Clinical decision support-assisted pharmacotherapy optimisation for older hospitalised patients

Lianne Huibers

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Clinical decision support-assisted pharmacotherapy optimisation for older hospitalised patients

Optimaliseren van farmacotherapie met behulp van een beslis-ondersteunend instrument voor in het ziekenhuis opgenomen oudere patiënten

(met een samenvatting in het Nederlands)

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"Medicine is a science of uncertainty and an art of probability."

- **Sir William Osler**

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AIMS AND OUTLINE OF THIS THESIS

"The person who takes medicine must recover twice, once from the disease and once from the medicine."

- **Sir William Osler**

GENERAL INTRODUCTION

This thesis focuses on in-hospital clinical decision support-assisted pharmacotherapy optimisation for older patients with polypharmacy and multimorbidity. To date, clinical trials that have aimed to reduce drug-related harmful outcomes, including drug-related hospital admissions and mortality in older patients with polypharmacy, failed to prove any impact of pharmacotherapy optimisation on such outcomes, both in primary and secondary care settings. The research presented in this thesis provides insights into the use of STOPP/START (Screening Tool of Older Persons' Prescriptions and Screening Tool to Alert to Right Treatment) criteria as a tool to reduce inappropriate prescribing and the feasibility of integrating the STOPP/START criteria into a clinical decision support system (CDSS). Additionally, this research explores the use of such a CDSS as part of an intervention involving a pharmacotherapy expert team in a clinical trial aimed at improving pharmacotherapy and related health outcomes for older hospitalised patients with polypharmacy. Furthermore, this thesis examines the involvement of healthcare professionals and patients in shared-decision-making (SDM) regarding in-hospital pharmacotherapy optimisation and highlights barriers and facilitators to this optimisation in a hospital setting. These insights may help improve the process of pharmacotherapy optimisation and ultimately reduce drug-related harm in older patients.

The ageing population with multimorbidity and polypharmacy

The population is ageing rapidly worldwide. According to the *World Population Prospects 2019*, by the year 2050, one in six people (16.7%) will be 65 years or over, while this was one in 11 people (9.1%) in 2019 (**Figure 1**). Globally, the survival beyond age 65 is increasing. A person who turned 65 between 2015 and 2020 can expect to live an additional 17 years, on average. This number is expected to increase to 19 years by 2050, while it was 14.3 years in 1950.[1,2]

Alongside this trend regarding ageing, common chronic health problems that are known to increase with age will become more prevalent. The prevalence of multimorbidity in older people, commonly defined as the coexistence of two or more chronic diseases, ranges from 55% to 98%.[4,5,6] Multimorbidity is associated with greater disability and functional decline, higher use of the healthcare system and a poorer quality of life.[6]

As chronic diseases are frequently managed with medications, the existence of multiple chronic diseases is often accompanied by polypharmacy, usually defined as the concomitant and chronic use of ≥ 5 medications.[7,8] Although polypharmacy is often indicated and is intended to relieve current symptoms and prevent future morbidity and mortality, it can also lead to negative health outcomes, such as adverse drug reactions, drug-related hospital admissions and functional decline.[9–11]

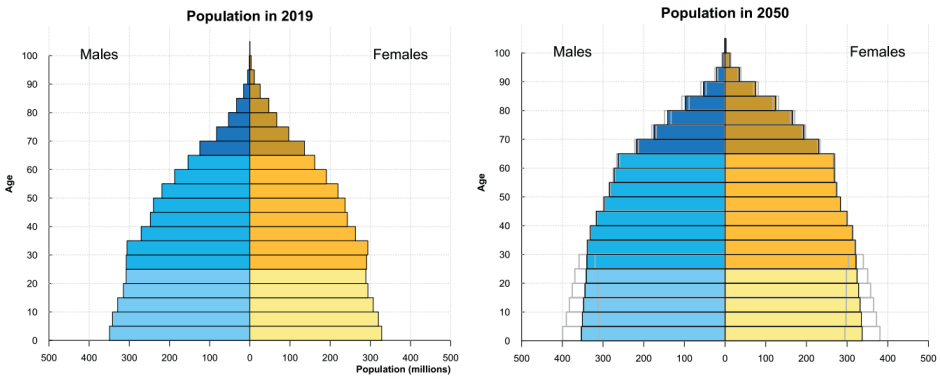


Figure 1: Population pyramids depicting the distribution of the world population by age group and sex. *Adopted from: United Nations, Department of Economic and Social Affairs, Population Division 2 World Population Prospects 2019, Volume II: Demographic Profiles*[3]

When the potential harms of pharmacotherapy outweigh the intended benefits for an individual patient, this is considered potentially inappropriate prescribing (PIP). PIP comprises both overtreatment expressed as potentially inappropriate medications (PIMs) as well as undertreatment, defined as potential prescribing omissions (PPOs). Up to 40% of older people are using PIMs according to recent studies.[12] The PPO prevalence among older patients in primary care settings is around 21%. Conversely, PIM and PPO prevalence among older multimorbid hospitalised patients varied from 35 to 77% and 51 to 77%, respectively.[13–15] Many factors contribute to the higher risks associated with PIP in older people compared to younger individuals. These include age-related alterations in pharmacokinetics and -dynamics, lower physiological reserve and the presence of multimorbidity (risk of drug–disease interactions) and polypharmacy (risk of drug–drug interactions).[16,17] To detect PIP and, ultimately, to optimise pharmacotherapy for older patients with polypharmacy and multimorbidity, numerous screening tools and interventions have been developed.[18] Medication reviews, – in other words, the structured evaluation of a patient's medications with the aim of optimising pharmacotherapy and improving health outcomes, – are widely used to address PIP in both primary and secondary care settings by different health care professionals.[7]

Screening tools and interventions to reduce inappropriate prescribing

Currently, several screening tools, both implicit (judgement-based) and explicit (criterion-based), are available to assist health care professionals in detecting PIP in older patients. Explicit screening tools typically consist of lists of medications or medication classes that should be avoided in older patients because of their increased risk of adverse effects; these include the STOPP/START criteria, the Beers criteria, the FORTA (Fit fOR The Aged) list and the EU(7)-PIM list.[18–22] The STOPP/START criteria,

which are used throughout this thesis, were developed in Ireland in 2008 and last updated in 2015.[23,24] In addition to the PIM list included in STOPP criteria, this tool also contains an explicit list of PPOs in older patients, which are the START criteria. The STOPP/START criteria are now widely used in Europe and beyond to detect and manage PIP in older patients. Studies have demonstrated that when the STOPP/START criteria were applied as an intervention combined with usual pharmaceutical care, they have the potential to reduce PIP, decrease medication costs and decrease the incidence of adverse drug reactions (ADRs) among multimorbid older patients in a hospital setting.[25]

A potential advantage of explicit screening tools is that these are easy to use by all prescribers and are less time-consuming, compared to implicit tools. These tools alert prescribers to the most prevalent or high-risk PIMs and PPOs without necessarily requiring specific expertise in that field. The downside of these explicit tools is that they focus on the medication, usually without taking into account individual patients' risk factors, comorbidities, treatment goals and preferences. Implicit screening tools, in contrast, require specific knowledge and expertise and are more time-consuming than explicit tools. The main advantage of implicit tools is that these focus on the benefit–risk ratio of medications in the specific context of the individual patient at that moment.

The Systematic Tool to Reduce Inappropriate Prescribing (STRIP) is an implicit prescribing tool where explicit prescribing criteria can be incorporated into the pharmacotherapy review.[26] The STRIP method actively involves the patient and encourages collaboration between different healthcare providers such as physicians and pharmacists. Evaluation and monitoring of medication changes and follow-up regarding patients' preferences, needs and concerns relating to their pharmacotherapy are other important aspects of the STRIP method that are likely to improve patient satisfaction and adherence. Although it was originally developed for the primary care setting, the STRIP method can also be used in other settings, such as hospitals. The STRIP method consists of five consecutive steps[26] (**Figure 2**): medication assessment, pharmacotherapy review, pharmaceutical care plan, shared decision making and follow-up and monitoring.

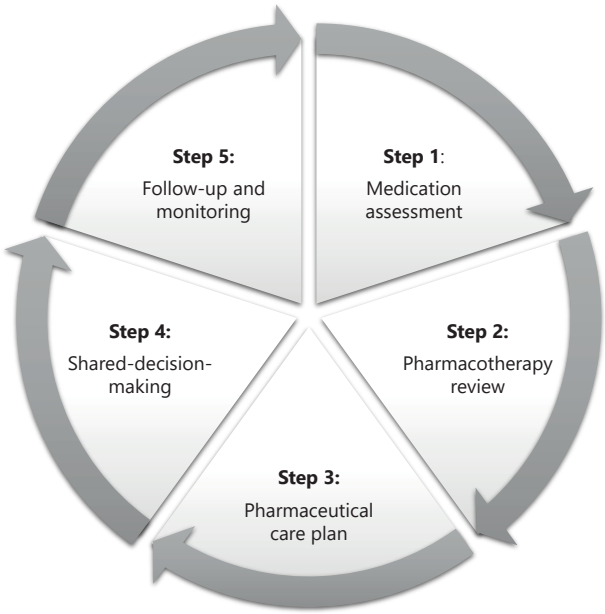
Clinical decision support systems in pharmacotherapy optimisation

To make the pharmacotherapy review (Step 2) within the STRIP method more time-efficient and to enable physicians and pharmacists to incorporate the STRIP method into the daily practice workflow, initiatives have been developed to integrate explicit criteria, such as STOPP/START, into CDSSs. The STRIP assistant has been developed as a stand-alone web application to assist pharmacists and general practitioners (GPs) with the pharmacotherapy review. The STRIP assistant can generate recommendations to optimise pharmacotherapy based on incorporated guidelines on clinical interactions,

double medication, contra-indications, dose strength and frequency, as well as recommendations based on the implemented STOPP/START criteria version 1.[23,28,29] In an online experiment involving 42 physicians, the STRIP assistant improved the effectiveness of medication reviews for polypharmacy patients (paper cases, compared with an expert panel), with an increase in appropriate decisions from 58% to 76% and a decrease in inappropriate decisions from 42% to 24%. However, participants spent significantly more time optimising pharmacotherapy with the STRIP assistant (24 min) than without it (13 min).[28] In a follow-up study involving teams of experts who performed medication reviews with the STRIP assistant, the time to perform a medication review statistically reduced over time as users gained more experience with the STRIP assistant.[30] Both studies suggest that CDSS-assisted pharmacotherapy optimisation may indeed be more time-efficient and lead to more appropriate decisions.

In medicine, CDSSs are increasingly used in interventions and implementation studies to support healthcare professionals and to better and more efficiently implement the intervention. A recent systematic review included 18 interventions that investigated the effect of CDSS in the care of older hospitalised patients.[31] The interventions included in this review focussed, for example, on delirium, falls, functional decline and medication review. In total, 72% of CDSS-assisted interventions were effective in improving care. The impact was based on process-related outcomes in 77% of effective interventions and only 8% on patient-related outcomes (e.g., falls and adverse drug reactions). No significant impact was found on length of stay and 30-day readmission rate. Multifaced interventions were associated with greater effectiveness.

Clinical trials aimed at optimising pharmacotherapy in older patients with polypharmacy also increasingly use CDSS in medication reviews. A recent systematic review and meta-analysis of computerised interventions that are designed to reduce PIP in hospitalised older patients concluded that CDSS-assisted interventions are capable of significantly reducing PIMs in this patient group. However, there was insufficient evidence that these interventions actually improve patient-related outcomes.[32] All included studies were single-centre studies – only two were randomised controlled trials (RCTs) – and all but one were conducted in the United States, which might have an impact on the generalisability of the findings. The acceptance rates of computer-generated recommendations varied significantly across the studies. The findings suggest that interventions targeting a smaller number of PIP instances may result in greater acceptance rates, as prescribers might be overwhelmed by the complexity of information provided in broader interventions. None of the included studies in this review targeted reducing medication underuse (i.e., PPOs) and no conclusions could be drawn regarding the cost-effectiveness of the intervention.



1	**Medication assessment:** Collect information on actual use and the patient's preferences, experiences and beliefs about medicines. The structured history taking of medication (SHiM) has proved to be valid for this purpose.[27]
2	**Pharmacotherapy review**: Identify potential pharmacotherapy-related problems. Check for under-prescribing, ineffective prescribing, over-prescribing, side effects, contra-indications, drug–drug and drug–disease interactions, dosing and practical issues. Explicit screening tools such as STOPP/START criteria can be implemented in this step.
3	**Pharmaceutical care plan**: Reach agreement between physician and pharmacist about therapeutic aims and how to achieve them.
4	**Shared-decision-making**: Meet the medication-related needs of the patient, establish goals of therapy and solve pharmacotherapy-related problems. Communication of all medication changes to the involved healthcare providers.
5	**Follow-up and monitoring**: Implementation of medication changes and evaluation of the impact. Planning of the next revision including the responsible health care provider.

Figure 2: Flowchart representing the Systematic Tool to Reduce Inappropriate Prescribing (STRIP). Reproduced with permission from ***Meulendijk et al***.[28]

The SENATOR (Software ENgine for the Assessment and optimisation of drug and non-drug Therapy in Older peRsons) trial was the first large-scale, multi-centre RCT assessing the impact of a software engine for electronic deployment of STOPP/START prescribing rules on incident ADRs in acutely hospitalised older patients with multimorbidity.[33] A total of 1,537 patients at six centres across Europe were randomised

in 13 medical and eight surgical clusters. The primary end point (non-trivial ADR) occurred in 190 (24.8%) control and 189 (24.5%) intervention patients (OR 0.98; 95% CI 0.77–1.24; p = 0.88). Adherence among the attending clinicians to the SENATOR software-generated medication recommendations was only 15%, on average, across the six participating centres, which was substantially lower than expected. This might be the most important explanation for the negative trial results. The authors conclude that it is important for future trials to combine efficient software delivery of prescribing advice with direct face-to-face contact between attending clinicians and trained physicians or pharmacists.[33,25] Additionally, a SENATOR-derived qualitative study investigating the factors affecting prescriber implementation of computer-generated medication recommendations revealed that, to enhance implementation, it is important for future CDSS-assisted interventions to provide informed rationale on how each recommendation was formed and to avoid unnecessary recommendations by adjusting the algorithms.[34]

In summary, CDSS-assisted pharmacotherapy optimisation indicated positive impacts on intervention implementation and process-related outcomes but no significant improvement in patient-related outcomes.[31,32] Prior trials demonstrated varying acceptance and implementation rates of CDSS-generated medication optimisation recommendations. This was related to the number of recommendations, the relevance of recommendations for the individual patient and the manner of communication (face-to-face versus written reports), amongst others. Large scale, multicentre RCTs are needed to investigate the effect of CDSS-assisted pharmacotherapy optimisation on patient-related outcomes in older hospitalised polypharmacy patients, taking into account the factors related to higher implementation rates of the recommendations. This will also require the active participation of all healthcare professionals and the patients involved.

Health care professionals' and patients' involvement in pharmacotherapy optimisation

The development and successful implementation of effective strategies for pharmacotherapy optimisation and the reduction of PIP-related negative health outcomes depends on multiple environmental factors (i.e., potential barriers and facilitators) and the people involved in the process. Ideally, the process of pharmacotherapy optimisation includes the patient, a physician and a pharmacist.[35,36] Pharmacists are important for their intimate knowledge of medication and the consequences of medication non-adherence and their ability to critically review and apply clinical guidelines to the medication care for individual patients.[37] Physicians are indispensable as prescribers who eventually alter the prescriptions and thereby implement medication adjustments. Additionally, physicians – especially those engaged in the care of older patients – are trained to weigh

the benefit/risk balance of pharmacotherapy for individual older patients who do not always fit into single-disease-oriented guidelines.[38] Moreover, active involvement of patients in decision-making regarding pharmacotherapy optimisation is important to improve medication adherence, patient satisfaction and, ultimately, patient outcomes.[39] Finally, the role of other healthcare professionals, such as home care nurses, could positively contribute to medication adherence and medication safety in older patients, as these nurses can provide informational, practical and emotional support to patients.[40] Furthermore, home care nurses can closely observe patients and recognise potential drug-related problems (DRPs).[41]

The pharmacist's role in patient care has increased in scope from the more traditional tasks of basic medication counselling and dispensing medications to intensive collaborations with other healthcare professionals and patients. The role of community pharmacists involves identifying, preventing and resolving DRPs in addition to promoting proper and safe use of medications and patient education.[42] Evidence of the positive contribution of community pharmacist-led interventions in improving patients' medication adherence and better disease control has increased. Community pharmacist-led medication reviews have demonstrated significant reductions in medication and/or health care costs, but findings regarding reductions of hospitalisations and mortality are inconclusive.[43–45]

In-hospital clinical pharmacist-led interventions have been the subject of several studies, including RCTs, over the past decade.[46–48] These trials focussed mainly on the prevention of DRPs and drug-related admissions (DRAs) through a variety of interventions, ranging from pharmacist-delivered medication reviews to multifaced interventions including motivational patient interviewing and follow-up with the GP and community pharmacist. One trial found a significant impact of the extended intervention (including patient interviews and follow-up) on 30-day readmission rate [HR], 0.62; 95% CI, 0.46-0.84), but no significant impact was found on drug-related readmissions. The other trials failed to significantly attenuate either of these endpoints. The role of clinical pharmacists in multidisciplinary teams on pharmacotherapy optimisation for older hospitalised patients needs be investigated further. Nevertheless, the importance of interdisciplinary collaboration between hospital pharmacists and hospital physicians in multidisciplinary teams to optimise patient outcomes has increased. A qualitative study of physician–pharmacist collaboration in the hospital setting revealed that the physicians lack knowledge about hospital pharmacists' roles, competencies and activities.[49] The authors conclude: "The presence, visibility and implication of hospital pharmacists needs to be improved, and physicians should be more aware of what the hospital pharmacists can offer them".[49]

Implementation of STOPP/START-based medication optimisation recommendations is significantly affected by the method of communication and the medium through which the recommendations are provided. Dalton et al. found that prescribing physicians were more likely to implement recommendations delivered by fellow physicians than those delivered by clinical pharmacists.[50] Additionally, the physicians communicated all recommendations verbally, whereas the pharmacists provided the recommendations in written form only in the majority of cases. The pharmacists, however, provided recommendations based on STOPP/START as well as a wider range of DRPs. This may contribute to information overload, resulting in the implementation of fewer recommendations. Thus, greater complexity of the intervention may result in lower implementation rates by attending prescribers. Prior research underlined that trust and "knowing" each other are key components to physician–pharmacist collaboration in primary care.[51] These potential interprofessional barriers may result in lower implementation rates of pharmacists' recommendations. Research on physicians' barriers and facilitators for implementation of pharmacist or physician recommendations in secondary care is scarce. Additionally, cost-effectiveness of the intervention delivered by either a pharmacist or physician needs to be further established in future research.[52,53] This is especially true because of the increasing extent of CDSS-assisted pharmacotherapy optimisation in both primary and secondary care, which might save time and expense.[54,55]

The third and possibly most important person in the chain of pharmacotherapy optimisation is the older patient with polypharmacy themself. Although many studies focus on patient-related outcomes such as readmissions and mortality associated with pharmacotherapy optimisation, not all studies actively involve patients in decision-making regarding their own pharmacotherapy. Studies report on prescriber implementation of recommendations, but patient satisfaction or agreement with these implemented recommendations is often not investigated or mentioned.

In the past years, SDM has attracted growing interest, and patient preferences regarding medication changes are considered important and are assumed to play a crucial role in medication adherence and persistence of medication changes.[56–58] Qualitative research reveals that few older people have a thorough understanding of the indication for which they are taking medications; moreover, the majority appear to have little to no knowledge of the potential adverse effects of their medications.[59–62] Many patients have complete trust in health care professionals and therefore feel no need to know all the indications or medications they are taking.[63] The experience of an effect and the absence of adverse effects from medication can act as a barrier to discontinue potentially inappropriate medication (i.e., deprescribing), whereas the lack of an effect or the presence of adverse effects could act as enablers to discontinue, especially among older adults with limited life expectancy.[59,61,64,65]

Patient-centred goal setting is important to identify patients' concerns, priorities and preferences regarding pharmacotherapy. Ideally, all treatment options, including the benefits and harms, are discussed to ensure a well-informed decision.[66] Deprescribing interventions targeting patients' motivation to deprescribe leads to successful outcomes when patients do not have internal competing desires to remain on drug therapy and health care providers are supportive.[67] Understanding a patient's perspective is an essential part of medication optimisation and SDM is not only considered ethically appropriate, it can also save time, resources and medications and may improve adherence and health outcomes.[68,69]

Although the potential advantages of SDM are well-known, the process is perceived as complex and time-consuming by many physicians.[70] The dynamic hospital setting can act as a barrier to engage in SDM. However, it might be the crucial step to maintain medication adjustments made during hospitalisation by promoting adherence through proper explanation and education regarding the indications and expected benefits to patients.

Evidence gap and rationale

Multimorbidity and polypharmacy become more prevalent with advancing age, increasing the risk of inappropriate prescribing and adverse drug reactions, due to the higher risk of drug–drug and drug–disease interactions in addition to age-related alterations in pharmacokinetics and -dynamics. Detection of potentially inappropriate prescribing and subsequent optimisation of pharmacotherapy to improve the benefit/risk balance of pharmacotherapy, in accordance with patient preferences and individual treatment goals, is an important objective in geriatric medicine. Despite the potential of pharmacotherapy optimisation to improve medication appropriateness and to reduce adverse drug events, until now, clinical trials aimed at reducing DRPs including DRAs and mortality, failed to prove the effect of pharmacotherapy optimisation on health-related outcomes in older patients with polypharmacy.

Trials aimed at investigating the efficacy of pharmacotherapy optimisation in older patients with polypharmacy have been conducted in a variety of settings, including primary and secondary care and nursing homes. Although optimisation of chronic pharmacotherapy might be considered the responsibility of GPs and community pharmacists, in-hospital pharmacotherapy optimisation could pose certain advantages over the primary care setting.[14] The prevalence of PIP appears to be higher among hospitalised older patients compared to community-dwelling older people.[10,15,71] Although the prevalence varies between studies, up to 30% of hospital admissions in older patients are classified as drug-related (main or contributory reason), and nearly 50% of those DRAs are potentially preventable.[72–75] Therefore, older hospitalised patients with multimorbidity and polypharmacy are an important target population for pharmacotherapy optimisation. The

reason for hospitalisation could be an important trigger to evaluate the pharmacotherapy regimen during admission. Additionally, patients admitted to the hospital can be easily approached at the wards and can be involved in shared decision-making regarding their pharmacotherapy. Conversely, the length of a hospital stay is often not sufficient to monitor side effects that evolve after initiation of new medications or withdrawal symptoms after discontinuation of chronic medication.

Systematic reviews and meta-analysis investigating the impact of interventions to improve appropriate prescribing – including medication reviews and complex, multi-faceted pharmaceutical care-based approaches, performed in both primary and secondary care settings – revealed no significant impact on clinical endpoints such as DRPs, hospital admissions and quality of life.[76] The use of CDSS in pharmacotherapy optimisation interventions has increased in recent years and may improve the efficacy and efficiency of the intervention. A CDSS aimed at prescribers (electronic alerts to guide to the appropriate treatment) has been successful in reducing PIP in older patients. The latest Cochrane systematic review by Rankin et al. on interventions to improve the appropriate use of polypharmacy in older people included only two studies that involved a CDSS in the intervention.[77,78] Both studies were conducted in primary care settings and measured only the reduction in PIP and no patient-related health outcomes. Therefore, large-scale trials are needed to create new evidence on the prevention of avoidable hospital admissions and other important patient-related health outcomes through CDSS-assisted pharmacotherapy optimisation in multimorbid older patients in the hospital setting.

To fill the evidence gap that exists regarding the impact of CDSS-assisted in-hospital pharmacotherapy optimisation for older patients on important clinical outcomes, the OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people (OPERAM) project was designed (**Figure 3**). OPERAM aims to examine the effect of a structured medication review (based on the STRIP method) supported by a CDSS (the STRIP assistant) on DRAs compared to usual pharmaceutical care.[55] The core element of the OPERAM project is a large-scale cluster RCT conducted in four European countries among hospitalised older patients (≥ 70 years) with multimorbidity (≥ 3 chronic medical conditions) and polypharmacy (concurrent use of ≥ 5 chronic medications). Patients will be recruited at both surgical and medical wards, both elective and through the emergency department. The attending ward physicians will be randomised to either control or intervention arms and, consequently, all patients admitted under the ward physician's care will be included in the same study arm. Patients will be screened and recruited by a member blinded to the allocation of the clusters to avoid bias. Patients will receive superficial information on the study objectives to minimise reporting bias during follow-up, and ward physicians will sign a non-disclosure contract to limit unblinding

during the trial. A blinded team member will conduct follow-up at two, six and 12 months by telephone to assess trigger events for the primary outcome (DRA) and all secondary outcomes. Blinded, independent teams of pharmacists and physicians at each trial site will adjudicate the primary outcome using a standardised chart review method.[55]

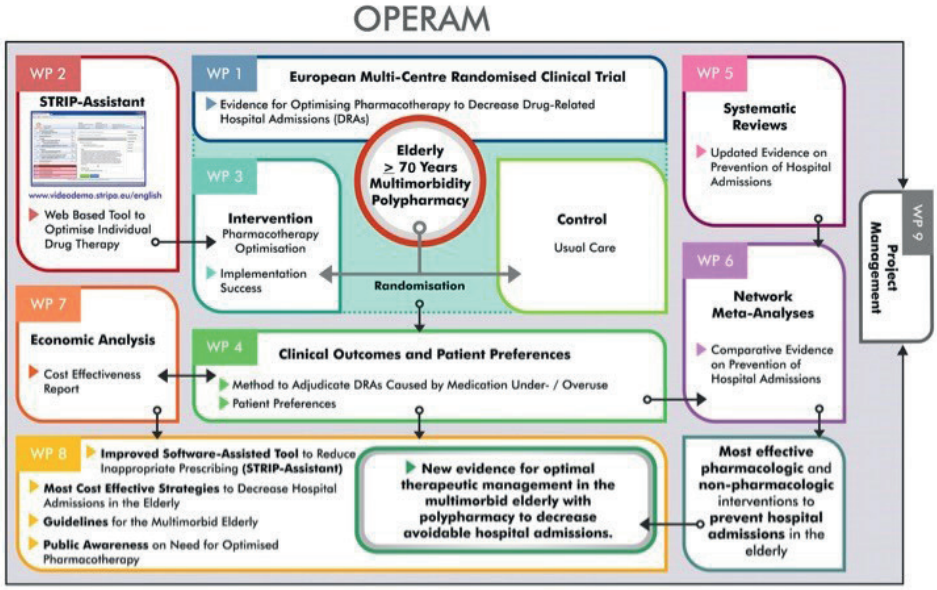


Figure 3: Overall concept of the OPERAM project. Adopted from Baumgartner et al.[79]

The OPERAM intervention is a complex, multicomponent intervention, based on the five steps of the STRIP method. It involves a structured history-taking of medication (SHiM), a medication review performed jointly by a physician and pharmacist and assisted by a CDSS known as the STRIP assistant (STRIPA) with integrated STOPP/START criteria (version 2), followed by shared decision-making with both patient and attending ward physician. An overview of all recommendations – implemented, rejected and postponed – will be sent to the patient's GP.

The OPERAM researchers aim to increase the impact of prescribing recommendations on patient care by promoting the collaboration of pharmacists and physicians, patient involvement in decision-making and clear communication of prescribing information and recommendations to the GP. Direct face-to-face communication of the pharmacotherapy optimisation recommendations between the researchers and the attending ward physicians will likely enhance implementation of the recommendations which should result in higher implementation rates than the 15% found in SENATOR.[33,80]

"The scientist is not a person
who gives the right answers,
he's one who asks the right questions."

- Claude Lévi-Strauss

AIMS OF THIS THESIS

This thesis focusses on various aspects of CDSS-assisted pharmacotherapy optimisation for older patients with polypharmacy and multimorbidity in the hospital setting.

The main aims of this thesis are:

- To assess the applicability of STOPP/START criteria for individual older hospitalised patients and to investigate the feasibility of translating the criteria into coded algorithms for software systems.
- To investigate the applicability of a CDSS, with integrated STOPP/START criteria, in medication reviews performed in a clinical trial setting among older hospitalised patients.
- To evaluate patients' and hospital physicians' perspectives on and involvement in decision-making regarding pharmacotherapy optimisation and to identify barriers and facilitators for implementation of pharmacotherapy optimisation in the hospital setting.

OUTLINE OF THIS THESIS

This thesis consists of three parts. The first part focusses on the applicability of STOPP/START criteria as a screening tool to detect inappropriate prescribing in older patients with multimorbidity and polypharmacy. These criteria can detect both over-prescribing (STOPP) and under-prescribing (START) and are used throughout this thesis. **Chapter 2** describes the process of converting the textual STOPP/START recommendations into coded algorithms suitable for implementation in software systems, including CDSS, through a multidisciplinary consensus procedure. **Chapter 3** reports the results of a quality appraisal study aimed at evaluation of the clinical applicability of the population-based STOPP/START criteria in daily patient care by assessing the clarity of singular criteria on a language level. We aim to provide directions to improve the clarity of future screening tools or clinical practice guidelines and to enhance clinical applicability.

The second part of this thesis covers various aspects of in-hospital CDSS assisted medications reviews in clinical trial settings. **Chapter 4** describes a cluster RCT in a preoperative assessment at the geriatric outpatient clinic. The aim of this study is to evaluate the impact of pharmacotherapy optimisation recommendations provided to the attending resident, supported by a CDSS with integrated STOPP/START criteria, on appropriate prescribing and three month mortality. **Chapter 5** provides a detailed description of the complex multi-component intervention of the OPERAM clinical trial.

The intervention consists of several consecutive steps according to the STRIP method including a structured, CDSS-assisted medication review with integrated STOPP/START criteria. **Chapter 6** discusses the frequency and subsequent acceptance, after evaluation for appropriateness for the individual patient, of the CDSS-generated STOPP/START signals by the pharmacotherapy team within the OPERAM trial.

The third part of this thesis highlights the involvement of hospital physicians and older patients in decision-making regarding pharmacotherapy optimisation in the hospital setting. **Chapter 7** presents the level of agreement (including reasons for disagreement) of hospital physicians and older hospitalised patients with individualised STOPP/START-based medication optimisation recommendations from a pharmacotherapy team. The results represent the Dutch OPERAM intervention group. Finally, **Chapter 8** explores hospital residents' perceived barriers and facilitators for pharmacotherapy optimisation in older hospitalised patients with polypharmacy in a qualitative study.

DECLARATIONS

Authors' contributions

This general introduction was written by Lianne Huibers (**CJAH**). Wilma Knol (WK), Ingeborg Wilting (IW), Rob van Marum (RvM) and Toine Egberts (TE) reviewed this introduction critically and approved the final version.

Competing interest

The author(s) declare that they have no competing interests.

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PART I

TRANSLATION OF STOPP/START CRITERIA INTO CLINICAL DECISION SUPPORT ALGORITHMS

Conversion of STOPP/START criteria version 2 into coded algorithms for software implementation: A multidisciplinary consensus procedure

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ABSTRACT

Background: The rapid digitalisation of medical practice has attracted growing interest in developing software applications for clinical guidelines and explicit screening tools to detect potentially inappropriate prescribing, such as STOPP/START criteria. The aim of the current study was to develop and provide logically unambiguous algorithms of STOPP/START criteria version 2, encoded with international disease and medication classification codes, to facilitate the development of software applications for multiple purposes.

Methods: A four round multidisciplinary consensus and validation procedure was conducted to develop implementable coded algorithms for software applications of STOPP/START criteria version 2, based on ICD, ICPC, LOINC and ATC classification databases.

Results: Consensus was reached for all 34 START criteria and 76 out of 80 STOPP criteria. The resulting 110 algorithms, modelled as inference rules in decision tables, are provided as supplementary data.

Conclusion: This is the first study providing implementable algorithms for software applications based on STOPP/START version 2, validated in a computer decision support system. These algorithms could serve as a template for applying STOPP/START criteria version 2 to any software application, allowing for adaptations of the included ICD, ICPC and ATC codes and changing the cut-off levels for laboratory measurements to match local guidelines or clinical expertise.

INTRODUCTION

Along with the rapidly aging population, the prevalence of multimorbidity and polypharmacy is increasing.[1,2] Polypharmacy increases the risk of inappropriate medications and is associated with adverse drug reactions (ADRs), poorer drug adherence, higher health care costs, more emergency department visits, hospital admissions and overall mortality.[3,4] Several implicit (judgement based) and explicit (criterion based) tools have been developed to detect inappropriate prescribing in multimorbid older people.[5–7] It appears to be challenging to incorporate these tools into daily clinical practice. Since the publication of the first version of STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert to Right Treatment) criteria in 2008, this explicit screening tool to detect potentially inappropriate prescribing (PIP) in older people has become the European alternative for the American Beers list, with a higher sensitivity for identifying ADR associated potentially inappropriate medications (PIMs).[8–10] When applied as an intervention, STOPP/START criteria significantly improved medication appropriateness in older patients admitted for acute illnesses and significantly reduced ADRs.[11,12] In 2015, the STOPP/START criteria were updated resulting in a 31% increase in the total number of criteria compared to version 1.[13] Due to the extensiveness of the list, currently comprising 114 criteria, there has been growing interest in developing STOPP/START software applications for clinical decision support systems (CDSS) as well as research studies in large databases.[14–16] More recently, the PIM-check was developed.[17] This international electronic prescription screening checklist was designed to detect PIMs in internal medicine patients. This checklist includes 160 statements in 17 medical domains and 56 pathologies. Comparison of PIM-Check and nondigital version of STOPP/START criteria applied to internal medicine patients revealed a substantially shorter screening time for PIMCheck compared to STOPP/START (4 vs 10 min) due to its electronic interface.[18] This emphasises the need for digitalisation of (explicit) screening tools. Nearly half of the detected PIMs, however, were judged to be non-clinically relevant for both tools. The consensus based specification of STOPP/START criteria version 1 implemented in a CDSS, improved the effectiveness of a medication review, expressed as an increase in appropriate decisions and a decrease in inappropriate decisions in accordance with an expert panel, compared to a traditional (non-digitalised) medication review.[19,20] Some criteria from STOPP/START are rather non-specific and ambiguous. Consequently, undesirable variations in interpretation and application could emerge. In order to develop software applications based on STOPP/START version 2, these criteria need further specification. Consensus is required to define STOPP/START version 2 more clearly.[15] The aim of the current study was to develop and provide logically unambiguous algorithms of STOPP/START criteria version 2, encoded with international disease and medication classification codes, to facilitate the development of software applications for multiple purposes.

METHODS

The current study involved a multidisciplinary consensus and validation procedure in order to develop a specification of STOPP/START criteria version 2, encoded with international disease and medication classification codes, ultimately providing implementable coded algorithms for software applications.

STOPP/START criteria

For this study we used the original Irish version 2 of STOPP/START as published by O'Mahony et al. consisting of 80 STOPP and 34 START criteria.[13]

Classification databases

To facilitate extractions both in hospital and general practices, two widely used classification systems for coding diseases were selected: the International Classification of Disease (ICD) version 9 and 10 and the International Classification of Primary Care (ICPC) version 1 and 2.[21–23] Medication was specified according to the Anatomic Therapeutic Chemical (ATC) classification system formulated by the World Health Organization Collaborating Centre for drug statistics methodology. They were defined as either medication classes (ATC 3 and 4 level) or singular drug compounds (ATC 5 level).[24] The Logical Observation Identifiers Names and Codes (LOINC) database was used to code laboratory values and measurements.[25] All these databases are freely accessible.

Consensus procedure

The multidisciplinary consensus procedure consisted of four rounds. A flowchart illustrating the consensus procedure is shown in **Figure 1**.

First round

A preparation panel consisting of 2 physicians (DdG; GP in training and CD; geriatric resident) prepared a draft algorithm together with a PhD in informatics (MM) for all 114 STOPP/START version 2 criteria. Therefore, the individual criteria needed to be itemised into 'codable' pieces. Roughly three categories were distinguished: (1) Diseases and/ or medical conditions specified by ICPC 1, 2 and ICD-9 and 10; (2) drug (classes) (with or without specified doses or duration) at ATC 3, 4, or 5 level; (3) laboratory values and measurements (with or without cut-off values) specified in LOINC. After specifying all the codes, they were converted into separate logical algorithms per criterion.

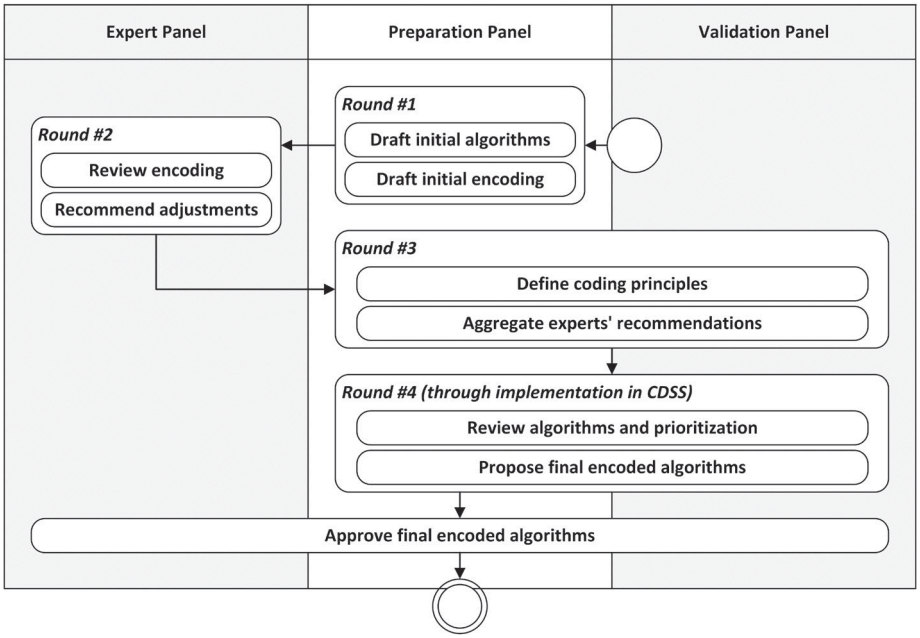

Figure 1: Flowchart illustrating the consensus procedure.

Second round

For the second round, an expert panel was consulted to review the draft algorithms. The expert panel consisted of a geriatrician-clinical pharmacologist (RvM), a geriatrician (JvC), a clinical pharmacologist (JH), a hospital pharmacist (AV) and a general practitioner (MB). All members of the expert panel received a copy of the draft algorithms, with web links to the ICPC, ATC and ICD databases. The algorithms were accompanied by a code dictionary containing all incorporated codes, categorized per STOPP/START criterion. The experts were asked to review all the assigned codes as well as the interpretation of the criteria by the preparation panel. A teleconference meeting was organized to discuss the suggested modifications by the expert panel and to reach consensus. During this meeting suggestions to in- and exclude certain ATC-codes (e.g. specifying DMARDs, anticholinergics, high potency opioids) and ICPC/ICD-codes were discussed per STOPP/START criterion, based on clinical guidelines, scientific literature and the (clinical) expertise of the panelists.

Third round

During the teleconference meeting, discussion between the panelists elucidated the ambiguity of some criteria leading to different interpretations of STOPP/START recommendations and consequent choices regarding the codes (both ICD/ICPC and ATC) to be included in

the algorithms. To improve the inter-rater reliability, a set of basic principles for coding the algorithms (**Table 1**) was deemed necessary. A physician (CH; geriatric resident and PhD researcher) and a pharmacist (BS; hospital pharmacist in training and PhD researcher) were consulted as a validation panel, based on their experience with developing and implementing STOPP/START algorithms in a CDSS. During the third round, the validation and preparation panel (DdG, MM, CH and BS) reviewed and discussed all coded algorithms in three face-to-face meetings according to the coding principles, focusing both on content (i.e. completeness and consistency of incorporated ICD, ICPC and ATC codes) and on logic (i.e. the interrelationship of different items within one algorithm).

Table 1: Coding principles defined during the third round

	Defined coding principles
1.	We intend to follow the original criteria as closely as possible. If criteria require additional specification in order to be encoded, this is conducted without essentially altering the content of the criterion.
2.	We assume the availability of recent laboratory values or measurements and prioritise these values over ICD or ICPC codes. If condition (1) is not satisfied, condition (2) will be evaluated for availability.
3.	If medication is specified as a class where an exact specification of the included medications within this class (i.e.) is mentioned, only those drugs are included (ATC 5 level). If medication is specified as a class on ATC 3 or 4 level, where no or some examples (e.g.) are mentioned, the most important medications within this class are included according to expert consensus.
4.	Some medical conditions can contain several underlying diagnoses that are not specifically mentioned. Therefore, the most common and/or most important diagnoses will be included based on consensus within the expert panel.
5.	In order to minimise false positive triggers in the practical application of our algorithms, we will add *optional* conditions to the criteria incorporating common (lack of) indications for certain medications and diseases (that are not actually present in the original criteria).

Fourth round

The validation panel applied the input of the experts to the algorithm and performed a functionality check for each criterion on logic, integrality and inter- and intra-item consistency using the defined coding principles. The draft version of the algorithm and the dictionary were updated accordingly. After consensus was reached regarding the content of the coded criteria, the ICD, ATC and LOINC based algorithms were implemented in a stand-alone, web-based CDSS (STRIP Assistant).[20] This round was an ultimate test to verify whether the content and logic, as theoretically approved in the third round, would reveal any unexpected errors if used in a computer system. Therefore,

all coded criteria were systematically tested in order to find false positive and false negative triggers, as well as logical errors within the algorithm. The conditions required to trigger an individual STOPP/START criterion were entered in the CDSS. If a specific criterion was not triggered while expected based on the data input into the CDSS, the algorithms were checked again to assess whether this was due to a coding problem based on content (i.e. ICD or ATC mismatch) or a logical problem within the algorithm itself. This process was repeated for all coded algorithms independently. A schematic representation of the approach is displayed in **Figure 2**. During this functionality check, it was found that the omission of exceptions within certain criteria generated false positive triggers if the algorithms were applied without any clinical judgement. For those criteria, the validation panel decided - in accordance with the experts - to add 'optional (excluding) conditions' to the algorithm, that were not actually present in the original STOPP/START criteria, to enhance (clinical) applicability of the algorithms. The adjusted set of algorithms was sent to all members of the expert panel for final approval.

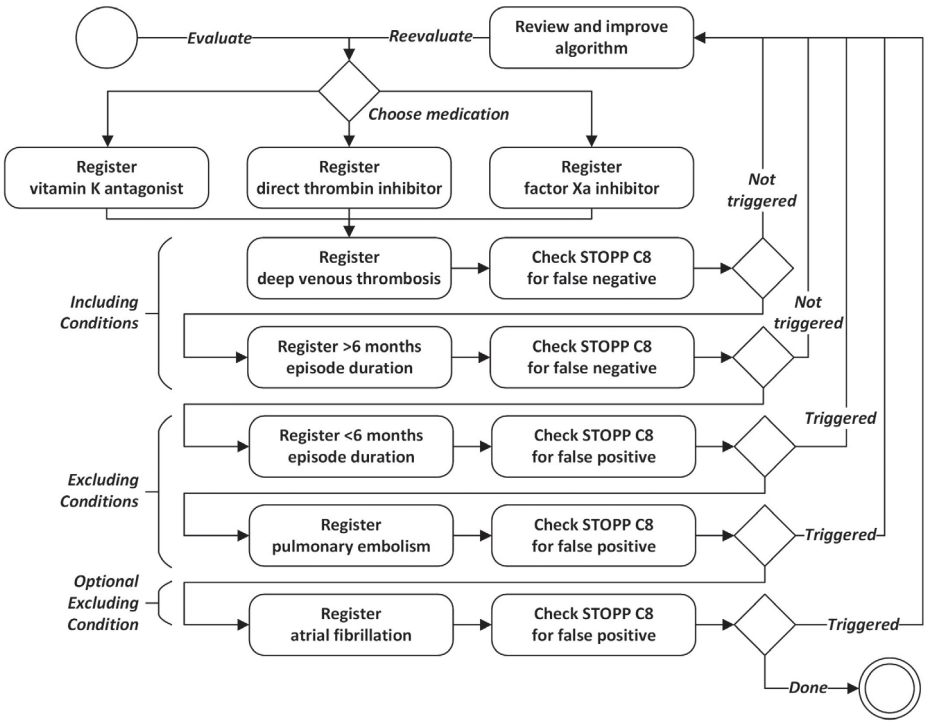

Figure 2: Systematic evaluation of STOPP criterion C8 as a flowchart

Schematic representation of STOPP criterion C8 'Stop vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for >6 months' illustrating the evaluation process (i.e. functionality check within a CDSS).

RESULTS

Consensus procedure

The consensus procedure resulted in the final list of algorithms as presented in the supplementary data (**Appendix A**). Any consensus based diversion from the original STOPP/START criteria is explained as a remark below the corresponding algorithm, including the addition of optional (excluding) conditions. During the consensus procedure, several challenges were faced while converting the textual STOPP/START recommendations and considerations into algorithms for software applications. A few examples illustrating the consequences of applying the coding principles to the algorithms are shown in **Table 2**.

Not all textual criteria could be converted into algorithms due to limitations in the coding databases as well as the presence of uncodable textual elements in the STOPP/START-criteria themselves. As a result, some criteria could not be coded at all (**Table 3**); others could be partially coded, leaving some uncodable elements out of the algorithms, thereby resulting in a simplification of the criterion. An overview of all optional (excluding) conditions included in the final algorithms is displayed in **Table 4**. During the (first) functionality check, 23 (68%) of 34 START criteria were correctly triggered, 5 (15%) could be improved and 6 (17%) did not show up within the CDSS. Regarding STOPP criteria, 41 (51%) were triggered accurately during first evaluation. Eleven (14%) could be improved and 28 (35%) did not show up. The reasons for incorrect triggering (both false positive and false negative) varied from simply dots instead of commas in the algorithms (logical error) to non-present ATC code for a specific medication in the algorithm (content). For all algorithms that were not triggered when expected or that could be improved, the logic was re-evaluated on errors and the content adjusted, as depicted in **Figure 2**, until all algorithms were functional and correct.

The algorithms

From a total of 114 criteria, we were able to code all 34 START criteria and 76 out of 80 STOPP criteria, corresponding with 96% of all criteria. The final 110 algorithms are attached as **Appendix A** in the online Supplementary Data. All ICPC 1, ICPC 2, ICD-9, ICD-10 and ATC codes used to convert individual STOPP/START criteria are listed as a code dictionary in **Appendix B**.

Technical aspects

From the initial draft onwards, the algorithms were described using decision tables, a commonly used approach to modelling inference rules.[26] Decision tables have the advantage of being easily understandable for domain experts while being logically unambiguous. We created a coloured domain-specific decision table format to optimise the readability as much as possible. All criteria were modelled using this format. A (simplified) example of the decision table format for START criterion C3 is shown in **Table 5**.

The first five rows of each decision table are reserved for specifications about their components. Each component covers one column. The first row indicates what type of information the column describes: metadata about the criterion, a condition, or an action. The four subsequent rows contain information on the object acted upon, its attribute, the operator, and a user-readable comment. The remaining rows contain values that, together with the first five rows, form a proposition for the criterion. In **Table 5**, Lewy body dementia (text) is identified as an episode (episode exists) being registered (equals (=)) with a specific ICD10-code (icd10), G31.8.

A criterion can contain multiple rows of values, indicating that it can be inferred through several conjunctions. In such cases, rows are prioritised to indicate which inference rule takes precedence. In the given example, a different drug is prescribed for Lewy body dementia compared with Alzheimer's dementia. As a result, Lewy body dementia is separately identified (in the inference rule with priority 2) and linked to the specific drug rivastigmine (N06DA03), and not the entire class acetylcholinesterase inhibitors (N06DA) as is the case for Alzheimer's dementia.

Table 2: Implications of applying the coding principles to the criteria

Coding principle	Examples
1.	**STOPP D1**: 'TCAs with dementia, narrow angle glaucoma, cardiac conduction abnormalities…' **STOPP B11**: 'ACE inhibitors or Angiotensin Receptor Blockers in patients with hyperkalemia' **START A1**: 'Vitamin K antagonist…presence of chronic atrial fibrillation'
2.	**STOPP B8**: 'Thiazide diuretic with current significant hypokalemia (i.e. serum K+ < 3.0 mmol/l), hyponatremia (i.e. serum Na+ < 130 mmol/l) hypercalcemia (i.e. corrected serum calcium > 2.65 mmol/l)…'
3.	**START A3**: "Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor)…" **STOPP C6**: "Antiplatelet therapy with vitamin K antagonist…"
4.	**START A6**: 'Angiotensin Converting Enzyme (ACE) inhibitor with a systolic heart failure and/or documented coronary artery disease'
5.	**STOPP C8/C9** "Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitor for first deep venous thrombosis/pulmonary embolus…' **STOPP B6**: 'Loop diuretic as first line treatment of hypertension'

**The examples shown here are randomly selected from all coded criteria to illustrate the process of consensus, based on the coding principles.*

Table 3: Criteria not coded

STOPP criterion	Addressed disease/diagnosis	Concerning medication (-group)
A1, A2	-	Any drug without indication or beyond recommended duration
A3	-	Any duplicated drug class
L3	Break-through pain	Long-acting opioids without short acting opioids

	Solution based on ICD-10* coding
	Not specified: Both **I44** '*Atrioventricular and left bundle-branch block*' and **I45**: '*Other conduction disorders*' including all sub categories are included. No cut-off value specified. We decided to define ≥5.0 mmol/L as hyperkalemia in all criteria addressing this condition without mentioned cut-off values (i.e. **STOPP B12**) Exact match in ICD-10 **I48.2** "Chronic atrial fibrillation" exists and preferred over **I48:** "atrial fibrillation and flutter"
	Laboratory values coded as LOINC term with cut-off levels Priority in the algorithm is given to LOINC codes over ICD10 diagnosis **E87.5** "hyperkalemia"
	Specification of individual drugs: only these four were included in the algorithm. All antiplatelet agents registered under ATC **B01AC*** were included
	Included ICD-10 codes according to expert consensus: **I20** Angina pectoris **I21** Acute myocardial infarction **I22** Subsequent myocardial infarction **I24** Other acute ischemic heart diseases **I25** Chronic ischemic heart disease **Z95.1** Presence of aortocoronary bypass graft and **Z95.5** Presence of coronary angioplasty implant and graft
	Not applicable if diagnosis "atrial fibrillation" is present: anticoagulant more likely prescribed for this condition. **I48** "Atrial fibrillation and flutter" was added as an optional excluding condition to trigger this rule. Not applicable in case of concomitant heart failure. Heart failure (**I50**) added as an optional excluding condition for this rule.
	*Similar decisions were made for several other criteria and codings. These decisions and their rationale are displayed below each corresponding STOPP/START criterion in **Appendix A**.*

	Reason for the impossibility to code
	Not possible to specify and code
	Too comprehensive to code. Also, some duplicated drug classes are justified (e.g. concurrent use of aspirin and clopidogrel shortly after coronary stent implantation)
	Database related limitation. Long-acting and short-acting opioids cannot be distinguished, due to similar ATC codes.

Table 4: An overview of all optional (excluding) conditions included in the final algorithms.

Criterion	Original criterion text
START	
E2	Bisphosphonates and vitamin D and calcium in patients taking ***long-term*** systemic corticosteroid therapy
G1, G2	Start alpha-1 receptor blocker and/or start 5-alpha reductase inhibitor with symptomatic prostatism, ***where prostatectomy is not considered necessary.***
STOPP	
B1	Stop digoxin for heart failure with normal systolic ventricular
B6	Loop diuretic as first-line treatment for hypertension
B7	Loop diuretic for dependent ankle edema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure
B9	Loop diuretic for treatment of hypertension with concurrent urinary incontinence
C6	Stop antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with ***stable coronary, cerebrovascular or peripheral arterial disease***
C8, C9	Stop vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmonary embolus or first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 12 months or > 6 months respectively.
D9	Stop neuroleptic antipsychotic in patients with behavioral and psychological symptoms of dementia (BPSD) ***unless symptoms are severe and other non-pharmacological treatments have failed.***
D13	Stop levodopa or dopamine agonists for benign essential tremor
H4	Stop long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis

** indicates that all subcategories starting with the letter/number combinations prior to the asterisk are included*

	Additional (excluding) condition	Justification
	Treatment duration >3 months for corticosteroids (only taken into account when starting date is entered)	*'Long-term'* not defined. Cut-off duration of 3 months was chosen, according to the Dutch local version.
	ICD-9 code 'prostatectomy' present as excluding condition	Condition *'where prostatectomy is not considered necessary'* not codable. Status post-prostatectomy was defined as (additional) excluding condition
	ICD-10 code I48* 'Atrial fibrillation' is encoded as additional condition, excluding this rule.	In patients suffering from both heart failure and atrial fibrillation, digoxin is most likely prescribed for atrial fibrillation.
	ICD-10 code I50* 'Heart failure' is encoded as additional condition, excluding this rule.	In patients suffering from both hypertension and heart failure, loop diuretics are most likely prescribed for heart failure.
	ICD-10 code I50* 'Heart failure' is encoded as additional condition, excluding this rule.	In patients with ankle edema and concomitant diagnosis of heart failure, loop diuretics are most likely prescribed for heart failure.
	See explanation STOPP B6	See explanation STOPP B6
	ICD-10 code Z95.5 'Presence of coronary angioplasty implant and graft' is encoded as additional condition, excluding this rule AND with a duration shorter than 12 months.	*Stable coronary, cerebrovascular or peripheral arterial disease'* not codable. The exception to this rule is the presence of a coronary stent for less than 12 months.
	ICD-10 code I48* 'Atrial fibrillation' is encoded as additional condition, excluding this rule.	A history of first pulmonary embolus > 12 months ago or first deep venous thrombosis > 6 months ago AND presence of atrial fibrillation, anticoagulant most likely prescribed for atrial fibrillation
	ICD-10 code F20*, F25* en F29 'Schizophrenic disorders/psychotic disorder NOS' AND coexistent ICD-10 code F51.0 or G47.0 'sleeping disorder' encoded as additional condition, excluding this rule.	*'unless symptoms are….have failed'* not codable. Sleeping disorders due to psychosis coded as additional excluding condition as mentioned in STOPP D10.
	ICD-10 code G20, G21*, G23.1, G23.2, G31.8, G90.3 'Parkinson/parkinsonism' added as additional excluding condition.	In patients with a history of Parkinson/ parkinsonism, levodopa or dopamine agonists most likely prescribed for this
	Additional excluding condition is concurrent use of a DMARD.	If DMARDs are used, corticosteroids are not used as monotherapy (monotherapy not codable otherwise)

Table 5: Simplified decision table for START criterion C3, "Start acetylcholinesterase inhibitor for mild-moderate Alzheimer's dementia or Lewy Body dementia".

