28]. Future strategies and educational interventions aiming to optimise medication use and prescribing should involve a multidisciplinary approach and behaviour change techniques for patients and healthcare professionals.

3.3 Optimising medication use: Medication Review and Deprescribing

To optimise medications and provide the best care to patients, it is essential to incorporate medication reviews and deprescribing into the patients' regular care [7, 79-81]. Each one of these terms is defined below.

Medication Review

Medication review is a common approach to managing polypharmacy. A medication review is usually defined as a structured evaluation of a patient's medications, including identifying medication-related problems and making concrete suggestions for improvement [82, 83]. The aim of a medication review is to optimise medication use and improve health outcomes [82, 83]. Although some definitions for medication review exist, they are not universal. Usually, medication review involves a systematic assessment of the patient's medications, in which the indication for each medication, potential drug interactions, appropriateness, safety, effectiveness, and adherence are evaluated by a healthcare professional [82, 83]. However, due to the lack of a unique definition of medication review, healthcare providers may interpret this term in different ways [84, 85]. For instance, a study reported that when pharmacy and medical students were asked about the meaning of the term 'medication review', medical students focused on clinical aspects while pharmacy students focused on the patient experience [86]. Differences in the definitions and interpretations of medication review need to be taken into account when comparing interventions and research studies in the field of medication review [84].

The process of medication review can be led by a pharmacist or other healthcare professional, individually or within interdisciplinary teams [87]. Incorporating interprofessional collaboration and specific training on medication review has been shown to enhance the implementation of medication reviews in clinical practice [26, 28, 88, 89]. When healthcare professionals include medication review in the patient's regular care, they are promoting safer prescribing practices and enhancing their patients' quality of life. Indeed, implementing medication reviews in clinical settings has been associated with lower mortality rates and decreased use of potentially inappropriate medications [90]. However, more research is needed to identify ways to improve the collaboration among healthcare professionals involved in this process.

Medication reviews can also be followed by other strategies to manage medications. For instance, when medications that are no longer appropriate are identified during the medication review process, deprescribing should be considered [81, 84, 91].

Deprescribing

Deprescribing is commonly defined as the process of stopping or reducing inappropriate medications, supervised by a healthcare professional [7, 79, 92]. Deprescribing is crucial to

prevent inappropriate polypharmacy and its related adverse outcomes and unnecessary costs, reducing the risks associated with the use of multiple medications [79, 93]. Deprescribing specifically targets to reduce or stop medications whose risks outweigh the benefits and those that are no longer appropriate [79]. Both medication reviews and deprescribing aim to optimise medications and promote patients' health and quality of life, and both focus mainly on older adults with polypharmacy [81, 83, 94]. Nevertheless, although they share some similar goals, these strategies complement each other in optimising medication use and improving patient outcomes [81].

The research on deprescribing has been increasing in the last decades, but there are still gaps to improve its implementation in clinical practice. Indeed, studies have identified factors that can influence the implementation of deprescribing decisions in clinical practice [94, 95]. For instance, deprescribing outcomes seem to vary among different care settings, geographic location, and medication type [81, 94]. Medications like vitamins, minerals, antihistamines, analgesics, and proton pump inhibitors have been reported to be often considered for deprescribing [53, 94]. On the other hand, antipsychotics and antidepressants seem to have less success in being deprescribed, possibly because these drugs are usually prescribed by specialists [53, 94]. Most of the research on deprescribing focuses on GPs', pharmacists', and nurses' attitudes towards deprescribing, and these professionals may be hesitant to recommend deprescribe for drugs from a speciality that they do not know so much about [94, 96]. Nevertheless, it is still not clear which medications have the better deprescribing outcomes and it seems to depend on the setting in which deprescribing is implemented. For instance, while some studies have identified PPIs as medications with high success rates, other studies have reported them to be among the medication types with less successful deprescribing outcomes [94, 96]. Understanding which factors and how these differences affect the implementation of deprescribing decisions provides important information for the development of future interventions.

GPs, pharmacists, and other healthcare professionals have a crucial role in facilitating the implementation of deprescribing decisions and medication reviews. Not only by evaluating the patient's medications, but also by encouraging patients to be involved in the shared decision-making process of medication reviews and deprescribing, providing enough information and evidence to their patients regarding treatment options and risks and benefits, and also by monitoring their patients' health outcomes. So that patients can be actively involved in the

process, which in turn results in tailored interventions that consider patients' views and preferences.

3.4 Patients' Attitudes Towards Deprescribing and Medication Optimisation

Shared decision-making has a crucial role in deprescribing, and decisions about whether and how to stop or reduce medications should consider patients' views and preferences [13, 14]. In this context, it is important to understand patients' attitudes towards deprescribing.

To assess patients' willingness to have medication deprescribed, the revised Patients' Attitudes Towards Deprescribing (rPATD) questionnaire has been widely used [97]. Most patients report being willing to have their medication deprescribed if their doctor said it was possible [98, 99]. Nevertheless, their willingness may be not enough to reach successful deprescribing outcomes. It has been reported that often patients are not interested in having medications deprescribed after discussing deprescribing opportunities with their physicians [100, 101]. In addition, while an association between the willingness to have medications deprescribed assessed by the ePATD and deprescribing outcomes has been reported [102], there seems to be a discrepancy between patients' self-reported willingness and their behaviour in practice and clinical trials [103, 104]. Some studies have identified that the patients' reported willingness to have medication deprescribed is much higher than their willingness to actually change their medications [105]. In addition, the way in which patients have been inquired about their willingness to stop or reduce medications seems also to affect the rate of reported willingness to deprescribe. For instance, when the rPATD question *'If my doctor said it was possible, I would be willing to stop one or more of my regular medications'* is used, 84-88% of the patients have been reported to be willing to have medication deprescribed [99, 106]. However, when the rPATD question *'I would like to try stopping one of my medicines to see how I feel without it'* is used, this prevalence seems lower [107]. This discrepancy may be related to the fact that in the first question deprescribing was a physician's recommendation. Although associations between patients' reported attitudes towards deprescribing and actual behaviour in implementing deprescribing decisions have been reported, many patients are not willing to participate in deprescribing trials [102, 104]. There is still a lack of evidence on how the different ways of assessing patients' willingness to

deprescribe compare and what is the most accurate way to assess patients' willingness to have medications deprescribed.

Patients' attitudes towards deprescribing can influence both the suitability of deprescribing and their willingness to deprescribe [96]. For instance, some patient characteristics such as high satisfaction with medications, evidence available on the harm of taking too many medications, and good relationship with the GP seem to act as enablers to deprescribing [94, 98, 105, 108]. On the other hand, perceived health benefits from taking medications and fear of the return of symptoms have been identified as barriers to deprescribing [94, 98, 105, 108]. Enablers and barriers to deprescribing should be considered and addressed when designing deprescribing interventions.

Furthermore, understanding patients' attitudes towards deprescribing specific medication can facilitate deprescribing decisions. When there is more than a unique inappropriate medication, the deprescribing process can start with the medication(s) that the patient is more willing to stop or reduce [14, 79]. Of note, although many studies have explored the overall willingness of patients to have medication deprescribed, there is a lack of evidence on which specific medications patients would be more willing to have deprescribed and why.

Patients' preferences for their involvement in medication optimisation are highly individual [99, 105, 109]. While some patients seem to prefer to be engaged in deprescribing decisions, others would rather defer decisions regarding their medications to their physicians and prefer to have a less proactive role [109]. Although their preferences may vary, most patients report wanting to be involved in medication optimisation and other health-related decisions [13, 14, 110]. Furthermore, when undergoing through the process of deprescribing, patients may feel more vulnerable to the consequences of changes in their medications. To mitigate their fears and feelings of vulnerability, trust in their physician also plays a crucial role in the implementation of deprescribing decisions [13, 79, 111, 112]. Given the impact of shared decision-making and trust in the physician in deprescribing [13, 79, 111], understanding how patients feel about their current medications and building a trusting relationship between physicians and patients is crucial.

Understanding patients' preferences in deprescribing will help to design and implement tailored deprescribing interventions in clinical practice. Therefore, it is important that healthcare professionals encourage their patients to be involved in the process of medication

optimisation and deprescribing, addressing their concerns and promoting positive attitudes towards deprescribing. For that, it is essential that healthcare professionals take the time to educate their patients about the risks and benefits of medications, as well as about the rationale for their treatment or deprescribing recommendation. Promoting patient engagement in this process can empower patients to make informed decisions and actively participate in the deprescribing process. Furthermore, when patients are involved in the process of optimising medications, healthcare professionals are more likely to be able to collect information about all substances the patient is taking, not only the medications prescribed by the healthcare professionals themselves, but also non-prescription medications and dietary supplements that can be obtained over the counter, but still contribute with polypharmacy.

3.5 Optimising Medications Use: What About the Use of Dietary Supplements?

Older patients with polypharmacy do not only use prescription medications, but also over-the-counter substances, such as dietary supplements [15, 94]. Therefore, it is crucial not only to focus on prescription drugs when exploring ways to optimise medication use, but also to consider the use of dietary supplements.

The use of dietary supplements is widespread, and it has been increasing, especially among older adults [15-17, 94]. Dietary supplements are often associated with a healthier life and are perceived as being risk-free [17, 20, 21, 113]. Indeed, dietary supplements are important for vulnerable groups at risk for nutritional deficiency, but there is no evidence of benefits from the overuse of dietary supplements without a clear indication [114, 115]. Given the low-risk perception towards dietary supplements and their easy accessibility, many patients do not disclose their use of supplements to their GPs and other healthcare providers [20, 21, 116, 117]. For a successful implementation of medication reviews, however, GPs should be aware of all the medications used, including supplements.

Indeed, dietary supplements may lead to adverse events, drug interactions, and hospital admissions, especially in older adults in which drug metabolism is compromised [118-120]. Furthermore, the regulations and studies on dietary supplements are not as strict as for prescription medications, making the safety and composition of dietary supplements also questionable [121]. For instance, the composition of dietary supplements is not standardized worldwide, and many supplements do not comply with national regulations nor are not strictly

monitored [122, 123]. Therefore, dietary supplements should be used with caution, with guidance and monitoring from healthcare professionals to ensure a safe and effective use of supplements.

Dietary supplements containing herbs seem to present more risk for interactions with drugs than vitamins and minerals [124]. St John's Wort, ginkgo biloba, garlic, and ginseng are among the dietary supplements with higher risk for interactions with drugs, while warfarin is among the prescription medications with higher risk for interactions with dietary supplements [124-126]. Although some supplements do not pose a high risk for adverse effects and drug interactions, dietary supplements are also often used when there is a lack of indication [53, 117, 127, 128]. When an indication for the use is not present, these supplements are only contributing to patients' pill burden and present an unnecessary financial burden [20, 129, 130]. Besides that, with the intense advertisements on the supposed benefits of dietary supplements and given the common misleading perception that "natural is always better", some patients are stopping taking their prescription medication to replace them with dietary supplements [131]. Dietary supplements contribute to polypharmacy and might be easy targets for deprescribing [20, 94]. However, there is a lack of studies focusing on provider and patient attitudes towards deprescribing potentially inappropriate supplements [20, 132].

To better implement deprescribing and medication reviews, healthcare providers should consider all substances used by the patients [117, 133]. When healthcare providers are unaware of patients' use of dietary supplements, they may not associate patients' symptoms with adverse effects caused by supplements. Instead, they may approach these symptoms as a new condition, starting a new drug to treat it, and thereby initiating a prescribing cascade and contributing to polypharmacy [1, 134]. To safely use dietary supplements, patients should seek guidance from healthcare providers to make informed choices tailored to their individual needs. However, there is limited information on how often older adults disclose their supplement use to their healthcare providers [20, 116, 117].

Although no deprescribing studies are focusing on dietary supplements specifically, many providers make their deprescribing recommendations targeting medications with questionable efficacy, such as dietary supplements [53, 94, 135]. However, these studies are focused on the overall willingness to deprescribe, and while some deprescribing studies include dietary supplements among the patients' medications, others do not consider these substances when

exploring deprescribing decisions [136]. Therefore, more research is needed to understand patients' and healthcare providers' attitudes towards deprescribing dietary supplements.

3.6 Pharmacists' Roles and Preferences in Medication Optimisation and Interprofessional Collaboration in the Context of Deprescribing

Collaboration between healthcare professionals from different backgrounds seems to enhance the process of medication optimisation [110]. For instance, multidisciplinary interventions including pharmacists have been shown to facilitate the implementation of deprescribing and medication reviews [22-28, 94]. Indeed, the roles and responsibilities of pharmacists in patient care have been expanding in several countries [137]. However, there is little evidence about pharmacists' preferences for interprofessional collaboration for medication optimisation in the Swiss context.

Pharmacists are healthcare professionals who are in constant contact with patients, they have excellent knowledge about medications, and therefore they are equipped to play a key role in deprescribing and medication optimisation [28, 138-140]. Indeed, multidisciplinary interventions involving pharmacists had a positive impact on deprescribing in long-term care facilities [22-25] and facilitated deprescribing in primary care settings [26-28, 141, 142]. Therefore, the collaboration between pharmacists and GPs is promising for the conduct of medication optimisation efforts [26, 28]. Understanding pharmacists' wishes for interprofessional collaboration in optimising medications is crucial to enhancing their collaboration with physicians in the context of deprescribing and medication review.

In these interprofessional collaborations, the pharmacists' role is often described as making deprescribing recommendations to physicians and proposing treatment plan modifications. Physicians and pharmacists seem to have a good agreement on the medications they target for deprescribing, suggesting that both professionals could benefit from shared decision-making when implementing deprescribing decisions [143]. A study in nursing homes conducted in the French-speaking part of Switzerland reported that pharmacists were more willing to put deprescribing into practice, while nurses and physicians were more cautious [144]. However, studies in other countries found that pharmacists were less willing to deprescribe medications compared to physicians [143, 145]. Such variations can be related

to the different roles and responsibilities of pharmacists in different working settings and across different countries.

Despite the promising involvement of pharmacists in medication optimisation, there are also many barriers to effective interprofessional collaboration in this context [143, 145, 146]. For instance, pharmacists' fear of making deprescribing recommendations to physicians and lack of access to patients' information have been described as barriers to effective interprofessional collaboration in real-life settings [143, 145-147]. Indeed, having access to complete patient information not only allows pharmacists to make better-informed recommendations based on patient health, but also to share these recommendations more efficiently [110]. Furthermore, interprofessional training on polypharmacy and deprescribing seems to improve the practice and collaboration of healthcare professionals in optimising medications [135]. Besides pharmacist-physician collaboration, efforts are still needed to enhance the relationship between pharmacists and patients, including guidelines and training for pharmacists on how to involve patients in the deprescribing process [148]. Understanding the challenges that pharmacists face in their daily work in the context of interprofessional collaboration for medication optimisation, as well as their preferences and wishes to improve their practice is crucial for the development of future deprescribing interventions.

3.7 Recruitment of Healthcare Professionals to Participate in Research Projects

Research in the field of healthcare and medicine is important to support evidence-based healthcare practices. To carry out high-quality research that involves human beings, it is crucial to plan the recruitment of participants in an effective way [149]. The recruitment of participants for a research project is time-consuming and demanding, and when study participants are healthcare professionals, it poses unique challenges [149, 150].

Healthcare professionals usually have demanding schedules and responsibilities in clinical practice, with very little time available to participate in research studies. Patient appointments, administrative tasks, and continuing education requirements are usually competing priorities of physicians, pharmacists, and other healthcare professionals. As a result, little time is left to engage in research activities, especially if there are no incentives or clear benefits for their participation. Providing clear information on time commitments, support, and resources

available may facilitate the time management of healthcare professionals and shed light on the feasibility of their participation [150-152].

The lack of awareness or interest of healthcare professionals in research may also be a barrier to recruiting these professionals to participate in research studies [149, 150, 153]. Some healthcare professionals may be not so familiar with research and clinical studies and therefore may be not completely aware of the importance of their participation in research studies. Promoting educational and training opportunities is crucial for raising healthcare professionals' awareness and interest in participating in research. Also, involving healthcare professionals in the study by asking for feedback, considering their insights, and disseminating the study results can create a sense of "ownership", which can encourage their participation. Another potential barrier to the recruitment of healthcare professionals is the lack of incentives to participate in research studies [149, 150, 153]. Training, acknowledgement, and recognition are necessary to promote intrinsic motivations, such as the desire to improve clinical research. Financial compensation, recognition of credits, or the opportunity to be involved in the manuscript resulting from the study can also encourage the participation of healthcare professionals.

Self-administered questionnaires are a common and financially feasible way to collect data for research studies. Nevertheless, low response rates may reduce the effective sample size and induce bias [153]. Finding ways to encourage healthcare professionals to respond to survey studies will therefore enhance the quality of future research. Not only raising awareness and interest, providing necessary support and resources, incentives, and recognition, but also simply strategies such as personalised invitations addressing the healthcare professionals by their names, and clearly explaining the significance and impact of the study are approaches that can enhance the recruitment and participation of healthcare professionals in survey studies and research projects.

4. Thesis Hypotheses and Aim

This PhD thesis is a cumulative work of a set of publications aiming to investigate patients' and healthcare professionals' behaviours and views on different aspects related to optimising medication use in primary care, including the use of dietary supplements. The specific hypothesis and aims of this thesis are presented in four original research manuscripts and one study protocol:

4.1 Article 1. Inappropriate proton-pump inhibitor prescribing in primary care – an observational study with quality circles

Hypothesis: Studies have shown that the prevalence of potentially inappropriate proton pump inhibitors (PPI) is high. I hypothesized that in our sample of Swiss primary care patients, many PPI prescriptions would also be classified as potentially inappropriate. In addition, I hypothesized that only raising GPs' awareness of potentially inappropriate PPI prescribing is not enough to successfully implement deprescribing of such inappropriate PPIs prescriptions in primary care.

Aim: To investigate the prevalence of potentially inappropriate PPI prescribing in a sample of patients in Swiss primary care settings and to evaluate how GPs manage patients with potentially inappropriate PPI prescribing after participating in an awareness campaign in a quality circle (meetings in which GPs reflect together to improve their care practice).

4.2 Article 2. Understanding older patients' willingness to have medications deprescribed in primary care: a protocol for a cross-sectional survey study in nine European countries

Hypothesis: Understanding patients' attitudes towards deprescribing at the individual and country levels may reveal effective ways to involve older adults in decisions about medications and help implement deprescribing in primary care settings. I hypothesized that patient attitudes towards deprescribing are different across countries.

Aim: To investigate older adults' perceptions and views on deprescribing in different European countries. Specifically, this study protocol aimed to provide a detailed plan outlining the objectives, design, methodology, and procedures for conducting Articles 2.1 and 3.

4.3 Article 2.1. Understanding older patients' attitudes towards deprescribing in primary care: A cross-sectional survey study in 14 countries

Hypothesis: When patients are asked about their willingness to have their medications deprescribed, most of them report being willing to stop or reduce medications. However, little is known about their willingness to have specific medications deprescribed from their own medication list, and how this willingness varies across countries. I hypothesized that patients' willingness to have medications deprescribed varies across countries and with patients' characteristics. In addition, I hypothesized that patients are more willing to have medications deprescribed because of their side effects.

Aim: To explore patients' attitudes towards deprescribing specific medications in 14 countries, which medications they are most willing to have deprescribed and the reasons why, and which patients' factors are associated with patients' willingness to have medications deprescribed.

4.4 Article 3. Exploring views of older adults with polypharmacy on their use of dietary supplements and their willingness towards deprescribing those: Results from an observational survey study conducted in Swiss primary care settings

Hypothesis: To optimise medication use, GPs ideally are aware of all the substances their patients take, including dietary supplements. I hypothesized that GPs are not aware of all dietary supplements used by their patients. I also hypothesized that the willingness of patients to have dietary supplements deprescribed is low, while GPs have a higher willingness to deprescribe dietary supplements.

Aim: To investigate the use of dietary supplements by older patients with polypharmacy, the rate at which they disclose this use to their GPs, and to compare patients' and GPs' attitudes towards discontinuing dietary supplements.

4.5 Article 4. Pharmacists' attitudes towards interprofessional collaboration to optimise medication use in older patients in Switzerland: A survey study

Hypothesis: The involvement of pharmacists is crucial for making and implementing deprescribing decisions and medication reviews in primary care settings. I hypothesized that pharmacists are willing to make deprescribing recommendations and that patients'

cardiovascular risk and dependency in activities of daily living are associated with pharmacists' deprescribing recommendations. I also hypothesized that pharmacists would like to be more involved with physicians in the process of medication reviews.

Aim: To explore pharmacists' perspectives on medication optimisation and deprescribing, as well as their preferences for interprofessional collaboration regarding medication optimisation within primary care settings.

5. Results

5.1 Article 1. Inappropriate proton-pump inhibitor prescribing in primary care – an observational study with quality circles

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Inappropriate proton-pump inhibitor prescribing in primary care – an observational study with quality circles

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Summary

INTRODUCTION: Proton-pump inhibitors (PPIs) should be deprescribed when an indication is lacking or the dose is too high. Academic and media reports have tried to raise awareness and thereby reduce the inappropriate prescribing of PPIs. However, pharmacoepidemiologic studies have shown an unchanged frequency of such inappropriate prescribing over time. Little is known about whether or how general practitioners (GPs) adapt their prescribing practices once their awareness of inappropriate PPI prescribing has been raised.

OBJECTIVE: We aimed to investigate the prevalence of potentially inappropriate PPI prescribing (too high dose or no indication) in a consecutive sample of patients in Swiss primary care settings. Our goal was then to evaluate how GPs managed the patients with potentially inappropriate PPI prescribing over 12 months after flagging these patients.

METHODS: In this observational study, 11 GPs from the canton of Bern in Switzerland used their medical records to identify 20 patients who had been prescribed a PPI for ≥8 weeks and flagged potentially inappropriate PPI prescribing in their records. After 12 months, we asked the same GPs whether the PPI prescriptions of those patients had changed and, if so, how.

RESULTS: Of 1,376 patients consecutively screened, 206 (15%) had been prescribed a PPI for ≥8 weeks. Of these 206 patients, 85 (41%) had a potentially inappropriate PPI prescription. Of these 85 patients, 55 (65%) had no indication for PPI, and 30 (35%) had a too-high dose. After one year, only 29 (35%) of the 84 flagged potentially inappropriate PPIs were stopped or reduced. The most frequently mentioned reasons that deprescribing was not possible were a lack of discussion with the patient (no contact or no time), the presence of symptoms requiring the PPI, or the unwillingness of the patient to deprescribe.

CONCLUSION: In the Swiss primary care setting, the rate of potentially inappropriate PPI prescribing is high. Having GPs flag potentially inappropriate PPI prescribing did not result in PPI deprescribing in most patients over 12 months. Our findings suggest that more personalised and targeted interventions are necessary to successfully implement the deprescribing of potentially inappropriate PPIs. We see the need to co-design interventions with patients and providers and test behavioural change techniques to enable the deprescribing of inappropriate PPIs.

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Introduction

Proton-pump inhibitors (PPIs) are among the most widely prescribed drug classes in the world [1–3]. A study in Germany found that around 15% of women and 13% of men received a PPI prescription in 2018 [3]. In Switzerland, the annual incidence of PPI prescriptions in adults was 23% in 2017 [4]. PPIs are usually prescribed for the treatment of gastric acid-related diseases such as gastroesophageal reflux disease, dyspepsia, reflux oesophagitis, peptic ulcer disease, hypersecretory conditions and *Helicobacter pylori* bacterial infections [5–7]. The long-term use of PPIs has been associated with an increased risk of hypocalcaemia, hypomagnesaemia, fractures, *Clostridium difficile* infections, pneumonia, vitamin B12 malabsorption and gastric pre-malignant lesions [8–13]. The inappropriate prescribing of PPIs leads to unnecessary costs and can be a burden to the healthcare system [1, 14–16]. Studies have shown that around 40–60% of patients who use PPIs have an inappropriate indication [5, 17–19]. The inappropriateness of PPI prescriptions can be verified by the dosage and the reason for use. Inappropriate prescribing of PPIs is often due to off-label indications and prophylaxis, such as corticosteroid and anticoagulant therapy to prevent gastrointestinal bleeding, and stress ulcer prophylaxis in non-intensive care units [5, 20–23]. Many patients during hospital stays receive a PPI prescription that is not discontinued thereafter: although the initial indication is no longer present, the PPI use is maintained [5].

The long-term use of PPIs is rarely necessary, and deprescribing is usually recommended after four to eight weeks [24]. Deprescribing is commonly defined as "the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes" [25]. Tapering medications is also part of deprescribing [24]. PPI de-

prescribing can be carried out by stopping, reducing the dosage or switching to "on-demand" use [24, 26]. Safely deprescribing PPIs can lead to reduced inappropriate polypharmacy while increasing the patient's overall health status and reducing health care costs [24]. Although academic and media reports have tried to raise awareness and reduce the inappropriate prescription of PPIs, the number of PPI prescriptions has increased in recent years [4, 24, 27–31]. For instance, in 2017, around 23% of Swiss people had at least one PPI prescribed, compared to 20% in 2012 [4].

The Smarter Medicine movement [30] in Switzerland recommends that at least once per year, prescribers should attempt to stop or reduce the dosage of PPIs and evaluate whether at least one indication for use is still present [30]. This movement also recommends that the continuation of PPI use should be discussed with patients, considering the adverse effects and benefits [30]. PPI supplies can only be obtained over the counter in Switzerland for a maximum of two weeks (packages with a maximum of 14 tablets), and long-term prescriptions can only be made by physicians. General practitioners (GPs) usually have a long-term relationship with their patients, gathering knowledge of their medical history, personal characteristics and preferences, thus playing a crucial role in the optimisation of PPI use. Knowing how potentially inappropriate PPI prescriptions evolve over time in primary care settings will help to better understand how they are managed by GPs. We also need to better understand how PPI prescribing evolves in patients after their GPs are part of an awareness campaign. In turn, this will help to tailor deprescribing interventions and optimise the prescribing of PPIs.

Objectives

We aimed to investigate the prevalence of potentially inappropriate PPI prescriptions in a sample of primary care patients in Switzerland. We also evaluated how GPs managed those patients over 12 months, with the only new strategy implemented being flagging these patients as having potentially inappropriate PPI prescribing. Additionally, we explored which patient characteristics were associated with inappropriate PPI prescriptions and the success of deprescribing.

Methods

Study design and participants

This observational study was carried out in the canton of Bern in Switzerland. A group of 11 GPs of the same quality circle (meetings in which a small group of GPs reflect together to improve their care practice [32]) was invited to participate. This quality circle takes place around 10 times a year, with each meeting lasting 1.5 hours. Only GPs, and no other health care providers, participated in this quality circle. All the GPs participating in the study were actively practising in the canton of Bern. This quality circle meeting aimed to raise the GPs' awareness of optimising PPI prescriptions by flagging patients as having a potentially inappropriate PPI prescription. They had not received any guidelines on how to reduce inappropriate PPI prescribing. We used a convenience sampling strategy, in which GPs were asked to use their electronic medical records to screen all patients they had seen before the baseline (June 1, 2021) until they found the first 20 with an active PPI prescription for ≥8 weeks. This consecutive sampling method was chosen to reduce the risk of selection bias. GPs did not receive any compensation for their participation in the study.

The study did not fall within the scope of Swiss human research law because it was initially designed as a quality improvement study. Therefore, a waiver of non-responsibility was obtained from the Ethics Committee of the Canton of Bern (BASEC-Nr: Req-2021-01213).

The inclusion criteria for GPs were attending the quality circle and agreeing in participating in the study. The selection criteria for patients were having been prescribed a PPI commercially available in Switzerland for ≥8 weeks before June 1, 2021, and being patients of one of the 11 GPs participating in the quality circle in which the study took place.

Data collection and data management

In the first round of data collection at the baseline, the participating GPs assessed their patients' electronic medical records to identify the first 20 who had an active PPI prescription for ≥8 weeks. They determined the length of PPI prescription by assessing repeated prescriptions in their records. The GPs were asked to report patients' age, gender, polypharmacy (taking ≥5 medications), name of the PPI's active substance, daily dose and indication for use. The indication for the PPI prescription was reported by GPs providing information on the following categories to the study team at the baseline: dose too high, no indication, risk of gastrointestinal bleeding (steroids plus anticoagulants; long-term use of non-steroidal anti-inflammatory drugs [NSAIDs]), peptic ulcer or gastroesophageal reflux disease. GPs also had the opportunity to provide additional information as free text. They were responsible for identifying potentially inappropriate PPI prescriptions based on their clinical judgement and the quality circle discussions. Those patients flagged as potentially having an inappropriate PPI prescription (dose too high or no indication) were followed up for one year, and all others were not. In addition, the GPs reported how many patients they had screened to find the first 20 with a PPI prescribed.

In the second round of data collection a year later, the GPs were asked to use their electronic medical records to report the updated status of PPI prescriptions of the same patients who had an inappropriate PPI prescription at baseline and report eventual changes in these prescriptions (e.g., tentative deprescribing of the PPI, return of symptoms, changes in the PPI dosage, whether deprescribing was successful and the reason). They also provided information on whether any attempt to deprescribe the PPI had been followed by a restart of the drug. Cases in which restarting the dose was necessary, but at a reduced dose compared to the baseline, were also considered successful deprescribing. To allow assessing the reasons why deprescribing was not possible, GPs used the information in their patients' electronic medical records to report this information as free text. They also used these records to determine whether the PPI prescription was still active at the second screening.

In both rounds of data collection, the GPs reported the information using an Excel spreadsheet provided by the research team. Data from the baseline and after one year were gathered and merged using the patient's identification number. We used age as a whole number and, to standardise the doses of different PPIs, we used pantoprazole as a reference drug. For that, we divided the actual PPI dose by its respective defined daily dose value according to the World Health Organization [33] to calculate a standardisation factor. We then multiplied this standardisation factor for each PPI by the defined daily dose of pantoprazole to obtain the standardised dose of each PPI relative to pantoprazole.

Statistical analysis

Baseline characteristics are presented as proportion for categorical variables and median and interquartile range (IQR) for continuous variables. The total number of patients that GPs had to screen to find the first 20 with a PPI prescription is reported as mean and range. We calculated absolute standardised differences (ASDs) to assess the balance of clinical and sociodemographic characteristics between those with an inappropriate PPI prescription and those with an appropriate prescription. An ASD of 0 is usually interpreted as a perfect balance between two groups, whereas an ASD of greater than 0.2 is considered an indication of meaningful imbalance [34]. We used multilevel logistic regression to analyse the association between patient characteristics and the frequency of deprescribing. The multi-level logistic regression was adjusted for clustering effects at the GP level (intracluster correlation coefficient [ICC] <0.01). We chose this approach considering that patients of the same GP were likely to be more similar to each other than patients of different GPs. Using a multilevel logistic regression clustered at the GP level can account for clustering effects even with a low ICC. The results remained similar in the sensitivity analysis using multivariable logistic regression. The co-variable selection strategy was based on clinical rationale. We chose the method of complete case analysis for dealing with missing data; therefore, the one patient lost to follow-up was excluded from the analyses. The most common inappropriate indications for PPI and the reasons that deprescribing was not successful were extracted from the free text, coded into themes, and described in numbers and percentages. Patients who had the PPI re-prescribed at a lower dose were considered successful deprescribing. Analyses were performed with Stata 16.1 (StataCorp, College Station, TX, USA), and R version 1.3.1093 was used for the alluvial diagram. A two-sided p-value of 0.05 was considered statistically significant.

Results

In our consecutive sample strategy, GPs had to screen 125 (range: 55 to 224) patients on average to identify the 20 who had a PPI prescription for ≥8 weeks. This means that on average, 15% of the patients had a PPI prescription.Of the participating GPs, five were women, and six were men. All GPs were practising in the canton of Bern in Switzerland. In total, the GPs identified 206 patients who had been prescribed a PPI at the baseline. Ten GPs recruited 20 patients each, and one GP recruited six patients. Of these, 85 patients had a potentially inappropriate PPI prescription and qualified for the one-year follow-up. A slight difference was found in the gender distribution between those with a potentially inappropriate PPI and those with an appropriate prescription (ASD = 0.201). We found no statistically significant difference in the other clinical or sociodemographic characteristics between patients with a potentially inappropriate PPI prescription and those with an appropriate prescription (table 1). We used the CONSORT flow diagram [35] to show the screening and recruitment of participants (figure 1). During the one-year follow-up, one patient died and was thus excluded from the analysis (figure 1). Data on 84 patients were available for the follow-up analysis. At the baseline, of the 206 patients, 109 (53%) were women, the median age was 70 (IQR 59–77) years, 147 (71.4%) had polypharmacy and the median PPI daily dose was 40 mg (IQR 20–40; table 1). The most frequent prescriptions were 138 (67%) of pantoprazole, followed by 30 (15%) of esomeprazole and 22 (11%) of omeprazole.

Regarding the indication for using a PPI, of the 206 patients, 85 (41%) had a potentially inappropriate PPI prescription (55 had no indication for PPI, and 30 had a too-high dose), 82 (40%) had gastroesophageal reflux disease and 22 (11%) had a risk of gastrointestinal bleeding (table 2). In the free text, the most frequently mentioned inappropriate PPI indications were gastritis (n = 13) and the short use of NSAIDs (n = 11), anticoagulants (n = 9) and corticosteroids (n = 7). Figure 2 shows how the inappropriate PPI prescribing progressed over one year. The GPs attempted to stop the PPI for 21 patients, reduce the dose for 16 and increase the dose for one. They reported stopping and then re-prescribing the PPI for 8 patients. During the one-year follow-up, GPs did not change the inap-

Table 1:
Number (percentage) or median (interquartile range) of participants' characteristics according to the appropriateness of prescription of proton-pump inhibitors at baseline. Categorical variables: number (percentage). Continuous variables: median (interquartile range).

	Total	Inappropriate*	Appropriate	Absolute standardised difference **
	n = 206 (100%)	n = 85 (41.3%)	n = 121 (58.7%)	
Women	109 (52.9%)	50 (58.8%)	59 (48.8%)	0.201
Age at baseline	70 (18.0)	71 (20.0)	69 (16.0)	0.163
Polypharmacy (≥5 medications)	147 (71.4%)	62 (71.8%)	85 (71.1%)	0.015
Daily dose PPI in mg***	40 (20.0)	40 (20.0)	26.71 (20.0)	0.136

* Inappropriate PPI due to lack of indication or dose too high according to GPs' classification. 0 missing.

** An absolute standardised difference of 0 indicates a perfect balance between two groups, whereas an absolute standardised difference of greater than 0.2 is typically considered indicative of meaningful imbalance.

*** PPI dose was standardised using pantoprazole as a reference drug.

propriate PPI prescription for 55 (65%) patients, whereas deprescribing was successful for 29 (35%) patients. The most common reason that deprescribing an inappropriate PPI was not successful among those 55 patients was a lack of discussion with the patient (23 cases; either because the patient did not come back for another consultation [n = 3] or because the GP did not have time to address the PPI use during the consultation). Other reasons were the PPI becoming indicated over time (n = 8); the presence of symptoms or conditions such as anaemia, nausea, stomach pain and gastritis (n = 6); the unwillingness of the patient to stop (n = 5); hospital or other health care provider recommendation (n = 2) and the return of the patient's symptoms (n = 1; table 3). Associations between patient characteristics (e.g., age, gender, PPI dose), GP gender, and the success of deprescribing are shown in table 4. The success of deprescribing was associated with neither GP gender (Odds Ratio female = 0.68, 95% CI 0.27 to 1. 68) nor patient characteristics (table 4). No statistical evidence existed for ICC at the GP level (ICC <0.01) in our multi-level logistic regression. The lack of correlation may be due to the small sample size.