				Column		
	1	**METADATA**	**METADATA**	**CONDITION**	**CONDITION**	**ACTION**
	2	ID	Priority	Episode exists	Episode exists	Medicine
	3	value	value	icd10	icd10	ATC
	4	equals (=)	equals (=)	equals (=)	equals (=)	start if not present
Row	5			*Alzheimer's dementia*	*Lewy body dementia*	*acetylcholinesterase inhibitor*
		START C3	1	G30*, F00*		N06DA*
			2		G31.8	N06DA03

** indicates that all subcategories starting with the letter/number combinations prior to the asterisk are included*

Note that the decision table format allows for some derivatives in notation to improve readability. Cells may be merged if their values are used in multiple prioritised inference rules. In **Table 5**, the criterion's ID (START C3) serves both inference rule #1 and #2. Explicit conditions do not have to be specified for medications that are to be started or stopped. In **Table 5**, the operator 'start if not present' in the action column also acts as an implicit condition; acetylcholinesterase inhibitors should not yet have been prescribed to the patient. In **Figure 3**, the simplified START criterion C3 from **Table 5** is shown as a flowchart. The priorities, conditions and actions in **Table 5** are transformed into an algorithm, which follows the routes, choices and activities shown in **Figure 3**.

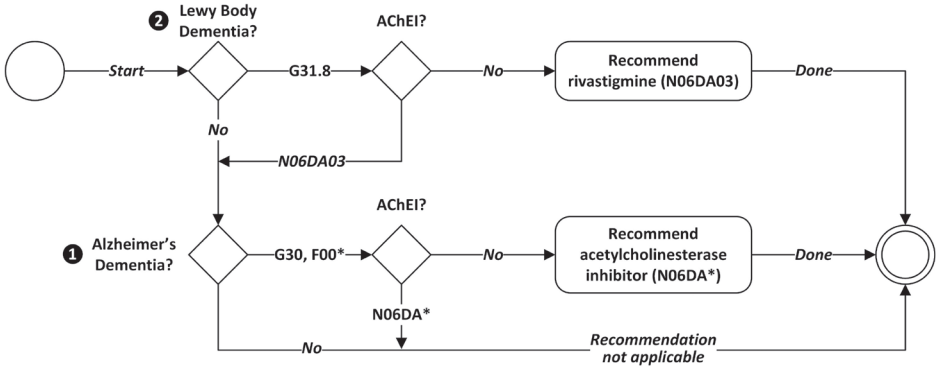

Figure 3: START criterion C3 as a flowchart.

DISCUSSION

Main findings

For this study STOPP/START criteria version 2 were converted into coded algorithms implementable in software applications. During four multidisciplinary consensus rounds we converted all 34 START criteria and 76 STOPP criteria into algorithms. Consensus based decisions on interpretation are necessary to convert STOPP/START elements requiring clinical context and knowledge of individual patients' history into coded algorithms. Five principles for universal coding were formulated to prevent essentially altering the content of criteria by elucidating the underlying intention of a criterion and to minimise the risk of bias.

Strengths

To the best of our knowledge, this is the first study providing implementable algorithms for software applications based on STOPP/START version 2. For the development of these algorithms, experts, trained in the use of STOPP/START in daily practice and familiar with international guidelines regarding pharmacotherapy in older people were consulted. Experts from both general practices and hospital settings were involved, of which the majority also cooperated in the specification of STOPP/START version 1.[19] Additionally, the experience and resources of two researchers involved in the development and application of a STOPP/START version 2 based CDSS were used. This allowed for evaluating our developed algorithms within this CDSS. We followed the original Irish STOPP/START criteria as closely as possible. By providing the actual algorithms and code dictionary with this publication, users are given the resources to make different choices about included ICD, ICPC and ATC codes or change cut-off levels for laboratory measurements following local guidelines. Therefore, these algorithms could serve as a template for applying STOPP/START criteria version 2 (or a subset of the criteria) to any software application.

Limitations

Despite maximal effort to be as complete and punctual as possible, several limitations to this study need to be addressed. For the algorithms presented here, the original Irish STOPP/START criteria, as published in Age & Aging in 2015, were used.[13] However, many local versions of these criteria exist in different countries based on variations in local guidelines. This may reduce the applicability of the algorithms to the country-specific situation. However, by providing our algorithms accompanied by a code dictionary including all the mentioned and coded diseases and medications per criterion, users can easily adapt the algorithm to match their local versions of STOPP/ START. In our coding strategy, we decided to translate the criteria as accurately as conceivable, assuming

that data registration in research databases and patients' health records is carried out perfectly by health care professionals. For instance, if a criterion is restricted to the condition of 'chronic atrial fibrillation', as is the case in START A1 and A2, we have coded this as the exact matching term ICD-10 I48.2: 'chronic atrial fibrillation' instead of I48: 'atrial fibrillation and flutter'. When applying the algorithm to a database using ICD-10 codes, this decision may lead to under detection of START A1 and A2, as atrial fibrillation is not always documented as either chronic or paroxysmal. Physicians and other health care professionals (HCP) should be encouraged to accurately code diseases and diagnoses according to international classification databases to enable data extraction. Educational programs to train HCPs in meticulous registration is crucial to successfully implement coded algorithms into electronic health records. Furthermore, expert based choices had to be made in cases where criteria were ambiguous or not matching the database terminology. For instance, opioids are not classified as either high or low-potency (START H1) in the WHO-ATC database and required expert consensus. In addition, cut-off values needed to be determined where these were not explicitly mentioned in the criteria. The potential hazard of hyperkalaemia is addressed in several criteria, like STOPP B11: 'ACE inhibitor or Angiotensin Receptor Blockers in patients with hyperkalaemia'. We defined hyperkalaemia as ≥ 5.0 mmol/L, a generally accepted cut-off value within laboratory testing of potassium.[27,28] Whether this value is already an indication to stop a presumed indicated medication like an ACE inhibitor in a clinical setting, remains debatable. Therefore, future applicators of the algorithm might decide differently, depending on their own expertise. Additionally, the expert panel consulted for this study comprised a limited number of professionals from one country. This might restrict the extrapolation of the results to other countries. Supplementary international validation through a Delphi method could be considered.

STOPP/START related restrictions

The majority of STOPP/START criteria are designed for clinicians facing the difficulties of polypharmacy in individual patients, presuming knowledge or at least accessible documentation of this patient's medical history and prior treatment regimens. However, converting these criteria into coded algorithms is challenging and sometimes even infeasible. In STOPP D2; 'initiation of TCAs as first-line antidepressant treatment' for example, a clinician might know immediately how to act, but 'first-line treatment' is not convertible into a code. The same reasoning applies to START G1 and G2; Alpha-1 receptor blocker/5-alpha reductase inhibitor with symptomatic prostatism, where prostatectomy is not considered necessary.' This restriction cannot be coded, let alone be extracted from a database or health record if it were codable. Consequently, leaving incodable elements out of the algorithm, led to a simplification of certain criteria. Moreover, when all STOPP/START criteria based algorithms are implemented together in a database or

CDSS to detect PIP, one must keep in mind that several criteria addressing overlapping diagnoses can result in conflicting recommendations. In STOPP L2 for example, the use of opioids without concomitant laxative is undesirable and the opioid is identified here as PIM, while in START H2 laxatives are recommended for the same patient using opioids. In START F1, an ACE inhibitor is recommended in patients with type 2 diabetes mellitus with renal disease, while in case of concurrent hyperkalaemia this is contraindicated according to STOPP A11 and STOPP A12. Additionally, in START A7 and A8, a beta blocker is recommended in patients with ischemic heart disease and/or stable systolic heart failure. However, in patients already using verapamil or diltiazem or in case of present bradycardia, this is undesirable because of the increased risk of (total) heart block according to STOPP B3 and B4. In this same hypothetical patient, the use of verapamil or diltiazem will also trigger STOPP B2:' Verapamil or diltiazem with NYHA Class III or IV heart failure'. If this recommendation is followed, starting a beta blocker will most likely be appropriate advice after all. This illustrates the complexity of applying (coded or non-coded) criteria to both databases and individual patients without clinical judgement, as no inter-criterion priority is predefined when multiple criteria are relevant to one patient. Application of the algorithms to real patients should reveal whether false positive triggers remain an issue, potentially causing alert fatigue [29], despite the addition of optional excluding conditions to minimise this. Therefore, actual validation of the complete set of algorithms together in one patient, preferably in a clinical trial setting, will be an important next step. Finally, we would like to emphasize that STOPP/START criteria are developed as a screening tool for potentially inappropriate prescribing, not an absolute guiding principle. Clinical judgement determining the applicability of the criteria for individual patients will remain indispensable. Our algorithms should be utilised as an extension of this principle.

Focus for future research

As concluded previously by Anrys et al.[15], many criteria within STOPP/START version 2 lack sufficient explicitness for translation into coded algorithms. By setting rules for universal coding and using multiple rounds of consensus and validation, we have attempted to overcome this problem. Unfortunately, this led to a simplification of certain criteria, as some parts are just not convertible into codes. For the development of STOPP/START version 3 or other sets of explicit criteria, we advise the developers to be as clear and unequivocal as possible. This includes mentioning clear cut-off values or numbers instead of 'hyperkalaemia' or 'recurrent episodes' and avoid ambiguous wordings such as 'first-line', 'long-term', 'radiological evidence' and 'continuing provoking risk factors'. With the growing digitalisation of medical practice, future guidelines and explicit screening tools should complement and facilitate the possibility for software applications.

DECLARATIONS

Authors' contributions

All authors certify that they have participated sufficiently in the work to take public responsibility for the content. Study concept and design: DdG, MM, RvM, **CJAH**, BTGMS. Data acquisition, analysis and/or interpretation of data: DdG, CD, MM (preparation panel), MB, JvC, JH, AV, RvM (expert panel), **CJAH**, BS (validation panel). Drafting the manuscript: **CJAH**. Revising the manuscript critically: all authors. We have not received substantial contributions from non-authors.

Competing interests

The author(s) declare that they have no competing interests.

Data availability statement

All supplementary data mentioned in this article is available online under a Creative Commons Attribution 4.0 license. The algorithms have been made available for download as a single spreadsheet. Additional file formats and data structures (including XML, JSON, and separate Excel spreadsheets for each criterion), which allow for easier implementation into software applications, are also available under a Creative Commons Attribution 4.0 license on request.

Ethics approval

Ethics approval was not required for this study since no humans or animals were involved.

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SUPPLEMENTARY DATA
APPENDIX A

Reading Instruction & Implementation Guideline

The 34 START and 76 STOPP algorithms described in the paper are supplied as a single Excel spreadsheet (.xlsx) of the original publication:

Huibers CJA, Sallevelt BTGM, de Groot DA *et al.* **Conversion of STOPP/START version 2 into coded algorithms for software implementation: A multidisciplinary consensus procedure**. Int J Med Inform. 2019 May;125:110-117. doi: 10.1016/j.ijmedinf.2018.12.010.

In order to implement these algorithms, please follow the steps described in this document. For additional file formats (such as XML or JSON), please contact the authors (mail@michielmeulendijk.nl).

Each criterion is encoded as a separate decision table, which leads to one or more inference rules per criterion. These rules are meant to run on a dataset composed of a single patient's health record, including his or her episodes, medicines, and measurements. These values are expected to be complete and accurate.

Each criterion has a number of columns containing metadata, conditions, and actions. These columns span five rows each and are formatted as such:

Table 1. Sample rule with Metadata, Condition, and Action columns.

Name	Sample Metadata	Sample Condition	Sample Action
Type	METADATA	[ADDITIONAL] CONDITION	ACTION
Object	ID	Episode exists	Medicine
Attribute	value	icd10	atc
Operator	equals (=)	equals (=)	start if not present
Description	*Criterion ID*	*Atrial fibrillation*	*Vitamin K antagonist*
Value	**START A1**	**I48**	**B01AA01**

The rows following the first five ones of each criterion contain values for these metadata, conditions, and actions. Values on the same row are treated as conjunctions (i.e. AND), while values on different rows are treated as disjunctions (i.e. OR). The sample rule shown in **Table 1** would read (provided all values were specified on the same row):

> ***If an episode with ICD10-code I48 exists, and if no medicine with ATC-code B01AA01 exists, then start a medicine with ATC-code B01AA01.***

Note that the medicine in the action column also acts as a condition; *start if not present* implies that no medicine with that ATC-code may exist.

Similarly, *stop if present* implies that a specific medicine should exist before the rule can be inferred.

Objects may need to satisfy several criteria before they match a condition. Multiple conditions on a single object are specified using the *(previous)* keyword, as illustrated here:

Table 2. Sample rule demonstrating (previous) objects.

Name		**Sample Condition**	
Type	CONDITION	CONDITION	CONDITION
Object	Measurement exists	(previous)	(previous)
Attribute	loinc	value	unit
Operator	equals (=)	greater than (>)	equals (=)
Description	*microalbumin*	*> 30 mg/24 hours*	*> 30 mg/24 hours*
Value	**14956-7**	**30**	**mg/(24.h)**

The sample rule specified in **Table 2** would read:

> ***If a measurement with LOINC-code 14956-7 and a value greater than 30 mg/24 hours exists, then …***

Often, conditions or actions contain several values in the same column, separated by commas. This means that they can be matched by an object matching one of these values. For example, matching diabetes mellitus in ICPC1NL can be specified as *T90, T90.1, T90.2*. A patient suffering from diabetes mellitus type 2 (*T90.2*) would satisfy this condition. Alternatively, this expression can be written using a wildcard (*). Wildcards imply that any code starting with the text before the asterisk match the condition. The diabetes example could thus be shortened to *T90**, which would match patients with *T90*, *T90.1*, or *T90.2*. In the case of *start if not present* actions, the recommendation implies that *one* of the medications should be started; if, for example, medicines with ATC-codes *A01BA01, A01BA02, A01BB** are recommended, users can follow up by prescribing *A01BB01*. In the case of *stop if present* actions, criteria are only inferred on a single medicine. If multiple medications are specified (and the patient uses several of them) the rule is inferred multiple times; for example, if medications with ATC-codes *A01BA01, A01BA02* are recommended to be stopped, the rule would be executed for both *A01BA01* and *A01BA02*.

Criteria with multiple rows of values can be inferred through several rules. In those cases, each row is preceded by a priority number (*1, 2, 3, …*). The row with the **highest** number takes precedence over the others; if the dataset does not match this rule, the row with the second highest number is checked, and so on.

Figure 1 illustrates the relations between a criterion's inference rules, their metadata, conditions, and actions. It also briefly lists the possible values each type of column can have. The next sections list in detail which attributes, operators, and values each object can have.

STOPP/START criteria v2 encoded in ICPC1 (NL), ICPC2, ICD9, ICD10, ATC, AND LOINC

The ten examples below were randomly selected from the total of 34 START algorithms and 76 STOPP algorithms. The complete Excel sheet including all 110 algorithms can be found as Supplementary Data of the original publication:

Huibers CJA, Sallevelt BTGM, de Groot DA *et al.* **Conversion of STOPP/START version 2 into coded algorithms for software implementation: A multidisciplinary consensus procedure**. Int J Med Inform. 2019 May;125:110-117. doi: 10.1016/j.ijmedinf.2018.12.010.

Table 3. Metadata columns and their allowed objects, attributes, and operators.

#	Object	Attribute	Operator
1	ID	value	equals (=)
2	Priority	value	
3	Description	value	
4	(previous)	language	

Table 4. Episode columns and their allowed objects, attributes, and operators.

#	Object	Attribute	Operator
	Episode [not] exists	icpc1nl	equals (=), not equals (!=)
		icpc2	
		icd9	
		icd10	
		frequency	equals (=), not equals (!=), greater than (>), less than (<)
		duration	
		interval	equals (=)
		active	equals (=), not equals (!=)

Table 5. Medicine columns and their allowed objects, attributes, and operators.

#	Object	Attribute	Operator
	Medicine [not] exists, Medicine	atc	equals (=), not equals (!=)
		frequency	equals (=), not equals (!=), greater than (>), less than (<)
		duration	
		interval	equals (=)
		daily dose	equals (=), not equals (!=), greater than (>), less than (<)
		unit	equals (=)

	Value Explanation
	Contains the STOPP- or START-criterion's key (e.g. *STOPP C1*).
	Contains an integer (e.g. *1, 2, 3*) indicating in which order rows should be checked for matches. Note that higher number take precedence over lower numbers. Also note that the real order in which rows occur in the spreadsheet is irrelevant.
	Contains the STOPP- or START-criterion's English description (e.g. *Stop vitamin K …*).
	Contains the description's language; in all cases *en*.

	Value Explanation
	Contains one or more (Dutch) ICPC1 codes (e.g. *T90*), optionally with sub codes (e.g. *T90.1*) or wildcards (e.g. *T90**), separated by commas (e.g. *T90, T91*).
	Contains one or more ICPC2 codes (e.g. *T90*), optionally with wildcards (e.g. *T90**), separated by commas (e.g. *T90, T91*).
	Contains one or more ICD9 codes (e.g. *427*), optionally with sub codes (e.g. *427.31*) or wildcards (e.g. *427.3**), separated by commas (e.g. *427.31, 428*).
	Contains one or more ICD10 codes (e.g. *I48*), optionally with sub codes (e.g. *I48.2*) or wildcards (e.g. *I48**), separated by commas (e.g. *I48.2, I50*).
	Contains a number indicating the frequency of the episode occurrence, for example for hypoglycaemic episodes (e.g. *1, 2*). Is always followed by *interval*.
	Contains a number indicating how long the episode has been active (e.g. *1, 2*). Is always followed by *interval*.
	Contains one of the following characters indicating a time interval: *Y (years), M (months), W (weeks)*. Always preceded by *frequency* or *duration*.
	Contains a yes/no value indicating whether the episode is currently active or historical (i.e. *YES, NO*).

	Value Explanation
	Contains one or more ATC codes (e.g. *B01AC06*), optionally with wildcards (e.g. *B01A**), separated by commas (e.g. *B01AC06, B01AC08*).
	Contains a number indicating the frequency of the medicine prescription, for example for yearly vaccines (e.g. *1, 2*). Is always followed by *interval*.
	Contains a number indicating how long the medicine has been prescribed (e.g. *1, 2*). Is always followed by *interval*.
	Contains one of the following characters indicating a time interval: *Y (years), M (months), W (weeks)*. Always preceded by *frequency* or *duration*.
	Contains a number indicating the medicine's daily dosage (e.g. *2.5, 50*). Is always followed by *unit*.
	Contains one of the following abbreviations indicating a unit of measurement: *G (gram), MG (milligram)*. Always preceded by *daily dose*.

Table 6. Measurement columns and their allowed objects, attributes, and operators.

#	Object	Attribute	Operator
	Measurement [not] exists	loinc	equals (=), not equals (!=)
		value	equals (=), not equals (!=), greater than (>), less than (<)
		unit	equals (=)
		age	equals (=), not equals (!=), greater than (>), less than (<)
		interval	equals (=)

	Value Explanation
	Contains a LOINC code (e.g. *11556-8*). Most LOINC codes have predetermined units of measurement for results. If not, a *unit* attribute is included to specify the unit of measurement.
	Contains a number indicating the measurement's result (e.g. *60*).
	Contains a unit of measurement (e.g. *mg/(24.h)*).
	Contains a number indicating the age of the measurement, for example for monthly repeated measurements (e.g. *1*, *2*). Is always followed by *interval*.
	Contains one of the following characters indicating a time interval: *Y (years)*, *M (months)*, *W (weeks)*. Always preceded by *age*.

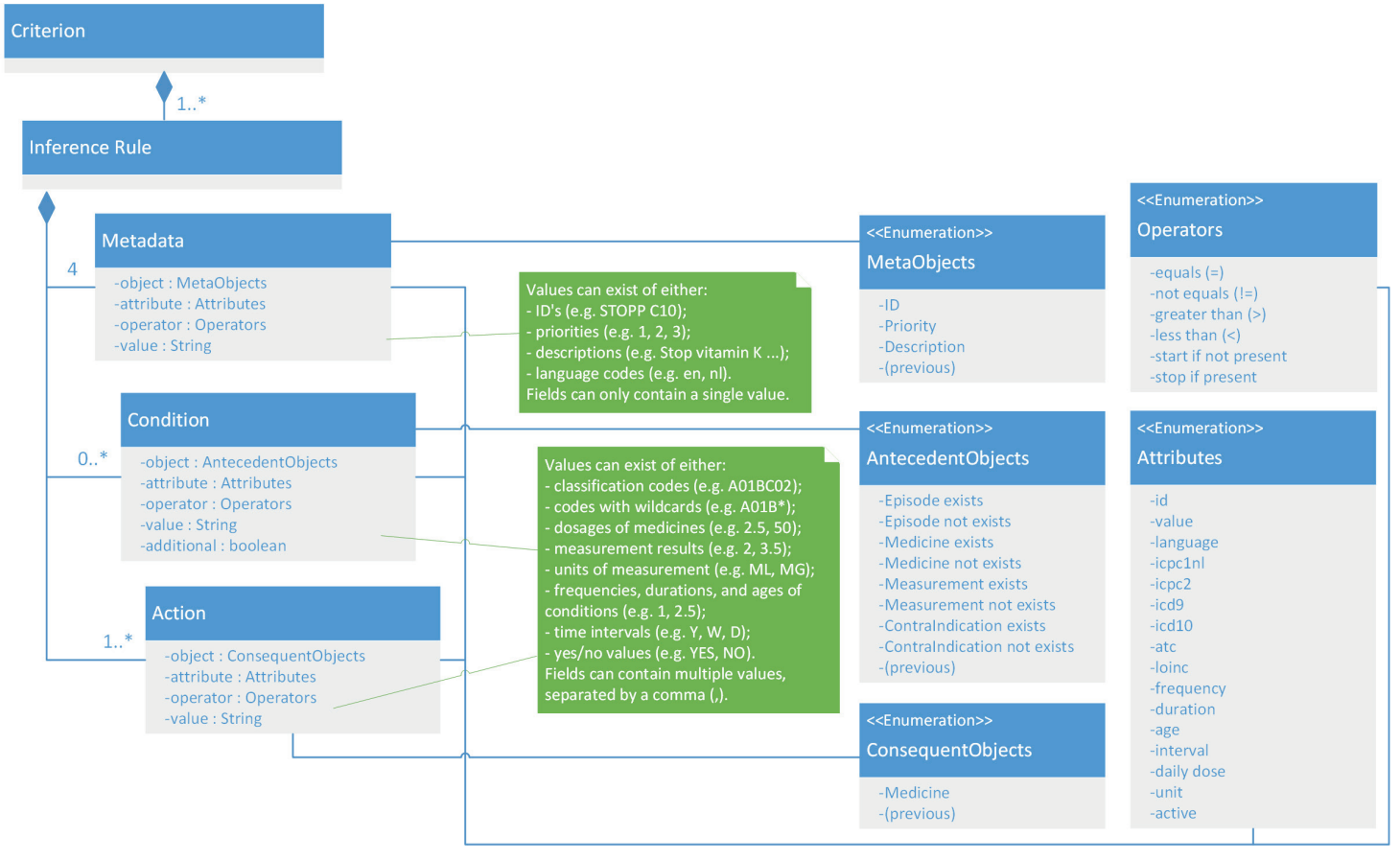

Figure 1. Diagram showing the relations between a criterion's inference rules, metadata, conditions, and actions, and their allowed values.

START algorithms

METADATA **ID** value equals (=)	METADATA **Priority** value equals (=)	METADATA **Description** value equals (=)	METADATA **(previous)** language equals (=)	CONDITION **Episode exists** icpc1nl equals (=) *atrial fibrillation*	CONDITION **Episode exists** icpc2 equals (=) *atrial fibrillation*	CONDITION **Episode exists** icd9 equals (=) *atrial fibrillation*	CONDITION **Episode exists** icd10 equals (=) *atrial fibrillation*	ACTION **Medicine** atc start if not present *Vit K antagonists, direct thrombin inhibitors or factor Xa inhibitors.*
START A1	1	Start vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation.	en	K78				B01AA*, B01AE*, B01AF*
	2				K78			
	3					427.31		
	4						I48.2	
Comments:	*Chronic atrial fibrillation is codable in ICD-9 and ICD-10, exact matching codes are used. For ICPC 'atrial fibrillation and flutter' is only available as general group.*							

METADATA **ID** value equals (=)	METADATA **Priority** value equals (=)	METADATA **Description** value equals (=)	METADATA **(previous)** language equals (=)	CONDITION **Episode exists** icpc1nl equals (=) *ischaemic heart disease*	CONDITION **Episode exists** icpc2 equals (=) *ischaemic heart disease*	CONDITION **Episode exists** icd9 equals (=) *ischaemic heart disease*	CONDITION **Episode exists** icd10 equals (=) *ischaemic heart disease*	ACTION **Medicine** atc start if not present *betablocker*
START A7	1	Start beta-blocker with ischaemic heart disease.	en	K74*, K75, K76*				C07*
	2				K74, K75, K76			
	3					410*, 411*, 412*, 413*, 414*, V45.81, V45.82, 36.0*, 36.1*		
	4						I20*, I21*, I22*, I24*, I25*, Z95.1, Z95.5	
Comments:	*Codes for coronary stents (Z95.5) and bypass surgery (Z95.1) also included as indicators of 'ischemic heart disease'*							

METADATA **ID** value equals (=)	METADATA **Priority** value equals (=)	METADATA **Description** value equals (=)	METADATA **(previous)** language equals (=)	CONDITION **Episode exists** icpc1nl equals (=) *Parkinson's disease*	CONDITION **Episode exists** icpc2 equals (=) *Parkinson's disease*	CONDITION **Episode exists** icd9 equals (=) *Parkinson's disease*	CONDITION **Episode exists** icd10 equals (=) *Parkinson's disease*	ACTION **Medicine** atc start if not present *L-dopa or dopamine agonist*
START C1	1	Start L-DOPA or a dopamine agonist in idiopathic Parkinson's disease with functional impairment and resultant disability.	en	N87.01				N04B*
	2				N87			
	3					332, 332.0		
	4						G20	
Comments:	*Not possible to code 'functional impairment and resultant disability'*							

METADATA **ID** value equals (=)	METADATA **Priority** value equals (=)	METADATA **Description** value equals (=)	METADATA **(previous)** language equals (=)	CONDITION **Episode exists** icpc1nl equals (=) *depression*	CONDITION **Episode exists** icpc2 equals (=) *depression*	CONDITION **Episode exists** icd9 equals (=) *depression*	CONDITION **Episode exists** icd10 equals (=) *depression*	ACTION **Medicine** atc start if not present *non-TCA antidepressant drug*
START C2	1	Start non-TCA antidepressant drug in the presence of persistent major depressive symptoms.	en	P76*				N06AB*, N06AF*, N06AG*, N06AX*, N06CA03
	2				P76			
	3					296.2, 296.3		
	4						F32*, F33*	
Comments:	*Not possible to code 'persistent, major'*							

METADATA **ID** value equals (=)	METADATA **Priority** value equals (=)	METADATA **Description** value equals (=)	METADATA **(previous)** language equals (=)	CONDITION **Episode exists** icpc1nl equals (=) *rheumatoid disease*	CONDITION **Episode exists** icpc2 equals (=) *rheumatoid disease*	CONDITION **Episode exists** icd9 equals (=) *rheumatoid disease*	CONDITION **Episode exists** icd10 equals (=) *rheumatoid disease*	ACTION **Medicine** atc start if not present *DMARD*
START E1	1	Start disease-modifying anti-rheumatic drug (DMARD) with active, disabling rheumatoid disease.	en	L88*				L04AX01, L04AX03, L04AA13, L04AD01, A07EC01, P01BA*, M01CB*, M01CC*
	2				L88			
	3					714.0, 714.1, 714.2		
	4						M05*, M06*	
Comments:	*Not possible to code 'active, disabling'*							

STOPP algorithms

METADATA **ID** value equals (=)	METADATA **Priority** value equals (=)	METADATA **Description** value equals (=)	METADATA **(previous)** language equals (=)	CONDITION **Episode exists** icpc1nl equals (=) *supraventricular tachyarrhythmias*	CONDITION **Episode exists** icpc2 equals (=) *supraventricular tachyarrhythmias*	CONDITION **Episode exists** icd9 equals (=) *supraventricular tachyarrhythmias*	CONDITION **Episode exists** icd10 equals (=) *supraventricular tachyarrhythmias*	ACTION **Medicine** atc stop if present *amiodarone*
STOPP B5	1	Stop amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias (higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem)	en	K79.01				C01BD01
	2				K79			
	3					427.0, 427.3		
	4						I47.1, I48*	
Comments:	*Not possible to code 'first-line treatment'. The presence of amiodaron will trigger this rule (with concomitant tachyarrhytmias)*							

METADATA **ID** value equals (=)	METADATA **Priority** value equals (=)	METADATA **Description** value equals (=)	METADATA **(previous)** language equals (=)	CONDITION **Measurement exists** loinc equals (=) *serum potassium*	CONDITION **(previous)** value greater than (>) *greater than 5*	CONDITION **Episode exists** icd9 equals (=) *current hyperkalaemia*	CONDITION **Episode exists** icd10 equals (=) *current hyperkalaemia*	ACTION **Medicine** atc stop if present *ACE inhibitors or angiotensin receptor blockers*
STOPP B11	1	Stop ACE inhibitors or Angiotensin Receptor Blockers in patients with hyperkalaemia.	en	2823-3	4.9			C09*
	2					276.7		
	3						E87.5	
Comments:	*Hyperkalamia' was defined as serum potassium >4.9. If no measurement available, ICD9 and 10 codes for hyperkalaemia will trigger the rule as well.*							

METADATA **ID** value equals (=)	METADATA **Priority** value equals (=)	METADATA **Description** value equals (=)	METADATA **(previous)** language equals (=)	ACTION **Medicine** atc stop if present *salicylates*	ACTION **(previous)** daily dose greater than (>) *160 or 200*	ACTION **(previous)** unit equals (=) *mg / day*	CONDITION **Episode exists** icd10 equals (=) *current hyperkalaemia*	ACTION **Medicine** atc stop if present *ACE inhibitors or angiotensin receptor blockers*
STOPP C1	1	Stop long-term aspirin at doses greater than 160mg per day (increased risk of bleeding, no evidence for increased efficacy).	en	B01AC06	160	MG		C09*
	2			B01AC08	200			
Comments:	*'Long-term' not defined and therefore not coded. Equivalent dose of carbasalate calcium added.*						E87.5	

METADATA **ID** value equals (=)	METADATA **Priority** value equals (=)	METADATA **Description** value equals (=)	METADATA **(previous)** language equals (=)	ADDITIONAL CONDITION **Episode not exists** icd9 equals (=) *implant*	ADDITIONAL CONDITION **Episode not exists** icd10 equals (=) *implant*	ADDITIONAL CONDITION **(previous)** duration less than (<) *12*	ADDITIONAL CONDITION **(previous)** interval equals (=) *months*	CONDITION **Medicine exists** atc equals (=) *Vit K antagonist, direct thrombin inhibitor or factor Xa inhibitors*	ACTION **Medicine** atc stop if present *antiplatelet agents*
STOPP C6	1	Stop antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease (No added benefit from dual therapy).	en	36.0*		12	M	B01AA*, B01AE*, B01AF*	B01AC*
	2				Z95.5				
Comments:	*'Stable coronary, cerebrovascular or peripheral arterial disease' not included as diagnoses. The exception to this rule is the presence of a coronary stent less than 12 months.*								

METADATA **ID** value equals (=)	METADATA **Priority** value equals (=)	METADATA **Description** value equals (=)	METADATA **(previous)** language equals (=)	ACTION **Medicine** atc stop if present *PPI*	ACTION **(previous)** daily dose greater than (>) *dosage*	ACTION **(previous)** unit equals (=) *mg / day*	ACTION **(previous)** duration greater than (>) *duration*	ACTION **(previous)** interval equals (=) *in weeks*
STOPP F2	1	Stop PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks (dose reduction or earlier discontinuation indicated).	en	A02BC01	39	MG	8	W
	2			A02BC02	79			
	3			A02BC03	59			
	4			A02BC04	19			
	5			A02BC05	39			
	6			A02BC06	29			
Comments:	*'Full therapeutic dose' defined as twice the daily defined dose (DDD) per PPI.*							

APPENDIX B

Medical conditions in STOPP & START Criteria V2 (example page, full document available online)

Table 1: medical conditions in STOPP & START Criteria V2

Medical condition	Description
Hypertension	Essential hypertension
Hypertension	Secondary hypertension
Hypertension	Elevated blood pressure
Hypotension	Orthostatic hypotension
Hypotension	Chronic hypotension
Hypotension	Iatrogenic hypotension
Hypotension	Other specified hypotension
Hypotension	Unspecified hypotension
Hypotension	Idiopathic hypotension
Syncope	Syncope (excl. orthostatic hypotension)
Syncope	Syncope/fainting (excl. micturition syncope)
Heart failure	Heart decompensation
Heart failure	Heart decompensation
Heart failure	Congestive heart failure, unspecified
Heart failure	Left heart failure
Heart failure	Systolic heart failure
Heart failure	Diastolic heart failure
Heart failure	Combined systolic and diastolic heart failure
Heart failure	(Malignant) hypertensive heart disease with heart failure
Heart failure	(Malignant) hypertensive heart disease with heart failure
Heart failure	Benign hypertensive heart disease with heart failure
Heart failure	Unspecified hypertensive heart disease with heart failure

ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
401	I10	K86, K87	K86, K87	B6, H2	A4
405	I15			B6, H2	A4
		K85	K85	B6, H2	A4
458	I95.1	K88	K88	I2, K3	
458,1	I95.8				
458,2	I95.2				
458,8					
458,9	I95.9				
	I95.0				
780,2		A06	A06	D11, I2	
	R55				
	I50	K77	K77	B1, B2, B6, B7 ,B9, B13, H2, J2	A6, A8
428				B1, B2, B6, B7 ,B9, B13, H2, J2	
428					
428,1					
428,2					A6, A8
428,3					
428,4					A6, A8
	I11.0			B1, B2, B6, B7, B9, B13, H2, J2	A6, A8
402,01				B1, B2, B6, B7, B9, B13, H2, J2	
402,11				B1, B2, B6, B7, B9, B13, H2, J2	
402,91				B1, B2, B6, B7, B9, B13, H2, J2	

Medications in STOPP & START Criteria V2 (example page, full document available online)

Table 2: Medication(groups) in STOPP & START Criteria V2

Drug Class (ATC)	ATC Code
Antidepressants	N06AA
Antidepressants	N06AB
Antidepressants	N06AF
Antidepressants	N06AG
Antidepressants	N06AX
Antidepressants	N06AX16
Psycholeptics and psychoanaleptics combinations	N06CA01
Psycholeptics and psychoanaleptics combinations	N06CA02
Psycholeptics and psychoanaleptics combinations	N06CA03
Antidepressants	N06AX21
Other anti-epileptics	N03AX16
Anti-inflammatory and antirheumatic products, non-steroids	M01A
Anti-inflammatory and antirheumatic products, non-steroids	M01AA
Anti-inflammatory and antirheumatic products, non-steroids	M01AB
Anti-inflammatory and antirheumatic products, non-steroids	M01AC
Anti-inflammatory and antirheumatic products, non-steroids	M01AE
Anti-inflammatory and antirheumatic products, non-steroids	M01AG
Anti-inflammatory and antirheumatic products, non-steroids	M01AH

Description (ATC)	STOPP Criteria	START Criteria	Comments
Non-selective monoamine reuptake inhibitors	N, D1, D2		
Selective serotonin reuptake inhibitors	A3, D2, D4	C2, C5	
Monoamine oxidase inhibitors, non-selective		C2	
Monoamine oxidase A inhibitors		C2	
Other antidepressants	D2	C2	
venlafaxine		C5	
amitriptyline and Psycholeptics	D1, D2		
melitracen and Psycholeptics	D1, D2		
fluoxetine and Psycholeptics	A3, D2, D4	C2, C5	
duloxetine		C5	
pregabalin		C5	
Antiinflammatory and antirheumatic products, non-steroids	A3, C10, C11, E4, H2, H3, H6, H8, L1	H1	
Butyl pyrazolidines	H1	H1	
Acetic acid derivatives and related substances	H1	H1	
Oxicams	H1	H1	
Propionic acid derivatives	H1	H1	
Fenamates	H1	H1	
Coxibs	H7	H1	

Evaluation of clarity of the STOPP/START criteria for clinical applicability in prescribing for older people:

A quality appraisal study

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BMJ Open. *2020;10(2):e033721.*

ABSTRACT

Objectives: Appropriate prescribing in older people continues to be challenging. Studies still report a high prevalence of inappropriate prescribing in older people. To reduce the problem of underprescribing and overprescribing in this population, explicit drug optimisation tools like Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) have been developed. The aim of this study was to evaluate the clinical applicability of STOPP/START criteria in daily patient care by assessing the clarity of singular criteria.

Design: Quality appraisal study.

Methods For each of the 114 STOPP/START criteria V.2, elements describing the action (what/how to do), condition (when to do) and explanation (why to do) were identified. Next, the clarity of these three elements was quantified on a 7-point Likert scale using tools provided by the Appraisal of Guidelines for Research and Evaluation (AGREE) Consortium.

Primary and secondary outcomes: The primary outcome measure was the clarity rating per element, categorised into high (>67.7%), moderate (33.3%–67.7%) or low (<33.3%). Secondary, factors that positively or negatively affected clarity most were identified. Additionally, the nature of the conditions was further classified into five descriptive components: disease, sign, symptom, laboratory finding and medication.

Results: STOPP recommendations had an average clarity rating of 64%, 60% and 69% for actions, conditions and explanations, respectively. The average clarity rating in START recommendations was 60% and 57% for actions and conditions, respectively. There were no statements present to substantiate the prescription of potential omissions for the 34 START criteria.

Conclusions: Our results show that the clarity of the STOPP/START criteria can be improved. For future development of explicit drug optimisation tools, such as STOPP/START, our findings identified facilitators (high clarity) and barriers (low clarity) that can be used to improve the clarity of clinical practice guidelines on a language level and therefore enhance clinical applicability.

INTRODUCTION

Clinical practice guidelines (CPGs) are instruments intended to provide guidance to healthcare professionals in patient care. Translation of healthcare knowledge, evidence and experience into clear recommendations for patient care, however, is challenging. Studies in the USA and the Netherlands suggest that about 30%–40% of patients do not receive care according to evidence based guidelines. A clear description of the desired behaviour has been associated with better compliance with guideline recommendations.[1,2]

Recommendations about safe and effective pharmacotherapy are an important part of CPGs. However, it is often unclear whether recommendations also apply to older people.[3–5] A complicating factor is that older people experience more concomitant morbidities, while CPGs often focus on best treatment for a single disease. Ambiguity among prescribers about pharmacotherapy in older people results in inappropriate prescribing, which causes adverse drug reactions, drug-related hospitalisations, decreased quality of life and even death.[6,7]

Due to the lack of clear statements in CPGs about (in)appropriate prescribing in older people with multimorbidity, several explicit screening tools have been developed.[8,9] The most widely used are the Beers criteria[10] and the Screening Tool of Older Persons' potentially inappropriate Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) criteria.[11] CPG recommendations are rarely specified in precise behavioural terms such as what, how, when and why to stop or start a drug, while explicit screening tools are designed to make clear statements and therefore ease clinical implementation.[2] However, studies continue to report a high prevalence of inappropriate prescribing in older people.[12–14] This suggests that implementation can still be improved.

Although STOPP/START criteria have shown good inter-rater reliability in studies involving physicians and (hospital)pharmacists working in geriatric units, data on how physicians less familiar with medication optimisation would interpret STOPP/START criteria are lacking.[15,16] The question then arises whether the recommended actions are formulated clearly enough to guide prescribers less experienced in geriatric patient care.

The aim of this study was to evaluate the clinical applicability of STOPP/START criteria in daily patient care by assessing the clarity of singular criteria with the purpose of improving future clinical guideline recommendations for appropriate prescribing in older people.

METHODS

STOPP/START criteria

The STOPP/START criteria were first published in 2008 and have been updated in 2015 to STOPP/START V.2.[17] STOPP/START is a product of two Delphi rounds by 19 experts from 13 European countries.

For this study, the supplementary data of the corrigendum of the STOPP/START criteria V.2 as published in November 2017 were used.[18] STOPP/START V.2 consists of a list of 80 potentially inappropriate medications (STOPP criteria) and 34 potential prescribing omissions (START criteria).

Clarity assessment

The Appraisal of Guidelines for Research & Evaluation (AGREE) II Instrument and Guideline Implementability Decision Excellence Model (GUIDE-M) were used to develop a framework to assess the clarity of language used in STOPP/START. AGREE II Instrument is an internationally validated tool to rate the quality of CPGs, developed by the AGREE Consortium.[19] In addition to the AGREE II Instrument, AGREE developed a GUIDE-M.[20] This model identifies 'communicating content' as a core tactic for CPG implementability. Obviously, language is an important domain of this tactic. The language subdomain promotes a clear, simple and persuasive message.

The relevant part of the AGREE II Instrument ('clarity of presentation', domain 4, item 15) states that recommendations should be 'specific and unambiguous', which is defined as 'a concrete and precise description of which option is appropriate for which situation and for what population group'. In line with this statement and the corresponding section of the AGREE II Instrument, three elements were identified that influence the clarity of recommendations:

- **Action**: description of the recommended action, i.e. what to do and how to act?
- **Condition**: identification of the relevant target population and statements about patients or conditions for whom the recommendations would apply or not apply, i.e. when?
- **Explanation**: identification of the intent or purpose of the recommended action, i.e. why?

In order to quantify the clarity of STOPP/START criteria, the three elements of each recommendation were rated independently on a 7-point Likert scale by a panel of two appraisers, consisting of a geriatric resident (CJAH) and a hospital pharmacy

resident (BTGMS), both experienced with the application of STOPP/START criteria in daily practice. The clarity for each of these three elements was rated from the perspective of a 'junior' physician or pharmacist with a basic level of knowledge (≤ 5 years of clinical postgraduate experience). The appraisers were trained with a rating guidance, developed and approved by senior clinicians (TE/EvP/IW/WK) prior to rating the elements independently. If ratings differed more than 1 point, a senior hospital pharmacist/clinical pharmacologist (IW) or a senior geriatrician/clinical pharmacologist (WK) was consulted as a third appraiser until consensus was reached.

Descriptive components of conditions

In addition to the calculation of clarity ratings for the action, condition and explanation, the nature of the conditions was further explored. The condition identifies the target population and is the most heterogeneous element. By stratifying the conditions into descriptive components, the nature of the components in relation to their clarity could be assessed. These components could lead to different strategies to optimise 'specific and unambiguous' wording in describing conditions.

The conditions were subdivided into five components that were considered essential for identification of the target population: disease, sign, symptom, laboratory finding and medication. Definitions of four components were based on the ontology as described by Scheuermann et al.[21] Signs are defined as bodily features observed in a physical examination including measurements (e.g. blood pressure), while symptoms are bodily features experienced by a patient (e.g. restless legs). Since optimisation of polypharmacy is the main focus of the STOPP/START, the target population can also be described by (co)medication. Medication is not defined by Scheuermann et al. Therefore, medication was added as a fifth component using the definition for medicinal products by the European Medicines Agency as 'a substance or combination of substances that is intended to treat, prevent or diagnose a disease or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action'.[22]

Data analysis

Clarity ratings for each of the three elements (action, condition, explanation) were calculated as a percentage of the obtained scores given by appraiser 1 and 2 divided by the maximum score.

$$Clarity\ rating\ (\%) = \frac{obtained\ score\ (sum\ of\ 2\ appraisers) - minimum\ possible\ score\ (2)}{maximum\ possible\ score\ (14) - minimum\ possible\ score\ (2)}$$

This calculation method is in accordance with the approach provided by AGREE II Instrument. The scores of appraisers 1 and 2 were both replaced by the consensus score if a third appraiser was consulted. After scoring the elements, clarity ratings were categorised into low (<33.3%), moderate (33.3%–67.7%) and high (>67.7%).

Patient and public involvement

Since this is an appraisal study of clinical guideline recommendations intended to be used by clinicians, this research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

RESULTS

The elements 'action' and 'condition' in STOPP and START recommendations were rated on their clarity, resulting in 80 and 34 scores per element, respectively. The element 'explanation' was present in all but three (A1, A2, B11) STOPP recommendations, resulting in 77 scores. None of the START criteria contained an explanation to substantiate the prescription of potential omissions. Therefore, Likert scores for explanations were only assessed in STOPP recommendations.

The agreement among the two appraisers for Likert scores was high and ranged from 76.3% (STOPP—condition) to 91.3% (STOPP—action). Forty-four out of 305 (14.4%) scores were replaced after consensus meetings with a third appraiser. Replacements did not alter average Likert scores per element with more than 0.2 points compared with the average scores prior to consensus.

Average clarity ratings for STOPP recommendations were 64%, 60% and 69% for actions, conditions and explanations, respectively. Average clarity ratings for START recommendations were 60% and 57% for actions and conditions, respectively (**Figure 1**).

In 80 STOPP and 34 START recommendations, the clarity ratings of 35 actions were categorised as high (30.7%), 65 as moderate (57.0%) and 14 as low (12.3%). 38 (33.3%), 67 (58.8%) and 9 (7.9%) conditions had a high, moderate or low clarity rating, respectively. In 77 STOPP criteria, the clarity ratings of 41 (53,2%) explanations were categorised as high, 35 (45.5%) as moderate and 1 (1.3%) as low.

13 STOPP criteria (C1, C2, C4, C7, D6, D12, D13, E5, E6, F1, G1, H1, H9) had high clarity ratings for all three elements. 4 START criteria (B3, G3, I1, I2) had high clarity ratings for both action and condition. Detailed information of clarity ratings per element for all individual STOPP/START-criteria can be found in the *Supplementary data*.

Elements with high (>67.7%) and moderate or low (≤67.7%) clarity ratings were analysed in more detail to identify factors that either positively or negatively affected 'specific and unambiguous' language most. These findings for actions, conditions and explanations with illustrative examples for STOPP and START recommendations are presented in **Table 1**.

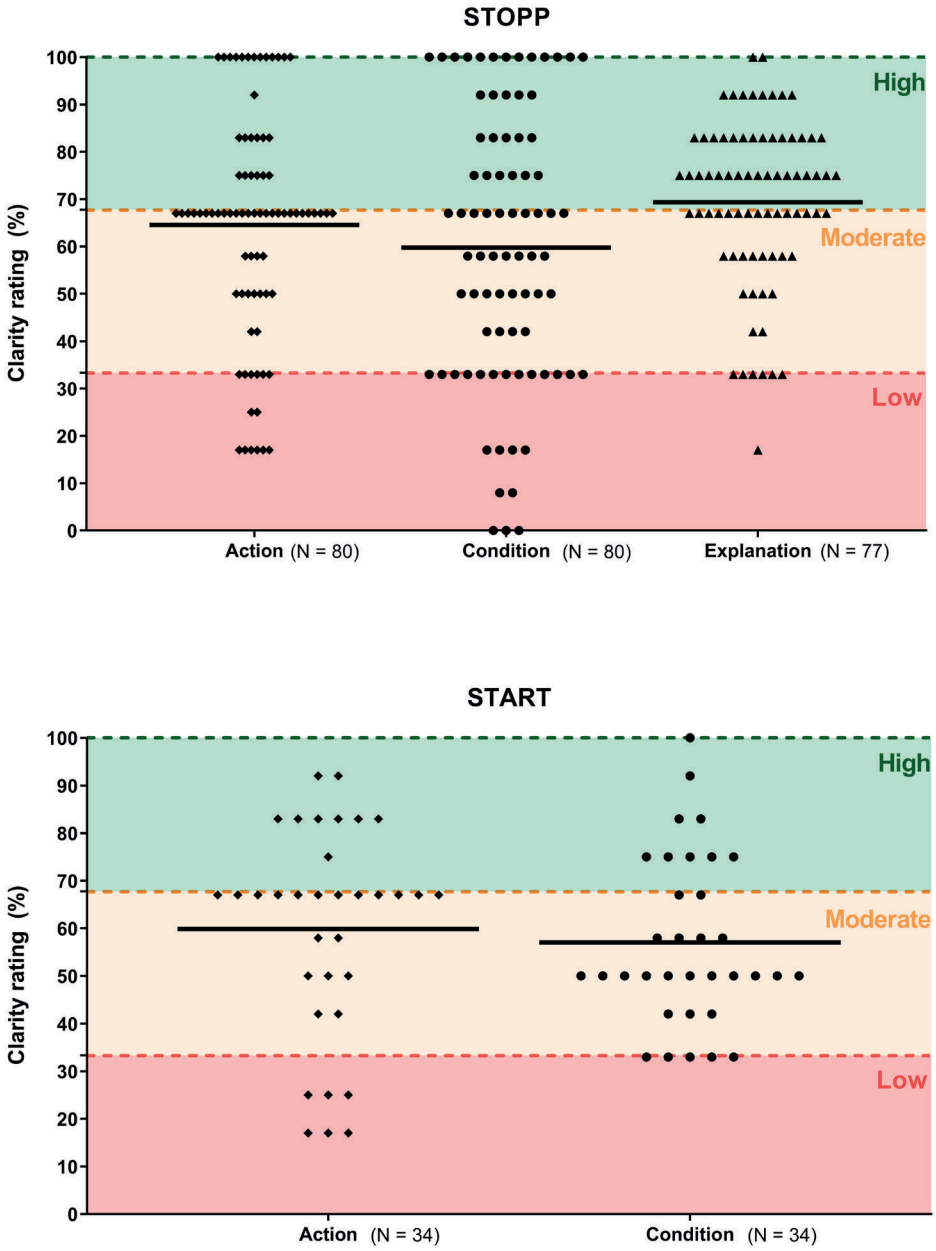

Figure 1: Distribution of clarity ratings for STOPP and START recommendations per element.

Average clarity ratings for STOPP recommendations were 64%, 60% and 69% for actions, conditions and explanations, respectively. Average clarity ratings for START recommendations were 60% and 57% for actions and conditions, respectively. STOPP/START = Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert to Right Treatment.

Table 1. *Main barriers and facilitators that affected clarity of the elements action, condition and explanation of STOPP/START recommendations.*

Barriers	Example [a] (clarity rating, %)
ACTION	
Lack of explicit drug (class)	STOPP D7/8. **Anticholinergics / antimuscarinics** (17%)
• 'e.g.' represents a non-limitative list and is therefore inconclusive	STOPP B10. Centrally-acting antihypertensives (**e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine**) (33%)
• Use of adjectives that need further investigation to allow use	STOPP D14. **First-generation** antihistamines (17%) START H1. **High potency** opioids (17%)
Lack of drug deprescribing schedules while considered necessary	STOPP K2. **Neuroleptic drugs** (17%)
Starting dose and target dose not mentioned	START C2. **Angiotensin Converting Enzyme (ACE) inhibitor** with systolic heart failure (67%)
Lack of directions how and what to monitor after starting a drug	START E1. **Disease-modifying anti-rheumatic drug** (DMARD) (25%)
CONDITION	
General - Patient population for whom recommendations would not apply was not (clearly / unambiguously) defined	
• In patients with a strong indication for a potentially inappropriate drug, it may be harmful to stop it	STOPP B5. **as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias** (33%)
• In patients with potential omissions, warnings for important contra indications are lacking / not clearly defined	START A2. **where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated** (33%)
Medication – see also *action*	
• Ambiguous adjectives were used	STOPP D2. **as first-line antidepressant treatment** (33%)
• Description of drug therapy (substance / dosage) not specific enough	START E7. in patients taking **methotrexate** (33%)
Disease - Clinical interpretation of 'disease (state)' for defining population needed	STOPP D1. with **dementia**, narrow angle glaucoma, **cardiac conduction abnormalities**, prostatism, or **prior history of urinary retention** (33%) START A5**.** with a documented **history of coronary, cerebral or peripheral vascular disease** (33%)

Table 1. *Continued.*

Sign - Measurement or scores were not described unambiguously	STOPP H2. with **severe hypertension** or **severe heart failure** (33%) START E1. with **active**, **disabling rheumatoid disease** (42%)
Symptom - Symptoms were not described unambiguously	STOPP K-section. Not clear whether the occurrence of **'falls'** - as mentioned only in the title of section K - is a prerequisite for the applicability of the recommendation or only used to address the increased risk of falls. If 'falls' is considered a condition, the frequency of 'falls' is not specified. (0%) STOPP D10. unless **sleep disorder** is due to (33%) START C2. with **persistent major depressive symptoms** (33%)
Laboratory finding - Parameters lack clear cut-off levels with reference ranges	START C6. once **iron deficiency** and **severe renal failure** have been excluded (33%)
EXPLANATION	
Risk of continuing therapy not clearly described: explanation does not cover clinical relevance of benefit / harm balance (specific adverse drug reactions, toxicity).	STOPP D7. **(risk of anticholinergic toxicity)** (17%) START N/A
Facilitators	**Example** [a] (clarity rating, %)
ACTION	
Drugs were specified on individual drug level and -if necessary- route / dosage was specified	STOPP C7. **Ticlopidine** (100%) START A2. **Aspirin (75 mg – 160 mg once daily)** (92%)
CONDITION	
Medication – see also *action* Specific description of drug therapy (substance / dosage) to clearly identify the target population (i.e. patients using a certain drug regimen).	STOPP B3. in combination with **verapamil** or **diltiazem** (92%) START I2. **at least once after age 65 according to national guidelines** (83%)
Disease - Diseases clearly described, the target population could be easily identified	STOPP H9. in patients **with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding** (92%) START C4. for **primary open-angle glaucoma**. (100%)
Signs - Signs clearly described as scores or measurements and therefore unambiguous	START B3. with documented chronic hypoxaemia **(i.e. pO2 < 8.0 kPa or 60 mmHg or SaO2 < 89%)** (92%)

Table 1. *Continued.*

Symptom - Symptoms clearly and unambiguous described	STOPP F1. with **Parkinsonism** (92%)
Laboratory findings - Clear cut-off levels with reference ranges present	STOPP E6. if **eGFR < 30 ml/min/1.73m2** (100%)
EXPLANATION	
Risk of discontinuing clearly described	STOPP D5. (**no indication for longer treatment**; **risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for > 2 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly**). (100%) START N/A

[a] *The examples shown are selected from elements with low and moderate (≤67.7%) clarity ratings for barriers and from high (>67.7%) clarity ratings for facilitators to substantiate the main findings. An overview of all clarity ratings can be found in the Supplementary data.*

The results of stratifying the element 'condition' into the five descriptive components medication, disease, sign, symptom and laboratory finding are shown per STOPP/START recommendation in **Figure 2**. Clarity ratings were scored on the level of condition as an element and not on the sublevel of the five descriptive components. Therefore, all components of one condition share the same colouring for their clarity.

In 33 (41%) STOPP criteria and 17 (50%) START criteria, the condition consisted of more than one component. No strong association was found between the clarity of conditions and the nature of the descriptive components, as the clarity ratings of the condition section varied regardless of the nature of the component. However, laboratory findings used to identify the target population were discovered to have the highest clarity rating compared to other descriptive components in STOPP recommendations; 9 out of 13 laboratory-based conditions had a high clarity rating (>67.7%).

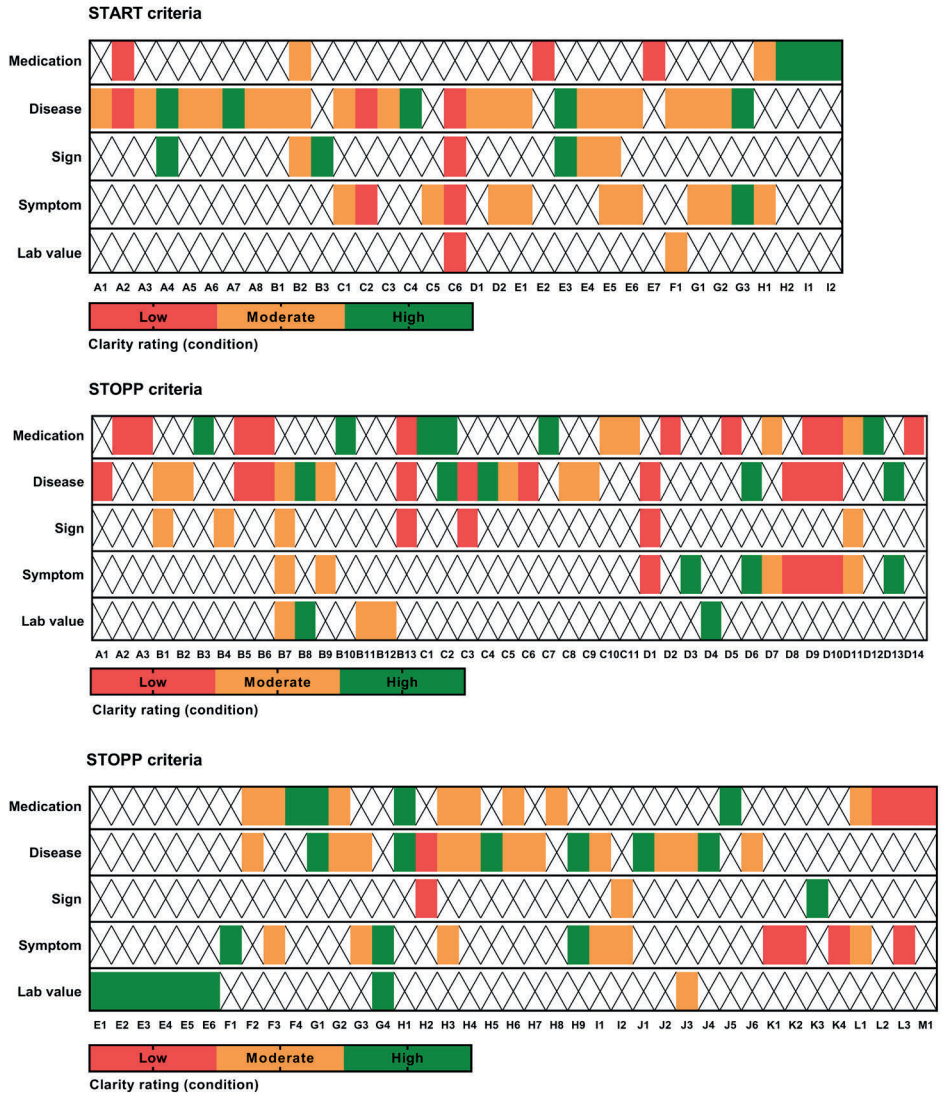

Figure 2: Clarity ratings of conditions for STOPP and START criteria related to five descriptive categories.

Green, **orange** and **red** colours correspond with high (>67.7%), moderate (33.3%–67.7%) or low (<33.3%) clarity ratings of conditions. STOPP/START = Screening Tool of Older Persons Prescriptions/ Screening Tool to Alert to Right Treatment.

DISCUSSION

Main findings

In this study, we evaluated the clinical applicability of STOPP/START criteria in daily patient care by assessing the clarity of singular criteria. We found that 13 out of 80 STOPP and 4 out of 34 START criteria had a high clarity rating for the three elements action, condition and explanation. To improve clarity of the recommendations, element-specific strategies can be formulated (**Table 1**).

Actions were considered unclear if recommendations included non-explicitly specified drug classes (e.g. 'anticholinergics'). To improve clear description of the action (*what and how*) we advise to specify drugs at an individual substance level. The addition of how to start or stop a drug (immediately versus gradually, including monitoring guidelines and deprescribing schedules), route of administration and dosage were considered necessary for some actions to further improve clarity.

The definition of the condition (*the when*) had the lowest average clarity rating in both START and STOPP. Low clarity ratings for conditions resulted from insufficient distinctiveness in the identification of patients for whom recommendations do or do not apply. Conditions were described by medication, diseases, signs, symptoms and laboratory findings. To increase the clarity of the conditions, laboratory findings and signs have the highest potential to be optimised by adding statements about clear cut-off levels (e.g. 'potassium >5.0 mmol/L' instead of 'hyperkalaemia') and measurements (e.g. 'systolic blood pressure >160 mmHg' instead of 'uncontrolled severe hypertension'). For conditions defined by medication use, the same improvements as suggested for actions apply. In some cases even a description on a drug substance level was not specific enough. For instance, folic acid for patients on methotrexate therapy (START E7) only applies to patients using a low dose, weekly methotrexate schedule and not for patients on high dose methotrexate. In such cases, a more detailed description of a drug dosage, route or indication was deemed necessary. Conditions described by diseases - like 'heart failure' - might seem clear at first, but often need further specification (reduced vs. preserved ejection fraction) to avoid ambiguity. Moreover, international cardiology guidelines distinguish between these subtypes of heart failure, subsequently affecting treatment recommendations. Adherence to terminology of internationally used dictionaries to describe diseases, such as International Classification of Primary Care (ICPC) and International Classification of Diseases (ICD), could be a solution.

Furthermore, no explanations were present for START criteria to substantiate *why* a potential omitted drug should be initiated. Even though the reason to start a drug might seem obvious in most cases, the risk-benefit balance should always be addressed to assist a physician's decision-making process whether or not to expose a patient to additional drug therapies.

Other remarks

STOPP/START criteria provide best evidence-based practices for the over- and undertreatment of single conditions. However, it should be noted that STOPP/START criteria provide conflicting recommendations. For example, if a patient has a clear indication for a beta blocker to treat ischaemic heart disease (START A7), this is contradicted if a patient is already using verapamil or diltiazem (STOPP B3). Merging such recommendations could increase implementation and prevent potential patient harm by overlooking relevant contra-indications.

Besides making the *what*, *how*, *when* and *why* as clear as possible, guideline developers should consider whether recommendations are tailored for its intended end-users (i.e. the *who*). Explicit screening tools to detect inappropriate prescribing in older people such as Beers criteria and STOPP/START, are likely to be developed to reach all professionals involved in prescribing, as all prescribers encounter the problem of under- and overprescribing in older people. Clinicians with high affinity for geriatric medicine may not need explicit treatment recommendation to provide best patient care, whereas some clinicians - such as e.g. surgical specialists - who treat older people but may be less experienced with (in)appropriate prescribing in older people, probably require more clear guidance. Clear recommendations are therefore important to reach all prescribers, because the success of STOPP/START criteria as an intervention depends on its integration and implementation in clinical practice.[23] Some recommendations may be best applied by physicians with a certain expertise, such as to start an 'acetylcholinesterase inhibitor for mild-moderate Alzheimer's dementia or Lewy Body dementia (START C3)'. In such cases, the focus for all clinicians should probably be the recognition and detection of a potential omission, rather than to actually start drug treatment. An explicit action could be to refer such patients to a geriatrician or neurologist, thus separating the trigger for potential undertreatment from the actual prescriber.

Strengths and limitations

To the best of our knowledge, this is the first study that explores the clarity of STOPP/START criteria. By systematically reviewing the clarity of the given action, condition and explanation, we identified facilitators (high clarity) and barriers (low clarity) that may be used to improve the content on a language level. As a result, element-specific strategies

can be extracted to improve items requiring refinement. Although no previous studies have reviewed the clarity of singular recommendations of explicit drug screening tools, comparable research has been conducted concerning clarity of monitoring instructions in CPGs and drug labels. Their conclusions to improve ambiguous instructions concerning the monitoring of laboratory values are in line with our suggestions to add clear statements about the *what*, *why*, *when* and *how* of recommendations.[24,25]

Moreover, studies to refine the methodology of developing deprescribing guidelines to facilitate the deprescribing process were conducted.[26,27] A good example are the tools provided by the Bruyère Research Institute, based on their research about the development of deprescribing guidelines. The Bruyère research group has published evidence-based clinical practice guidelines (for instance how to deprescribe benzodiazepines), accompanied by clear algorithms including well-described populations (including for which patients the recommendation does not apply), a list of available drugs and dosages, monitoring recommendations and tapering regimes, thereby complementing the clarity some STOPP-recommendations are lacking.[28]

Tools that have been developed to review the quality of entire CPGs underline the importance of clear and unambiguous recommendations[29], but no validated tool exists to rate singular clinical recommendations. As clarity of presentation is both part of the AGREE II Instrument and described by GUIDE-M, we used tools from the AGREE Consortium to develop a review method. Moreover, the AGREE II Instrument is internationally formally endorsed for guideline assessment and provides a Likert scale that allowed us to quantify clarity.

Clarity ratings were scored by appraisers who are experienced in applying STOPP/START criteria in clinical practice, as they contributed to a large multicentre, randomised controlled trial that evaluated the impact of a STOPP/START-based medication review in older people with polypharmacy. We believe that these experiences allowed clear identification of difficulties prescribers not familiar with STOPP/START may encounter. Although the scoring process remains partly subjective, the consensus ratings show high inter-rater agreement. Differences (>1 point) were discussed with a third appraiser and consensus was reached for all items. Therefore, the final clarity ratings were considered reliable.

One concern of further specifying recommendations might be that they 'replace' important clinical considerations made by physicians. However, guideline recommendations are never meant to fully substitute clinical judgement to treat individual patients. This is why the explanation of a recommendation – next to the action and condition sections – is important for facilitating translation to an individual patient level.

A lack of strong evidence to support the recommended actions could impede formulating clear explanations. For example, clear statements on numbers needed to treat (NNT) or numbers needed to harm (NNH) might be difficult to extract from currently available evidence. In such cases, the addition of the strength of recommendations and supporting evidence could further direct clinicians. This is also endorsed by internationally renowned CPG quality assessment tools from AGREE and GRADE.[30]

Furthermore, our study only highlights barriers that could be optimised to prevent unintentional deviations from STOPP/START due to unclear language. Apart from the clarity of presentation, many other factors attribute to clinical implementation of evidence-based recommendations.[27,31]

Implications

To clarify the action, condition and explanation sections of a recommendation, a more detailed statement is often required. This may directly affect choices regarding the presentation of recommendations. In addition to improvements in 'language', the presentation style or 'format' of a guideline could have a high impact on applicability as well. In a time where almost all evidence-based knowledge is electronically requested, a dynamic, electronical format could be used to integrate information that will improve clarity of presentation without making recommendations too extensive. Integrating clinical rules within electronic healthcare systems – with an option to request more detailed information - could contribute to a continuing learning cycle as part of (but without slowing down) the usual care process. For example, a drug class (stop benzodiazepines) may be provided with a hyperlink including information on drug substance levels (ATC5-codes) and a deprescribing tool, accessible upon request. Once a prescriber has become familiar with all the details of a certain recommendation, such information is no longer required. However, converting recommendations into effective software assistance starts with a clear message of the initial statements.

To make the current version of STOPP/START criteria suitable for software engines, multiple multidisciplinary expert rounds turned out to be necessary to reach consensus on how to interpret ambiguous wordings.[32] For instance, due to different lists of anticholinergic drugs in current literature, expert opinion is needed to translate this drug class to clinically relevant, individual drugs with high anticholinergic burden. Furthermore, it was found that some recommendations, such as to 'stop any drug beyond the recommended duration (STOPP A3)' were too general or unspecific to convert into an algorithm. Selecting specific recommendations concerning potentially inappropriate long-term use of medication, such as long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis (STOPP H4) or continuing bisphosphonates >5

years without evaluating efficacy (not a criterion), will probably result in a better uptake among clinicians and can be easily integrated into clinical decision support systems. Consequently, the lack of clear statements may impede software implementation.[32,33]

Another advantage of presenting clear recommendations in an electronic, dynamic format, is that content could be easily modified based on updates in evidence, country specific guidelines, available drugs and local expertise. Collaboration of guideline developers with experts in medical informatics for considering content formatting could therefore be of great value to facilitate future implementation of recommendations in clinical practice.

Conclusion

In conclusion, for future development of clinical practice guidelines (CPGs), our findings provide direction to assure the clarity of recommendations. We believe in the opportunity to transform STOPP/START from a tool to *detect* inappropriate prescribing to a guideline that provides clear statements on how to *act* after detection. The use of specific and unambiguous language in CPG recommendations is likely to assist physicians in prescribing the right drug to the right patient at the right time.

DECLARATIONS

Authors' contributions

All authors certify that they have participated sufficiently in the work to take public responsibility for the content. Study concept and design: BTGMS, **CJAH**, WK, EvP, TE and IW. Data acquisition: BTGMS, **CJAH**, WK and IW. Analysis and/or interpretation of data: BTGMS, **CJAH**, WK, EvP, TE and IW. Drafting the manuscript: BTGMS. Revising the manuscript critically for important intellectual content: BTGMS, **CJAH**, WK, EvP, TE and IW. We have not received substantial contributions from non-authors.

Competing interests

The author(s) declare that they have no competing interests.

Data availability statement

All data relevant to the study are included in the article or uploaded as online supplementary information.

Ethics approval

Ethics approval was not required for this appraisal study since no humans or animals were involved.

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SUPPLEMENTARY DATA

Table 1: Clarity ratings for **STOPP** criteria
Table 2: STOPP: Clarity ratings of a*ctions*, from lowest through highest ranking
Table 3: STOPP: Clarity ratings of *conditions*, from lowest through highest ranking
Table 4: STOPP: Clarity ratings of e*xplanations*, from lowest through highest ranking
Table 5: Clarity ratings for **START** criteria
Table 6: START: Clarity ratings of *actions*, from lowest through highest ranking
Table 7: START: Clarity ratings of *conditions*, from lowest through highest ranking

Clarity ratings per element for 80 STOPP and 34 START recommendations

Table 1: Clarity ratings for STOPP criteria

STOPP	Action	Clarity rating	Condition
A			
A1	Any drug	100%	prescribed without an evidence-based clinical indication.
A2	Any drug	100%	prescribed beyond the recommended duration, where treatment duration is well defined
A3	Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants	33%	*[users with…duplicate drug class prescription]*
B			
B1	Digoxin	100%	for heart failure with normal systolic ventricular function
B2	Verapamil or diltiazem	100%	with NYHA Class III or IV heart failure
B3	Beta-blocker	67%	in combination with verapamil or diltiazem
B4	Beta blocker	67%	with bradycardia (< 50/min) , type II heart block or complete heart block
B5	Amiodarone	100%	as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias
B6	Loop diuretic	67%	as first-line treatment for hypertension
B7	Loop diuretic	67%	for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure

	Clarity rating	Explanation	Clarity rating
	8%		N/A
	8%		N/A
	17%	(optimisation of monotherapy within a single drug class should be observed prior to considering a new agent).	33%
	58%	(no clear evidence of benefit).	58%
	58%	(may worsen heart failure).	75%
	92%	(risk of heart block).	75%
	42%	(risk of profound hypotension, asystole).	75%
	33%	(higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem)	83%
	33%	(lack of outcome data for this indication; safer, more effective alternatives available).	33%
	58%	(leg elevation and /or compression hosiery usually more appropriate)	75%

Table 1: Continued.

STOPP	Action	Clarity rating	Condition
B8	Thiazide diuretic	67%	with current significant hypokalaemia (i.e. serum K+ < 3.0 mmol/l), hyponatraemia (i.e. serum Na+ < 130 mmol/l) hypercalcaemia (i.e. corrected serum calcium > 2.65 mmol/l) or with a history of gout
B9	Loop diuretic	67%	for treatment of hypertension with concurrent urinary incontinence
B10	Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine),	33%	unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives
B11	ACE inhibitors or Angiotensin Receptor Blockers	67%	in patients with hyperkalaemia.
B12	Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene)	50%	without monitoring of serum potassium
B13	Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil)	50%	in severe heart failure characterised by hypotension i.e. systolic BP < 90 mmHg, or concurrent nitrate therapy for angina
C			
C1	Long-term aspirin at doses greater than 160mg per day	83%	
C2	Aspirin	92%	with a past history of peptic ulcer disease without concomitant PPI
C3	Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors	67%	with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding
C4	Aspirin plus clopidogrel	100%	as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis

	Clarity rating	Explanation	Clarity rating
	75%	(hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic).	83%
	67%	(may exacerbate incontinence).	58%
	75%	(centrally-active antihypertensives are generally less well tolerated by older people than younger people).	50%
	50%		N/A
	67%	(risk of dangerous hyperkalaemia i.e. > 6.0 mmol/l – serum K should be monitored regularly, i.e. at least every 6 months).	92%
	33%	(risk of cardiovascular collapse).	67%
	92%	(increased risk of bleeding, no evidence for increased efficacy).	75%
	100%	(risk of recurrent peptic ulcer).	83%
	33%	(high risk of bleeding)..	58%
	83%	(no evidence of added benefit over clopidogrel monotherapy) .	83%

Table 1: Continued.

STOPP	Action	Clarity rating	Condition
C5	Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	100%	in patients with chronic atrial fibrillation
C6	Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%	in patients with stable coronary, cerebrovascular or peripheral arterial disease
C7	Ticlopidine	100%	in any circumstances
C8	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%	for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months,
C9	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%	for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months
C10	NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%	in combination
C11	NSAID	67%	with concurrent antiplatelet agent(s) without PPI prophylaxis
D			
D1	Tricyclic Antidepressants (TCAs)	67%	with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention
D2	Initiation of Tricyclic Antidepressants (TCAs)	67%	as first-line antidepressant treatment
D3	Neuroleptics with moderate-marked antimuscarinic/ anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol)	33%	with a history of prostatism or previous urinary retention
D4	Selective serotonin re-uptake inhibitors (SSRI's)	67%	with current or recent significant hyponatraemia i.e. serum Na+ < 130 mmol/l

	Clarity rating	Explanation	Clarity rating
	67%	(no added benefit from aspirin).	83%
	33%	(no added benefit from dual therapy).	67%
	100%	(clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects)..	92%
	67%	(no proven added benefit).	83%
	67%	(no proven added benefit).	83%
	67%	(risk of gastrointestinal bleeding).	67%
	67%	(increased risk of peptic ulcer disease)	67%
	33%	(risk of worsening these conditions).	50%
	33%	(higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).	42%
	75%	(high risk of urinary retention).	92%
	75%	(risk of exacerbating or precipitating hyponatraemia).	92%

Table 1: Continued.

STOPP	Action	Clarity rating	Condition
D5	Benzodiazepines	67%	for ≥ 4 weeks
D6	Antipsychotics (i.e. other than quetiapine or clozapine)	75%	in those with parkinsonism or Lewy Body Disease
D7	Anticholinergics/ antimuscarinics	17%	to treat extra-pyramidal side-effects of neuroleptic medications
D8	Anticholinergics/ antimuscarinics	17%	in patients with delirium or dementia
D9	Neuroleptic antipsychotic	25%	in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed
D10	Neuroleptics	33%	as hypnotics, unless sleep disorder is due to psychosis or dementia
D11	Acetylcholinesterase inhibitors	67%	with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil
D12	Phenothiazines	75%	as first-line treatment,
D13	Levodopa or dopamine agonists	83%	for benign essential tremor
D14	First-generation antihistamines	17%	*[users of…first-generation antihistamines]*
E			
E1	Digoxin at a long-term dose greater than 125µg/day	100%	if eGFR < 30 ml/min/1.73m2
E2	Direct thrombin inhibitors (e.g. dabigatran)	58%	if eGFR < 30 ml/min/1.73m2
E3	Factor Xa inhibitors (e.g. rivaroxaban, apixaban)	58%	if eGFR < 15 ml/min/1.73m2
E4	NSAID's	42%	if eGFR < 50 ml/min/1.73m2
E5	Colchicine	100%	if eGFR < 10 ml/min/1.73m2
E6	Metformin	100%	if eGFR < 30 ml/min/1.73m2

Clarity rating	Explanation	Clarity rating
33%	(no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for > 2 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).	100%
100%	(risk of severe extra-pyramidal symptoms)	83%
50%	(risk of anticholinergic toxicity),	50%
33%	(risk of exacerbation of cognitive impairment).	75%
33%	(increased risk of stroke).	33%
33%	(risk of confusion, hypotension, extra-pyramidal side effects, falls).	67%
50%	(risk of cardiac conduction failure, syncope and injury).	92%
83%	since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care).	92%
100%	(no evidence of efficacy)	83%
33%	(safer, less toxic antihistamines now widely available).	75%
83%	(risk of digoxin toxicity if plasma levels not measured).	67%
100%	(risk of bleeding)	67%
100%	(risk of bleeding)	67%
100%	(risk of deterioration in renal function).	75%
100%	(risk of colchicine toxicity).	83%
100%	(risk of lactic acidosis).	83%

Table 1: Continued.

STOPP	Action	Clarity rating	Condition
F			
F1	Prochlorperazine or metoclopramide	100%	with Parkinsonism
F2	PPI	58%	for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks
F3	Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids)	33%	in patients with chronic constipation where non-constipating alternatives are available
F4	Oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate> 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate> 1800 mg/day;	50%	
G			
G1	Theophylline	100%	as monotherapy for COPD
G2	Systemic corticosteroids	75%	instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD
G3	Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium)	50%	with a history of narrow angle glaucoma or bladder outflow obstruction
G4	Benzodiazepines	67%	with acute or chronic respiratory failure i.e. pO_2 < 8.0 kPa ± pCO_2 > 6.5 kPa
H			
H1	Non-steroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents	75%	with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist
H2	NSAID	67%	with severe hypertension or severe heart failure
H3	Long-term use of NSAID (>3 months)	75%	for symptom relief of osteoarthritis pain where paracetamol has not been tried
H4	Long-term corticosteroids (>3 months)	83%	as monotherapy for rheumatoid arthrtitis

	Clarity rating	Explanation	Clarity rating
	92%	(risk of exacerbating Parkinsonian symptoms).	92%
	50%	(dose reduction or earlier discontinuation indicated).	33%
	67%	(risk of exacerbation of constipation).	100%
	100%	(no evidence of enhanced iron absorption above these doses).	75%
	75%	(safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).	75%
	67%	(unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available).	75%
	42%	(may cause urinary retention).	50%
	92%	(risk of exacerbation of respiratory failure).	67%
	100%	(risk of peptic ulcer relapse).	75%
	33%	(risk of exacerbation of hypertension/heart failure)	67%
	58%	(simple analgesics preferable and usually as effective for pain relief)	42%
	67%	(risk of systemic corticosteroid side-effects).	58%

Table 1: Continued.

STOPP	Action	Clarity rating	Condition
H5	Corticosteroids (other than periodic intra-articular injections for mono-articular pain)	83%	for osteoarthritis
H6	Long-term NSAID or colchicine (>3 months)	67%	for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor e.g. allopurinol, febuxostat
H7	COX-2 selective NSAIDs	83%	with concurrent cardiovascular disease
H8	NSAID	58%	with concurrent corticosteroids without PPI prophylaxis
H9	Oral bisphosphonates	75%	in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding
I			
I1	Antimuscarinic drugs	17%	with dementia, or chronic cognitive impairment or narrow-angle glaucoma or chronic prostatism
I2	Selective alpha-1 selective alpha blockers	67%	in those with symptomatic orthostatic hypotension or micturition syncope
J			
J1	Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride)	50%	with type 2 diabetes mellitus
J2	Thiazolidenediones (e.g. rosiglitazone, pioglitazone)	50%	in patients with heart failure
J3	Beta-blockers	67%	in diabetes mellitus with frequent hypoglycaemic episodes
J4	Oestrogens	67%	with a history of breast cancer or venous thromboembolism
J5	Oral oestrogens	83%	without progestogen in patients with intact uterus
J6	Androgens (male sex hormones)	67%	in the absence of primary or secondary hypogonadism
K			
K1	Benzodiazepines	67%	*[falls]*
K2	Neuroleptic drugs	17%	*[falls]*

	Clarity rating	Explanation	Clarity rating
	100%	(risk of systemic corticosteroid side-effects).	58%
	50%	(xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).	33%
	42%	(increased risk of myocardial infarction and stroke).	75%
	58%	(increased risk of peptic ulcer disease).	75%
	92%	(risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture)	83%
	42%	(risk of increased confusion, agitation / risk of urinary retention).	67%
	50%	(risk of precipitating recurrent syncope).	75%
	75%	(risk of prolonged hypoglycaemia).	75%
	58%	(risk of exacerbation of heart failure).	67%
	50%	(risk of suppressing hypoglycaemic symptoms).	83%
	83%	(increased risk of recurrence).	67%
	100%	(risk of endometrial cancer).	67%
	58%	(risk of androgen toxicity; no proven benefit outside of hypogonadism indication).	92%
	0%	(sedative, may cause reduced sensorium, impair balance).	58%
	0%	(may cause gait dyspraxia, Parkinsonism).	58%

Table 1: Continued.

STOPP	Action	Clarity rating	Condition
K3	Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers,)	33%	with persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥ 20mmHg
K4	Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon	50%	*[falls]*
L			
L1	Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine)	42%	as first line therapy for mild pain
L2	Use of regular (as distinct from PRN) opioids	67%	without concomitant laxative
L3	Long-acting opioids	17%	without short-acting opioids for break-through pain
M			
M1	Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines)	25%	*[users with…concomitant use of two or more drugs with antimuscarinic/anticholinergic properties]*

	Clarity rating	Explanation	Clarity rating
	83%	(risk of syncope, falls).	75%
	0%	(may cause protracted daytime sedation, ataxia).	58%
	50%	(WHO analgesic ladder not observed).	33%
	17%	(risk of severe constipation).	83%
	17%	(risk of non-control of severe pain)	67%
	17%	(risk of increased antimuscarinic/anticholinergic toxicity)	17%

Table 2: STOPP: Clarity ratings of actions, from lowest through highest ranking

STOPP n=80	Action	Clarity rate
D7	Anticholinergics/antimuscarinics	17%
D8	Anticholinergics/antimuscarinics	17%
D14	First-generation antihistamines	17%
I1	Antimuscarinic drugs	17%
K2	Neuroleptic drugs	17%
L3	Long-acting opioids	17%
D9	Neuroleptic antipsychotic	25%
M1	Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines)	25%
A3	Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants	33%
B10	Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine),	33%
D3	Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol)	33%
D10	Neuroleptics	33%
F3	Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids)	33%
K3	Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers,)	33%
E4	NSAID's	42%
L1	Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine)	42%
B12	Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene)	50%
B13	Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil)	50%
F4	Oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate > 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate > 1800 mg/day;	50%
G3	Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium)	50%
J1	Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride)	50%
J2	Thiazolidenediones (e.g. rosiglitazone, pioglitazone)	50%
K4	Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon	50%
E2	Direct thrombin inhibitors (e.g. dabigatran)	58%

Table 2: Continued.

STOPP n=80	Action	Clarity rate
E3	Factor Xa inhibitors (e.g. rivaroxaban, apixaban)	58%
F2	PPI	58%
H8	NSAID	58%
B3	Beta-blocker	67%
B4	Beta blocker	67%
B6	Loop diuretic	67%
B7	Loop diuretic	67%
B8	Thiazide diuretic	67%
B9	Loop diuretic	67%
B11	ACE inhibitors or Angiotensin Receptor Blockers	67%
C3	Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors	67%
C6	Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%
C8	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%
C9	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%
C10	NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%
C11	NSAID	67%
D1	Tricyclic Antidepressants (TCAs)	67%
D2	Initiation of Tricyclic Antidepressants (TCAs)	67%
D4	Selective serotonin re-uptake inhibitors (SSRI's)	67%
D5	Benzodiazepines	67%
D11	Acetylcholinesterase inhibitors	67%
G4	Benzodiazepines	67%
H2	NSAID	67%
H6	Long-term NSAID or colchicine (>3 months)	67%
I2	Selective alpha-1 selective alpha blockers	67%
J3	Beta-blockers	67%
J4	Oestrogens	67%
J6	Androgens (male sex hormones)	67%
K1	Benzodiazepines	67%
L2	Use of regular (as distinct from PRN) opioids	67%
D6	Antipsychotics (i.e. other than quetiapine or clozapine)	75%
D12	Phenothiazines	75%
G2	Systemic corticosteroids	75%

Table 2: Continued.

STOPP n=80	Action	Clarity rate
H1	Non-steroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents	75%
H3	Long-term use of NSAID (>3 months)	75%
H9	Oral bisphosphonates	75%
C1	Long-term aspirin at doses greater than 160mg per day	83%
D13	Levodopa or dopamine agonists	83%
H4	Long-term corticosteroids (>3 months)	83%
H5	Corticosteroids (other than periodic intra-articular injections for mono-articular pain)	83%
H7	COX-2 selective NSAIDs	83%
J5	Oral oestrogens	83%
C2	Aspirin	92%
A1	Any drug	100%
A2	Any drug	100%
B1	Digoxin	100%
B2	Verapamil or diltiazem	100%
B5	Amiodarone	100%
C4	Aspirin plus clopidogrel	100%
C5	Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	100%
C7	Ticlopidine	100%
E1	Digoxin at a long-term dose greater than 125µg/day	100%
E5	Colchicine	100%
E6	Metformin	100%
F1	Prochlorperazine or metoclopramide	100%
G1	Theophylline	100%

Table 3: STOPP: Clarity ratings of conditions, from lowest through highest ranking

STOPP n=80	Condition	Clarity rate
K1	*[falls]*	0%
K2	*[falls]*	0%
K4	*[falls]*	0%
A1	prescribed without an evidence-based clinical indication.	8%
A2	prescribed beyond the recommended duration, where treatment duration is well defined	8%
A3	*[users with…duplicate drug class prescription]*	17%
L2	without concomitant laxative	17%
L3	without short-acting opioids for break-through pain	17%
M1	*[users with…concomitant use of two or more drugs with antimuscarinic/ anticholinergic properties]*	17%
B5	as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias	33%
B6	as first-line treatment for hypertension	33%
B13	in severe heart failure characterised by hypotension i.e. systolic BP < 90 mmHg, or concurrent nitrate therapy for angina	33%
C3	with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding	33%
C6	in patients with stable coronary, cerebrovascular or peripheral arterial disease	33%
D1	with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention	33%
D2	as first-line antidepressant treatment	33%
D5	for ≥ 4 weeks	33%
D8	in patients with delirium or dementia	33%
D9	in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed	33%
D10	as hypnotics, unless sleep disorder is due to psychosis or dementia	33%
D14	*[users of…first-generation antihistamines]*	33%
H2	with severe hypertension or severe heart failure	33%
B4	with bradycardia (< 50/min) , type II heart block or complete heart block	42%
G3	with a history of narrow angle glaucoma or bladder outflow obstruction	42%
H7	with concurrent cardiovascular disease	42%
I1	with dementia, or chronic cognitive impairment or narrow-angle glaucoma or chronic prostatism	42%
B11	in patients with hyperkalaemia.	50%
D7	to treat extra-pyramidal side-effects of neuroleptic medications	50%

Table 3: Continued.

STOPP n=80	Condition	Clarity rate
D11	with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil	50%
F2	for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks	50%
H6	for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor e.g. allopurinol, febuxostat	50%
I2	in those with symptomatic orthostatic hypotension or micturition syncope	50%
J3	in diabetes mellitus with frequent hypoglycaemic episodes	50%
L1	as first line therapy for mild pain	50%
B1	for heart failure with normal systolic ventricular function	58%
B2	with NYHA Class III or IV heart failure	58%
B7	for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure	58%
H3	for symptom relief of osteoarthritis pain where paracetamol has not been tried	58%
H8	with concurrent corticosteroids without PPI prophylaxis	58%
J2	in patients with heart failure	58%
J6	in the absence of primary or secondary hypogonadism	58%
B9	for treatment of hypertension with concurrent urinary incontinence	67%
B12	without monitoring of serum potassium	67%
C5	in patients with chronic atrial fibrillation	67%
C8	for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months,	67%
C9	for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months	67%
C10	in combination	67%
C11	with concurrent antiplatelet agent(s) without PPI prophylaxis	67%
F3	in patients with chronic constipation where non-constipating alternatives are available	67%
G2	instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD	67%
H4	as monotherapy for rheumatoid arthrtitis	67%
B8	with current significant hypokalaemia (i.e. serum K+ < 3.0 mmol/l), hyponatraemia (i.e. serum Na+ < 130 mmol/l) hypercalcaemia (i.e. corrected serum calcium > 2.65 mmol/l) or with a history of gout	75%

Table 3: Continued.

STOPP n=80	Condition	Clarity rate
B10	unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives	75%
D3	with a history of prostatism or previous urinary retention	75%
D4	with current or recent significant hyponatraemia i.e. serum Na+ < 130 mmol/l	75%
G1	as monotherapy for COPD	75%
J1	with type 2 diabetes mellitus	75%
C4	as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis	83%
D12	as first-line treatment,	83%
E1	if eGFR < 30 ml/min/1.73m2	83%
J4	with a history of breast cancer or venous thromboembolism	83%
K3	with persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥ 20mmHg	83%
B3	in combination with verapamil or diltiazem	92%
C1	[Long-term aspirin at doses greater than 160mg per day]	92%
F1	with Parkinsonism	92%
G4	with acute or chronic respiratory failure i.e. pO2 < 8.0 kPa ± pCO2 > 6.5 kPa	92%
H9	in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding	92%
C2	with a past history of peptic ulcer disease without concomitant PPI	100%
C7	in any circumstances	100%
D6	in those with parkinsonism or Lewy Body Disease	100%
D13	for benign essential tremor	100%
E2	if eGFR < 30 ml/min/1.73m2	100%
E3	if eGFR < 15 ml/min/1.73m2	100%
E4	if eGFR < 50 ml/min/1.73m2	100%
E5	if eGFR < 10 ml/min/1.73m2	100%
E6	if eGFR < 30 ml/min/1.73m2	100%
F4	*[Oral elemental iron doses greater than 200 mg daily]*	100%
H1	with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist	100%
H5	for osteoarthritis	100%
J5	without progestogen in patients with intact uterus	100%

Table 4: STOPP: Clarity ratings of explanations, from lowest through highest ranking

STOPP n=77	Explanation	Clarity rating
M1	(risk of increased antimuscarinic/anticholinergic toxicity)	17%
A3	(optimisation of monotherapy within a single drug class should be observed prior to considering a new agent).	33%
B6	(lack of outcome data for this indication; safer, more effective alternatives available).	33%
D9	(increased risk of stroke).	33%
F2	(dose reduction or earlier discontinuation indicated).	33%
H6	(xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).	33%
L1	(WHO analgesic ladder not observed).	33%
D2	(higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).	42%
H3	(simple analgesics preferable and usually as effective for pain relief)	42%
B10	(centrally-active antihypertensives are generally less well tolerated by older people than younger people).	50%
D1	(risk of worsening these conditions).	50%
D7	(risk of anticholinergic toxicity),	50%
G3	(may cause urinary retention).	50%
B1	(no clear evidence of benefit).	58%
B9	(may exacerbate incontinence).	58%
C3	(high risk of bleeding)..	58%
H4	(risk of systemic corticosteroid side-effects).	58%
H5	(risk of systemic corticosteroid side-effects).	58%
K1	(sedative, may cause reduced sensorium, impair balance).	58%
K2	(may cause gait dyspraxia, Parkinsonism).	58%
K4	(may cause protracted daytime sedation, ataxia).	58%
B13	(risk of cardiovascular collapse).	67%
C6	(no added benefit from dual therapy).	67%
C10	(risk of gastrointestinal bleeding).	67%
C11	(increased risk of peptic ulcer disease)	67%
D10	(risk of confusion, hypotension, extra-pyramidal side effects, falls).	67%
E1	(risk of digoxin toxicity if plasma levels not measured).	67%
E2	(risk of bleeding)	67%
E3	(risk of bleeding)	67%
G4	(risk of exacerbation of respiratory failure).	67%
H2	(risk of exacerbation of hypertension/heart failure)	67%
I1	(risk of increased confusion, agitation / risk of urinary retention).	67%

Table 4: Continued.

STOPP n=77	Explanation	Clarity rating
J2	(risk of exacerbation of heart failure).	67%
J4	(increased risk of recurrence).	67%
J5	(risk of endometrial cancer).	67%
L3	(risk of non-control of severe pain)	67%
B2	(may worsen heart failure).	75%
B3	(risk of heart block).	75%
B4	(risk of profound hypotension, asystole).	75%
B7	(leg elevation and /or compression hosiery usually more appropriate)	75%
C1	(increased risk of bleeding, no evidence for increased efficacy).	75%
D8	(risk of exacerbation of cognitive impairment).	75%
D14	(safer, less toxic antihistamines now widely available).	75%
E4	(risk of deterioration in renal function).	75%
F4	(no evidence of enhanced iron absorption above these doses).	75%
G1	(safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).	75%
G2	(unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available).	75%
H1	(risk of peptic ulcer relapse).	75%
H7	(increased risk of myocardial infarction and stroke).	75%
H8	(increased risk of peptic ulcer disease).	75%
I2	(risk of precipitating recurrent syncope).	75%
J1	(risk of prolonged hypoglycaemia).	75%
K3	(risk of syncope, falls).	75%
B5	(higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem)	83%
B8	(hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic).	83%
C2	(risk of recurrent peptic ulcer).	83%
C4	(no evidence of added benefit over clopidogrel monotherapy) .	83%
C5	(no added benefit from aspirin).	83%
C8	(no proven added benefit).	83%
C9	(no proven added benefit).	83%
D6	(risk of severe extra-pyramidal symptoms)	83%
D13	(no evidence of efficacy)	83%
E5	(risk of colchicine toxicity).	83%
E6	(risk of lactic acidosis).	83%

Table 4: Continued.

STOPP n=77	Explanation	Clarity rating
H9	(risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture)	83%
J3	(risk of suppressing hypoglycaemic symptoms).	83%
L2	(risk of severe constipation).	83%
B12	(risk of dangerous hyperkalaemia i.e. > 6.0 mmol/l – serum K should be monitored regularly, i.e. at least every 6 months).	92%
C7	(clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects)..	92%
D3	(high risk of urinary retention).	92%
D4	(risk of exacerbating or precipitating hyponatraemia).	92%
D11	(risk of cardiac conduction failure, syncope and injury).	92%
D12	since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care).	92%
F1	(risk of exacerbating Parkinsonian symptoms).	92%
J6	(risk of androgen toxicity; no proven benefit outside of hypogonadism indication).	92%
D5	(no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for > 2 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).	100%
F3	(risk of exacerbation of constipation).	100%

Table 5: Clarity ratings for START criteria

START	Action	Clarity rating
A		
A1	Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors	67%
A2	Aspirin (75 mg – 160 mg once daily)	92%
A3	Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor)	75%
A4	Antihypertensive therapy	25%
A5	Statin therapy	67%
A6	Angiotensin Converting Enzyme (ACE) inhibitor	67%
A7	Beta-blocker	67%
A8	Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol)	83%
B		
B1	Regular inhaled B2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium)	58%
B2	Regular inhaled corticosteroid	58%
B3	Home continuous oxygen	83%
C		
C1	L-DOPA or a dopamine agonist	67%
C2	Non-TCA antidepressant drug	25%
C3	Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine)	50%
C4	Topical prostaglandin, prostamide or beta-blocker	67%
C5	Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated)	67%
C6	Dopamine agonist (ropinirole or pramipexole or rotigotine)	83%

	Condition	Clarity rating	Explanation	Clarity rating
	in the presence of chronic atrial fibrillation.	50%		N/A
	in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated.	33%		N/A
	with a documented history of coronary, cerebral or peripheral vascular disease.	58%		N/A
	where systolic blood pressure consistently > 160 mmHg and/ or diastolic blood pressure consistently >90 mmHg; if systolic blood pressure > 140 mmHg and /or diastolic blood pressure > 90 mmHg, if diabetic.	75%		N/A
	with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years.	42%		N/A
	with systolic heart failure and/or documented coronary artery disease.	58%		N/A
	with ischaemic heart disease.	75%		N/A
	with stable systolic heart failure.	67%		N/A
	for mild to moderate asthma or COPD.	50%		N/A
	for moderate-severe asthma or COPD, where FEV1 <50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.	50%		N/A
	with documented chronic hypoxaemia (i.e. pO2 < 8.0 kPa or 60 mmHg or SaO2 < 89%)	92%		N/A
	in idiopathic Parkinson's disease with functional impairment and resultant disability.	50%		N/A
	in the presence of persistent major depressive symptoms.	33%		N/A
	for mild-moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).	42%		N/A
	for primary open-angle glaucoma.	100%		N/A
	for persistent severe anxiety that interferes with independent functioning.	50%		N/A
	for Restless Legs Syndrome, once iron deficiency and severe renal failure have been excluded.	33%		N/A

Table 5: Continued.

START	Action	Clarity rating
D		
D1	Proton Pump Inhibitor	67%
D2	Fibre supplements (e.g. bran, ispaghula, methylcellulose, sterculia)	50%
E		
E1	Disease-modifying anti-rheumatic drug (DMARD)	25%
E2	Bisphosphonates and vitamin D and calcium	67%
E3	Vitamin D and calcium supplement	17%
E4	Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab)	42%
E5	Vitamin D supplement	42%
E6	Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat)	50%
E7	Folic acid supplement	92%
F		
F1	ACE inhibitor or Angiotensin Receptor Blocker (if intolerant of ACE inhibitor)	67%
G		
G1	Alpha-1 receptor blocker	67%
G2	5-alpha reductase inhibitor	67%
G3	Topical vaginal oestrogen or vaginal oestrogen pessary	83%
H		
H1	High-potency opioids	17%
H2	Laxatives	17%
I		
I1	Seasonal trivalent influenza vaccine	83%
I2	Pneumococcal vaccine	83%

	Condition	Clarity rating	Explanation	Clarity rating
	with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation.	50%		N/A
	for diverticulosis with a history of constipation.	58%		N/A
	with active, disabling rheumatoid disease.	42%		N/A
	in patients taking long-term systemic corticosteroid therapy.	33%		N/A
	in patients with known osteoporosis and/or previous fragility fracture(s) and/or Bone Mineral Density T-scores more than -2.5 in multiple sites.	75%		N/A
	in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists (Bone Mineral Density T-scores -> 2.5 in multiple sites) and/or previous history of fragility fracture(s).	58%		N/A
	in older people who are housebound or experiencing falls or with osteopenia (Bone Mineral Density T-score is > -1.0 but < -2.5 in multiple sites).	50%		N/A
	with a history of recurrent episodes of gout.	50%		N/A
	in patients taking methotexate.	33%		N/A
	in diabetes with evidence of renal disease i.e. dipstick proteinuria or microalbuminuria (>30mg/24 hours) with or without serum biochemical renal impairment.	67%		N/A
	with symptomatic prostatism, where prostatectomy is not considered necessary.	50%		N/A
	with symptomatic prostatism, where prostatectomy is not considered necessary.	50%		N/A
	for symptomatic atrophic vaginitis	75%		N/A
	in moderate-severe pain, where paracetamol, NSAIDs or low-potency opioids are not appropriate to the pain severity or have been ineffective.	50%		N/A
	in patients receiving opioids regularly.	75%		N/A
	annually	83%		N/A
	at least once after age 65 according to national guidelines	83%		N/A

Table 6: START: Clarity ratings of actions, from lowest through highest ranking

START n=34	Action	Clarity rating
E3	Vitamin D and calcium supplement	17%
H1	High-potency opioids	17%
H2	Laxatives	17%
A4	Antihypertensive therapy	25%
C2	Non-TCA antidepressant drug	25%
E1	Disease-modifying anti-rheumatic drug (DMARD)	25%
E4	Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab)	42%
E5	Vitamin D supplement	42%
C3	Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine)	50%
D2	Fibre supplements (e.g. bran, ispaghula, methylcellulose, sterculia)	50%
E6	Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat)	50%
B1	Regular inhaled B2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium)	58%
B2	Regular inhaled corticosteroid	58%
A1	Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors	67%
A5	Statin therapy	67%
A6	Angiotensin Converting Enzyme (ACE) inhibitor	67%
A7	Beta-blocker	67%
C1	L-DOPA or a dopamine agonist	67%
C4	Topical prostaglandin, prostamide or beta-blocker	67%
C5	Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated)	67%
D1	Proton Pump Inhibitor	67%
E2	Bisphosphonates and vitamin D and calcium	67%
F1	ACE inhibitor or Angiotensin Receptor Blocker (if intolerant of ACE inhibitor)	67%
G1	Alpha-1 receptor blocker	67%
G2	5-alpha reductase inhibitor	67%
A3	Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor)	75%
A8	Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol)	83%
B3	Home continuous oxygen	83%
C6	Dopamine agonist (ropinirole or pramipexole or rotigotine)	83%
G3	Topical vaginal oestrogen or vaginal oestrogen pessary	83%
I1	Seasonal trivalent influenza vaccine	83%
I2	Pneumococcal vaccine	83%
A2	Aspirin (75 mg – 160 mg once daily)	92%
E7	Folic acid supplement	92%

Table 7: START: Clarity ratings of conditions, from lowest through highest ranking

START n=34	Condition	Clarity rating
A2	in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated.	33%
C2	in the presence of persistent major depressive symptoms.	33%
C6	for Restless Legs Syndrome, once iron deficiency and severe renal failure have been excluded.	33%
E2	in patients taking long-term systemic corticosteroid therapy.	33%
E7	in patients taking methotexate.	33%
A5	with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years.	42%
C3	for mild-moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).	42%
E1	with active, disabling rheumatoid disease.	42%
A1	in the presence of chronic atrial fibrillation.	50%
B1	for mild to moderate asthma or COPD.	50%
B2	for moderate-severe asthma or COPD, where FEV1 < 50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.	50%
C1	in idiopathic Parkinson's disease with functional impairment and resultant disability.	50%
C5	for persistent severe anxiety that interferes with independent functioning.	50%
D1	with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation.	50%
E5	in older people who are housebound or experiencing falls or with osteopenia (Bone Mineral Density T-score is > -1.0 but < -2.5 in multiple sites).	50%
E6	with a history of recurrent episodes of gout.	50%
G1	with symptomatic prostatism, where prostatectomy is not considered necessary.	50%
G2	with symptomatic prostatism, where prostatectomy is not considered necessary.	50%
H1	in moderate-severe pain, where paracetamol, NSAIDs or low-potency opioids are not appropriate to the pain severity or have been ineffective.	50%
A3	with a documented history of coronary, cerebral or peripheral vascular disease.	58%
A6	with systolic heart failure and/or documented coronary artery disease.	58%
D2	for diverticulosis with a history of constipation.	58%

Table 7: Continued

START n=34	Condition	Clarity rating
E4	in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists (Bone Mineral Density T-scores -> 2.5 in multiple sites) and/or previous history of fragility fracture(s).	58%
A8	with stable systolic heart failure.	67%
F1	in diabetes with evidence of renal disease i.e. dipstick proteinuria or microalbuminuria (>30mg/24 hours) with or without serum biochemical renal impairment.	67%
A4	where systolic blood pressure consistently > 160 mmHg and/or diastolic blood pressure consistently >90 mmHg; if systolic blood pressure > 140 mmHg and /or diastolic blood pressure > 90 mmHg, if diabetic.	75%
A7	with ischaemic heart disease.	75%
E3	in patients with known osteoporosis and/or previous fragility fracture(s) and/or Bone Mineral Density T-scores more than -2.5 in multiple sites.	75%
G3	for symptomatic atrophic vaginitis	75%
H2	in patients receiving opioids regularly.	75%
I1	annually	83%
I2	at least once after age 65 according to national guidelines	83%
B3	with documented chronic hypoxaemia (i.e. pO2 < 8.0 kPa or 60 mmHg or SaO2 < 89%)	92%
C4	for primary open-angle glaucoma.	100%

PART II

EVALUATION OF CLINICAL DECISION SUPPORT-ASSISTED PHARMACOTHERAPY OPTIMISATION IN THE HOSPITAL SETTING

The effect of providing prescribing recommendations on appropriate prescribing: A cluster-randomised controlled trial in older adults in a preoperative setting

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ABSTRACT

Aims: The Systematic Tool to Reduce Inappropriate Prescribing (STRIP) is a method to assess patient's medication and has been incorporated into a clinical decision support system (CDSS): STRIP Assistant. Our aim was to evaluate the effect of recommendations generated using STRIP Assistant on appropriate prescribing and mortality among older patients in a preoperative setting.

Methods: This cluster-randomised controlled trial was carried out at the preoperative geriatric outpatient clinic. Residents who performed a comprehensive geriatric assessment were randomised to the control group and intervention group in a 1:1 ratio. Visiting patients aged 70 years or older on 5 or more medications were included. Intervention: prescribing recommendations were generated by a physician using STRIP Assistant and provided to the resident. Control group residents performed a medication review according to usual care. Primary outcome: number of medication changes made based on potential prescribing omissions (PPOs), potentially inappropriate medications (PIMs), and suboptimal dosages according to the prescribing recommendations. Secondary outcome: 3-month postoperative mortality.

Results: 65 intervention and 59 control patients were included, attended by 34 residents. Significantly more medication changes based on PPOs and PIMs were made in the intervention group than in the control group (PPOs 26.2% *vs* 3.4%, OR 0.04 [95% CI 0.003–0.46] $P < 0.05$; PIMS 46.2% *vs* 15.3% OR 0.14 [95% CI 0.07–0.57] $P < 0.005$). There were no differences in dose adjustments or postoperative mortality.

Conclusion: Prescribing recommendations generated with the help of STRIP Assistant improved appropriate prescribing in a preoperative geriatric outpatient clinic without affecting postoperative mortality.

INTRODUCTION

Inappropriate prescribing is common among older people and may have serious consequences, such as inefficacy, adverse drug events, falls, (re)hospitalisation or death.[1-5] The screening tool of older person's prescriptions/screening tool to alert to right treatment (STOPP/START) criteria provide a structured format to evaluate patients' medications for the presence of potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs).[6] Prior research has shown that the use of the STOPP/START criteria improves appropriate prescribing, measured with the Medication Appropriate Index and Assessment of Underutilisation Index in a hospital setting.[7] Furthermore, 51.7% of the PIMs that caused a serious adverse drug event were detected when the STOPP/START criteria were used.[2] Additonally, the use of the STOPP/START criteria significantly reduced the number of PIMs and PPOs and the number of falls in a geriatric chronic care facility.[8]

Explicit screening tools such as STOPP/START are included in the Systematic Tool to Reduce Inappropriate Prescribing (STRIP). STRIP consists of 5 steps to optimise an individual patient's medication regimen and has proven to be effective in reducing inappropriate prescribing when used by final-year medical students[9] and in detecting drug-related problems (mainly PIMs) in patients with an intellectual disability.[10] STRIP is currently considered best practice in the Netherlands.[11,12]

A web-based application was developed to help physicians to conduct a medication review using the STRIP method: the STRIP Assistant. STRIP Assistant helps users to formulate medication recommendations based on STOPP/START criteria version 1 and G-standard.[6,12-14] G-standard is a database comprising all medications registered in the Netherlands, and includes guidelines on established clinical interactions, duplicate medications, contraindications, dosage, and frequency of administration recommendations. The G-standard forms the basis of pharmacovigilance in the Netherlands.[13] Studies have revealed that the use of STRIP Assistant by general practitioners and pharmacists increases appropriate medication decisions (58–76%), decreases inappropriate decisions (42–24%) and increases the percentage of solved drug-related problems in test cases from general practice.[14,15] As little is known about the effect of STRIP Assistant-generated prescribing recommendations in a hospital setting, we evaluated whether prescribing recommendations established with the use of the STRIP Assistant, improved prescribing in a preoperative geriatric outpatient population. The primary outcome was the number of resident-implemented medication changes made based on PIMs, PPOs, and suboptimal dosages; a secondary outcome was 3-month postoperative mortality.

METHODS

Design, setting and participants

This cluster-randomised controlled trial investigated the effect of written prescribing recommendations generated by a research physician using STRIP Assistant on medication changes made by residents during a preoperative comprehensive geriatric assessment. A cluster randomised design was chosen to avoid bias resulting from residents learning from the recommendations. All residents working at the geriatric outpatient clinic of the University Medical Centre Utrecht (UMCU) during the inclusion period were included except for 3 residents who participated as research physicians in this study. A random number generator was used to randomly assign the residents to the intervention group (even numbers) and the control group (odd numbers) in a 1:1 ratio.

Due to the nature of the intervention, participating residents and the research physicians generating the prescribing recommendations, could not be blinded. However, patients, supervisors of the residents and the nurses, who gathered information about comorbidity, cognitive function and functional status, were blinded for the allocation of the intervention. Residents from the intervention group were asked not to discuss the prescribing recommendations they received with colleagues, to prevent contamination of the control group.

Cluster size was determined by the number of patients eligible for inclusion treated by one resident. The work schedule of the residents was not modified by or for this study. In the UMCU, patients aged 70 years or older scheduled for elective surgery are invited for a comprehensive geriatric assessment (CGA) at the preoperative geriatric outpatient clinic. Participation is voluntarily. During this visit, patients were informed that their data could be used for research projects, unless they object.

Patients scheduled for the preoperative screening at the geriatric outpatient clinic of the UMCU between October 2014 and July 2016 were assessed for eligibility. Inclusion criteria were polypharmacy defined as the use of 5 or more different medications, including topical, inhaled and acute medications, and the availability of a Structured History taking of Medication use (SHiM) taken by a pharmacy assistant before the patient visited the geriatric outpatient clinic.[16]

Exclusion criterion was the inability to provide prescribing recommendation due to practical issues such as patient no-show, surgery cancellation etc.

Usual care

A pharmacy assistant took the SHiM as part of usual care, prior to the CGA. Findings were recorded in the patient's electronic medical record. The standard CGA, performed by a resident and supported by a nurse, provided information about smoking habits and alcohol use, the Charlson Comorbidity Index (CCI), 15-point Katz Index of Independence in Activities of Daily Living (Katz-ADL), and mini-mental state examination (MMSE). The resident also reviewed the patients' medication. Any medication changes made by the resident (direct changes as well as recommendations to the surgeon or general practitioner regarding the medication regimen) were registered in the medical record.

Intervention

The intervention consisted of written prescribing recommendations prepared by an independent, clinically experienced research physician using the STRIP Assistant. The input data consisted of medication use (as reported by the SHiM use), age, sex, medical history, current medical problems and medical history, blood pressure, pulse and estimated glomerular filtration rate. Prescribing recommendations were based on PPOs, PIMs and suboptimal dosages identified by STRIP Assistant and the research physician. The recommendations were provided to the resident before the CGA. Whether these recommendations were implemented, either direct changes to medication regimen or recommendations deferred to the surgeon or general practitioner, was at the resident's discretion.

Outcome measures

The primary outcomes were the number of implemented medication changes per patient made by a resident during the CGA, corresponding with the PPOs and PIMs, and suboptimal dosages identified by the research physician using the STRIP Assistant. To compare intervention and control groups, prescribing recommendations were retrospectively generated using STRIP Assistant for the control group. In the control group, a recommendation was considered implemented when the resident identified the same PPO or PIM as recommended by the STRIP Assistant. A dose adjustment for suboptimal dosage was considered implemented when a resident adjusted the dose in the same direction (a decrease or increase) as recommended by the research physician. Secondary outcomes were prescribing appropriateness according to STOPP/START criteria version 2, three-month and one-year postoperative mortality rates and three-month changes in MMSE, Katz-ADL and Fried criteria.

Standardisation of intervention

To check the accuracy and consistency of the prescribing recommendations generated by the research physician using STRIP Assistant, the recommendations for the first 39 patients (both intervention and controls) were compared with consensus recommendations from an expert panel consisting of a geriatrician–clinical pharmacologist and a clinical pharmacist–clinical pharmacologist. This resulted in 11 instructions to standardise the application of STOPP/START criteria and dose adjustments in order to improve the consistency of the intervention (**Table 1**). These instructions were applied to all patients included after the first 61 patients (64.4% of control group and 35.4% of intervention group). The effect of these instructions on the primary outcome was investigated.