Discussion

In our observational study in primary care settings in Switzerland, 11 GPs consecutively selected 206 patients with a PPI prescription for ≥8 weeks and identified 85 (41%) of these as inappropriate. Of these 85 patients, 26% (55) had no indication, and 15% (30) had a dose too high. Instructing GPs to flag patients with a potentially inappropriate PPI prescription in their electronic medical record resulted in only 35% of these potentially inappropriate prescriptions being discontinued or reduced to a lower dose. In this setup, we found that raising awareness by flagging patients was not enough to improve the appropriateness of PPI use.

The number of inappropriate PPI prescriptions in our study is in line with the results of other studies that found the

Figure 1: Flow diagram: screening and recruitment of patients.

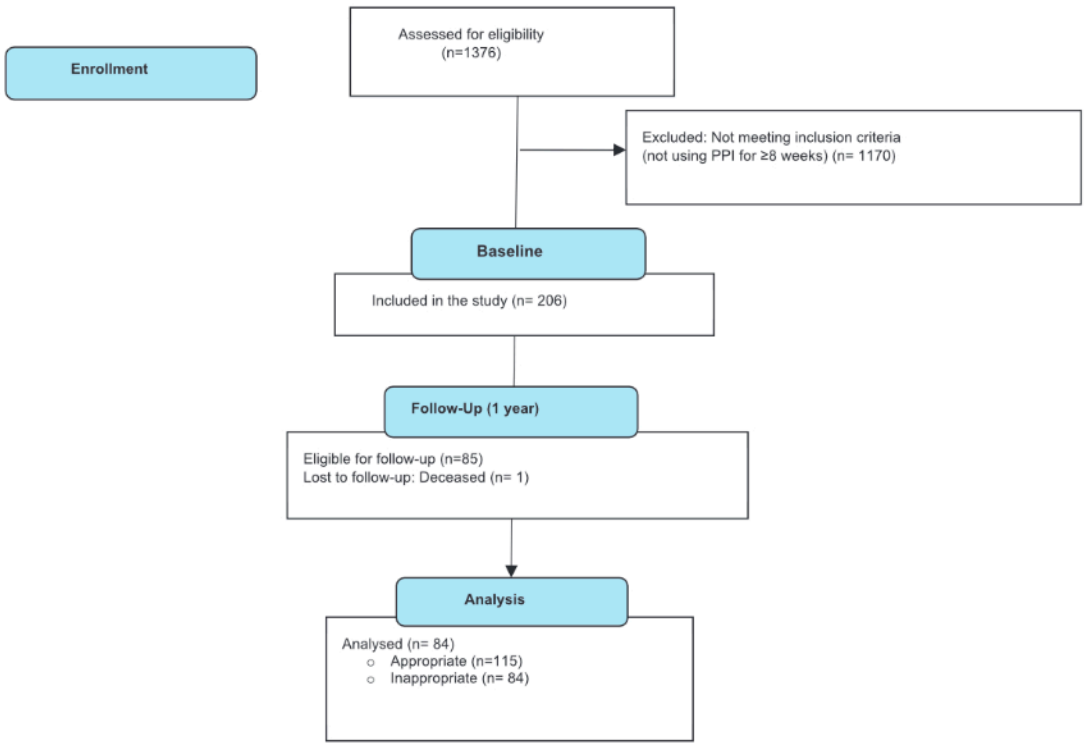

Table 2:
Numbers and percentages of proton-pump inhibitor indications at baseline.

Indication	Number (percentage) of patients
No indication	55 (26.7%)
Dose too high	30 (14.6%)
Gastroesophageal reflux disease	82 (39.8%)
Peptic ulcer	7 (3.4%)
Risk of gastrointestinal bleeding	22 (10.7%)
Gastroesophageal reflux disease and peptic ulcer	1 (0.5%)
Gastroesophageal reflux disease and risk of gastrointestinal bleeding	6 (2.9%)
Peptic ulcer and risk of gastrointestinal bleeding	3 (1.5%)
Total	206 (100.0%)

presence of inappropriate PPI prescribing between 35% and 63% [36–40]. Inappropriate PPI prescribing increased in Switzerland from 13.9% in 2012 to 28% in 2017 [4], and our study indicates that this number might be even higher. Other studies have also reported the lack of an appropriate indication as one of the most common reasons for the potentially inappropriate prescribing of PPIs [37, 39, 41]. In our study, according to GPs, doses were too high for 30 (15%) of the 206 patients with a PPI prescription, similar to a recent study in Iceland, in which 21% of the patients remained in higher-dose treatment after one year [42]. PPIs should be administrated using the lowest dose and for the shortest duration possible [43]. Only a few studies have investigated the appropriateness of PPIs regarding too-high doses, and recommendations are lacking on PPI dose reduction [4, 22]. Inappropriate indications for PPIs have been related to the lack of discontinuation after hospital discharge and automatic renewal of PPI pre-

Figure 2: Alluvial diagram illustrating the participant flow according to proton-pump inhibitor prescription and successful deprescribing (n = 84).

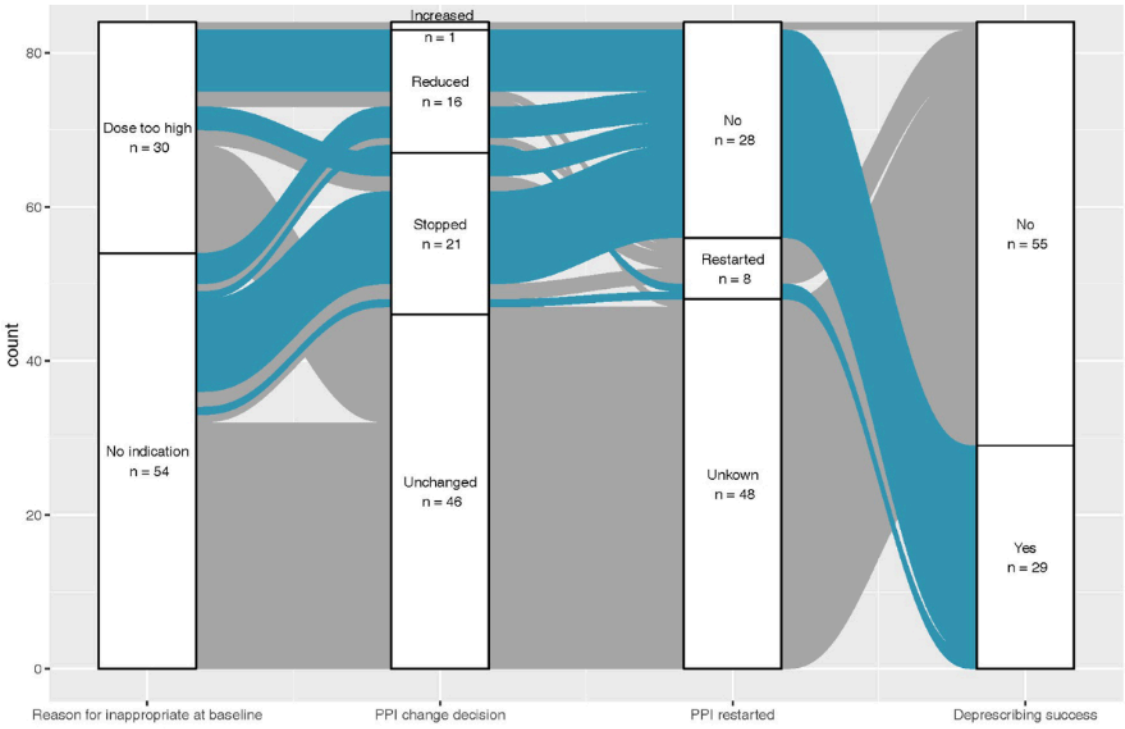

Table 3:
Most common reasons that deprescribing proton-pump inhibitors was not successful in patients with an inappropriate proton-pump inhibitor prescription at baseline.

Reason	Number of patients
It was not discussed yet	23 (42%)
Not specified	10 (18%)
Indication changed to appropriate	8 (15%)
Patient was symptomatic*	6 (11%)
Patient did not want to stop	5 (9%)
Hospital or other health care provider recommendation	2 (4%)
Recurrence of symptoms	1 (2%)
Total	55 (100%)

* Patient had symptoms and conditions such as anaemia, nausea, stomach pain and gastritis.

Table 4:
Association between patient characteristics and successful deprescribing of proton-pump inhibitors using a multi-level logistic regression adjusted for clustering effects at GP level. (n = 84; one patient was excluded from the analysis due to loss to follow-up.)

	Crude Odds Ratio (95% CI)	P-value	Adjusted* Odds Ratio (95% CI)	P-value
Age (by 10-year increase)	1.07 (0.78 to 1.47)	0.665	1.28 (0.89 to 1.90)	0.212
Female patient (vs male)	0.66 (0.27 to 1.64)	0373	0.50 (0.19 to 1.34)	0.170
Polypharmacy ≥5 medications (vs no polypharmacy)	0.65 (0.24 to 1.72)	0.385	0.52 (0.16 to 1.70)	0.276
Daily dose PPI in mg (by 1 mg increase) **	1.00 (0.97 to 1.02)	0.605	1.00 (0.97 to 1.02)	0.886
Female GP (vs male)	0.68 (0.27 to 1.68)	0.938	0.60 (0.23 to 1.57)	0.297

* Multi-level logistic regression adjusted for GP cluster as random effect and covariates in the table.

** Daily PPI doses were standardised using pantoprazole as a reference drug.

scriptions without adequate appraisal [19, 43]. Other common reasons for inappropriate prescriptions in our study were gastritis (n = 13) and the short use of NSAIDs (n = 11), anticoagulants (n = 9) and corticosteroids (n = 7), in line with other studies [5, 20-23, 44–47]. Additionally, PPI indications for bariatric surgery, chemotherapy and oesophageal varices were mentioned, although these do not qualify for an appropriate long-term PPI prescription [23, 41]. Women were slightly more likely than men to have an inappropriate PPI prescription (table 1). Female gender has been associated with the use of potentially inappropriate medication in other studies [48–50]. We found no significant association between age, gender, polypharmacy or PPI dose and inappropriate prescribing of PPIs, although other studies have shown that older age and polypharmacy were associated with inappropriate PPI prescription [20, 51, 52]. The lack of these associations could be due to the small number of participants in this study.

In this study, the GPs were simply asked to screen patients who were taking a PPI and flag those who had a potentially inappropriate prescription, not receiving any intervention, although they had a raised awareness of the topic. After the one-year follow-up, inappropriate PPIs were successfully deprescribed in 29 (35%) of the 84 patients with a potentially inappropriate PPI prescription. The GPs did not receive any information on how to involve patients or carry out deprescribing interventions. Other studies have found that involving the patient in the deprescribing attempt is important to reach a higher success rate [53] and that the implementation of behaviour change techniques (BCT) may influence deprescribing outcomes [54, 55]. If patients had been involved in the process and an intervention had focused on BCT, the success rate of deprescribing PPIs may have been higher. Furthermore, our results may have been different if the GPs had received instructions on how to deprescribe PPIs. Current guidelines on deprescribing PPIs suggest incorporating tapering as a crucial part of the process. First reducing the PPI to the lowest effective dose has been recommended, followed by the management of the patient's symptoms, and only then discontinuing the PPI [24]. In our study, the most mentioned reason that deprescribing an inappropriate PPI was not successful was a lack of discussion with the patient, mostly because the GP did not have time to address the PPI use during the consultation. An unpublished pilot survey by Streit et al. from September to October 2021 with 88 GPs from the German part of Switzerland found that 48 (55%) reported seeing patients with inappropriate PPI prescriptions often or very often but lacked the time to deprescribe PPIs in their everyday clinical practice. In that study, 58% of GPs stated that they would like a guideline on PPI deprescribing, and 26% wanted information material on this topic.

Strengths and limitations

To our knowledge, this is the first study to investigate the prescribing of potentially inappropriate PPIs in Swiss primary care settings using data directly reported by GPs. This overcomes the problems of epidemiological studies where the indication of a PPI is unknown or not recorded or the duration of the prescription might not be clear. A random sample would not have been feasible in our study. Therefore, we chose a simple but feasible consecutive sampling approach to recruit patients with a PPI prescription for ≥8 weeks. The consecutive sampling approach has the advantage of reducing selection bias, limiting the chances of GPs choosing which patients they would like to follow. GPs were responsible for identifying potentially inappropriate PPI prescriptions and too-high doses on their own. This comes with the limitation that the definitions of too-high doses were not standardised and GPs may have interpreted the indications differently. However, this simple self-definition also reflects the usual care in the GPs' practices. The simplicity of our definition of appropriate and inappropriate PPIs allowed for GPs to quickly browse through their lists of recently consulted patients, but we acknowledge that more sophisticated definitions of inappropriate PPIs exist. This study has a pilot character, with a small sample of 200 patients using PPIs for ≥8 weeks. However, the findings are comparable to larger pharmacoepidemiologic studies that show that inappropriate prescribing is frequent. We only collected information on selected variables; therefore, in the regression analysis, unmeasured confounding cannot be ruled out. Although most GPs throughout Switzerland regularly participate in quality circles, our findings cannot be generalised to other Swiss cantons or other countries because the GPs were part of a specific quality circle in the canton of Bern.

Conclusion

In this small Swiss primary care sample of consecutive patients prescribed a PPI for ≥8 weeks, inappropriate prescription of PPIs was common. Nearly half of the patients taking a PPI had a potentially inappropriate prescription at the baseline. Only raising awareness in GPs by flagging inappropriate PPI prescribing did not result in PPI deprescribing in most patients over 12 months. Inappropriate PPI prescribing is an important issue in Swiss health care that must be addressed and needs more attention from GPs. Further interventions based on BCT are needed to investigate how to successfully deprescribe PPIs in Swiss primary care settings.

Availability of data and materials

The data used and analysed in this study may be made available upon reasonable request.

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5.2 Article 2. Understanding older patients' willingness to have medications deprescribed in primary care: a protocol for a cross-sectional survey study in nine European countries

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My contributions: Together with Katharina Jungo, Kristie Weir, Zsofia Rozsnyai, and Sven Streit, we planned the study design, data collection, ethical application, study protocol, and created the study questionnaire. I drafted the manuscript, created all figures and tables for the manuscript, and implemented revisions from co-authors and from the peer-review process. I was responsible for the communication with all the co-authors.

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STUDY PROTOCOL

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Understanding older patients' willingness to have medications deprescribed in primary care: a protocol for a cross-sectional survey study in nine European countries

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Abstract

Introduction: To reduce inappropriate polypharmacy, deprescribing should be part of patients' regular care. Yet deprescribing is difficult to implement, as shown in several studies. Understanding patients' attitudes towards deprescribing at the individual and country level may reveal effective ways to involve older adults in decisions about medications and help to implement deprescribing in primary care settings. In this study we aim to investigate older adults' perceptions and views on deprescribing in different European countries. Specific objectives are to investigate the patients' willingness to have medications deprescribed by medication type and to have herbal or dietary supplements reduced or stopped, the role of the Patient Typology (on medication perspectives), and the impact of the patient-GP relationship in these decisions.

Methods and analysis: This cross-sectional survey study has two parts: Part A and Part B. Data collection for Part A will take place in nine countries, in which per country 10 GPs will recruit 10 older patients (≥65 years old) each ($n = 900$). Part B will be conducted in Switzerland only, in which an additional 35 GPs will recruit five patients each and respond to a questionnaire themselves, with questions about the patients' medications, their willingness to deprescribe those, and their patient-provider relationship. For both Part A and part B, a questionnaire will be used to assess the willingness of older patients with polypharmacy to have medications deprescribed and other relevant information. For Part B, this same questionnaire will have additional questions on the use of herbal and dietary supplements.

Discussion: The international study design will allow comparisons of patient perspectives on deprescribing from different countries. We will collect information about willingness to have medications deprescribed by medication type and regarding herbal and dietary supplements, which adds important information to the literature on patients' preferences. In addition, GPs in Switzerland will also be surveyed, allowing us to compare GPs' and patients' views and preferences on stopping or reducing specific medications. Our findings will help to understand patients' attitudes

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towards deprescribing, contributing to improvements in the design and implementation of deprescribing interventions that are better tailored to patients' preferences.

Keywords: Deprescribing, Polypharmacy, Primary care, Survey study, Older adults

Introduction

The high rate of polypharmacy, commonly defined as the regular use of ≥5 medications [1], is a worldwide public health problem. Recent studies have found that the prevalence of polypharmacy in older adults is rising in the last years, ranging from 26 to 40% in Europe [2–5]. There is also evidence that patients with polypharmacy are at higher risk of inappropriate medication use [6]. Inappropriate medication use has been associated with adverse outcomes, including the increased risk for falls [7], adverse drug reactions [8], declined functional ability, cognitive capacity, and nutritional status [9, 10], poor treatment adherence [11], and impaired quality of life [12]. In Switzerland, 21% of patients with polypharmacy take at least one potentially inappropriate medication (PIM) [13]. Indeed, the prevalence of PIMs is high among older adults worldwide [14, 15]. A medication is considered inappropriate when potential harms outweigh potential benefits in an individual [16]. Adverse effects of inappropriate medication mostly affect older adults due to pharmacokinetic and pharmacodynamic changes with age, increasing vulnerability and probability of drug side effects [17, 18]. The increased awareness of the harms associated with polypharmacy has led to research that focuses on deprescribing, which is defined as "the process of withdrawal (or reduction) of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes" (definition adapted from [19]).

Deprescribing should be implemented in primary care routinely for any patient who is affected by inappropriate medication use, especially older adults [20–23]. While the evidence for deprescribing is growing, individual patients face barriers and concerns when it comes to making deprescribing decisions [24]. Previous research has shown patients' lack of knowledge about the harms of inappropriate polypharmacy is an important barrier, while a good patient-GP relationship acts as an enabler to deprescribing [25, 26]. Additionally, some patients may fear that the offer of deprescribing is an indication that their doctor is withdrawing care or neglecting them [27]. However, the barriers and enablers faced by older adults are highly individual. As shown in Table 1, the Patient Typology was developed by Weir et al. which identified three types of older adults who vary in their attitudes towards medications, preferences for involvement in decision-making, and openness to deprescribing [28]. This can help to understand more deeply how older patients are experiencing their medications and may help to achieve patient-centred decisions about deprescribing.

In recent years there has been focus on patients' hypothetical willingness to have their medications deprescribed. A recent systematic review and meta-analysis found that most of adults (84%) are willing to have a medication deprescribed [29] and similar findings have been shown in Switzerland [25, 30]. Of note, the studies conducted varied in terms of study design, population, and setting. Associations between willingness to deprescribe, clinical and participant characteristics were inconsistent across studies [29]. Furthermore, the literature mostly focuses on individual survey studies rather than systematic studies looking at deprescribing in different countries. Despite the high hypothetical willingness to have medications deprescribed, the literature shows that there is a much smaller percentage of patients, who agree with the statement: "*I feel that I may be taking one or more medications that I no longer need*". Furthermore, patients also report a high level of satisfaction with their medications [29] and often indicate not being fully aware of the reasons for taking them or the potential harms caused by medications [31]. Despite the growing research on patients' willingness to deprescribe, it remains unknown which medications patients would like to stop taking and why. Knowing this, will help designing and implementing deprescribing interventions.

Shared decision-making and patient-physician trust play an essential role in taking and implementing deprescribing decisions [32, 33]. Little is known about patients and health professionals deprescribing preferences and how these preferences compare. A recent study [33]

Table 1 Three 'types' of older adults from the Patient Typology[1]

Type 1:	Positive attitudes towards medicines, left decisions to their doctor or were strongly guided by them, resistant to deprescribing.
Type 2:	Ambivalent attitudes towards medicines, preferred a proactive role in decision-making, were open to deprescribing.
Type 3:	Gave medicines little thought, deferred decisions to their doctor or companion, unaware deprescribing is an option.

[1] Previous qualitative study developing the Patient Typology [28]

found that patients seem to prefer continuing the use of sedatives and pain killers, but prescribers would rather discontinue these. However, this study was restricted to patients with cognitive disorders, younger than 60 years of age. In this context, it is important to better understand how GPs' deprescribing suggestions are aligned with their patients' preferences and how the patient–GP relationship influences deprescribing decisions. Having a better understanding of this will help to reduce disagreement in clinical practice by developing interventions that consider eventual differences [34].

While most of the literature on deprescribing focuses on prescription drugs only, for optimal medication management, GPs should be aware of all the medications used, including such supplements. Herbal and dietary supplements can be PIMs and are commonly used in many countries, including Switzerland [3, 35–39]. For instance, multivitamins are among the most frequently used PIMs [22, 40]. According to the Beers list and STOPPFrail criteria, Ferrous sulfate (iron), multivitamins, and caffeine are examples of PIMs and should be discontinued when prescribed for prophylaxis rather than treatment [41, 42]. Patients are commonly unaware of the potential risks of self-medication [36] and the use of such supplements is often not disclosed to GPs [39]. In this study we focus on supplements (e.g., multivitamins, vitamin D, calcium, iron, magnesium) as they are commonly used over a longer period, as compared to other medications (e.g., cold and flu medications) that can be bought over the counter in Switzerland.

Study objectives

The overall aim of this study is to investigate older adults' perceptions and views on the use and deprescribing of prescription medications and supplements in different European countries.

Specific objectives for all participating countries are:

1) To explore older patients' views on deprescribing and compare how they differ by country.
2) To assess patients' willingness to have medications deprescribed by medication type.
3) To analyse if and how patients' hypothetical deprescribing decisions are associated with the three types of the Patient Typology (a qualitative framework).
4) To analyse the association between patients' perceived trust and relationships with their GP and their willingness to make deprescribing decisions.

Additional objectives for Switzerland, where we do a patient-GP matched survey and collect additional data on herbal and dietary supplements, are:

1) To compare patients' and GPs' hypothetical deprescribing decisions and to examine the role of patient-provider relationships with regards to the agreement between patients and GPs.
2) To explore the views of patients on the use and on the reduction or stopping of herbal and dietary supplements.

Methods and analysis

Study design

This cross-sectional study contains two parts: Part A and Part B. Part A involves nine European countries (Fig. 1) with anonymous data collection on older adults' willingness to have medications deprescribed. Part B is a nested sub-study in Switzerland only, which extends Part A by collecting additional data from older patients and GPs.

In both Part A and Part B, we are using a questionnaire to assess patients' willingness to have their medications deprescribed, Patient Typology, and other relevant sociodemographic and clinical information on older patients with polypharmacy. For Part B, an additional questionnaire will be distributed to GPs in Switzerland, which will contain questions about the patients' medications and the GP-patient relationship. Patients in Part B will be asked about their use of herbal and dietary supplements and their willingness to stop or reduce them. Table 2 shows further details.

Setting

The study will be conducted in primary care settings in nine European countries. It is coordinated by the central study team in Switzerland at the Institute of Primary Health Care (BIHAM) of the University of Bern and conducted in collaboration with a group of GPs from the European General Practice Research Network (EGPRN) – a proven successful collaboration [43–45]. Seventeen National Coordinators from 13 different countries were invited to participate in the study, of which 11, coming from 8 different countries, accepted to participate (Fig. 1). Four National Coordinators are participating from different locations in Germany. The list of participant countries is subject to changes.

Participants

Eligibility criteria

For both parts, patients will be included if they are 65 years or older and have polypharmacy (taking ≥5 prescribed medications regularly). Patients are not eligible if they are unable to give informed consent or if they do not reside in one of the participating countries. For Part

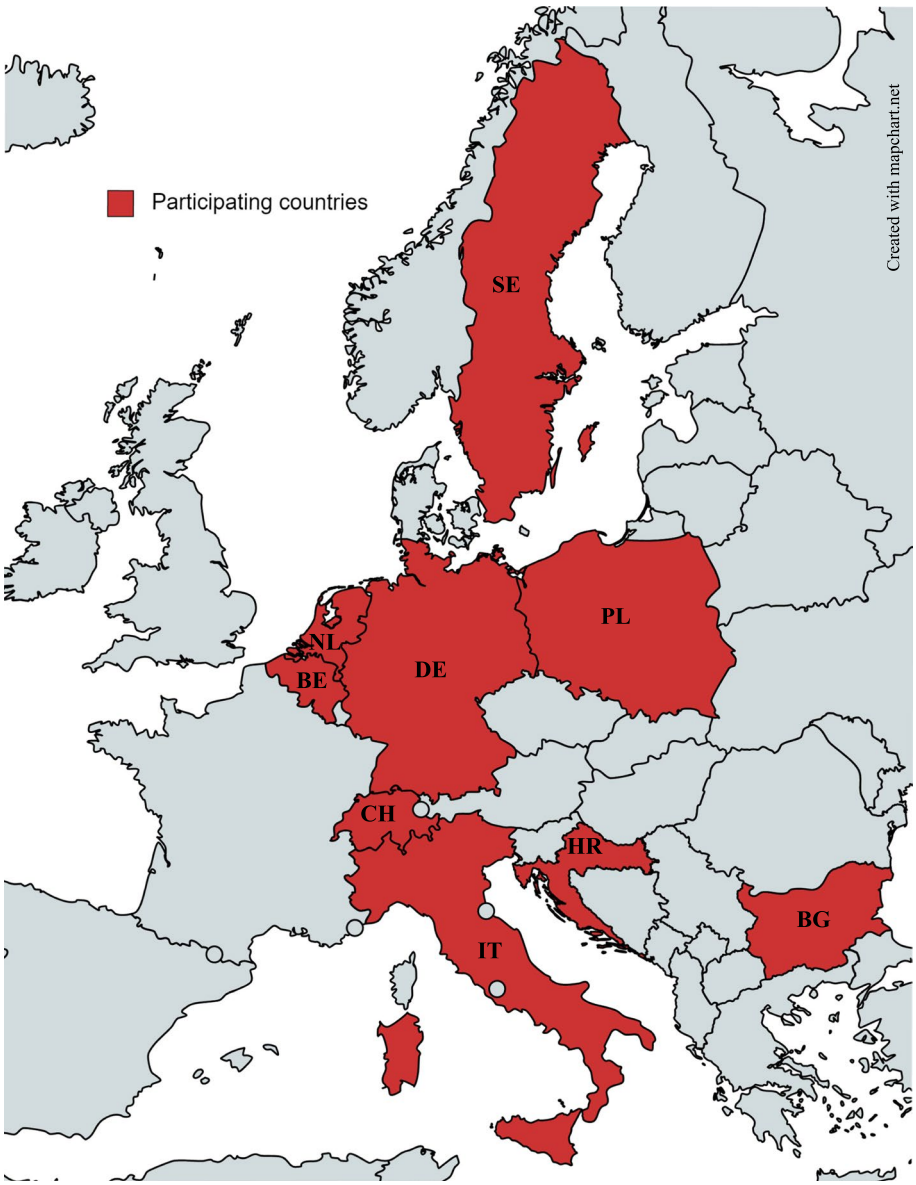

Fig. 1 Map of participating countries created with MapChart.net. Maps created with MapChart can be freely used, edited and modified for publications, as long as mapchart.net is referenced (https://mapchart.net/terms.html, accessed July 15, 2022)

B, due to language reasons, the inclusion criterium for the GPs participating in the additional data collection is to be a practicing GP in the German-speaking part of Switzerland.

Screening and recruitment

Starting in May 2022, through the networks of the National Coordinators at each site, we aim to recruit GPs who will in turn recruit patients. For study Part A, our goal is to recruit a total of 900 primary care patients, which corresponds to approximately 100 patients per country (around 10 per GP). For Part B we will recruit an additional 35 GPs, who will invite five patients each to respond to a questionnaire and will also complete a questionnaire themselves for each of the recruited patients.

For Part A and B, primary care patients will be recruited through their GP. GPs will be recruited through the National Coordinators at the participating sites and the study team at BIHAM in Switzerland. GPs will be given screening criteria to be able to screen and recruit primary care patients in their practice. Screening criteria will be sent to all the participating GPs. Screening

Table 2 Summary of Part A and B of the project

	Part A	Part B
Countries involved	Switzerland, Germany, Poland, Sweden, French-speaking part of Belgium, Bulgaria, Italy, Croatia, and Netherlands	German-speaking part of Switzerland
Anonymization	Anonymized	Pseudonymized
Subjects	Patients	Patients and their GPs
Questionnaires used	Patient questionnaires in local language(s)	Patient questionnaire including part on herbal and dietary supplements, GP questionnaires
Number of recruited GPs	10 per country	35 in the Swiss German part of Switzerland
Role of the GPs	Screen and recruit eligible patients	Screen and recruit eligible patients, complete questionnaires themselves
Number of recruited patients	100 per country (10 per GP) = 900 in total	5 per GP = 175 in total

and recruitment of the patients will take place during the regular consultation hours of the GPs. They will be instructed to screen their patients consecutively (e.g., on a work half-day) to reduce selection bias. In the Netherlands, GPs are able to screen their patients in their electronic medical records and then invite a random sample of them.

Due to the anonymous design of Part A, patients will give their informed consent by replying to the question "by clicking yes here, I agree to participate in this study". If they click "no", they cannot participate in the study. For Part B, patients will have to give their written informed consent to participate. As soon as all questionnaires from one GP practice have been completed, the GP will return the questionnaire to the study team in Switzerland or to the respective National Coordinator of the participating sites.

Questionnaire

Cross-cultural adaptation of the questionnaire will be carried out by the National Coordinator in each participating country. Translations will be validated by performing back-translations to English and solving eventual inconsistences.

For patients (Part A and B), the questionnaire contains questions on demographic characteristics, educational level, housing and living situation, health literacy, medication management and information on life circumstances. Patients will be asked to specify any medications they would potentially discontinue, for what reason, and the support they would need to do this. Furthermore, the survey will contain questions on trust in the physician and questions on the Patient Typology. In Part B, patients will also be asked about herbal and dietary supplements. In Part B, GPs will be asked to attach the

Table 3 Study objectives and survey tools

Objective	Data collection tool
Part A: European data collection	
1) To explore patients' views on deprescribing specific medications and compare how they differ by country.	1) Two questions from the revised Patients' Attitudes Towards Deprescribing (rPATD) questionnaire [47].
2) To assess patients' willingness to have medications deprescribed by medication type.	2) Questions on hypothetical deprescribing decisions related to patients' own medications.
3) To analyse if and how patients' hypothetical deprescribing decisions are associated with the three types of the Patient Typology (a qualitative framework).	3) Questions based on the typology of three 'types' of older adults (the Patient Typology) [28].
4) To analyse the association between patients' perceived trust and relationships with their GP and their willingness to make deprescribing decisions.	4) Questions from the abbreviated Wake Forest Trust in Physician Scale [48].
Part B: Patient-GP data collection in Switzerland	
5) To compare patients' and GPs' hypothetical deprescribing decisions and to examine the role of patient-provider relationships with regards to the agreement between patients and GPs.	5) GP questionnaire asking if and why GPs would stop/reduce any of their patients' medications, questions regarding their relationship with the patient, and sociodemographic questions. We also use adapted questions from the Control Preference Scale [49], GP typology [46], and Prescribers' Perceptions of Medication Discontinuation Survey [50].
6) To explore the views of older adults on the use and deprescribing of herbal and dietary supplements.	6) Questions on the use of herbal or dietary supplement by patients.

patient's medication list to the questionnaire and indicate which medications they would be willing to deprescribe. The GP questionnaire will contain sociodemographic questions, questions about work practices, and decision-making preferences ("GP profile") based on previous qualitative research [46]. Details on the individual components of the questionnaire, and how they related to the study objectives, are provided in Table 3.

Data collection and data management

Paper and online versions of the questionnaire will be available to participants. Part A is anonymized and thus complies with the European General Data Protection Regulation (GDPR). Part B is pseudonymized and not anonymized, as we need to be able to match GPs and patients for the analysis.

We are programming the online survey using REDCap [51], which provides role-based user access control and audit trails [52]. The questionnaire will either be entered into REDCap by the National Coordinators, or the participant can fill in the survey directly online using REDCAp survey function. Only selected members of the research team will have access to the full database in REDCap.

Sample size

A recent systematic review found that 84% of patients strongly agree to have one or more of their medications deprescribed [29]. In Switzerland the results were similar with 77% of patients agreeing to deprescribe one or more of their medications [25]. For the sample size calculations, we used the more conservative estimate of 77%. The sample size calculation accounts for the clustered nature of data for patients within the same GP (ICC = 0.10), which is more conservative than the Intra-cluster correlations (ICC) of 0.01 to 0.05 that were reported for binary outcomes in cluster clinical trials of older individuals [53]. We did all sample size calculations using the power one proportion function in Stata, which allows to account for the clustered nature of the data.

Calculations for Part A

Based on the assumption that 77% of patients would be willing to deprescribe (yes/no), assuming an ICC of 0.10, we need a total of 80 clusters (i.e., GPs recruiting patients and distributing surveys, around 8 per site), and 8 patients recruited per GP, to have an effect size of 0.06 at a power of 0.90. To account for potential missing data, we increased the number of GPs per site to 10 and the number of patients per cluster to 10.

Calculations for Part B

This part of the study is powered for the GP-patient agreement related to deprescribing specific medications. In line with the literature on the agreement between GPs and patients with regards to which medication to (dis-) continue, in around half of the cases patients and GPs were in agreement regarding which medications to continue [33]. Assuming an ICC of 0.10, we need a total of 33 clusters (GPs) and 4 patients with a minimum of 5 medications each per cluster to have an effect size of 0.10 at a power of 0.90. Overall, to account for missing data, we aim to recruit 35 GPs from the German-speaking part of Switzerland, who will be instructed to recruit 5 patients each. This will result in around 175 patients and a sufficient number of medications that were rated by both GPs and patients (willing to deprescribe yes/no). There will be a minimum of 875 medications if each study participant has a minimum of 5 medications. Likely, there will be more medications to compare though, since in a previous study with a similar study population the mean number of medications was 8 [25].

Statistical analysis

Part a

From the rPATD [47], we are using the question *'If my doctor said it was possible, I would be willing to stop one or more of my regular medications'* to assess the primary outcome for objective 1. In a sensitivity analysis, we also use the question '*I would like to try stopping one of my medicines to see how I feel without it*' from the rPATD. The rPATD questions with 5-point Likert scale responses will be dichotomized into *"strongly agree/agree"* versus *"unsure/disagree/strongly disagree"*. If patients agree or strongly agree with this statement, they will be considered to be willing to deprescribe. Descriptive statistics will report baseline characteristics of the sample stratified by willingness to deprescribe. Where appropriate, the t-test and Chi-square test will be used to compare participants who were willing to deprescribe versus not willing to deprescribe. To explore the patients' willingness to have medications deprescribed, we will assess univariate and multivariate associations between sociodemographic and clinical characteristics (e.g., age, sex, medication management, living status, education level, number of medications, etc.) and their willingness to have medications deprescribed using mixed-effects logistic regression models. Models will be adjusted for clustering effects at GP and country level. We will use a hypothesis-driven approach to select the confounders we have to adjust for. To analyse how the views on deprescribing differ among the participating sites, we will use the same regression model, but stratify by country.