Statistical analyses

Differences between intervention and control groups regarding patient characteristics, numbers of PPOs and PIMs at baseline identified with STOPP/START criteria version 2, resident characteristics, and clinical data were analysed using descriptive statistics. Normally distributed data are presented as means with standard deviations and analysed using *t*-tests. Non- parametric data are reported as median and interquartile range (IQR) and analysed using the Pearson $\chi 2$ test, Mann–Whitney *U* test and Fisher exact test.

As a result of the clustered design, generalised estimating equation (GEE) regression models were used for the primary outcome to adjust for the numbers of recommended medication changes based on PPOs and PIMs. GEE regression models were also used to investigate the appropriateness of prescribing according to STOPP/START criteria adjusted for baseline PPOs and PIMs, the effect of the intervention on mortality adjusted for age, sex, and CCI at screening, and to investigate the effect of the standardisation instructions by comparing the control group and the intervention group before and after application of instructions. To measure any effect of learning or contamination of the control group, the effect of the duration of the residents' participation in the study (in months) on the number of resident-implemented PPO and PIM changes was measured using GEE regression models. Statistical significance levels were set at $P < 0.05$ (two-tailed). Statistical analyses were performed using IBM SPSS Statistics version 21 (IBM SPSS, Chicago, IL, USA).

Sample size

The study size was calculated by assuming that the number of PIM changes made by the resident would be 0.5 per patient in the intervention group and 0.2 per patient in the control group. This was based on a detection rate, using STOPP criteria, of 0.86 in a study involving hospitalised older adults[17] and 0.36 in a study involving

primary care patients older than 70 years.[18] Standard levels for type I and II errors ($\alpha = 0.05$, $\beta = 0.8$) were used. The calculated number of patients was multiplied by 1.15 because of the cluster randomised design, with an expected mean cluster size of four patients and $\rho = 0.05$ $(1 + (\text{cluster size} - 1)\rho)$, resulting in a required number of 50 patients per study arm.

Ethics

The Research Ethics Committee of University Medical Centre Utrecht confirmed that the Medical Research involving Human Subjects Act was not applicable to this study, and a waiver was granted.

Table 1: Consensus-based instructions to standardise the prescribing recommendations

STOPP/START criteria	Ambiguity leading to potential discrepancies in interpretation	Instructions how to interpret STOPP/START criteria and guidelines panel
PPO		
1.START, A6/7	ACE inhibitor and β-blocker in all patients with coronary disease or only in patients who experienced cardiac ischaemia?	Beta-blocker in patients with a history of coronary bypass or coronary stent (myocardial infarction not prerequisite) and ACE inhibitor (only) in patients with history of acute myocardial infarction.
2.	The number of available blood pressure measurements was often limited. Should advice be given on the basis of fewer than 3 measurements?	Antihypertensive medication in patients in whom the target blood pressure was not achieved, regardless of the number of blood pressure measurements.
3. START E5	Do all older patients need to use vitamin D supplement?	Vitamin D supplement in patients with known osteoporosis or other musculoskeletal disease (e.g. rheumatoid arthritis, intermittent claudication) and insufficient sunlight exposure.
4. START E3	Do all older patients need to use calcium supplement?	Calcium supplement in patients with osteoporosis in combination with low dietary intake.
PIM		
5. STOPP A1	Antidepressant use without a documented depression or anxiety disorder in medical history. Possibly the available medical history is not complete.	Antidepressant without documented depression in medical history.

Table 1: Continued

STOPP/START criteria	Ambiguity leading to potential discrepancies in interpretation	Instructions how to interpret STOPP/START criteria and guidelines panel
6. STOPP A1	Analgesic use without documentation of pain or disease that causes pain. Possibly the available medical history is not complete.	Analgesic without documentation of pain or disease that causes pain (e.g. osteoporosis, rheumatoid disease, (metastatic) cancer, surgery within 2 weeks) in medical history.
Dose adjustment		
7.	Should the maximum dose for acetaminophen be 3 times daily or 4 times daily?	Acetaminophen >1 g 3 times daily adjust to a maximum 1 g 3 times daily in patients with chronic use.
8. START A5	Which dose should be advised for statins?	Simvastatin adjusted to 40 mg once daily, atorvastatin adjusted to dose 20 or 40 mg once daily
9. STOPP F2	Which dose should be advised for proton-pump inhibitors?	Proton-pump inhibitor pantoprazole or omeprazole as prophylaxis adjusted to 20 mg once daily.
Change in medication		
10. START A7	Should the following medication be changed?	Change drug when the patient is not using the first choice drug according to guidelines, for example:
10A.		Metoprolol instead of propranolol in a patient with a history of myocardial infarction
10B.		Metoprolol instead of sotalol or digoxin in a patient with a history of permanent atrial fibrillation.
10C.		Thiazide diuretic instead of diltiazem in a patient with a history of hypertension.
Other considerations		
11.	Is angiotensin inhibitor an alternative when there is an indication for an ACE inhibitor?	Angiotensin inhibitor is considered equivalent to an ACE inhibitor.

ACE = angiotensin-converting-enzyme; PIM = potentially inappropriate medication; PPO = potential prescribing omission; START = screening tool to alert doctors to right treatment; STOPP = screening tool of older person's prescriptions

RESULTS

All 34 randomised residents (i.e. the clusters) participated in the study, 19 were assigned to the intervention group and 15 to the control group; the median number of patients per cluster was 3 (IQR 1–4; Figure 1). The trial ended after the calculated sample size was reached for both groups. No data are available for the patients who rejected the invitation for the preoperative CGA. None of the included patients objected to participation in research. After randomisation of 170 eligible patients, 45 patients had to be excluded, mainly because of patient no-show (**Figure 1**). The data of 124 included patients could be analysed for the primary outcome.

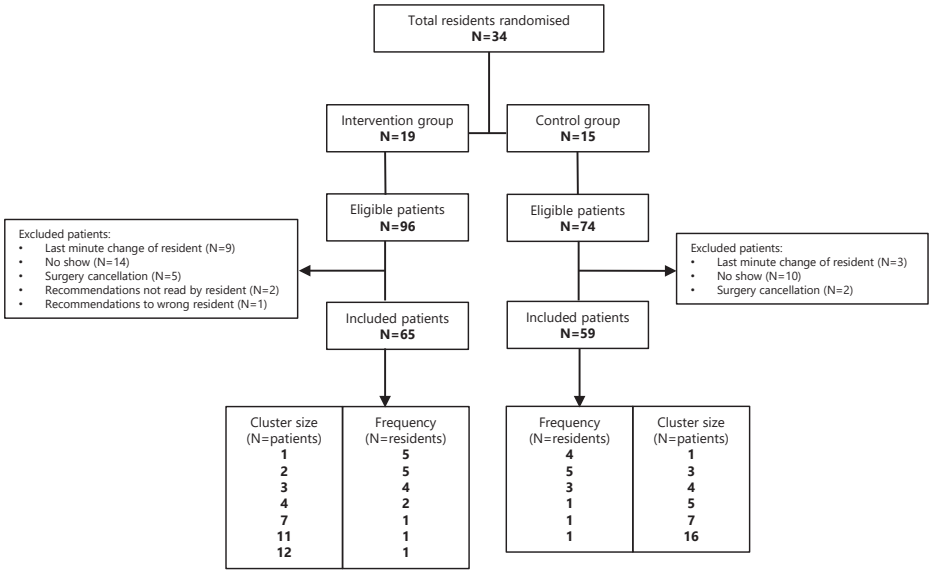

Figure 1 Participant flow and cluster size

Patients in the intervention (*n* = 65) and control (*n* = 59) groups did not differ regarding age (mean 77.8 ± 5.7, *vs* 79, ± 6.0 respectively), sex, smoking, alcohol consumption, renal function, number of medications (median; IQR; 9; 6–12 and 9; 7–12 respectively), prescribing appropriateness, surgical specialty, comorbidity, cognitive function or functional status at baseline (**Table 2**). Residents in the control group were generally more experienced and were more often specialising in geriatrics, whereas the residents in the intervention group were more often specialising in nursing home medicine (**Table 2**). The primary outcome was the number of resident-implemented medication changes made based on PIMs, PPOs and suboptimal dosages. More recommended PPO and PIM

changes were implemented in the intervention group than in the control group (PPOs 26.2% *vs* 3.4%, $P < 0.001$; PIMs 46.2% *vs* 15.3%, $P < 0.001$; Table 3). When the number of implemented PPO and PIM changes was adjusted for the number of recommended PPO and PIM changes, this difference remained significant (PPOs odds ratio (OR) 0.04, [95% confidence interval (CI) 0.003–0.46] $P < 0.05$; PIMs OR 0.14 [95% CI 0.07–0.57] $P < 0.005$). The number of dose changes made based on suboptimal dosages was very low and did not differ significantly between the 2 groups (4.6% *vs* 0.0%, $p = 0.1$). Changes in dosing frequency were recommended twice in the control group.

In addition to the medication changes based on PPOs, PIMs, and suboptimal dosages, made in accordance with the prescribing recommendations of the research physician with the STRIP Assistant, the residents also identified additional PPO, PIM and suboptimal dosage changes that were not included in the prescribing recommendations (**Figure 2**).

These numbers did not significantly differ between the groups (PPOs 9.3% *vs* 8.5%, $P = 0.843$; PIMs 7.7% *vs* 3.4%, $P = 0.308$; suboptimal dosages 4.6% *vs* 6.8%, $P = 0.603$). When combining these additional PPO, PIM and suboptimal dosage changes with the implemented prescribing recommendations, the difference between the total number of PPO and PIM changes made by the residents in the 2 groups remained significant (PPOs 35.4% *vs* 10.2%, $p < 0.05$; PIMs 47.7% *vs* 16.9%, $p < 0.01$; dose adjustment changes 9.2% *vs* 6.8%, $p = 0.618$; **Figure 2**). The appropriateness of prescribing measured by the numbers of PPOs and PIMs identified by STOPP/START criteria version 2 before and after the intervention, increased significantly in the intervention group for the number of PIMs (OR 0.14 [95% CI 0.08–0.25] $p < 0.001$). The number of PIM changes made in the control group and the number of PPO changes made in the intervention group and control group did not differ before and after the intervention or usual care (**Table 4**).

Three-month postoperative mortality did not significantly differ between intervention and control groups; eight patients in the intervention group (13.1%) and seven in the control group (12.1%) died (OR 1.01 [95% CI 0.40–3.05], $p = 0.859$). Due to missing data, the difference in MMSE (62.9% missing), Katz-ADL (28.2% missing), Fried criteria (24.2% missing) between baseline and 3 months postoperatively, and 1 year postoperative mortality (47.9% missing) could not be analysed. Standardisation instructions for the application of STOPP/START criteria and guidelines were introduced after 61 patients had been included and were based on a sample of 39 patients from both groups.

Table 2: Baseline characteristics

Characteristics	**Intervention group** (N=65)	**Control group** (N=59)	P=value
Sex, n (%), male	34 (53.8)	30 (50.8)	0.94[c]
Age (years)[a]	77.8 ± 5.7	79.0 ± 6.0	0.29[e]
Renal function (eGFR ml/min/1,73m2)[b]	69.0 (52.0–84.0)	69.5 (52.0–85.0)	0.92[e]
Smoking, n (%), yes	10 (16.1)	6 (10.2)	0.43[d]
Alcohol consumption, n (%) >1 unit/day	10 (16.1)	8 (13.5)	0.72[c]
Total number of medications used by patient[b]	9 (6–12)	9 (7–12)	0.86[f]
Number of PPOs per patient[b]	1 (0–2)	1 (0–2)	0.08[f]
Number of PIMs per patient[b]	3 (1–5)	2 (0.5–3.5)	0.87[f]
Referring specialty, n (%)			0.13[d]
General surgery	3 (4.6)	9 (15.3)	
Cardiology	12 (18.5)	13 (22.0)	
Oncology	23 (35.4)	14 (23.7)	
Orthopaedics	15 (23.0)	13 (22.0)	
Urology	5 (7.7)	1 (1.7)	
Vascular Surgery	7 (10.8)	7 (11.7)	
Other	0 (0)	2 (3.4)	
Charlson Comorbidity Index (CCI)[b]	3 (0–9)	3 (0–10)	0.74[f]
MMSE <24, n (%)	5 (8.2)	4 (6.8)	0 .81[c]
Katz-ADL ≥ 7, n (%)	9 (14.1)	3 (5.5)	0 .06[d]
Specialty and year of residency cluster resident, n (%)			<0.001[c]
Geriatric medicine			
2nd	0	1 (1.7)	
3rd	9 (13.6)	3 (5.1)	
4th	4 (6.1)	4 (6.8)	
5th	17 (26.2)	13 (22.0)	
6th	0	17 (27.1)	
Internal medicine 1st	0	1 (1.7)	
General practice 2nd	10 (16.7)	10 (16.9)	
Nursing home medicine 2nd	25 (38.5)	10 (16.9)	

PPOs = potential prescribing omissions STOPP/START criteria version 2; PIMs = potentially inappropriate medications based on STOPP/START criteria version 2; Katz-ADL = 15 point Katz Index of Independence in Activities of Daily Living; MMSE = mini-mental state examination. Missings (N): Renal function (7), smoking (5), alcohol consumption (5), CCI (4), MMSE (6), Katz-ADL index (5). [a] mean ± SD; [b] median (IQR); [c] based on χ2-test; [d] based on Fisher exact test (2-sided); [e] based on independent Student *t* test; [f] based on Mann–Whitney *U* test.

Table 3: Number of resident-implemented medication changes based on potential prescribing omission (PPO), potentially inappropriate medication (PIM) and suboptimal dosages made per patient by the resident in accordance with prescribing recommendations.

	Intervention group (N=65)	**Control group** (N=59)	P-value
Numbers of PPO changes	Patients, N (%)	Patients, N (%)	<0.001[a]
0	48 (73.8)	57 (96.6)	<0.05[b]
1	11 (16.9))	2 (3.4	
2	6 (9.2)	0	
Numbers of PIM changes	Patients, N (%)	Patients, N (%)	<0.001[a]
0	35 (53.8)	50 (84.7)	<0.005[b]
1	14 (21.5)	8 (13.6)	
2	8 (12.3)	0	
≥3	8 (12.3)	1 (1.7)	
Number of suboptimal dosage changes	Patients, N (%)	Patients, N (%)	
0	62 (95.4)	59 (100)	0.096[a]
1	3 (4.6)	0	

[a] *P* value based on Mann–Whitney *U*. [b] *P* value based on generalised estimating equation analysis of association between intervention and number of patients with 0 or ≥ 1 PPOs/PIMs. Adjusted for the number of recommended PPO/PIM medication changes.

Comparison of periods before and after the introduction of these instructions revealed no significant difference in resident-implemented PPO and PIM changes before and after the introduction within the intervention group (**Table 4**). Moreover, the difference in resident-implemented recommended PPO and PIM changes between intervention and control groups remained significant when the total control group was compared with both the intervention group before and intervention group after introduction of standardisation instructions (PPOs before: OR 0.03 [95% CI 0.002–0.66] $P < 0.05$ and after OR 0.04 [95% CI 0.004–0.45] $P < 0.01$ respectively; PIMs: before OR 0.17 [95% CI 0.06–0.47] $P < 0.005$ and after OR 0.20 [95% CI 0.06–0.74] $P < 0.05$, respectively).

The duration of the residents' participation in the study did not affect the number of resident-implemented PPO and PIM changes. The most frequently recommended and implemented recommendations regarding PPOs involved vitamin D, angiotensin-converting enzyme inhibitors and statins. The most frequently recommended and implemented recommendations regarding PIMs involved proton pump inhibitors, benzodiazepines, analgesics and antiplatelet drugs.

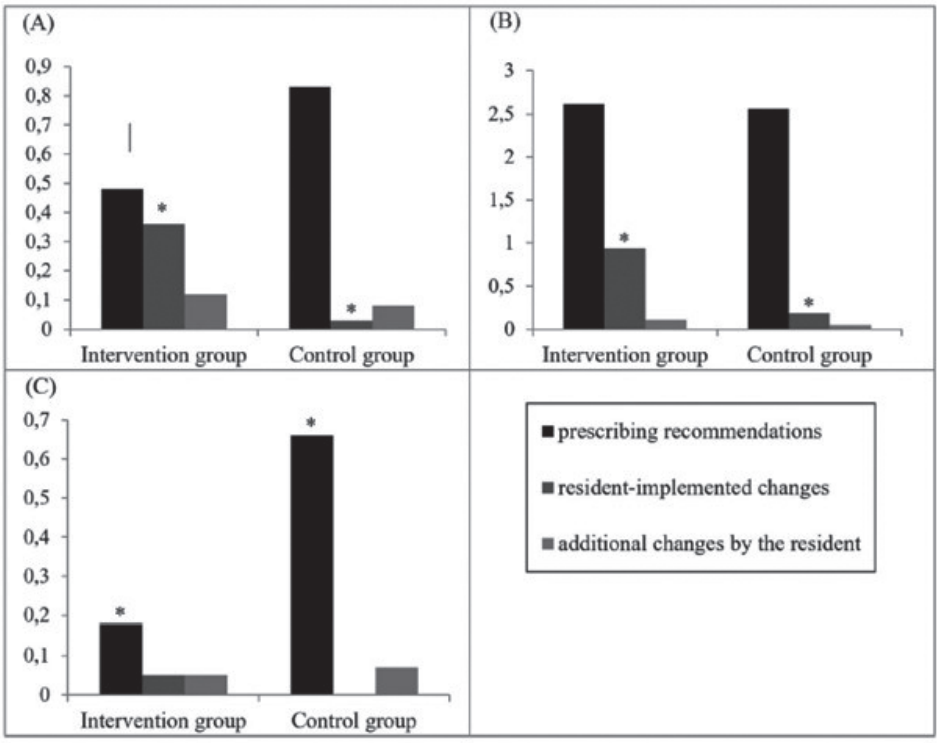

Figure 2: Average number of prescribing recommendations per patient, average number of medication changes in accordance with prescribing recommendations, and average number of additional changes by the resident per patient, because of potential prescribing omissions (PPOs); (A), potentially inappropriate medications (PIMs); (B), and suboptimal dosages (C) in the control and intervention groups. *$P < 0.001$. P values calculated using Mann–Whitney U

Table 4: Number of potential prescribing omissions (PPOs) and potentially inappropriate medications (PIMs) before and after intervention/usual care identified with STOPP/START criteria version 2.

Intervention group	**Before intervention**	**After intervention**
Number of PPOs	Patients, N (%)	Patients, N(%)
0	30 (46.2)	36 (55.4)
1	19 (29.2)	17 (26.2)
2	14 (21.5)	10 (15.4)
≥3	2 (3.0)	2 (3.0)
Number of PIMS	Patients, N (%)	Patients, N (%)
0	8 (12.3)	12 (18.5)
1	12 (18.5)	16 (24.6)
2	10 (15.4)	11 (16.9)
≥3	35 (53.8)	26 (40.0)
Control group	**Before usual care**	**After usual care**
Number of PPOS	Patients, N (%)	Patients, N (%)
0	20 (33.9)	21 (35.6)
1	18 (30.5)	16 (27.1)
2	13 (22.0)	15 (25.4)
≥3	8 (13.6)	7 (11.9)
Number of PIMS	Patients, N (%)	Patients, N (%)
0	0 (1.7)	3 (5.1)
1	15 (25.4)	15 (25.4)
2	15 (25.4)	14 (23.7)
≥3	28 (47.6)	27 (45.9)

P values were based on generalised estimating equation regression model analysis of association between intervention and number of patients with 0 or ≥ 1 PPO/PIM, adjusted by the number of PPOs/PIMs at baseline. PPOs P = 0.36. PIMs P < 0.001.

DISCUSSION

Individualised prescribing recommendations generated by a research physician using STRIP Assistant increased appropriate prescribing in patients visiting a geriatric preoperative outpatient clinic. The number of resident-implemented recommended medication changes based on PPOs and PIMs was significantly higher in the intervention group than in the control group. The appropriateness of prescribing improved by the intervention, based on the decrease in PIMs identified with STOPP/START version 2. No statistically significant effect on 3-month postoperative mortality was found.

The high number of PIMs detected by the research physician using STRIP Assistant in this study (average of 2.59 per patient) as compared to earlier studies (average of 0.47–1.81) might be explained by the higher number of medications used by patients in our study (mean 9.5 *vs* 6–9.5).[2,17-20] Furthermore, the incorporated guidelines withinin the STRIP Assistant might lead to a higher detection rate when compared with STOPP/START criteria alone. In contrast, the lack of relevant clinical information could have resulted in the identification of unjustified PIMs by the research physician. The lack of relevant clinical information might also explain the discrepancy between recommended and implemented changes regarding PPOs, PIMs and suboptimal dosages. Dalleur *et al.*[17] found that the average number of PIMs identified per patient after a CGA was 0.86, whereas the number of implemented changes made after discharge was 0.26. This illustrates that even recommended changes based on a CGA are not fully implemented.

The most frequently recommended and implemented changes based on PIMs involved proton pump inhibitors, benzodiazepines, analgesics and antiplatelet drugs, as reported earlier by other researchers.[2,17-20] These PIMs are clinically relevant because antiplatelet drugs and medications that act on the central nervous system are major causes of medication-related hospital admissions.[1] The most frequently recommended and implemented changes regarding PPOs in our study involved vitamin D, angiotensin-converting-enzyme inhibitors and statins, and are comparable with the main PPOs found by Dalleur et al. (vitamin D, statins).[20] The fact that we did not find a significant difference in mortality is probably the result of the small sample size and the short follow-up period. However, a Cochrane meta-analysis including 3218 patients did not reveal a significant effect of medication review on 1-year mortality rates in hospitalised patients.[21]

There is no gold standard to determine the best medication regimen for individual patients.[21] In our study, the Individualised prescribing recommendations were considered most appropriate since the STRIP Assistant combines the explicit STOPP/START criteria with other prescribing guidelines, clinical parameters and judgement of

an experienced physician. Therefore, the prescribing recommendations provided by the research physician and subsequently implemented by the residents were considered appropriate. Residents within the control group could be expected to make different medication changes or dose adjustments as they did not receive the prescribing recommendations. However, we detected a trend towards more changes additional to the prescribing recommendations in the intervention group than in the control group.

In contrast to the decrease in PIMs, the number of PPOs according to the STOPP/START criteria version 2 did not significantly decrease by the intervention or usual care. However, there was a trend towards less PPOs after the intervention and usual care compared to baseline. This lack of significance could be attributed to the fact that the study was not powered for this outcome.

The input for the research physician using the STRIP Assistant was the SHiM, the medical history, blood pressure, heart rate and estimated glomerular filtration rate. The residents in both groups used information gathered during the CGA. Consequently, the residents had access to more information than the research physician who used the STRIP Assistant, such as complaints, expectations, previous (negative) experiences, and more physical and biochemical information. The residents in both groups identified PPOs additional to those identified by the research physician using the STRIP Assistant, possibly as a result of this extra information and the process of shared-decision-making. This underlines the importance of a clinical evaluation as part of a medication review.

The discrepancy between the recommended and implemented PPO, PIM and suboptimal dose changes can also be explained by the specific choices made by residents. For example, in a hypertensive patient on a low dose of an antihypertensive, both a dose increase (dose adjustment) and starting a new antihypertensive agent (PPO) can be advised.

A potential limitation of this study is that the control group contained more experienced residents, more residents specialising in geriatrics, and fewer residents specialising in nursing home medicine. This might have caused bias, since there may be a difference in willingness to implement recommendations and a difference in capability to identify inappropriate medication between more and less-experienced residents. Another potential limitation is the variable and small cluster size (median of three), which was determined by the number of patients per resident. Since the objective of this study was to measure the effect of the prescribing recommendations in clinical practice, we decided not to interfere with the working schedule of the residents and thereby accepting the variable and small cluster size.

Consensus-based instructions to standardise the prescribing recommendations were introduced during the study, which could have changed the intervention. However, the impact was negligible. When the groups were analysed for the 2 different periods (before and after standardisation) the difference between the control group and the intervention group persisted without a significant difference between the intervention group before and after the standardisation.

While both the research physicians and residents could have gained experience in generating prescribing recommendations, this learning effect over time was expected to be similar in the two groups. Although residents from the intervention group were instructed not to discuss the prescribing recommendations with colleagues, there might have been contamination of the control group due to joined care for other patients with residents from the intervention group. However, this contamination is considered to be minor since most residents worked for only three to four months at our centre. Furthermore, the number of resident-implemented recommended PPO and PIM changes did not increase during the participation of the residents in the study.

Lastly, the STRIP Assistant generates prescribing recommendations according to STOPP/START version 1, which is not the most recent version at the moment. However, by the time of patient inclusion, this version was the most recent available version.

This study showed that prescribing recommendations generated with the use of the STRIP Assistant resulted in more appropriate prescribing at a preoperative geriatric outpatient clinic. Therefore, we recommend the use of a CDSS, such as the STRIP Assistant, by the attending health care professional in clinical practice. Additionally, this study underlines the importance of clinical evaluation and judgement as part of a medication review. Further research should focus on the effect of prescribing recommendations on clinical, patient-reported and economic outcomes.

DECLARATIONS

Authors' contributions

All authors certify that they have participated sufficiently in the work to take public responsibility for the content. Study concept and design: **CJAH**, MNB, IW, WK, MHE. Data acquisition: MNB, **CJAH**, ACD. Analysis and/or interpretation of data: MNB, **CJAH**, IW, WK. Drafting the manuscript: MNB. Revising the manuscript critically and approval of the final version: all authors. We have not received substantial contributions from non-authors.

Competing interests

The author(s) declare that they have no competing interests.

Data availability statement

All data relevant to the study are included in the article or uploaded as online supplementary information.

Ethics approval

The Research Ethics Committee of University Medical Centre Utrecht confirmed that the Medical Research involving Human Subjects Act was not applicable to this study, and a waiver was granted.

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Intervention protocol: OPtimising thERapy to prevent avoidable hospital Admission in the Multi-morbid elderly (OPERAM):

A structured medication review with support of a computerised decision support system

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ABSTRACT

Background: Several approaches to medication optimisation by identifying drug-related problems in older people have been described. Although some interventions have shown reductions in drug-related problems (DRPs), evidence supporting the effectiveness of medication reviews on clinical and economic outcomes is lacking. Application of the STOPP/START (version 2) explicit screening tool for inappropriate prescribing has decreased inappropriate prescribing and significantly reduced adverse drug reactions (ADRs) and associated healthcare costs in older patients with multi-morbidity and polypharmacy. Therefore, application of STOPP/START criteria during a medication review is likely to be beneficial.

Incorporation of explicit screening tools into clinical decision support systems (CDSS) has gained traction as a means to improve both quality and efficiency in the rather time-consuming medication review process. Although CDSS can generate more potential inappropriate medication recommendations, some of these have been shown to be less clinically relevant, resulting in alert fatigue. Moreover, explicit tools such as STOPP/START do not cover all relevant DRPs on an individual patient level. The OPERAM study aims to assess the impact of a structured drug review on the quality of pharmacotherapy in older people with multi-morbidity and polypharmacy. The aim of this paper is to describe the structured, multi-component intervention of the OPERAM trial and compare it with the approach in the comparator arm.

Method: This paper describes a multi-component intervention, integrating interventions that have demonstrated effectiveness in defining DRPs. The intervention involves a structured history-taking of medication (SHiM), a medication review according to the systemic tool to reduce inappropriate prescribing (STRIP) method, assisted by a clinical decision support system (STRIP Assistant, STRIPA) with integrated STOPP/START criteria (version 2), followed by shared decision-making with both patient and attending physician. The developed method integrates patient input, patient data, involvement from other healthcare professionals and CDSS-assistance into one structured intervention.

Discussion: The clinical and economical effectiveness of this experimental intervention will be evaluated in a cohort of hospitalised, older patients with multi-morbidity and polypharmacy in the multicentre, randomised controlled OPERAM trial (OPtimising thERapy to prevent Avoidable hospital admissions in the Multi-morbid elderly), which will be completed in the last quarter of 2019.

BACKGROUND

The global population aged over 65 years is rapidly increasing such that by 2060 approximately one-third of the European population is projected to be over 65 years.[1] In this ageing population, there is a higher prevalence of multi-morbidity, which is in turn associated with greater mortality[2], decreased quality of life (QoL) and increased number of hospital admissions.[3] Moreover, these patients are frequently exposed to multiple medications in the context of their multi-morbidity i.e. multiple chronic diseases usually engender multiple prescriptions, also known as polypharmacy. Although polypharmacy has several definitions, the most broadly accepted is that of the concurrent use of ≥5 medications.[4] Polypharmacy in older patients has been repeatedly shown to result in negative consequences such as increased healthcare costs, adverse drug reactions (ADRs), adverse drug-drug interactions (DDI) and drug-related hospital admissions.[5-7] Importantly, the risk of either ADR or DDI occurrence increases with the number of medications prescribed.[8,9] Despite this, a recent study demonstrated that across specific European countries, the issue of problematic polypharmacy has not been widely addressed.[10]

Several different approaches to optimise prescription medication in older people have been reported.[11,12] In spite of a general lack of evidence for their significant impact on health-related outcomes, a Cochrane review did find that one particular approach was beneficial in reducing inappropriate polypharmacy[13], i.e. the novel geriatric-specific inappropriate prescribing criteria called Screening Tool of Older Persons' Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START).[14] The first of a series of 5 randomised controlled trials (RCTs) using the STOPP/START criteria as an intervention demonstrated that the use of these criteria significantly improved prescribing appropriateness up to 6 months after discharge in a cohort of older, hospitalised patients.[9] Further refinements to the criteria resulted in the publication of STOPP/START version 2[15] and subsequent studies have shown that application of STOPP/START criteria can reduce both the incidence of ADRs and medication costs in older, hospitalised patients.[16,17] Application of the STOPP/START version 2 criteria into a structured medication review process is defined as the Systematic Tool to Reduce Inappropriate Prescribing (STRIP).[18]

More recently, the European Commission and Swiss Government-funded OPERAM (OPtimising thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly) project was established based on the use of the STRIP medication review. The STRIP process encompasses the use of a customised software-based tool known as the STRIP Assistant (STRIPA), which was developed to support healthcare professionals

to perform the STRIP medication review process. The STRIPA process then generates a report with prescribing recommendations addressing potentially inappropriate prescribing (PIP) or potential prescribing omissions (PPOs).[19]

STRIPA consists of four main components, i.e. functional architecture, user interface, decision rule engine, and semantic interoperability.[20] For the purpose of the multicentre OPERAM trial, the STRIPA software was translated into four languages; English, German, French and Dutch.

Integration of STOPP/START criteria into a standalone web-based clinical decision support system (CDSS) could improve the detection of inappropriate prescribing. A recent review has demonstrated that computerized interventions can significantly decrease PIP in hospitalised older adults, although the authors highlight that larger scale multinational RCTs are needed to support this contention.[21] Interestingly, other studies that investigated the benefits of medication review software based on clinical tools such as STOPP/START confirm the high identification rate of PIP, but address the fact that this can result in less clinically relevant recommendations being made.[22] Furthermore, it has been shown that the majority of DRPs identified during medication review may not be associated with the STOPP/START criteria.[23] Taken together, these results suggest that the application of STOPP/START alone does not adequately detect all drug-related errors and that consequently a more complex intervention is necessary to optimise the medication review process. Therefore, a structured assessment, including a patient interview that identifies health and medication issues, combined with a medication review facilitated by a CDSS and evaluated by trained healthcare professionals, could potentially identify the most relevant drug-related problems. The aim of the OPERAM study is to assess the impact of a structured drug review utilising the STRIP method, including STRIPA software, on the quality of pharmacotherapy and whether such optimisation of pharmacotherapy in older people can reduce the number of drug-related hospital admissions in older patients with multi-morbidity and polypharmacy hospitalised previously (i.e. at enrolment into OPERAM).[24] The trial protocol has been described elsewhere;[25] the aim of this report is to describe the structured, multicomponent intervention and compare it with the approach in the comparator arm (see **Figure 1**: Flowchart of STRIP and STRIPA intervention process). This protocol has been written in line with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) recommendations (see Additional File 1).

METHODS AND DESIGN

Intervention arm: the STRIP intervention as performed in OPERAM

***Step 1**: Structured History-taking of Medication (SHiM)*

In order to optimise patients' pharmacotherapy during their hospital stay, their medication lists have to be as accurate as possible at the point of arrival. Several studies have shown that older patients' medication lists on admission to hospital significantly differ from what they actually take at home.[26–29] These differences can be of clinical significance, causing adverse drug events (ADEs) or patient harm[30,31] and older patients are particularly at risk from these events.[32] Medicines reconciliation as an intervention has repeatedly been shown to reduce medication discrepancies and to improve the accuracy of medication lists[26,29], although there is no clear consensus on the most accurate method of carrying out medicines' reconciliation. Different sources for obtaining information on medication history include letters from referring physicians, community pharmacy dispensing lists and patients' own medications, although none of these methods is completely accurate when taken in isolation and the use of several sources is recommended.[31] To address this problem, the Structured History-taking of Medication (SHiM) was devised by Spee and colleagues[33] who developed a 21-item questionnaire that can be used to fully interrogate a patient's current medication use (including non-prescription medications), patient's attitudes and beliefs towards their own medication regime, any perceived barriers to medication use as well as any known medication allergies or intolerances.[28] Application of the SHiM has been shown to successfully detect discrepancies in medication lists in up to 92% of patients being admitted to hospital, reducing potential patient harm as a result of addressing these errors.[28,34]

In OPERAM, a SHiM assessment is conducted for all intervention patients, either with the patients themselves or their next-of-kin in the case of patients with cognitive impairment, typically between 24 and 72 h after inclusion in the trial. It is completed by a trained researcher (pharmacist, physician or nurse) and is performed separately to the routine clinical history-taking which is completed on admission by a member of the attending medical team. In OPERAM, a modified version of the SHiM is used, which has removed the final 7 questions from previously described versions[28] (see **Table 1**. Questions in the modified SHiM used in the OPERAM trial). In addition to the SHiM, at least one other source is consulted. Preferably, a complete medication dispensing list is obtained from the community pharmacy and/or the general practitioner (GP), or if not available, a list of medications on admission is taken from the patient's medical records or from the primary care physician's referral letter.

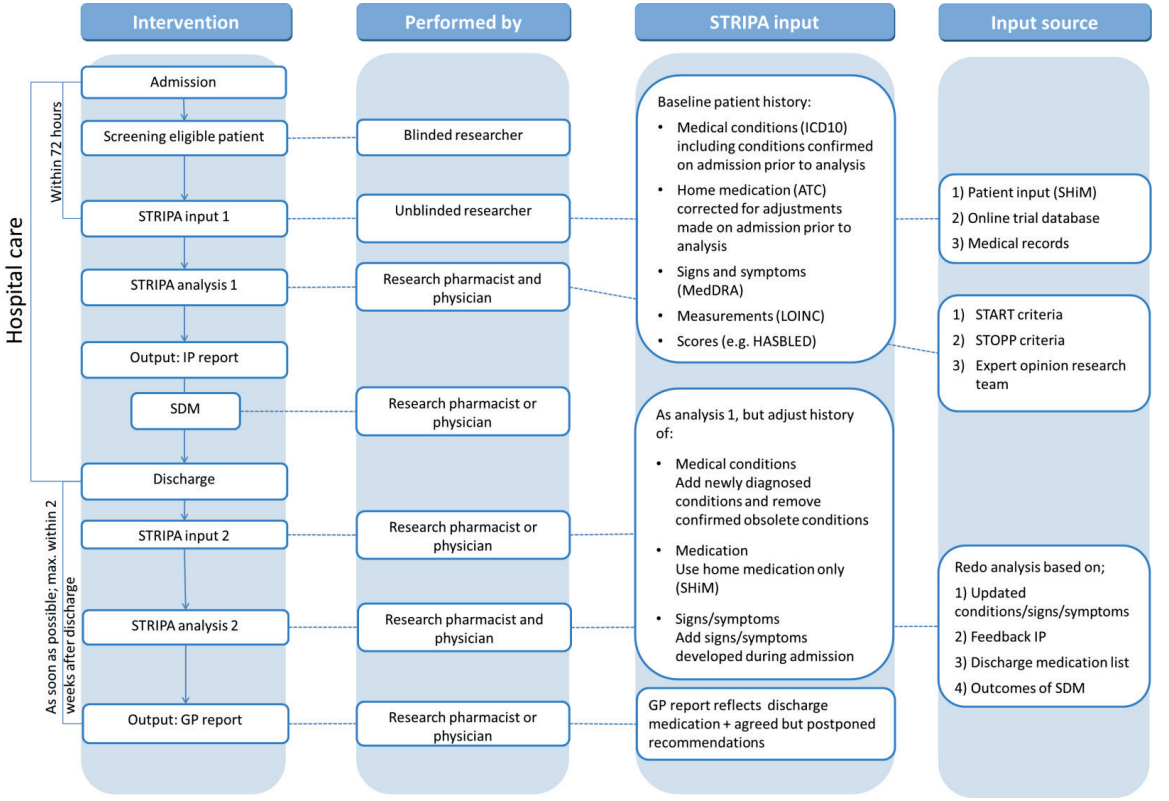


Figure 1: Flowchart of STRIP and STRIPA intervention process.

Abbreviations: STRIPA = Systematic Tool to Reduce Inappropriate Prescribing Assistant; SDM = shared decision making; IP = internal physician; ICD-10 = International Statistical Classification of Disease and related Health Problems, 10th revision; ATC = Anatomical Therapeutic Chemical; LOINC = Logical Observation Identifiers Names and Codes; SHiM = structured history-taking of medication; GP = general practitioner

Table 1 Questions in the modified SHiM used in the OPERAM trial

Questions on individual drug level
1. Are you using this drug as prescribed? (dosage, dose frequency and dosage form)
2. If not, what is the reason for deviating (from dosage, frequency or form) or not taking the drug at all?
3. Are you experiencing any side-effects from taking this drug?
Questions on a general level
4. Are you using any other prescription drugs that are not mentioned on this list?
5. Are you using non-prescription drugs?
6. Are you using homeopathic drugs or herbal medicines?
7. Are you using drugs that belong to family members or friends?
8. Are you using any 'as needed' drugs?
9. Are you using drugs that are no longer prescribed?
10. Do you have any drug allergies?
11. Do you have any drug intolerances?

***Step 2**: Clinical Decision Support System with integrated STOPP/START (STRIPA)*

The pharmaceutical analysis within the OPERAM trial is carried out by a trained research physician and a trained research pharmacist in mutually supportive roles assisted by the STRIPA software. STOPP/START criteria (version 2) were converted into clinical rules though an extensive, multi-disciplinary process, and these rules were then incorporated into the stand-alone CDSS to assist clinicians in detection of PIP and PPOs. However, suggestions can also be manually entered based on expert opinion by the trained research physician or pharmacist. Within STRIPA, the patient demographic data are entered anonymously, and baseline data including details of age, gender and race are recorded. Race is entered as either black or non-black for the sole purpose of calculating the estimated Glomerular Filtration Rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[35,36]

The patient's clinical data are then entered as medical conditions using the International Statistical Classification of Disease and related Health Problems, 10th revision (ICD-10) codes, current medications as Anatomical Therapeutic Chemical (ATC; level 5) codes and measurements such as blood pressure, bone mineral density and laboratory values using Logical Observation Identifiers Names and Codes (LOINC) codes. The different steps taken during data entry and analysis will now be described in greater detail.

Data entry

After entering the baseline patient characteristics, the patient's medical data are entered in five sequential steps:

(1) All relevant medical conditions (either chronic or acute) are entered using ICD-10 codes. Surgical interventions not requiring (current) medical treatment are not considered for data input. Coronary artery stent deployment, for example, is entered as this treatment requires antiplatelet therapy for 6– 12 months. For some medical conditions, the date of onset is important and this can also be entered during this step.

(2) All current medications are entered (including those upon admission) at ATC-5 level (generic drug names), including frequency and route of administration. This may differ from the patient's home medication. Additionally, drugs with a long-term indication that have been withheld upon admission due to the specific nature of the patient's presenting illness are included, as their re-initiation after hospitalization is likely.

(3) All patient-reported signs and symptoms are entered. They are either elicited from the patient during SHiM or found in the medical records or in the laboratory results. A predefined list of signs and symptoms present in START and STOPP criteria in the form of checkboxes is available in STRIPA, and includes for example constipation, dizziness, blurred vision and ankle oedema, among others. Other signs or symptoms can be entered manually and then selected from the Medical Dictionary for Regulatory Activities (MedDRA) database, a medical dictionary developed by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), integrated with STRIPA.

(4) All available vital and laboratory measurements are reviewed. However, only those parameters present within one or more of the STOPP and START criteria are available within STRIPA. These can either be entered manually or selected from the predefined list of parameters present.

(5) The final step in the data entry process comprises different measurements, specifically the HAS-BLED score[37], clinical parameters such as urea and electrolyte values, heart rate and blood pressure, patient height and weight as well as the pneumococcal and influenza vaccination status. Additionally, allergies and ADRs can be entered here as plain text.

STRIPA analysis

The pharmaceutical analysis consists of six steps, according to the Prescribing Optimisation Method[38], at the end of which a report with prescribing recommendations is generated. These steps are as follows:

(1) Assignment of medication to the recorded diagnoses: the STRIPA user assigns all the entered medications to the present ICD-10 codes representing the patient's medical conditions (see **Figure 2:** Screenshot of STRIPA process during which medications are assigned to relevant medical conditions). This can be achieved by 'dragging' the medications by screen cursor on the 'right side' of the screen to the corresponding indicated medical condition on the 'left side' of the screen. Where no appropriate indication for a medication is present, this medication can be assigned to ICD-10 code 'R69- unknown and unspecified causes of morbidity', i.e. a so-called 'dummy condition'.

(2) Screening for under-treatment: during this step, the entered medications and medical conditions are checked for under-treatment according to START criteria (see **Figure 3:** A screenshot of triggered START criteria). All medications assigned to a medical condition are evaluated, regardless of the specific medical condition they were assigned to. For instance, where an ACE inhibitor is assigned to hypertension instead of heart failure, START rule A6 ("Angiotensin Converting Enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease") will not be triggered as the ACE inhibitor is already present in the medication list. The intervention team will evaluate all generated START rules on their appropriateness for a specific patient by either accepting or rejecting the advice. In the event of a rejected recommendation, the reasons for rejection are not recorded within the STRIPA software. When a START recommendation is accepted, the user can choose any medication on an ATC-5 level, including preferred dose, within the advised class from a drop-down menu. This drug is then automatically assigned to the medical condition triggering the rule. When more than one criterion is triggered advising the same drug (or drug class), the best matching criterion is chosen by the intervention team and the others are then automatically disabled. At the end of this step, the updated medication list is evaluated for potential under-treatment not highlighted in START criteria, but considered relevant according to the STRIPA software user. In such cases, these drugs can be manually added to the designated medical condition and will appear on the final advice report as 'expert opinion' instead of triggered by START criteria.

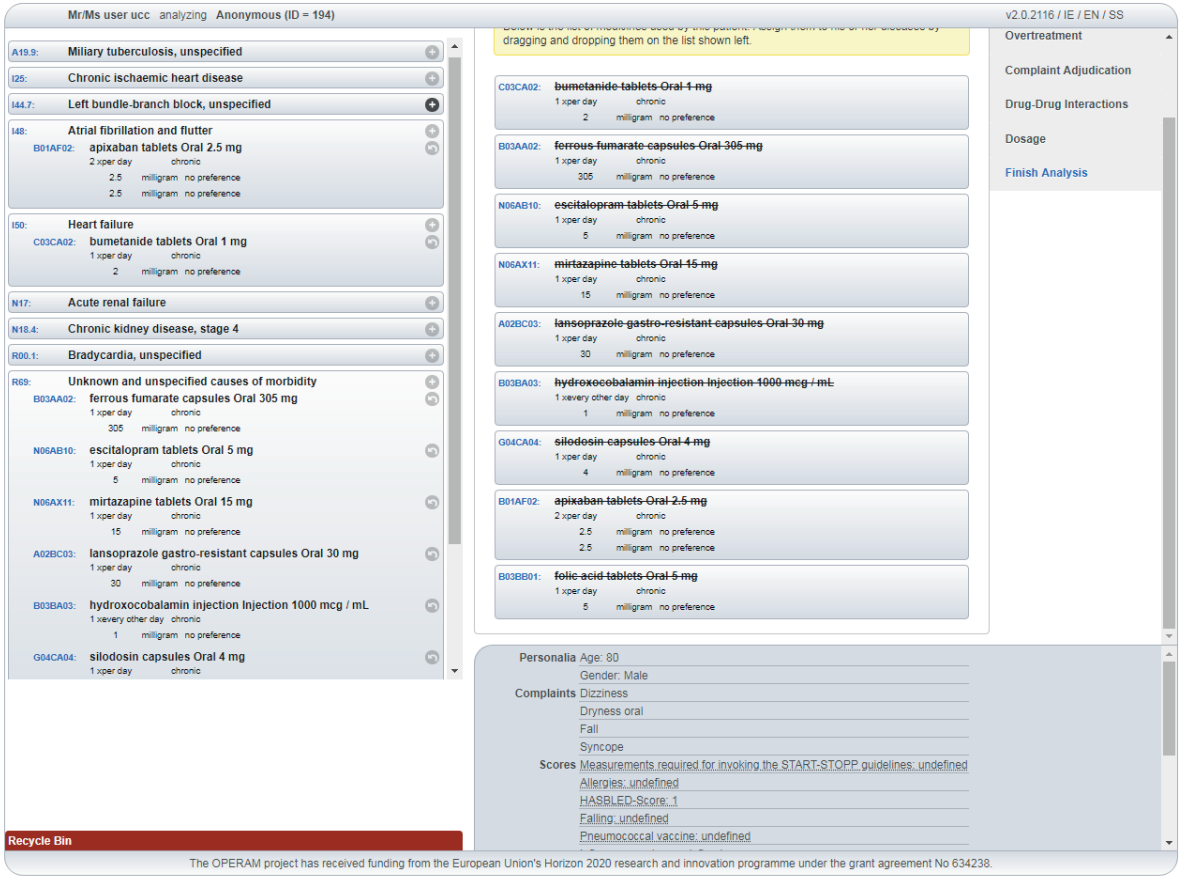


Figure 2: Screenshot of STRIPA process during which medications are assigned to relevant medical conditions

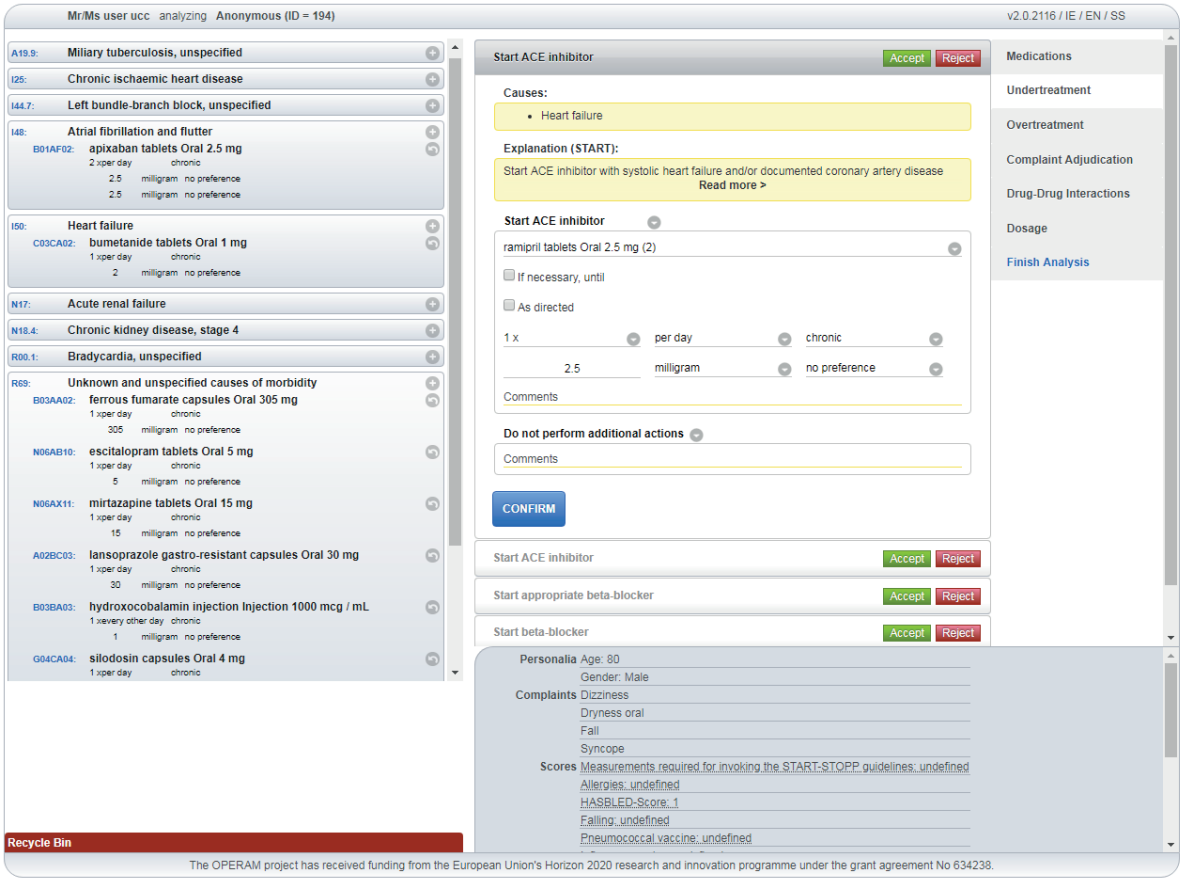


Figure 3: A screenshot of triggered START criteria

(3) Screening for over-treatment: this step involves evaluation of over-treatment according to STOPP criteria. All medications including those initiated in the prior step are evaluated based on the medical conditions and known biomedical parameters and symptoms or complaints. During this step, the newly initiated medications, including START criteria-based recommendations accepted during the previous step, could also appear as STOPP recommendations. For example, in the previous step an ACE inhibitor was started according to START rule A6. However, due to the presence of hyperkalaemia, STOPP rule B11 ("ACE Inhibitors or Angiotensin Receptor Blockers in patients with hyperkalaemia") would then be triggered. The user decides whether these STOPP recommendations are relevant to the patient under review. If a recommendation is followed, the medication in question will then be removed from the recommended medications list. They will appear on the final report as 'medication advised to be stopped'. All medications that could not be assigned to an appropriate medical condition and have therefore been allocated the ICD-10 code 'R69' are considered potential overtreatment. Moreover, the STOPP criteria addressing impaired renal function and combinations with certain medications (e.g. digoxin and eGFR < 30 ml/min) will be triggered here, based on either entered eGFR values or an ICD-10 diagnosis of renal insufficiency. In addition to stopping medications, the user could also decide to recommend a dose adjustment (both manually and based on STOPP criteria).

(4) Medication-Disease Interactions (ADEs): this step encompasses the adjudication of clinical signs or symptoms entered which are based on the predefined list of symptoms and signs that may be attributable to medications or medical conditions. The software user, based on expert opinion, can assign symptoms and signs manually to medications and a drop-down menu with three possible actions appears: (A) The symptom/sign can be registered as 'side effect' of the concerning medication; (B) The medication can be either maintained, stopped or adjusted; (C) Adaptations to other drugs can be made including stopping, adjusting or starting new drugs. All assigned symptoms and signs will appear on the report linked to their possible causative medication.

(5) Medication-Medication Interactions: during the fifth step, the medication list will be checked for drug-drug interactions based upon the incorporated or local interaction database (dependent on licensing) within the software. If an interaction is identified, the user can again choose to act upon or ignore the prompt. An explanation about the interaction is present to assist the software user in this decision process. When a drug-drug interaction is addressed, the software user must decide which medication

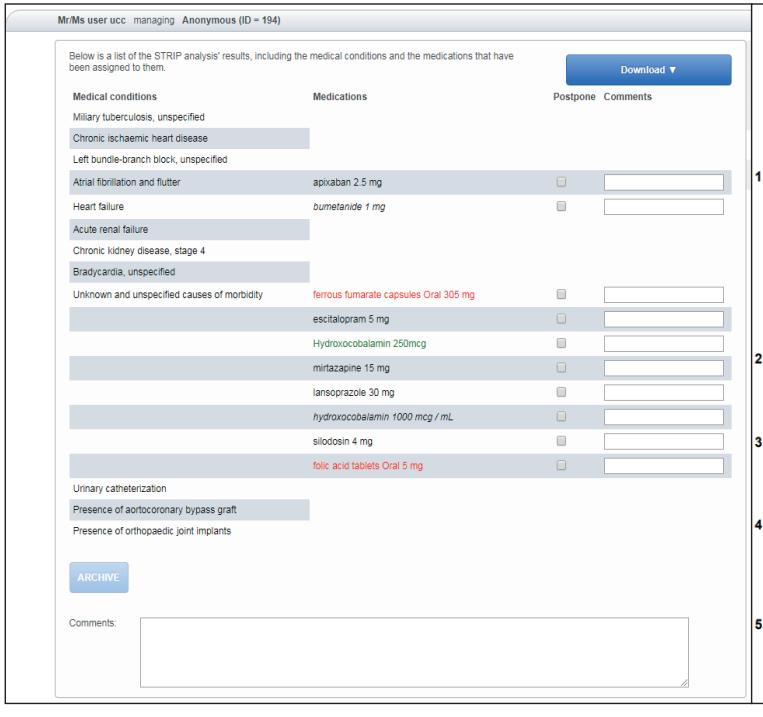
to maintain, stop or adjust. Also, other drugs from the medication list can be adapted here and a new medication can be initiated, for instance to replace one of the interacting medications.

(6) Dosage: the final step consists of dose adjustment recommendations based on the Dutch KNMP Kennisbank® database and the patient's calculated eGFR. When a recommendation is acted upon, the software user can choose to maintain, stop or adjust the concerned medication and/or take other actions including adjustment of other medications in the list or starting a new medication.

After completing the steps above, the analysis is finalized. All choices made are then saved within the STRIPA system and tracked in the background. However, the different steps of the analysis can be revisited at all times, if necessary. When the analysis is considered complete, an overview of all the adaptations to the medication list can be viewed in the 'advice tab'. Here, all suggested medications to be discontinued are shown in red, newly started medications are in green and manually adjusted medications appear in italics. The medications are still linked to the corresponding medical condition and will appear correspondingly on the report. In the advice tab, the user can manually adapt the plain text of both medical conditions and medications to enhance the final report presented to the patient's prescribing (internal) physician (see **Figure 4:** The internal physician report: (A) final screen in the STRIPA process, and (B) completed report). This will not affect the underlying ATC and ICD-10 codes saved in the STRIPA track. Furthermore, comments on the recommendations (other than explanations of STOPP and START criteria which will appear on the report regardless) can be added by the user according to each proposed medication change in order to convince the prescribing physician to follow the advice or to emphasize the importance of the recommendation. Moreover, recommendations can be deferred to the patient's primary care physician when they are not deemed appropriate to the current acute clinical situation. Lastly, a general comment box exists where the software users can enter extra information or considerations regarding the recommendation or general points of attention relevant to this patient.

After all adaptations are made, the report known as the 'internal physician report' (see Fig. 4b. The internal physician report: (A) final screen in the STRIPA process, and (B) completed report) can be downloaded and printed for discussion with the prescribing hospital physician.

A



B

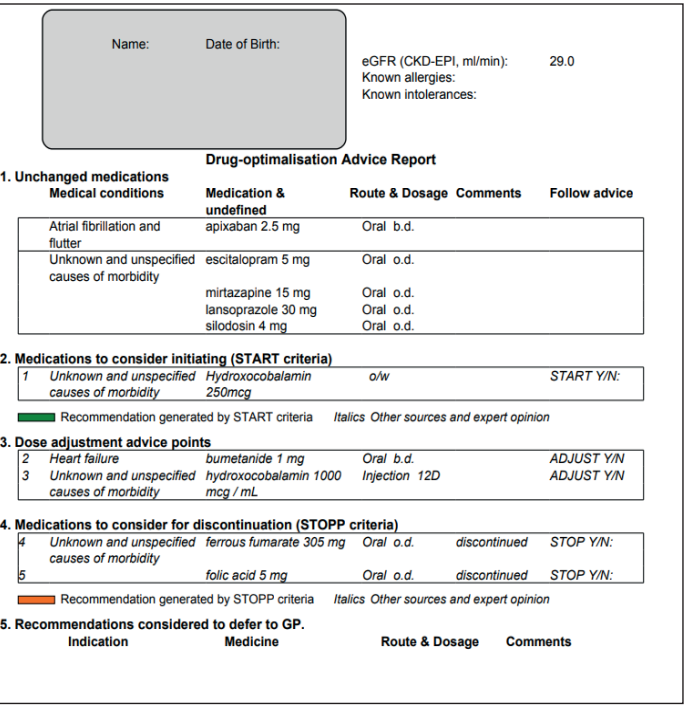


Figure 4: The internal physician report: (**A**) final screen in the STRIPA process, and (**B**) completed report

Step 3: Communication and discussion of the STRIPA report with the prescribing physician
After the first analysis has been conducted and the prescribing physician report is complete, the research pharmacist and research physician contact the prescribing physician and discuss the implementation of the STRIPA-generated recommendations. The objective is to incorporate the prescribing recommendations with the insight that the prescribing physician can provide with regards to the overall functional capacity of the patient to reach a consensus about the recommendations that should be implemented to prevent both ADRs during the hospital stay, and later drug-related readmissions (i.e. the primary endpoint of the OPERAM trial).

Step 4. Shared-decision making with the patient
Subsequently, once consensus has been reached between the researchers and the prescribing physician, the process of shared decision-making (SDM) can take place if the prescribing physician has identified preference sensitive decisions with regard to stopping, starting, continuing or selecting medications for discussion with the patient. SDM has been defined as *"an approach where healthcare professionals and patients share the best available evidence when faced with making decisions regarding healthcare, and where patients are supported to consider options to achieve informed preferences"*.[39] This process addresses patients' autonomy and promotes patient engagement,[39] and it has repeatedly been shown to play an integral role in a successful de-prescribing of harmful drugs.[40-42]

The model for SDM has previously been described elsewhere.[43] Briefly, it is centred around 4 main principles i.e. 'choice talk', 'option talk', 'preference talk' and 'decision talk'.[43] All patients, in particular patients with cognitive impairment, should be facilitated to have another relevant person (e.g. close family member) present when making any decisions in the SDM process. Collectively, the research team and the patient agree on definitive medication changes to be made and then proceed to develop a pharmaceutical care plan. Changes after the SDM process are communicated to the prescribing physician, and in some cases, the SDM can be deferred to the patient's GP; if so, this is documented on the GP information letter, as will be discussed in the next section.

Step 5: Discharge and the GP information report
Once recommendations are agreed between the research team, the prescribing physician and the patient, the changes to the patient's medications are entered into STRIPA and a report known as the "GP report" is generated. Where the prescribing physician has accepted STRIPA recommendations, these recommendations are included in the GP report. Where the prescribing physician has made changes unrelated to STRIPA, these changes are entered manually. In cases where SDM is deferred to the GP, instructions for

the GP are written by either the research physician or research pharmacist in the section of the GP report entitled "recommendations not yet applied during hospitalization". The GP report should then be identical to the patient's discharge prescription, and is mailed to the GP after the patient is discharged from hospital.

Control arm and SHAM intervention

Patients in the control group receive usual care, with the potential of a medication review by the prescribing physician in accordance with usual pharmaceutical care. Patients from both groups complete the 8-item Moriskey Medication Adherence Scale questionnaire (MMAS-8)[44] with a trained member of the intervention team. This is to prevent potential unblinding in the event of unblinded team members approaching patients when attending patients' wards.

Device deficiency

Due to a software tool being used in this trial, there is the potential for a so-called device deficiency, defined by the European Medical Device Vigilance System (MEDDEV) 2.7/3 as an "Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance.[45] This may include malfunctions, use error, or inadequacy in the information supplied by the manufacture." All technical problems with the STRIPA system are reported, using the designated STRIPA feedback form, within 24h to the software developers, who then assess whether the problem in question is a possible device deficiency. They will then report back within 72h to the clinical site in question with details of the investigation of the issue and determine any actions to be taken. If corrective actions are required at all sites, all co-Principal Investigators (PIs) including the co-ordinating PI are informed within another 48h.

Safety section

The STRIPA software provides general recommendations and is not intended to impose firm decisions. It does not replace decision-making and clinical judgements made by physicians and pharmacists and this is explicitly stated in the disclaimer on the printed reports. It is expected that prescription recommendations made by the STRIPA system that turn out to be inappropriate for an individual patient are detected by a pharmacist or physician conducting the intervention and addressed appropriately to safeguard patients' welfare. The prescribing physicians remain responsible for all final medical decisions concerning their patients.

DISCUSSION

ADRs, which are particularly likely to occur during acute hospital admission, cause significant morbidity in older patients and contribute to increased healthcare costs.[4,5] ADRs are common in older multi-morbid patients and often lead to acute hospitalization despite reports that approximately 50% of these drug-related admissions (DRA) are likely to be preventable.[7,46] Growing evidence indicates that optimising pharmacotherapy, through various interventional designs, mitigates inappropriate prescribing as well as the incidence of ADRs and associated costs in this high-risk patient population.[11,15,16] Although there is insufficient data to support the use of a single validated intervention, a recent review highlighted the value of several methods including close liaison between physicians and clinical pharmacists as well as the use of implicit and explicit prescribing criteria such as STOPP/START.[11] A particular strength of the OPERAM trial is its novelty, i.e. it is one of the first computerised interventions designed to incorporate a structured medication review to look at potentially inappropriate prescribing and potential prescribing omissions in older hospitalised patients, and assesses whether it reduces drug-related hospital admissions. It also recognises the importance of the identification of patient-reported clinical signs and symptoms that may be related to PIP. Moreover, it relies on multidisciplinary input and collaboration between physicians and pharmacists and clear communication of prescribing information with GPs, which will likely increase the impact of prescribing recommendations on patient care. Finally, the SDM process allows for greater emphasis to be placed on a patient-centred approach, encouraging patient engagement with their own healthcare. The integration of multiple interventions that have demonstrated benefit is anticipated to have a synergistic effect on pharmacotherapy quality. The study can also demonstrate the feasibility of a multi-component intervention in a hospital environment. A key strength of the OPERAM trial will be its demonstration of feasibility in differing healthcare environments of the EU and non-EU countries. The OPERAM trial will also analyze the intervention from a health economics perspective and will allow for the determination of the benefit that the intervention can provide to society in general through a reduction in healthcare expenditure. Recruitment for the OPERAM trial began in December 2016 and finished in October 2018. Trial follow-up will be completed in October 2019 and trial results are expected in the first quarter of 2020.

DECLARATIONS

Authors' contributions

EKC, BTGMS, **CJAH**, KDM, EM, AL, MF, NS, LA made substantial contributions to the design of the intervention. MS and ZS were involved in the creation of software used in the intervention. **CJAH** en BTGMS developed en tested the algoritms used for the CDSS in the clinical trial and EKC, BTGMS, **CJAH**, KDM, WK, SB, and DOM have drafted the work or substantively revised it. All authors have approved the submitted version and have agreed to be personally accountable for their own contributions. We have not received substantial contributions from non-authors.

Competing interests

The author(s) declare that they have no competing interests.

Data availability statement

Data will be deposited in the Bern Open Repository and Information System (BORIS) (www.boris.unibe.ch). BORIS allows searching and is indexed by search engines. All items are stored with a unique Digital Object Identifier (DOI) that can be referenced in respective publication. The whole study database will be in csv format, and will include README files, metadata, information about the performed processing and analytical steps, variable definitions, and references to vocabularies used to help secondary users to understand and reuse the data. Data will only be shared upon request. Data use proposals will be evaluated by the OPERAM publication committee. The data is owned by the sponsor-investigators. In case of data sharing, a data-sharing agreement between the external party and the sponsor-investigator will need to be agreed on and signed.

Ethics approval

The OPERAM study received ethical approval from the following ethics committees:

- Belgium: Comité d'éthique hospitalo-facultaire cliniques universitaires SaintLuc UCL Bruxelles
- Ireland: Clinical Research Ethics Committee of the Cork Teaching Hospitals
- Netherlands: Medisch Ethische Toetsingscommissie Utrecht
- Switzerland: Kantonale Ethikkomission Bern

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(SERI) under contract number 15.0137. The opinions expressed and arguments employed herein are those of the authors and do not necessarily reflect the official views of the EC and the Swiss government. Trial management, recruitment, analysis, and publication were independent of the funding bodies.

Informed consent

Written consent was obtained from patients participating in the OPERAM trial and written consent was obtained from a patient's next-of-kin for participating patients with cognitive impairment.

Trial registration

Universal Trial Number: U1111-1181-9400 Clinicaltrials.gov: NCT02986425, Registered 08 December 2016. FOPH (Swiss national portal): SNCTP000002183. Netherlands Trial Register: NTR6012 (07-10-2016).

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Frequency and acceptance of clinical decision support system-generated STOPP/START signals for hospitalised older patients with polypharmacy and multimorbidity

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ABSTRACT

Background: The Screening Tool of Older Persons' Prescriptions (STOPP)/Screening Tool to Alert to Right Treatment (START) instrument is used to evaluate the appropriateness of medication in older people. The STOPP/START criteria have been converted into software algorithms and implemented in a clinical decision support system (CDSS) to facilitate their use in clinical practice.

Objective: To determine the frequency of CDSS-generated STOPP/START signals and subsequent acceptance by a pharmacotherapy team in a hospital setting.

Design and methods: Hospitalised older patients with polypharmacy and multimorbidity allocated to the intervention arm of the OPtimising thERapy to Prevent Avoidable Hospital Admissions in the Multimorbid Elderly (OPERAM) trial received a CDSS-assisted structured medication review in four European hospitals. We evaluated the frequency of CDSS-generated STOPP/START signals and the subsequent acceptance of these signals by a trained pharmacotherapy team consisting of a physician and pharmacist after evaluation of clinical applicability to the individual patient, prior to discussing pharmacotherapy optimisation recommendations with the patient and attending physicians. Multivariate linear regression analysis was used to investigate potential patient-related (e.g. age, number of co-morbidities and medications) and setting-related (e.g. ward type, country of inclusion) determinants for acceptance of STOPP and START signals.

Results: In 819/826 (99%) of the patients, at least one STOPP/START signal was generated using a set of 110 algorithms based on STOPP/START v2 criteria. Overall, 39% of the 5080 signals were accepted by the pharmacotherapy team. There was a high variability in the frequency and the subsequent acceptance of the individual STOPP/START criteria. The acceptance ranged from 2.5% to 75.8% for the top ten most frequently generated STOPP and START signals. The signal to stop a drug without a clinical indication was most frequently generated (28%), with more than half of the signals accepted (54%). No difference in mean acceptance of STOPP versus START signals was found. In multivariate analysis, most patient-related determinants did not predict acceptance, although the acceptance of START signals increased in patients with ≥1 hospital admissions (+7.9 [95% CI 1.6-14.1]) or ≥1 falls in the previous year (+7.1 [95% CI 0.7-13.4]). A higher number of co-morbidities was associated with lower acceptance of STOPP (-11.8% [95% CI, -19.2 to -4.5]) and START signals (-11.0% [95% CI -19.4 to -2.6]) for patients with >9 and 7-9 co-morbidities, respectively. For setting-related determinants, the acceptance differed significantly between the participating trial sites. Compared to

Switzerland, the acceptance was higher in Ireland (+26.8% [95% CI 16.8-36.7] for STOPP; +31.1% [95% CI 18.2-44.0] for START) and the Netherlands (+14.7% [95% CI 7.8-21.7] for STOPP). Admission to a surgical ward was positively associated with acceptance of STOPP signals (+10.3% [95% CI 3.8-16.8]).

Conclusion: The involvement of an expert team in translating population-based CDSS signals to individual patients is essential, as more than half of the signals for potential overuse, underuse and misuse were not deemed clinically appropriate in a hospital setting. Patient-related potential determinants were poor predictors of acceptance. Future research investigating factors that affect patients' and physicians' agreement with medication changes recommended by expert teams may gain further insights relevant for implementation in clinical practice.

BACKGROUND

Polypharmacy poses an increasing challenge in health care and is largely driven by the steadily growing multimorbid elderly population and prescribers' adherence to single-disease oriented guidelines.[1] Polypharmacy is, as a negative by-product of the benefits of pharmacotherapy, associated with an increased risk of negative health outcomes, such as adverse drug events, falls, decline in cognitive function, hospitalisation and even death, especially in frailer older people.[2] Therefore, the potential benefits should outweigh the potential risks of pharmacotherapy for each patient, and this balance should be evaluated both on treatment initiation and regularly during long-term follow-up through medication review.

Explicit screening tools, such as the Screening Tool of Older Persons' Prescriptions (STOPP) and the Screening Tool to Alert to Right Treatment (START), have been developed to facilitate the detection of potentially inappropriate prescribing in the process of regular medication review in older people.[3-6] Research has shown that the use of STOPP/START criteria in patient care can lead to a reduction of polypharmacy, inappropriate prescribing and adverse drug reactions.[5,6] However, application of STOPP/START v2 – which comprises 114 criteria – is time-consuming, which hampers its use in everyday clinical practice.[7] Hence, STOPP/START criteria v2 were converted into software algorithms that can be implemented into a clinical decision support system (CDSS) to facilitate their application.[8,9]

A recent systematic review concluded that the use of CDSS-generated signals is likely to reduce potentially inappropriate prescriptions in older patients. However, studies reported adherence values to these signals by clinicians ranging from 33%-55%.[10] Too many irrelevant signals can result in alert fatigue and inappropriate alert overrides, impeding the effectiveness of CDSS in clinical practice.[11,12] The STOPP/START criteria are *population-based* recommendations to detect medication overuse, misuse (STOPP) and underuse (START) and require clinicians' careful consideration concerning their applicability to *individual* patients. Investigating the relevance of CDSS-assisted detection of potential medication overuse, underuse and misuse by STOPP/START for individual patients in clinical practice is necessary to gain insight into the applicability of these population-based recommendations to individual patient care.

This study aimed to determine the frequency of CDSS-generated STOPP/START signals and subsequent acceptance by a pharmacotherapy team for use in individual hospitalised older patients with polypharmacy and multimorbidity. In addition, measurable determinants that may be associated with acceptance were investigated.

METHODS

Setting, design and study population

This study was embedded in the OPtimising thERapy to Prevent Avoidable Hospital Admissions in the Multimorbid Elderly (OPERAM) trial – a cluster-randomised controlled trial investigating the effect of a structured medication review on drug-related hospital admissions (DRAs). As previously described in detail, in-hospital patients were recruited from four hospitals in four countries (Switzerland, Belgium, Ireland, the Netherlands) and randomised to receive usual pharmaceutical care (control group) or a CDSS-assisted structured medication review (intervention group).[13] Inclusion criteria were age ≥ 70 years, multimorbidity (defined as ≥ 3 chronic conditions), and polypharmacy (defined as the use of ≥ 5 regular medications for over 30 days prior to admission). There were two exclusion criteria: 1) patients admitted to palliative care within 24 hours after hospital admission and 2) patients undergoing a structured medication review other than the trial intervention or having received a medication review during the two months preceding the index hospitalisation to reduce the risk of contamination bias. Both medical (e.g. internal medicine, cardiology, pulmonology, neurology) and surgical (e.g. general surgery, vascular surgery, orthopaedics, neurosurgery) wards were eligible for inclusion. However, geriatric wards were excluded to comply with the exclusion criteria, because medication optimisation was considered standard of geriatric care in all participating trial sites. The OPERAM trial was approved by the participating hospitals' medical ethics committees and registered under trial registration number NCT02986425.

In this study, OPERAM intervention patients for whom data from the in-hospital CDSS-assisted medication review were available, were included for analysis.

The structured medication review was conducted by a team of a physician and a pharmacist (hereafter pharmacotherapy team) who were trained by standardised operating procedures in all sites. The medication review was performed according to the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) method[14] and consisted of five consecutive steps:[15] 1) a structured history taking of medication use (SHiM)[16] and data entry of relevant and available patient information into the CDSS (i.e. current in-hospital medication list updated by information from SHiM, medical conditions, laboratory values, signs and patient-reported symptoms); 2) digitalised screening of the current medication list for medication over- and underuse by STOPP/START algorithms; 3) a pharmacotherapy analysis by the pharmacotherapy team who evaluated CDSS-generated signals for clinical applicability to each patient based on the patient's medical status. Accepted signals were translated into patient-specific medication optimisation

recommendations and presented on a feedback report in a standardised format; 4) discussion of the feedback report with both the attending physician and the patient; and 5) generating a discharge report for the patient's general practitioner, which included in-hospital medication changes and recommendations which were agreed upon by the attending physician and the patient but deferred to the general practitioner for implementation.

This research focused on the first three steps of the medication review process and ends at the stage of either acceptance or rejection of CDSS signals by the pharmacotherapy team that resulted in medication optimisation recommendations to be discussed with the attending physician and the patient, prior to the implementation of medication changes. All consecutive steps of the OPERAM intervention and the focus of this study (step 1-3) are summarised in **Figure 1**.

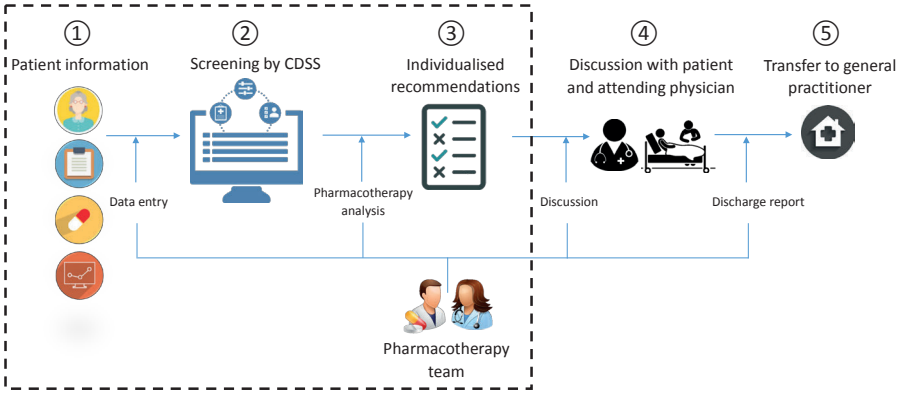

Figure 1. Summary of all consecutive steps (1–5) of the medication review within the OPERAM trial and the focus of this study: the acceptance of CDSS-generated STOPP/START signals by the pharmacotherapy team (steps 1–3) prior to discussion with the attending hospital physician and the patient. CDSS = clinical decision support system.

CDSS with integrated STOPP/START algorithms

The CDSS used for pharmacotherapy analysis was the STRIP Assistant (STRIPA), a web-based CDSS developed to perform a digitalised STRIP analysis with integrated STOPP/START criteria v2.[8,17] International coding systems were used for translating the STOPP/START v2 into algorithms, using the International Statistical Classification of Disease and related Health Problems, 10th revision (ICD-10) codes for diseases, the Anatomical Therapeutic Chemical (ATC) coding system for medication, the Logical Observation

Identifiers Names and Codes (LOINC) database for measurements (e.g. blood pressure, bone mineral density, laboratory values). The Medical Dictionary for Regulatory Activities (MedDRA) dictionary was used to register patient-reported symptoms (e.g. dizziness, fatigue).[9,15]

Seventy-nine out of 80 original STOPP criteria were encoded into algorithms. Only STOPP A2 *'any drug prescribed beyond the recommended duration, where treatment duration is well defined'* could not be converted into an algorithm. Thirty-four original START criteria were converted to 33 algorithms as START A1 (*'Start vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation'*) and START A2 (*'Start aspirin if START A1 is contraindicated'*) were merged into one algorithm (START A1/2). START I1 and I2 (*'Start influenza and pneumococcal vaccines'*) were excluded from analysis because CDSS custom settings differed per country for these two criteria based on national vaccination programmes. This resulted in a total of 110 STOPP/START algorithms available for analysis. Details of the CDSS and the intervention as performed in the OPERAM trial have been published previously.[15]

Outcomes

The primary outcome was the frequency and subsequent acceptance of CDSS-generated STOPP/START signals by the pharmacotherapy team **(Figure 1**, step 2–3). Frequency was defined as the number of population-based STOPP/START signals generated by the CDSS. Acceptance was defined as the percentage of STOPP/START signals accepted by the pharmacotherapy team after evaluation for clinical applicability to the individual patient. Accepted signals resulted in recommendations for the attending hospital physicians to initiate a drug based on START signals, or in recommendations to discontinue or reduce dosage (e.g. drug tapering of benzodiazepines, antidepressants) based on STOPP signals. Data regarding both the accepted and rejected STOPP/START signals by the pharmacotherapy team were saved within the CDSS and available for analysis. The mean acceptance – namely, the percentage of accepted STOPP and START signals on the individual patient's level – was used to investigate determinants that may affect signal acceptance.

Potential determinants

Signal type (STOPP vs START), patient-related factors and setting-related factors were investigated as potential determinants. Patient-related factors included gender, age, number of co-morbidities, number of medications, history of falls, history of hospital admissions, renal function, systolic blood pressure, and being housebound or not. Setting-related factors included ward type (medical vs surgical), admission type (elective vs non-elective), length of hospital stay and country of inclusion. Potential determinants

with continuous values were dichotomised or categorised into tertiles based on patient distribution or based on clinically accepted cut-off values for measurements (renal function <30 ml/min, 30-50 ml/min, >50 ml/min, systolic blood pressure <120 mmHg, 120-140 mmHg, >140 mmHg). Data on potential determinants were captured during the index hospitalisation in an electronic case report form (eCRF) for all OPERAM patients. The included potential determinants were selected after expert consensus and based on a potential relation with STOPP/START (e.g. falls – section STOPP K; renal function – section STOPP E, STOPP B7, START F1; systolic blood pressure – START A4, STOPP K3) and database availability.

Data analysis

Data analysis was performed with IBM SPSS Statistics v.25.0.0.2. An unpaired, two-sided student's t-test ($\alpha = 0.05$, $\beta = 0.2$) was used to test the difference in percentages of mean acceptance for STOPP vs START signals. The effect of patient- and setting-related determinants on mean acceptance was investigated separately for STOPP and START signals in a univariate linear regression analysis and entered in a multivariate linear regression model after examination of model assumptions.

RESULTS

Study population

A total of 2,008 patients were included in the OPERAM study, 963 of whom were assigned to the intervention group. Data on the CDSS-assisted structured medication review during hospital admission were incomplete for 137 (14.2%) intervention patients. The study population therefore consisted of 826 patients who underwent a structured in-hospital medication review as part of the OPERAM intervention (**Figure 2**).

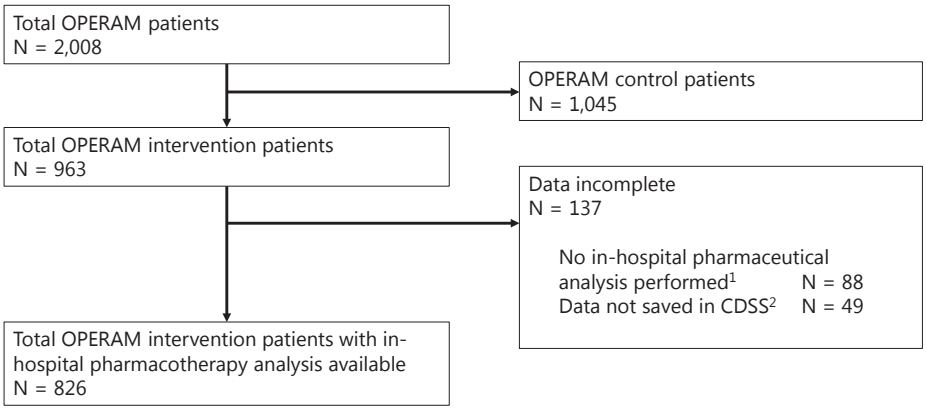

Figure 2. Flowchart of the study population.

[1]Reasons why no in-hospital pharmacotherapy analysis was performed in 88 (9%) of the OPERAM intervention patients were not collected on patient level but included: patient was discharged or transferred from ward, patient died, patient withdrew from study, other reasons. [2]The pharmacotherapy team had to actively save the results into the CDSS. Due to technical failure, results were not saved in the CDSS in 49 (5%) of the OPERAM intervention patients.

The distribution of patients among the four participating trial sites was 399 (48.3%), 132 (16.0%), 92 (11.1%) and 203 (24.6%) for Switzerland, Belgium, Ireland, and the Netherlands, respectively. The study population had a median age of 78 (IQR 74–84); the median number of co-morbidities was 11 (IQR 8–17), and the median number of medications was 10 (IQR 7–13). 8.4% of the study patients were nursing home residents, and the Barthel Index of Activities of Daily Living score[18] was high (median 95; IQR 75–100) (**Table 1**).

Table 1. Baseline characteristics of the study population.

	***N* = 826**
Age in years, median (IQR)	78 (74–84)
Gender, % female (*n*)	46.4 (383)
Number of co-morbidities, median (IQR)	11 (8–17)
Number of medications, median (IQR)	10 (7–13)
Renal function, CKD-EPI; ml/min/1.73m^2, median (IQR)	61 (43–79)
Nursing home residents, % (*n*)	8.4 (69)
Housebound, % (*n*)	13.3 (110)
Barthel Index of ADL[1], median (IQR)	95 (75–100)
Patients with ≥1 fall(s) in the previous year, % (*n*)	37.9 (313)
Number of falls in the previous year, median (IQR)	0 (0–1)
Patients with ≥1 hospital admission in the previous year, % (*n*)	50.1 (414)
Number of hospital admissions in the previous year, median (IQR)	1 (0–1)
Length of hospital stay (days), median (IQR)	8 (6–12)
Admission type, % (*n*)	
• Elective	25.3 (209)
• Non-elective	74.1 (612)
Ward, % (*n*)	
• Medical	78.1 (645)
• Surgical	21.9 (181)
Country of inclusion, % (*n*)	
• Switzerland	48.3 (399)
• Belgium	16.0 (132)
• Ireland	11.1 (92)
• The Netherlands	24.6 (203)

Data represent numbers and percentages for categorical variables or median and interquartile range (IQR) for continuous variables. Missing data: renal function: 74 (9.0%); nursing home residents: 3 (0.4%); Barthel Index of ADL: 11 (1.3%); housebound: 2 (0.2%); number of falls during the previous year: 9 (1.1%); number of hospitalisations in the previous year: 3 (0.4%); Length of stay during index hospitalisation: 2 (0.2%); admission type: 5 (0.6%). [1]ADL: Basic Activities of Daily Living, as measured by the Barthel Index. Values ranged from 0 to 100. Higher values indicate higher functional independence.[15]

Frequency of STOPP/START signals

In total, 5,080 STOPP/START signals were generated in 826 patients. The median was 6 (IQR 4–8) generated signals per patient. No signals were generated in 0.8% (*n*=7) of the patients, whereas 1–3, 4–6 and >6 signals were generated in 39%, 38% and 22% of the patients, respectively.

Of the generated signals, 68.2% (*n*=3,465) were based on STOPP criteria. In 96% (*n*=791) of patients, ≥1 STOPP signals were generated with a median of 4 (IQR 2–6) per patient, and 31.8% (*n*=1,615) of the generated signals were based on START criteria. In 82% (*n*=681)

of cases, ≥1 START signals were generated with a median of 2 (IQR 1–3) per patient. The distribution of generated signals per patient was comparable across countries and ranged between 93–98% for ≥1 STOPP signal and 80–87% for ≥1 START signal.

Sixty-eight of the 79 implemented STOPP criteria and 29 of the 31 START criteria generated a signal by the CDSS based on actual medical data on diagnosis, medication use, measurements, and laboratory values. The ten most frequently generated STOPP and START signals and their subsequent acceptance as well as the eleven STOPP and two START signals that were never generated are listed in **Table 2**.

Acceptance of STOPP/START signals

Overall, the pharmacotherapy team accepted 39.1% (*n*=1,990) of all 5,080 generated STOPP/START signals which corresponds with a median of 2 (IQR 1–3) per patient. As for STOPP signals, 40.1% (*n*=1,390) were accepted by the pharmacotherapy team, resulting in a recommendation to the attending hospital physician and the patient. The median number of accepted STOPP signals was 1 (IQR 0–2) per patient. As for START signals, 37.2% (*n*=600) were accepted and resulted in a recommendation to initiate a drug (median 0; IQR 0–1).

In general, there was a high variability in the acceptance of individual STOPP/START signals. Acceptance of the top ten most frequently generated STOPP/START signals ranged from 2.5%-75.8%. STOPP A1 ('*Stop any drug prescribed without an evidence-based clinical indication*') covered 28% of all generated signals with more than half of the signals accepted (54%). Drugs for acid related disorders were the most often recommended drug class for discontinuation based on STOPP A1 (22.5%) followed by mineral supplements (calcium) (8.0%) and psychoanaleptics (7.3%). The recommended drug classes for discontinuation based on STOPP A1 are outlined in **Figure 3**.

Other STOPP signals from the top ten that resulted in a recommendation in more than 25% of cases included benzodiazepines (STOPP D5 – 64%), proton-pump inhibitors (STOPP F2 – 35%), unindicated dual anticoagulant and antiplatelet therapy (STOPP C5 – 32%) and duplicated drug classes (STOPP A3 – 26%).

The most frequently generated START signal was a high potency opioid in moderate-severe pain (START H1), but this signal was almost never accepted (3%). From the top ten most frequently generated signals based on START criteria, signals to initiate vitamin D, calcium or bone anti-resorptive therapy in osteoporosis (START E5 – 76%; START E3 – 61%; START E4 – 43%); a laxative with concurrent opioid use (START H2 – 48%); statin therapy with known coronary, cerebral or peripheral vascular disease (START

A5 – 63%); an angiotensin-converting enzyme inhibitor with systolic heart failure and/or documented coronary artery disease (START A6 – 51%) or an anticoagulant with chronic atrial fibrillation (START A1A2 – 50%) were accepted in > 25% of cases (**Table 2**). Detailed information on frequencies and subsequent acceptance for all STOPP/START criteria – in total and stratified per country – can be found in Supplementary Information SI1. An overview of the drugs (on ATC-2 level) involved in the medication optimisation recommendations based on accepted STOPP/START signals is provided in Supplementary Information SI2 (online).

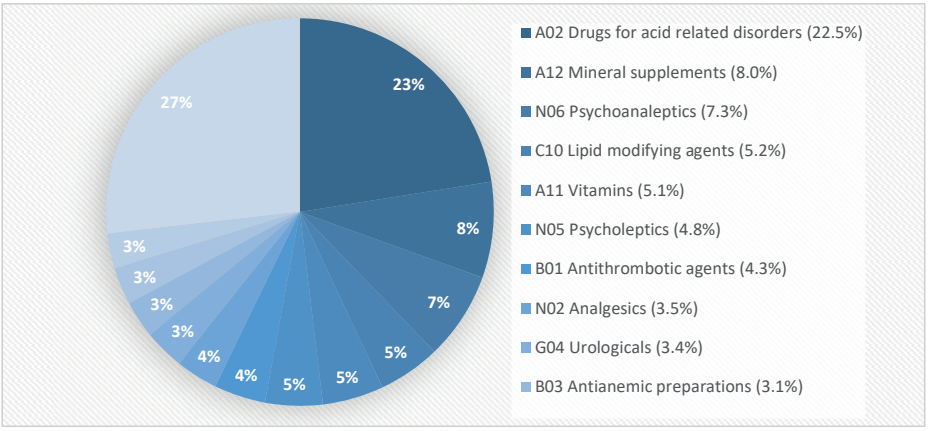

Figure 3. Distribution of drugs on ATC-2 level that were recommended for discontinuation because of a lack of an evidence-based clinical indication (STOPP A1). Drugs that resulted in a recommendation < 20 times were categorized as 'X00 Other'. 766 out of 1412 generated STOPP A1 signals were accepted by the pharmacotherapy team.

For 9.1% (n=181) of all accepted signals, the pharmacotherapy team added the advice to defer implementing the recommended action to the patient's general practitioner. The accepted signals that were most frequently (>10 times) recommended for deferral were: to stop a drug without indication (STOPP A1; n=43), to stop a benzodiazepine (STOPP D5; n=22), to start bone anti-resorptive therapy (START E4; n=19) and to start an ACE-inhibitor (START A6; n=16). These deferred recommendations were all included in the top ten most generated signals (**Table 2**).

Table 2: Overview of the frequency and subsequent acceptance of generated STOPP/START signals

Top 10 most frequently generated STOPP signals	Frequency, N	Acceptance, %
STOPP A1 – Any drug prescribed without an evidence-based clinical indication.	1,412	54.2%
STOPP A3 – Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE-I, anticoagulants	503	26.0%
STOPP D5 – Benzodiazepines for ≥ 4 weeks	181	64.1%
STOPP F2 – PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks	146	34.9%
STOPP B6 – Loop diuretic as first-line treatment for hypertension	101	22.8%
STOPP C3 – Aspirin, clopidogrel, dipyridamole, VKA, direct thrombin inhibitors or factor Xa inhibitors with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding.	75	4.0%
STOPP F3 – Drugs likely to cause constipation in patients with chronic constipation where non-constipating alternatives are available	75	20.0%
STOPP G2 – Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD	63	6.3%
STOPP C5 – Aspirin in combination with VKA, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic atrial fibrillation	60	31.7%
STOPP L2 – Use of regular (as distinct from PRN) opioids without concomitant laxative	56	12.5%
Total	793	32.2%
STOPP signals that were never generated		
STOPP C7 – Ticlopidine in any circumstances	0	N/A
STOPP D3 – Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects with a history of prostatism or previous urinary retention	0	N/A
STOPP D6 – Antipsychotics (i.e. other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Disease	0	N/A
STOPP D7 – Anticholinergics/antimuscarinics to treat extra-pyramidal side-effects of neuroleptic medications	0	N/A
STOPP E5 – Colchicine if eGFR < 10 ml/min/1.73m2	0	N/A
STOPP F1 – Prochlorperazine or metoclopramide with Parkinsonism	0	N/A
STOPP G1 – Theophylline as monotherapy for COPD	0	N/A
STOPP H1 – NSAID other than COX-2 selective agents with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist	0	N/A
STOPP J2 – Thiazolidenediones in patients with heart failure	0	N/A
STOPP J4 – Oestrogens with a history of breast cancer or venous thromboembolism	0	N/A

Table 2: Continued.

STOPP M1 – Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties	0	N/A
Total	**3,465**	**40.1%**
Top 10 most frequently generated START signals	**Frequency, N**	**Acceptance, %**
START H1 – High potency opioids in moderate-severe pain, where paracetamol, NSAIDs or low-potency opioids are not appropriate to the pain severity or have been ineffective.	162	2.5%
START A6 – ACE-I with systolic heart failure and/or documented coronary artery disease.	133	51.1%
START E4 – Bone anti-resorptive or anabolic therapy in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists and/or previous history of fragility fracture(s).	118	43.2%
START H2 – Laxatives in patients receiving opioids regularly.	115	47.8%
START E3 – Vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s) and/or Bone Mineral Density T-scores more than -2.5 in multiple sites.	110	60.9%
START E5 – Vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia.	99	75.8%
START A5 – Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years.	80	62.5%
START G2 – 5-alpha reductase inhibitor with symptomatic prostatism, where prostatectomy is not considered necessary.	79	15.2%
START D2 – Fibre supplements for diverticulosis with a history of constipation.	76	18.4%
START A1A2 – VKA or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation. If an oral anticoagulant is contraindicated, start aspirin (75-160 mg) instead.	72	50.0%
Total	571	29.4%
START signals that were never generated		
START C4 - Topical prostaglandin, prostamide or beta-blocker for primary open-angle glaucoma.	0	N/A
START G3. Topical vaginal oestrogen or vaginal oestrogen pessary for symptomatic atrophic vaginitis.	0	N/A
Total	**1,615**	**37.2%**

Detailed information on frequency and acceptance for all STOPP/START signals – in total and per country – can be found in Supplementary Information SI1 (online). Note: some of the original STOPP/START criteria v2 titles are shortened. VKA = vitamin K antagonist; NSAID = non-steroid anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitors; ACE-I = Angiotensin-converting enzyme inhibitors; PPI = Proton-pump inhibitor; PRN = pro re nata (as needed); eGFR = estimated glomerular filtration rate.

Determinants

There was no difference in mean acceptance of STOPP versus START signals (+2.1; 95% confidence interval [CI] −1.5 to 5.7]). Linear regression analysis was performed on potential patient- and setting-related determinants for STOPP and START signals. For STOPP signals, mean acceptance significantly decreased after multivariate linear regression analysis for patients with a higher number of co-morbidities (>9: −11.8%; 95% CI −19.2 to −4.5; **Table 3**). Admission to a surgical ward was positively associated with acceptance (+10.3%; 95% CI 3.8–16.8). The rate of acceptance was higher in Ireland (+26.8%; 95% CI 16.8–36.7) and the Netherlands (+14.7; 95% CI 7.8–21.7) than in Switzerland as reference country.

For START signals, mean acceptance significantly decreased by −11.0% (95% CI −19.4 to −2.6) for patients with seven to nine co-morbidities after multivariate analysis. ≥1 falls (+7.1%; 95% CI 0.7–13.4) and ≥1 hospital admissions in the previous year (+7.9; 95% CI 1.6–14.1) were positively associated with acceptance of START signals. Compared with Switzerland, a higher acceptance rate was only found in Ireland (+31.1%; 95% CI 18.2–44.0). **Table 3** presents the results of univariate and multivariate linear regression analysis of patient- and setting-related determinants on mean acceptance of STOPP and START signals.

Table 3. Univariate and multivariate linear regression of patient and setting related determinants on mean acceptance.

	Patients, *N*	Univariate, % [95% CI]
PATIENT-RELATED		
Gender		
Male	421	37.7
Female	370	**+5.5 [1.0; 9.9]***
Age		
<75	226	38.6
75-80	249	+0.9 [-4.8; 6.7]
>80	316	+3.3 [-2.1; 8.8]
Number of co-morbidities		
<7	282	48.7
7-9	257	**-7.5 [-12.7; -2.2]***
>9	252	**-19.0 [-24.3; -13.7]***
Number of medications		
<9	287	39.3
9-12	275	+2.9 [-2.4; 8.2]
>12	229	-0.4 [-6.0; 5.1]
Number of falls in the previous year		
0	480	41.1
≥1	302	-1.7 [-6.4; 2.9]
Number of hospital admissions in the previous year		
0	386	43.4
≥1	402	**-5.9 [-10.4; -1.5]***
Housebound		
No	687	40.0
Yes	102	+1.2 [-5.5; 7.9]
Renal function (eGFR;CKD-EPI; ml/min/1.73m^2)		
>50	477	39.4
30-50	169	-1.6 [-7.2; 4.0]
<30	76	0.2 [-7.5; 8.0]
Systolic blood pressure (mmHg)		
120-140	298	39.8
<120	243	-2.8 [-8.1; 2.7]
>140	235	+3.9 [-1.6; 9.4]

Multivariate, % [95% CI]	Patients, *N*	Univariate, % [95% CI]	Multivariate, % [95% CI]
Reference	374	37.0	Reference
+2.8 [-1.9; 7.5]	307	+2.5 [-3.4; 8.3]	-0.8 [-7.1; 5.5]
Reference	193	37.2	Reference
+1.0 [-4.8; 6.9]	211	+0.7 [-6.8; 8.3]	+0.9 [-7.0; 8.8]
+2.7 [-3.1; 8.5]	277	+1.9 [-5.2; 9.0]	+1.9 [-5.8; 9.7]
Reference	234	42.6	Reference
-5.4 [-11.6; 0.8]	224	**-7.1 [-14.1; -0.04]***	**-11.0 [-19.4; -2.6]***
-11.8 [-19.2; -4.5]*	223	-6.5 [-13.6; 0.5]	-7.1 [-17.2; 3.0]
Reference	252	38.7	Reference
+2.7 [-2.9; 8.3]	239	-0.4 [-7.2; 6.4]	-2.9 [-10.3; 4.6]
+5.2 [-0.9; 11.2]	190	-1.5 [-8.8; 5.8]	-2.1 [-10.2; 6.1]
Reference	403	35.8	Reference
+0.2 [-4.6; 4.9]	269	+5.0 [-0.9; 10.9]	**+7.1 [0.7; 13.4]***
Reference	319	34.2	Reference
-3.5 [-8.1; 1.2]	359	**+7.2 [1.4; 13.0]***	**+7.9 [1.6; 14.1]***
Reference	589	36.8	Reference
-4.9 [-12.5; 2.7]	90	+9.1 [0.6; 17.6]	-0.0 [-10.0; 10.0]
Reference	407	36.6	Reference
-2.0 [-7.6; 3.6]	149	+2.5 [-4.7; 9.7]	+2.1 [-5.5; 9.6]
+1.6 [-6.0; 9.3]	69	-1.0 [-10.7; 8.8]	-1.0 [-11.1; 9.1]
Reference	261	37.2	Reference
-0.0 [-5.5; 5.5]	209	-0.3 [-7.3; 6.7]	-1.1 [-8.4; 6.2]
+3.0 [-2.6; 8.6]	199	+3.3 [-3.8; 10.4]	+4.7 [-2.9; 12.2]

Table 3. Univariate and multivariate linear regression of patient and setting related determinants on mean acceptance.

	Patients, *N*	**Univariate, % [95% CI]**
SETTING-RELATED		
Ward		
Medical	618	38.6
Surgical	173	**+7.2 [1.8;12.6]***
Admission type		
Elective	198	39.1
Non-elective	589	+1.5 [-3.7; 6.7]
Length of hospital stay (days)		
<6	194	38.6
6-10	332	+2.2 [-3.5; 7.9]
>10	263	+2.2 [-3.8; 8.2]
Country of inclusion		
Switzerland	392	30.7
Belgium	122	**+9.6 [3.5; 15.8]***
Ireland	88	**+27.7 [20.7; 34.7]***
The Netherlands	189	**+20.8 [15.6; 26.1]***

All determinants were entered in the multivariate linear regression model for mean acceptance of STOPP and START signals. Statistical significant values ($p < 0.05$) are in bold and denoted with (*).

	Multivariate, % [95% CI]	Patients, *N*	Univariate, % [95% CI]	Multivariate, % [95% CI]
	Reference	535	38.1	Reference
	+10.3 [3.8; 16.8]*	146	+0.2 [-6.9; 7.3]	-1.8 [-10.5; 6.9]
	Reference	163	38.6	Reference
	+4.8 [-1.2; 10.8]	514	-0.4 [-7.2; 6.4]	+1.4 [-6.8; 9.7]
	Reference	151	35.9	Reference
	-1.5 [-7.4; 4.4]	385	+1.4 [-6.2; 9.0]	-0.8 [-8.9; 7.3]
	-3.8 [-10.2; 2.5]	244	+4.8 [-3.0; 12.6]	+3.9 [-4.6; 12.4]
	Reference	320	31.3	Reference
	+4.2 [-4.4; 12.8]	107	**+11.6 [3.4; 19.9]***	+8.8 [-2.7; 20.2]
	+26.8 [16.8; 36.7]*	78	**+26.2 [16.9; 35.5]***	**+31.1 [18.2; 44.0]***
	+14.7 [7.8; 21.7]*	176	**+7.8 [0.9; 14.8]***	-2.3 [-7.1; 11.6]

DISCUSSION

Frequency and acceptance

In 819 out of 826 patients (99%), at least one signal for potential inappropriate prescribing was generated by the CDSS using a set of 110 algorithms based on STOPP/START criteria v2.[3] In 96% of patients ≥ 1 STOPP signals and in 82% of patients ≥ 1 START signals were generated. The pharmacotherapy team accepted 39% (*n*=1,990) of the total of 5,080 CDSS-generated STOPP/START signals. Overall, there was high variability in both the frequency and acceptance of the individual criteria. To discontinue a drug without a clinical indication (STOPP A1) was the most frequently generated signal (28% of all signals) and accepted in 54% of cases. Although more STOPP (68%) than START (32%) signals were generated, no significant difference was found between their respective mean acceptance rates.

The detection of potential inappropriate prescribing in older patients has been investigated in several studies using a CDSS in a hospital setting. Heterogeneity in reported frequencies of medication overuse, underuse and misuse can generally be explained by differences in the study population, types of tools used and differences in tool application (e.g. prospective vs retrospective). For instance, a recent study found a lower prevalence for potential overuse (56%) and for potential underuse (58%) after application of STOPP/START v2 algorithms on a database with medical information from older hospitalised patients.[19] Retrospective database studies are often limited by incomplete documentation of relevant medical information directly affecting the prevalence of STOPP/START signals. Dalton et al. included four controlled studies in a systematic review reporting acceptance (range 29.3%–95.0%) of computer-generated recommendations for medication overuse in hospitalised older adults.[20] However, the computerised intervention tools were rather heterogeneous and did not include detection of potential underuse, which impedes comparison with our findings.

More comparable to our research in relation to the study design and population is the SENATOR trial. This multicenter clinical trial investigated the impact of CDSS-generated STOPP/START criteria v2 on the occurrence of adverse drug reactions (ADRs) within 14 days of inclusion of in-hospital multimorbid older patients.[21] The frequency of generated START signals (1.8 vs 2 per patient) was similar to our findings, but we detected higher overuse (2.8 vs 4.0 per patient) which may be explained by the exclusion of STOPP A1 (no clinical indication for the drug) in the SENATOR trial. In contrast to the medication review process in OPERAM, CDSS-generated signals were directly presented to the attending physicians without assessment for clinical applicability by a pharmacotherapy team. The clinical relevance of the CDSS-generated signals according

to attending physicians was not prospectively measured, but a *post hoc* analysis of the SENATOR trial showed that only 15% of generated signals were implemented by the attending physicians.[22] However, after retrospective examination of signals by a pharmacist-physician pair, it was found that 39% of all generated signals were deemed to be of possibly important or very important clinical relevance.[22] This percentage is in line with the acceptance of signals by the pharmacotherapy team found in our study.

Determinants

Country of recruitment was the most important determinant for which a significant difference in acceptance for both STOPP and START signals was found compared to Switzerland as the country of reference. The higher acceptance of signals by the pharmacotherapy team from Cork (Ireland) - the originator of STOPP/START version 1 - may be partly explained by familiarity with applying these criteria in their hospital. However, the STOPP/START criteria are widely used across Europe nowadays and the pharmacotherapy teams were trained according to standardised operating procedures prior to performing the intervention. Therefore, site-specific differences in rotation and level of clinical experience of the pharmacotherapy teams may be more likely to explain the variability in acceptance across sites, with Switzerland having a high turnover of physician-pharmacist pairs that performed the intervention compared to the other countries.

The impact of other significant patient- and setting- related determinants on acceptance was relatively low, ranging from -11.8% to +10.3. Acceptance was positively associated with admission to a surgical ward for STOPP signals (+10.3%), which suggest that special attention to deprescribing in patients on surgical wards may be beneficial. From the investigated patient-related factors, a negative association between an increased number of co-morbidities and the acceptance of STOPP and START signals was found. This may indicate that the population-based STOPP/START criteria are less suitable for application to individual patients with multiple conditions, for instance because co-existing relevant contra-indications could impede medication changes. From the patient-related determinants, one or more hospital admissions in the previous year and a history of falls were positively associated with acceptance of START signals. The higher acceptance in patients with a history of falls could be explained by the high number of accepted signals related to vitamin D, calcium supplements and bone-antiresorptive therapy. Although these patient-related factors were statistically significant, differences were considered too small to define a clear in-hospital patient population for whom the application of STOPP/START would be of lower or higher value from a clinical perspective.

CDSS-related restrictions

In order to incorporate guideline recommendations into a CDSS, STOPP/START criteria were converted into algorithms; however, many were found to lack sufficient clarity for translation.[9,23,24] STOPP A2 – '*Any drug prescribed beyond the recommended duration, where treatment duration is well defined*' – could not be coded at all, and some elements of other criteria were left out (e.g. for START A5 – '*…unless the patient's status is end-of-life*'). For other ambiguous criteria (e.g. STOPP M1 – '*drugs with antimuscarinic/anticholinergic properties*'), experts consisting of senior physicians and clinical pharmacists were consulted to reach consensus on which conditions or drugs should be included in the algorithms. Risk of over-detection rather than under-detection was chosen as a strategy for converting STOPP/START criteria into algorithms within the OPERAM trial. Consequently, simplifying certain criteria probably led to false-positive signals and negatively affected acceptance.

In addition, multiple STOPP and START criteria could be generated recommending medication changes for the same drug, while the CDSS allowed the pharmacotherapy team to accept only one recommendation for each drug per patient. For instance, STOPP L2 – '*use of regular (as distinct from PRN) opioids without concomitant laxative*' and START H2 – '*laxatives in patients receiving opioids regularly*' would both be generated in a patient using opioids without a laxative. In such cases, the pharmacotherapy team could either reject both signals, or – if a drug change was clinically indicated – accept the most appropriate signal of the two, which resulted more frequently in a recommendation to initiate a laxative (**Table 2**, START H2: frequency n=115; acceptance 47.8%), rather than to discontinue the opioid (**Table 2**, STOPP L2: frequency n=56; acceptance 12.5%).

Setting-related restrictions

The pharmacotherapy analysis was performed in a hospital setting. Decisions to accept or reject STOPP/START signals may be influenced by the clinical setting, as well as the willingness of patients and physicians to implement medication changes. Hospitalisations have a significant impact on the continuity of pharmacotherapy, whereas STOPP/START criteria mainly focus on chronic drug use.[25-27] However, the pharmacotherapy team could also decide to accept but defer the implementation (e.g. drug tapering) of a clinically relevant signal until after discharge, and those signals were counted as accepted. In addition, our geriatric population was relatively functionally independent with only 8.4% of participants living in nursing homes. Results from a study investigating the impact of STOPP/START criteria (v1) in frail geriatric chronic care residents found that 82.4% of STOPP and 92.6% of START recommendations made by a research pharmacist were implemented by the attending physician[28,29], whereas only 62.2% of all OPERAM patients had ≥1 STOPP/START recommendation implemented at two months follow up.[30]

Interestingly, the implementation of recommendations to discontinue benzodiazepines was lower in the geriatric chronic care setting (23%; n=3/13) than in the OPERAM trial at two months follow up (39.1%; n=45/115).[28,30] These differences may illustrate that decisions to optimise pharmacotherapy are likely to differ in a hospitalised population compared to those made for long-term care facility residents or in primary care.

Strengths and limitations

In our study, medical information at the time of pharmacotherapy analysis was prospectively collected and assessed for clinical applicability by physicians and pharmacists with clinical experience in caring for older adults with full access to the patient's actual medical file. Unlike retrospective studies, essential factors, such as life expectancy, drug exposure length and time until benefit, were considered by the pharmacotherapy team. Carvalho et al.[31] have reported that only one-third of all STOPP criteria and just one START criterion can be adequately applied if only a patient's medication list is available without diagnostic data. Consequently, applying STOPP/START using medical databases without clinical evaluation is hampered compared to its use on real-time patient data. Our structured prospective evaluation of STOPP/START signals in a large group of in-hospital older people provides accurate insight into clinically relevant signals of over- and under-prescribing in this population.

A limitation of this study was the relatively large number of missing data (*n*=137). After performing a pharmacotherapy analysis, the pharmacotherapy team had to actively save the results into the CDSS. Due to technical failure, results were not saved in the CDSS in 49 of the OPERAM intervention patients (5%). No in-hospital pharmacotherapy analysis was performed for the other missing patients due to various factors, such as early discharge from the hospital, transfer to another ward, or withdrawal before intervention.

The acceptance reflects the pharmacotherapy team's treatment recommendations regarding presumed overuse, underuse and misuse; however, information about individualised treatment goals and patient preferences was not always available during the pharmacotherapy analysis. The proposed recommendations' implementation after discussion with both the attending hospital physician and the patient and the persistence after discharge, were not included in the design of this study. In the main OPERAM trial results, data on implementation of recommendations at two months after index hospitalisation were provided.[30] However, different choices were made in this substudy to define the study population and to define the term 'recommendations' compared to the OPERAM main trial, which is explained in Supplementary Information SI3 (available online).

Lastly, the reasons for rejection of CDSS-generated STOPP/START signals were not collected, which makes it difficult to distinguish whether CDSS-related or setting-related restrictions had a larger impact on low acceptance of signals by the pharmacotherapy teams.

Implications

The use of STOPP/START v2 criteria as algorithms is a helpful approach to detect medication overuse, underuse and misuse in older patients within a hospital setting, but it may also result in signal overload. Given that more than half of all generated signals were rejected, an expert team's involvement in translating population-based CDSS signals to individual patients is essential. Furthermore, our most frequently recommended action was '*to stop a drug without a clear indication*' (STOPP A1), which requires critical clinical evaluation. Without such an expert team, signal overload will probably lead to low implementation rates in usual care, as shown in the SENATOR trial (15%).[22]

Our detailed description of the combined frequency and acceptance of STOPP/START v2 within a large European hospital population could help to differentiate which STOPP/START algorithms provide the highest clinical benefit in a hospital setting. Future research investigating factors that affect patients' and physicians' agreement with medication changes recommended by expert teams may gain further insights relevant for implementation in clinical practice. In addition, our results were based on decisions made by a pharmacotherapy team in a hospital setting, which may not be the most appropriate setting to change chronic medication. It would be highly interesting to compare the results of this study with those of the OPTICA (Optimising PharmacoTherapy In the multimorbid elderly in primary CAre) trial, in which the application of a similar STOPP/START-based CDSS is being investigated in a primary care setting.[32]

Conclusion

In conclusion, nearly all hospitalised patients with polypharmacy and multimorbidity had at least one signal for potential medication overuse, underuse or misuse, and 39% of them were accepted by a pharmacotherapy team on the individual patient level. There was a high variability in the frequency and subsequent acceptance of individual STOPP/START v2 signals. In general, the investigated patient-related determinants were poor predictors for STOPP/START v2 recommendation acceptance in a hospital setting. The moderate overall acceptance and the site-specific differences in acceptance emphasize the important role of a pharmacotherapy team in translating population-based STOPP/START signals to individual patients.