For objective 2, we will descriptively analyse which types of medications patients were most likely to report as willing to stop or reduce from their own medication use. We will also compare the reasons provided for stopping or reducing by medication type. Using multivariate mixed-effects logistic regression analyses, we will also investigate patients' sociodemographic and clinical characteristics associated with being willing to have certain medication types deprescribed.

For objective 3, we will assess the association between the three "types" of the Patient Typology *Dimension* participants identify with and patients' hypothetical deprescribing decisions. To do so we will use a multivariate mixed-effects logistic regression model that will be adjusted for patient sociodemographic and clinical characteristics and clustering at the GP and country level.

For objective 4, we will analyze the associations between patient-provider relationships (reported by patients) and patients' willingness to make deprescribing decisions using multivariate mixed-effects logistic regression analyses that will be adjusted for patient sociodemographic and clinical characteristics and clustering at the GP and the country level.

Part B

For objective 5, we will analyse the agreement between patients' and GPs' hypothetical deprescribing decisions. We will use descriptive statistics to describe the percentage of (dis) agreement between patients and GPs and which types of medications they most commonly (dis) agree about. Logistic regression models will be used to assess the association between GP-patient trust, patient and GP characteristics, and the agreement between GPs' and patients' willingness to make hypothetical deprescribing decisions.

Finally, for objective 6, we will investigate the use, beliefs, and motivations of patients for taking herbal and dietary supplements and their willingness to stop or reduce using such supplements. Descriptive statistics will be used to determine the percentage of patients who use supplements. Logistic regression models will be used to assess the association between patients' demographic, behavioural, and health characteristics, the use of supplements, and patients' willingness to deprescribe those. The analyses will be adjusted for clustering at the GP level.

Baseline characteristics will be presented in proportions (categorical variables) and means ± SD (or medians and IQR) (continuous variables). A two-sided p-value of 0.05 will be considered statistically significant. Analyses will be performed with STATA 16.1 (StataCorp, College Station, TX, USA).

Discussion

Overall, the aim of our study from 9 European countries about older primary care patients' willingness to have medications deprescribed is to better understand patients' attitudes towards deprescribing at the individual and country level. Eventually, the study's goal is to inform effective ways to involve older adults in decisions about their pharmacological treatment. To the best of our knowledge, this is one of the first studies comparing patients' willingness to have medications deprescribed across countries. It will also be one of the first studies to look at both the willingness to have prescription medications and supplements stopped or reduced. A better understanding of the enablers and barriers of the willingness to deprescribe in older patients with polypharmacy by answering the questions raised in this project, may contribute to improvements in the design and implementation of deprescribing interventions that are better tailored to patients' preferences. This in turn will directly help GPs and other health professionals to optimise the process of approaching and implementing deprescribing in patients with polypharmacy. This will provide a better understanding of the management of polypharmacy and medication optimization, especially in older individuals. Ultimately this may improve patients' overall health, reduce adverse effects caused by inappropriate polypharmacy, and eventually reduce the burden of polypharmacy on different health care systems in Europe and worldwide.

This study is strengthened by its approach to patient and public involvement, National Coordinators are partners of the Swiss central study team, and they have

Table 4 Involvement of National Coordinators in study design and planning of the data collection

Question	Decisions made
Timeline	Data collection begins in May 2022 in Switzerland and in June 2022 in the other countries (depending on how the COVID-19 situation evolves).
Data collection format	Offer patients both online and on paper questionnaires so that they can chose a suitable format.
Survey tool	The questionnaire will be translated into German, French, Italian, Bulgarian, Swedish, Croatian, Polish, and Dutch, and culturally adapted by the National Coordinators.
Data collection procedure	GPs will collect the questionnaires from patients and send them to the National Coordinators, who will enter the data into REDCap.

helped shape several aspects of the study, such as the recruitment strategy. Therefore, we aligned the data collection with all countries, to ensure feasibility of the project in regard to the format of the questionnaire, timeline of the data collection, etc. Each of the National Coordinators signed a Research Collaboration Agreement, in which the duties, tasks, qualifications for co-authorship and data use are clarified. More details on the decisions taken together with the National Coordinators are shown in Table 4. Although in Switzerland, primary care research is gaining attention, it is still a difficult context in which to conduct research. However, our team succeeded in overcoming such difficulties when conducting research involving GPs and patient recruitment in the past [43, 54]. The questionnaires (both paper-based and online version) used in this study have been piloted with 6 patients and 4 GPs and were revised based on their feedback.

Strengths and limitations

As this will be a cross-sectional study design and we will ask hypothetical deprescribing questions, the directionality of the associations cannot be confirmed. Nevertheless, our study will add important information to the literature comparing GPs' and patients' preferences on deprescribing specific medication types. We are limited by GDPR and the available funding and therefore cannot compare GPs' and patients' preferences in all participating countries but will focus on Switzerland. For Part A, due to the irreversible anonymization, we are not able to track the response rate nor are we able to adjust the analyses for the clustering effect at the GP level. However, we will be able to adjust the analyses for GP-level variables.

This study is strengthened by the fact that it will investigate which specific medications patients would prefer to deprescribe and for which reason. Another strength will be the international study design with 12 participating sites, which will allow us to compare patient perspectives on deprescribing from different European countries.

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Authors' contributions

RL, KTJ, KW, and ZR wrote the first draft of this protocol paper. Critical review and feedback were made by RVL, KTJ, KRW, AKG, BS, DK, DMGW, FP, HT, HL, RA, RKEP, VL, ZR, SS. All authors were involved in the study design decisions and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. All authors approved the final version of the manuscript.

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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. The questionnaires used in this study are available upon request.

Declarations

Ethics approval and consent to participate

The local ethics committee in Switzerland (Kantonale Ethikkommission Bern) approved the study protocol in January 2022 for Part A and B (Project-ID 2022–00035). This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [55], the principles of Good Clinical Practice, the Human Research Act (HRA) [56] and the Human Research Ordinance (HRO) [57] as well as other locally relevant regulations in the participating countries. In addition, for Part A, in order to respect privacy rights under the European regulation, the requirements of the European General Data Protection Regulation (GDPR) will be fulfilled by anonymization and/or data source protection. Patients from Part A give their informed consent by replying to the question "by clicking yes here, I agree to participate in this study". If they click "no", they cannot participate in the study. Patients from Part B will provide written informed consent before completing the study questionnaire. All sites will also adhere to all local and national ethical guidelines for conducting research and apply for ethical approval, if necessary.

The results of this study will be disseminated through peer-reviewed journals, conference presentations and the doctoral thesis of the first author. We also aim to diffuse our results in journals commonly read by GPs (for instance, the Swiss journal ***Primary and Hospital Care***) to enable knowledge transfer.

Consent for publication

Not applicable.

Competing interests

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

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Publisher's Note

5.3 Article 2.1. Understanding older patients' attitudes towards deprescribing in primary care: A cross-sectional survey study in 14 countries

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My contributions: Together with Katharina Tabea Jungo, Kristie Weir, Zsofia Rozsnyai, and Sven Streit, I worked in the study planning and design, acquired ethical approval, wrote the study protocol, and recruited participants. Together with Katharina Tabea Jungo I drafted the manuscript, created all figures and tables shown in the manuscript, implemented revisions from co-authors, entered data from paper into REDCap, was responsible for data cleaning and performed the statistical analysis. I was responsible for communication with the national coordinators and study coordination.

Status: This is still a working paper. We aim to submit this manuscript in spring 2024.

Understanding older patients' attitudes towards deprescribing in primary care: A cross-sectional survey study in 14 countries

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Abstract

Background: Deprescribing medications for which potential harms outweigh benefits is a key intervention in reducing medication-related harms in older adults. To design effective deprescribing interventions we must better understand patient attitudes towards stopping or reducing specific medication types. We investigated older adults' attitudes towards deprescribing, by investigating which medications patients were most willing to have deprescribed, the reasons why, and patient factors associated with willingness to deprescribe.

Methods: This cross-sectional study was conducted in primary care settings across 17 sites in 14 countries. From May 2022 to December 2023, 10 GPs per country each recruited 10 patients aged ≥65 years old, taking ≥5 medications who completed a survey about their attitudes towards deprescribing. We assessed patient attitudes towards deprescribing, as well as the number and types of medications patients reported to be willing to deprescribe. We used multilevel logistic regression analysis adjusted for the clustering effect at country level to investigate the association between patient characteristics and willingness to have medications deprescribed.

Findings: Of the 1,340 patients (average 96 per country), 82% (n=1,089) reported being satisfied with their medications, 81% (n=1,088) were willing to deprescribe ≥1 of their medications if their doctor said it was possible, and 44% (n=589) named ≥1 medication when asked about stopping or reducing their own medications. The three most reported medication types for deprescribing were diuretics (n=111, 11%), lipid modifying agents (n=109, 11%), and agents acting on the renin–angiotensin system (n=83, 8%). The odds of willingness to deprescribe specific medications were higher for patients with less satisfaction with medications (OR=0.31, 95%CI 0.21 to 0.47) and lower trust in their GP (OR=0.96, 95%CI 0.93 to 1.00).

Interpretation: Our findings show that patients' willingness to stop or reduce medications is lower when patients are asked about specific medications compared to when they are asked unspecific questions assessing their overall willingness to deprescribe. The association between patients' satisfaction with medications, trust in their GP, and willingness to deprescribe specific medications highlights the importance of patient-provider communication in deprescribing.

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Evidence before this study

The majority of previous studies on patient attitudes towards deprescribing used the revised Patients' Attitudes Towards Deprescribing (rPATD) [1]. Studies using the question *'If my doctor said it was possible, I would be willing to stop one or more of my regular medications'* from the rPATD to assess patients' willingness to deprescribe found that 84-88% of the patients were willing to have medication deprescribed [2,3]. Patient's willingness assessed using the rPATD question '*I would like to try stopping one of my medicines to see how I feel without it'* seemed lower [4]. However, little is known about patients' attitudes towards deprescribing specific medications from their own medication lists. Furthermore, willingness to deprescribe varies across different settings (e.g., different countries). While research on patients' willingness to deprescribe has been conducted in different countries, not many previous studies have simultaneously collected data in different countries, which limits their comparability [2,3].

Added value of this study

Our research adds to the literature in two different, innovative ways: a) by collecting data in multiple countries, and b) by asking patients about specific medications they would be willing to have deprescribed from their own medication list. Therefore, in this study patients' willingness to have medications deprescribed is assessed through the question *'Thinking about your current medication list, are there any medications that you would like to stop taking or reduce the dose of?'.* This approach allowed us to explore what types of medications patients are more willing to stop or reduce. Our study is strengthened by the fact that we collected data in 14 countries, which allowed us to study how patient attitudes towards deprescribing specific medications varied across countries.

Implications of all the available evidence

The results from this study are informative for the development of future deprescribing interventions. First, variations in patients' willingness to deprescribe across countries demonstrate that patient-facing intervention materials must be tailored for different settings. Second, the fact that the currently most frequently used assessment tools to evaluate overall patient attitudes

towards deprescribing lead to an overestimation could be one of the reasons why deprescribing willingness has not yet been found to translate to real-world medication changes [3-5], highlighting the need for more accurate measures to reflect patient attitudes in real-life situations. Third, better understanding which specific medications patients would rather stop or reduce and the reasons why will inform future deprescribing interventions (e.g., tailored patient-facing intervention materials). Furthermore, our findings highlight the importance of trust and patient-provider relationships when implementing deprescribing decisions in real-world clinical settings.

Introduction

The prevalence of polypharmacy (use of ≥5 medications [6,7]), among older adults is high [8,9]. When medications do not have an indication, are used in too high doses, or their potential harms outweigh potential benefits, they are considered inappropriate [7,10,11]. Due to the high rates of inappropriate polypharmacy and its associated harms, the interest in deprescribing (the process of stopping or reducing inappropriate medications[12]) has been increasing [13-17]. Deprescribing is a key intervention in the management of polypharmacy and helps reduce medication-related harms. Although the overall reported patient willingness to have medications deprescribe is high, studies have shown that this willingness varies across different settings [2,3]. For instance, patients from higher-income countries seem to be more willing to have medications deprescribed [2,3]. To successfully implement deprescribing, we need to better understand patient attitudes towards deprescribing in different settings.

Some patient factors seem to act as enablers and barriers to deprescribing. For instance, high satisfaction with medications, perceived health benefits from medications, and fear of the return of symptoms have been identified as barriers to deprescribing, while a good patient-physician relationship has been identified as an enabler [18,19]. Studies have shown that most patients report being willing to have their medication deprescribed if their doctor said it was possible [3,18]. However, there seems to be a discrepancy between patients' self-reported willingness and their behaviour in practice and clinical trials [3-5,20]. Furthermore, little is known about older adults' willingness to have specific medications deprescribed from their own medication list.

When designing deprescribing interventions, however, it is important to better understand patient attitudes towards deprescribing considering specific medications and differences across

medication types. In this study we aimed to investigate older adults' attitudes towards deprescribing across 14 countries, to assess which medications patients were most willing to have deprescribed and the reasons why, as well as the patients' factors associated with their willingness to have medications deprescribed.

Methods

Study design and study participants

This is a cross-sectional study conducted in primary care settings of 17 sites in 14 different countries (Belgium, Bulgaria, Croatia, Germany, Hungary, Ireland, Israel, Italy, Netherlands, Poland, Portugal, Spain, Sweden, and Switzerland). Each site had at least one national coordinator responsible for recruiting a minimum of 100 patients per country (Supplementary File Figure S1). To be eligible to participate in the study, patients had to be ≥65 years old and take ≥5 medications regularly. Exclusion criteria were inability to give informed consent and/or residency outside of the participating countries. Further details on the study design were published in the study protocol[21]. The competent ethics committee in Switzerland (Kantonale Ethikkommission Bern) approved this research (Project-ID 2022–00035).

Data source and data collection

The study questionnaire (Supplementary File e1) was anonymous and could be completed on paper or online directly in REDCap. Each national coordinator recruited GPs who in turn recruited eligible patients to respond to the questionnaire. GPs were instructed to recruit patients consecutively to reduce selection bias. In the Netherlands, GPs from different practices used patients' medical records to invite random samples of participants. Patients gave their informed consent to participate.

The questionnaire contained questions on patients' socio-demographic characteristics, trust in the GP, and attitudes towards deprescribing. Patients' willingness to have specific medications deprescribed was assessed through the binary question '*Thinking about your current medication list, are there any medications that you would like to stop taking or reduce the dose of?*'. In addition, we included the two global questions from the rPATD about patients' willingness to have

medications deprescribe [1]: *If my doctor said it was possible, I would be willing to stop one or more of my regular* and *'I would like to try stopping one of my medications to see how I feel without it*'.

Variables and data management

Questionnaires from all sites were appended and analysed together. Patients who responded '*yes*' to the *'Thinking about your current medication list, are there any medications that you would like to stop taking or reduce the dose of?'* question, were considered to be willing to deprescribe specific medications. Patients who responded '*yes*' to this question could enter the name of a minimum of one and maximum of four medications they would be willing to stop or reduce, as well as the reason(s) why they chose each specific medication. Patients named the medications they would consider deprescribing using the brands or substance names. Patients who responded '*no*' to this question could choose the reason(s) why they do not want to stop any medication. Reasons for not being willing to have medications deprescribed were shown in a pre-determined list based on the study from Vordenberg, et al., 2023[22]. To classify the medications named for deprescribing, we used ATC codes at the second anatomical level to standardize the medication classification, which allowed us to group medications into specific therapeutic or pharmacological subcategories. For instance, within the anatomical group 'C Cardiovascular System,' the second-level ATC codes can include subdivisions like 'C01 Antiarrhythmics,' 'C02 Antihypertensives,' and 'C03 Diuretics'. Since medication information was collected in different countries in different languages, we translated the medication names to German and classified the medications using ATC codes from the Swiss government list [23]. For medications that were not on the list, the ATC codes were added from WHO website [24].

Statistical analyses

We used descriptive statistics to report participant characteristics, the frequency (number and percentage) of patients willing to deprescribe, the reasons provided for being willing to have specific medications deprescribed, and the reasons for not wanting to have any medication deprescribed. Continuous variables were presented as means and standard deviations (SD) and categorical variables as frequencies and percentages. We stratified willingness to deprescribe the

three most frequent medication types by patient gender and country. To study the associations between patient characteristics (gender, number of medications, GP gender, financial status, confidence in filling medical forms, self-rated health, satisfaction with medications, and trust in the GP) and patients' willingness to have medications deprescribed, we performed a mixed-effects logistic regression, adjusted for clustering effects at the country level. We used a hypothesis-driven approach to select the covariates. A two-sided p-value of 0.05 was considered statistically significant. We identified missing data at random and used a complete case analysis method to handle missingness. We used Stata 16.1 [25] to perform the analysis.

Role of the funding source

The funders had no role in the study design, data collection, data analysis and interpretation, writing the report, or in the decision to submit the paper for publication.

Results

1,423 participants consented to participate in the study. 1,340 met the inclusion criteria and were included in the analysis (Supplementary File Figure S1). Patient characteristics are shown in Table 1. 55% (n=736) of the participants were female, 44% (n=580) had secondary school as the highest educational level, 34% (n=458) were '*quite a bit confident'* in filling out medical forms, and 45% (n=597) rated their overall health as *'average'*. Participants were taking an average of 7 regular medications (SD=2). 82% (n=1,089) of the patients reported to be satisfied with their medications.

Table 1. Patient characteristics (n = 1,340).

Patients' characteristics	**n (%)**
'What is your gender?' [a]	
Female	736 (55%)
Male	598 (45%)
'What is your highest completed education?'	
None	44 (3%)
Primary school	329 (25%)
Secondary school	580 (43%)
Third level education	376 (28%)
'How easily do you make ends meet?'	
Without any problems	340 (25%)
Quite easily	451 (34%)
With some difficulty	450 (34%)
With great difficulty	84 (6%)
'How confident are you filling out medical forms by yourself?'	
Extremely	258 (19%)
Quite a bit	458 (34%)
Somewhat	340 (25%)
A little bit	173 (13%)
Not at all	104 (8%)
'Where were you born?'	
In the country I currently live in	1221 (91%)
In another country	108 (8%)
'In general, how would you describe your health today?'	
Excellent	5 (1%)
Very good	68 (5%)
Good	462 (34%)
Average	597 (45%)
Poor	198 (15%)
'How many different medications do you take regularly?' mean (SD)	7 (2)
'Do you prepare your medication by yourself?'	
Yes, I prepare and take it myself according to the prescription.	1165 (87%)
No, I receive support in preparing/taking my medication.	168 (13%)
Trust in the GP [c] ***mean (IQR)***	20 (5)
'How long have you been seeing your GP?' [d]	
0-9 years	617 (46%)
10-19 years	375 (28%)
20-29 years	178 (13%)
30+ years	117 (9%)
'The gender of my GPs is…' [d]	
Female	696 (52%)
Male	549 (41%)
Other	16 (1%) [b]
'My GP's practice is located…' [d]	
In an urban area	772 (58%)
In a suburban area	297 (22%)
In the countryside	155 (12%)

The missing data was ≤1% for all variables, except for: 'How many different kinds of medications do you take regularly?' (3%); 'How long have you been seeing this GP?' (4%); 'My GPs is…' (6%); 'My GP's practice is…' (9%).

[a] No patient chose the option 'other' to the question 'What is your gender?'

[b] 8 GPs classified as "other" were from the Netherlands, where the patients in our sample did not have a unique fixed GP.

[c] Score of the abbreviated Wake Forest Trust in Physician Scale [26]. Range of the score: 5 to 25 - with higher values indicating higher trust.

[d] Only shown for participants who responded 'yes' to the question Do you have your own GP/family doctor (definition: when you have a health problem, you usually consult the same family doctor, except in emergencies)? (n=1,295)

Regarding their willingness to deprescribe, 81% (n=1,088) of patients agreed or strongly agreed with the statement from the rPATD[1] *'If my doctor said it was possible, I would be willing to stop one or more of my regular medications'* and 48% (n=648) of patients agreed or strongly agreed with the statement *'I would like to try stopping one of my medications to see how I feel without it*' (Supplementary File Figure S2). Meanwhile, when patients were asked about their willingness to stop or reduce specific medications (*Thinking about your current medication list, are there any medications that you would like to stop taking or reduce the dose of?'*), their willingness to deprescribe dropped to 44% (n=589).

Figure 1 shows patients' willingness to deprescribe per country and reveals some geographic variation across countries. The willingness to deprescribe specific medications was highest in Poland (n=86/109, 79%) and in Italy (n=68/92, 75%), and lowest in Croatia (n=6/27, 24%) and Bulgaria (n=21/96, 23%).

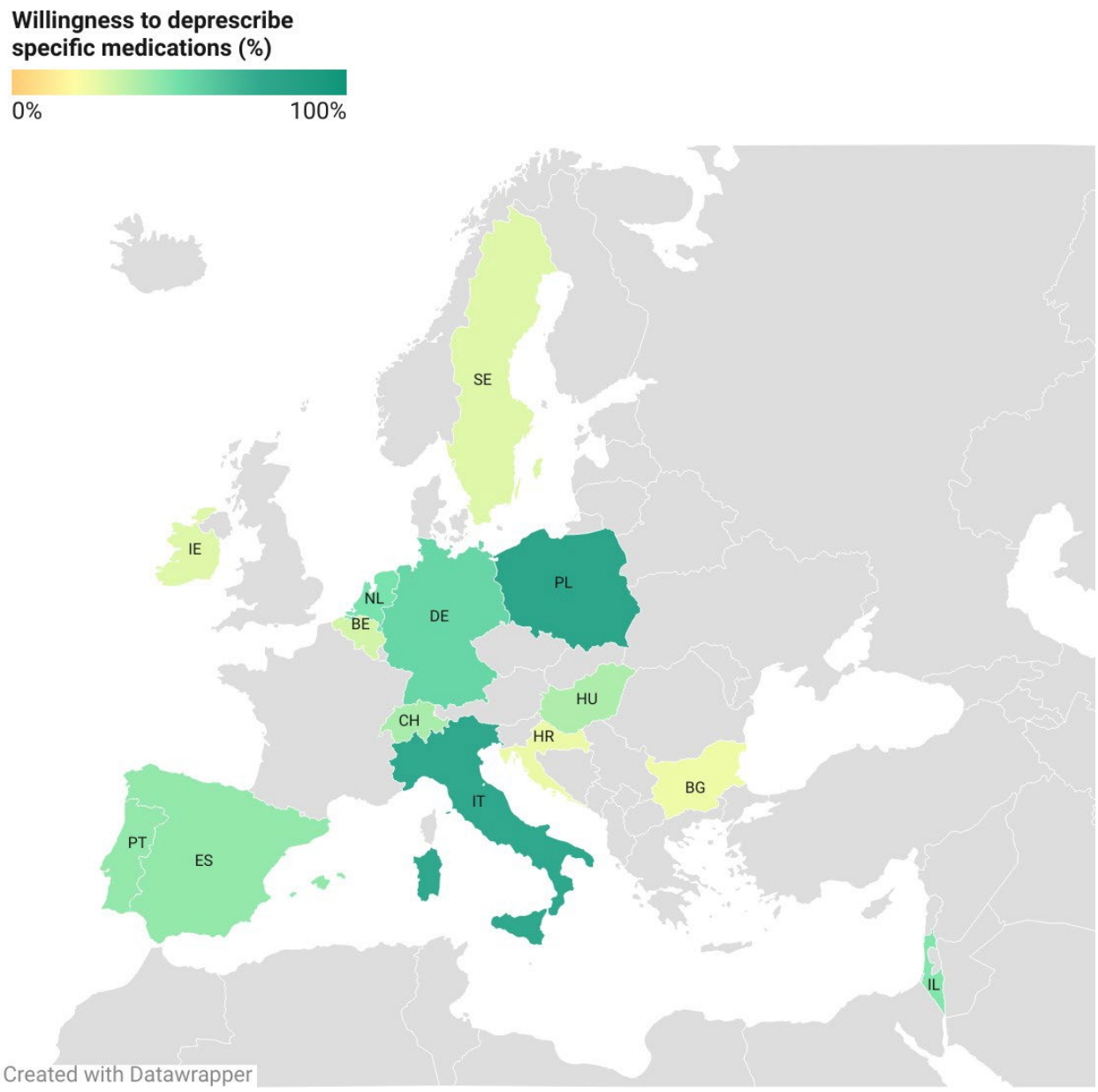

Figure 1. Percentage of older adults willing to have at least one medication deprescribed per country according to the question '*Thinking about your current medication list, are there any medications that you would like to stop taking or reduce the dose of?'*.
Map created with *Datawrapper*.

When asked about specific medications to stop or reduce, patients named 1,002 medications. The medications most frequently named were diuretics (n=109, 11%) and lipid modifying agents (n=107, 11%) (Figure 2). Supplementary File Table S1 shows the most frequently named

medication types, stratified by patients' gender and countries. Diuretics were among the most commonly named medication for both women (n=63, 11%) and men (n=45, 11%), but when stratifying the analysis by country, diuretics were the top 1 only for Italy (n=20, 13%) and Poland (n=54, 21%).

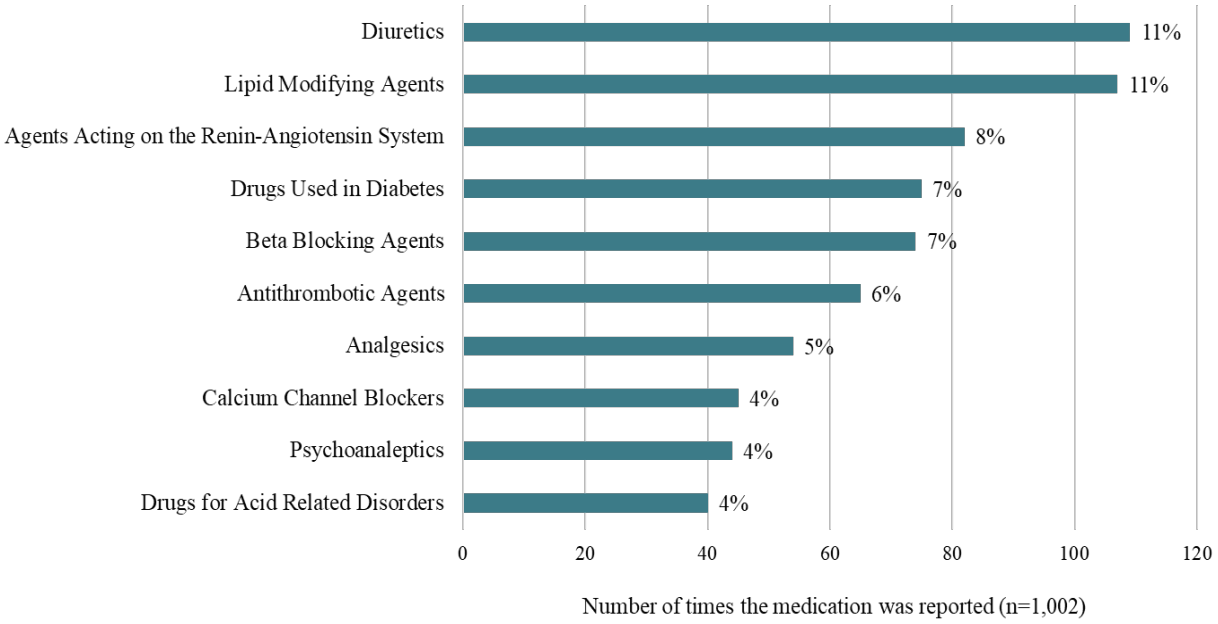

Figure 2. Frequency of top 10 medication types patients reported to be willing to stop or reduce.

When patients were asked why they would be willing to stop or reduce the medications they named, the most reported reasons overall were the presence of side effects associated with the medication (n=271, 20%), dislike of medications (n=144, 11%), and the inconvenience of taking the medication (n=131, 10%). Indeed, presence of side effects was also the most reported reason for willingness to stop or reduce for any of the top five medications (Supplementary File Figure S3). The reasons patients preferred not to stop or reduce any specific medication were due to the benefits of the medication (n=422, 58%), the belief that doctors only prescribe necessary medication(s) (n=366, 50%), and the habit of taking the medicine for a long time (n=294, 41%) (Figure 4).

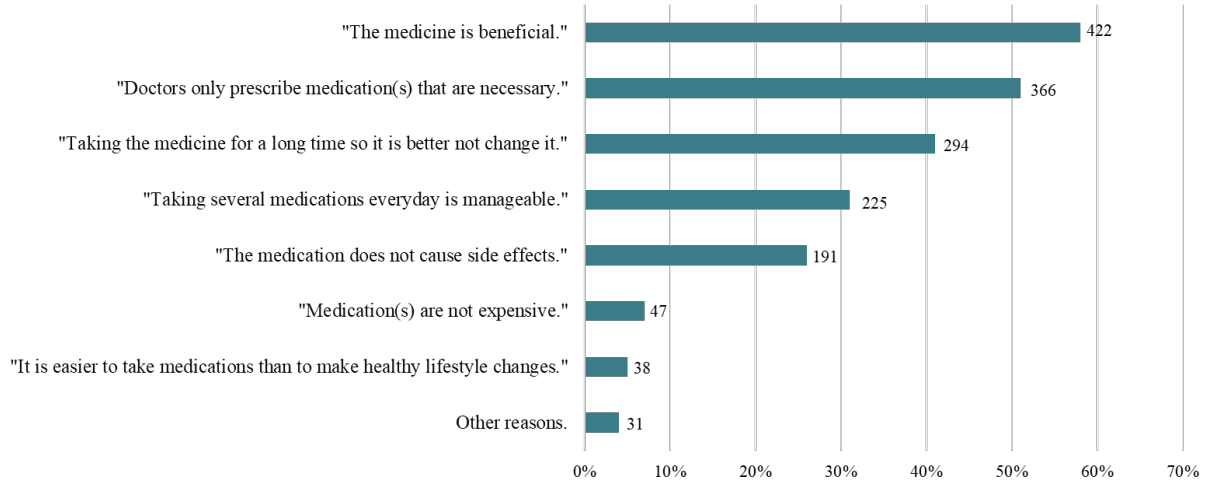

Figure 3. Reason for unwillingness to deprescribe any medication (n=726). Participants could choose multiple responses.

The results of the association between willingness to deprescribe and patient factors are presented in Table 2. Patients with lower satisfaction with medications (OR=0.31, 95% CI 0.21 to 0.47) and lower trust in their GP (OR=0.96, 95% CI 0.93 to 1.00) had higher odds of willingness to deprescribe specific medications. In the unadjusted analysis, the odds of willingness to deprescribe were higher with higher number of medications (OR=1.05, 95% CI 1.00 to 1.11).

Table 2. Patient willingness to deprescribe any specific medication[#] adjusted for sociodemographic characteristics and country clusters (n=1,081).

	Crude Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI)	p-value [a]
Patient gender (ref. male)				
Female	1.08 (0.85 to 1.36)	0.524	1.12 (0.86 to 1.50)	0.403
Number of medications				
per unit increase	1.05 (1.00 to 1.11)	**0.036**	1.05 (0.99 to 1.12)	0.106
GP gender (ref. female)				
Male	1.24 (0.97 to 1.60)	0.087	1.27 (0.96 to 1.69)	0.095
Other	1.05 (0.35 to 3.15)	0.926	1.25 (0.33 to 4.69)	0.745
'How do you make ends financially?' (ref. With great difficulty)				
Without any problems	0.84 (0.49 to 1.44)	0.524	0.83 (0.44 to 1.55)	0.551
Quite easily	0.66 (0.39 to 1.10)	0.112	0.66 (0.36 to 1.22)	0.184
With some difficulty	0.94 (0.56 to 1.55)	0.794	0.94 (0.53 to 1.68)	0.846
'How confident are you filling out medical forms by yourself?' (ref. not at all)				
Extremely	0.82 (0.49 to 1.37)	0.454	1.26 (0.69 to 2.30)	0.448
Quite a bit	1.00 (0.63 to 1.61)	0.985	1.55 (0.88 to 2.72)	0.126
Somewhat	0.99 (0.61 to 1.60)	0.955	1.35 (0.76 to 2.39)	0.304
A little bit	0.82 (0.47 to 1.42)	0.481	1.17 (0.62 to 2.20)	0.626
Self-rated health [b] (ref. not good health state)				
Good health state	0.80 (0.63 to 1.02)	0.076	1.00 (0.74 to 1.34)	0.996
'Overall, I am satisfied with my current medications' [c] (ref. no)				
Yes	0.29 (0.20 to 0.40)	**0.000**	0.31 (0.21 to 0.47)	**0.000**
Trust in the GP [d]				
per unit increase	0.95 (0.92 to 0.98)	**0.002**	0.96 (0.93 to 1.00)	**0.040**

[#] Patients who responded *'yes'* to the question '*Thinking about your current medication list, are there any medications that you would like to stop taking or reduce the dose of?'.* were considered willing to deprescribe specific medications.

[a] Mixed-models logistic regression adjusted at the county level. Dependent variable: willingness to deprescribe[#]. ICC = 0.102.

[b] Self-rated health was dichotomised considering '*good*', '*very good'* and *'excellent'* as '*good health state'* and *'average'* and *'poor'* as 'not *good health state'*.

[c] Satisfaction with currently medication was assessed by the 5-point Likert scale question *'Overall, I am satisfied with my current medications.'* from Reeve et al., 2016 [1]. 5-point Likert scale question was dichotomised. Responses '*agree*' or '*strongly agree'* were considered as '*yes*'.

[d] Score of the abbreviated Wake Forest Trust in Physician Scale [26]. Score is within 5 to 25, with higher values indicating higher trust.

Discussion

In this international study with 1,340 participants from 14 different countries, nearly half of older adults with polypharmacy were willing to stop or reduce at least one of their on average 7 medications. Patients' attitudes towards deprescribing varied across countries, with willingness to deprescribe varying between 23% in Bulgaria and 79% in Poland. Our findings demonstrate that older adults seemed to be most willing to deprescribe medications used for treatment and prevention of cardiovascular diseases, especially due to the side effects associated with the

medication. Older adults' satisfaction with their medications and their trust in their GP influenced their willingness to have medications deprescribed.

The overall willingness to deprescribe in our study using the global question from the rPATD *'If my doctor said it was possible, I would be willing to stop one or more of my regular medications'* was high with 81% of the older adults reporting to be willing to deprescribe any of their medications if their doctor recommended it. This finding is similar to other studies that used the same question [3]. However, the willingness to deprescribe specific medications dropped to 44% when older adults were asked about their willingness to stop or reduce specific medications they were using. While both questions were hypothetical, this shows that asking patients about specific medications on their medication list rather than a general question about their overall willingness to deprescribe, leads to a more conservative estimate of patient attitudes towards deprescribing. Other studies have reported a gap between reported willingness and actual behaviour in implementing deprescribing decisions in clinical practice [3-5]. There are different plausible explanations for this difference. First, the rPATD global question *'If my doctor said it was possible, I would be willing to stop one or more of my regular medications'* specifically mentions a doctor's recommendation, which may make patients more likely to agree with this statement. Although shared decision-making is crucial for successful deprescribing outcomes, not all patients like to be involved in deprescribing decisions and many defer the responsibility to their physicians [27]. Second, the question '*Thinking about your current medication list, are there any medications that you would like to stop taking or reduce the dose of'* specifically focuses on the patient's own medication list. It is plausible that patients are less likely to agree with stopping or reducing a specific medication rather than any unspecific medication. Nevertheless, the willingness to deprescribe specific medications remained relatively high, with almost half of older adults willing to stop or reduce at least one of their regular medications.