DECLARATIONS

Authors' contributions

The authors certify that they have participated in the aspects of conception and design (BTGMS, **CJAH**, TE, EvP, DOM, AS, NR, IW, WK), acquisition of data (BTGMS, **CJAH**, JoH) and intrepreration of the data (BTGMS, **CJAH**, JoH, IS, TE, EvP, IW, WK, NR, AS, DOM), drafting the article (**CJAH**, BTGMS) and revising it critically for important intellectual content (all authors). All authors have approved the final article. We have not received substantial contributions from non-authors.

Competing interests

DOM has a patent A Prescription Decision Support System (based on screening tool of older person's prescriptions and screening tool to alert to the right treatment (STOPP/START) prescribing rules) issued to European Patent Office (Munich). MS reports a 2011 grant and personal fees from Spru IT, before the conduct of the study; in addition, MS reports a settlement agreement between Spru IT and Utrecht University, in which all systematic tool to reduce inappropriate prescribing (STRIP) assistant IP is transferred to Utrecht University, in exchange for obtaining a free but non-exclusive right to provide STRIP assistant consultancy or support services, or both on a commercial basis, and to update the STRIP assistant, until June 2023.

Data availability statement

Data for this study will be made available to others in the scientific community upon request after publication. Data will be made available for scientific purposes for researchers whose proposed use of the data has been approved by a publication committee.

Ethics approval

The OPERAM trial was approved by the independent research ethics committees at each participating site (lead ethics committee: Cantonal Ethics Committee Bern, Switzerland, ID 2016-01200; Medical Research Ethics Committee Utrecht, Netherlands, ID 15-522/D; Comité d'Ethique Hospitalo-Facultaire Saint-LucUCL: 2016/20JUL/347– Belgian registration No: B403201629175; Cork University Teaching Hospitals Clinical Ethics Committee, Cork, Republic of Ireland; ID ECM 4 (o) 07/02/17), and Swissmedic as responsible regulatory authority.

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Informed consent

Written informed consent was obtained from the patients or their legal representatives before enrolment in the OPERAM trial.

Trial registration

ClinicalTrials.gov Identifier: NCT02986425

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PART III

HOSPITAL PHYSICIANS' AND OLDER PATIENTS' PERSPECTIVES ON IN-HOSPITAL PHARMACOTHERAPY OPTIMISATION

Hospital physicians' and older patients' agreement with individualised STOPP/START based medication optimisation recommendations in a clinical trial setting

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ABSTRACT

Objective: To evaluate the agreement of hospital physicians and older patients with individualised STOPP/START based medication optimisation recommendations from a pharmacotherapy team.

Methods: This study was embedded within a large European, multicentre, cluster randomised controlled trial examining the effect of a structured medication review on drug-related hospital admissions in multimorbid (≥ 3 chronic conditions) older people (≥ 70 years) with polypharmacy (≥ 5 chronic medications), called OPERAM. Data from the Dutch intervention arm of this trial were used for this study. Medication review was performed jointly by a physician and pharmacist (i.e. pharmacotherapy team) supported by a Clinical Decision Support System (CDSS) with integrated STOPP/START criteria. Individualised STOPP/START based medication optimisation recommendations were discussed with patients and attending hospital physicians.

Results: 139 patients were included, mean (SD) age 78.3 (5.1) years, 47% male and median (IQR) number of medications at admission 11 (9-14). In total, 371 recommendations were discussed with patients and physicians, overall agreement was 61.6% for STOPP and 60.7% for START recommendations. Highest agreement was found for initiation of osteoporosis agents and discontinuation of proton pump inhibitors (both 74%). Factors associated with higher agreement in multivariate analysis were: female gender (+17.1% [3.7;30.4]), ≥ 1 falls in the past year (+15.0% [1.5;28.5]) and renal impairment defined as eGFR 30-50 ml/min/1.73m^2; (+18.0% [2.0;34.0]). The main reason for disagreement (40%) was patients' reluctance to discontinue or initiate medication.

Conclusion: Better patient and physician education regarding the benefit/risk balance of pharmacotherapy, in addition to more precise and up-to-date medical records to avoid irrelevant recommendations, will likely result in higher adherence with future pharmacotherapy optimisation recommendations.

BACKGROUND

Multimorbidity and polypharmacy remain challenging in the context of rapidly ageing populations globally. Although polypharmacy is often indicated in older patients with multimorbidity, it is also associated with an increased risk of negative health outcomes including adverse drug reactions (ADRs) and drug-related hospital admissions (DRAs).[1,2,3] Periodic evaluation of the individual patient's pharmacotherapy by medication review is important to ensure an optimised balance between therapeutic and preventive benefit and potential harms of treatment.[4,5,6]

Several screening tools, both implicit and explicit, have been developed to assist physicians and pharmacists in performing medication reviews.[7] The STOPP/START criteria are explicit criteria that are widely used in medication reviews for older people, especially in Europe.[8,9] It can, however, be challenging to translate the general population-based STOPP/START recommendations into specific recommendations for the individual patient. An important element of medication review is alignment of a patient's pharmacotherapy with individual patient's preferences.[10] Prior research shows that taking patients' preferences into account will likely result in higher agreement with recommendations.[11,12,13] Prescriber implementation of pharmacotherapy optimisation recommendations provided by physicians or pharmacists showed large variation in previous studies.[14] Therefore, it is important to investigate the factors that influence the willingness of patients and their attending physicians to follow pharmacotherapy optimisation recommendations and to understand patients' and physicians' reasons for disagreement with the recommendations. This could help to improve the effectiveness of medication reviews, increase appropriate prescribing and ultimately reduce negative health outcomes.

The aim of the current study was to evaluate the level of agreement, including reasons for disagreement, of hospital physicians and older patients with polypharmacy and multimorbidity with individualised STOPP/START based medication optimisation recommendations from a pharmacotherapy team.

METHODS

Setting, design and study population

This study was embedded within The OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people (OPERAM) clinical trial.[15] In brief, OPERAM was a large European, multicentre, cluster randomised controlled trial examining the effect of a structured medication review on drug-related hospital admissions (DRAs) in multimorbid (≥3 chronic conditions) older people (≥70 years) with polypharmacy (≥5 chronic medications). In-hospital patients were recruited in Switzerland (Bern), Belgium (Louvain), Ireland (Cork) and the Netherlands (Utrecht) i.e. one centre per country. All patients were admitted to the participating hospitals, either electively or non-electively through the emergency department and were recruited in both surgical and medical wards. Geriatric specialist wards were excluded from the OPERAM trial to avoid contamination of the trial arising from routine medication reconciliation and optimisation in such wards. Only data from the Dutch intervention patients were eligible for the present study, as data regarding agreement with the recommendations and reasons for disagreement by both patients and physicians were only systematically collected at the St. Antonius Hospital, a large non-academic teaching hospital, located in Utrecht and Nieuwegein. Data were collected between January 2017 and October 2018 during the recruitment phase of the OPERAM trial. Baseline characteristics were registered in and extracted from the electronic Case Report Form (eCRF) deployed in each randomised patient.

Intervention

The intervention within the OPERAM trial consisted of a structured medication review based on the software-supported Systematic Tool to Reduce Inappropriate Prescribing (STRIP) method performed by a pharmacotherapy team (PT), consisting of a physician and a pharmacist, both experienced with geriatric pharmacotherapy optimisation and trained by standardised operating procedures in all trial sites.[7,16] The Dutch PT consisted of one physician/pharmacist pair performing the intervention throughout the trial. The intervention consisted of five consecutive steps and occurred within 72 hours after trial enrolment: 1) Structured History taking of Medication use (SHiM)[17] and collection of patient data including medical conditions, laboratory data and clinical parameters; 2) digitalised screening of pharmacotherapy supported by a Clinical Decision Support System (CDSS) with integrated STOPP/START criteria (version 2);[18,19] START and STOPP signals generated by the CDSS were based on the patient data and current pharmacotherapy; 3) pharmacotherapy analysis resulted in a report with individualised recommendations: the CDSS-generated STOPP/START signals were assessed for appropriateness for the individual patient by the PT based on additional information from the patient's medical records, such as prior use and effectiveness, side-

effects or known drug allergies; 4) discussion of individualised medication optimisation recommendations with the patient and attending physician by the PT. Recommendations were first discussed with the patient. The recommendations agreed upon by the patient were then suggested to the attending physician. In case the attending physician did not agree or did not feel qualified to adjust the medication, these recommendations were then transferred to the GP in case both the attending physician and the patient consented; 5) an overview of the recommendations (both implemented during hospital admission and postponed) was transferred to the patient's general practitioner as a written advice report. The GP was asked to review the postponed recommendations for implementation after hospital discharge in collaboration with the patient. All consecutive steps and the focus of this study (step 4) are summarised in **Figure 1**.

Ethics approval

The local ethics committee at each participating trial site approved the OPERAM study protocol, registered under Trial Registration Number NCT02986425. No additional ethical approval was needed for this study, as the data collected and analysed were part of the main trial.[20]

Primary outcome

The primary outcome of this study was defined as the STOPP/START recommendations provided by the PT that were agreed upon by both patient and attending hospital physician after discussion with the PT, as illustrated in **Figure 1** (step 4).

Secondary outcome

Reasons for disagreement with the STOPP/START recommendations by the patient and/or attending hospital physician were collected and analysed.

Determinants

Potential determinants of agreement with the recommendations were investigated. Potential determinants with continuous values were dichotomised or categorised into tertiles based on patient distribution (age, comorbidities, number of medications) or based on clinically accepted cut-off values for measurements (renal function). STOPP/START criteria-related variables were: type of recommendation (STOPP versus START), medication involved (i.e. drug class) and number of recommendations per patient. Patient-related variables include: sex, age group (70-79 years, 80-89 years, ≥90 years), number of comorbidities (<7, 7-9 or ≥9), renal function (eGFR <30, 30-50 or ≥50 ml/min/1.73m^2), occurrence of falls in the past year (defined categorically as 0 or ≥1), and number of long term daily medications at inclusion (<9, 9-12 or ≥12). Setting-related variables were: ward type (medical or surgical) and hospital length of stay (<7, 7-14, >14 days).

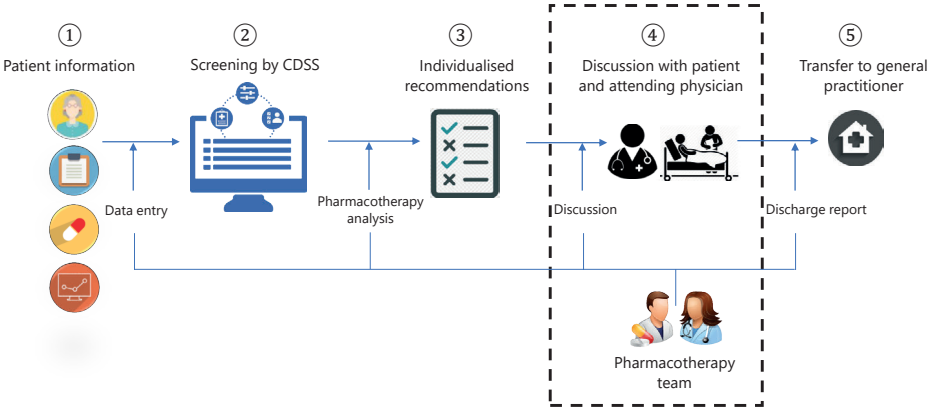

Figure 1: Summary of all consecutive steps (1-5) of the intervention within the OPERAM trial and the focus of this study highlighted: the agreement of recommendations by patients and attending physicians after discussion with the pharmacotherapy team (step 4).

Data analyses

Data analysis was performed with IBM SPSS® Statistics v.25.0.0.2. Baseline characteristics and agreement with STOPP/START recommendations were analysed using descriptive statistics. The outcome agreement was binary on a recommendation level (yes/no) and continuous on an individual patient level (percentage of recommendations agreed upon), as multiple recommendations could be applicable to one patient. Potential determinants of agreement were investigated on an individual patient level using a univariate and multivariate linear regression model (method: enter). For subgroup analyses on a recommendation level, relative risks (RR) and 95% confidence intervals (CIs) were calculated. P-values <0.05 were considered statistically significant.

RESULTS

Study population

A total of 452 patients were included in the OPERAM cohort at the Utrecht trial site, of whom 229 (50.7%) were allocated to the intervention group. Four patients (1.7%) withdrew from the trial prior to the intervention. The medication review including CDSS-assisted pharmacotherapy analysis was not completed in 23 of 225 patients (10.2%) due to several (mostly logistic) factors, such as early discharge, transfer to another ward (including the Intensive Care Unit) or to another hospital. Data from one patient were missing from the database. In 24 patients, the pharmacotherapy analysis did not result in START/STOPP recommendations. In 22 patients, discussion with patient and physician was not performed and for 16 patients recommendations were only discussed with the attending physicians and not with the patients. These 16 patients were excluded from the final analysis. For 139 of the 155 eligible patients (89.7%), the medication review including discussion with both patient and attending physician was successfully completed. These 139 patients comprised the study population. A flowchart illustrating the data flow is presented in **Figure 2**.

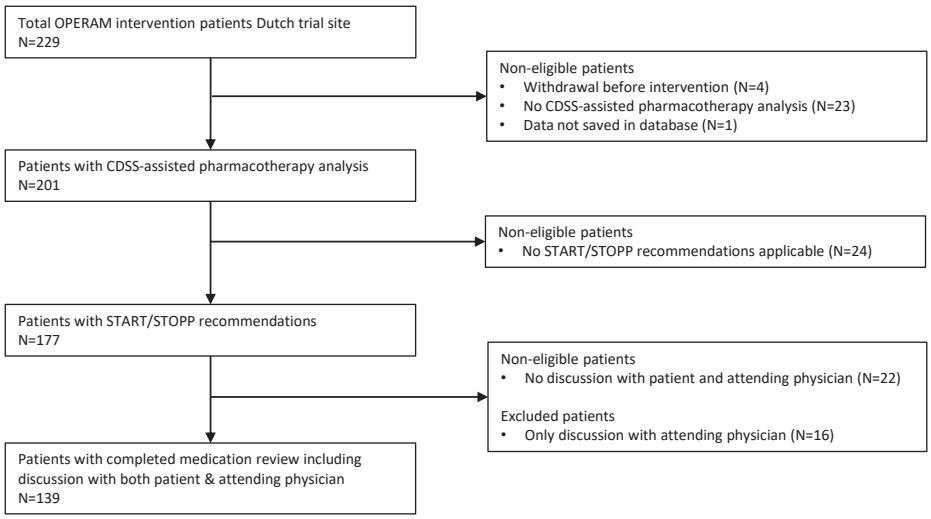

Figure 2: Study population flowchart. Non-eligible patients did not fulfil the inclusion criteria of this OPERAM substudy i.e. discussion of recommendations with patient and attending physician in order to determine agreement with recommendations.

The mean (SD) age of the study population was 78.3 (5.1) years, 65 patients (47%) were male and the median (IQR) number of prescribed long term daily medications prior to admission was 11 (9-14). All baseline characteristics are presented in **Table 1**. CDSS-

assisted pharmacotherapy analysis by the PT resulted in a total of 371 recommendations for 139 patients, comprising 237 STOPP recommendations (median (IQR): 1 (1-2) per patient) and 134 START (1 (0-1) per patient) recommendations. Overall STOPP/START recommendation agreement was 61.2%, with no significant difference in agreement proportion between STOPP (61.6%) and START (60.7%) recommendations.

Table 1: Baseline characteristics of study population.

Characteristics	
Patients, N	139
Age in years, mean (SD)	78.3 (5.1)
Gender (Male), N (%)	66 (47.5%)
Number of comorbidities, median (IQR)	8 (6-11)
Number of prescribed medications (admission), median (IQR)	11 (9-14)
Nursing home residents, N (%)	6 (4.3%)
Housebound patients, N (%)	19 (13.7%)
Barthel Index of ADL, median (IQR)	92.5 (85-100)
Patients with ≥1 fall(s) in the past year, N (%)	57 (41.9%)
Patients with ≥1 hospital admission in the past year, %	67 (48.2%)
Length of stay index hospitalisation in days, median (IQR)	9 (6-18)
Estimated GFR (CKD-EPI, mL/min/1.73m^2) Mean (SD)	59.1 (20.6)
Estimated GFR 30-50 ml/min/1.73m2 N (%)	36 (25.9%)
Estimated GFR ≤ 30 ml/min/1.73m2 N (%)	13 (9.4%)
Ward (N, %)	
Medical	109 (78.4)
Surgical	30 (21.6)
Admission type (N, %)	
Elective	34 (24.5)
Non-elective	105 (75.5)

Missing data: number of comorbidities 3 (2.2%) renal function 5 (3.6%) nursing home residents & housebound 1 (0.7%) Barthel Index 1 (0.7%) Falls 3 (2.2%) hospitalisations 1 (0.7%)

Agreement with recommendations based on STOPP criteria

Among all 237 STOPP recommendations discussed, 146 (61.6%) were agreed upon by both patient and physician. More than half (52.7%) of the STOPP recommendations discussed with the patients and physicians were based on criterion 'no evidence-based clinical indication' (STOPP A1), of which there was consensus to discontinue in 60.8% after discussion. Within the STOPP A1 criterion ('no evidence-based clinical indication'), drugs for acid related disorders (including PPIs) represented 43.2% of the recommendations. After discussion with both patient and attending physician, 74.1% of these recommendations relating to

drugs for acid related disorders were agreed upon. Other medication groups within STOPP A1 were heterogeneous and contained small numbers with varying agreement e.g. inhaled bronchodilators (N=12; 33.3% agreement), analgesics (N=7; agreement 28.6%).

The 10 most prevalent STOPP recommendations, comprising 87.3% (N=207) of all discussed STOPP recommendations and their subsequent agreement by both patient and attending physician after discussion with PT are listed in **Figure 3**. Some of these individual criteria contain STOPP recommendations for the same medication (or drug class) but were based on other reasons for inappropriateness. For example, implementing STOPP criteria D5 and K1 both result in discontinuation advice for benzodiazepines.

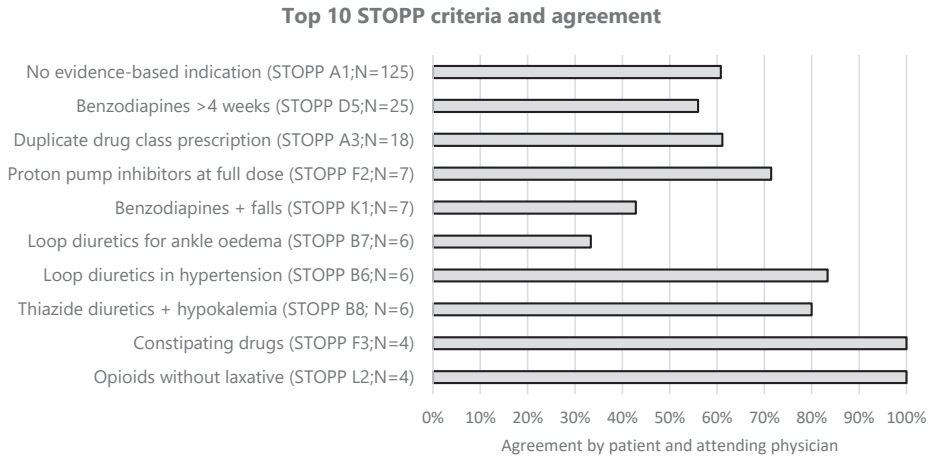

Figure 3: Top 10 STOPP recommendations and corresponding agreement by patient and attending physician after discussion with PT. STOPP A1: 'No evidence-based clinical indication' contains stop recommendations for multiple medications with 'drugs for acid related disorders' being the most prevalent (43.2% of STOPP A1).

Agreement with recommendations based on START criteria

Of the 134 START criteria discussed with patients and their attending physicians by the PT, 60.7% were agreed upon. An overview of the 10 most prevalent START recommendations, comprising 89.6% (N=120) of all START recommendations discussed and subsequent agreement, is displayed in **Figure 4**.

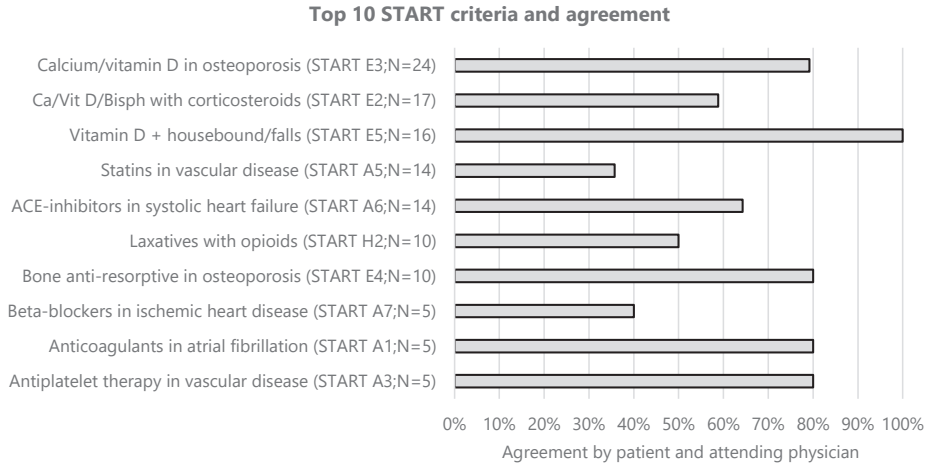

Figure 4. Top 10 START recommendations and corresponding agreement by patient and attending physician after discussion with PT. START E3 consist of recommendations for both calcium and/or vitamin D. START E2 consist of recommendations for calcium, vitamin D and/or bisphosphonates (i.e. Ca/Vit D/Bisph in the figure).

Determinants of agreement

Potential determinants of agreement were investigated on a patient level (N=139). Multivariate linear regression revealed three patient-related factors significantly associated with higher mean agreement (with STOPP/START recommendations taken together) i.e. female gender (+17.1% [3.7;30.4]), ≥1 falls in the past year (+15.0% [1.5;28.5]) and moderately diminished renal function defined as eGFR 30-50 ml/min/1.73m^2 (+18.0% [2.0;34.0]). None of the investigated setting-related factors (ward type, admission type, length of stay) was associated with lower/higher agreement. All determinants included in the univariate and multivariate analyses are displayed in **Table 2**.

Table 2. Statistical analysis of determinants of agreement.

Determinant	Patients (N)	Mean agreement (%)	Linear regression (% [95%-CI])	
			Univariate	Multivariate
PATIENT RELATED DETERMINANTS				
Gender				
Male	66	52.9	Ref	Ref
Female	73	68.7	**+15.8 [3.2;28.4]**	**+17.1 [3.7;30.4]**
Age				
<75	43	62.2	Ref	Ref
75-80	45	56.6	-5.7 [-21.7;10.4]	-3.9 [-19.9;12.1]
>80	51	64.3	+2.0 [-13.7;17.6]	-2.4 [-18.8;14.1]

Table 2. Continued.

Determinant	Patients (N)	Mean agreement (%)	Linear regression (% [95%-CI])	
			Univariate	Multivariate
PATIENT RELATED DETERMINANTS				
Number of co-morbidities				
<7	38	63.1	Ref	Ref
7-9	52	59.8	-3.3 [-19.5;12.9]	-6.8 [-23.6;9.9]
>9	49	61.2	-1.9 [-18.3;14.5]	-3.4 [-21.1;14.4]
Number of medications				
<9	34	57.4	Ref	Ref
9-12	54	61.2	+3.8 [-12.8;20.4]	-7.7 [-24.6;9.3]
>12	51	63.7	+5.52 [-11.42;22.45]	-8.1 [-25.9;9.7]
Number of falls in the past year				
0	79	55.1	Ref	Ref
≥1	57	69.3	**+14.1 [1.3;27.0]**	**+15.0 [1.5;28.5**]
Number of hospital admissions in the past year				
0	70	65.0	Ref	Ref
≥1	68	56.7	-8.3 [-21.1;4.5]	-6.1 [-19.2;7.0]
Renal function (eGFR;CKD-EPI; ml/min/1.73m^2)				
>50	86	57.8	Ref	Ref
30-50	37	72.9	**+15.1 [0.5;29.8]**	**+18.0 [2.0;34.0**]
<30	13	53.0	-4.8 [-27.0;17.4]	-6.3 [-29.6;17.1]
SETTING RELATED DETERMINANTS				
Ward				
Medical	109	60.0	Ref	
Surgical	30	65.3	+5.3 [-10.3;20.9]	
Admission type				
Elective	34	60.1	Ref	
Non-elective	105	61.5	+1.4 [-13.5;16.4]	
Length of stay (days)				
<7	38	57.0	Ref	
7-14	58	60.6	+3.6 [-12.2;19.4]	
>14	43	65.7	+8.7 [-8.2;25.5]	

All patient and setting related determinants were included in univariate linear regression model. Determinants significantly associated with higher agreement were included in the multivariate model (cut-off value P <0.2). Other variables of interest (age, number of comorbities and number of medications) were also included in the mutivariate analysis. All values including 95% confidence intervals are shown. Statistically significant values are in **bold**. Ref = reference category

For the individual STOPP and START recommendations (N=371), potential determinants of agreement were investigated as well. No difference was found between STOPP and START recommendations and no significant relationship was found between the number of recommendations discussed (range 1-7) and subsequent agreement. All individual STOPP and START recommendations were categorised into subgroups according to the medication class involved and their occurrence. This resulted in 4 subgroups: 1) cardiovascular & antithrombotic agents (N=83;22.4%), 2) drugs for acid related disorders (N=61;16.4%), psychotropic drugs including benzodiazepines/Z-drugs (N=59;15.9%), 3) osteoporosis agents (vitamin D, calcium and bisphosphonates; N=70;18.9%) and 4) miscellaneous others (all other medications, N=98;26.4%). The levels of agreement with PT recommendations within these groups is displayed in **Figure 5**. Within these medication groups, agreement varied when stratified for gender, with significantly higher agreement in females for cardiovascular medications i.e. 66.7% versus 41.5% by males (RR 1.61; 95%CI 1.05-2.45; p=0.0274) and osteoporosis drugs i.e. 91.9% versus 54.5% (RR 1.68; 95%CI 1.21-2.33; p=0.0017). A history of ≥1 falls in the previous year resulted in significantly higher agreement with recommendations regarding osteoporosis drugs i.e. 94.6% versus 51.5% among patients with no falls (RR 1.84; 95%CI 1.31-2.58; p=0.0005).

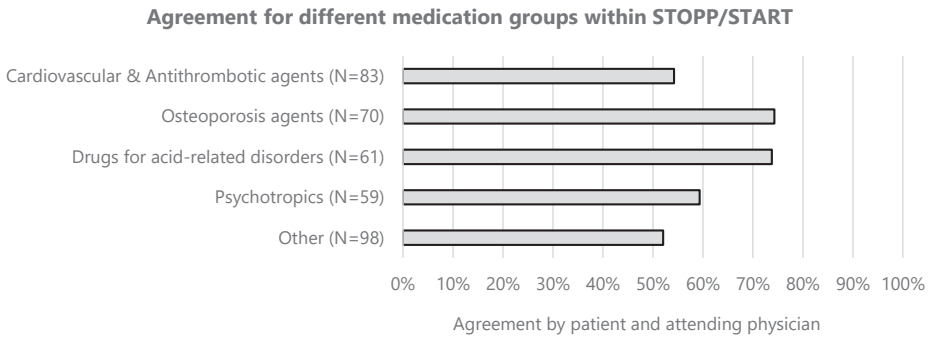

Figure 5: Categorisation of individual STOPP/START recommendations (N=371) into 5 medication groups and subsequent agreement after discussion with patient and attending physician.

Note: Groups 'psychotropics' and 'drugs for acid related disorders' contain only STOPP recommendations, 'osteoporosis agents' 3 STOPP and 67 START, 'cardiovascular & antithrombotic agents' 35 STOPP and 48 START and the group 'other' contained 79 STOPP and 19 START recommendations.

Reasons for disagreement with recommendations

From the total of 371 STOPP/START recommendations that were discussed with both patient and attending physician, 143 (38.5%) were not agreed upon with 'patient does not agree' being the most prevalent documented reason for disagreement (39.9%).

The majority of recommendations to discontinue *drugs for acid related disorders* (N=61; of which 95.1% involved PPIs) were agreed upon (73.8%, **Figure 5**). Disagreement within this drug class occurred in 31% due to reluctance to discontinue by the patient, mainly relating to previous ineffective attempts to discontinue the medication. In another 31% of recommendations, the medication adjustment decision was deferred to the patient's GP. In 19% of recommendations, they were no longer applicable at the time of discussion, indicating that new information had emerged during the discussion that was not present in the patient's medical records. The remaining 19% of non-agreed recommendations were defined as 'other' or 'unknown' reason.

Within the psychotropic medication group, 49 recommendations involved stopping benzodiazepines or Z-drugs. Of these, 27 recommendations (55.1%) were agreed upon by both patient and physician. Disagreement, when it occurred, was in the great majority (90.9%) due to reluctance to discontinue by the patient. The most common reasons given were chronic use without side-effects (falls or sleepiness) and self-reported dependence by patients.

Recommendations to start osteoporosis drugs (N=67) were agreed upon by both patient and physician in 74.3% of cases. Reasons for disagreement included recommendation no longer applicable (41%) based on new information obtained during discussion with patient/physician, patient not agreeing (35%) based on lack of motivation to take more tablets, and patient preference to discuss the matter with their GP rather than stopping in hospital. For 12 recommendations (18%), the decision was deferred to the GP and in the remaining 4 recommendations (6%), the reason for disagreement was unknown.

Medication within the cardiovascular & antithrombotic agents group contained both START recommendations (N=48) and STOPP recommendations (N=35) with identical mean levels of agreement for both categories i.e. 54%. In cases of disagreement, the most important reason was 'physician does not agree or does not feel qualified to advise' (30%). In 24% of recommendations, the decision was deferred to the GP. In 19% of recommendations, the reason was 'patient does not agree'. In 5%, the recommendation was no longer applicable and in 22% other reasons were applicable or the reason was not known.

DISCUSSION

In this study we evaluated older patients' and their attending hospital physicians' agreement/disagreement with individualised STOPP/START criteria-based medication optimisation recommendations from a pharmacotherapy team. Overall agreement was 61.6% for STOPP recommendations and 60.7% for START recommendations, after discussion of 371 recommendations with 139 patients and their attending physicians. The most frequently discussed recommendation was 'no evidence-based clinical indication' (STOPP A1;33.7% of all recommendations). Highest agreement was found for initiation of osteoporosis agents and discontinuation of drugs for acid related disorders (both 74%).

Few studies have explored patients' or physicians' agreement with in-hospital pharmacotherapy optimisation recommendations. In a non-randomised study among older patients admitted to a specialist geriatric unit, physicians' agreements with STOPP recommendations, including benzodiazepines, was 87% compared to 62% in our study, presumably explained by the lack of patient involvement in decision making in contrast to our study.[21] Reasons for disagreement with STOPP/START recommendations in that study were predominantly 'therapeutic prioritisation' (STOPP) and 'severe mental or physical disability' (START). Differences may be explained by a different study population (mean age 88.5, high prevalence of severe dementia (32%) and high prevalence of severe ADL deficiencies (50%)) compared to our study.[21]

In the present study, reasons for disagreement varied between medication groups. Disagreement with stopping of benzodiazepines and Z-drugs was, in 90.9% of instances, due to reluctance to discontinue by the patient (e.g. self-reported dependence, lack of side effects). Low perceived necessity to discontinue medication, as with benzodiazepines in our study, acted as a barrier to agreement with in-hospital medication changes in a qualitative study among older polypharmacy patients.[22] Conversely, the majority of these patients reported acceptance of the hospital-initiated medication changes with high perceived importance (e.g. usual treatment ineffective or causing side-effects). This could explain our findings that initiation of osteoporosis drugs in patients who experienced a fall in the previous year had significantly higher agreement than in patients with no falls (94.6% versus 51.5%).

Research shows that many patients expressed the wish to reduce their daily number of medications.[22] However, patients' willingness to deprescribe specific medications, like benzodiazepines/Z-drugs, was considerably lower in our study than the hypothetical willingness to discontinue medication reported by other researchers (around 90%), investigating patients' attitudes, beliefs and willingness related to medication

deprescribing through questionnaires.[12,23] This might partly be explained by the hospital setting in the present study. In addition, potentially inappropriate medication (PIM) use was not associated with patients' willingness to deprescribe one or more of their medications (74.3% without PIMs versus 79.9% with PIMs) in prior studies.[24] Female gender was associated with more PIM use (based on Beers criteria), especially benzodiazepines, Z-drugs and ≥3 concurrent psychoactive drugs, but not with willingness to deprescribe. We found no gender difference in PIM or PPO prevalence, but we did find an association between female gender and higher agreement with recommendations (both STOPP and START). This is an interesting new finding that needs to be confirmed in future research.

Although patients' reluctance to medication adjustments was an important reason for disagreement, factors within the attending physician and environmental constraints were also prevalent. Postponed recommendations to the GP (21% in total) were frequently associated with attending physicians feeling ill-equipped to take responsibility for suggested medication changes beyond their area of expertise, as we found for cardiovascular medication. These factors correspond relatively well with those found by Dalton et al., who investigated factors affecting prescriber implementation of computer-generated medication recommendations within the SENATOR trial.[25,26] Although the SENATOR-derived study significantly differs in methodology and outcome from our study, four important barriers for implementation were elucidated, of which some were partly overcome in our trial i.e. 1) computerised output leading to recommendations with low clinical relevance, thereby limiting their uptake; 2) the hospital environment with associated time constraints within the busy clinical environment and desire to devolve responsibility of managing older patients' pharmacotherapy to GPs; 3) prescriber factors, particularly prescriber inertia and lack of awareness of the highly prevalent ADRs, reluctance to prescribe outside their therapeutic specialty; 4) patient factors, particularly the overriding focus on the patient's acute status, where reviewing the prescribing recommendations was not a high priority for many attending physicians.[25] All pharmacotherapy optimisation recommendations that were discussed with the patient and the physician in our study, were already evaluated for appropriateness for the individual patient by the PT. This resulted in rejection of 603 out of 1059 (56.9%) STOPP/START signals generated by the CDSS during pharmacotherapy analysis in Dutch patients, based on information present in the patients' medical records (results of this evaluation process are published elsewhere).[16,27] Therefore, the category 'computerised output' was not applicable to our study, as all recommendations discussed were considered relevant to the patient by the PT. Additionally, our output was discussed face-to-face with both patient and attending physician, in contrast to providing a printed report with recommendations to the attending physician and nothing more. These factors

would likely contribute to higher implementation rates than those found in the SENATOR trial (15%) and could explain the overall agreement of 60% we found in our study.[26] In the OPERAM main trial, at least one of the recommendations was successfully implemented at 2 months follow-up in 62.2% of the patients who received ≥1 recommendation during the intervention (across all participating countries). This primarily concerned the discontinuation of potentially inappropriate medications (STOPP A1) and duplicate drug class prescriptions (STOPP A3).[28] Interestingly, the recommendation by PTs to discontinue benzodiazepines used ≥4 weeks (STOPP D5), was implemented in 39.1% at 2 months, suggesting that the majority (80%) of these recommendations agreed upon during discussion (55.1% in our study) were actually implemented after discharge and still discontinued at 2 months. As for START criteria, implementation was considerably lower at 2 months ranging from 12.7% for 'bone antiresorptive treatment' in osteoporosis (START E4) to 38.8% for vitamin D supplements in housebound patients (START E5). Although these OPERAM results reflect all participating trial sites and the agreement presented in this study concerns only the Dutch trial site, these numbers confirm our hypothesis that many possible factors impede the actual and persistent implementation of (verbally) agreed upon recommendations after hospital discharge.

Limitations

This study has some limitations. Firstly, data were collected in a single centre and represent a relatively small sample. Secondly, the entire intervention including CDSS analysis and discussion with both patient and attending hospital physician (in cases where STOPP/START recommendations were applicable), as intended by the OPERAM trial protocol[15], was not completed in 66 of 229 (28.8%) Dutch patients which could have introduced bias to the results. Also, according to the OPERAM protocol, only numbers of diseases and medications, rather than the prevalence of common diseases and medications, are presented at baseline.[28] This might compromise the generalisability of the results. Thirdly, reasons for disagreement were collected by the PT after discussion with patients and attending physicians, thereby possibly introducing bias during documentation of the reasons. In addition, the 'patient does not agree' option could also be interpreted as 'PT failed to convince the patient' in some cases. Furthermore, agreement with recommendations mentioned in our study was based on 'oral consent' to follow the suggested recommendations by both patients and physicians. Although these percentages might considerably change over time, agreement/disagreement was not re-evaluated after discharge. Moreover, actual implementation of the STOPP and START recommendations at hospital discharge was at the discretion of the attending physician and not measured in this OPERAM substudy. It is likely, however, that whilst attending physicians agreed upon medication adjustments verbally, implementation rates were lower due to practical/logistical reasons (e.g. busy clinical practice, pressure to discharge

patients once stable etc.) or patient-related factors like additional changes in medication due to (acute) intercurrent conditions such as sepsis, pain or dehydration. Lastly, communication with the GP was solely through a written report with recommendations to consider after discharge (separately from the hospital discharge letter) and could easily have been missed by the GP. It is likely that adherence by GPs to the postponed recommendations could be improved by discussion through follow-up phone calls to explain and motivate the patients' GPs to implement prescribing recommendations post-discharge.

Implications

In this study high willingness among hospitalised multimorbid older patients and their attending physicians to follow pharmacotherapy optimisation recommendations was found, however, some important areas for improvement were also identified. Disagreement with recommendations was related to the patient's reluctance to change pharmacotherapy in approximately 40% of cases. Better patient education regarding the potential benefits and harms of pharmacotherapy and training of physicians/pharmacists in shared-decision-making (SDM) to more effectively communicate this information to the patient could attribute to better informed decision-making and possibly higher agreement.[29] More and better education and explanation about the potential benefits of implementing the suggested pharmacotherapy recommendations is also important for the hospital physicians, because they felt that some medication groups were beyond their own area of expertise. The discussion with the patient and physician revealed that medical records were not always up to date, making 13% of the recommendations irrelevant at the time of discussion. To increase the specificity of CDSS-assisted medication reviews, it is important that the necessary clinical information in medical records is current and accurate. Low implementation rates of pharmacotherapy optimisation recommendations in clinical trials impedes drawing firm conclusions about the impact of medication reviews on clinical end points like readmissions and mortality, as was recently found in the OPERAM trial.[26] Also, medication reviews should not be performed at a single time point during admission, but need to be repeated after discharge in close collaboration with the GP and community pharmacists, since nearly 50% of patients are unable to recall medication changes implemented in-hospital.[22,30] The effects of medication adjustments (both positive and negative) should be closely monitored and recommendations continuously evaluated and adjusted when necessary. In addition, discussion of medication changes with older patients during hospital admissions for acute illnesses and corresponding disturbances of homeostasis, may not be the ideal time to optimise long-term pharmacotherapy. Both patients and prescribers often have other priorities and certain medication changes could have detrimental effects in unstable patients. Not surprisingly, the patient's GP appears to have particularly strong influence on medication withdrawal (both for and against).[31,32]

Trials focusing on optimising pharmacotherapy in multimorbid older people conducted in, or in close collaboration with, primary care physicians are needed to assess whether the clinical setting and the health care professional involved have significant influence on recommendation agreement, implementation, monitoring and prevention of adverse events within this population.

Conclusion

Hospital physicians' and older patients' agreement with individualised STOPP/START based medication optimisation recommendations after discussion with a pharmacotherapy team was approximately 60%. Highest agreement was found for initiation of osteoporosis drugs and stopping of PPIs. Female gender, history of falls and eGFR 30-50 ml/min/1.73m^2 were significantly associated with higher agreement levels with proposed medication adjustments. Patients' own reluctance to change (40%) was the most important reason for disagreement. Better patient and physician education regarding the benefit/risk balance of pharmacotherapy in addition to more precise and up-to-date medical records will likely result in higher agreement with and implementation of pharmacotherapy optimisation recommendations in the future.

DECLARATIONS

Authors' contributions

The authors certify that they have participated in the aspects conception and design (**CJAH**, BTGMS, TE, RvM, IW, WK), acquisition of the data (**CJAH**, BTGMS, JOH), interpretation of the data (**CJAH**, BTGMS, JOH, TE, IW, WK, RvM, NR, OD, DOM), drafting the article (**CJAH**) and revising it critically for important intellectual content (all authors). All authors have approved the final article. We have not received substantial contributions from non-authors.

Competing interests

DOM has a patent: a Prescription Decision Support System (based on screening tool of older person's prescriptions and screening tool to alert to the right treatment (STOPP/START) prescribing rules) issued to European Patent Office (Munich)

Data availability statement

Data for this study will be made available to others in the scientific community upon request after publication. Data will be made available for scientific purposes for researchers whose proposed use of the data has been approved by a publication committee

Ethics approval

The OPERAM trial was approved by the independent research ethics committees at each participating site (lead ethics committee: Cantonal Ethics Committee Bern, Switzerland, ID 2016-01200; Medical Research Ethics Committee Utrecht, Netherlands, ID 15-522/D; Comité d'Ethique Hospitalo-Facultaire Saint-LucUCL: 2016/20JUL/347– Belgian registration No: B403201629175; Cork University Teaching Hospitals Clinical Ethics Committee, Cork, Republic of Ireland; ID ECM 4 (o) 07/02/17), and Swissmedic as responsible regulatory authority.

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Informed consent

Written informed consent was obtained from the patients or their legal representatives before enrolment in the OPERAM trial.

Trial registration

ClinicalTrials.gov Identifier: NCT02986425

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Hospital residents' perceived barriers and facilitators for pharmacotherapy optimisation for hospitalised older patients with polypharmacy

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ABSTRACT

Background: Despite the well-documented harms, the prevalence of inappropriate prescribing remains high among older patients with polypharmacy. In order to develop and implement effective strategies to reduce inappropriate prescribing and subsequent negative health outcomes, it is important to identify and understand patient- and prescriber-related factors that positively or negatively influence implementation of in-hospital medication review strategies. The objective of this study was to explore hospital physicians' perceived barriers and facilitators for pharmacotherapy optimisation for hospitalised older patients with polypharmacy.

Methods: A qualitative study was performed with semi-structured interviews among hospital residents from both surgical and non-surgical specialties, in the Netherlands and Belgium. Content analysis was conducted including deductive and inductive analysis. The deductive analysis was based on categories drawn from social cognitive theories that have been associated with health care professionals' intentions and actual behaviour in prior research (i.e. Fishbein and Ajzen's 'theory of reasoned action' (TRA) and it's extension the 'theory of planned behaviour' (TPB), combined with Triandis' theory of interpersonal behaviour (TIB)). Qualitative data analysis software (NVivo®) was used to facilitate coding and analysis.

Results: Thirteen hospital residents participated in the study. The residents came from eight medical specialties across three hospitals in two countries. The barriers and facilitators identified emerged within two main themes: prescriber- and environment/setting-related factors. The most important barriers to in-hospital pharmacotherapy optimisation mentioned by hospital residents were: lack of time, patients' lack of knowledge of their own treatment and reluctance to change, absence of a long-term patient relationship, the specific hospital setting where patients are sick/unstable and the residents' lack of knowledge/skills to perform medication reviews. The facilitators elucidated were: the presence of certain triggers (e.g. suspected side effects) related to evaluation of the medication, supervisors acting as role models, more education and training concerning appropriate prescribing and consulting medication optimisation teams.

Conclusion: Assisting hospital residents in identifying patients at risk for inappropriate prescribing and drug-related problems combined with providing consulting pharmacotherapy optimisation teams, will likely improve prescribing for hospitalised older patients and ultimately reduce drug-related problems and readmissions.

BACKGROUND

The prevalence of inappropriate prescribing and the use of potentially inappropriate medications (PIMs) remains high among older patients, despite the well-documented harms such as an increased risk of adverse drug reactions leading to more emergency department visits, hospital (re)admissions and overall mortality.[1,2] Periodic evaluation and optimisation of an individual patient's pharmacotherapy – that is medication review – aims to reduce inappropriate prescribing and ultimately improve patient outcomes.[2,3] To date, however, trials aimed at reducing drug-related problems, including drug-related admissions (DRAs), have failed to prove the effect of medication review on health-related outcomes in older patients.[4–6] Nevertheless, the majority of trials have been heterogenous in methodology and had a high risk of bias.[5] Additionally, pharmacotherapy optimisation recommendations from researchers (pharmacists and/or physicians) had low implementation rates in several trials, compromising the possibility to draw firm conclusions concerning the actual effect of pharmacotherapy optimisation interventions.[6–8] Moreover, the interpretation of the findings from trials investigating complex multicomponent interventions is difficult without an analysis of the underlying care process and the context in which the interventions were performed.[9,10] In particular, in the case of an unsuccessful intervention, process evaluation is important to distinguish between interventions that are inherently faulty (failure of intervention theory or concept) and interventions that are poorly delivered (implementation failure).[9–11]

To develop and implement effective strategies to reduce inappropriate prescribing and negative health outcomes, it is important to identify and understand patient- and prescriber-related factors that may positively or negatively influence implementation of medication review strategies. Patients' decisions to (dis)continue medication have been found to be influenced by multiple competing barriers and facilitators, such as a positive or negative attitude towards medication, perceived appropriateness of the prescription and the experience of side effects versus perceived or expected benefit. Trust in the health care professional proposing the medication changes has shown to be an important facilitator for the cessation of PIMs.[12–14] Barriers to identifying and managing PIMs on a prescriber level have been found to be related to knowledge and/or skill deficits, including the difficulty surrounding balancing the benefits and harms of therapy, recognising adverse drug events and establishing appropriate indications for medication. In addition, extrinsic factors such as the (older) patient, the work setting/environment, the health-care system and cultural factors can influence (appropriate) prescribing.[15,16]

Studies on barriers and facilitators to pharmacotherapy optimisation have mainly investigated the views of primary care physicians rather than those of hospital prescribers and have primarily focussed on single PIMs or drug classes and not on optimising the entire pharmacotherapeutic regimen in older patients with polypharmacy.[15,17] As hospital residents usually prescribe medication on admission, during hospitalisation and on discharge, they are also important (potential) stakeholders for performing clinical medication reviews and implementing pharmacotherapy optimisation recommendations from consultants. Therefore, identifying hospital residents' barriers and facilitators for in-hospital pharmacotherapy optimisation for older patients with polypharmacy could help determine the focus for future interventions and enhance implementation of pharmacotherapy optimisation recommendations to improve older patients' pharmacotherapy and related outcomes.

The objective of this study was to explore hospital physicians' perceived barriers and facilitators for pharmacotherapy optimisation for hospitalised older patients with polypharmacy.

METHODS

Setting, study design and study population

A qualitative study was performed among hospital residents from different medical specialties. Residents were chosen (instead of senior physicians)as they perform the majority of prescribing in the ward on admission and discharge. The residents were recruited from two hospitals in the Netherlands – one academic (University Medical Centre Utrecht) and one non-academic (St. Antonius Hospital Nieuwegein) – and one academic hospital in Belgium (Clinique Universitaires Saint-Luc). The inclusion criteria were involvement as a ward physician in the daily care of multimorbid older patients with polypharmacy, experience with receiving pharmacotherapy optimisation advice from consultants and oral consent for the researchers to conduct and audio record the interview. No exclusion criteria were applicable. The participating hospital residents were recruited from both surgical and non-surgical wards between January 2018 and February 2019.

The majority of the recruited residents also participated in in the "OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people" (OPERAM) randomised clinical trial. Details of OPERAM have been published elsewhere.[18,19] In brief, the intervention within the OPERAM trial consisted of a medication review according to the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) method.[3] Physicians in the intervention arm of OPERAM received pharmacotherapy optimisation recommendations from a research physician and pharmacist for their patients. Physicians in the control group treated their patients according to usual care without medication advice from the research team. For the present study, physicians from both OPERAM intervention and control arms were included. To ensure a diverse sample, the individual physicians were selected through *purposeful sampling*. *Purposeful sampling* is a technique used in qualitative research for the identification and selection of participants based on both characteristics of a population and the study objective.[20] This study included both surgical and non-surgical residents from different medical specialties (e.g. pulmonology, urology, internal medicine and general surgery) from the three mentioned hospitals. Residents working in the geriatric department were not included in this study due to their presumed high standard of care regarding medication reconciliation and optimisation (consistent with the OPERAM trial). The sample was further augmented through *theoretical sampling,* whereby new participants were selected based on their potential additional value to the data set and the developing theory. In this phase, physicians not involved in the OPERAM clinical trial were added to the sample to represent the views of (general) surgeons. Based on prior qualitative research by other researchers using semi-structured interviews,[15] we aimed to include 12

to 15 residents. However, the sampling was a cyclical process which continued until data saturation was reached. Data saturation was considered achieved once no new codes emerged during the analysis of the last two interviews up to that moment.

Data collection and analysis

The semi-structured face-to-face interviews were conducted in the local language by the members of the research team (NL: C.H. and J.O.H.; BE: C.P. and A.C.), all of whom have been trained in qualitative data collection and analysis, possess sufficient knowledge regarding pharmacotherapy in multimorbid older people and had prior experience conducting interviews.

A topic guide for the interviews, with open-ended questions was developed based on existing social cognitive theories frequently used for the prediction of (health-related) behaviours.[21,22] The social cognitive theories used for the topic guide were: Fishbein and Ajzen's 'theory of reasoned action' (TRA)[23] and it's extension the 'theory of planned behaviour' (TPB),[24] combined with Triandis' theory of interpersonal behaviour (TIB).[25] In many behavioural models, such as the TRA, TPB and TIB, intention is the immediate antecedent and key determinant of behaviour. A systematic review performed by Godin et al. aimed to quantify to what extent studies based on social cognitive theories explain the intention of health-care professionals (HCPs) concerning the adoption of clinical behaviours and predict health professionals' clinical behaviour.[22] The conclusion of Godin et al. was that TRA/TPB predicts HCPs' behaviour significantly more accurately than other theories. However, regarding the prediction of underlying behavioural intention, studies based on TIB have been shown to best predict HCPs' intentions. The most important determinants of intended behaviour found by Godin et al. were *beliefs about capabilities* (i.e. control belief in TPB), *beliefs about consequences*, *moral norm* (i.e. behavioural belief in TPB), *social influences* and *role and identity*. The cognitive determinants most consistently associated with HCPs actual behaviour were *beliefs about capabilities* and *intention* (to perform the behaviour). Other relevant reported determinants were *past behaviour/experience* and *knowledge*. As no single theory predicted both HCPs intention and behaviour with accuracy, we combined the significant determinants of intention and behaviour from the TRA/TPB and TIB. To visualise all these significant determinants and their presumed relation with intended and actual behaviour we combined the determinants into one figure; this figure was then used for the development of our topic guide (**Figure 1**).

The interview topic guide was developed in Dutch and translated into English and French. The topic guide was piloted with two residents in each country, which led to the creation of the final version (**Appendix 1**). The participating residents were asked

to elaborate on their experiences with and perspectives on the prescribing process and optimising pharmacotherapy in the clinical setting, focussing on our target population (i.e. hospitalised multimorbid older patients with polypharmacy), based on a representative case scenario. Physicians were encouraged to discuss their current working process (actual behaviour) and share their experiences with and perspectives on optimising pharmacotherapy (behavioural intentions) in the clinical setting. The interviews consisted of eight open ended questions with follow-up questions and probes to address all the important domains and to discover underlying motivation to perform the behaviour (**Appendix 1**). Interviews lasted 30 to 45 minutes on average.

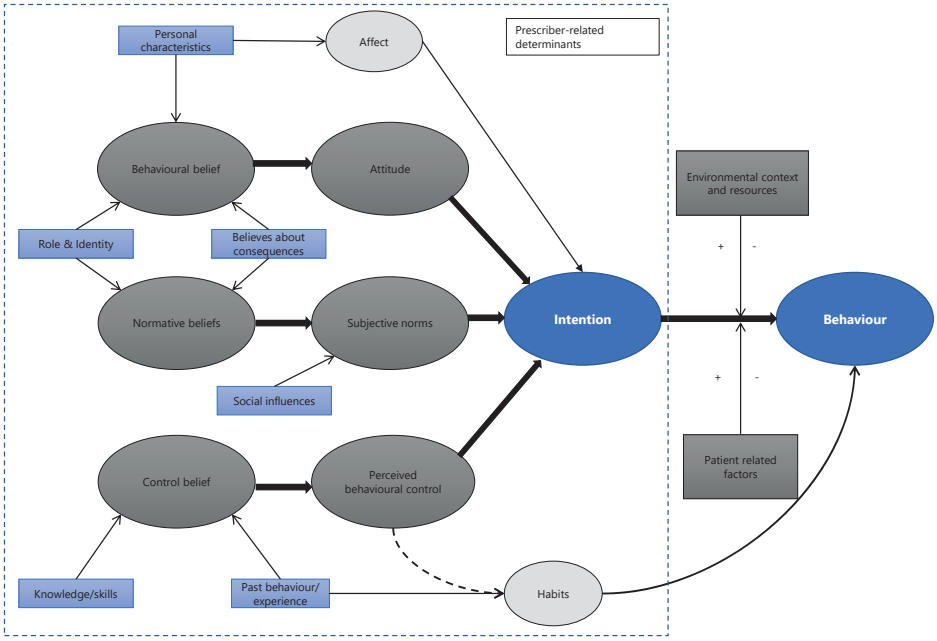

Figure 1: Visualisation of potential determinants of physicians' behaviour and intention to perform the behaviour based on TRA/TPB and TIB used for the development of the topic guide for this study.

For both countries the interviews were audio recorded with permission of the interviewed hospital resident and transcribed verbatim by the local researchers in the local language. The resulting transcripts were anonymous, with no specific information on the residents included. Data collection and data analysis occurred simultaneously following the model for qualitative research developed by Mays and Pope.[26] Content analysis was performed including both deductive and inductive analysis.[27] The deductive analysis allowed for exploration of the residents' perspectives based on the topic guide and the predefined factors/domains derived from the social cognitive theories. The inductive

analysis made discovering unexpected findings possible, including findings within the deductive categories. The transcripts were independently coded in English, by two different researchers per country. Based on this step, a code dictionary was developed following transcription of the first interviews. The researchers met afterwards to reach consensus about the assigned codes. This dictionary was further supplemented with new codes once new information emerged. Qualitative data analysis software (NVivo® version 11 and 12) was used to facilitate storing, coding and analysis of the data.

After finishing the coding process and completion of the code dictionary, data were interpreted with the aim of developing themes that may provide explanations for the findings. Theoretical concepts were generated through the use of analytical memos, comparison with existing literature and discussion between the researchers. Data saturation was reached after 13 interviews were analysed.

Ethical committee

For the current study the Ethical Board of the University Medical Centre Utrecht provided a declaration for non-liability to the Dutch law for medical research on humans. The protocol was submitted to and approved by the Belgian Ethical Board.

RESULTS

Description of participants

In total, 25 hospital residents were approached. 13 residents from different medical specialties across three hospitals in two countries agreed to participate in this study. The participating residents worked in eight different medical specialties: pulmonology (2), internal medicine (2), neurology (1), urology (1), general surgery (2), neurosurgery (1), orthopaedics (3) and cardiology (1). Nine of the residents involved in this study also participated in the OPERAM trial, while four did not (these four were all recruited from the University Medical Centre Utrecht). Working experience as a prescribing resident varied from <1 to >5 years (median 2.5 years), mean age was 28.8 (range 25–32) years old and 53.8% were female.

Barriers and facilitators for in-hospital pharmacotherapy optimisation

The identified barriers and facilitators for in-hospital pharmacotherapy optimisation identified were divided into two main themes: ***prescriber-related factors*** and ***environment/setting-related factors.*** Presciber-related factors referred to elements intrinsic (e.g. role and identity) or related (e.g. social influences) to the prescriber and environment/setting-related factors were those related to the dynamic hospital setting and (digital) infrastructure.

In the results in the following section, the terms accurate prescribing and pharmacotherapy optimisation are used to describe different processes. *Accurate prescribing* concerns medication prescribing on admission, including the medication reconciliation process. *Optimising pharmacotherapy* involves the critical evaluation of a patient's pharmacotherapy, including a comprehensive medication review, carried out after the initial prescribing process is completed.

Prescriber-related factors

Professional role and identity

Barriers

Although all participants claimed to feel responsible for the medication they prescribe to patients admitted to their ward, approximately half of the residents have experienced mixed feelings about this responsibility. In particular, these mixed feelings occurred in case of continuation of home medication that was initially prescribed by other physicians or when it concerned medications beyond their area of expertise.

> *"It doesn't always feel fair to be responsible for medication you did not prescribe in the first place".*

"Legally, I am responsible, but you don't always have the time or the expertise to check everything and take your responsibility afterwards".

In terms of optimising a patient's pharmacotherapy, the feeling of responsibility was experienced slightly differently amongst the participants. The physicians with a more surgical background argued that medication review and subsequent pharmacotherapy optimisation are primarily the responsibility of the general practitioner (GP).

"I don't think it's your responsibility as a ward physician to conduct a comprehensive STOPP/START review for every patient. And maybe that's the problem – nobody really feels responsible".

One of the reasons for this lesser feeling of responsibility mentioned was the long-term relationship between the GP and the patient, as well as the follow-up and monitoring that need to be coordinated by the GP after hospital discharge. Some surgical residents mentioned (appropriate) medication prescription is not their main priority – *"surgery comes first"* – while others felt all doctors should have some knowledge and skills regarding (appropriate) prescribing and optimising pharmacotherapy. Most physicians thought (appropriate) prescribing and optimising pharmacotherapy are important but did not necessarily believe that they are the right person to perform a medication review.

"I am not sure whether you are the right person to do this [as a ward physician], because you only see the patient once … But I still think it's your responsibility as a ward physician to evaluate a patient's pharmacotherapy regimen critically".

Most surgical residents explicitly mentioned they do not consider it as the role of a surgeon to optimise pharmacotherapy.

"I am not someone who just stops all kinds of medications – I don't think it's my role as a surgeon to do that".

The degree of active detection of and subsequent action concerning drug-related problems differed between the participants. Where some experienced responsibility to check these problems at some time during admission, others felt it was the responsibility of the initial prescriber of the drug or the GP to monitor drug-related problems.

Facilitators

All participants reported feeling a certain extent of responsibility for the medication they prescribe to patients admitted to their ward.

"I believe the moment you prescribe something you're responsible, even if the patient has been using it for over 300 years (so to speak)".

The majority of residents considered it a ward physicians' duty to ensure no harm is caused by prescribing medication to a patient, both in the case of continuing home medication and that of new medication being started by the ward physicians themselves.

"Everything that happens to a patient during hospital admission is the responsibility of the ward physician, including the medication prescribed".

Some residents felt it was their responsibility to critically evaluate their patient's pharmacotherapy regimen during admission, particularly when the residents started their patient on new medications or when side effects were suspected. However, the interview participants generally agreed that, due to time constraints, such critical evaluation is not always possible. Moreover, when a patient experiences problems, some residents consult the pharmacist or geriatrician to evaluate the patient's medication and obtain recommendations. Thereby, these residents have often transferred the responsibility of medication changes to professionals deemed more qualified.

"If we get medication advice from other specialists we are responsible to implement the changes and if we don't feel qualified, it's our responsibility to make sure there will be follow-up by the GP or the specialist concerned".

Social influences and subjective norms

Barriers

The Belgian residents outlined the need to obtain an accurate medication list by asking the patient or retrieving the information from the medical file. The participants expressed trust in lists composed by a geriatrician or internist, however, such lists are not always available in the patients' file. The Dutch residents said they rely mainly on the pharmacy technician to obtain the list from the community pharmacy and verify with the patient.

Overall, participants found that medications prescribed by a cardiologist are difficult to adjust. Some residents stated they never adjust cardiovascular medication, while others call the prescribing cardiologist and discuss whether medication could be stopped or is actually indicated.

"If the indication of certain drugs is unclear I try to figure out who prescribed it, for instance the cardiologist or the GP and then consult them by phone or email".

When a patient is admitted through the Emergency Department and a colleague prescribed the medication, nearly all residents acknowledged they would rely on their colleague's work and expect them to have discovered any problems or inconsistencies within the medication regimen of the patient.

> *"In all honesty I must admit that due to the workload I rely on my colleague for accurately prescribing the medication on admission – also because this colleague made a plan for the patient and a differential diagnosis where medication-related problems are included in the considerations".*

Not many residents have discussed patients' medication with their direct colleagues. Sometimes a supervisor has been involved in medication decisions, but this was said to be helpful only when it concerned medication from the supervisor's own field of expertise. In case of polypharmacy and optimising treatment, the consensus according to the interviewed residents was that most supervisors do not significantly contribute.

> *"I think 75% of the supervisors never even prescribe medications and they probably don't even know how it works. So, I don't expect anything from them in this".*

While the non-surgical residents stated intention to evaluate the medication for all their admitted patients, surgical residents said they do not evaluate the medication of their patients with the aim to optimise treatment. Surgical residents outlined how they work with interaction signals and adjust medication accordingly, if necessary, but they do not actively ask patients if they are experiencing side effects, for example, nor evaluate the indication of chronic medication.

> *"Sometimes a patient really stands out with the number of drugs he takes. Then I think: Yeah, let's scroll down. Do I need to take something into account? But that's a global check, not a comprehensive review".*

Facilitators

All the interviewed Dutch residents had experience with medication verification performed by a pharmacy technician and generally expressed reliance on these technicians to define the most accurate list of medications used by the patient. In case of discrepancies between two sources, the GP is consulted to clarify and, if needed, identify indications for certain medications.

"In case of discrepancies between the medication list from the pharmacy and the patient, I will trust the pharmacy to be the most reliable source. Most older patients don't know exactly what they are taking or they forget or don't use it properly".

When drug-related problems are detected involving medications outside the ward physicians' field of expertise, most interviewed residents said they feel free to consult different specialists. The most consulted specialties were internal medicine and cardiology.

"Sometimes I consult other specialist like internists or cardiologist when I have a question about medications they prescribed and that do not go well together with new drugs we like to start. But this does not happen often".

Two residents stated they always check and evaluate the medication of all patients at least once during admission. One resident mentioned that he/she would only be triggered to reassess the medication prescribed by a colleague to see if anything should be adjusted in case the patient "is not doing well".

"...Unless the patient is not doing well, then I re-assess the medication list to see if anything needs be adapted or stopped. But I trust the work of my colleague and when the patient is fine, then I don't check it again".

The residents stated that, in general, when a consulting specialist proposes medication changes for a patient admitted under the resident's responsibility, the specialist's judgement is trusted and their recommendations likely followed.

"I never consult the geriatrician solely for medication optimisation. But, if the patient has orthostatic hypotension and other vague geriatric things in combination with 20 different medications, then I do".

Further, it was found to be very important that supervisors set an example and perform medication reviews more often. The interviewed residents tended to feel that supervisors should act more like a role model for their residents.

"What would really help in my opinion is when supervisors would do it more often. Like for example: 'Okay, let's take a look at this medication list together.' Because now I feel that for them it is not really a priority"

Knowledge and skills

Barriers

Insufficient pharmacotherapy knowledge emerged as a self-reported barrier for nearly all residents. Participating residents were asked to rate their own pharmacotherapy knowledge on a scale from 0 to 100 (Appendix 1). Scores ranged from 30% to 75% with a median of 60%, whereby their own desired score was between 80% and 90%. The majority of residents expressed willingness to follow courses to improve their pharmacotherapy knowledge, but had experienced a lack of opportunities to do so.

> *"If I am honest, I think my knowledge is deteriorating … A course to freshen up this knowledge would be an idea. It needs to be aimed at surgeons though – we don't have to learn the same as geriatricians".*

> *"I don't know what a structured medication review is, so I don't think I did it before".*

Another knowledge/skill-related barrier mentioned by most residents was the discrepancy between the attention towards pharmacotherapy during medical school and lack of focus on appropriate prescribing in clinical practice.

> *"The thing I find disappointing is that we get everything explained so well during education, but in clinical practice it is not really implemented".*

> *"I don't feel qualified to do a medication review. We've had this in college, but we don't possess the know-how to do it properly I think".*

Nearly all residents felt their pharmacotherapy knowledge could be improved, but not all residents aspired to take steps to achieve this. Some surgeons mentioned a tendency to delegate medication-related tasks to other specialists more often.

> *"Do I want to know more? That's always the question. I think we tend to delegate more and more. For instance, when a diabetic patient is admitted we consult the internist to regulate the blood sugars, however, glucose control is not that complicated. So, in a way, we could do better".*

Facilitators

Most residents stated they would like to have more education about pharmacotherapy and the related optimisation during their clinical training. Tools such as the STOPP/START criteria were known by some (non-surgical) residents, however, those tools were

said to be mainly used in educational settings. These tools were reported as helpful but not structurally used in clinical practice; when they have been used, the use has usually been only as a reference for specific medications or indications.

> *"Maybe more education about this would help, and also more recommendations for your patients from others would help. I learn much more from clinical practice than from education and paper cases. This helps me for future patients as well".*

> *"I've had education about STOPP/START criteria a few times and I have some of those criteria in my head. If I have doubts about something I Google those quickly. I do not use them structurally, but I think I use most of them".*

Most physicians thought more education and practice would help them to improve their knowledge and skills and that such education and practice should be repeated on a regular basis.

> *"I think there should be more focus on optimising pharmacotherapy during medical school and also during your residency. Especially with the ongoing ageing of the ppopulation it should be embedded in every training, as every specialty (except for paediatrics) will come across elderly patients and thus polypharmacy".*

Some residents said that medication evaluation should be incorporated in their daily practice as standard of care – when it is part of daily routine, it will not be forgotten. Additionally, increased practice would help to improve residents' skills and make residents more efficient at conducting medication reviews.

> *"It just has to be incorporated in your daily practice. So, I think you have to find yourself a predetermined moment per patient to do this. "*

Receiving pharmacotherapy optimisation advice from consultants, such as geriatricians or pharmacist, was reported to be experienced as very valuable. Recommendations provided by these consultants were said to almost always be implemented.

> *"Consulting a specialist, for example the geriatrician, could be really helpful because everything is critically evaluated and it leads to specific advice. I think not all my colleagues know the possibility of referring a polypharmacy patient to the geriatrician. More visibility and familiarisation would help".*

One resident stated he/she regularly consults an internist as early as the prescribing process in case of renal insufficiency or doubt about the safety of some medications at that moment for that patient.

Past behaviour/experience

Barriers

All interviewed hospital residents worked with older polypharmacy patients on a daily basis. There was consensus regarding more complex prescribing in this patient group compared to other patient groups, not only because these patients use more medications, but because they are more prone to side effects, interactions and complications during hospitalisation. On the part of the resident in these scenarios, prescribing was experienced as more time-consuming and required more effort than in patient groups without polypharmacy or frailty.

> *"My experience with these patients is that it's a lot of work to verify all the medication and approve it, including all the adjustments the pharmacy has made. In comparison to other patients there are more interactions you need to take into account while prescribing medication".*

> *"In older patients with polypharmacy I am more aware of drug-related problems when I prescribe medication and that I must do dose adjustments more often than in other patient groups".*

> *"My experience with these patients when they are admitted to the hospital is that they are frail and frequently use a lot of medications. It's a very fragile balance and after surgery many things could dysregulate, like development of delirium and electrolyte disorders".*

The fact that many older patients do not know exactly what medication they have been using was stated to be an important barrier for accurate prescribing (i.e. not making prescription errors) and subsequent pharmacotherapy optimisation by the residents.

> *"In my experience most of these older polypharmacy patients do not know what they are taking and when they are taking it, which leads to errors. I think in pulmonary medicine there's a high risk group of patients that neglect themselves including not taking proper care of their medication as well. I think this is a big problem".*

Discussion about pharmacotherapy optimisation was experienced as difficult if patients are not aware of their own prescriptions and related indications for which they are using these prescriptions. It was stated that, usually there are many different sources for obtaining the medication list (patient, relative, GP, pharmacy) and the residents find it difficult to determine which is the most accurate.

> *"The really old patients usually don't remember what medications they are taking. So, I don't trust them with that and rely on the hospital pharmacy then".*

> *"There are a lot of different sources for medication overview and sometimes there are discrepancies. This is difficult and could lead to errors. During office hours I would rely on our pharmacy, and during the night shift I have to trust the patient".*

Most residents mentioned that sometimes the patients themselves prevent optimising pharmacotherapy because of their reluctance to stop chronic medications, especially benzodiazepines.

> *"It's difficult to stop benzodiazepines in patients. You can try to stop, but in the end you must prescribe them again".*

> *"In case of side effects from medications the patient is really attached to, it's a negotiation with the patient: does he suffer more from the side effect or is he more attached to the drug? I always try to explain it to them and see if we can find an alternative with fewer side effects. If the patient persists on continuing the medication nonetheless, that's up to them".*

Facilitators

When prescribing a patient's medication, most residents said they would like an accurate medication list to start with. Some residents mentioned they simply copy the list the patient brings without further research or questioning, while others rely on the pharmacy technician to register the actual medications first.

> *"At first, I copy the home medication list 1:1, unless there are medications that don't match with admission diagnosis or have another reason to be stopped".*

> *"I always ask the pharmacy technician to verify the medication first. I don't do that myself".*

Certain triggers within the patient or the medication list were found to facilitate pharmacotherapy optimisation. Blood pressure medication was said to be regularly adjusted or even stopped by the residents during admission, and in cases of falling or confusion the use of benzodiazepines is re-evaluated. The maximal daily dose of pain killers is adapted frequently (to a lower dose in older patients) and a proton pump inhibitor is prescribed more often as co-medication. Renal function is frequently diminished in older patients and most residents check if related dose adjustments are needed, especially when antibiotics are prescribed.

> *"If a patient is really old or confused or has a high risk of falling I usually evaluate if benzodiazepines are really necessary and see whether there's no inappropriate medication that can be stopped".*

> *"I am more cautious in older patients. The maximal frequency of oxycodone is 6 times daily, but in older patients I don't start with this. Also, paracetamol I prescribe 3 times 1000mg instead of 4".*

Environment/setting related factors

Electronic prescribing systems

Barriers

Residents stated they mainly use electronic prescribing systems to detect potential interactions, both between medications already used by the patient as outlined on admission and with newly prescribed medications during admission. Such systems were reported as helpful by most residents, however, due to the high number of alerts and warnings (especially in polypharmacy patients) which are not always clinically relevant, many residents tend to click the majority of alerts and warnings away (alert fatigue). The residents acknowledged this could result in the missing of relevant alerts and potentially cause harm to the patient. Some interactions are well-known, but less familiar ones are sometimes discussed with the pharmacist, most often to verify the clinical relevance and the desired action from the resident.

> *"In patients with polypharmacy you will get a very long list of alerts and it's not always relevant. Then one relevant alert in this long list could easily be missed".*

> *"I once had an incident where I prescribed digoxin wrongly in the middle of the night. We had 2 different tablets available differing in dose 1,000-fold. This was an unrealistic dose and the system should have prevented me from prescribing this".*

Facilitators

Residents would like the pharmacist or pharmacy technician to reconcile and register all home medications for every newly admitted patient, including outside office hours. The interviewed residents believed this would increase efficiency and could prevent prescribing errors due to the lack of time to check everything themselves.

> *"If a pharmacy technician were present in the Emergency Department they could register the right medication in the prescribing system and then I can approve it. This would lead to less prescribing errors".*

The electronic prescribing systems were reported as helpful in detecting interactions, and could also be used as an important first step in optimising pharmacotherapy, as suggested by some residents. One (non-surgical) resident suggested these systems would be a useful medium to implement screening tools, such as STOPP/START criteria, to help residents in optimising therapy.

> *"I am familiar with a lot of interactions already, but I check the ones I don't know yet to learn for the next time. I investigate further if I get a lot of alerts for one patient. "*

> *"The most important ones [interactions] you know, for instance with renal insufficiency or important medication interactions. However, there are also a lot of less familiar interactions you don't know, so that's when these systems really help".*

> *"...I think it would be an opportunity to integrate the STOPP/START criteria in such systems. This will remind you, for instance, to think about osteoporosis prophylaxis when you are prescribing prednisone".*

Clinical setting

Barriers

The most important barrier to perform a medication review during hospital admission was found to be the lack of time. Ward residents reported experiencing a high workload and therefore limited time to spend on a medication review.

> *"Time. Time is the biggest issue. You just don't have enough time to do all this. And if you do this, and I think it's important, it takes you about 15 to 30 minutes per patient. And that time is just not available. That's the most important barrier".*

"If you really want to evaluate the medication critically, it takes a lot of time – at least that's the scenario everyone has in mind. Finding all the indications could indeed be time-consuming".

"Do I think it's realistic with the workload we have? No, I really don't".

The unfamiliarity with certain medications prescribed to patients and the lack of clear indications for those medications and information regarding the primary prescriber was another barrier identified for pharmacotherapy optimisation. Further, the residents mentioned that the absence of a long-term relationship with admitted patients means the residents do not always have the responsibility to optimise chronic pharmacotherapy.

"I think commonly mentioned reasons are high workload, and that you're not the regular ward physician but you only stepped in for one day and therefore don't feel responsible".

In addition, some patients have a short length of stay, especially those admitted for elective surgical procedures. In such cases, there is no time for medication review. Additionally, some residents expressed doubt regarding whether the clinical setting is appropriate for performing a medication review because patients can be very unstable.

"Maybe, the clinical setting with all the chaos, is not the right place to do it. If you really want to do a medication review you should not do it when the patient is ill and many other patients are ill too".

Facilitators

The possible advantage of performing a medication review during hospitalisation was stated to be the presence of the patient and the availability of expertise from different medical specialists. Close collaboration between (surgical) wards and geriatric consultants was mentioned by some residents as an opportunity to improve pharmacotherapy in older adults during hospitalisation. An additional potential facilitator mentioned was multidisciplinary meetings with pharmacists and/or geriatricians to discuss patients' pharmacotherapy.

"Basically, the hospital is a good setting to perform a medication review, because there is a lot of knowledge available and we have a lot of patients fulfilling the criteria, so you could reach a lot of patients at once".

"I think it would be good to have a sort of multidisciplinary meeting including the pharmacist where patients' medication is discussed, like happens now at the GP. "

"I think it should be standard of care for surgical wards to work together with the geriatricians. They could then also focus on medication optimisation".

The presence of certain triggers can facilitate performing a medication review during hospital admission and also help convince patients to optimise their pharmacotherapy. The triggers mentioned were complaints/symptoms (e.g. confusion or falling) that could possibly be side effects, a palliative setting, diminished renal function and unfamiliarity with certain medications.

"In case a patient is admitted for a complaint or electrolyte disorders, that will get me thinking: could it also be medication-related? I think I am more triggered by the reason for admission and evaluate the medication while working on that then the other way around".

"If a patient presents at the Emergency Department with symptoms likely to be side effects, something needs to be changed – you cannot send the patient home with the same medication then".

DISCUSSION

This study provides an in-depth exploration of hospital residents' perceived barriers and facilitators for optimising pharmacotherapy for older patients with polypharmacy during hospital admission in both surgical and non-surgical wards. We identified barriers and facilitators within two main themes: prescriber-related and environment/setting-related.

The most important barriers mentioned were the high workload experienced in the wards, which results in a lack of time to evaluate patients' pharmacotherapy, together with discrepancies between different sources of medication and patients' lack of knowledge of their own treatment. In addition, the absence of a long-term relationship with the patient (in contrast to a GP), patients' reluctance to change chronic medications and the clinical setting where patients are usually sick and unstable were mentioned as critical barriers. Some residents do not feel qualified to perform a medication review or have never performed one. The surgical residents mentioned that they did not consider it the role of the surgeon to optimise pharmacotherapy, yet they do feel responsibility for the medication prescribed during admission. The facilitators for optimisation elucidated were the presence of certain triggers (e.g. suspected side effects, a palliative setting and renal insufficiency) to cause evaluation of the medication, an example set by a supervisor (role model), increased education and training on appropriate prescribing and medication optimisation advice from consultants. Screening tools such as the STOPP/START criteria could be helpful once incorporated in electronic prescribing systems; otherwise, the use of such criteria is considered too time-consuming.

These findings correspond relatively closely with the barriers identified by Cullinan et al. through their semi-structured interviews with hospital physicians based on the theoretical domains framework (TDF).[16] Cullinan et al. reported four main barriers to appropriate prescribing: an environment conducive to sub-optimal prescribing (e.g. lack of IT structure), constrained resources (e.g. lack of targeted pharmacy input on the wards), lack of specific training (e.g. geriatric pharmacotherapy and feeling ill-equipped to prescribe appropriately), poor patient education (e.g. patients' poor knowledge of own medication). However, their study only included internal medicine and geriatric physicians and therefore does not take the perspectives of surgical physicians into account. The majority of surgical residents in our study believe medication reviews are not their job and they do not have the expertise to perform them, therefore, the interview participants expected they will probably not perform such reviews in the future regardless of the other mentioned barriers.

Recently, Lau et al. performed a scoping review exploring the barriers for effective prescribing in older people by applying the TDF in an ambulatory setting.[28] Multiple domains were elicited as barriers to effective prescribing including physician-related factors such as 'knowledge', 'skills' and 'social/professional role and identity' on top of issues surrounding 'environmental context and resources' and the impact of 'social influences' and 'emotion' on prescribing behaviour. Furthermore, this review identified three major stakeholders that influence effective prescribing: the patient, the physician and the health care system as a whole. The reviews' findings correspond with the barriers identified by the interviewed hospital residents for this study, which not only included barriers intrinsic to the prescriber, but system(environment)-related factors as well. Patient-related factors were not specifically investigated in our study, as we only focused on older hospitalised patients with polypharmacy – no other patient groups. However, changing the prescribing climate will require interventions that target all the stakeholders identified in the scoping review by Lau et al., including health care policy makers.[28] The results of our qualitative study support these conclusions.

Another important potential facilitator – or barrier when not implemented well – to improve prescribing during and after hospitalisation is patient involvement in decision-making regarding pharmacotherapy optimisation, as was reported by Thevelin et al., who interviewed OPERAM participants about their experiences regarding hospital-initiated medication changes.[29] In the MedBridge trial, Kempen et al. identified facilitators and barriers to performing comprehensive medication reviews and post-discharge follow-up in older hospitalised patients from the health care professional's perspective as part of a process evaluation.[30,31] Unfortunately, the MedBridge trial did not find a decreased incidence of unplanned hospital visits in hospitalised older patients that received a medication review plus post-discharge follow-up.[30] In the related qualitative study the focus was on collaboration between hospital physicians and ward pharmacists involved in the trial, regarding in-hospital medication review. Six main themes were found regarding barriers and facilitators (a) medication reviews and follow-up are needed, but not in all patients; (b) there is a general belief in positive effects; (c) lack of resources is an issue, although the performance of medication reviews may save time; (d) pharmacists' knowledge and skills are valuable, but they need more clinical competence; (e) compatibility with hospital practice is challenging, and roles and responsibilities are unclear and (f) personal contact in the ward is essential for physician-pharmacist collaboration.[31] The role of the (ward) pharmacist in performing the medication reviews was not so prominently discussed by the residents in our study, as such a process is not (yet) widely implemented in most wards in Dutch and Belgian hospitals. However, regarding the expressed aspiration to receive more pharmacotherapy optimisation advice from consultants, involving the clinical pharmacists more in the ward could be potential new strategy to investigate in future trials.

Limitations

As with all qualitative research, the results presented here cannot be generalised to other settings. Additionally, due to the conducting of the interviews in two different languages (Dutch and French) and translation into English for data analysis, some nuances might have been lost. All interviewed physicians were residents with relatively short prescribing experience (median of 2.5 years), however, we believe this reflects daily clinical practice relatively well, as most prescribing in the hospital wards is completed by this group of "junior" doctors.

This was a qualitative study exploring hospital residents' theoretical intention and behaviours rather than measuring or observing the target behaviour. Therefore, the relative contribution of the different determinants of intention and behaviour cannot be established from these results. Objective assessment of behaviour might be less subject to several biases (including reporting bias) than self-reports. However, the principle of correspondence between intention and behaviour, as recommended by Fishbein and Ajzen, cannot always be applied in studies using objective measures.

Moreover, our interview topic guide was based on a combination of social cognitive theories (TRA/TPB and TIB), while the TDF was developed and validated to examine HCPs' behaviour. Nevertheless, the results we found correspond relatively well with the categories identified by Cullinan et al. who used the TDF.

Patient-related factors were not specifically investigated in this study, as we only focussed on older hospitalised patients with polypharmacy. No comparison with other patient groups was made. Patient-related factors might, however, act as additional barriers or facilitators to pharmacotherapy optimisation in the hospital setting.

Finally, content analysis is a qualitative data analysis method developed to validate or extend a (conceptual) theory, primarily focussing on deductive category application. This could lead to bias as finding evidence supportive of the theory is more likely than finding non-supportive evidence.

Implications

Increased focus and priority on pharmacotherapy optimisation amongst physicians should contribute to improved implementation of medication evaluation in daily clinical practice. However, in our opinion, the aim should not be to train all hospital residents/physicians to perform comprehensive medication reviews for their patients in the ward, but to assist those physicians in identifying patients at risk for drug-related problems and subsequently consulting other specialists (like geriatricians or pharmacists) to help

them with optimising pharmacotherapy for those patients. In our study, certain triggers were identified in which case the residents were more likely to evaluate the patient's pharmacotherapy (such as palliative setting or suspected side effects). In the future, physicians might interpret an older hospitalised patient with polypharmacy itself as a trigger to perform a medication review or consult a geriatrician/pharmacist for advice. Such a step could help to identify potential drug-related problems or important missing medications that are not directly overt when looking at the medication list.

Finally, introducing consulting pharmacotherapy optimisation teams in wards, especially surgical wards, may result in improved prescribing for hospitalised older patients, as trust in other specialists such as internists and geriatricians appears to be high and recommendations made by these teams will therefore very likely be implemented.

Conclusion

The willingness to contribute to the optimisation of pharmacotherapy in older hospitalised patients, within the restrictions of their capabilities and the working environment, was high among the participating hospital residents. Assisting hospital residents (both surgical and non-surgical) with identifying patients at risk for inappropriate prescribing and drug-related problems, combined with the introduction of consulting pharmacotherapy optimisation teams, will likely result in improved prescribing for hospitalised older patients and ultimately reduce drug-related problems and hospital readmissions.

DECLARATIONS

Authors' contributions

The authors certify that they have participated in the aspects conception and design (**CJAH**, TE, RvM, IW, WK), acquisition of the data (i.e. conduction and coding of the interviews: **CJAH**, JOH, CP), and interpretation of the data (**CJAH**, JOH, CP, AS, TE, IW, WK, RvM), drafting the article (**CJAH**) and revising it critically for important intellectual content (all authors). All authors have approved the final article. We have not received substantial contributions from non-authors.

Competing interests

The author(s) declare that they have no competing interests.

Data availability statement

Data for this study will be made available to others in the scientific community upon request after publication. Data will be made available for scientific purposes for researchers whose proposed use of the data has been approved by a publication committee.

Ethics approval

For the current study the Ethical Board of the University Medical Centre Utrecht provided a declaration for non-liability to the Dutch law for medical research on humans. The protocol was submitted to and approved by the Belgian Ethical Board.

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Informed consent

Verbal informed consent was obtained from the participating residents to conduct and audiorecord the interviews.

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SUPPLEMENTARY DATA
APPENDIX 1– INTERVIEW TOPIC GUIDE

Introduction

Thank you for your participation in this interview. This interview is part of study focusing on the hospital residents' perspectives on optimising polypharmacy in multimorbid older patients and aims to identify potential barriers and enablers to appropriate prescribing in this population. This interview will be audio recorded to be able to transcribe all the given answers afterwards. Everything you say will remain strictly confidential. Do you agree?

To gain insight into your background as a physician, I will start with some short questions.

- Could you tell me your age and gender?
- What is your current medical specialty? How long have you been working in this field?
- Do you have working experience in other fields? How long?
- In your daily practice; how often do you come across older patients with polypharmacy? *(estimated percentage among all patients)*
- What is your overall experience with these patients admitted on the ward?

I will now start to ask you some open ended questions regarding pharmacotherapy and medication management in older patients during hospitalisation. I am inviting you to tell me as much as possible. There are no right or wrong answers, honesty is more important.

I would like to start with a case scenario. Please imagine this situation:
You are a ward physician and a new patient is admitted (electively) on the ward under your responsibility. It concerns an 80 years old Ms H, suffering from a fairly extensive medical history, including: diabetes, hypertension, myocardial infarction, peripheral vascular disease, cerebral infarction and breast cancer. She is currently using 10 different medications. Her last known eGFR = 28ml/min.

1. How would you proceed regarding the medication? (i.e. prescribing process)
    - What steps do you take?
    - Why are you taking these steps?
    - What problems do you face with these steps? What circumstances make it more difficult?
    - What is helpful/what would make these steps easier?
    - are you satisfied with how you perform these steps? Why (not)? What would be needed to make you satisfied?

Probes

- Medication prescribing process:
  - Who does verify the medication? What is your role? Why verify? How?
- Copy pharmacy list
- Verification with the patient or their pharmacy/GP?
- How do you handle inconsistencies?
- Medication related problems like side effects:
  - Ask patient for side effects?
  - Consider side effects to be a potential cause of a patient's complaint? How would you deal with this?
- If yes, then when do you evaluate the patient's pharmacotherapy?
  - During or after prescribing? Why?
  - Do you act upon abnormalities? Which abnormalities? What do you do? Why?
- Do you check for drug-drug interactions?
  - How do you check? And in case they're present: how do you deal with it?
- Do you ever consult colleagues or a supervisor for medication related problems or medication reviews for your patients?
  - If not: why not?
  - If yes?
- Who do you consult?
- Why do you consult?
- Who is, in your opinion, responsible for a patient's clinically prescribed medication?

2. *If these topics have not yet been discussed, please continue with these questions:*

Is your working procedure different depending on the reason for admission and why does it differ? (If not noted, check: what if this patient suffers from recurrent falling?)

3. Does your policy change when the patient is admitted through the Emergency Department (and the medication is already prescribed by your colleague)? *If yes, why does this change your policy and how?*

4. During admission, do you:
   - Start new medications?
     - Special considerations when starting new medication in older patients with polypharmacy?
   - What considerations?
   - Why these considerations?
   - Considerations different from other patient groups? Why?
     - If not noted, then check: do you check for and act upon:

- Interactions (if yes: how? If not: why not?)
- Contraindications (e.g. comorbidities) (if yes: how? If not: why not?)
- Dose adjustments necessary based on age or renal function? (If yes: how? If not: why not?)
- Stopping medication?
    - Reasons to stop?
- If not noted, check: do you stop inappropriate medication?
    - Special considerations when stopping medication in older patients with polypharmacy?
- What considerations?
- Why these considerations?
- Considerations different from other patient groups? Why?
    - If not noted, then check:

How do you deal with (potentially inappropriate) medication prescribed by another specialist? Do you feel reluctance to stop these drugs? Why?

5. In what percentage of the patients > 75 years with polypharmacy do you perform some kind of medication review?
    - If not (0%): why not?
    - Satisfied with this percentage?
    - Satisfied with extend of your medication review?
        - Percentage patients you perform a minimal medication review?
            - What is your procedure for a minimal medication review?
            - How much time does it take on average?
        - Percentage patients you perform a completed (structured) medication review?
            - What is the procedure for maximal medication review?
            - How much time does it cost on average?
    - Do percentages differ for other patient groups? How and why?
        - Would you like these percentages to be it different, how different?
            - If no: why not?
            - If yes: What do you need to make it different?
        - Have you've always done it like this or did your procedure or percentage change over time?
            - Why change?

If they perform medication reviews to some extend (check over- and undertreatment, side effects and interactions) in patients during hospital admission: then ask:

- At what moment?
- Triggers for performing them?
- How do you handle this?
- Do you use specific guidelines/tools?

6. If they spontaneously bring up the STOPP/START criteria:
    - Experience with these criteria?
    - If applying:
    - How?
    - Helpful?

Different factors could function as barriers or enablers to perform medication reviews during clinical admission.

Please imagine a case you were actually involved in and where you did not perform a medication review in a >75 y old patient with polypharmacy.
(First, let them imagine and tell something about this case), then ask:
- What were reasons for not performing the review?

Now please imagine a case that you were actually involved in and where you did perform a medication review in a >75 y old patient with polypharmacy
(let them imagine and tell something about it), then ask:
- What were reasons for performing the review?
- How did it differ from the first case in which you did not?
- What would be needed/required in order to do this in every patients >75 years with polypharmacy?

Probes
- (lack of) time
- Patients' resistance to change
- Frailty in patients
- Not primarily my responsibility
- The clinical setting is not appropriate (better in outpatient setting or first line)
- My pharmacotherapy knowledge is insufficient
- My supervisor's pharmacotherapy knowledge is insufficient
- Lacking facilities (e.g. tools, accessible guidelines etc.)

What are your experiences with the medication reviews performed by the research team or consulting teams? (Helpful, annoying, dependent on physician/ pharmacist … etc….)

What would help to make this intervention better?

If you were to say something about your current pharmacotherapy knowledge, specifically regarding polypharmacy in multimorbid older patients, how would you estimate your knowledge?

8. Could you rate your presumed knowledge on a scale from 0 to 100?
    - Is this score based on what you think you should know (considering your specialty etc.) or how you would rate yourself compared to your direct colleagues?
    - What score would you aspire to or are you satisfied as it is? (in case of dissatisfaction: how do you think you can improve this? What do you need?)

Those were all the questions I wanted to ask you. Do you have any additions to or questions about the items we have discussed?

Then I would really like to thank you for your participation and your cooperation. I will now end the audio recording.

PART IV

GENERAL DISCUSSION & SUMMARY

GENERAL DISCUSSION

"Science never solves a problem without creating ten more."

- George Bernard Shaw

GENERAL DISCUSSION

Background

Worldwide, the population is ageing rapidly, and life expectancy beyond the age of 65 is increasing. As multimorbidity and polypharmacy become more prevalent with advancing age, the risk of receiving inappropriate prescriptions and their associated negative health outcomes increases accordingly. Drug-related problems (DRPs) such as adverse drug reactions (ADRs) and drug-related hospital admissions occur more frequently in older patients with multimorbidity and polypharmacy, due to the higher risk of drug–drug and drug–disease interactions combined with age-related alterations in pharmacokinetics and -dynamics. The prevalence of potentially inappropriate prescribing (PIP) is higher among hospitalised older patients compared to community-dwelling older people. Additionally, up to 30% of hospital admissions are drug-related and nearly half of these are potentially preventable.

Many implicit and explicit tools are available for health care professionals to detect PIP in older patients. The Screening Tool of Older Persons' Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria are the most frequently used and investigated explicit criteria in Europe. Balancing the benefit/risk ratio of pharmacotherapy for individual patients, in accordance with patient preferences and individual treatment goals, is considered pharmacotherapy optimisation. Despite the potential value of pharmacotherapy optimisation in the reduction of DRPs and negative health outcomes, clinical trials aimed at reducing DRPs, including drug-related admissions (DRAs) and mortality, failed to prove the effect of pharmacotherapy optimisation on these outcomes in older patients with multimorbidity and polypharmacy. However, many trials had a high risk of bias.

A clinical decision support system (CDSS) is increasingly used in implementation and intervention studies to support health care professionals and to make interventions more efficient. Therefore, integrating explicit screening tools, such as STOPP/START criteria, into CDSS is promising. A recent systematic review and meta-analysis concluded that CDSS-assisted pharmacotherapy interventions are capable of significantly reducing PIP in hospitalised older patients, but there is insufficient evidence that these interventions reduce negative patient-related outcomes. In addition, prior trials demonstrated varying acceptance rates of CDSS-assisted pharmacotherapy optimisation recommendations, thereby compromising the effect of the intervention. Furthermore, the active involvement of health care professionals and patients in decision-making regarding pharmacotherapy and identifying potential barriers and facilitators for in-hospital pharmacotherapy optimisation is important to increase the

implementation and maintenance of optimisation recommendations and, ultimately, reduce negative health outcomes. When taking all of these factors into account, multiple approaches, both quantitative and qualitative, are needed to investigate whether CDSS-assisted pharmacotherapy optimisation can reduce medication-related negative health outcomes in older hospitalised patients with polypharmacy.

In this thesis we focussed on CDSS-assisted pharmacotherapy optimisation for older hospitalised patients with polypharmacy. In **Part I** we assessed the applicability of STOPP/START criteria for individual older hospitalised patients and investigated the feasibility of translating the criteria into coded algorithms for software systems (**Chapters 2 and 3**). In **Part II** we investigated the usability of a CDSS, with integrated STOPP/START criteria, in medication reviews performed in a clinical trial setting among older hospitalised patients (**Chapters 4, 5 and 6**). Finally, in **Part III** we evaluated patients' and hospital physicians' perspectives on and involvement in decision-making regarding pharmacotherapy optimisation and aimed to identify barriers and facilitators for the implementation of pharmacotherapy optimisation in the hospital setting (**Chapters 7 and 8**).

In this general discussion, I first summarise the main findings of this thesis and subsequently discuss these findings in a broader perspective. I elaborate on five main themes:

- The usability of STOPP/START criteria in medication reviews for older hospitalised patients.
- Challenges of in-hospital pharmacotherapy optimisation for older patients with polypharmacy.
- DRAs as an outcome in pharmacotherapy optimisation trials.
- The role of health care professionals and settings in pharmacotherapy optimisation.
- Older patients' involvement in decision-making regarding pharmacotherapy optimisation.

I conclude with the clinical implications of the findings within this thesis and finally discuss future perspectives.

SUMMARY OF THE MAIN FINDINGS

Critical evaluation of population-based STOPP/START recommendations by experienced clinicians is important when applying STOPP/START criteria to individual older patients to optimise pharmacotherapy and prevent patient harm by inappropriate decisions (**Chapters 2 and 3**).

Explicit criteria, such as STOPP/START criteria, can be converted into algorithms for software systems and integrated into CDSS to enhance application and help ensure greater efficiency for medication reviews (**Chapter 2**).

Clarity of presentation of the individual STOPP/START criteria can be improved on a language level, and explanations to justify the recommendations could help clinicians in deciding on the applicability of the recommendations to the individual older patient with polypharmacy (**Chapter 3**).

Individualised prescribing recommendations generated by a CDSS with integrated STOPP/START criteria improve appropriate prescribing in a geriatric outpatient clinic, without affecting three months mortality (**Chapter 4**).

The involvement of an expert team to evaluate the applicability of CDSS-generated signals for individual patients is essential, as more than half of the signals for potential overuse, underuse and misuse were not deemed appropriate for patients in the hospital setting (**Chapter 6**).

Patients' and physicians' agreement with in-hospital pharmacotherapy optimisation recommendations in a clinical trial setting was >60%. Patients' reluctance to change was the main reason for disagreement (**Chapter 7**).

Better patient and physician education regarding the benefit/risk balance of pharmacotherapy, in addition to more precise and up-to-date medical records to avoid irrelevant recommendations, will likely result in higher adherence with future pharmacotherapy optimisation recommendations (**Chapter 7**).

The most important resident-perceived barriers to in-hospital pharmacotherapy optimisation were: lack of time, patients' lack of knowledge of their own treatment and reluctance to change, absence of a long-term patient relationship, the hospital setting in which patients are sick/unstable and the lack of knowledge/skills to perform medication reviews (**Chapter 8**).

Important facilitators include: the presence of certain triggers (e.g. suspected side effects) to evaluate the medication, a supervisor as a role model, more education and training about appropriate prescribing and consultation of medication optimisation teams (**Chapter 8**).

The usability of STOPP/START criteria in medication reviews for older hospitalised patients

Although a medication review comprises far more than the application of explicit screening tools such as STOPP/START criteria, it is also important to evaluate the feasibility of the STOPP/START criteria for detecting and managing PIP in older hospitalised patients with polypharmacy. In **Chapters 2** and **3** we converted the textual STOPP/START criteria into coded algorithms and evaluated the clarity of presentation of the singular criteria for applicability for individual patients.[1,2] Important lessons learned from these processes are that, in contrast to the initial intended purpose of explicit screening tools (i.e. application by less experienced prescribers), the research presented in this thesis promotes application of the explicit STOPP/START criteria by experienced clinicians with physical access to the patient and the patient's medical file to prevent potential patient harm resulting from inappropriate decisions. Additionally, we emphasised the need for specification of the intended users of the criteria or subsets of the criteria. The STOPP/START criteria are developed to detect PIP in older people; however, their original publication does not mention who should apply those criteria in this patient group and when. Although the criteria focus mainly on chronic prescriptions that are predominantly monitored by the general practitioner (GP), STOPP/START criteria have been used as an in-hospital intervention to improve medication appropriateness and to reduce DRPs such as ADRs and readmissions.[3] When it is used in the clinical or non-trial setting, however, who will conduct this intervention for the admitted older patient with polypharmacy? Are surgeons the designated physicians to start betablockers in patients with a history of ischemic heart disease during an admission for elective cholecystectomy? Cardiologists, on the other hand, likely do not need these criteria to point them towards optimal treatment for their ischemic heart disease patients, as they follow their own guidelines on top of their clinical experience and expertise. In addition, a cardiologist is not likely to initiate an acetylcholinesterase inhibitor in patients with dementia, although the screening tools might alert them to this example of undertreatment. The findings in this thesis underpin the importance of specifying the intended users of the criteria and the necessity of providing some guidance on how follow-up and monitoring should be organised and who is responsible. Simply implementing STOPP/START-based algorithms into electronic prescribing systems to alert physicians to PIP and expecting them to make the right decisions regarding pharmacotherapy optimisation for individual older patients is not enough and can even cause patient harm. For instance, restarting medication that caused an ADR in the past or starting new medication that needs intensive monitoring by a specialist (e.g. disease-modifying antirheumatic drugs (DMARDs) for rheumatoid arthritis) should not be among the screening tools used to optimise an individual patient's pharmacotherapy by all physicians. Additionally, following some recommendations might possibly introduce new PIPs, for instance through the introduction of new drug–drug or drug–disease interactions.

The importance of critical evaluation of all criteria that are possibly relevant to an individual patient by competent health care professionals was emphasised earlier in this thesis. In **Chapter 6** we reported that 61% of the CDSS-generated STOPP/START signals were not accepted by the pharmacotherapy team, after they critically evaluated the signals for clinical applicability for each patient based on the patient's medical file, including medical history, prior use and certain measurements, for example.[4] This can be explained, in part, by the difficulty of translating theoretical criteria into computer algorithms (**Chapter 2**), leading to 'over triggering' caused by a simplification of certain criteria, as not all elements or conditions can be coded.[1,5] Implicit judgement of the applicability of that signal for that specific patient, therefore, is indispensable and may result in the signal being rejected. In addition to the more technical issues, specific expertise and knowledge of the medication or medication group involved is also important. It is probably not the best of care if all physicians begin prescribing angiotensin-converting-enzyme (ACE) inhibitors for heart failure because the electronic prescribing system told them to do so. Prior research indicated that a large proportion (61%) of computer-generated STOPP/START signals were of potential 'adverse significance', of 'no clinical relevance' or of 'possibly low relevance'.[6] There was a significantly higher likelihood of implementation of the recommendations with a higher clinical relevance, as was also demonstrated in a related qualitative study.[7] However, in case many signals are generated with no clinical relevance or even potential adverse relevance in daily clinical practice, this could cause alert fatigue among prescribers, resulting in non-implementation of relevant recommendations.[8–10] It could also cause patient harm when the prescribers who are less experienced with pharmacotherapy optimisation make the 'wrong' decisions. Another possibility is that some signals to alert prescribers to inappropriate prescribing, although acknowledged to be relevant, are ignored or overruled by the prescribers, as was recently investigated for the prescription of benzodiazepines and sedative-hypnotics.[11] In a retrospective review of primary-care clinicians' interaction with an electronic medical record-based support system that triggered when benzodiazepines or sedative-hypnotic drugs were prescribed, more than 99% of these triggers were ignored (16%) or overridden (83%). The most frequently reported reason (49%) for overriding was 'alternatives ineffective or contraindicated'. In 15% of the cases the prescription was based on patient preferences. This study demonstrated the limited ability of electronic decision support systems to influence clinicians' inappropriate prescribing patterns for older adults when implemented in isolation. The authors state that future interventions would benefit from the early involvement of key stakeholders such as prescribers and pharmacists to ensure that alerts are appropriate, motivated and actionable.[11]

Implementation of STOPP/START or other explicit screening tool-based algorithms into electronic prescribing systems could, however, be helpful in assisting (hospital) prescribers in identifying patients at risk for PIP. Instead of following recommendations that may fall outside their area of expertise, prescribers could then consult other health care professionals such as pharmacists or geriatricians to help optimise pharmacotherapy for this patient. Furthermore, to prevent alert fatigue and ensure that relevant alerts are not ignored or overruled, it might be worthwhile to prioritise for the prescriber in advance and implement only the most relevant or most dangerous alerts instead of complete sets of screening tools.

In conclusion, explicit screening tools such as STOPP/START criteria can be useful in detecting and managing PIP for individual multimorbid hospitalised older patients when applied by experienced clinicians or they can help less experienced clinicians identify patients at risk for PIP. Future explicit screening instruments should specify the intended users of the criteria and substantiate the underlying rationale of the recommendations to promote implementation and avoid inappropriate decisions and potential patient harm.

Challenges of in-hospital pharmacotherapy optimisation for older patients with polypharmacy

Systematic reviews and meta-analyses published thus far reported associations between the existence of PIP in older patients and health-related outcomes such as ADRs, functional decline and hospital admissions.[12] As optimising pharmacotherapy is considered one of the most important interventions to reduce PIP, the logically derived hypothesis would be that optimising pharmacotherapy in older patients would also reduce negative health outcomes associated with PIP. However, systematic reviews and meta-analyses of trials investigating the effect of interventions to reduce PIP on frequently reported clinical outcomes like medication related admissions and mortality were inconclusive or had a high risk of bias.[12–15] The interventions that were investigated varied from unifaceted interventions such as a simple review of patients' prescriptions to more complex multicomponent interventions including geriatric assessment, shared decision-making (SDM) and follow-up. The interventions were performed by various health care professionals such as pharmacists, GPs and hospital prescribers, working solely or jointly. Interventions were conducted in both primary- and secondary-care settings. Although the interventions in some trials improved medication appropriateness as measured by an implicit tool, not one single intervention demonstrated significant improvement regarding important DRPs such as ADRs, DRAs and mortality.[14,16]

The OPERAM trial was designed to fill the gap that existed regarding pharmacotherapy optimisation for hospitalised older patients, presumably addressing pitfalls from prior trials.[17,18] The only exclusion criteria applicable were a palliative setting or a prior recent medication review. All patients aged 70 years or older with polypharmacy and multimorbidity admitted to the hospital, both elective and non-elective, were eligible for participation. The complex multicomponent intervention (**Figure 1**), which included a CDSS-assisted medication review performed by a pharmacotherapy team consisting of a trained physician and pharmacist and SDM with both patients and attending ward physicians, was compared to usual care (**Chapter 5**).[18] The follow-up duration was 12 months. The results of the OPERAM main trial are not presented in this thesis, but, in brief, OPERAM did not find a significant effect of the CDSS-assisted structured medication review on its primary endpoint, drug-related readmissions, nor on its secondary outcomes such as all-cause mortality.[19]

In total, 2,008 hospitalised older patients were randomised and enrolled in 54 intervention (963 patients) and 56 control clusters (1,045 patients). The prevalence of inappropriate prescribing in the intervention group was high, 86.1% and 62.2% (n = 491) had ≥ 1 recommendation successfully implemented at two months. In the intervention group, 211 patients (21.9%) experienced a drug-related hospital admission, compared with 234 (22.4%) in the control group. The hazard ratio for a drug-related hospital admission was 0.91 (0.69 to 1.19) according to the per protocol analysis.

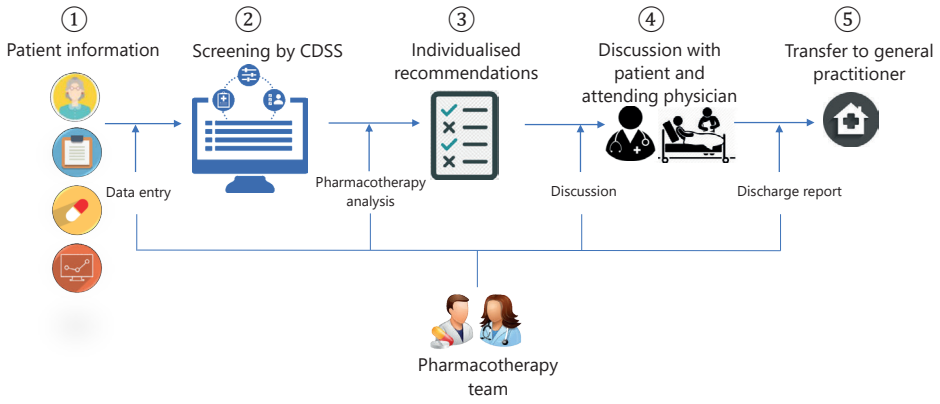

Figure 1: Summary of all consecutive steps (1–5) of the intervention within the OPERAM trial

It is important to investigate and understand why the complex OPERAM intervention was not effective in reducing DRAs, despite all of the precautions that were taken to address issues from prior trials. Already in 2006, Oakley et al. emphasised the importance

of investigating the process involved in implementing an intervention, whereas most randomised controlled trials focus primarily on outcomes.[20] The interpretation of the findings from trials investigating complex multicomponent interventions is difficult without an analysis of the underlying care process and the context in which the intervention was performed.[20,21] Especially in the case of an unsuccessful intervention such as that in the OPERAM trial, process evaluation is helpful in differentiating between interventions that are inherently faulty (failure of intervention theory or concept) and interventions that are poorly delivered (implementation failure).[20–22] Since process evaluation of complex interventions does not necessarily provide an understanding of the causal assumptions underpinning the interventions, it is also important to investigate other factors that may affect the intervention such as 'past experience' and 'common sense' and the context in which the intervention was delivered (**Figure 2**). The context comprises everything external to the intervention that may act as a barrier or facilitator to its implementation.[21]

The complex multicomponent interventions focussed on pharmacotherapy optimisation that are used in some trials, including OPTICA, SENATOR and OPERAM, are designed to increase generalisability of the results, as they mimic clinical practice without standardisation for trial purposes.[19,23,24] However, the heterogeneity of patients and interventions makes it difficult to compare such trials and, if significant results are found, to extrapolate the results to other settings or populations, especially to individual patients. Another downside of these complex multicomponent interventions is that many variables must be considered when analysing and interpreting the data and results. Especially in the case of negative trial results, it is important to understand the underlying process (i.e. process evaluation) and investigate whether these negative results can be attributed to one specific facet of the intervention or several. In addition, it is important to assess whether the complete intervention was applied and/or implemented in all intervention patients according to the study protocol.

In the case of the OPERAM trial, the intervention consisted of CDSS-assisted pharmacotherapy optimisation by a pharmacotherapy team. It is difficult, however, to 'measure' or report optimisation of pharmacotherapy, as the result of pharmacotherapy optimisation is different for all patients (i.e. an individualised intervention).[25] The optimisation of pharmacotherapy might result in a prescription of vitamin D for patient X who is housebound and may result in the discontinuation of the beta blocker in patient Y due to severe bradycardia. Both patients will be followed up for DRAs in the next 12 months and adjudicated as if they received the same intervention. The question then arises, however, whether these patients and interventions are comparable and what potentially positive trial results of such interventions imply for future individual patients.

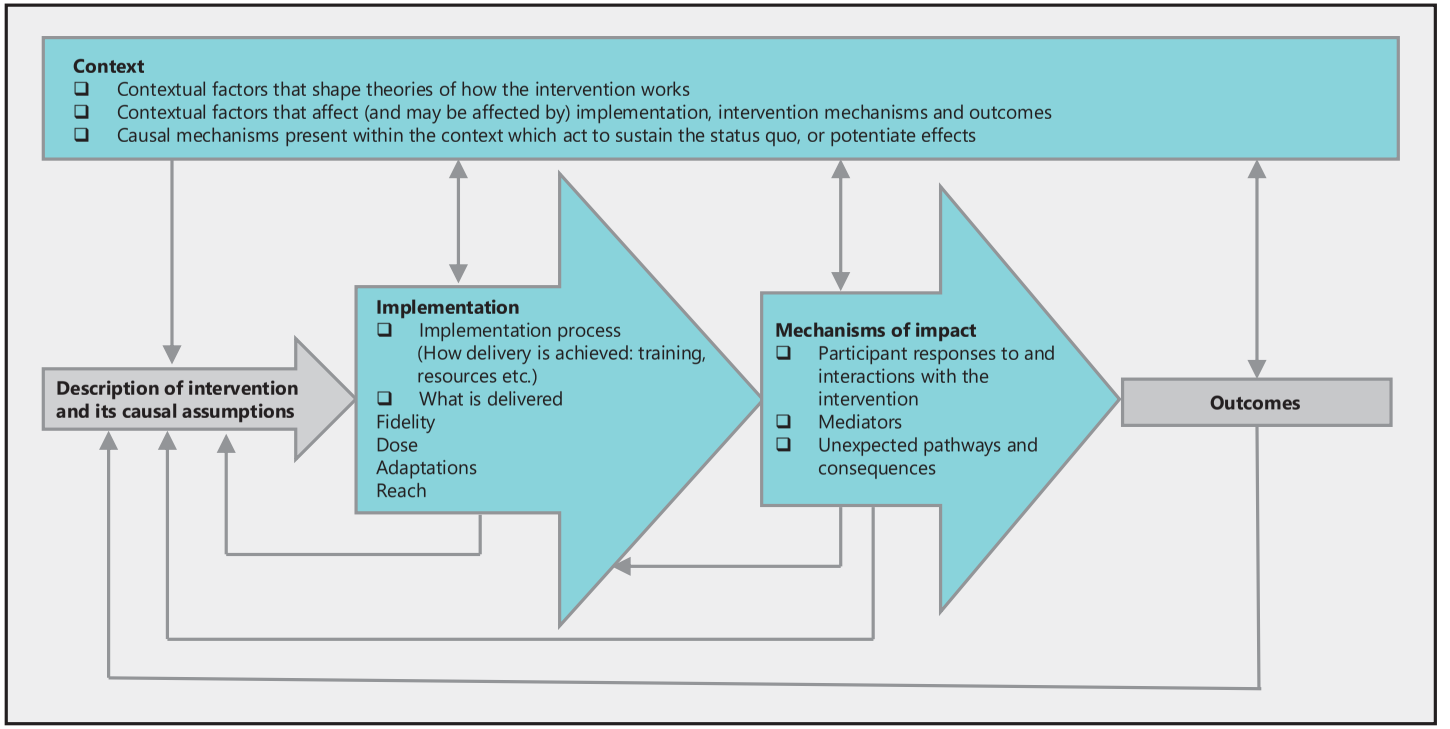

Figure 2 Key functions of process evaluation and relations among them.