Despite the overall high willingness to deprescribe, we observed some geographic variation in our findings. Such variations may be due to differences in health literacy, income, healthcare systems, and out of pocket spending on medications. It has been shown that the willingness to deprescribe varies across countries and seems to be higher in patients from higher-income countries [2,3]. Variation in the willingness to deprescribe across different French-speaking countries (Belgium, Canada (province of Quebec), France, and Switzerland) has also been reported [28]. Our findings

show that not only GP attitudes towards deprescribing [29], which our team investigated in a previous study, but also patient attitudes towards deprescribing differ across countries. Willingness to deprescribe is context-specific, and such differences should be taken into account when designing and implementing deprescribing interventions.

The drugs most frequently named by older adults with polypharmacy for deprescribing were drugs usually used in the treatment or prevention of cardiovascular diseases (e.g., diuretics, lipid modifying agents, and agents acting on the renin-angiotensin system), which is in line with findings from a study in the United States of America involving adults between 50 and 80 years old [30]. Side effects from drugs used in the treatment of cardiovascular diseases are commonly noticed quicker than their benefits. Furthermore, for preventive cardiovascular medications, the benefits will become visible to patients in the long term and are visible in clinical tests rather than patients' perceptions of their health status. Hence patients may be more likely to stop medications for which they do not perceive an immediate effect. In light of these considerations about how patients perceive the benefits and side effects of their medications, the most frequent reasons for being willing to deprescribe identified in this research (e.g., presence of side effects, dislike of medication, inconvenience of taking the medication) are plausible. And on the flipside, the most frequent reasons for older adults with polypharmacy not being willing to deprescribe were the benefits associated with using medications. This is in line with other studies that reported favourable perceptions of medications as a barrier to deprescribing [18,19,31].

Older adults not willing to stop or reduce any specific medication also reported that they believed that doctors only prescribe necessary medications, highlighting the importance of communication, trust in the GP, and physician education on medication optimisation. Our findings show that older adults with lower satisfaction with medication and lower trust in their GP were more likely to be willing to have medications deprescribed. Indeed, low satisfaction with medications has been reported as an enabler to deprescribing [18,19]. As expected, when patients are satisfied with their current medications, they have no incentive to change it. Furthermore, patients who trust their GPs may be more satisfied with their overall care and less likely to challenge their GPs' decisions regarding medications [27]. Nevertheless, other studies reported that trust in the physician is an enabler in following the physician's recommendation to deprescribe [18,19,31]. This difference can be

explained by the fact that we did not specify in our question that deprescribing was a physician's recommendation.

This study is strengthened by its novel aspect of investigating which specific medications patients would prefer to deprescribe and for which reason. Another strength is its international design involving 17 sites from 14 countries, which allows us to compare patients' attitudes towards deprescribing across countries. This study also comes with several limitations. First, due to the hypothetical nature of the deprescribing decisions, the reported deprescribing decisions may not reflect patients' deprescribing decisions in real-world situations. Second, since patients were able to name any of their medications as deprescribing candidates, not all of them were suitable deprescribing candidates. Furthermore, since we did not have any information about patients' diagnoses and other relevant clinical information about patients' health status, we were unable to assess the appropriateness of their deprescribing preferences. In addition, patients could only name a maximum of four medications for deprescribing. Nevertheless, the information provided by patients about the specific medication types adds important information to the current literature on patient attitudes towards deprescribing different medication types. Third, due to the cross-sectional design of this study, causal relationships cannot be determined. Fourth, the fact that (except for the Netherlands) the samples at the country level were not representative limits their generalisability. Although GPs were instructed to recruit the patients consecutively to have a representative sample of patients, we cannot rule out selection bias. Fifth, due to the anonymous data collection via national coordinators and GPs in the different countries, we were unable to track the recruitment and response rate.

Implications and future research

The results from this study are informative for the development of future deprescribing interventions. First, despite being unable to study the exact reasons for the geographic variation across countries, the observed variation in patients' willingness to deprescribe across countries demonstrates that patient-facing intervention materials might be more impactful when adjusted to local context and different settings. Second, the fact that the currently used assessment tools to evaluate patient attitudes towards deprescribing likely lead to an overestimation could be one of the reasons why deprescribing willingness has not yet been found to translate to real-world

medication changes. Future deprescribing interventions would benefit from measures that reflect patients' deprescribing attitudes in real-life clinical situations more accurately. Third, when scoping future deprescribing interventions the types of medications patients are more willing to deprescribe should be considered. For instance, in the presence of more than one medication targeted for deprescribing, the deprescribing process can start with the medications that patients are most willing to have deprescribed. Furthermore, when making deprescribing recommendations, it also is important that physicians explain the rationale for the deprescribing choice, so that patients can understand how they will benefit from it. Future research should aim at better understanding the relationship between trust and patient-provider relationships and how this influences the implementation of deprescribing decisions in real-world clinical settings.

Contributors

RVL and KTJ wrote the first draft of the paper with support from KRW, ZR, and SS. RVL and KTJ were responsible for the statistical analysis. ZR and SS acquired the grant that funded this research. RVL, KTJ, KRW, ZR, and SS were involved in the study design decisions. KTJ and SS supervised the project. RVL, KTJ, KRW, LA, RA, SAB, MB, TF, GH, AAJ, DK, VL, HL, SM, AP, FP, RKEP, AS, DW, ER, ZR, and SS supported the data collection. All authors critically reviewed the manuscript and provided feedback. All authors approved the final version of the manuscript.

Data sharing statement

The data for this study are available to other researchers on request. The data will be made available for scientific research purposes, after the proposed analysis plan has been approved. Data and documentation will be made available through a secure file exchange platform after approval of the proposal. In addition, a data transfer agreement must be signed (which defines obligations that the data requester must adhere to regarding privacy and data handling). For data access, please contact the corresponding author.

Ethical approval and patient informed consent

The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the competent local ethics committee in Switzerland (Kantonale Ethikkommission Bern) in January 2022 (Project-ID 2022–00035). This study was conducted according to the relevant regulations at the participating sites and each national coordinator sought local ethical approval where necessary. To respect privacy rights under the European regulation, the requirements of the European General Data Protection Regulation (GDPR) were fulfilled by anonymization and data source protection. Patients gave their informed consent by replying to the question "by clicking yes here, I agree to participate in this study". If they clicked "no", they could not complete the survey.

Declarations of interest

The authors declare no conflicts of interest.

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5.4 Article 3. Exploring views of older adults with polypharmacy on their use of dietary supplements and their willingness towards deprescribing those: Results from observational survey study conducted in Swiss primary care settings

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My contributions: Together with Katharina Jungo, Kristie Weir, Zsofia Rozsnyai, and Sven Streit, we planned the study design, acquired ethical approval, submitted the study protocol, wrote the questionnaire, and recruited participants. I drafted the manuscript, created all figures and tables for the manuscript, implemented revisions from co-authors, entered data from paper on REDCap, was responsible for data cleaning and performed the statistical analysis.

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Exploring views of older adults with polypharmacy on their use of dietary supplements and their willingness towards deprescribing those: Results from an observational survey study conducted in Swiss primary care settings

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Abstract

Background: Dietary supplements are commonly used by older adults, but their inappropriate use may lead to adverse events and unnecessary costs. To optimise medication use, general practitioners (GPs) ideally are aware of all substances patients take, including supplements. This cross-sectional study explored the use of older patients with polypharmacy of dietary supplements, the rate at which they disclosed this use to their GPs, and compared patients' and GPs' attitudes towards discontinuing dietary supplements. **Methods:** GPs and their respective patients from Swiss primary care settings were invited to complete a survey on patients' use of dietary supplements and attitudes towards deprescribing those. We described and compared their responses. We assessed the association of supplement disclosure with patients' characteristics using multilevel logistic regression analysis. **Results:** We collected data from 10 GPs (3 (30%) female, average age 52 years (SD=8)) and 65 of their patients (29 (45%) female, average 7 patients per GP). 70% of the patients (n=45) were taking ≥1 supplement. On average patients reported to be using 3 supplements (SD=2). In 60% (n=39) of patients, GPs were unaware of ≥1 supplement used. 8% (n=5) of patients and 60% (n=6) of GPs reported ≥1 supplement they would be willing to deprescribe and none of the supplements reported by GPs and patients to deprescribe matched. **Conclusion:** Swiss GPs were unaware of many dietary supplements used by their older patients, which may affect medication optimisation efforts.

Keywords: Primary care, dietary supplements, deprescribing, polypharmacy, older adults, patient preferences.

Background

Dietary supplements are defined as products containing vitamins, minerals, herbs or other botanicals, amino acids and/or other dietary substances used to supplement a person's diet [1, 2]. The use of supplements is common and has been increasing in older adults, despite the underreporting of use in health surveys [3-8]. In Switzerland, the prevalence of dietary

supplement use among the adult population was between 26% and 53% from 2009 to 2023 [6, 9, 10]. According to the annual report of a Swiss health insurance, vitamin D was one of the most commonly purchased substances in 2021 and the use of vitamin B12 increased by 36% from 2021 to 2022 [11, 12]. Despite their widespread use, there are still gaps regarding the use and views of older adults with polypharmacy regarding dietary supplements.

Dietary supplements are often associated with a healthier life and are perceived as being risk-free [13-16]. Indeed, dietary supplements are important for vulnerable groups at risk for nutritional deficiency, but the benefits of taking many supplements are inconclusive for the general old population [17-19]. Given the low-risk perception towards dietary supplements and their easy accessibility, many patients do not disclose their use of supplements to their general practitioners (GPs) and other healthcare providers [5, 14, 16, 17, 20]. However, dietary supplements may also lead to adverse events, drug interactions, and hospital admissions, especially in older adults in which drug metabolism is compromised [19, 21, 22]. Furthermore, dietary supplements are often used when there is a lack of indication [3-5, 23]. When an indication for the use of the dietary supplement is not present, these are only contributing to patients' pill burden and present an unnecessary financial burden [14, 24]. Dietary supplements contribute to polypharmacy (use of ≥5 medications) and might be easy targets for deprescribing (stopping or reducing substances that are non-longer needed [25-27])[14, 28]. However, there is a lack of studies focusing on provider and patient attitudes towards deprescribing potentially inappropriate supplements [14, 29].

Firstly, when GPs are unaware of patients' use of dietary supplements, they may not associate patients' symptoms with adverse effects caused by supplements. Instead, they may approach these symptoms as a new condition, starting a new drug to treat it, and thereby initiate a prescribing cascade and contribute to polypharmacy [30, 31]. Therefore, GPs should not only consider prescription medications, but also supplements when carrying out medication reviews

and deprescribing efforts. To be able to identify and manage patients at risk of potentially inappropriate use of supplements, GPs and other healthcare providers must be informed about which supplements patients are using [5, 32]. However, there is limited information on how often older adults disclose their supplement use to their healthcare providers [5, 14, 17].

Secondly, although most of the research on deprescribing focuses on prescription drugs only, when healthcare professionals are asked which medications they would be more willing to stop or reduce in their patients, dietary supplements are often mentioned and seem to have promising deprescribing outcomes [28, 33]. However, these studies are focused on overall willingness to deprescribe, considering prescription and non-prescription medications, with little information focusing on patients' and GPs' willingness to stop or reduce supplements specifically. Studies that focus on overall willingness to deprescribe are limited by the lack of information on whether all prescribers accounted for all supplements when making deprescribing decisions. For instance, in different settings (e.g., different countries), dietary supplements might be part of the patients' medication list, but in others, they are not. Also, supplements that are not prescribed are not always included in medication lists. Little is also known about how patient and GP attitudes towards deprescribing supplements compare.

In this context, we aimed to investigate a) the use, beliefs, and motivations of older patients with polypharmacy for using dietary supplements, b) the rate at which the use of supplements is disclosed to GPs by patients, and c) to explore and compare older patients' and their GPs' attitudes towards deprescribing dietary supplements.

Materials and Methods

Settings and Study Design

This cross-sectional study is part of the "Understanding older patients' willingness to have medications deprescribed in primary care" [34]. GPs practising in the German-speaking part of

Switzerland were invited to participate in the study. The inclusion criteria for GPs were to be actively working in primary care in the German-speaking part of Switzerland. Each GP was asked to consecutively recruit a sample of five to ten of their primary care patients aged ≥65 years old with polypharmacy (≥5 long-term medications). The recruitment was from May 2022 to November 2023. Written informed consent was documented for each patient. More details on the study design have been described in the study protocol [34]. The competent ethics committee in Switzerland (*Kantonale Ethikkommission Bern*) approved the present study in January 2022 (Project-ID 2022–00035).

Data Source and Data Collection

GPs and their recruited patients were invited to complete a survey, which could be completed either online or on paper. For paper surveys, patients had four weeks to return the completed questionnaire in a sealed envelope to their GP practice. GPs then returned the sealed envelopes from patients and their own (which they had completed for each of the recruited patients) to the research team at the University of Bern, who then entered the data into the REDCap study database [35, 36].

Questionnaire

The content of the survey was based on the literature and on investigating the study aims [7, 13, 37-39]. The GP survey contained questions on background information (e.g., age, gender, years of work experience), dietary supplements disclosed to be taken by or prescribed to each of the recruited patients, and attitudes towards deprescribing those. The survey for patients contained questions on sociodemographic characteristics, use of dietary supplements, attitudes and beliefs towards dietary supplements, attitudes towards having those deprescribed and trust in their physician [40]. The English version of the questionnaires can be found in the supporting material (Additional File 1 and Additional File 2).

Variables and Data Management

To be able to match GPs' and patients' questionnaires, we collected encrypted information about patients' and GPs' names. Identifiable variables (GPs' and patients' names) were only used to certify the merging of the questionnaires and deleted afterwards.

Outcomes

Patient reported supplement use: Was assessed the use of supplement according to the question '*Do you regularly take vitamins, mineral or herbal supplements?'.* To assess which dietary supplements patients were using, each patient received a list of 24 commonly used dietary supplements, from which they could choose which one(s) they were currently taking (see Additional File 1). In addition, they were able to report in free text additional supplements by choosing the option '*other*'. Each supplement reported in free text was individualised coded according to the specific types (e.g., Q10, Halibut fish oil) for the analysis. Dietary supplements in free text were categorized according to the supplement substance (e.g., vitamin C, Iron, Calcium, Valerian, etc) and defined as vitamins, minerals, amino acids, essential fatty acids, plants and/or herbal extracts [1, 2]. For feasibility reasons, patients could choose a maximum of three dietary supplements to give more information on the reasons why they use these supplements and who recommended these supplements to them.

GP reported supplement use: GPs received the same list of 24 dietary supplements. Based on their knowledge, GPs selected the supplements the believed their patients were using. GPs were able to report additional supplements in free text by choosing the option '*other*' (see Additional File 2).

Disclosure of supplement use: To explore whether patients disclosed their dietary supplement use to their GPs, we compared the responses of GPs and patients. Disclosure was defined as follows: i) when both the GP and the patient reported the same specific supplement(s), we

assumed that the supplement use was disclosed (i.e., the GP knew about the supplement taken); ii) when the supplement was reported by either the patient or the GP, we assumed that the supplement had not been disclosed.

Willingness to stop/reduce supplement use: GPs reported the supplements they would be willing to deprescribe in free text. Patients reported the supplements they would be willing to deprescribe by responding to the 5-point Likert scale question *'I would be willing to stop or reduce the dosage of this supplement'* for each supplement they were currently taking. These responses were dichotomised considering the options '*strongly agree'* and *'agree*' as willingness to deprescribe each specific supplement. Willingness to deprescribe was considered for individual supplements.

Agreement to stop/reduce: In situations in which GPs and patients chose the same supplement for deprescribing, we considered this as agreement to deprescribe. When GPs and patients mentioned different supplements, we considered it as disagreement.

Statistical Analysis

We used descriptive statistics to report patients' and GPs characteristics, the frequency and reasons for using dietary supplements, and the beliefs of older adults regarding dietary supplements. Continuous variables were presented as means and standard deviation (SD) and categorical variables as frequencies and percentages. To analyse the association between the disclosure of the use of dietary supplements with patients' characteristics, we performed a multilevel logistic regression at the supplement level, accounting for cluster at the GP and patient level. To investigate and compare the willingness of patients and their GPs to stop or reduce the use of dietary supplements, we used descriptive statistics (numbers and percentages). To assess the deprescribing agreement, we described the number and percentage of situations in which patients and GPs agreed. We handled missing data by

carrying sensitivity analysis, restricting, and comparing responses of those who did and who did not fully complete the questionnaire, identifying missingness at random for all the variables. We used a complete case analysis to treat missing data. We used Stata 16.1 (StataCorp, College Station, TX, USA) to perform the analysis. A two-sided p-value of 0.05 was considered statistically significant.

Results

We collected data from 10 GPs (3 (30%) female, average age 52 years (SD=8)) and 65 of their patients (29 (45%) female, average of 7 patients per GP). **Table 1** shows the sociodemographic characteristics of patients and GPs. 65% (n=42) of the patients had at least secondary school level, 48% (n=31) reported to making ends financially quite easily, 89% (n=58) were born in Switzerland, 58% (n=38) self-rated their overall health as good or excellent, and 53% (n=35) were quite or extremely confident in filling out medical forms. The score of the abbreviated Wake Forest Trust in Physician Scale [40] was 22 (SD=4, range: 5-25, with higher values indicating higher trust). 51% (n=33) of the patients had been seeing their current GP for more than 9 years. 70% (n=45) of the patients reported to be taking at least one dietary supplement, and the average of supplements taken by patient was 3 (SD=2). 67% (n=30) of the 45 patients using dietary supplements responded that they talk to the GP or pharmacist before taking any dietary supplement, and 67% (n=43) of the overall sample agreed or strongly agreed that they should speak to their GP, a pharmacist, or another health professional before using any supplement.

Patients reported to be taking on average 7 (SD=3) prescription medications, while GPs reported that patients were taking on average 9 (SD=3) prescription medications. GPs had on average 15 years of work experience as a GP (SD=6). GPs reported that they recommended dietary supplements for 52% (n=31) of the patients and responded to be aware that 63% (n=41) of the patients were currently using ≥1 dietary supplement. Supplements most commonly

recommended were vitamin D, vitamin B12, and magnesium. 44% (n=20) of the patients using dietary supplements reported to buy their dietary supplements at a pharmacy, 18% (n=8) at the supermarket, 18% (n=8) at the GP practice[1], 8% (n=4) at the drugstore, 5% (n=2) on the internet, 2% (n=1) at the health food store. 75% (n=34) of the patients taking supplements said it was recommended by their GP, 31% (n=14) that they decided to take it themselves, and 20% (n=9) that it was recommended by another physician. The overall average score of 24 (SD=2) of the beliefs on dietary supplements was similar among users and non-users of supplements (score between 8 to 40, with higher values representing more positive beliefs).

[1] In some regions of Switzerland, physicians can dispense medications directly to their patients (self-dispensation cantons).

Table 1. Patient characteristics according to patients' reported use of dietary supplements

Patient characteristics	**Total (n=65), *n (%)***	**Use of dietary supplements (n = 45) [£]**	**No use of dietary supplements (n= 18) [£]**
Female gender, n (%) [a]	29 (45%)	25 (56%)	3 (17%)
What is your highest completed education?			
None, n (%)	2 (3%)	2 (4%)	0
Primary school, n (%)	20 (31%)	14 (31%)	4 (22%)
Secondary school, n (%)	33 (51%)	23 (51%)	10 (56%)
Third level education, n (%)	9 (14%)	5 (11%)	4 (22%)
How do you make ends financially?			
Without any problem, n (%)	26 (40%)	20 (44%)	5 (28%)
Quite easily, n (%)	31 (48%)	20 (44%)	10 (56%)
With some difficulty, n (%)	6 (9%)	3 (7%)	3 (17%)
With great difficulty, n (%)	1 (2%)	1 (2%)	0
Born in Switzerland, n (%)	58 (89%)	39 (87%)	18 (100%)
In general, how would you describe your health today?			
Excellent, n (%)	2 (3%)	1 (2%)	1 (6%)
Good, n (%)	36 (55%)	25 (56%)	10 (56%)
Average, n **(**%)	21 (32%)	15 (33%)	6 (33%)
Poor, n (%)	4 (6%)	2 (4%)	1 (6%)
How confident are you filling out medical forms by yourself?			
Extremely, n (%)	12 (18%)	2 (4)	2 (11%)
Quite a bit, n (%)	23 (43%)	4 (9)	11 (61%)
Somewhat, n (%)	16 (25%)	13 (29%)	3 (17%)
A little bit, n (%)	7 (11%)	4 (9%)	2 (11%)
Not at all, n (%)	2 (3%)	2 (4%)	0
How many different medications do you use regularly?			
Mean (SD)	7 (2)	7 (2)	6 (2)
Trust in the physician, mean (SD) [c]	22 (4)	22 (5)	22 (3)
How long have you been seeing your GP?			
0-9 years, n (%)	30 (46%)	21 (47%)	9 (59%)
10-19 years, n (%)	18 (28%)	14 (31%)	4 (22%)
20-29 years, n (%)	13 (20%)	9 (20%)	4 (22%)
30+ years, n (%)	2 (3%)	0	0
Number of dietary supplements used, mean (SD)	-	3 (2)	-
Score perceptions towards dietary supplements [b]			
Mean (SD)	24 (2)	24 (2)	24 (2)
Talk to GP or pharmacist about taking dietary supplements, n (%)	-	30 (67%)	-
I should speak to my GP/ pharmacist/another health professional before taking any herbal, vitamin, or mineral supplement.			
Strongly disagree, n (%)	1 (2%)	1 (2%)	0
Disagree, n (%)	5 (8%)	2 (4%)	3 (17%)
I do not know, n (%)	8 (12%)	4 (9%)	3 (17%)
Agree, n (%)	27 (42%)	18 (40%)	9 (50%)
Strongly Agree, n (%)	16 (25%)	14 (31%)	1 (6%)

SD, Standard deviation

[£] 3 (5%) missing responses on the question *"Do you regularly take vitamins, mineral or herbal supplements?"*

For all variables presented the missingness was 0. Exceptions: Gender, higher education, financial status, birth country: n=1 (2%); Patient health status, time seeing the GP: n=2 (3%); Number of medications: n=4 (6%); Perceptions towards dietary supplements: n=12 (18%); 'I should speak to my GP [...]' and Trust: n=8 (12%).

[a] None of the participants chose the option "other" for gender.

[b] According to eight 5-point Likert scale questions. Scores are between 8 to 40. Higher scores indicate more positive perceptions towards dietary supplements.

[c] Score of the abbreviated Wake Forest Trust in Physician Scale [40]. Score is within 5 to 25, with higher values indicating higher trust.

Patients' attitudes towards dietary supplements are shown in **Figure 1**. For most of the statements, most patients were unsure about their beliefs. Regarding benefits, 77% (n=46) of patients agreed or strongly agreed that supplements are beneficial and 54% (n=31) that they may prevent diseases. Despite these positive beliefs, only 7% (n=4) of the patients believed that everyone needs dietary supplements. Regarding risk perception towards dietary supplements, 48% (n=26) believe that supplements can interact with other drugs. Additional File 3 - Figure S1 shows the differences in agreement with each statement among users and non-users of dietary supplements. 75% (n=34) of users versus 61% (n=11) of non-users agreed or strongly agreed that supplements can have positive effects on one's health, 49% (n=22) of users and 39% (n=7) of non-users believed that supplements may prevent diseases, and 17%(n=8) of users versus 6% (n=1) of non-users believed that supplements treat diseases.

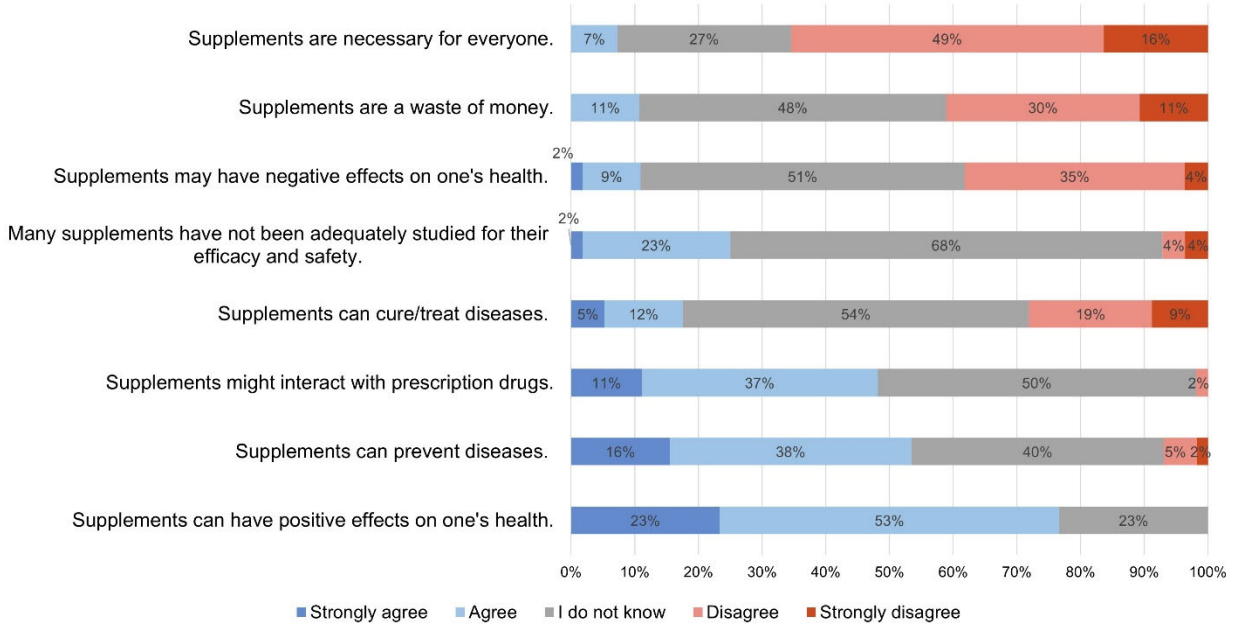

Figure 1. Perceptions towards dietary supplements in older patients with polypharmacy (n=65).

The three most common supplement categories reported by patients were vitamins minerals, and herbs. The dietary supplements most frequently mentioned by GPs were vitamin D (n=25), magnesium (n=10) and vitamin B12 (n=10). The same supplements were the most frequently mentioned by patients: magnesium (n=23), vitamin D (n= 20), and vitamin B12 (n=9) (Additional File 3 - Figure S2). Most common reasons for taking dietary supplements reported by patients were to improve general health and due to discomfort with muscles, joints or for bone health (**Figure 2**).

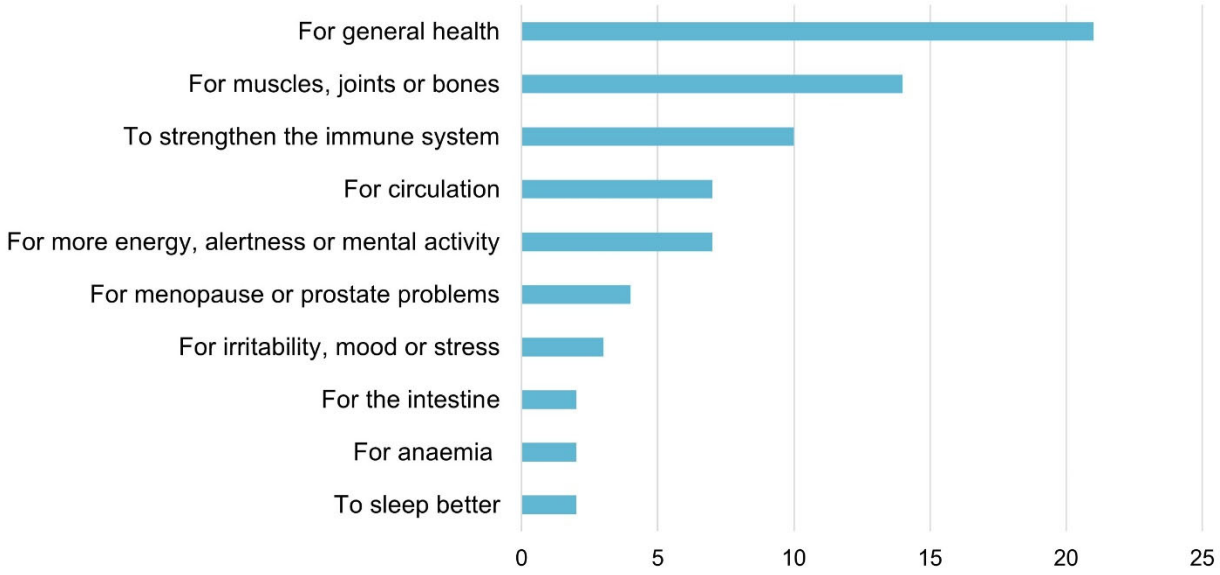

Figure 2. Reasons why older adults with polypharmacy living in the German part of Switzerland use dietary supplements (n=45).
Multiple answers were possible.

GPs and patients reported in total 156 supplements. Comparing supplement use reported by GPs and their patients demonstrated that 22% (n=35) of the supplements were classified as disclosed (reported by both parties), whereas 78% (n=121) were not disclosed (only reported by one of the parties). GPs were unaware of 82 (53%) supplements taken by 39 (60%) of their patients. 39 (25%) of the supplements were reported by GPs, but not by the patients. Supplements that had a complete match and were reported by both patients and GPs were vitamin B12, vitamin D and

magnesium. **Table 2** shows the association between the disclosure of the use of dietary supplements with patient characteristics and trust in their physician. The odds of supplement disclosure tend to be higher among women (OR = 2.10, 95%CI 0.81 to 5.48) and lower with higher reported trust in the physician (OR= 0.97, 95%CI 0.88 to 1.08).

Table 2. Association between the disclosure of the use of dietary supplements with patient characteristics and patient trust in their physician (n=123)

	Crude Odds Ratio (95% IC)	**p-value**	**Adjusted Odds Ratio (95% CI)**	**p-value [a]**
Female patient (*reference: male*)	2.14 (0.91 to 5.05)	0.081	2.10 (0.81 to 5.48)	0.129
Score trust in the physician [b] (*by unit increase*)	0.98 (0.89 to 1.07)	0.599	0.97 (0.88 to 1.08)	0.593
Patients' higher education (*reference: lower education*) [c]	0.60 (0.23 to 1.61)	0.311	1.28 (0.44 to 3.72)	0.655
Vitamin/minerals (*reference: other supplements*)	1.86 (0.70 to 4.95)	0.217	1.52 (0.55 to 4.15)	0.418

[a] Multilevel logistic regression adjusted at GP (ICC = 0.057) and patient (ICC = 0.058) level. Dependent variable: disclosure of dietary supplement, assessed by the match of each supplement reported by patients and their GPs.
[b] Score of the abbreviated Wake Forest Trust in Physician Scale [40]. Score is within 5 to 25, with higher values indicating higher trust.
[c] Secondary School or Third level education *versus* Primary School or None.

Of the 45 patients, only five (11%) reported at least one dietary supplement they would be willing to deprescribe if their GP suggested to do so. Of the ten GPs, six (60%) reported at least one dietary supplement they would be willing to deprescribe for 12 of their patients. In total, patients reported eight dietary supplements that they would be willing to deprescribe, and GPs reported 14. Patients reported they would be willing to deprescribe vitamins and minerals (n=4), herbs (n=2), and fish oil (n=2). GPs reported they would be willing to deprescribe vitamins and minerals (n=6), followed by herbs (n=4), fish oil (n=2), and others (n=2). Looking at patient-GP pairs, there were no matches of dietary supplements chosen for deprescribing selected by both patients and GPs.

Discussion

In our sample of GPs from Swiss primary care settings and a sample of their older patients with polypharmacy, most of the patients were taking at least one dietary supplement, and GPs seemed to be unaware of most dietary supplements taken by their patients. When GPs were asked about their willingness to deprescribe dietary supplements from their patients' medication list, 60% of the GPs reported at least one supplement they would be willing to stop or reduce. Only 11% of patients reported at least one supplement they would be willing to stop or reduce.

The percentage of 70% of patients reporting to be taking at least one dietary supplement is higher than in previous studies conducted in Switzerland, which reported the prevalence of supplement use between 26 to 53% [6, 9, 10]. However, these studies did not focus on the older population with polypharmacy, and the use of dietary supplements has been associated with older age [6, 7, 32]. Although other studies have reported that people who take dietary supplements have better overall health [14, 39], in our study the self-reported health status was comparable between users and non-users.

In our sample of older primary care patients with polypharmacy, the most common reasons for taking dietary supplements were to improve general health and due to discomfort with muscles, joints or for bone health. Other studies have also reported health maintenance or improvement [7, 13, 38, 39] and bone health [7, 39] as the main reasons for using supplements. However, the comparison with other studies should be considered with caution, as most of the studies on the beliefs and reasons for using dietary supplements did not specifically focus on older adults. The most commonly used supplement types were vitamins and minerals, which is in line with previous studies in Switzerland that showed that vitamins and minerals were the most commonly used [6, 10, 15]. Specifically, vitamin D, magnesium, and vitamin B12 were the most frequently reported dietary supplements by both patients and GPs. This corroborates the findings of a report from a Swiss health insurance company, in which the use of vitamin D and vitamin B12 were reported as frequently used in Switzerland in 2021 and 2022 [11, 12].

Considering patients' beliefs towards dietary supplements, most of the patients in our study believed that supplements are beneficial, that they may prevent diseases, and that they are worth the money spent on them. Although in our study patients held generally positive beliefs about dietary supplements, which is in line with previous studies [13, 37, 39], most participants also believed that supplements are not necessary for everyone and that they may interact with other medications. When we explored beliefs towards dietary supplements between users and non-users, users tended to have slightly more positive beliefs than non-users, which is plausible considering that patients with more positive beliefs may be more likely to purchase supplements for themselves. Despite the high use of dietary supplements by the patients in our study, many reported to be unsure regarding the risks and benefits of supplements. Other studies have also shown that there is lack of knowledge regarding dietary of supplements, but at the same time there also is an interest in learning more about those [13]. Patients' decision-making regarding supplement use would benefit from a better understanding of risks and benefits associated with dietary supplement use.

When comparing dietary supplements reported by GPs and their patients, we found that GPs seemed to be unaware of more than half of the dietary supplements taken by their older patients with polypharmacy. Controversially, most patients believed that they should talk to their GP or another healthcare provider about the use of dietary supplements, and most of the users of dietary supplements responded that they do talk to their GP or pharmacist about taking supplements. Other studies have also reported that patients usually did not disclose their dietary supplements use to their GPs or other health care professionals [5, 14, 41-44]. A systematic review reported that disclosure rate varied between 12% and 78% [5]. However, most of these studies were conducted in the United States of America, were published before 2010, and collected the disclosure information simply by asking patients whether they disclose the use of dietary supplements to their physicians or healthcare providers or not.

Another interesting finding in our study is that when GPs and patients were asked about the number of prescription medications the patient is currently taking, GPs reported on average two medications more than their patients, and many supplements were reported by GPs, but not by the patients. These findings are worth to be explored in future studies, as it likely reflects older patients' medication adherence. The discrepancy in the number of supplements reported by GPs and patients, demonstrates that a particular emphasis must be put on establishing adequate medication lists (including supplements) in future medication optimisation efforts.

The odds of supplement disclosure tended to be lower with increased trust in the physician. This counterintuitive finding can be due the overall high trust in the physician reported by the patients. Other studies have shown that patient-provider communication plays a role in the disclosure of dietary supplements [43-45]. Patients who trust their physician more are more likely to ask questions about their medications and less likely to feel judged when talking about the use of dietary supplements. Although patients were often unsure about the benefits of dietary supplements, and many understand that supplements may interact with other drugs, many still did not discuss the use of supplements with their GPs, demonstrating a lack of communication between older patients and GPs. Strategies to improve this communication and to optimise medication safety in primary care are thus required.

In our study, the only supplements that were reported by both patients and GPs were vitamin B12, vitamin D and magnesium. These supplements are commonly prescribed in Switzerland, which would explain why GPs are aware of the use of these supplements, but not other over-the-counter supplements. Other studies have identified potential risk of interactions between prescribed medications and dietary supplements when these are used concomitantly [5, 46]. For instance, one patient in our study was taking *St John's wort*, and two patients were taking *Ginkgo biloba. St John's wort* is one of the supplements with more risk for interactions with other drugs, and *Ginkgo biloba* poses a high risk of bleeding when used with other medications such as aspirin and warfarin, which are commonly used among older adults [5, 47]. The finding that many

supplements are not disclosed reinforces the fact that GPs should actively ask their patients about their use of dietary supplements including non-prescription ones, so that they can identify potential risks, drug-supplement and supplement-disease interactions, and lack of indications [44, 45].

Most of the older patients in our study were not willing to have any dietary supplements deprescribed. This is in line with the results from another study that found that older adults were resistant to having non-prescription medications (including dietary supplements) deprescribed [48]. The low patients' willingness to have supplements deprescribed could be explained by the finding of patients' positive attitudes towards supplements and overall lack of information regarding dietary supplements. Studies have identified barriers and concerns towards deprescribing prescription medications [49-51]. For instance, patients may be reluctant to change prescription medications that they have been taking for a long time [49-51]. In line with this, patients in our study may also be reluctant to change supplements they have been using for extended periods of time. Also, patients may feel more "ownership" in taking dietary supplements, as they are easily accessible, which could also pose a barrier to stop or reducing their use.

Despite the low awareness, most GPs were willing to stop or reduce at least one dietary supplement for at least one of their patients. If they had been aware of all supplements used by patients, they likely would have made even more deprescribing suggestions. Dietary supplements are easy targets for reduction or discontinuation. Although there are no studies focusing on GPs' attitudes towards deprescribing dietary supplements specifically, GPs and other health care providers often suggest dietary supplements as deprescribing targets [28, 33]. When comparing patient and provider attitudes towards deprescribing, none of the supplements chosen by GPs and by patients matched. This discrepancy could be one of the reasons explaining the low implementation rate of deprescribing suggestions in real-world clinical settings. In future research, it will be worthwhile to also compare GP-provider agreement with regards to deprescribing prescription medications.

It is important to note that dietary supplements are important for vulnerable groups at risk for nutritional deficiency, but their use should be individualised and accompanied by a GP, pharmacist, dietitian, or other healthcare professional to avoid interactions and adverse events. Supplements are often used without an indication, can cause harm, and lead to unnecessary costs. Medications - including supplements - that do not contribute to patients' health should be considered for deprescribing to avoid risks and unnecessary costs [25, 52]. However, only when GPs aware of all substances used by their patients, they can provide personalised treatments and make deprescribing recommendations. Our findings shed light on the need of raising GP awareness on actively asking their patients about the use of dietary supplements when conducting medication optimisation efforts.

Strengths and Limitations

To the best of our knowledge, this is the first study investigating and comparing older patients' and GPs' attitudes towards deprescribing dietary supplements. This study is strengthened by the fact that we collected information directly from patients and their GPs, allowing the comparison of their responses. Although we sought to avoid selection bias by instructing GPs to use a consecutive sampling approach when recruiting patients, we cannot rule out selection bias by GPs. At the patient level, we have the limitation that due to feasibility reasons patients could only report a maximum of three supplements in the questionnaire. However, only 10 patients (15%) reported three supplements. We cannot rule out recall bias, as participants may not have reported all their supplements, or volunteer bias, as participants could have been more interested in the study topic compared to non-participants. Given the cross-sectional design we cannot establish causality in our results. However, our exploratory and hypothesis-generating findings provide valuable insights for future research on the use and deprescribing of dietary supplements in older adults with polypharmacy. The findings of the present study cannot be generalised, given its sample size and restricted location in the German-speaking part of Switzerland. Despite the small

sample size, some of our analyses were carried out at the supplement level, allowing a more detailed examination of the dietary supplements disclosed by patients to their GPs. Nevertheless, due to the small sample size the confidence intervals in the logistic regression model were wide and imprecise.

Conclusions

GPs in Swiss primary care settings were not aware of more than half of dietary supplements used by their older patients with polypharmacy. Patients seemed to be unsure about the benefits, necessity, and possible risks of dietary supplements and were not willing to have those deprescribed. To optimise the use of dietary supplements by older adults, is crucial for GPs and other health care providers to identify which dietary supplements are used by their patients. By actively asking patients about their supplement use as part of medication optimisation efforts, healthcare professionals can help reduce medication-related harm.

Declarations

Ethics Approval and Consent to Participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the local ethics committee in Switzerland (*Kantonale Ethikkommission Bern*) in January 2022 (Project-ID 2022–00035). Informed consent was obtained from all subjects involved in the study.

Consent for publication

Not applicable.

Competing Interests

The authors declare no conflicts of interest.

Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors on request.

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Author Contributions

Conceptualization, RVL, KTJ, KRW, ZR, SS; Design, RVL, KTJ, KRW, ZR, SS; Methodology, RVL, KTJ, KRW, ZR, SS; Data acquisition, RVL, KTJ, KRW, ZR, SS; Data Analysis, RVL, KTJ; Data interpretation, RVL, KTJ, KRW, ZR, SS; Writing – Original Draft Preparation, RVL, KTJ; Writing – Review & Editing, RVL, KRW, ZR, SS; Funding Acquisition, ZR, SS. RVL, KTJ, KRW, ZR, and SS have approved the submitted and published version of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Supplementary Information

The online version contains supplementary material available at

Additional Files

Additional File 1.pdf – Study questionnaire for patients

Additional File 2.pdf – Questionnaire for General Practitioners

Additional File 3.docx - **Figure S1.** Beliefs about dietary supplements of users and non-users and **Figure S2.** Dietary supplements used by older patients with polypharmacy living in the German part of Switzerland.

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5.5 Article 4. Pharmacists' attitudes towards interprofessional collaboration to optimise medication use in older patients in Switzerland: A survey study

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My contributions: Together with Katharina Jungo and Sven Streit, we planned the study design and acquired ethical waiver of non-responsibility. I drafted the questionnaire and implemented suggestions from all co-authors. I drafted the manuscript, created all figures and tables shown in the manuscript, implemented revisions from co-authors, was responsible for the data cleaning performed the statistical analysis.

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Pharmacists' attitudes towards interprofessional collaboration to optimise medication use in older patients in Switzerland: A survey study

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Abstract

Background: Collaboration between physicians and pharmacists facilitates the conduct of medication optimisation efforts. In the context of deprescribing, pharmacists' roles are often described as making deprescribing recommendations to physicians. Little is known about factors associated with pharmacists' willingness to make deprescribing recommendations and their interprofessional collaboration with physicians in Swiss primary care settings.

Objective: To explore pharmacists' perspectives on medication optimisation and deprescribing in older adults, and their preferences for interprofessional collaboration in Swiss primary care settings.

Methods: In this cross-sectional study, a random sample of 1000 pharmacist members of the Swiss Pharmacists Association pharmaSuisse was invited to participate in a survey on medication optimisation, deprescribing, and interprofessional collaboration. The survey contained three case vignettes of multimorbid patients with polypharmacy aged ≥80 years old, with different levels of dependency in activities in daily living (ADL) and cardiovascular disease (CVD). For each case vignette, pharmacists were asked if and which medications they would deprescribe. We calculated proportions of pharmacists' willingness to deprescribe by case vignette and performed a multilevel logistic regression to assess associations between CVD, ADL and willingness to deprescribe.

Results: 138 (14%) pharmacists responded to the survey: 113 (82%) were female, their mean age was 44 years (SD=11)**,** and 66% (n=77) reported having never received any specific training on how to conduct structured medication reviews. 83 (72%) pharmacists reported to be confident in identifying deprescribing opportunities. All pharmacists were willing to deprescribe ≥1 medication in all vignettes. Patients with CVD were at lower odds of having medications deprescribed (OR=0.27, 95%CI 0.21 to 0.36). Willingness to deprescribe was lower with higher dependency in ADL (medium versus low dependency: OR=0.68, 95%CI 0.54 to 0.87, high versus

low dependency: OR=0.72, 95%CI 0.56 to 0.91). However, the effect of dependency in ADL on willingness to deprescribe was significantly modified by the history of CVD. 88 (81%) pharmacists wished to be more involved in deprescribing and medication review.

Conclusion: Pharmacists were willing to make deprescribing suggestions for older patients with polypharmacy, but two-thirds reported having received no formal training on how to perform structured medication reviews. Pharmacists would like to be more involved in the process of medication review and deprescribing, which should be leveraged in the context of Swiss primary care settings.

Keywords: Polypharmacy, medication review, interprofessional collaboration, older adults, deprescribing

Background

The worldwide ageing population has been leading to new challenges in the health care of older adults. With ageing, older adults are more susceptible to having multiple diseases (known as multimorbidity), which often leads to polypharmacy (commonly defined as the regular use of ≥5 medications) [1-3]. Inappropriate polypharmacy usually refers to the use or prescribing of medications without a clinical indication, and it is common among older adults [3-7]. Due to the age-related pharmacokinetics and pharmacodynamics changes in the body, older adults are at high risk for adverse events led by inappropriate polypharmacy [5, 8]. Inappropriate polypharmacy has been associated with several health issues, such as an increased fall risk, cognitive decline, and adverse drug reactions [8-10]. Studies have shown that many older adults are receiving medications without an indication (overprescribing) or are not receiving the appropriate treatment (underprescribing) [11, 12]. To address over- and underprescribing medication reviews and

deprescribing (stopping or reducing medications for which risks outweigh benefits) should be part of patient care [13-15].

Older adults with multimorbidity and polypharmacy commonly see different healthcare providers due to their complex healthcare needs. To optimise older adults' medication use, collaboration among health professionals is crucial [16, 17]. Pharmacists are healthcare professionals who are in constant contact with patients, they have excellent knowledge about medications, and therefore they are equipped to play a key role in deprescribing and medication optimisation [18-21]. The collaboration between pharmacists and general practitioners (GPs) is promising for the conduct of medication optimisation efforts [19, 22]. Several studies have shown that a multidisciplinary intervention, including pharmacists, had a positive impact on deprescribing in long-term care facilities [23-26] and facilitated deprescribing in primary care settings [19, 22, 27].

In these interprofessional collaborations, the role of pharmacists is often described as making deprescribing recommendations to physicians and proposing treatment plan modifications. A study in nursing homes conducted in the French-speaking part of Switzerland found that pharmacists seemed to be more willing to put deprescribing into practice, while nurses and physicians were more cautious [28]. Studies in other countries, however, reported pharmacists to be less willing to deprescribe medications compared to physicians [29, 30]. Despite the promising involvement of pharmacists in medication optimisation, there are also many barriers to effective interprofessional collaborations [29-31]. For instance, pharmacists are sometimes hesitant to make recommendations to physicians due to the fear of jeopardising their collaboration and they fear that their recommendations could be perceived as inappropriate [31]. Lack of access to the patients' health information has also been reported as a barrier for interprofessional collaboration [29, 32]. These barriers are likely also true in the context of Swiss primary care settings. Little is known about interprofessional collaboration for optimising medications in Swiss primary care settings.

In this survey study, we aimed i) to explore the current practices of pharmacists working in Switzerland related to conducting medication reviews, ii) to understand pharmacists' attitudes towards making deprescribing recommendations in adults ≥80 years with polypharmacy and how patients' history of cardiovascular disease (CVD) and dependency in activities of daily living (ADL) are associated with pharmacists' willingness to make deprescribing recommendations, and iii) to explore pharmacists' experiences with and wishes for interprofessional collaboration between pharmacists and physicians with regards to medication optimisation.

Methods

Study design and data collection

In this cross-sectional survey study, a random sample of 1000 pharmacist members of the Swiss Pharmacists Association (pharmaSuisse) were invited to participate in an online survey. Participants were invited in two batches of 500 each. The first batch received a reminder and the second one received one email. Data was collected between June and December 2023. The questionnaire was available in German and French on SurveyMonkey [33] (for the English translation see additional File 1). Seven pharmacists piloted the survey before the start of the data collection. The questionnaire was anonymous, and pharmacists did not receive any compensation.

Inclusion criteria

Inclusion criteria were to work as a pharmacist in a community pharmacy, hospital, nursing home or home care in Switzerland, and to be an active member of pharmaSuisse. Pharmacists working in other settings (e.g., industry) were excluded because we were interested in pharmacists with direct patient contact.

Questionnaire

The questionnaire contained 41 questions regarding pharmacists' sociodemographic characteristics and work settings, familiarity, and experiences with deprescribing and medication reviews, and their interprofessional collaboration with physicians. In our questionnaire, *medication review* was defined as "*a structured evaluation of a patients' medications, including identifying medication-related problems and making concrete suggestions for improvement. The aim of a medication review is to identify, solve and prevent drug-related problems to optimise drug therapy, reduce drug side effects and improve clinical outcomes*" (adapted from [34]). To assess pharmacists' experiences with medication reviews, we adapted the *Tool for Assessing Ambulatory Care Pharmacist Practice* (TAAPP) [35]. To assess confidence in deprescribing, we used the confidence scale from Heinrich et al. [18]. To assess pharmacists' experiences with and wishes for interprofessional collaboration, we adapted the questions from the *Physician/Pharmacist Collaboration Index* (PPCI) so that they addressed collaboration with physicians in general and not one specific physician [36]. The adapted score from the PPCI ranged from 10 to 70, with higher scores indicating greater collaboration. Next, we presented three case vignettes describing hypothetical patients aged ≥80 years with polypharmacy to the pharmacists to assess their willingness to deprescribe. We adapted the case vignettes from the study conducted by Jungo et al. with general practitioners in 31 countries [37]. Hypothetical patients in the case vignettes differed in terms of dependency in activities of daily living (ADL) and history of cardiovascular disease (CVD) (Additional File 2). Pharmacists were asked if and why they would stop or reduce any medication in each case vignette.

Sample size calculation

We used the power one proportion function in Stata to calculate the sample size. Based on the 74% of pharmacists found to be confident to discuss deprescribing interventions [1], we would need to recruit 106 pharmacists in Switzerland at a power 0.80 to reach an effect size of 0.1 to

detect a difference in the proportion of pharmacists who are confident to discuss deprescribing interventions. To account for potential missing data, we considered that around 20% of respondents would not complete the entire survey and verified that 3% of pharmacist members of pharmaSuisse were not working in an eligible setting. The minimum sample size was therefore 137 pharmacists.

Statistical analysis

We used descriptive statistics to report pharmacists' characteristics. Continuous variables were presented as means and standard deviations and categorical variables as frequencies and percentages. We used two-sample test of proportions to compare the percentages of deprescribing recommendations across the case vignettes. We performed a multilevel logistic regression at the medication level to assess the association between the willingness to deprescribe and pharmacists' and patient characteristics (CVD, dependency in ADL). We performed sensitivity analysis using the same regression model for patients with and without CVD. Covariables included in the model were selected based on clinical rationale: age, gender, specialization training in community pharmacy, frequency of interaction with older adults. We identified the data to be missing at random and used a complete case analysis method. Analyses were performed with Stata 16.1 [38]. A two-sided p-value of 0.05 was considered statistically significant. Free text responses were assigned to not pre-defined categories.

Ethical approval

This study did not fall within the scope of the Swiss Human Research act and therefore a waiver of non-responsibility was obtained from the competent ethics committee of the canton of Bern (Req-2021-01101).

Results

Sociodemographic characteristics

Of the 1000 pharmacists invited to respond to the survey, 138 (14%) pharmacists accepted to participate in our study. 113 (82%) were female, with a mean age of 44 years old (SD=11), and a mean of 18 (SD=11) years working as a pharmacist (Table 1). Regarding further training, 43 (31%) pharmacists had a specialist training (FPH) in community pharmacy and 57 (41%) a specific training (FPH) in anamneses in primary care. 132 (96%) of the pharmacists worked in a community pharmacy or pharmacy combined with drugstore. Pharmacists were working in 20 out 26 cantons in the different language regions of Switzerland (Additional File 3). Pharmacists reported that on average 40% (SD=22) of their daily patients are ≥70 years old and have polypharmacy.

Table 1. Characteristics of participating pharmacists (n=138).

Gender [a]	
Female, *n (%)*	113 (82%)
Male, *n (%)*	25 (18%)
Age in years	
Mean (SD)	44 (11)
Missing, *n (%)*	3 (2%)
Working settings (multiple responses possible)	
Community pharmacy, *n (%)*	121 (88%)
Community pharmacy combined with drugstore, *n (%)*	11 (8%)
Hospital, *n (%)*	12 (9%)
Homecare, *n (%)*	1 (1%)
Nursing home *n (%)*	4 (3%)
Do you work in a place where self-dispensing by physicians is permitted? [b]	
Yes *n (%)*	50 (36%)
No *n (%)*	70 (51%)
Mixed system *n (%)*	16 (12%)
Missing *n (%)*	2 (2%)
Do you have one of the following further training certifications? (multiple responses possible)	
FPH in anamneses and primary care *n (%)* [c]	57 (41%)
FPH in community pharmacy *n (%)* [c]	43 (31%)
FPH Vaccination and blood sample	94 (68%)
FPH Pharmaceutical counselling for healthcare institutions	3 (4%)
Further training (other FPH certificates/titles) *n (%)* [c]	24 (17%)
Certificate of Advanced Studies (CAS)/Master of Advanced Studies (MAS) *n (%)*	16 (12%)
PhD *n (%)*	13 (9%)
How many years have you been working as a pharmacist?	
Mean (SD)	18 (11)
Missing *n (%)*	16 (12%)
Estimate the percentage of daily interactions with patients ≥70 years old with polypharmacy	
Mean (SD)	40 (22)
Missing *n (%)*	17 (12%)

Variables for which missing was not reported, had no missing responses.

[a] None of the participants chose the responses 'non-binary' or 'Do not want to report' for this question.

[b] In Switzerland, self-dispensing cantons are regions in which physicians can dispense medications directly to their patients. In non-self-dispensing cantons medication dispensing is restricted to pharmacists. In mixed cantons, the legislation varies within the canton.

[c] FPH*: Foederatio Pharmaceutica Helvetiae* is the certification organisation for pharmacists in Switzerland, overseeing postgraduate and continued education.

Attitudes towards medication review and deprescribing

Current practices of pharmacists working in Switzerland related to conducting medication reviews and attitudes towards deprescribing are shown in Table 2. Of the 116 pharmacists who responded to this part of the questionnaire, most reported creating a complete and updated medication list (n=68, 59%) and identifying medication-related issues (n=92, 79%) at least once a week. Overall, 34% (n=39) had received specific training on how to perform structured medication reviews, and of the 38 respondents with a FPH in community pharmacy, 76% (n= 29) had received specific training on medication reviews. 98 (85%) pharmacists reported encountering a situation in which deprescribing would be possible at least once a week. Pharmacists that reported to conduct medication reviews stated that the medication review process takes an average of 31 minutes (SD=32).

Table 2. Current practices of pharmacists working in Switzerland related to conducting medication reviews and attitudes towards deprescribing (n=116)[#]

Question	n (%)
Medication optimisation	
I ask patients questions to assess adherence to medication therapy [a]	
At least once a week	101 (87%)
Less often than once a week	14 (12%)
Missing	1 (1%)
I review all medications (prescription, over-the-counter medications, herbals, and supplements) with the patient to create an updated and complete medication list [a]	
At least once a week	68 (59%)
Less often than once a week	47 (40%)
Missing	1 (1%)
I review complete medication list to identify medication-related issues [a]	
At least once a week	92 (79%)
Less often than once a week	24 (21%)
How long does the medication review process take for you?	
Minutes, mean (SD)	31 (32)
Which tools do you use to check medication appropriateness of patients ≥70 years with >5 medications? (multiple responses possible) [b]	
Lists of potentially inappropriate medications (e.g., Priscus, Beers, START/STOPP)	42 (36%)
Documents/tools for polymedication check [c]	46 (40%)
Other interaction databases (e.g. Pharmavista, Compendium)	95 (82%)
Other	13 (11%)
Have you ever received training on how to conduct a detailed medication reviews?	
Yes (versus no)	39 (34%)
If yes, did this training take place during your studies at university or afterwards? [b]	
At university	13 (33%)
In further education/training	21 (54%)
Other	5 (13%)
Attitudes towards deprescribing	
From 1 to 10, how familiar were you with deprescribing before starting this questionnaire? [d]	
Low familiarity (1-3)	32 (28%)
Average familiarity (4-7)	54 (47%)
High familiarity (8-10)	30 (26%)
What priority should deprescribing have in your daily work?	
High/very high priority	58 (50%)
Neither high nor low priority/undecided	48 (41%)
No priority/low priority	10 (9%)
How often does a situation arise in your daily work in which deprescribing would be possible? [b]	
Everyday	24 (21%)
Several times a week	42 (36%)
Once a week	32 (28%)
Once a month	11 (10%)
Fewer than that	7 (6%)

[#]Of the 138 pharmacists, 22 (16%) stopped responding the questionnaire in this section. Therefore, the percentages are regarding the total of 116 who responded to this session to the questionnaire.

[a] Adapted from Bradley et al., 2018 [35].

[b] No one responded "none"/"never" to these questions.

[c] *Polymedication* check: Medication review tool used in Swiss pharmacies with patients taking ≥4 medications for longer than 3 months [39].

[d] Score varying from 0 to 10. Higher scores indicate higher familiarity with the concept of deprescribing.

Pharmacists' confidence in undertaking deprescribing behaviours and medication review in daily practice is shown in Figure 1. 83 (72%) of 116 pharmacists agreed or strongly agreed in being able to identify suitable deprescribing targets, while 49 (42%) disagreed or strongly disagreed that their pharmacy training prepared them to discuss deprescribing opportunities with patients. Regarding medication reviews, 81% (n=88) of the 109 respondents reported that they would like to be more involved in the process of medication reviews, but 65% (n=70) disagreed or strongly disagreed with having enough information about their patients' health status to conduct medication reviews. 56% (n=61) reported to often see patients for whom they would recommend deprescribing, but as they were not responsible for the prescription they do not react in this situation (e.g., contacting their physician).

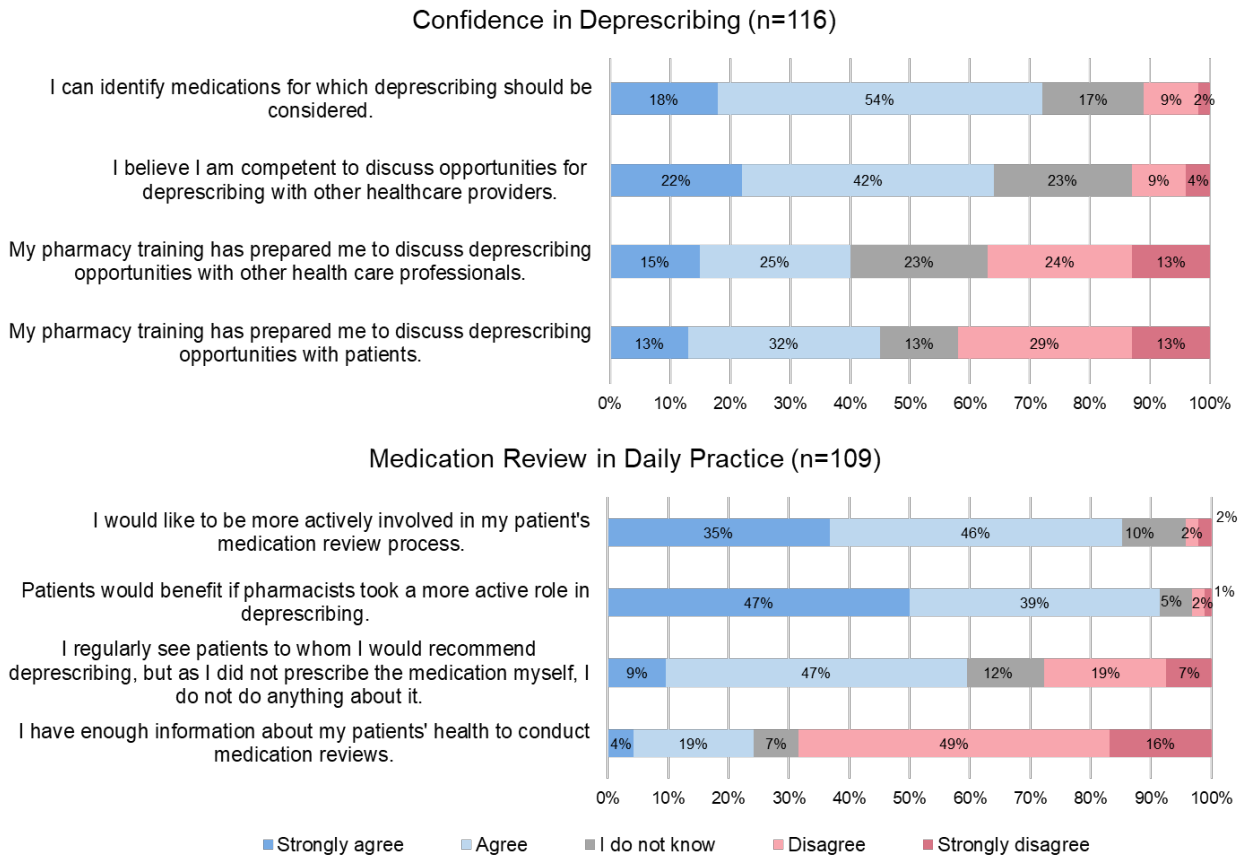

Figure 1. Pharmacists' views on medication review and their confidence in undertaking deprescribing behaviours.

Adapted from Heinrich et al., 2022 [18].

Case vignettes

All pharmacists were willing to deprescribe at least one medication in each case vignette. Pharmacists suggested an average of 4 (SD=3) medications for deprescribing in case vignette 1 (low dependency in ADL), and an average of 3 (SD=3) medications for vignettes 2 and 3 (medium and low dependency in ADL). When comparing deprescribing recommendations by case vignette, pharmacists were less willing to deprescribe for patients with a history of CVD in all case vignettes (Additional File 4). For instance, in case vignette 1 (low dependency in ADL), the difference of willingness to deprescribe at least one medication between patients without and with history of CVD was 24% (95%CI 12% to 36%). This difference of willingness to deprescribe for patients with

and without CVD decreased to 10% (2% to 23%) for patients with higher dependency in ADL. In addition, the percentages of medications suggested for deprescribing tended to be lower with higher level of dependency in ADL (Additional File 4). When exploring the willingness to deprescribe by medication type (Additional File 5), we found that the willingness to deprescribe was lower for all medications in all case vignettes when the patient had a history of cardiovascular disease. For instance, in case vignette 1 (low dependency in ADL), pharmacists' willingness to deprescribe aspirin fell from 41% to 1% when the same hypothetical patient was presented with a history of cardiovascular disease, and for pantoprazole from 65% to 47%. The history of CVD had a lower impact on the willingness to deprescribe antihypertensive medications (e.g., enalapril; decrease from 6% to 3%), for which pharmacists' willingness to deprescribe was low to begin with. Of the 98 pharmacists who responded to the case vignetter-related questions, 89% (n=87) responded that they perceived enalapril as the most important medication for the patient in case vignette 1 (low cardiovascular risk and low level of dependency in ADL), and 86% (n=84) that pantoprazole as the least important. In all case vignettes, the most common reason reported for deprescribing was the possibility of adverse events (case vignette 1: n=68, 69%; case vignette 2: n=71, 72%; case vignette 3: n=64, 65%).

Association of patient and pharmacist characteristics with pharmacists' willingness to deprescribe

The associations between pharmacists' willingness to make deprescribing recommendations and patients' history of CVD and level of dependency in ADL are shown in Table 3. The odds of recommending deprescribing were lower in patients with a history of CVD (OR=0.27, 95%CI 0.21 to 0.36) and lower in patients with higher dependency in ADL compared with low dependency (medium dependency: OR=0.68, 95%CI 0.54 to 0.87, high dependency: OR=0.72, 95%CI 0.56 to 0.91). However, the joint presence of medium/high dependency in activities of daily living and a history of CVD increased the odds of making a deprescribing suggestion (CVD x medium dependency: OR=1.61 95%CI 1.11 to 2.33, CVD x high dependency: OR= 1.75 95%CI 1.21 to

2.52). In sensitivity analysis higher levels of dependency in ADL were had lower odds of willingness to recommend deprescribing only in cases without history of CVD (medium versus low dependency: OR=0.69, 95%CI 0.54 to 0.87, high versus low dependency: OR=0.72, 95%CI 0.57 to 0.91), but it was different in cases with history of CVD (medium versus low dependency: OR=1.10, 95%CI 0.83 to 1.47, high versus low dependency: OR=1.26, 95%CI 0.95 to 1.67) (Additional File 6). The odds of recommending deprescribing were also higher for pharmacists that had received a training in medication review (OR=2.48, 95%CI 1.38 to 4.44).

Table 3. Association between making deprescribing recommendations in each case vignette and the patients' history of cardiovascular disease and dependency in activities in daily living (ADL), and pharmacists' characteristics (n=98 pharmacists, n=4,788 observations)

	Crude Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI) [a]	p-value [a]
Cardiovascular disease (CVD) (*ref: no history of cardiovascular* disease*)*				
History of cardiovascular disease	0.39 (0.33 to 0.45)	0.000	0.27 (0.21 to 0.36)	0.000
Dependency in activities of daily living (ADL) *(ref: low)*				
Medium	0.84 (0.70 to 1.00)	0.052	0.68 (0.54 to 0.87)	0.002
High	0.91 (0.76 to 1.08)	0.281	0.72 (0.56 to 0.91)	0.006
Interaction Terms *(ref:* CVD x low dependency*)*				
CVD x medium dependency	-	-	1.61 (1.11 to 2.33)	0.012
CVD x high dependency	-	-	1.75 (1.21 to 2.52)	0.003
Pharmacist age				
Per 10-year increase	0.86 (0.66 to 1.12)	0.262	0.93 (0.77 to 1.14)	0.629
Gender *(ref: male)*				
Female	0.81 (0.39 to 1.70)	0.577	0.77 (0.38 to 1.56)	0.465
Frequency of seeing patients ≥70 years old with polypharmacy (0-100)				
Per 10-percentage increase	0.90 (0.80 to 1.02)	0.110	0.88 (0.78 to 0.99)	0.041
FPH in community pharmacy *(ref: not having a FPH title in community pharmacy)*				
Specialized in community pharmacy	0.78 (0.58 to 1.34)	0.406	0.84 (0.47 to 1.52)	0.573
Training in Medication Review *(ref. not having a training in medication review)*				
Having a medication review training	2.42 (1.38 to 4.26)	0.002	2.48 (1.38 to 4.44)	0.002

[a] Multilevel logistic regression adjusted for patients' and pharmacists' characteristics. Dependent variable: Willing to deprescribe each medication. ICC: 0.351.

FPH*: Foederatio Pharmaceutica Helvetiae* is the certification organisation for pharmacists in Switzerland, overseeing postgraduate and continued education. The FPH in community pharmacy is required in order to obtain authorization to practice as a pharmacist in the private sector under their own professional responsibility and to bill the compulsory health insurance.

Interprofessional collaboration in the context of medication review and deprescribing

Pharmacists' experiences with interprofessional collaboration between pharmacists and physicians with regards to deprescribing are reported in Table 4. 97% (n=105) of the pharmacists reported to interact with physicians to clarify questions regarding prescriptions at least once a

week. 65% (n=68) of respondents stated that they believe their communication with physicians to be two-way, and 59% (n=64) reported having an interest in supporting physicians to improve their prescribing practices (Additional File 7). Additional File 8 presents pharmacists' ideas to improve collaboration between pharmacists and general practitioners with regards to medication optimisation based on the free text responses provided: respondents wished for more shared decision-making (n=32, 43%), more efficient ways to communicate with physicians (n=31, 40%), and acceptance of their recommendations and expertise by physicians (n=25, 33%).

Table 4. Pharmacists' experiences with interprofessional collaboration between pharmacists and physicians with regards to deprescribing (n=109[¥]).

Question	Mean (SD) or n (%)
How often do you interact with physicians to clarify questions regarding medications prescribed to your patients?	
Everyday	43 (40%)
Several times a week	46 (42%)
Once a week	16 (15%)
Once a month	2 (2%)
Rarer	2 (2%)
Never	0 (0%)
How often do you make suggestions to physicians about patients' medication use?	
Everyday	19 (18%)
Several times week	30 (28%)
Once a week	28 (26%)
Once a month	16 (15%)
Rarer	15 (14%)
Never	0 (0%)
Score of the interprofessional collaboration with physicians (min. 10 to max. 70)[#]	
Mean (SD)	45 (10)

SD: Standard Deviation

[¥] Missing: 29 (21%) stopped responding the questionnaire in this section. Percentages are regarding the 109 pharmacists who responded to this section.

[#] Score range: 10 – 70, adapted from Zillich et al., 2006 [36]. Higher scores indicate greater collaboration.

Discussion

In our sample of pharmacists working mainly in community pharmacies in Switzerland, all were willing to deprescribe at least one medication in each case vignette of oldest-old adults with polypharmacy. The willingness to recommend deprescribing was lower in patients with a history of CVD and lower in patients with higher dependency in ADL. However, the joint presence of

medium/high dependency in activities of daily living and a history of CVD increased the odds of making a deprescribing suggestion. Pharmacists who reported having a specific training on structured medication review were also more willing to recommend deprescribing. Most pharmacists perceived themselves as capable of identifying drugs suitable for deprescribing and reported to be willing to be more involved in the process of optimising medication use. Regarding their collaboration with physicians in medication reviews, pharmacists wished for more shared decision-making, and more efficient ways to communicate with physicians.

Only a third of pharmacists reported having had sufficient training on how to conduct structured medication reviews and deprescribing, which highlights the need for expanded training opportunities in this area. Of note, it must be considered that only a minority of the participants had a specific training (FPH) in community pharmacy and that their mean age was 41 years, which means that they are likely not representative of the most recent generation of pharmacy graduates in Switzerland. Since 2018, it has been mandatory for all pharmacists to obtain the federal postgraduate title FPH in community pharmacy to obtain a licence allowing them to practice the profession under their own professional responsibility and to bill the compulsory health insurance. This specialist qualification covers training on how to perform medication reviews. If our study had focused only on recent graduates, our results would likely have been different.

Pharmacists reported that on average 40% of their daily patients are ≥70 years old and have polypharmacy. These daily interactions could be a great opportunity to identify and manage situations of inappropriate polypharmacy, which are common among older adults [40]. Most of the pharmacists reported reviewing patients' medication lists at least once a week, and that they take on average half an hour to perform medication reviews. However, previous studies have shown that performing medication reviews can take up to 2-3 hours [41, 42]. This discrepancy may be explained by the fact that the term *medication review* can be interpreted in different ways, and

while some definitions exist they are not universal [34]. Although pharmacists reported performing medication reviews in their daily work, two third of them reported to have never received training on how to perform structured medication reviews. This finding raises awareness of the need for additional continued education and training sessions offered to pharmacists that do not have the federal postgraduate title FPH in community pharmacy, considering that the training for obtaining this FPH title covers the topic of structured medication reviews. Nevertheless, we also must consider that despite providing a definition of medication reviews in our questionnaire, medication reviews may have interpreted differently by pharmacists in our sample.

Even though only a third of participants reported having obtained training in conducting structured medication reviews, most of them reported being confident in identifying deprescribing opportunities and discussing them with other healthcare providers. These findings could reflect different aspects: On the one hand, this could indicate that pharmacists in our study felt confident in analysing medication lists despite not having received specialised training on how to conduct structured medication reviews. On the other hand, this finding could also indicate that they were overconfident in their ability to assess medication lists, which could also be reflected in the lower amount of time spent on medication reviews. Finally, pharmacists in our sample could have had different views on what a medication review is, as the definition of medication review varies and can be interpreted differently. For instance, in Switzerland pharmacists provide different services in which they are asked to check medication lists (e.g., “polymedication check” [39]), but that are not exactly a structured medication review.

Most of the pharmacists reported to be confident in implementing deprescribing, in line a study in Ireland [18]. Despite the reported high confidence in identifying suitable deprescribing candidates, only 43% reported being confident in discussing deprescribing suggestions with patients, which highlights the need of training on patient involvement in medication optimisation. Furthermore, the finding that more than half of the respondents reported to not react to deprescribing

opportunities (e.g., not contact physician with specific suggestions) could indicate a lack of "ownership" of what medications they dispense to their patients. This is plausible in the context of the findings from another study, which found pharmacists to be hesitant to make deprescribing recommendations to physicians [30]. Nevertheless, pharmacists are legally equally responsible for the medications dispensed as the prescribing physicians. A further explanation for this inertia could be the lack of knowledge about their patients' health status since most pharmacists reported lacking information on this aspect. Many pharmacists wished to have access to more patient health information and believed that this would facilitate their collaboration with physicians. Access to complete patient health records not only allows pharmacists to make better-informed deprescribing recommendations based on patients' health status, but also to share these recommendations more efficiently [43], which reinforces the need for pharmacists to have a better access to patient information.

Pharmacists in our study were willing to make deprescribing recommendations for patients with polypharmacy aged ≥80 years, and all were willing to deprescribe at least one medication in each case vignette. In the LESS study with general practitioners [37, 44], in which the same case vignettes were used in 31 countries, GPs' willingness to deprescribe was lower compared to the pharmacists' willingness in the present study. Both our study and the studies with GPs found the willingness to deprescribe to be lower in patients with a history of CVD. In our study, the odds of recommending deprescribing were lower for patients with higher dependency in ADL. However, we identified an interaction effect between history of CVD and dependency in ADL; meaning that the effect of dependency in ADL on the outcome was significantly modified by the history of CVD. This is why the finding that the odds to deprescribe are lower in patients with higher dependency should be interpreted with caution. When considering only patients without a history of CVD, pharmacists' willingness to deprescribe was lower in patients with higher dependency in ADL, but it was not the case for patients with history of CVD. Interestingly, previous studies with GPs

reported the willingness to deprescribe to be higher with higher dependency in ADL [37, 44, 45]. In addition, pharmacists who reported having received a specific training on how to perform structured medication reviews were more willing to deprescribe, which highlights again the importance of specific courses on medication review offered by pharmacists.

The history of CVD seemed to have a greater impact on pharmacists' deprescribing choices than in GPs' choices, especially regarding cardiovascular medications [37]. For instance, in this present study, in case vignette 1 (low dependency in ADL) pharmacists' willingness to deprescribe aspirin fell from 41% to 1% and pantoprazole from 65% to 47% once the hypothetical patient was presented with a history of cardiovascular disease. For antihypertensive medications, the history of CVD had a low impact on the willingness to deprescribe, which is in line with the GP study using the same case vignettes [37]. Proton pump inhibitors were the medication most commonly chosen for deprescribing in all cases vignettes, which again is in line with the GP study [37]. However, when Swiss GPs received the same case vignettes [44], cardiovascular preventive medications like atorvastatin were the most commonly chosen deprescribing candidate, and pantoprazole was the second.

In our study, the most commonly reported reason for deprescribing was the risk of adverse events, followed by lack of benefits, which is in line with the study with GPs [37]. The similarities in the deprescribing decisions of pharmacists in our study and GPs who responded to the same case vignettes evidence the feasibility of collaboration between these professionals in the context of deprescribing. Other studies have reported that physicians are willing to accept deprescribing recommendations from pharmacists, and their similar decisions could be an enabler for their collaboration [29, 30]. We also identified several barriers to the collaboration between pharmacists and physicians in the context of medication optimisation. Pharmacists in our study wished for more opportunities to interact with physicians, quicker and more efficient communication channels between them, more opportunities for shared decision-making between them, and more access to patient information, which is in line with other studies [31, 46-48].

Our findings have significant implications for clinical practice and future research on medication optimisation within the context of Swiss primary care settings. The high willingness of pharmacists to make deprescribing recommendations, their confidence in identifying deprescribing opportunities, and their wish for being more involved in this process, indicate that the involvement of pharmacists can facilitate the implementation of deprescribing and medication optimisation efforts. In addition, our study highlights the need of more training on medications reviews offered to pharmacists, including information on deprescribing-related communication with patients and physicians. Our study raises awareness the need for facilitating interprofessional collaboration between physicians and pharmacists in the context of medication optimisation. To improve the implementation of medications reviews, future interventions should focus on ways to improve communication between pharmacists and physicians, shared decision-making between them, and access to patient information.

Our survey study is strengthened by the fact that we invited a random sample of Swiss pharmacists to participate in our study. Indeed, pharmacists working in 20 out of 26 cantons in the different language regions of Switzerland completed the survey. Nevertheless, our findings may not be generalizable to other countries. Our study also comes with several limitations. First, the use of hypothetical case vignettes may not fully capture how pharmacists regularly manage older adults with polypharmacy in real-life clinical practice. Second, we cannot rule out volunteer bias, as the pharmacists who participated in our study may be more interested in medication optimisation than those who chose not to participate. Third, we managed to recruit the target sample size, but the fact that not all pharmacists responded to all the questions decreased our sample size for some analyses. For feasibility reasons, we were unable to extend the recruitment period. The regression model however was performed at the medication level for the case vignettes, which allowed for a sufficiently big sample.

Conclusion

All pharmacists in this study were willing to recommend deprescribing for at least one medication in oldest-old patients with polypharmacy. Willingness was higher for patients with lower cardiovascular risk and lower in patients with higher dependency in ADL. Pharmacists were confident in their capacity to make deprescribing recommendations and would like to be more involved in the process of medication review and deprescribing, which provides great potential for medication optimisation efforts in Swiss primary care settings.

Declarations

Ethics approval and consent to participate

This study did not fall within the scope of the Swiss Human Research act and therefore a waiver of non-responsibility was obtained from the competent ethics committee of the canton of Bern (Req-2021-01101). Hence, the consent to participate was not necessary from the participants.

Consent for publication

Not applicable.

Availability of data and materials

The dataset used and analysed during the current study is available from the corresponding author upon reasonable request. The questionnaire used in this study is available in the Additional File 1. The case vignettes are available in the Additional File 2.

Competing interests

The authors do not have any competing interests to declare.

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Authors' contributions

RVL, KTJ, SS, DC, and SPJ were involved in the study planning, study design, and development of the study questionnaire. SPJ was responsible for the sampling of pharmacists. RVL wrote the original draft of this paper with the support of KTJ. KTJ and SS supervised the project. Critical review and feedback were made by KTJ, SS, DC, and SPJ. All authors approved the final version of the manuscript.

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6. Overall discussion

6.1 Summary of Findings

6.1.1 Article 1. Inappropriate proton-pump inhibitor prescribing in primary care – an observational study with quality circles

In Article 1, I investigated how GPs in the canton of Bern in Switzerland manage potentially inappropriate PPI prescribing after being aware of such inappropriate prescribing among their patients. GPs retrospectively selected 206 patients in their medical records with a PPI prescription ≥8 weeks. Potentially inappropriate PPI prescriptions were common in our sample, with 85 (41%) patients having a potentially inappropriate PPI prescription. Of these 85 patients, 55 (65%) had no indication for PPI, and 30 (35%) had a too high dose. After one year, only 29 (35%) of the 84 flagged potentially inappropriate PPIs were stopped or reduced. The most frequently mentioned reasons that deprescribing was not possible were a lack of discussion with the patient (no contact or no time), the presence of symptoms requiring the PPI, or the unwillingness of the patient to deprescribe.

6.1.2 Article 2 . Understanding older patients' willingness to have medications deprescribed in primary care: a protocol for a cross-sectional survey study in nine European countries

In this study protocol, we explained the detailed study planning, design, settings, methodology, rationale, and objectives of a project involving different countries, of which the overall aim of was to investigate older adults' perceptions and views on the use and deprescribing of specific medications. This project resulted in different sub-studies. In this thesis specifically, Article 2.1 and Article 3 are studies resulted from this study protocol. When this study protocol was published, there were nine countries involved in the study, but with the development of the project and increasing international collaborations, we completed data collection in 14 countries.

6.1.3 Article 2.1. Understanding older patients' attitudes towards deprescribing in primary care: A cross-sectional survey study in 14 countries

In Article 2.1, we recruited 1340 patients from 14 countries (average 96 per country), of which 82% (n=1,089) were satisfied with their medications, 81% (n=1,088) were willing to deprescribe if their doctor suggested doing so, and 44% (n=589) said they would be willing to

have at least one of their medications deprescribed. The three most commonly reported medication types for deprescribing were diuretics (n=111, 11%), lipid modifying agents (n=109, 11%), and agents acting on the renin–angiotensin system (n=83, 8%). The odds of being willing to have specific medications deprescribed were higher with lower trust in the physician (OR=0.96, 95%CI 0.93 to 1.00) and lower satisfaction with medications (OR=0.31, 95%CI 0.21 to 0.47). Patients' willingness to stop or reduce medications were lower when patients were asked about specific medications compared to when they were asked non-specific questions such as *'If my doctor said it was possible, I would be willing to stop one or more of my regular medications'* from the rPATD [97].

6.1.4 Article 3. Exploring views of older adults with polypharmacy on their use of dietary supplements and their willingness towards deprescribing those: Results from an observational survey study conducted in Swiss primary care settings

In Article 3, we collected data from 10 GPs in Switzerland, of which 3 (30%) were female, and the average age was 52 years (SD=8). In addition, we collected data from 65 of their patients, of which 29 (45%) were female, with an average of 7 patients per GP). 70% of the patients (n=45) were taking ≥1 supplement. On average patients reported to be using 3 supplements (SD=2). In 60% (n=39) of patients, GPs were unaware of ≥1 supplement used. 8% (n=5) of patients and 60% (n=6) of GPs reported ≥1 supplement they would be willing to deprescribe and none of the supplements reported by GPs and patients to deprescribe matched.

6.1.5 Article 4. Pharmacists' attitudes towards interprofessional collaboration to optimise medication use in older patients in Switzerland: A survey study

In article 4, we invited 1,000 pharmacists to respond to an online survey. Of these, 138 (14%) accepted to participate. 113 (82%) pharmacists were female, and their mean age was 44 years (SD=11). 77 (66%) pharmacists reported having never received any specific training on how to conduct structured medication reviews, while 83 (72%) reported being confident in identifying deprescribing opportunities. All pharmacists were willing to deprescribe at least one medication in all vignettes. We also assessed patients' and pharmacists' characteristics associated with the pharmacists' willingness to deprescribe and found that patients with CVD were at lower odds of having medications deprescribed (OR=0.27, 95%CI 0.21 to 0.36).

Pharmacists' willingness to deprescribe was lower with higher dependency in ADL (medium versus low dependency: OR=0.68, 95%CI 0.54 to 0.87, high versus low dependency: OR=0.72, 95%CI 0.56 to 0.91). However, the joint presence of medium/high dependency in activities of daily living and a history of CVD increased the odds of making a deprescribing suggestion (CVD x medium dependency: OR=1.61 95%CI 1.11 to 2.33, CVD x high dependency: OR= 1.75 95%CI 1.21 to 2.52). In sensitivity analysis higher levels of dependency in ADL were had lower odds of willingness to recommend deprescribing only in cases without history of CVD (medium versus low dependency: OR=0.69, 95%CI 0.54 to 0.87, high versus low dependency: OR=0.72, 95%CI 0.57 to 0.91), but it was different in cases with history of CVD (medium versus low dependency: OR=1.10, 95%CI 0.83 to 1.47, high versus low dependency: OR=1.26, 95%CI 0.95 to 1.67). The odds of recommending deprescribing were also higher for pharmacists that had received a training in medication review (OR=2.48, 95%CI 1.38 to 4.44). Regarding interprofessional collaborations for medication optimisation, 88 (81%) pharmacists wished to be more involved in the process of medication review and deprescribing, which provides great potential for medication optimisation efforts in Swiss primary care settings.

6.2 Strengths and Limitations

6.2.1 Strengths

The work presented in this thesis has several strengths. Article 1 brought information on how GPs manage patients with inappropriate PPIs after being aware of these inappropriate prescriptions using data collected directly by GPs, overcoming the problems of epidemiological studies where the indication and the duration of the PPI prescription might be unknown or unclear. The consecutive retrospective sampling approach has the advantage of reducing selection bias. Also, the fact that GPs were responsible for identifying potentially inappropriate PPI prescriptions and too high doses on their own reflects closer the usual care in the GPs' practices. The study presented in Articles 2, 2.1, and 3 adds important information to the literature by its novel aspect of assessing patients' attitudes on having specific medication types deprescribed, including dietary supplements. The international part of the study (Article 2.1) allowed us to explore allows us to compare patient's attitudes towards having specific medications deprescribed across countries. For the part in Switzerland (Article

3), collecting data directly from GPs allowed us to compare their responses and overcame limitations of studies that assessed the disclosure of dietary supplements simply by asking the patients whether they disclosed or not the use of supplements to their GPs. To the best of our knowledge, this is the first study investigating and comparing older patients' and GPs' attitudes towards deprescribing dietary supplements. Article 4 is strengthened by the random sample approach to recruit pharmacists. Pharmacists were from 20 out of 26 Swiss cantons, increasing national representativeness. In addition, using questionnaires allowed us to assess multiple variables in an inexpensive way.

6.2.2 Limitations

The studies presented in this thesis also have some limitations. Due to their cross-sectional design, none of the studies presented in this thesis can establish causality. Also, we cannot rule out volunteer bias, as participants (patients, GPs, and pharmacists) could have been more interested in the study topic compared to those who chose to not participate.

In Article 1, a random sample would have been better to prevent selection bias, but it was not feasible in our study as in Switzerland electronic medical records report past patients and not necessarily currently active patients. Also, definitions of too high doses of PPIs were not standardised and the provided information to assess PPI appropriateness was limited, therefore GPs may have interpreted it differently. Although we sought to avoid selection bias by instructing GPs to use a consecutive sampling approach when screening their medical records, we cannot rule out selection bias. Our findings cannot be generalised, as the GPs participating in the study were all practising in the canton of Bern in Switzerland. The study presented in Articles 2, 2.1, and 3 has the limitation of the hypothetical nature of the deprescribing choices, which may not reflect patients' and GPs' attitudes towards deprescribing in real-world settings. Due to feasibility reasons (e.g., length of the questionnaire), and considering the experience with piloting the questionnaire, we allowed patients to report a maximum of four medications and three supplements they would be willing to have deprescribed. Since the samples of participants at the country level were not representative, this limits the generalisability of our findings. Although GPs were instructed to use a consecutive sampling approach to recruit patients, selection bias by GPs cannot be ruled out. For the international part (Article 2.1), we did not have any information about patients' diagnoses and other relevant clinical information about patient health conditions and were therefore unable to assess the appropriateness of their deprescribing preferences. Due

to the irreversible anonymisation of the collected data, due to the General Data Protection Regulation (GDPR), we were not able to track the response rate nor were we able to adjust the analyses for the clustering effect at the GP level. For the part in Switzerland (Article 3), we cannot rule out recall bias, as participants may not have reported all the dietary supplements they were using. Article 4 has the limitation that the use of hypothetical case vignettes may not fully capture how pharmacists regularly manage older adults with polypharmacy in real-life clinical practice. Although we managed to recruit the target sample size, not all pharmacists responded to all the questions, which decreased the sample size for some analyses. As our survey was based on Swiss settings, our findings cannot be generalised to other countries.

6.3 Outlook

In this thesis, I investigated different aspects related to patients' and healthcare professionals' behaviours and views on optimising medication use in primary care settings, including the use of dietary supplements. For that, I presented my findings through five manuscripts, of which four are research articles and one is a study protocol. As of May 2024, of the research articles one is published (Article 1), two are under review (Articles 3 and 4), and one is being reviewed by co-authors (Article 2.1).

First, I took proton pump inhibitors (PPIs) as an example of common inappropriate medications to explore how GPs manage patients with potentially inappropriate medications after being aware of potentially inappropriate PPI prescriptions among their patients. Second, considering the lack of research on deprescribing focusing on specific medications, including dietary supplements, we designed an international study to explore i) attitudes of older patients with polypharmacy towards deprescribing specific medications and ii) patients' and their GP's attitudes towards dietary supplements and their willingness to deprescribe those. Third, in view of the importance of interprofessional collaborations to reach successful deprescribing outcomes, we investigated the willingness of pharmacists to make deprescribing recommendations and their preferences for interprofessional collaborations in medication review and deprescribing.

Through these different studies, I collected information directly from key actors in the process of medication optimisation and deprescribing: patients, pharmacists, and GPs. By assessing these different perspectives on deprescribing and medication optimisation, this thesis

gathered important information for future tailored deprescribing interventions that consider patient preferences, healthcare provider perspectives, and contextual factors, such as differences across countries.

6.4 Interpretations, Implications, and Perspective

Despite the growing evidence on medication optimisation and deprescribing, the implementation of these practices by GPs, pharmacists and other healthcare professionals still faces challenges and has barriers to be overcome [94, 95]. While our research has provided valuable insights into the behaviours and attitudes of patients and healthcare professionals towards deprescribing, there are still many questions in this area that need to be investigated in future research with different populations and using different study designs.

First, my findings highlight the need for more personalised and targeted interventions to successfully implement deprescribing in clinical practice. While educational initiatives have been shown to enhance GPs' and other healthcare professionals' awareness of inappropriate polypharmacy [73-75], just raising awareness of potentially inappropriate medications may be not enough to impact successful deprescribing outcomes. Of note, we also need to consider that patient involvement and interprofessional collaboration facilitate the implementation of deprescribing [96, 110, 111]. Therefore, it is possible that if GPs in our study had received information on how to involve patients in the deprescribing attempt and if patients and other healthcare professionals had been actively involved in the process of deprescribing potentially inappropriate PPIs, our results would have been different. To reach higher success deprescribing rates, it is necessary to co-design interventions that provide enough training, knowledge, evidence, and guidance to healthcare professionals. In addition, future deprescribing interventions should provide guidance on how to involve the patient in the deprescribing attempt and make use of behaviour change techniques to enable the deprescribing of inappropriate medications. Precisely, the findings from Article 1 provided useful information also for the currently DepRescribing inapprOpriate Proton Pump InibiTors – DROPIT Trial, a cluster randomized controlled trial in Swiss primary care settings, which aims to investigate the effectiveness of an intervention for patients and GPs to deprescribe inappropriate PPIs in primary care patients in Switzerland.

Second, my research also sheds light on the importance of accurately assessing patients' willingness to deprescribe specific medications. While previous studies have indicated high levels of willingness of patients to have medication deprescribed [99, 106], my results suggest that patients' willingness may vary when patients are asked about specific medications. Most studies investigating patient attitudes towards deprescribing have used the revised rPATD to investigate patients' willingness to have medications deprescribed [97]. Using the question *'If my doctor said it was possible, I would be willing to stop one or more of my regular medications'* from the rPATD, 84-88% of the patients were willing to have medications deprescribed [99, 106]. Meanwhile, using the question *'Thinking about your current medication list, are there any medications that you would like to stop taking or reduce the dose of?'* we found that 44% of older patients with polypharmacy were willing to have medications deprescribed. To better understand patient attitudes towards deprescribing, we need to identify and develop new measures that capture patients' deprescribing attitudes more accurately, ensuring that deprescribing interventions are aligned with patient preferences and priorities. In addition, the findings of Article 2 and Article 2.2 shed light on variations in patients' willingness to deprescribe across countries, demonstrating that patient-facing intervention materials might be more impactful when adjusted to local contexts and different settings.

Third, this thesis identified an important gap in deprescribing interventions. While there are several tools and guidelines on deprescribing and medication optimisation, there is still a lack of interventions and guidelines focusing on and involving dietary supplements in the context of medication optimisation and deprescribing [41, 53, 60, 61, 132]. Nevertheless, all substances used by the patient - including dietary supplements - that do not contribute to the patient's health should be considered for deprescribing to avoid potential risks and unnecessary costs [7, 154]. GPs must be aware of all substances used by their patients to be able to provide personalised treatments and make deprescribing recommendations. However, in our sample of Swiss primary care older patients with polypharmacy, many did not disclose the use of dietary supplements to their GPs, which is in line with other studies reporting low disclosure of dietary supplements use to GPs and other healthcare professionals [20, 21, 116, 117, 155]. Our finding of low disclosure of supplement use reinforces the fact that GPs should actively ask their patients about their use of dietary supplements. Future deprescribing interventions should aim to enhance patient-provider communication, guiding GPs and other healthcare providers to actively ask their patients about their use of dietary supplements.

Fourth, my research also sheds light on ways to improve the interprofessional collaboration between pharmacists and physicians in the context of medication optimisation in Swiss primary care settings. As well as GPs, pharmacists are also in constant contact with patients, having a crucial role in the implementation of deprescribing and medication reviews [28, 138-140]. Our findings are in line with other studies that reported that pharmacists have confidence and willingness to recommend deprescribing potentially inappropriate medications [138, 144], indicating that their involvement can facilitate the implementation of deprescribing and medication optimisation efforts. In addition, our study highlights the need for more training on medication reviews offered to pharmacists, involving communication with patients and physicians. To better implement interprofessional medication reviews, future interventions should aim to find ways to improve communication between pharmacists and physicians, facilitate shared decision-making between these healthcare providers and with patients, and explore ways to enhance the access to patient information by all healthcare providers involved in medication-related decisions.

My thesis contributed to addressing significant gaps in the field of medication optimisation and deprescribing. My findings are informative for designing future deprescribing interventions that consider not only patients' preferences, but also attitudes of GPs and pharmacists towards deprescribing and medication optimisation, contributing to future research and clinical practice in the context of deprescribing and medication reviews.

7. Curriculum Vitae

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Curriculum Vitae

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EDUCATION

Jul/2021 - Present	**PhD Student - Epidemiology and Biostatistics** *PhD Thesis: "Exploring different aspects related to making and implementing deprescribing decisions in primary care settings"* Institute of Primary Health Care (BIHAM) University of Bern, Switzerland
Feb 2015 - Feb 2017	**Master of Science (MSc) - Public Health Nutrition** *Master's Thesis: "Vitamin D in intestinal microbiota modulation: Associations with inflammatory and cardiometabolic profiles"* School of Public Health, University of São Paulo (USP), Brazil
Jan 2011 - Dez 2014	**Bachelor of Science (BSc) - Nutrition and Dietetics** University São Camilo, Brazil

EXPERIENCE

July 2021 - Present	**Research Assistant and Doctoral Researcher** Institute of Primary Health Care (BIHAM), University of Bern, Switzerland
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Sep 2020 - Jun 2021	**Researcher Trainee - Clinical Evolutionary Medicine Group**
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Feb 2015 – Mar 2017	**Research Assistant and Master's Researcher**
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Mar 2014 - Jan 2015	**Research Assistant - Cohort study - Gut Microbiota and Nutrition**
	School of Public Health - University of São Paulo (FSP/USP), Brazil
Jan 2013 – Jan 2014	**Internships – Clinical Dietitian/ Nutritionist/ Researcher**
	Federal University of São Paulo – UNIFESP, Brazil
	Hospital of Medical School of the University of São Paulo – HCFMUSP, Brazil
	Hospital 9 de Julho, Brazil
	Hospital Samaritano, Brazil
	Equilibrium Latam - Nutritional consultancy, Brazil
	Compass Group (GRSA), Brazil

RESEARCH PROJECTS

2021 - Present	Exploring different aspects related to making deprescribing decisions in primary care settings
2015 - 2017	Vitamin D in the modulation of intestinal microbiota: Associations with inflammatory and cardiometabolic profile

2014 - 2015	Validation of web-based self-reported anthropometric data in the Nutritionists' Health Study (NutriHS)
2014	Benefits of nutrients and nutritional status control in oncologic patients

RESPONSIBILITIES

Coordination of the "Understanding older patients' attitudes towards deprescribing in primary care: A cross-sectional survey study in 14 countries" (2021-present)

Organization of "Research Q&A" of the pharmacy team at the Institute of Primary Healthcare (BIHAM), University of Bern (2022-present)

SUPERVISION OF STUDENTS

Co-supervision of master's student Demi Verhagen (2024)

Co-supervision of master's student Anne Centeno Neelen (2023)

Co-supervision of master's student Esther Werkman (2023)

FELLOWSHIPS

CNPq fellowship - MSc in Public Health Nutrition, 2015-2017

Capes fellowship - Undergraduate Research Project in Public Health Nutrition, 2014-2015

SKILLS

Language: Portuguese (native), English (fluent), German (B2), Italian (basic)

Computer: STATA, SPSS, R (basic), REDCap, Endnote, Excel, Microsoft Word, PowerPoint

CARREER BREAK

Nanny / German School – Zurich, Switzerland - 2018 – 2020

Mothers help/ Nanny - London, United Kingdom - 2017- 2018

During 2017-2020 I also attended several courses on nutrition and health/life sciences.

8. List of Publications

8.1 Published Peer-Reviewed Publications

Google Scholar Profile - https://scholar.google.com.br/citations?user=1LWabPgAAAAJ

During the PhD

i. **Lüthold, RV,** et al. Inappropriate proton-pump inhibitor prescribing in primary care - an observational study with quality circles. Swiss medical weekly. 2023 Sep 21;153(40119).
ii. **Lüthold, RV,** et al. Understanding older patients' willingness to have medications deprescribed in primary care: a protocol for a cross-sectional survey study in nine European countries. BMC Geriatr 2022; 22, 920.
iii. Jungo, K.T., (…), **Lüthold, RV**, (…), et al. A mixed methods analysis of the medication review intervention centered around the use of the 'Systematic Tool to Reduce Inappropriate Prescribing' Assistant (STRIPA) in Swiss primary care practices. BMC Health Serv Res 24, 350 (2024).

Before the PhD

i. WILLI, S, **Lüthold, R**, et al. COVID-19 Sequelae in adults aged less than 50 years: A Systematic Review. Travel medicine and infectious disease 2021; 101995.
ii. **Lüthold, RV**, et al. Gut microbiota interactions with the immunomodulatory role of vitamin D in normal individuals. Metabolism 2017; 69: 76-86.

8.2 Publications in Process

i. **Lüthold, RV**, Pharmacists' attitudes towards interprofessional collaboration to optimise medication use in older patients in Switzerland: A survey study.
ii. **Lüthold, RV**, et al. Exploring older adults' views on their use of dietary supplements and their willingness towards deprescribing those: An observational study in Swiss primary care settings.
iii. **Lüthold, RV**, et al. Understanding older patients' attitudes towards deprescribing in primary care: A cross-sectional survey study in 14 countries.
iv. Dupuis, M, Weir, KW, **Lüthold, RV**, et al.Social determinants of antidepressant continuation during pregnancy in the USA: Findings from the ABCD cohort study

9. List of Conference Presentations

During the PhD

i. Inappropriate proton-pump inhibitor prescribing in primary care - an observational study with quality circles. GHS Symposium, 2022, Bern, Switzerland.
ii. Exploring GPs' and patients' views on the use and deprescribing of herbal and dietary supplements. GHS Symposium, 2022, Bern, Switzerland.
iii. Patients' willingness to have medications deprescribed in Europe: Protocol for a cross-sectional survey study. 1st International Conference on Deprescribing (ICOD), 2022, Kolding, Denmark.
iv. Exploring GPs' and patients' views on the use and deprescribing of herbal and dietary supplements. 1st International Conference on Deprescribing (ICOD), 2022, Kolding, Denmark.

Before the PhD

i. Web-Based Self-Reported Anthropometry in The Nutritionist Health Study: Validation. The Epidemiology Congress of the Americas, 2016, Miami, United States. American College of Epidemiology, 2016. v. unico. p. 1635-S/P-1635-S/P.
ii. Is Birth Weight Associated with Body Adiposity and Glucose Metabolism in Youngsters? The Epidemiology Congress of the Americas, 2016, Miami, United States. American College of Epidemiology, 2016. v. unico. p. 0910-0910.
iii. Abdominal visceral tissue measured by DXA is associated with a cardiometabolic risk profile even in healthy young people from Nutritionists Health Study. In: Congresso Paulista de diabetes e metabolismo, 2016, São Paulo. Congresso Paulista de diabetes e metabolismo, 2016.
iv. Knowledge Acquired in Nutrition Reverses to Healthier Life Habits? 13º Congresso Nacional da Sociedade Brasileira de Alimentação e Nutrição - SBAN, 2015, São Paulo, Brazil. NUTRIRE, 2015. v. 40. p. 199-199.
v. E-NUTRIHS: A Web-Based System for a Brazilian Cohort Study. 13º Congresso Nacional da Sociedade Brasileira de Alimentação e Nutrição - SBAN, 2015, São Paulo, Brazil. NUTRIRE, 2015. v. 40. p. 436-436.

vi. Validation of web-based self-reported anthropometric data in the NutriHS. 13º Congresso Nacional da Sociedade Brasileira de Alimentação e Nutrição - SBAN, 2015, São Paulo, Brazil. NUTRIRE, 2015. v. 40. p. 667-667.

vii. Benefits of nutrients and nutritional status control in oncologic patients. XIX Jornada Cientifica Sao Camilo, 2015, Sao Paulo, Brazil.

viii. Sodium content in lunch meals - consumption by employees in the Municipality of São Paulo. XVIII Jornada Cientifica Sao Camilo, 2014, Sao Paulo, Brazil.

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12. Supplementary Material

12.1 Article 2.1. Understanding older patients' attitudes towards deprescribing in primary care: A cross-sectional survey study in 14 countries

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Supplementary File e1. Study Questionnaire

Patient Questionnaire

Dear Madam or Sir,

Thank you for your interest in participating in this study. It is being conducted by the Institute of Primary Health Care (BIHAM) of the University of Bern with collaborators from various European countries.

You were informed about this study in your GP's practice and received this survey because your GP thinks you fulfill the inclusion criteria. We are conducting this study with adults who are 65 years or older and regularly take 5 or more medications. The aim of this project is to find out your opinion about stopping or reducing the dose of your medication. This is a survey only and no changes will be made to your medication as part of this project. The study ends after you have completed the survey.

In total, about 1000 patients from 14 countries are taking part in this survey. By taking part in this study, you contribute to better understanding how this group (adults aged 65 years or older, taking five or more medicines) think and feel about their medication. The results, which are based on the views of all the patients surveyed in this study, may be important in the future to help GPs care for their patients, by improving the process of stopping or reducing unnecessary medication.

Your answers will be kept anonymous. This means that neither your GP nor the study team can identify you or your answers.

You have the option of completing the questionnaire online or on paper. If you fill in the paper questionnaire, please return it to your GP in a sealed envelope. If you choose to complete the questionnaire online, please use this link or the QR-code above: _____

In this case, you do not need to return the hard copy of the questionnaire to your GP. We ask that you do not mention any names or addresses on the questionnaire to keep your anonymity.

This study is approved by the Ethics Committee of the Canton of Bern and complies with the legal requirements for research with anonymous medical data. The data will be securely stored electronically.

By answering "yes" to the question below and completing this questionnaire, you agree to participate in the study and the research team will collect your responses for the purpose of this study.

It will take about 15-30 minutes to complete the questionnaire.

Your help means a lot to us. Thank you again for taking the time to complete this questionnaire. If you have any questions or comments, please contact the study team:

Email: (Add email national coordinator)

Yours sincerely,

(Add national coordinator)

Prof. Sven Streit, PhD MD MSc
Principal Investigator of the LESS study
Institute of Primary Health Care (BIHAM)
University of Bern

Informed consent

Do you agree to participate in this study in which we will collect information about your medication use?

If you check "Yes", you agree to participate.

o Yes *(please continue to the next question)*

o No *(end of study participation)*

1) Questions about the inclusion criteria

1. How old are you (in years)?
   - o 65 years old or older *(please continue to the next question)*
   - o 64 years old or younger *(end of study participation, you are not eligible for this study*)

2. Do you regularly take 5 or more medications? (Regularly means: every day or most days for 30 days or more)
   - o Yes *(please continue to the next question)*
   - o No *(end of study participation, you are not eligible for this study*)

3. Do you live in (add country)
    - Yes *(please continue to the next question)*
    - No *(end of study participation, you are not eligible for this study*)

2) Socio-demographic questions

We will now ask you some questions to understand a bit more about you.

4. What is your gender?
    - male
    - female
    - other

5. What area do you live in?
    - urban
    - suburban
    - rural

6. Do you live alone in your household?
    - yes
    - no

7. What is your living situation?
    - Own your house or apartment
    - Rented house or apartment

8. What is your highest completed education?
    - None
    - Primary school
    - Secondary school (high school or vocational training)
    - Third level education (university or equivalent training)

9. How do you make ends meet financially?
    - With great difficulty
    - With some difficulty
    - Quite easily

- Without any problems

10. Where were you born?
    - In the country where I currently live
    - Other country: Please specify country_____

11. What is your first language?
    - Official language of the country where I live in
    - Other language: Please specify language_____

12. How confident are you filling out medical forms by yourself?
    - Not at all
    - A little bit
    - Somewhat
    - Quite a bit
    - Extremely

13. In general, how would you describe your health today?
    - Excellent
    - Very good
    - Good
    - Average
    - Poor

3) Questions about your GP

We will now ask you some questions about your GP.

14. Do you have your own GP/family doctor (definition: when you have a health problem, you usually consult the same family doctor, except in emergencies)?
    - Yes
    - No *(please go to Section 4) "questions about your use of medication")*
    - Unclear:
        - Reason: _____

15. How long have you been seeing this GP?

- 0–9 years
- 10–19 years
- 20–29 years
- 30+ years

16. My GP is:
    - male
    - female
    - other

17. My GP's practice is:
    - In an urban area
    - In a suburban area
    - In the countryside

4) Questions about your medication use

Now we would like to learn more about your experiences with taking medications.

18. Do you prepare your medication by yourself?
    - Yes, I prepare and take it myself according to the prescription.
    - No, I receive support in preparing/taking my medication from relatives, home carers, or at the pharmacy for example.

19. Overall, I am satisfied with my current medications.
    - Strongly agree
    - Agree
    - Don't know
    - Disagree
    - Strongly disagree

20. How many different kinds of medications do you take regularly? (Regularly means daily or on most days of the week.) Please indicate the number of different kinds of medications.
    Number of different medications: _____

5) Questions about your attitude towards and decisions about medication

Now we are going to ask you questions on your thoughts about stopping or reducing the dose of medicines.

21. If my doctor said it was possible I would be willing to stop one or more of my regular medications.
    - o Strongly agree
    - o Agree
    - o Don't know
    - o Disagree
    - o Strongly disagree

22. I would like to try stopping one of my medications to see how I feel without it.
    - o Strongly agree
    - o Agree
    - o Don't know
    - o Disagree
    - o Strongly disagree

23. Thinking about your current medication list, are there any medications that you would like to stop taking or reduce the dose of?
    - o Yes *(please continue to the next question)*
    - o No, I am not considering stopping or reducing the dose of any medication. *(Please go to Question 25)*

24. In the following table, please state the name(s) of the medication(s) that you would consider stopping or reducing, and the reason why.
    Any lines that are not applicable can be left empty.

Name(s) of the medication(s) that you would consider stopping or reducing	**Why did you choose this/these medication(s) to stop or reduce?** *Please check all answers that apply*

Name of the medication: ___________________________	○ It causes side effects. ○ I do not benefit from it. ○ I do not like the medication. ○ The medication is too expensive. ○ It is inconvenient for me to take this medication. ○ The tasks involved in taking the medication(s) (e.g. blood glucose monitoring) are stressful for me. ○ I often forget to take this medication. ○ Other reason:____________________________
Name of the medication: ___________________________	○ It causes side effects. ○ I do not benefit from it. ○ I do not like the medication. ○ The medication is too expensive. ○ It is inconvenient for me to take this medication. ○ The tasks involved in taking the medication(s) (e.g. blood glucose monitoring) are stressful for me. ○ I often forget to take this medication. ○ Other reason:____________________________
Name of the medication: ___________________________	○ It causes side effects. ○ I do not benefit from it. ○ I do not like the medication. ○ The medication is too expensive. ○ It is inconvenient for me to take this medication. ○ The tasks involved in taking the medication(s) (e.g. blood glucose monitoring) are stressful for me. ○ I often forget to take this medication. ○ Other reason:____________________________
Name of the medication: ___________________________	○ It causes side effects. ○ I do not benefit from it. ○ I do not like the medication. ○ The medication is too expensive. ○ It is inconvenient for me to take this medication. ○ The tasks involved in taking the medication(s) (e.g. blood glucose monitoring) are stressful for me. ○ I often forget to take this medication. ○ Other reason:____________________________

After the table please continue to section 6 "additional questions about stopping medications and your willingness to do so".

25. You may not want to stop taking a medication or reduce the dose. Here are some reasons why. Which one(s) do you think are the most important reasons for not stopping a medication? (Please select all that apply)
    - The medicine is beneficial.
    - Taking the medicine for a long time so it is better not change it.
    - Taking several medications every day is manageable.
    - The medication does not cause side effects.
    - Medication(s) are not expensive.
    - Doctors only prescribe medication(s) that are necessary.
    - It is easier to take medications than to make healthy lifestyle changes.
    - Other reasons: _____

6) Stopping medications and your doctor's involvement:

We will now ask you some questions about how you would stop or reduce the dose of your medications with your doctor.

26. I feel comfortable talking to my doctor about changes to my medication
    - Strongly agree
    - Agree
    - Don't know
    - Disagree
    - Strongly disagree

27. Who would you talk to about stopping or reducing the dose of a medication*? (Please check all that apply)*
    - GP
    - Specialist
    - Pharmacist
    - Family and friends
    - Other

28. What would help you to stop or reduce the dose of a medication? *(Please check all that apply)*
    - A plan or instructions for stopping or reducing the dosage
    - The support of my GP
    - An alternative medication instead
    - An alternative such as a lifestyle change, physiotherapy
    - The option to restart the medicine if I feel I need to, or my symptoms return
    - Other:_____

For each of the following, please select the statement that best aligns with your views.

29. What do you think about the medications you take?
    - My medications are important, they keep me alive and help me live well.
    - My medications do what they are supposed to do.
    - I don't really care much about my medications, I take them as my doctor tells me to.
30. How do you get information about your medications?
    - My doctor and I talk about my medications together.
    - I know about my medications – I ask my doctor or read the information leaflet or search online.
    - I don't know much about my medications.
31. How do you make decisions about your medications?
    - I want to be informed, but I trust my doctor to make decisions about my medications.
    - I make decisions about the medications I take, or share the decision with my doctor.
    - Other people (e.g. my doctor or my partner) make decisions for me about my medications.
32. What do you think about the idea of stopping or reducing the dose of one or more of your medications?
    - I would not like to stop any of my medications or reduce the dose.

- I wish I did not take so many medications and I would stop or reduce the dose of my medications if I could.
- If my doctor said that it is possible to stop or reduce the dose of a medication that would be ok with me.

7) Questions about your relationship to your family doctor

33. This section is about your relationship with your GP and your trust in them. Please indicate how strongly you agree with each of the statements. There are no right or wrong answers.

	Completely disagree	Disagree	Don't know	Agree	Completely agree
Sometimes my GP cares more about what is convenient for them than about my medical needs.					
My GP is extremely thorough and careful.					
I completely trust my GP's decision about which medical treatments are best for me.					
My GP is completely honest about the different treatment options available for my health problem.					
All in all, I have complete trust in my GP.					

8) Final questions

34. Did anyone help you with completing this questionnaire?

- Yes
  - If yes: Who? *(please check the answer that applies)*
    - Relatives
    - Friends
    - GP
    - GP practice staff
    - Other: _____
  - No

You had the opportunity to complete the questionnaire online or on paper. Please confirm that you **only completed one** of the versions of the questionnaire.

- “I confirm that I only completed one of the versions of the questionnaire.”

Thank you for taking the time to complete the questionnaire.

[Please return this questionnaire to your GPs office as soon as possible.]

If you have any questions, please do not hesitate to contact us.

Yours sincerely,

(Add national coordinator)

Prof. Sven Streit and the LESS Study team

Figure S1. Recruitment flow chart.

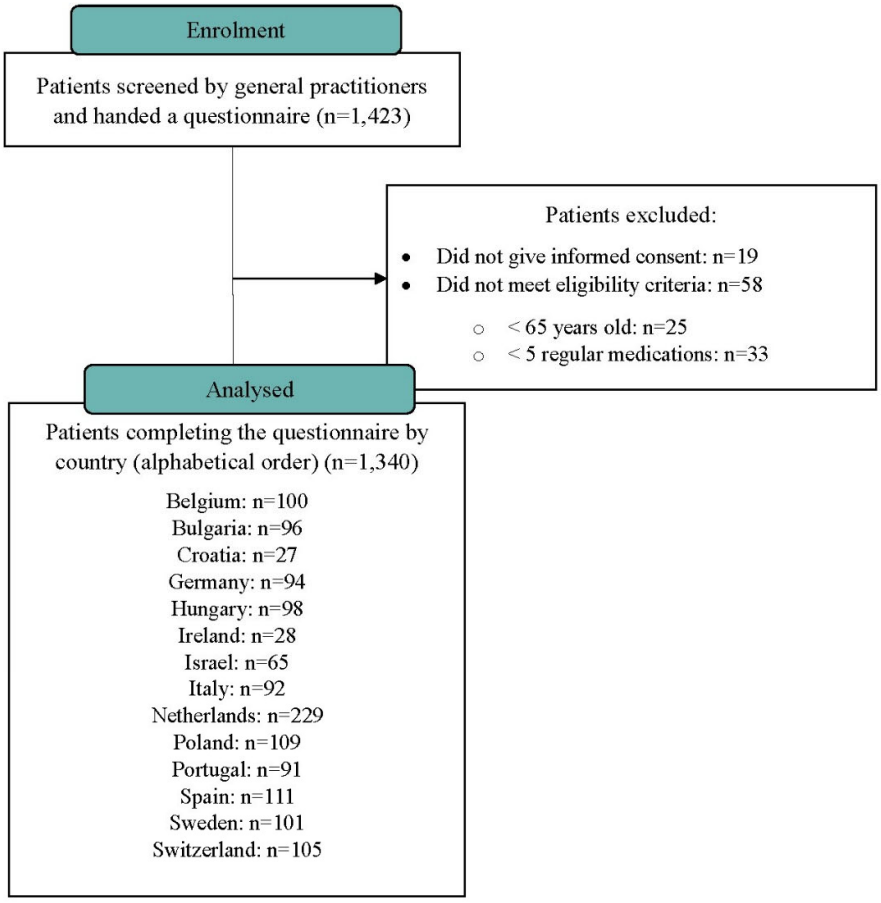
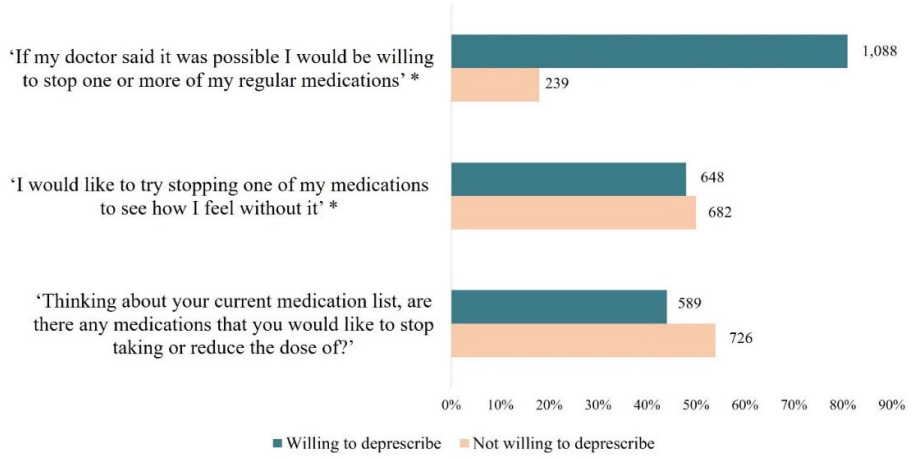


Figure S2. Patients' willingness to stop or reduce medications.



Patients who responded 'agree' or 'strongly agree' to the rPATD global questions *'If my doctor said it was possible, I would be willing to stop one or more of my regular medications'* and *'I would like to try stopping one of my medications to see how I feel without it'* were considered as willing to deprescribe. Patients who responded 'yes' to the question *'Thinking about your current medication list, are there any medications that you would like to stop taking or reduce the dose of?'* were considered willing to deprescribe.

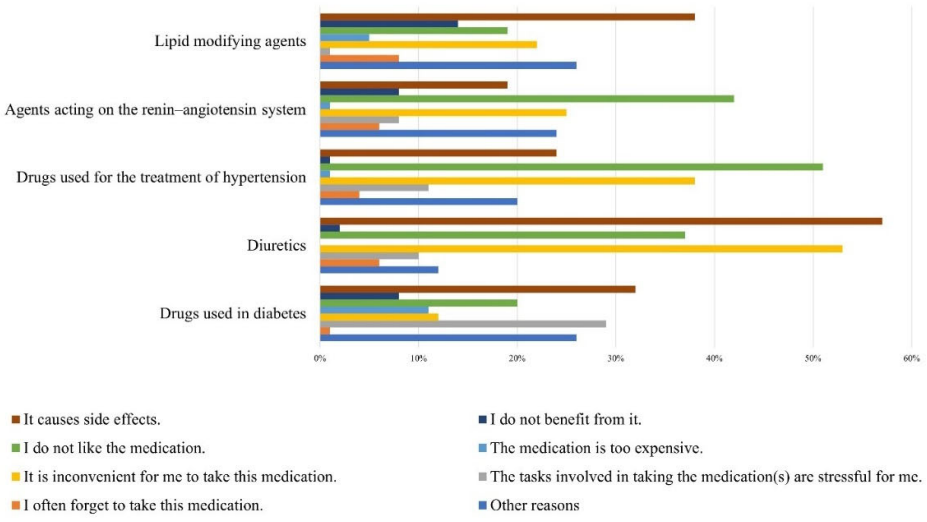
Reference: Reeve E, Low LF, Shakib S, Hilmer SN. Development and Validation of the Revised Patients' Attitudes Towards Deprescribing (rPATD) Questionnaire: Versions for Older Adults and Caregivers. Drugs Aging. 2016;33(12):913-28. doi:10.1007/s40266-016-0410-1.

Table S1. Patients' attitudes towards deprescribe: Most frequently mentioned medication classes, stratified by patient gender and country.

	1st medication class	2nd medication class	3rd medication class
Overall (n=1,002 medications)	diuretics (n=109)	lipid modifying agents (n=107)	agents acting on the renin-angiotensin system (n=82)
Gender			
Female (n=577)	diuretics (n=63)	lipid modifying agents (n=61)	agents acting on the renin-angiotensin system (n=46)
Male (n=425)	diuretics (n=46)	lipid modifying agents (n=46)	antithrombotic agents (n=39)
Country			
Belgium (n=14)	drugs used in diabetes (n=3)	psycholeptics (n=3)	antithrombotic agents (n=2)
Bulgaria (n=21)	lipid modifying agents (n=4)	diuretics (n=3)	psychoanaleptics (n=3)
Croatia (n=10)	psycholeptics (n=4)	analgesics (n=2)	drugs used in diabetes (n=1)
Germany (n=60)	lipid modifying agents (n=11)	antithrombotic agents (n=7)	agents acting on the renin-angiotensin syst. (n=7)
Hungary (n=51)	lipid modifying agents (n=7)	drugs used in diabetes (n=6)	agents acting on the renin-angiotensin syst. (n=4)
Ireland (n=10)	agents acting on the renin-angiotensin system (n=2)	lipid modifying agents (n=2)	psychoanaleptics (n=2)
Israel (n=33)	antithrombotic agents (n=7)	psychoanaleptics (n=4)	drugs for acid-related disorders (n=3)
Italy (n=157)	diuretics (n=20)	antithrombotic agents (n=13)	drugs for obstructive airway diseases (n=12)
Netherlands (n=170)	agents acting on the renin-angiotensin system (n=22)	lipid modifying agents (n=22)	drugs for acid-related disorders (n=20)
Poland (n=263)	diuretics (n=54)	beta blocking agents (n=42)	agents acting on the renin-angiotensin system (n=29)
Portugal (n=49)	lipid modifying agents (n=9)	antithrombotic agents (n=5)	diuretics (n=5)
Spain (n = 60)	analgesics (n=8)	drugs used in diabetes (n=7)	lipid modifying agents (n=5)
Sweden (n=46)	drugs used in diabetes (n=7)	lipid modifying agents (n=5)	antithrombotic agents (n=4)
Switzerland (n=58)	agents acting on the renin-angiotensin syst. (n=7)	lipid modifying agents (n=7)	analgesics (n=7)

Medication classes were defined using the Anatomical Therapeutic Chemical Classification (ATC) at the second anatomical level.

Figure S3. Reasons for willingness to stop or reduce medications according to the medication class of the five most mentioned medication classes. Multiple responses possible (n=454).



12.2 Article 3. Exploring views of older adults with polypharmacy on their use of dietary supplements and their willingness towards deprescribing those: Results from an observational survey study conducted in Swiss primary care settings

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Additional File 1. Study Questionnaire for Patients

Have you already signed the consent form together with your GP?

If you click/check "Yes", you agree to participate.

o Yes (automatic forwarding to the questionnaire)

o No (end of study participation)

1) Questions about the inclusion criteria

33. How old are you (in years)?
    - 65 years old or older (continue to the next question)
    - 64 years old or younger (end of study participation)

34. Do you regularly take 5 or more medications? (Regularly means: every day or most days for 30 days or more)
    - Yes (continue to the next question)
    - No (end of study participation)

35. Do you live in Switzerland?
    - Yes (go to next question)
    - No (end of study participation)

2) Information about your GP

36. What is the name of your general practitioner? Please enter his/her first and last names:

_____

37. What is the location of your GPs' office?

_____

38. What is the postcode of the practice?

_____

39. What is the name of the street where the GP practice is located?

    _____

40. Is this your family doctor? (Definition: if you have a health problem, you usually always consult the same family doctor - except in emergencies

    o Yes (continue with the next question number 9)
    o No (Please go directly to Section 3 Socio-demographic questions)

41. If yes, how long have you been going to this family doctor?

    o 0-9 years
    o 10-19 years
    o 20-29 years
    o 30+ years

3) Socio-demographic questions

We will now ask you some questions in order to better understand who answered our questionnaire.

42. What is your gender?
    - male
    - female
    - other

43. What area do you live in?
    - urban
    - suburban
    - rural

44. What is your postcode?

45. Do you live alone in your household?
    - yes
    - no

46. What is your living situation?
    - Own your house or apartment
    - Rented house or apartment

47. What is your highest completed education?
    - none
    - primary school
    - secondary education (apprenticeship or high school)
    - tertiary education (university or college studies)

48. How do you make ends meet financially?
    - With great difficulty
    - With some difficulty
    - Quite easily
    - Without any problems

49. Where were you born?
    - In the country where I currently live
    - Other country [Please specify country] _____

50. What is your first language?
    - Official language of the country where I currently live
    - Other language [Please specify language] _____

51. How confident are you in filling out medical forms by yourself?
    - Not at all
    - A little bit
    - Somewhat
    - Quite a bit
    - Extremely

52. Generally speaking, how would you describe your health today?
    - o Excellent
    - o Very good
    - o Good
    - o Average
    - o Poor

4) Questions about your use of medication

Now we would like to learn more about your experiences with taking medication.

53. I prepare my medication myself:
    - o Yes, I prepare and take it myself according to the prescription.
    - o No, I receive support in preparing/taking my medication from relatives, the Spitex or at the pharmacy for example.

54. Overall, I am satisfied with my current medications.
    - o Strongly agree
    - o Agree
    - o Don't know
    - o Disagree
    - o Strongly disagree

55. How many different kinds of medications do you take regularly? (Regularly means daily or on most days of the week.) Please indicate the number of different kinds of medications.

    Number of different medications: _____

56. Do you regularly take herbal, vitamin, or mineral supplements?
    - o Yes (continue to the next question)
    - o No (continue to section 5)

57. How many different vitamins, mineral supplements, or herbal medications do you take regularly?

    Number of different dietary supplements: _____

58. In the last week: What supplements have you taken? Please check all that apply.

□ Multivitamins
□ Iron
□ Calcium
□ Vitamin A
□ Vitamin E
□ Vitamin B12
□ Vitamin B6
□ Vitamin C
□ Vitamin D
□ Vitamin K
□ Vitamin B complex
□ Folic Acid
□ Magnesium
□ Zinc
□ Valerian root
□ Ginkgo biloba
□ Turmeric
□ Echinacea
□ St. John's wort
□ Garlic
□ Ginseng
□ Omega-3
□ Chondroitin sulphate
□ Glucosamine
□ Other(s): _____

_____

5) Questions about your attitude towards and decisions about medication

Now we are going to ask you questions on your thoughts about stopping or reducing the dose of medicines.

59. If my doctor said it was possible I would be willing to stop one or more of my regular medications.

- o Strongly agree
- o Agree
- o Don't know
- o Disagree
- o Strongly disagree

60. I would like to try stopping one of my medications to see how I feel without it.

- o Strongly agree
- o Agree
- o Don't know
- o Disagree
- o Strongly disagree

61. Thinking about your current medication list, are there any medications that you would like to stop taking or reduce the dose of?

- o Yes *(please continue to the next question)*
- o No, I am not considering stopping or reducing the dose of any medication. *(Please go to Question 31)*

62. In the following table, please state the name(s) of the medication(s) that you would consider stopping or reducing, and the reason why.

Any lines that are not applicable can be left empty.

Name(s) of the medication(s) that you would consider stopping or reducing	Why did you choose this/these medication(s) to stop or reduce? *Please check all answers that apply*
Name of the medication: _____	o It causes side effects. o I do not benefit from it. o I do not like the medication. o The medication is too expensive. o It is inconvenient for me to take this medication. o The tasks involved in taking the medication(s) (e.g. blood glucose monitoring) are stressful for me. o I often forget to take this medication. o Other reason:_____

Name of the medication: ___________________________	○ It causes side effects. ○ I do not benefit from it. ○ I do not like the medication. ○ The medication is too expensive. ○ It is inconvenient for me to take this medication. ○ The tasks involved in taking the medication(s) (e.g. blood glucose monitoring) are stressful for me. ○ I often forget to take this medication. ○ Other reason:____________________________
Name of the medication: ___________________________	○ It causes side effects. ○ I do not benefit from it. ○ I do not like the medication. ○ The medication is too expensive. ○ It is inconvenient for me to take this medication. ○ The tasks involved in taking the medication(s) (e.g. blood glucose monitoring) are stressful for me. ○ I often forget to take this medication. ○ Other reason:____________________________
Name of the medication: ___________________________	○ It causes side effects. ○ I do not benefit from it. ○ I do not like the medication. ○ The medication is too expensive. ○ It is inconvenient for me to take this medication. ○ The tasks involved in taking the medication(s) (e.g. blood glucose monitoring) are stressful for me. ○ I often forget to take this medication. ○ Other reason:____________________________

After the table please continue to section 6 “additional questions about stopping medications and your willingness to do o”.

63. You may not want to stop taking a medication or reduce the dose. Here are some reasons why. Which one(s) do you think are the most important reasons for not stopping a medication? (Please select all that apply)

    - ○ The medicine is beneficial.

- Taking the medicine for a long time so it is better not change it.
- Taking several medications every day is manageable.
- The medication does not cause side effects.
- Medication(s) are not expensive.
- Doctors only prescribe medication(s) that are necessary.
- It is easier to take medications than to make healthy lifestyle changes.

Other reasons: _____

64. Do you regularly take vitamins, mineral supplements or herbal medications?
    - Yes
    - No (*If you are not taking such supplements, please go directly. to section 6).*

If the answer is yes, please complete the table below by indicating the three dietary supplements you use most regularly/frequently.

If you are taking other supplements not mentioned above, please consider them as well. We then ask you to answer the following questions for each supplement by ticking the appropriate statements. An example of filling out the table can be found below. (If you are not using supplements, please leave the table blank.)

Name of the supplement	**Why do you use this supplement?**	**Who recommended that you take this supplement?**	**I would be willing to stop taking this supplement or reduce its dose.**
Example: *Vitamin D*  	o To improve my general health ✖ To strengthen my immune system o For my nerves, mood or stress o For more energy, alertness or mental activity o To improve blood or circulation o To improve sleep o For muscle, joint or bone problems o To regulate body weight or appetite o To improve skin, nails or hair o For complaints due to menopause or prostate o Other reasons: _____ o I don't have a reason.	○ My GP ○ Other doctor/specialist ○ Pharmacist ○ Other health professional ○ Relatives ○ Friends ✖ Myself ○ Other (please specify): _____	○ Strongly disagree ○ Disagree ✖ Don't know ○ Agree ○ Strongly agree
Supplement 1: Name: _____	o To improve my general health o To strengthen my immune system o For my nerves, mood or stress o For more energy, alertness or mental activity o To improve blood or circulation o To improve sleep o For muscle, joint or bone problems o To regulate body weight or appetite o To improve skin, nails or hair o For complaints due to menopause or with the prostate o Other reasons: _____ o I don't have a reason.	○ My GP ○ Other doctor/specialist ○ Pharmacist ○ Other health professional ○ Relatives ○ Friends ○ Myself ○ Other (please specify): _____	○ Strongly disagree ○ Disagree ○ Don't know ○ Agree ○ Completely agree

Name of the supplement	**Why do you use this supplement?**	**Who recommended that you take this supplement?**	**I would be willing to stop taking this supplement or reduce its dose.**
Supplement 2: Name: _____	o To improve my general health o To strengthen my immune system o For my nerves, mood or stress o For more energy, alertness or mental activity o To improve blood or circulation o To improve sleep o For muscle, joint or bone problems o To regulate body weight or appetite o To improve skin, nails or hair o For complaints due to menopause or with the prostate o Other reasons: _____ o I don't have a reason.	○ My GP ○ Other doctor/specialist ○ Pharmacist ○ Other health professional ○ Relatives ○ Friends ○ Myself ○ Other (please specify): _____	○ Strongly disagree ○ Disagree ○ Don't know ○ Agree ○ Strongly agree
Supplement 3: Name: _____	o To improve my general health o To strengthen my immune system o For my nerves, mood or stress o For more energy, alertness or mental activity o To improve blood or circulation o To improve sleep o For muscle, joint or bone problems o To regulate body weight or appetite o To improve skin, nails or hair o For complaints due to menopause or with the prostate o Other reasons: _____ o I don't have a reason.	○ My GP ○ Other doctor/specialist ○ Pharmacist ○ Other health professional ○ Relatives ○ Friends ○ Myself ○ Other (please specify): _____	○ Strongly disagree ○ Disagree ○ Don't know ○ Agree ○ Strongly agree

65. Where do you buy the supplements? Select all answer options that apply.

- Pharmacy
- Drugstore
- Supermarket
- Internet
- Natural food store
- In the gym
- Other location: _____

66. Do you talk to your family doctor or pharmacist about taking supplements?

- Yes
- No

6) Additional questions about stopping medication and your willingness to do so:

67. I feel comfortable talking to my doctor about changes to my medication

- Strongly agree
- Agree
- Don't know
- Disagree
- Strongly disagree

68. Who would you talk to about stopping or reducing the dose of a medication*? (Please check all that apply)*

- GP
- Specialist
- Pharmacist
- Family and friends
- Other
    a. Who?

69. What would help you to stop or reduce the dose of a medication? *(Please check all that apply)*

- A plan or instructions for stopping or reducing the dosage

- The support of my GP
- An alternative medication instead
- An alternative such as a lifestyle change, physiotherapy
- The option to restart the medicine if I feel I need to, or my symptoms return
- Other:_____

For each of the following, please select the statement that best aligns with your views.

70. What do you think about the medications you take?
    - My medications are important, they keep me alive and help me live well.
    - My medications do what they are supposed to do.
    - I don't really care much about my medications, I take them as my doctor tells me to.

71. How do you get information about your medications?
    - My doctor and I talk about my medications together.
    - I know about my medications – I ask my doctor or read the information leaflet or search online.
    - I don't know much about my medications.

72. How do you make decisions about your medications?
    - I want to be informed, but I trust my doctor to make decisions about my medications.
    - I make decisions about the medications I take, or share the decision with my doctor.
    - Other people (e.g. my doctor or my partner) make decisions for me about my medications.

73. What do you think about the idea of stopping or reducing the dose of one or more of your medications?

- I would not like to stop any of my medications or reduce the dose.
- I wish I did not take so many medications and I would stop or reduce the dose of my medications if I could.
- If my doctor said that it is possible to stop or reduce the dose of a medication that would be ok with me.

7) Questions about your relationship to your family doctor

42. This section is about your relationship with your GP and your trust in them. Please indicate how strongly you agree with each of the statements. There are no right or wrong answers.

	Completely disagree	Disagree	Don't know	Agree	Completely agree
Sometimes my GP cares more about what is convenient for them than about my medical needs.					
My GP is extremely thorough and careful.					
I completely trust my GP's decision about which medical treatments are best for me.					
My GP is completely honest about the different treatment options available for my health problem.					
All in all, I have complete trust in my GP.					

8) Questions about your use of herbal, vitamin or mineral supplements.

Now we want to hear your opinion about the most common herbal, vitamin or mineral supplements and other dietary supplements (e.g. multivitamins, vitamin D, calcium, valerian, ginkgo biloba, turmeric), even if you don't use any of them.

How much do you agree with the following statements about herbal supplements containing vitamins or minerals?

	Strongly disagree	Disagree	Don't know	Agree	Strongly agree
Supplements can have a positive effect on people's health.					
Supplements can prevent diseases.					
Supplements can cure/treat a disease.					
Supplements are necessary for everyone.					
Supplements can have a negative effect on people's health.					
Supplements are a waste of money.					
Many supplements have not been adequately studied for their efficacy and safety.					
Supplements can interact with prescription drugs.					
I should talk to my GP, pharmacist or other health professional before taking any herbal, vitamin or mineral supplement.					

9) Final questions

Did anyone help you with completing this questionnaire?

- No
- Yes
    - If yes: Who? (please check the answer that applies)
        - Relatives
        - Friends
        - GP
        - GP practice staff
        - Other: _____

You had the opportunity to complete the questionnaire online or on paper. Please confirm that you **only completed one** of the versions of the questionnaire.

- "I confirm that I only completed one of the versions of the questionnaire."

Thank you for your participation, you can now close the survey. If you completed the questionnaire online, you can now close the window. If you completed the questionnaire on paper, please return it to your GP practice as soon as possible.

Thank you for taking the time to complete the questionnaire.

If you have any questions, please do not hesitate to contact us.

Yours sincerely,

Prof. Sven Streit and the rest of the LESS study team

Additionla File 2. Study Questionnaire for General Practitioners

Part 1

GP Profile

Please complete once as part of this study.

Questions about yourself	
1. Name and first name	_____
2. Address of the practice where you work	_____
3. Town and postcode of the practice where you work	_____
4. Location of the practice where you work	*Please check the most appropriate answer.* □ urban □ suburban □ rural
5. Please indicate your gender	□ male □ female □ no answer
6. Please indicate your age (in years):	_____
7. What is your first language?	□ German/Swiss German □ French □ Italian □ Other: _____
8. Do you have an FMH title?	□ Yes □ No
If yes: Which FMH title do you have?	_____

Questions about your daily work

9. How much experience do you have as a general practitioner? (in years)	_____
10. On how many half-days per week do you see patients? (one half-day equals 10%)	_____ (please give a number between 1-10)
11. How many consultations do you have on an average workday (this corresponds to two half-days)?	□ <15 □ 15-25 □ 26-35 □ >35
12. What kind of practice do you work in?	□ Single practice □ Group practice
If group practice: How many GPs work in this practice?	_____
13. Before you were invited to participate in this project: Had you ever heard of the concept of deprescribing?	□ Yes □ No

General questions about your patients with polypharmacy

14. Please estimate the percentage of patients in your practice who have polypharmacy (i.e. who regularly take 5 or more medications)?	_____ (Please enter a number between 0-100)
15. Please estimate the percentage of patients in your practice who are eligible for stopping or dose reduction?	_____ (Please enter a number between 0-100)
16. For patients taking medications that could	_____

potentially be stopped or reduced: What percentage of them have you recommended this to?	(Please enter a number between 0-100)
17. If you did not recommend stopping or reducing the dose of medication, what were the main reasons?	***Please check all answers that apply.*** □ Lack of time □ The medication does not cause any problems. □ The patient wants to continue the medication. □ The patient's symptoms will return when the medication is stopped/reduced. □ Lack of scientific information (or guidelines, etc.) about stopping medication or reducing its dose □ Other reason: _____ _____
Questions about decision-making	
18. How important do you think it is to understand your patients' goals and preferences regarding their medications?	□ not at all important □ a little important □ somewhat important □ pretty important □ really important
19. How often do you talk to your patients about their goals and preferences?	□ never □ rarely □ sometimes □ frequently □ always
20. Please select the option that best reflects how you usually make decisions about stopping a medication or reducing its dose with a patient during your consultation.	□ The patient makes the final decision about stopping or reducing the dose of a medication. □ The patient makes the final decision about stopping a medication or reducing its dose after seriously considering my opinion. □ The patient and I share the responsibility of deciding which medication is best for them. □ I make the final decision about stopping a medication or reducing its dose, but seriously consider the patient's opinion. □ I make the final decision about stopping a medication or reducing its dose.
21. Please select the option that best describes how you	□ The patient makes the final decision about stopping or reducing the dose of a medication.

would like to make decisions about stopping a medication or reducing its dose with a patient in your consultation.	□ The patient makes the final decision about stopping a medication or reducing its dose after seriously considering my opinion. □ The patient and I share the responsibility of deciding which medication is best for them. □ I make the final decision about stopping a medication or reducing its dose, but seriously consider the patient's opinion. □ I make the final decision about stopping a medication or reducing its dose.

You had the opportunity to choose between filling out an online or a paper questionnaire: Please confirm that you only completed one of the two questionnaires.

o “I confirm that I have only completed one version of the two questionnaires”

Thank you very much for completing this questionnaire. We appreciate you taking the time to do so.

If you have not already done so, we now ask that you complete the other short questionnaires for each of the 5 patients recruited individually.

If you have any questions, please do not hesitate to contact us.

Yours sincerely,

Prof. Sven Streit and the rest of the LESS study team

Part 2

Questions about the hypothetical discontinuation of medications or reduction of their dose in the patients recruited by you

Please complete one form per patient recruited for this study.

Procedure:

1) After you have recruited 5 patients for this study, have their current medication list (digital or on paper) at hand.

2) Then fill out this short questionnaire for all 5 patients and send us their current medication lists (with your comments). You can do this by e-mail or by post

Questions about you

1. Name and first name

_____

We need this information in order to be able to assign the participating patients to the participating GPs.

Questions about the Patient

2. Patient's name and first name

_____

3. Patient's address

_____

4. How long has this patient been your patient?

□ 0-9 years

□ 10-9 years

□ 20-29 years

□ 30+ years

Questions about the patient's use of medication

5. How many long-term medications (prescribed for ≥30 days) are currently prescribed for this patient?

_____

Please enter a number.

6. Which long-term medications (prescribed for ≥30 days) are currently prescribed for this patient?

Please take the list of medications you have for this patient.

Mark an X for all long-term medications (prescribed for ≥30 days).

Example: **X** Pantoprazole 20mg, 1x per day

7. Which of these medications do you think are the most important?

Please **circle** them on the medication list.

Example: Pantoprazole 20mg, 1x am Tag

8. Which of these medicines do you think are the least important?

Please **cross them out** on the medication list.

Example: Pantoprazole 20mg, 1x per day

9. Would you stop or reduce the dose of any of the medications that the patient is currently taking?

□ Yes

□ No

10. If you were to think about stopping or reducing the dose of one of the medicines this patient is currently taking, which would it be?

Please **mark** these medicines with a **circle**.

Example: Pantoprazole 20mg, 1x per day **O**

11. Please indicate why you have chosen this/these medication(s) to discontinue or reduce their dose:

Mark all the answers that apply: The medication(s)...

□ has/have side effects

□ has/have no benefit

□ has/have no indication

□ is/are too expensive

□ my patient complains about this/these medicine(s)

□ Other reason:_____

Questions about taking non-prescription vitamin, mineral, herbal and/or other supplements

Such supplements may include iron capsules, fizzy drinks such as Berroca, or drops such as valerian root. Here are some examples: Multivitamins, iron, vitamin D, calcium, valerian root, ginkgo biloba, turmeric.

12. Have you ever recommended any supplement to this patient?

□ Yes

□ No

13. Do you know if this patient regularly takes supplement?

□ Yes

□ No

(including those you did not prescribe)

If yes: Which supplements?

□ Multivitamins
□ Iron
□ Calcium
□ Vitamin A
□ Vitamin E
□ Vitamin B12
□ Vitamin B6
□ Vitamin C
□ Vitamin D
□ Vitamin K
□ Vitamin B complex
□ Folic Acid

□ Magnesium
□ Zinc
□ Valerian root
□ Ginkgo biloba
□ Turmeric
□ Echinacea
□ St. John's wort
□ Garlic
□ Ginseng
□ Omega-3
□ Chondroitin sulphate
□ Glucosamine
□ Other(s): _____

14. Would you stop or reduce any dietary supplement for this patient?	□ Yes □ No
15. If yes, which dietary supplement?	_____

Now please go through the statements below and indicate to what extent you agree with them.

	Strongly disagree	Disagree	Don't know	Agree	Strongly agree
This patient tells me everything.					
Sometimes this patient does not follow my recommendations.					
This patient trusts me.					
This patient often disagrees with my recommendations.					

You had the opportunity to choose between filling out an online or a paper questionnaire: Please confirm that you only completed one of the two questionnaires.

o "I confirm that I have only completed one version of the two questionnaires"

Thank you for completing this questionnaire. We appreciate you taking the time to do this.

If you have not already done so, we now ask you to fill in the GP profile about yourself and how you work. You only need to complete this once.

If you have any questions, please do not hesitate to contact us.

Yours sincerely,

Prof. Sven Streit and the rest of the LESS study team

Additional File 3.

Figure S1. Beliefs about dietary supplements of users and non-users (n=65).

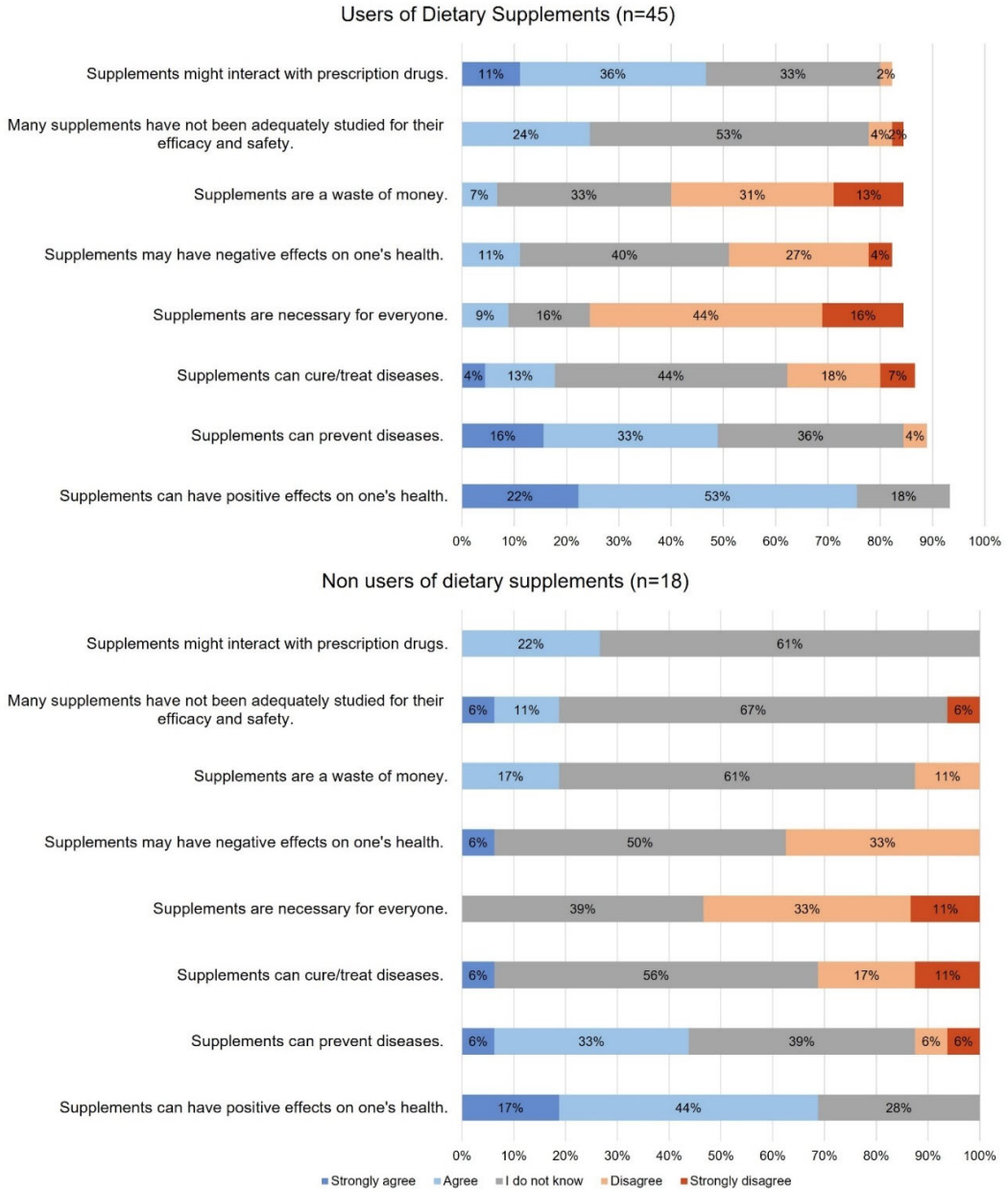
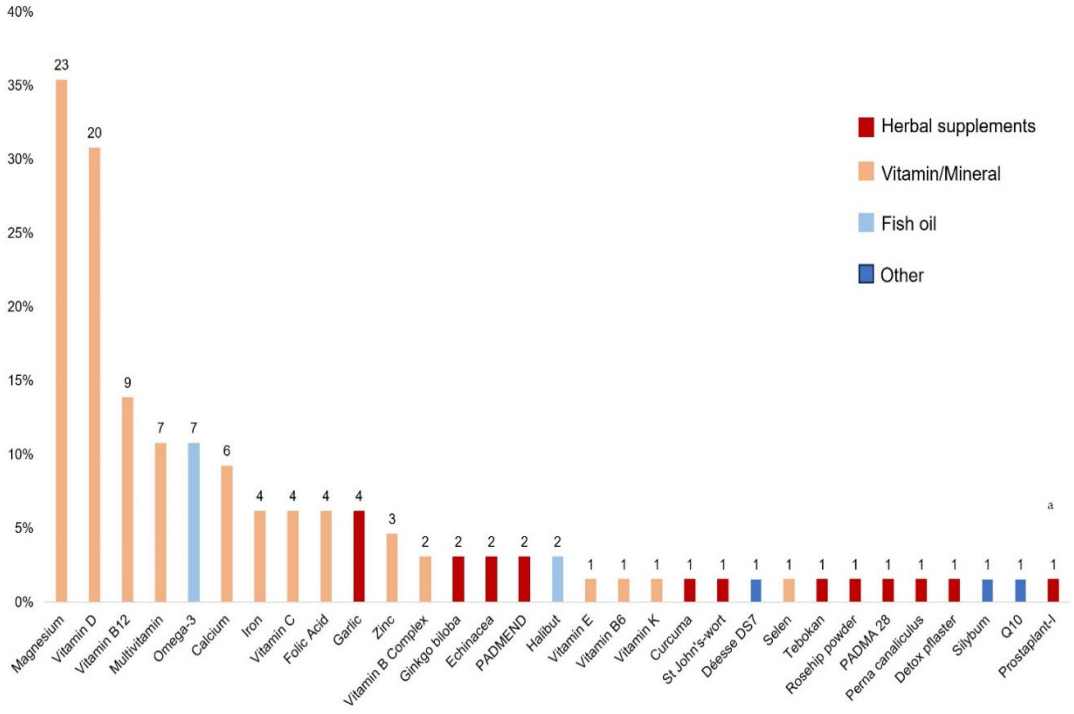


Figure S2. Dietary supplements used by older patients with polypharmacy living in the German part of Switzerland.



[a] Prostaplant-L is a phytotherapeutic product containing herbs.

12.3 Article 4. Pharmacists' attitudes towards interprofessional collaboration to optimise medication use in older patients in Switzerland: A survey study

Table of Contents

Additional File 1. Study questionnaire for pharmacists

Pharmacists' attitudes towards interprofessional collaboration to optimise medication use in older patients in Switzerland

Information for pharmacists

Dear Colleagues,

People on multiple medications (polypharmacy) are at particularly high risk for side effects and overtreatment. While it is often recommended to stop taking inappropriate medications or reduce their dosage (called deprescribing), this approach is challenging for both patients and general practitioners for a variety of reasons. In this context, the involvement of pharmacists and their collaboration with general practitioners can improve the deprescribing process. In this survey, we would like to learn more about pharmacists' views on the process of discontinuing or reducing medications and interprofessional collaboration in this context.

We would like to invite you to take part in this anonymous survey of around 15 - 20 minutes. This survey contains questions about your working practice, interprofessional collaboration, and your attitude towards reducing or stopping medications.
Do you work in a community pharmacy, hospital, nursing home or homecare facility? Then we cordially invite you to take part in this survey. The data is collected using SurveyMonkey and stored securely on a server at the University of Bern. Your answers will be treated confidentially and the data will be collected anonymously.
Thank you very much for your participation. We - a very motivated interprofessional team - really appreciate that you take the time to participate in this study.

Part A

Background information

For this survey we are interested in the views of pharmacists on the process of stopping potentially harmful medications or reducing their dosage in primary care. The survey was designed for who work in contact with patients.

1. Where do you work (multiple answer options)?
    - Community pharmacy
    - Combined pharmacy with drug-store
    - Hospital
    - Homecare
    - Nursing home
    - Other:(direct branching logic to the end of survey, to the explanation that they are not eligible to participate but still thank them!)

2. Please indicate your age in years: _____

3. Please indicate your gender.

    - Male
    - Female
    - Other (which):
    - Prefer to not answer.

4. In which canton do you currently work?

o Appenzell Innerrhoden (AI)	o Graubünden (GR)	o Solothurn (SO)
o Appenzell Ausserrhoden (AR)	o Jura (JU)	o Thurgau (TG)
o Aargau (AG)	o Luzern (LU)	o Tessin (TI)
o Bern (BE)	o Neuenburg (NE)	o Uri (UR)
o Basel Stadt (BS)	o Obwalden (OW)	o Wallis (VS)
o Basel Land (BL)	o Nidwalden (NW)	o Waadt (VD)
o Freiburg (FR)	o St. Gallen (SG)	o Zug (ZG)
o Genf (GE)	o Schaffhausen (SH)	o Zürich (ZH)
o Glarus (GL)	o Schwyz (SZ)	

5. Do you regularly work in more than one place?
    - Yes
    - No

6. (If yes) If you work in multiple pharmacies and the answer to a question varies depending on the pharmacy, please refer to the pharmacy where you work most often.

7. Do you work in a place where *self-dispensation* by doctors is permitted?
    - Yes
    - No
    - Mixed canton

8. (If «mixed canton») Can the nearest doctor give the medication directly to the patient?

9. Do you have any of the following further training courses/titles? Please check all that apply.
    - FPH in Anamnese in primary care
    - FPH in vaccination and blood collection
    - FPH in integrated care models
    - FPH consultant pharmacist for outpatient medication prescription
    - FPH in pharmaceutical support for healthcare institutions
    - FPH in community pharmacy
    - FPH is hospital
    - FPH in clinical pharmacy
    - Certificate of Advanced Studies (CAS) / Master of Advanced Studies (MAS)
    - PhD
    - Other:

10. How many years have you been working as pharmacist? (in number of years)

11. How much do you work according to your work contract? Please give your answer as a percentage between 0 and 100. A full-time position corresponds to 100 percent.

For the next few questions, we will use the word “patient” to refer to a person with whom you may interact during your work and provide pharmaceutical services. Please consider each patient/client/customer - of any gender - to answer these questions.

12. How often do you advise/serve patients who fulfil the following criteria?
    - Alter von ≥ 70 Jahren,
    - ≥ 5 Medikamente

    - Multiple times a day
    - Every day
    - Several times a week
    - Rarer

13. Thinking about all the recipes you see in a workday, what percentage of them are electronic and many of them are paper? (If you work in multiple pharmacies and the answer to a question varies depending on the pharmacy, please refer to the pharmacy where you work most often.) Please provide a number between 0-100% for each option.

        - Paper prescriptions sent by fax or scanned and sent by email
        - Recipes created by recipe software (i.e. not handwritten) and printed on paper
        - Prescriptions that are sent purely electronically

14. Do you use an electronic tool to edit and analyze patients' medication lists?
    - Yes
    - No

15. (Branching logic, if «yes»): What kind of electronic tool do you use in your work?

    - eMediplan
    - Other tools, please specify:

Part B

Familiarity with the concept of deprescribing

Deprescribing is commonly defined as the process of stopping inappropriate medications or reducing the dosage thereof, aiming the reduction of polypharmacy and the improvement of quality of life.

16. How familiar are you with the concept of deprescribing?
    - 1 (never heard about it)
    - 2
    - 3
    - 4
    - 5
    - 6
    - 7
    - 8
    - 9
    - 10 (very familiar)

17. For those who have heard of it before (branching logic): Where have you learnt about this topic? (Multiple responses possible)
    - scientific literature/magazines
    - Workshops/Further training (e.g., FPH, CAS)
    - Conferences, courses
    - Other (where?):

18. What priority should “deprescribing” have in your daily work?
    - No priority
    - Low priority
    - Neither low nor high priority
    - High priority
    - Very high priority
    - Undecided

19. How often does a situation arise for a possible deprescribing in your daily work??
    - every day
    - several times a week
    - once a week
    - once a month
    - less common
    - never

<u>Confidence in Undertaking Deprescribing Behaviours</u>

For each of the following questions, please indicate which of the statements best reflects your opinion. *We consider your previous pharmacist training to be all the university training, further education, trainings, etc. that you have completed so far.*

	Strongly disagree	Disagree	Neutral	Agree	Strongly Agree
20. My pharmacist training has prepared me to discuss deprescribing opportunities with patients.					
21. My pharmacist training has prepared me to discuss deprescribing opportunities with other health care professionals.					
22. I believe I am competent to discuss opportunities for deprescribing with other health care professionals.					
23. I can identify medications for which deprescribing should be considered.					

Part C

Work practices

Typical work month

Reflecting on a typical month at your workplace, please indicate, on average, how often you perform the following activities when indicated:

	Every working day	Multiple times a week	Once a week	Once a month	Less frequently than that	Never
24. Reviewed all medications (prescription, over- the-counter, herbals, and supplements) with the patient to create an updated and complete medication list						
25. Asked the patient questions to assess adherence to medication therapy						
26. Reviewed complete medication list to identify medication-related issues (i.e. incorrect dose, drug interaction)						

Medication Review in work practice (branching logic: show if response for 23 or 25: something other than Never)

Below you will find some questions about the *Medication review* process in your work practice. By the term *Medication review* we mean a structured evaluation of a patient's medications. This includes identifying medication-related problems and making concrete suggestions for improvement. The goal of a medication review is to identify, solve and prevent drug-related problems in order to generally optimize drug therapy, reduce drug side effects and improve clinical outcomes.

27. Have you ever received any training on how to conduct detailed medication reviews?
    - Yes
    - No

28. If so, did this training take place during your studies at university or after?
    - At university
    - In further education/training
    - Other: _____

29. Regarding patients who are older than 70 years and have polypharmacy (>5 medications): When checking their medications for appropriateness, which instruments/tools/auxiliary materials/etc. use? Check all that apply.
    - Lists of potentially inappropriate medications (e.g., Priscus, Beers, START/STOP)
    - Documents/tools for polymedication check
    - Other interaction databases (e.g. Pharmavista, Compendium)
    - Other:
    - None

For each of the following questions, please indicate which of the statements best reflects your opinion.

	Strongly disagree	Disagree	I do not know	Agree	Strongly Agree
30. I have enough information about my patient to perform medication reviews.					
31. I regularly see patients to whom I would recommend stopping/reducing medication. But since I didn't prescribe the medication myself, I didn't do anything about it.					

32. Patients would benefit if pharmacists had a more active role in deprescribing.						
33. I would like to be more actively involved in my patients' medication review process.						

34. What information are you missing to carry out medication reviews?

35. If you conduct medication reviews, how long does it take you on average? Please provide the answer in minutes.

36. Who do you contact if you determine that a medication should be reduced or discontinued? Check all that apply.

- To no one/I do not speak to anyone
- Directly to the patient
- To the patient's GP
- To the prescribing doctor
- If available: homecare
- Others:

Part D

<u>Interprofessional collaboration between pharmacists and physicians</u>

In this part of the survey we are interested in the interprofessional collaboration between pharmacists and physicians in the context of deprescribing and medication review.

36. Please indicate your agreement with the statements below.

	strongly disagree	disagree	somewhat disagree	neutral	somewhat agree	agree	strongly agree
I can count on physicians to do what they say.							
Communication between physicians and myself is two-way.							
My interactions with physicians are characterized by open communication of both parties.							

I spend time trying to learn how I can help physicians provide better care.							
I show an interest in helping physicians improve his/her practice.							
I provide information to physicians about specific patients.							
Physicians and I are mutually dependent on each other in caring for patients.							
Physicians depend on me as much as I depend on them.							
Physicians are willing to work with me to discuss and optimize our patients' drug therapy.							
Physicians accept my advice on our patients' drug therapy.							

Now, thinking about your contact with physicians, tick the answer that best applies to the questions below.

37. How often do you interact with physicians to clarify questions about the medications prescribed to your patients?
    - every day
    - several times a week
    - once a week
    - once a month
    - less common
    - never

38. How often do you make suggestions to physicians regarding medication use?
    - every day
    - several times a week
    - once a week
    - once a month
    - less common
    - never

Open question:

What would improve collaboration between pharmacists and family doctors? All ideas are welcome!

Additional File 2. Case Vignettes

Part E

Case Vignettes

In the following there will be three case-vignettes. Imagine a GP asked you to review 3 patient's medication lists and to suggest medications suitable for stopping or reducing (deprescribing). The situation of each patient is described in a case vignette. All the information that you need to make your decisions is described in the text and it is not possible to have any further information about the patient.

You will now see the three case-vignettes, which differ in terms of the patient's level of dependency in activities of daily living and overall complexity of health problems. The differences among each case vignette are written in *italic*.

After each case vignette there will be a few questions asking you which medications you would recommend to deprescribe.

Case vignette 1:

Patient 1, 82 years old

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 (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 a good physical functioning and somatic condition
- to be totally independent
- to be cognitively not impaired
- to have a low risk of cardiovascular events

➔ Which of these medicines do you think are most important to the patient's health status? Please tick all that apply.

- 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

➔ Which of these medicines do you think are least important to the patient's health status? Please tick all that apply.

- 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

➔ Would you suggest stopping or decreasing the dosage of one/several medication/s? (yes/no)

➔ (branching logic with question before) Which medication/s would you stop or decrease? Please tick all that apply.

- 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

➔ Why did you choose this medication? (free text, not mandatory)

Consider that Patient 1 now had a cardiovascular event in the past (e.g. myocardial infarction three years ago). Would you stop or reduce the dosage of one/several medication/s?

- Yes
- No

➔ Which medication/s would you suggest stopping or reducing when 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

Patient 3, 82 years of age:

Social history: retired carpenter*, lives together with his wife in a nursing home*

General health: *Patient 3 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?

- o Yes
- o 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 once daily
- Paracetamol 1g three times a day
- Tramadol 50 mg twice daily
- Pantoprazole 20 mg once daily

➔ 18. Consider that Patient 3 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 3 had a cardiovascular event in the past (e.g. myocardial infarction three years ago)?

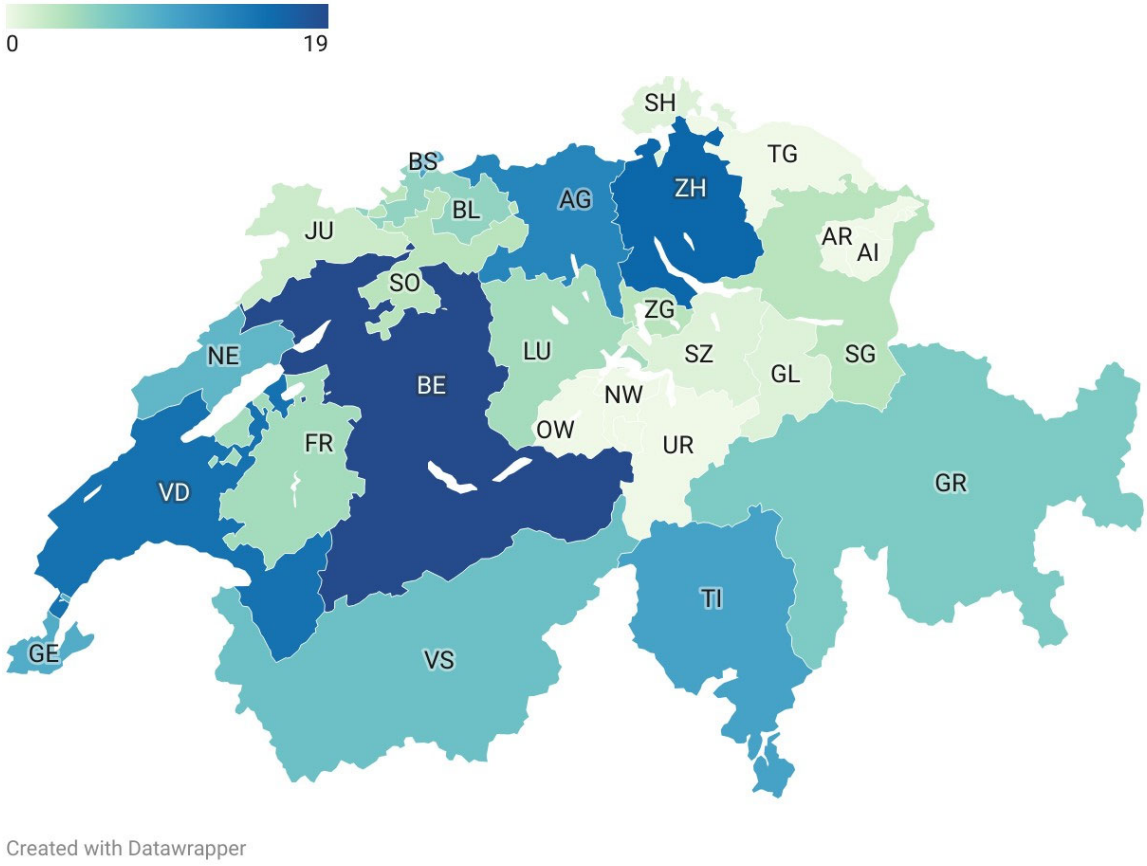
- Aspirin 100 mg once daily
- Atorvastatin 40 mg once daily
- Enalapril 10 mg once daily
- Amlodipine 5 mg once daily
- Paracetamol 1g three times a day
- Tramadol 50 mg twice daily
- Pantoprazole 20 mg once daily

End of survey

Thank you very much for your participation in our study.

We really appreciate that you took the time to do this.

Additional File 3. Figure S1. Workplace locations of respondents (n=138).



Multiple responses were possible. Map created with Datawrapper.

Additional File 4 - Table s1. Pharmacists' deprescribing recommendations per case vignette (n=138)[#]

Case vignette	Patients' dependency level	Deprescribing recommendation	No history of CVD[a] (95%CI)	With history of CVD[a] (95%CI)	Difference (95% CI)[b]
1	low	Min. 1 medication	79% (72% to 87%)	55% (46% to 64%)	24% (12% to 36%)
		Min. 2 medication	75% (67% to 83%)	36% (27% to 45%)	39% (27% to 51%)
		Min. 3 medication	53% (43% to 62%)	16% (10% to 23%)	36% (25% to 48%)
2	medium	Min. 1 medication	69% (61% to 77%)	57% (48% to 66%)	12% (-1% to 25%)
		Min. 2 medication	60% (51% to 69%)	42% (33% to 51%)	18% (5% to 31%)
		Min. 3 medication	41% (32% to 49%)	17% (10% to 24%)	23% (12% to 35%)
3	high	Min. 1 medication	66% (57% to 74%)	55% (46% to 64%)	10% (2% to 23%)
		Min. 2 medication	58% (49% to 67%)	44% (35% to 53%)	14% (1% to 27%)
		Min. 3 medication	41% (32% to 50%)	20% (13% to 27%)	22% (10% to 33%)

[#]Missing = 40.
CI: Confidence interval
[a]CVD= Cardiovascular disease
[b] Two-sample test of proportions

Additional File 5 - Table s2. Percentages of pharmacists' willingness to deprescribe each medication by case vignette according to the medication type, history of cardiovascular disease, and dependency level (n= 116)

Medication	Level of dependency in activities of daily living		
	Low (Case vignette 1)	Medium (Case vignette 2)	High (Case vignette 3)
	Percentage of Pharmacists (95% CI)	Percentage of Pharmacists (95% CI)	Percentage of Pharmacists (95% CI)
Pain medications			
Tramadol 50 mg, twice daily			
Without history of CVD	50% (41% to 59%)	54% (45% to 64%)	51% (41% to 60%)
With history of CVD	33% (24% to 42%)	46% (36% to 55%)	44% (35% to 53%)
Paracetamol 1 g, three times daily			
Without history of CVD	27% (13% to 36%)	19% (12% to 27%)	19% (12% to 27%)
With history of CVD	16% (10% to 24%)	15% (9% to 22%)	16% (9% to 23%)
Proton-pump inhibitor			
Pantoprazole 20 mg, once daily			
Without history of CVD	65% (55% to 73%)	56% (47% to 65%)	53% (43% to 62%)
With history of CVD	47% (38% to 57%)	46% (36% to 55%)	44% (35% to 53%)
Antihypertensive medications			
Amlodipine 5 mg, once daily			
Without history of CVD	15% (9% to 22%)	14% (8% to 21%)	15% (9% to 22%)
With history of CVD	6% (2% to 12%)	4% (1% to 10%)	8% (4% to 14%)
Enalapril 10 mg, once daily			
Without history of CVD	6% (2% to 12%)	4% (1% to 10%)	8% (4% to 14%)
With history of CVD	3% (1% to 7%)	3% (1% to 7%)	4% (1% to 10%)
Cholesterol-lowering medication			
Atorvastatin 40 mg, once daily			
Without history of CVD	42% (33% to 52%)	26% (18% to 35%)	36% (27% to 46%)
With history of CVD	5% (2% to 11%)	5% (2% to 11%)	12% (7% to 19%)
Antiplatelet medication			
Aspirin 100 mg, once daily			
Without history of CVD	41% (32% to 51%)	28% (20% to 37%)	25% (17% to 34%)
With history of CVD	1% (0% to 5%)	1% (0% to 5%)	3% (1% to 7%)

CI: Confidence interval; CVD: Cardiovascular disease; GP: General practitioner
Missing: Of the 138 respondents, there were 40 missing.

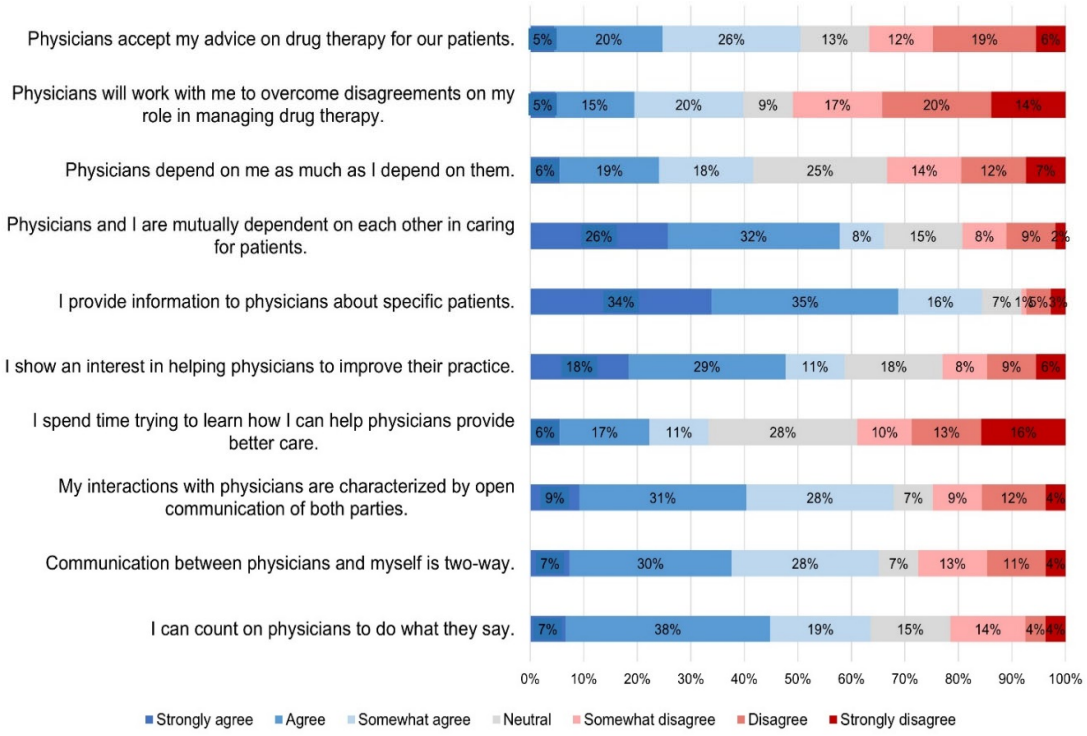
Additional File 6 - Table s3. Sensitivity analysis of the association between making deprescribing recommendations in each case vignette, dependency in activities in daily living and pharmacists' characteristics by patients' history of cardiovascular disease (n=98 pharmacists, n=2,394 observations)

	Adjusted Odds Ratio (95% CI) [a]	p-value [a]
Patients without cardiovascular disease		
Dependency in activities of daily living (ADL) *(ref: low)*		
Medium	0.69 (0.54 to 0.87)	0.002
High	0.72 (0.57 to 0.91)	0.006
Pharmacist age		
Per 10-year increase	0.98 (0.76 to 1.26)	0.881
Gender *(ref: male)*		
Female	0.89 (0.46 to 1.71)	0.717
Frequency of seeing patients ≥70 years old with polypharmacy (0-100)		
Per 10-percentage increase	0.88 (0.79 to 0.99)	0.026
FPH in community pharmacy *(ref: not having a FPH title in community pharmacy)*		
Specialized in community pharmacy	0.88 (0.52 to 1.51)	0.651
Training in Medication Review *(ref. not having a training in medication review)*		
Having a medication review training	2.37 (1.39 to 4.06)	0.002
Patients with cardiovascular disease		
Dependency in activities of daily living (ADL) *(ref: low)*		
Medium	1.10 (0.83 to 1.47)	0.510
High	1.26 (0.95 to 1.67)	0.113
Pharmacist age		
Per 10-year increase	0.87 (0.65 to 1.17)	0.360
Gender *(ref: male)*		
Female	0.66 (0.31 to 1.42)	0.290
Frequency of seeing patients ≥70 years old with polypharmacy (0-100)		
Per 10-percentage increase	0.91 (0.80 to 1.04)	0.163
FPH in community pharmacy *(ref: not having a FPH title in community pharmacy)*		
Specialized in community pharmacy	0.83 (0.44 to 1.57)	0.574
Training in Medication Review *(ref. not having a training in medication review)*		
Having a medication review training	2.38 (1.28 to 4.44)	0.006

[a] Multilevel logistic regression adjusted for patients' and pharmacists' characteristics. Dependent variable: Willing to deprescribe each medication. ICC: 0.347.

FPH*: Foederatio Pharmaceutica Helvetiae* is the certification organisation for pharmacists in Switzerland, overseeing postgraduate and continued education. The FPH in community pharmacy is required in order to obtain authorization to practice as a pharmacist in the private sector under their own professional responsibility and to bill the compulsory health insurance.

Additional File 7 – Figure s2. Interprofessional collaboration between pharmacists and physicians (n=109).



Adapted from 1.Zillich AJ, Milchak JL, Carter BL, Doucette WR. Utility of a questionnaire to measure physician-pharmacist collaborative relationships. J Am Pharm Assoc (2003). 2006;46(4):453-8.

Additional File 8 - Table s4. Suggestions made by pharmacists on how to improve collaboration between pharmacists and general practitioners with regards to medication optimisation in Swiss primary care settings (n=75)

Topic	Description	n (%)
Shared decision-making between pharmacists and physicians	Wish for more interprofessional work practices, teamwork, shared responsibilities, and wish for a higher acceptance of pharmacists' role by physicians.	32 (43%)
Efficient communication between pharmacists and physicians	Quicker responses from physicians, direct contact between pharmacists and physicians, easier access for pharmacists to physicians, and availability of an electronic platform to facilitate communication and data sharing.	31 (40%)
Equality in the workplace	More acceptance and respect from physicians towards pharmacists' (de)prescribing recommendations, understanding by physicians that both pharmacists and physician have equal importance in the medication optimisation process.	25 (33%)
Regular meetings between pharmacists and physicians (and other health care professionals)	Regular meetings like *quality circles*[1], in which physicians, pharmacists and other healthcare professionals discuss questions and issues that arise in their clinical practice. Through regular meetings they could get to know each other better, which would facilitate daily interactions.	23 (31%)
Access to detailed patient health information	Wish from pharmacists for shared digital patient health records that facilitate data sharing and allow them to access complete patients' health data (pharmacists in Switzerland currently do not have access to diagnoses, complete medication lists including the reasons for prescribing, laboratory or vital data).	22 (28%)
Exchange of physicians' and pharmacists' work experiences	Pharmacists visiting physicians' practices and physicians visiting pharmacies regularly would improve the understanding of both parties on what the daily clinical routines of the other party look like. Wish for more opportunities to interact and discuss patient scenarios.	19 (25%)
Acknowledgement and recognition of the pharmacists' role and knowledge by physicians	Wish that physicians had more awareness, respect, recognition, and understanding of the pharmacists' role in patient care. If physicians would learn more about pharmacists' education, capabilities, knowledge, and skills, this would facilitate interprofessional collaboration.	17 (23%)
Joint training for pharmacists and physicians	Physicians and pharmacists should have joint training sessions/educational opportunities (from the university setting to the continued education setting). Joint events could facilitate the teamwork in daily practice.	12 (16%)

Responses to the free-text question "*What would improve collaboration between pharmacists and family doctors?*" were analyzed using a quantitative text analysis.

[1] Quality circles are regular meetings among healthcare professionals (commonly among general practitioners), in which they discuss their general work practice.

13. Declaration of Originality

Declaration of Originality

Last name, first name: Vidonscky Lüthold, Renata

Matriculation number: 21-111-273

I hereby declare that this thesis represents my original work and that I have used no other sources except as noted by citations.

All data, tables, figures and text citations which have been reproduced from any other source, including the internet, have been explicitly acknowledged as such.

I am aware that in case of non-compliance, the Senate is entitled to withdraw the doctorate degree awarded to me on the basis of the present thesis, in accordance with the "Statut der Universität Bern (Universitätsstatut; UniSt)", Art. 69, of 7 June 2011.

Place, date

Bern, 05.04.2024

Signature

Renata Lüthold Digitally signed by Renata Lüthold
Date: 2024.04.05 14:28:11 +02'00'