Blue boxes are the key components of a process evaluation. Investigation of these components is shaped by a clear intervention description and informs interpretation of outcomes. Adopted from Moore et al.[21]

One of the most crucial factors within the OPERAM trial, however, is probably the fact that an important proportion of the recommendations provided by the pharmacotherapy team was not implemented at hospital discharge and/or not implemented upon follow-up two months later. In only 62.2% of the patients (n = 491) at least one STOPP/START recommendation was successfully implemented at two months. This means that for many intervention patients, pharmacotherapy was not actually optimised, or at least not completely, as a mean of 2.75 (SD 2.24) STOPP/START recommendations was considered applicable per patient during the intervention. Nevertheless, these patients, and the possible DRAs that occurred in these patients, were analysed as if they received complete pharmacotherapy optimisation (i.e. the intention-to-treat principle). This could very well dilute the effect present for those patients where pharmacotherapy was optimised (i.e. all recommendations implemented). The study was not powered for this subgroup analyses, so no definitive conclusion can be drawn from this.

Additionally, the follow-up period of 12 months was probably not long enough to reliably establish the effects of newly started preventative medications, while this was the largest group of START recommendations in the OPERAM trial.[4,26] It is likely that initiation of osteoporosis prophylaxis (vitamin D, calcium and/or bisphosphonates) will take longer than 12 months to reveal significant effects on fracture prevention. The time to benefit of bisphosphonate therapy in a recent meta-analysis was 12.4 months to prevent one nonvertebral fracture per 100 postmenopausal women with osteoporosis, supporting this assumption.[27]

Conversely, a 12-month follow-up period is quite long for a single-time-point intervention, especially when it concerns a complex intervention that needs follow-up and monitoring, such as pharmacotherapy optimisation. Newly initiated preventive medication, is cases where the patient does not experience a positive impact but does suffer from side effects, could easily be discontinued after discharge if monitoring and useful explanation about the expected long-term benefit is lacking.[28] Additionally, potentially inappropriate medication discontinued at hospital discharge (e.g. benzodiazepines) might be restarted in the case of withdrawal symptoms without patient education and proper guidance by the GP or simply in the case of insufficient communication about medication changes to the community pharmacy where the patient receives a refill prescription.[29–32] Moreover, there is cognitive bias that exists as a result of the visibility of new adverse events occurring after initiation of indicated medications, such as a minor/major bleeding in patients started on anticoagulant therapy for atrial fibrillation, in contrast to the imperceptibility of the strokes that have been prevented by this newly started medication. Conversely, anticoagulant therapy may be discontinued in very frail older patients with frequent falls to prevent bleeding complications. A small fraction

of these patients will develop a new stroke after discontinuation of the anticoagulant, but the number of prevented bleedings is unknown. In complex intervention trials on pharmacotherapy optimisation powered on drug-related readmissions as the primary outcome, such as OPERAM, only those new bleedings and strokes will be taken into account, and this will not be in favour of the intervention.

In conclusion, complex multicomponent interventions are designed to mimic clinical practice as closely as possible. However, many factors and determinants must be considered when interpreting trial results. Especially in the case of negative trial results, process evaluation is important to distinguish between failure of the *concept* of the intervention or failure of the *implementation* of the intervention. In the case of the OPERAM trial, implementation failure is much more likely, as an important proportion of the recommendations provided by the pharmacotherapy team were not implemented at hospital discharge and/or not implemented at two months follow-up.

Drug-related admissions as an outcome in pharmacotherapy optimisation trials

The primary outcome of the OPERAM trial was the first drug-related readmission. All readmissions that occurred in participating OPERAM patients within the follow-up period of 12 months were adjudicated for drug-relatedness by a blinded adjudication team consisting of senior physicians and pharmacists. The DRA adjudication guide was developed and published by Thevelin et al.[33] When a readmission was assigned by the adjudication team as a DRA (i.e. adverse drug event was the main or major contributory reason for hospitalisation), the primary outcome was reached for this patient and new hospitalisations were no longer adjudicated. The adjudication teams first assessed the preventability of the DRA by determining whether the DRA was caused by overuse, underuse or misuse of medication. If this was not the case, the DRA was considered non-preventable. The DRAs detected in the intervention group were not further analysed to determine whether the causative drug was already present (or absent in case of omission and, thus, potential underuse) at the time of the intervention. Investigating the relationship between the occurrence of potentially preventable DRAs and the detectability of PIP linked to these DRAs during an in-hospital medication review at a single time point prior to this DRA may help improving the pharmacotherapy optimisation process in future trials. Although this was not addressed in the the main trial, we decided to retrospectively analyse those DRAs in the intervention group for their potential preventability by the CDSS-assisted medication review performed in the OPERAM trial.[34] **Figure 3** depicts a graphical illustration of the relationship between the in-hospital medication review at index hospitalisation and the adjudication process

of hospital readmissions.[34] In total, 127 of the 211 DRAs identified in the intervention group were non-preventable. Of the 84 preventable DRAs, 72 could be analysed for detectability during the pharmacotherapy optimisation process of the intervention. Underuse was the most frequently identified PIP type (49.3%), followed by overuse (36.4%) and misuse (14.3%). The three most frequent clinical presentations associated with potentially preventable DRAs were heart failure exacerbation (26.0%), new fall and/or fracture (20.8%) and minor or major bleeding (10.4%). Nearly 50% of the PIP responsible (i.e. medication error) for the preventable DRA was not present at the time of the in-hospital medication review, and therefore was not detectable and not preventable by the CDSS-assisted pharmacotherapy optimisation at that time. In 50% of the PIPs that were present during the pharmacotherapy optimisation process, a recommendation was provided by the pharmacotherapy team; however, these recommendations were not implemented by the attending physicians.

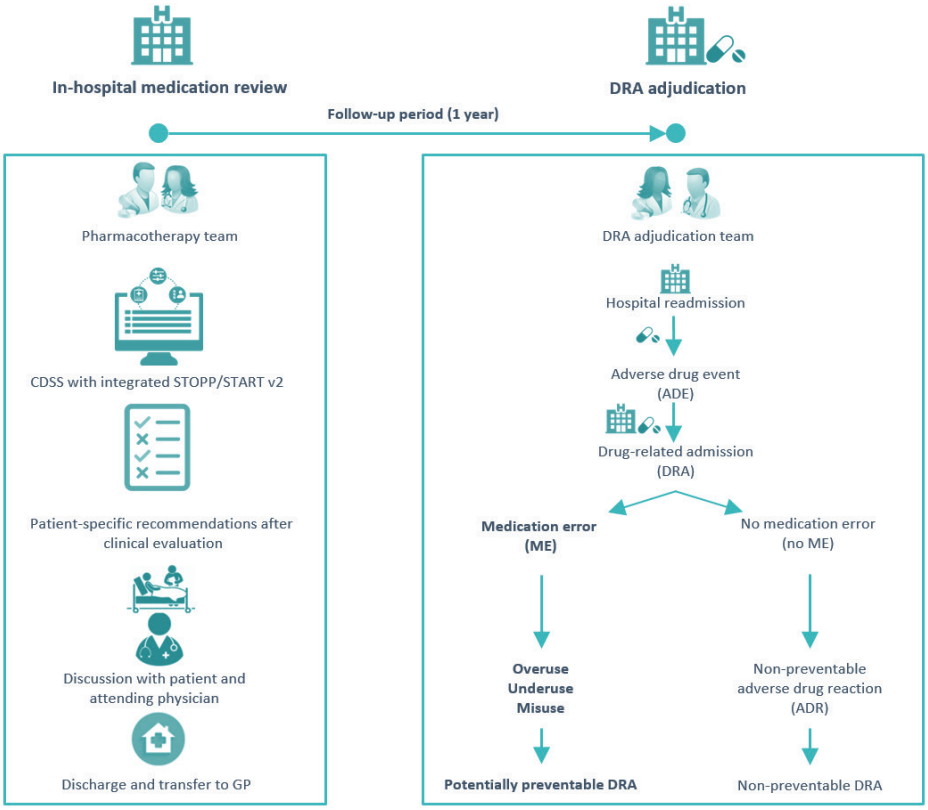

Figure 3: Graphical illustration of the relationship between the in-hospital medication review at index hospitalisation and the adjudication process of hospital readmissions within one year of the in-hospital medication review. Adopted from ***Sallevelt*** et al.[34]

These results suggest that a single-time-point, in-hospital medication review is not effective in preventing DRAs. New PIP can occur when new medications are added or when previously discontinued inappropriate medication is restarted. Additionally, chronic conditions can worsen (e.g. heart failure exacerbation) and patients can develop new conditions over time. Therefore, pharmacotherapy optimisation should be a continuous process, including follow-up, monitoring and reassessment of pharmacotherapy over time. This includes close collaboration among hospital prescribers, pharmacists and GPs, especially when the medication adjustments are conducted or recommended in the hospital setting and when patients are discharged home or to an outpatient setting. If this follow-up and monitoring had been better implemented in the OPERAM trial, it is likely that some of the PIP would have been detected earlier (50% was not yet present at the time of the intervention) and, perhaps, some of the DRAs could have been prevented. Therefore, it is important for future in-hospital pharmacotherapy optimisation trials to ensure this follow-up, monitoring and reassessment of pharmacotherapy is affirmed.

In conclusion, a DRA is an important outcome measure in medication optimisation trials. The majority of DRAs in the OPERAM trial were adjudicated as non-preventable. In the case of a potentially preventable DRA, 50% of the responsible PIP was not present at the time of the in-hospital medication review. In the 50% of the cases where the PIP was present, the recommendations provided by the pharmacotherapy team were not implemented by the attending physicians. Therefore, a single-time-point, in-hospital CDSS-assisted medication review such as that conducted in the OPERAM trial, was not effective in preventing DRAs.

The role of health care professionals and settings in pharmacotherapy optimisation

Another important finding of the detailed DRA analysis within the OPERAM trial was that when PIP was detected by the CDSS-assisted medication review and recommendations were made by the pharmacotherapy team, these recommendations were not implemented by the attending physicians in 50% of cases. It is important to use process evaluation to elucidate the underlying factors determining the reasons for not following these recommendations. In **Chapter 7** we investigated the level of agreement, including the reasons for disagreement, of these attending hospital physicians and patients who were involved with the STOPP/START-based pharmacotherapy optimisation recommendations provided by the pharmacotherapy team.[26] The results of this substudy indicated that the willingness of the attending physicians to follow the recommendations was high and that patients' reluctance to change was the most important reason for not following the recommendations. If the attending physician did not agree with the recommendations, this was mainly due to medication adjustments beyond their own area of expertise such as cardiovascular medication, or their preference

to defer the decision to the GP. This emphasises the importance of useful explanation about the underlying rationale of the optimisation recommendations and the potential risks of not following the recommendations.[7,35] Better and more frequent education about adequate pharmacotherapy and the risks of PIP for older patients with multimorbidity and polypharmacy is also important to create awareness and to better equip the (hospital) prescribers with pharmacotherapy optimisation knowledge and skills.[35,36] In addition, it is important to acknowledge when other professionals or experts can be consulted or when patients should be referred for pharmacotherapy optimisation.

Although this was not specifically investigated in this substudy, the discrepancy between the willingness to follow the recommendations and the actual implementation of recommendations at the two month follow-up suggests that there were other barriers for implementation than the patients' reluctance to change and the physicians feeling ill-equipped to adjust certain medications. It is likely, that the dynamic hospital setting poses particular challenges for physicians in prioritising among all of their tasks, and pharmacotherapy optimisation might not be the main priority for most of them. In **Chapter 8**, we interviewed hospital residents to identify perceived barriers and facilitators for pharmacotherapy optimisation in older hospitalised patients with polypharmacy. Process evaluation includes qualitative research to provide an in-depth understanding of the factors that cannot be measured but that play an important role in the successful implementation of an intervention.[20,21] The most important barrier to optimising pharmacotherapy during hospitalisation mentioned by the residents was the lack of time caused by all of the other tasks they have as a ward physician and the dynamic hospital setting in which many other patients are sick and unstable. On top of the lack of time, the majority of the residents also referred to their insufficient knowledge and skills to perform a medication review. The surgical residents stated that they do not consider it the role of a surgeon to optimise pharmacotherapy. Although it was not specifically mentioned by the interviewed residents, it is likely that the lack of financial resources to perform medication reviews during hospital admission plays an important role as well. Time spent on pharmacotherapy optimisation directly affects time available for other tasks that might be financially compensated. Possible facilitators elucidated were the need for more pharmacotherapy education and practice and the possibility to consult experts for specific advice regarding pharmacotherapy.

One possible conclusion from this qualitative study could be that the hospital setting is not suitable for the optimisation of chronic medication. This is due in part to barriers intrinsic to the hospital prescribers or related to the dynamic hospital environment, which includes many different tasks. Nevertheless, the lack of a long-term relationship with the patient and the possibility to closely monitor patients after medication changes play important roles as well.

The role of the community pharmacist (CP) in patient care, including medication safety, is evolving.[37] The demand for enhanced collaboration with physicians and other primary-care prescribers is increasing, and CPs are seen as the 'gatekeepers' for medication safety, as they are the last piece in the chain before the medication is dispensed.[38] As medication experts they can support physicians, and a successful collaboration between CPs and primary-care providers could help to reduce medication errors and improve patient outcomes.[38] CPs have access to information on patients' medication adherence and can inform GPs of adherence-related safety concerns.[39,40] In addition, CPs could help in patient education, ensuring appropriate use of medications and improving patients' knowledge of prescribed medication and its relationship to their diseases.[41] Although the role of CPs in medication management seems promising, a recent narrative review reported some barriers to collaboration with primary-care providers.[38] From the providers' perspective, the most important barriers were negative past experiences, difficulty in reaching CPs, infrequent interactions (i.e. not knowing each other), uncertainty about a pharmacist's competencies and the fear of being judged.[42] From the pharmacists' perspective, inadequate access to clinical information, non-acceptance of expertise by physicians and the lack of time were identified as the most important barriers for collaboration. From both perspectives the lack of role specification and the lack of direct, face-to-face, communication was mentioned.[43] Facilitators that may positively influence the interprofessional collaboration between CPs and GPs are co-location, joint education to understand each other's capabilities and compatible technologies to facilitate communication.[44] It is important to overcome these barriers for collaboration in the near future to ensure medication safety and to improve patient outcomes.

In conclusion, many barriers for in-hospital pharmacotherapy optimisation remain, both intrinsic to the hospital physician and related to the dynamic hospital environment. The role of the CP, in close collaboration with the GP, in pharmacotherapy optimisation and medication safety post-discharge is promising.

Older patients' involvement in decision-making regarding pharmacotherapy optimisation

The stakeholder who is the least represented in this thesis is the older hospitalised patient with polypharmacy. Nevertheless, this stakeholder may be the most important one when it comes to the maintenance of medication adjustments and the adherence to optimised pharmacotherapy. Active patient involvement in decision-making has attracted growing interest in recent decades and a paradigm shift from a paternalistic to more patient-centred care has arisen. A patient-centred approach in health care means respecting a patient's preferences, values and personal experiences and making the patient a member of the health care team.[45,46]

Not all patients are able to fulfil this role or are not aware of the possibility to join the health care team. Other patients may believe they are not competent enough to be involved in health-related decisions.[47] Although health care professionals are well trained to make these decisions and balance the benefits and risks of treatment options (i.e. they have the scientific knowledge), patients live with their conditions on a daily basis and should be considered experts when it comes to their experiences of illness and health (i.e. they have the experiential knowledge). Recognising the existence of both scientific and experiential knowledge is an important foundation of SDM, which is defined as 'an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences'. [45,48] The use of SDM in health care is promoted through both policy and research, yet its implementation in routine practice has evolved rather slowly.[49] Research on implementation of SDM in hospital settings in particular is a developing field, as most qualitative studies of barriers and facilitators to SDM implementation have been conducted in the past five years. In a recent systematic review, the barriers to SDM implementation specific to the hospital setting included busy and noisy ward environments and a lack of private spaces in which to engage in SDM conversations.[49]

SDM is an important tool for physicians and patients to make decisions together regarding multiple health-related issues, such as surgical or oncological treatments and pharmacotherapy options. Recently, a guideline from the Dutch Federation of Medical Specialist (FMS) was launched to guide physicians in conducting SDM, and the FMS aims to make SDM the standard of care by 2025.[50,51] To achieve this, the existing barriers for both patients and physicians must be addressed. Concerning SDM in pharmacotherapy, research focusses mainly on deprescribing, rather than on optimising pharmacotherapy, which includes potential prescribing omissions as well. Deprescribing is 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'.[52] Thevelin et al. conducted a mixed-methods study embedded within the OPERAM trial exploring older patients' perspectives on hospital-initiated medication changes, and patients in both the intervention and control groups from all four participating countries were interviewed. [53] In general, patients expressed a positive attitude towards medication review, yet emphasised the importance of a long-term relationship with the health care professional involved in their medication review, such as their GP. Many patients reported predominantly paternalistic decision-making and said they had experienced a lack of communication and information about their medication changes. Additionally, several patients had problems recalling the information received, which has been reported by previous studies. A recent Dutch study investigated 124 patients'

informational needs upon their hospital discharge and found that only half of them were able to recall the medication changes that had been implemented in the hospital.[31] In the OPERAM intervention arm, according to the study protocol, pharmacotherapy optimisation recommendations were discussed with the attending ward physician and the patient according to the SDM principle. Formal SDM includes three phases: (I) introducing choice; (II) describing options, often by integrating the use of patient decision support; and (III) helping patients explore preferences and make decisions, in accordance with the model proposed by Elwyn et al.[54] According to OPERAM trial implementation data, medication changes were discussed with 85% of the patients, and formal SDM, following all three phases, was performed with 70% of intervention patients However, the results of the mixed-methods study from Thevelin et al. suggest that SDM implementation was much lower from the patients' perspective, as only 23% of the interviewed patients stated that they experienced participation in decision-making.[53] The remaining 77% of patients reported predominantly paternalistic decision-making. This illustrates the challenge of incorporating SDM in daily clinical practice, as even in the OPERAM trial in which SDM was part of the intervention, the implementation was considerably lower than expected.

Although SDM should take place during the hospital admission when the medication changes are made, it is also important to follow up on the medication changes and to keep the patient involved in the process after discharge. Kayyali et al. investigated the experiences of patients with chronic conditions regarding SDM and the awareness of community pharmacy medication review services.[55] The interviewed patients stated that they experienced a lack of detailed medication counselling and involvement in SDM at hospital discharge. Although medication changes were made in 70% of patients, only a third of them said they were consulted about these changes. Furthermore, important topics related to side effects and life style changes were discussed with fewer than 40%. Additionally, there was an underutilisation of community pharmacy services due to the lack of awareness among target patients regarding the availability of medication optimisation and counselling services. Furthermore, the patients expressed a preference for receiving their discharge medication and counselling from the CP instead of in the hospital.[55]

In **Chapter 7**, we investigated the level of agreement and reasons for disagreement with recommendations of the pharmacotherapy team among the OPERAM intervention patients at the Dutch trial site. SDM was successfully conducted with 139 of the 177 (78.5%) SDM-eligible patients. During this SDM process, the recommendations that were deemed appropriate for that individual patient by the pharmacotherapy team were discussed with the patient. If the patient did not agree with the recommendations, they

were not provided to the attending ward physician, thereby empowering the patient in their decision. However, in these cases of disagreement, the patients were asked for permission to send the recommendations to their GPs so the discussions could continue with the GPs after discharge. Many patients expressed their trust in their GP during SDM with the pharmacotherapy team, saying they did not feel comfortable adjusting their medication without consultation with their GP. The exact numbers of the recommendations that were postponed to the GP and implemented after discharge are not known; however, given the implementation rates found in the OPERAM trial, we assume them to be low. Although a discharge report including all postponed recommendations was sent to the GP, it is likely that patients forgot to make an appointment with their GP to discuss the recommendations or that the GPs missed or lost the discharge report in their mail. Additionally, the pharmacotherapy team made no follow-up phone calls to the patient and/or to the GP. Such calls to remind patients to discuss the recommendations with their GP and to explain and justify the recommendations to the GPs might have increased the implementation rates.

Unfortunately, the results of the MedBridge trial indicated that a hospital-based medication review, including post-discharge follow-up, did not reduce the incidence of unplanned hospital visits within 12 months, compared with usual care.[56] However, a process evaluation of this trial, including semi-structured interviews with participating physicians and pharmacists, revealed that the post-discharge intervention in collaboration with the responsible physicians was not conducted successfully and that patients had a limited role in decision-making. This suggests implementation failure rather than failure of the concept of the intervention.[57] Therefore, it is important that future trials focussed on in-hospital pharmacotherapy optimisation in older polypharmacy patients actively involve patients in decision-making. Additionally, these future trials should include transitional care to increase the impact of the intervention by attempting to achieve implementation rates as high as possible. When all of these conditions are present, the impact of the entire intervention on patient-related outcomes such as DRAs can be more reliably established.

In conclusion, SDM is becoming the standard of care in many health related topics, including pharmacotherapy optimisation. Most patients want to be involved in decision-making regarding their pharmacotherapy, but they may have difficulty recalling everything that is discussed during their hospital admission or at discharge. Good transitional care from hospital to home is crucial, and close collaboration between GPs and CPs is important for intensive monitoring of hospital-initiated medication changes and to ensure medication safety by continuously evaluating individual patients' pharmacotherapy.

Future perspectives

With the major lessons learned from the research in this thesis in mind, how should we move on with pharmacotherapy optimisation for older patients with polypharmacy?

One important message from the interviewed medical residents (**Chapter 8**) was that they lacked proper education and training regarding pharmacotherapy optimisation, both during medical school and during their residency. Consequently, they feel ill-equipped to prescribe appropriately, especially for older patients with polypharmacy who are admitted to the hospital. It is important to sufficiently prepare all future physicians during medical school to ensure basic pharmacotherapy knowledge in all prescribers. Training and education should be repeated during residency, for instance through educational sessions or courses presented by pharmacists or clinical pharmacologists. The aim is not to encourage all prescribers to perform comprehensive medication reviews and optimise pharmacotherapy. The goal of this basic pharmacotherapy knowledge is merely to prevent medication-related problems such as side-effects and adverse drug-events by promoting adequate prescription. Although it is important for all prescribers not to harm patients, it is not realistic to expect every physician to optimise pharmacotherapy in older patients, not only because they lack the time to perform medication reviews but also because this is a skill that requires specific knowledge and expertise. Surgeons are trained to perform surgery, and that is what they should do. It is important, however, to help surgeons and other prescribers identify patients at risk for drug-related problems and promote adequate consultation with other health care professionals who can help optimise pharmacotherapy, especially when it concerns older patients with polypharmacy. This is where CDSS fits in. When a CDSS with integrated explicit screening criteria, such as STOPP/START, is incorporated into electronic prescribing systems, both in the hospital and at GPs' practices, this might alert prescribers to consider the patient as being at risk for inappropriate prescribing when multiple signals are triggered in one patient. For this process to work, it is important that medical files are accurate, up to date, and linked to the CDSS, especially regarding medical conditions and certain parameters such as recent blood pressure measurements and current renal function, for example. Additionally, this electronic prescribing system integrated with a CDSS may function as a tool to prevent inappropriate prescribing by warning physicians when they are about to order a potentially inappropriate medication (PIM) for a patient and suggest safer alternatives. In case the PIM is prescribed nonetheless, advice could be generated on how to monitor the patient and when. Prevention might be the most effective intervention to reduce inappropriate prescribing, as it appears to be rather difficult to deprescribe certain PIMs (e.g. benzodiazepines) after chronic use.[32] Therefore, prescribing them in the first place should be discouraged. Proper explanations about reasons for inappropriateness and the risk of prescribing the PIM should be provided

by the CDSS, and this information can be used for SDM with the patient.[11] It is crucial to involve the patient in decision-making early in this process. Discharge interventions to reduce readmissions appeared to be most effective when these interventions were oriented towards patient empowerment, compared to all other interventions.[58]

To effectively reduce inappropriate prescribing and to improve patient-related outcomes, it is crucial to make clear arrangements and to promote useful collaboration among all health care professionals involved in the patient's care. This includes good transitional care for older polypharmacy patients upon their discharge from the hospital. Hospital-initiated medication changes need follow-up and monitoring. This can be done by the GP, but it might be better to refer these patients to pharmacotherapy optimisation outpatient clinics that, ideally, would be operated by geriatricians and clinical pharmacists. Follow-up and monitoring are more effective when conducted by the same person who initiated the pharmacotherapy optimisation and who discussed the recommendations and rationale with the patient during hospitalisation. In addition, GPs do not always have the time to coordinate this and may not always possess the knowledge and skills to adequately monitor all medication adjustments and act accordingly when the patient experiences problems. Another promising alternative would be to involve non-dispensing pharmacist who would be located at the GPs' practices. It might be inconvenient, especially for older patients, to travel to outpatient clinics, and follow-up would preferably be conducted within their GP's practice or even at home visits. In addition to follow-up on hospital-initiated medication changes, a non-dispensing pharmacist could also conduct medication reviews for community-dwelling older people who are at risk for inappropriate prescribing and could play an important role in primary prevention of medication-related hospitalisations, as was recently investigated in the POINT trial.[59]

With the lessons learned from the OPERAM trial, new project initiatives have been launched. One of these projects is the LIMONCELLO study that will be conducted at 16 Dutch hospitals, including both university medical centres and non-academic hospitals. In this study a pharmacotherapy team consisting of a physician and a pharmacist will critically evaluate the older patients' pharmacotherapy regimen just before hospital discharge, and medication adjustments will be implemented together with the involved specialist. Different from the OPERAM trial, direct communication between the pharmacotherapy team, involved specialists and the patient's GP will be warranted and will include a digital letter outlining all recommendations and considerations. The GP will retain the central control over the patient. The primary outcome, drug-related readmissions, will be measured at three months, and the total follow-up duration will be 12 months. Cost-effectiveness will be determined so that if the intervention proves

successful and cost-effective, it can be implemented in future clinical practice. The LIMONCELLO researchers hope to achieve better implementation rates than those in the SENATOR and OPERAM trials and by closely cooperating with the GPs, monitoring and patient adherence are likely to improve.

Concluding remarks

Conducting clinical trials assessing the effect of optimising pharmacotherapy for multimorbid older patients with polypharmacy remains challenging, especially in the dynamic hospital setting. The results of the studies presented in this thesis and the process evaluation of the OPERAM clinical trial provide insights into how some of these challenges might be overcome in future research and clinical practice. Good transitional care is important to follow-up on hospital-initiated medication changes after a patient's discharge. Close collaboration among all health care professionals involved in the care of older patients with multimorbidity and polypharmacy, including the GP and the CP, is indispensable to improve patient-related outcomes and to reduce pharmacotherapy related patient harm. In addition, patient education and empowerment by active involvement in SDM are crucial to ensure adherence to implemented pharmacotherapy optimisation recommendations and to improve overall patient satisfaction.

DECLARATIONS

Authors' contributions

This general discussion was written by Lianne Huibers (**CJAH**). Wilma Knol (WK), Ingeborg Wilting (IW), Rob van Marum (RvM) and Toine Egberts (TE) reviewed the manuscript critically and approved the final version.

Competing interests

The author(s) declare that they have no competing interests.

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10

SUMMARY

"The absence of evidence
is not the evidence of absence."

- Carl Sagan

SUMMARY

The aim of this thesis was to explore the STOPP/START criteria as a tool for detection of inappropriate prescribing in older patients and to evaluate their clinical applicability for individual patients (**PART I**). In addition we aimed to investigate the applicability of clinical decision support systems (CDSS), with integrated STOPP/START criteria, in medication reviews performed in the hospital setting (**PART II**). Finally, we addressed the importance of older patients' and physicians' involvement in decision-making regarding pharmacotherapy optimisation and ultimately aimed to identify barriers and facilitators for implementation of pharmacotherapy optimisation in the hospital setting (**PART III**).

PART I - Translation of STOPP/START criteria into clinical decision support algorithms
In **Chapter 2** we described the process of converting the textual STOPP/START recommendations into coded algorithms to enable implementation in software systems. During this process we have encountered several challenges and restrictions related to the STOPP/START criteria and the classification databases used. Through four multidisciplinary consensus rounds we were able to convert all 34 START and 76 out of 80 STOPP criteria into algorithms. Expert based choices had to be made in case criteria were ambiguous or did not match the database terminology. Additionally, some elements were not codable at all and were therefore left out of the algorithms, which led to a simplification of certain criteria. Another issue we addressed in this chapter was the complexity of applying all (coded or non-coded) criteria to databases or individual patients without clinical judgement. As several criteria contain overlapping medications or diagnoses, this can result in conflicting recommendations. Moreover, no inter-criterion priority is predefined when multiple criteria are relevant to one patient, emphasising the need for critical evaluation of the recommendations by experienced clinicians with access to actual patient data. The algorithms and the coding dictionary are provided as supplementary data for users and can easily be adapted according to local guidelines or expert opinion.

The difficulties faced during the translation of STOPP/START criteria into algorithms led to the idea to evaluate the clarity of STOPP/START criteria for their clinical applicability in prescribing for older people, as we presented in **Chapter 3**. With this study we aimed to explore the effect of the language used within the individual STOPP/START criteria on clarity and the consequences for clinical implementation. For each of the 114 STOPP/START criteria, elements describing the action (*what/how* to do), condition (*when* to do) and explanation (*why* to do) were identified. Clarity rating was categorised into high (>67.7%), moderate (33.3%–67.7%) or low (<33.3%). We found an average clarity for STOPP recommendations of 64%, 60% and 69% for actions, conditions and

explanations, respectively. Average clarity for START recommendations was 60% and 57% for actions and conditions, respectively. No statements were present to justify the prescription of the potential omissions within the 34 START recommendations. Unintentional deviations from the recommendations by end-users, resulting from ambiguous wordings and the lack of clear rationales and supporting evidence to substantiate the recommendations, could lead to lower implementation rates. This can even cause patient harm when implemented without taking the individual patient's context into account, especially when less experienced physicians are involved. Our findings provide direction to improve the clarity of presentation for future guidelines and explicit screening tools.

PART II - Evaluation of clinical decision support-assisted pharmacotherapy optimisation in the hospital setting

Chapter 4 describes the results of a single centre cluster-randomised controlled trial performed in a pre-operative outpatient setting. The aim of this cluster RCT was to evaluate the effect of pharmacotherapy optimisation recommendations, supported by a CDSS with integrated STOPP/START criteria (version 1), on appropriate prescribing and 3 month postoperative mortality. Residents performing the Comprehensive Geriatric Assessment (CGA) in older patients (≥ 70 years) with polypharmacy (≥ 5 medications) visiting the preoperative geriatric outpatient clinic, were randomised to either control or intervention cluster. The recommendations to optimise pharmacotherapy were based on STOPP/START criteria and formulated by a research physician, supported by the CDSS. The recommendations needed to be implemented by the attending resident of the outpatient clinic. Primary outcome was the number of medication changes made based on potential prescribing omissions (PPOs) and potentially inappropriate medications (PIMs) according to the prescribing recommendations. In total, 65 intervention and 59 control patients were included in 34 clusters. Significantly more medication changes based on PPOs and PIMs were made in the intervention group compared to usual care: PPOs 26.2% vs 3.4% and PIMS 46.2% vs 15.3%, respectively. There were no differences in dose adjustments or postoperative mortality. Whether this more appropriate prescribing will lead to better patient outcomes, such as fewer drug-related problems and drug-related admissions (DRAs), needs to be investigated in larger trials.

The complex multi-component intervention conducted in the OPERAM trial is described in detail in **Chapter 5**. This intervention consisted of several steps according to the Systematic tool to reduce inappropriate prescribing (STRIP) method, including a structured history-taking of medication (SHiM) and a medication review supported by a clinical decision support system (CDSS) with integrated STOPP/START criteria (version 2). This pharmacotherapy analysis was carried out by a trained research physician and

research pharmacist in mutually supportive roles (i.e. the pharmacotherapy team). In addition to the CDSS generated STOPP/START recommendations, based on patient data entered into the CDSS by the pharmacotherapy team, expert recommendations (i.e. potential over- and undertreatment not part of STOPP/START) were added to the medication optimisation report. The recommendations resulting from the medication review were subsequently discussed with both patient and prescribing physician through Shared-Decision-Making (SDM). Finally, an information report with actual discharge medication and recommendations not yet applied during hospitalization was sent to the GP. The effect of this multi-component intervention on DRAs in multimorbid older patients was the primary outcome investigated in the OPERAM clinical trial.

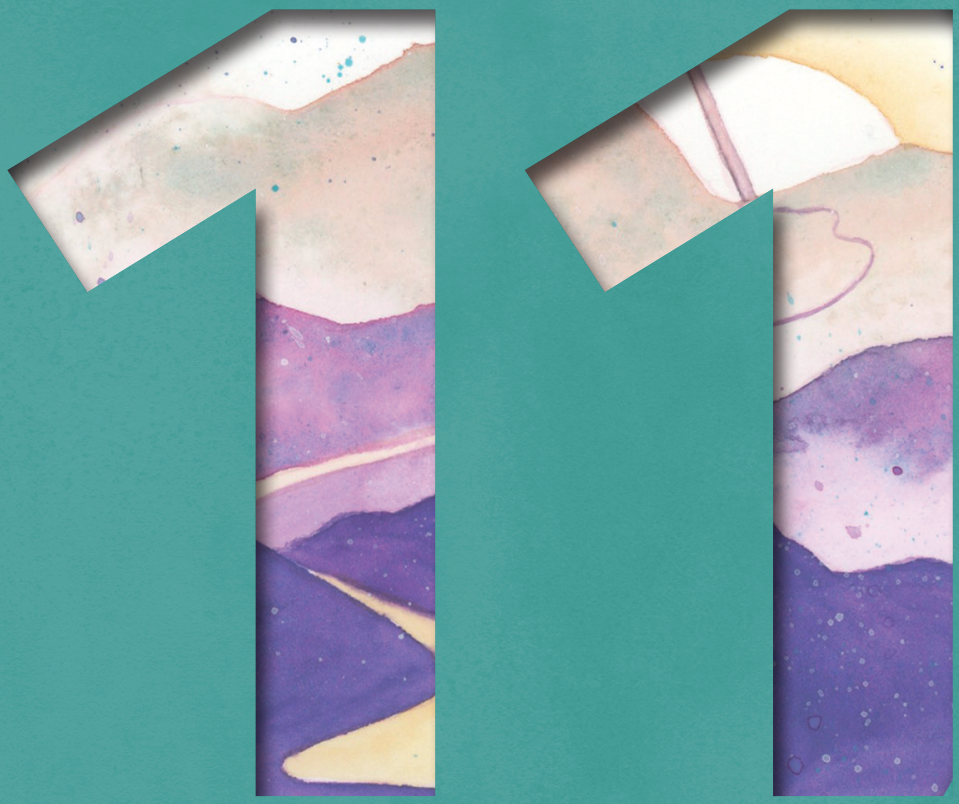
As all CDSS-generated STOPP/START-based recommendations during the pharmacotherapy analysis in the OPERAM trial were evaluated for appropriateness for the individual patient, certain recommendations were 'rejected' by the pharmacotherapy team. Data on which recommendations were frequently accepted and which were frequently rejected could provide insight into the clinical applicability of STOPP/START recommendations on an individual patient level. This resulted in **Chapter 6**, where we investigated the frequency and subsequent acceptance of the CDSS generated STOPP/START signals by the pharmacotherapy team within the OPERAM trial. We found that in nearly all patients at least one STOPP/START signal was generated. Overall, 39% of the CDSS generated signals were accepted by the pharmacotherapy team. The most frequently generated signal was to stop a drug without a clinical indication, accepted by the pharmacotherapy team in 54%. The most frequently involved medication group was 'drugs for acid related disorders'. The investigated patient-related determinants were poor predictors for acceptance of the STOPP/START recommendations, which means no target population could be identified for whom the application of STOPP/START criteria would have the most clinical value in the hospital setting. Furthermore, the results of this study emphasise the need for critical evaluation of CDSS-generated pharmacotherapy optimisation recommendations by experienced clinicians, to minimise over triggering and prevent potential patient harm by implementing all recommendations without clinical judgement tailored to the individual patient.

PART III - Hospital physicians' & older patients' perspectives on in-hospital pharmacotherapy optimisation

After the CDSS supported medication review was completed, the pharmacotherapy optimisation recommendations were discussed with patient and attending hospital physician by the pharmacotherapy team according to the intervention protocol as reported in **Chapter 5**. During this discussion both patient and prescribing physician could agree or disagree with the suggested medication changes by the pharmacotherapy

team and for different reasons. In **Chapter 7** we elaborated on this topic and presented the results of this discussion from the Dutch OPERAM intervention group. We found that although the recommendations were deemed appropriate for the individual patient by the pharmacotherapy team, overall agreement by patients and attending ward physicians was 61% for STOPP and START recommendations. Highest agreement (74%) was found for initiating osteoporosis agents and discontinuation of PPIs. Main reason for disagreement (40%) was reluctance to medication change by the patient. Most important lessons learned from these results, were the need for better patient and physician education regarding potential benefits and harms of pharmacotherapy and the discovery that medical records were not always up to date, resulting in many irrelevant recommendations (13%) as appeared during discussion with patient and physician.

Lastly, **Chapter 8** provided insights into hospital residents' perspectives on optimising pharmacotherapy through semi-structured interviews. In this qualitative study, residents from many different medical specialties elaborated on their experiences with multimorbid older patients with polypharmacy during hospital admission in respect to pharmacotherapy optimisation. All participating physicians, both surgical and non-surgical residents, felt responsible for the patients' medication and were aware of the potential harms of inappropriate prescribing in this vulnerable patient group. They acknowledged the importance of medication evaluation, yet experienced multiple barriers to conduct a medication review in the clinical setting. The most important barriers faced were the lack of time caused by the high work load experienced at the ward and the presence of other priorities during admission, on top of insufficient knowledge and skills to carry out a medication review. The surgical residents stated that they do not consider it the role of the surgeon to optimise pharmacotherapy. In addition to these barriers intrinsic to the prescriber, patient and system-related factors were also identified as limiting to pharmacotherapy optimisation. The facilitators elucidated were: the presence of certain triggers (e.g. suspected side effects, diminished renal function) to evaluate the medication, supervisors as a role model, more education and training about appropriate prescribing and consultation of a pharmacotherapy optimisation team. Changing the prescribing climate will require interventions targeting physicians, patients as well as the health care system as a whole.



NEDERLANDSE SAMENVATTING

"The greatest medicine of all
is teaching people how not to need it."

- Hippocrates

SAMENVATTING

Achtergrond

De wereldbevolking vergrijst in hoog tempo en de levensverwachting van mensen van 65 jaar of ouder neemt toe. Een persoon die tussen 2015 en 2020 de leeftijd van 65 jaar bereikt, heeft gemiddeld nog 17 jaar te leven en de verwachting is dat dit oploopt tot 19 jaar in 2050. Met deze vergrijzing neemt de prevalentie van chronische ziekten die vaak voorkomen op hogere leeftijd toe. Het hebben van twee of meer chronische ziekten, multimorbiditeit genoemd, is geassocieerd met functionele achteruitgang en afhankelijkheid, meer gebruik van gezondheidszorg en een slechtere kwaliteit van leven.

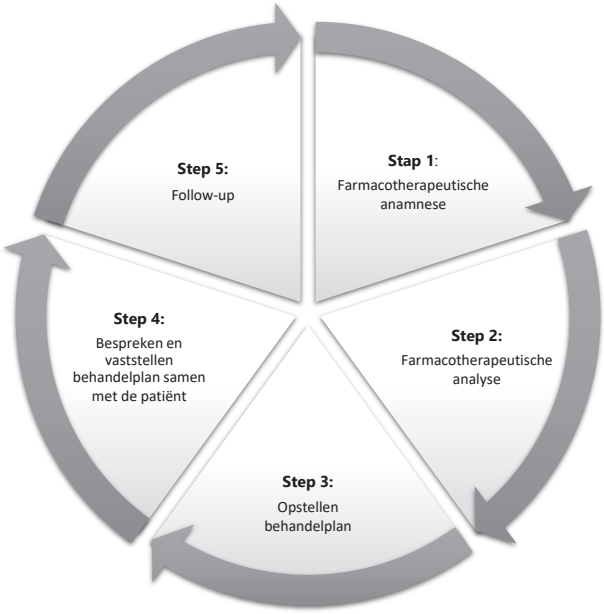
Omdat veel chronische ziekten vaak worden behandeld met medicatie, gaat multimorbiditeit vaak gepaard met het chronisch gebruik van 5 of meer geneesmiddelen, ook wel polyfarmacie genoemd. Naast de positieve effecten van medicatie is er ook een risico op gezondheidsschade. Zo hebben ouderen met multimorbiditeit en polyfarmacie een verhoogd risico op medicatie-gerelateerde problemen, zoals een medicatie-gerelateerde ziekenhuisopname. Naar schatting is tot ongeveer 30% van de van ziekenhuisopnames bij ouderen medicatie-gerelateerd, waarvan de helft potentieel vermijdbaar is. Het is daarom belangrijk om bij het voorschrijven van geneesmiddelen de potentiële voordelen zorgvuldig af te wegen tegen de potentiële risico's voor de individuele patiënt.

Om medicatie-gerelateerde problemen te voorkomen, is het belangrijk om potentieel ongeschikt medicatiegebruik bij ouderen op te sporen en indien mogelijk de farmacotherapie te optimaliseren. Hiervoor zijn diverse richtlijnen ontwikkeld. Het wordt aanbevolen om bij ouderen met polyfarmacie periodiek een gestructureerde medicatiebeoordeling uit te voeren.

In Nederland wordt hiervoor vaak de STRIP (Systematic Tool to Reduce Inappropriate Prescribing) methode gebruikt. De STRIP methode betrekt actief de patiënt en stimuleert de samenwerking tussen verschillende zorgverleners. De STRIP methode bestaat uit 5 opeenvolgende stappen zoals weergegeven in **Figuur 1**: 1. Farmacotherapeutische anamnese 2. Farmacotherapeutische analyse 3. Opstellen behandelplan 4. Bespreken en vaststellen behandelplan samen met de patiënt 5. Follow-up.

Er zijn meerdere screeningsinstrumenten ontwikkeld die kunnen helpen bij de medicatiebeoordeling om ongeschikt medicatiegebruik sneller op te sporen. Deze instrumenten kunnen worden ingebouwd in stap 2 (farmacotherapeutische analyse) van de STRIP methode. In Europa worden hiervoor de Screening Tool of Older Persons'

Prescriptions (STOPP) en Screening Tool to Alert to Right Treatment (START) criteria het meest gebruikt. Eerdere onderzoeken hebben laten zien dat het toepassen van de STOPP/START criteria als interventie kan leiden tot beter medicatiegebruik, minder bijwerkingen en lagere kosten.

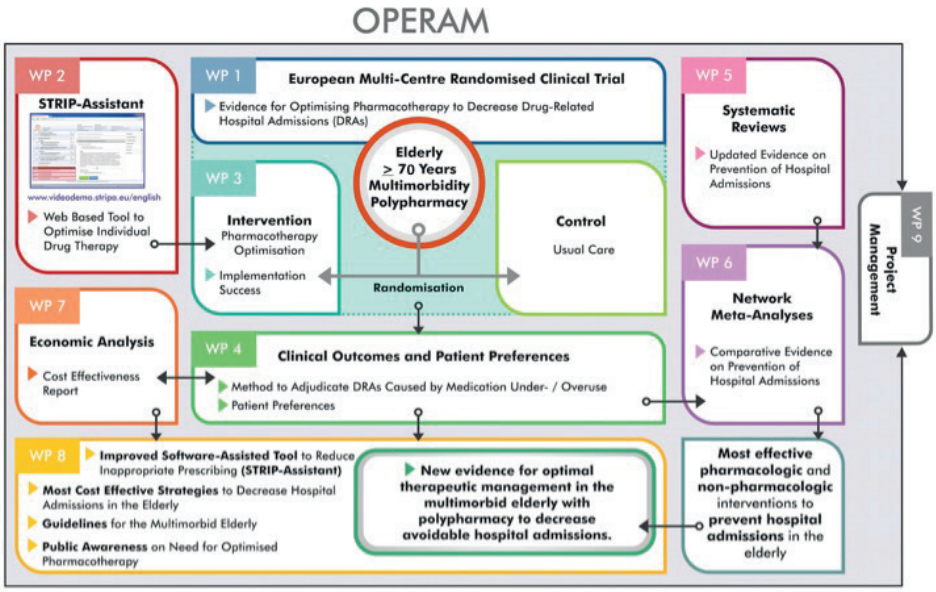


1	**Farmacotherapeutische anamnese:** Verzamelen van informatie over actueel medicatiegebruik en patiëntvoorkeuren. De 'Structured History-taking of Medication' (SHiM) vragenlijst is gevalideerd voor dit proces.
2	**Farmacotherapeutische analyse**: Vastellen van potentiële farmacotherapie-gerelateerde problemen. Checken op onderbehandeling, ineffectieve behandeling, overbehandeling, bijwerkingen, contra-indicaties, interacties, onjuiste dosering en praktische problemen. Screeningsinstrumenten zoals de STOPP/START criteria kunnen in deze stap worden gebruikt.
3	**Opstellen behandelplan**: Overeenstemming bereiken tussen arts en apotheker over de therapeutische doelen en hoe deze te bereiken.
4	**Vaststellen behandelplan met de patiënt**: Tegemoetkomen aan de medicatie-gerelateerde behoeften van de patiënt, behandeldoelen vaststellen en farmacotherapie-gerelateerde problemen oplossen. Communiceren van alle medicatiewijzigingen naar de betrokken zorgverleners.
5	**Follow-up**: Implementeren van medicatiewijzigingen en evaluatie van het effect. Plannen van het volgende bezoek aan de verantwoordelijke zorgverlener.

Figuur 1: Schematische weergave van de Systematic Tool to Reduce Inappropriate Prescribing (STRIP) methode.

Het gebruik van dergelijke screeningsinstrumenten kost vaak veel tijd. Om de farmacotherapeutische analyse efficiënter te maken zijn er allerlei initiatieven ontwikkeld om screeningsinstrumenten, zoals de STOPP/START criteria, in te bouwen in beslis-ondersteunende instrumenten (ook wel CDSS: clinical decision support systems). Een CDSS is een computergestuurde technologische oplossing die ingezet wordt ter ondersteuning van het nemen van beslissingen bij het oplossen van complexe problemen. Ook in onderzoeken naar farmacotherapie optimalisatie wordt steeds vaker gebruikt gemaakt van een dergelijk CDSS. Tot op heden is het echter nog niet gelukt om in grote studies naar farmacotherapie optimalisatie, met of zonder gebruik van CDSS, medicatie-gerelateerde problemen zoals medicatie-gerelateerde ziekenhuisopnames, te voorkomen.

Het onderzoek in dit proefschrift focust op het optimaliseren van farmacotherapie met behulp van een beslis-ondersteunend instrument bij oudere patiënten met polyfarmacie en multimorbiditeit die in het ziekenhuis zijn opgenomen. Met de onderzoeken die in dit proefschrift worden gepresenteerd streven we ernaar inzicht te verschaffen in het gebruik van de STOPP/START criteria als screeningsinstrument om ongewenst medicatiegebruik te verminderen en onderzoeken we de uitvoerbaarheid van het integreren van de STOPP/START criteria in beslis-ondersteunende instrumenten. Daarnaast onderzoeken we het gebruik van dit beslis-ondersteunend instrument als onderdeel van een interventie waarbij een farmacotherapie expert team betrokken is binnen een grote Europese klinische studie (OPERAM: OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people) met als doel farmacotherapie te optimaliseren en gezondheidsuitkomsten te verbeteren voor ouderen patiënten die zijn opgenomen in het ziekenhuis. Een overzicht van alle onderdelen van het OPERAM-project, inclusief de klinische studie, is weergegeven in **Figuur 2**. Daarnaast zal dit proefschrift inzoomen op de betrokkenheid van zorgverleners en patiënten bij gezamenlijke besluitvorming met betrekking tot farmacotherapie optimalisatie in de Nederlandse ziekenhuis-setting en belemmerende en bevorderende factoren om farmacotherapie in het ziekenhuis te optimaliseren uitlichten. Deze inzichten kunnen helpen om het proces van farmacotherapie optimalisatie te verbeteren en helpen bij het bereiken van positieve gezondheidseffecten en het verminderen van gezondheidsschade door geneesmiddelen bij oudere patiënten.



Figuur 2: Concept van het OPERAM-project.

OPERAM = OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people

Samenvattend, was het doel van dit proefschrift om de STOPP/START criteria als screeningsinstrument voor het opsporen van ongeschikt medicatiegebruik bij ouderen patiënten te onderzoeken en om de klinische toepasbaarheid van de STOPP/START criteria voor individuele patiënten te evalueren (**DEEL I**). Daarnaast hebben we de bruikbaarheid van een beslis-ondersteund instrument (CDSS), met geïntegreerde STOPP/START criteria, bij medicatiebeoordelingen in het ziekenhuis onderzocht (**DEEL II**). Tot slot hebben we het belang benadrukt van het betrekken van oudere patiënten en artsen bij gezamenlijke besluitvorming aangaande farmacotherapie optimalisatie en hebben we belemmerende en bevorderende factoren geïdentificeerd voor de implementatie van farmacotherapie optimalisatie in het ziekenhuis (**DEEL III**).

Deel I - Vertaling van STOPP/START criteria naar algoritmes voor beslis-ondersteunde instrumenten

In **hoofdstuk 2** is het proces beschreven van het vertalen van de tekstuele STOPP/START aanbevelingen naar gecodeerde algoritmes die geschikt zijn voor implementatie in software systemen, zoals CDSS. Tijdens dit proces kwamen we voor verschillende uitdagingen te staan en werden we geconfronteerd met de beperkingen van de STOPP/START criteria zelf en de classificatie databases die we hebben gebruikt voor het coderen. Middels 4 multidisciplinaire consensus rondes waren we in staat om alle 34 START criteria en 76 van de 80 STOPP criteria om te zetten naar gecodeerde algoritmes.

Het was nodig om keuzes te maken op basis van 'expert opinion' als de criteria niet eenduidig waren of niet overeenkwamen met de database terminologie. Daarnaast bleek dat sommige elementen binnen de STOPP/START criteria in het geheel niet te coderen waren waardoor deze elementen uit de algoritmes werden weggelaten. Dit heeft geleid tot een vereenvoudiging van sommige criteria.

Een ander belangrijk punt dat we met dit hoofdstuk willen benadrukken is dat het toepassen van alle criteria op databases of individuele patiënten erg complex is, zeker als er geen klinische beoordeling plaatsvindt. Mede doordat bepaalde criteria overlappende diagnoses of medicatie bevatten kan dit leiden tot tegenstrijdige aanbevelingen binnen één patiënt. Omdat er geen prioritering wordt aangegeven tussen de criteria die van toepassing zijn op de individuele patiënt is het belangrijk dat er kritische evaluatie plaats vindt door ervaren clinici met toegang tot de patiënt en/of patiënt data. De algoritmes hebben wij beschikbaar gesteld voor gebruik door andere zorgverleners, waarbij het mogelijk is om de data aan te passen aan de lokale richtlijnen of naar eigen inzicht van de zorgverlener.

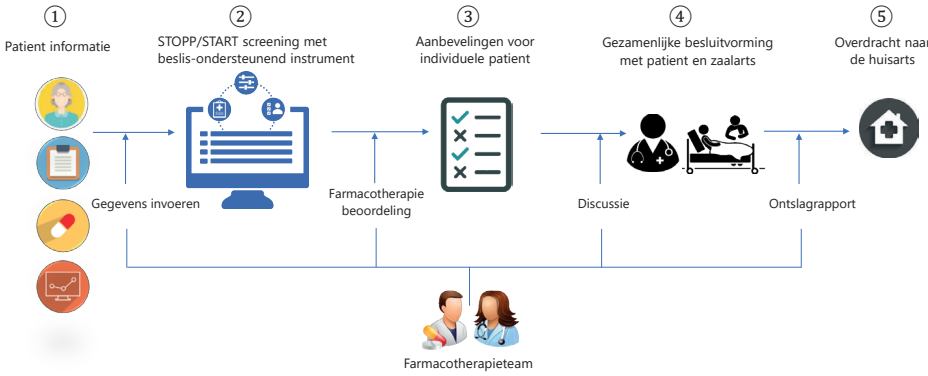
De uitdagingen die we tegenkwamen tijdens de vertaling van de STOPP/START criteria naar algoritmes leidde uiteindelijk tot het idee om de eenduidigheid van de STOPP/START criteria met betrekking tot hun klinische toepasbaarheid in de dagelijkse praktijk verder te onderzoeken. De uitkomsten hiervan zijn gepresenteerd in **hoofdstuk 3**. Met dit onderzoek wilden we het effect van de gebruikte taal en definities binnen de individuele START/STOPP criteria op de implementatie van de aanbevelingen in de klinische praktijk in kaart brengen. Voor alle 114 STOPP en START criteria werd de eenduidigheid van de aanbevolen *actie* (wat moet er gebeuren en hoe?), de *voorwaarde* (onder welke omstandigheden en voor wie geldt dit?) en de *toelichting* (waarom is dit van toepassing?) vastgesteld. Vervolgens werd de eenduidigheid gecategoriseerd als hoog (>67,7%), gemiddeld (33,3%–67,7%) of laag (<33,3%). De gemiddelde score op deze drie onderdelen was tussen de 57% en 69%. Bij de START criteria ontbrak de toelichting in alle gevallen, zodat het voor gebruikers niet altijd duidelijk is waarom een bepaald criteria van toepassing is en wat het belang is van het opvolgen van de aanbeveling voor de individuele patiënt.

De resultaten van deze studie laten zien dat gebrek aan eenduidig taalgebruik en gebrek aan toelichting om de aanbevelingen te onderbouwen kan leiden tot lagere implementatie van de aanbevelingen in de klinische praktijk. Daarnaast kan het zelfs leiden tot gezondheidsschade bij de patiënt als aanbevelingen klakkeloos worden overgenomen zonder dat de context van de patiënt wordt meegenomen in de overwegingen, vooral als ze worden toegepast door minder ervaren gebruikers.

Deel II - Bruikbaarheid van beslis-ondersteunde instrumenten bij medicatie-beoordelingen in het ziekenhuis

Hoofdstuk 4 beschrijft de resultaten van een cluster gerandomiseerde studie in een poliklinische patiëntenpopulatie van het UMC Utrecht. Het doel van deze studie was het effect onderzoeken van farmacotherapie optimalisatie adviezen op adequaat voorschrijven. Deze adviezen werden geformuleerd met behulp van een beslis-ondersteunend instrument waarin de STOPP/START waren geïntegreerd. Hierbij werden deze adviezen voorgelegd aan arts-assistenten in de interventiegroep, die een Comprehensive Geriatric Assessment (CGA) uitvoerden bij oudere patiënten (≥ 70 jaar) met polyfarmacie (≥ 5 geneesmiddelen) die de geriatrische pre-operatieve polikliniek bezochten. Het was vervolgens aan deze arts-assistenten om te bepalen of zij deze adviezen ook wilden overnemen. De primaire uitkomst was het aantal medicatiewijzigingen op basis van onderbehandeling of overbehandeling als gevolg van de farmacotherapie optimalisatie adviezen. Er werden 65 patiënten in de interventiegroep en 59 in de controle groep geïncludeerd. Er werden significant meer medicatiewijzigingen doorgevoerd in de interventiegroep, vergeleken met de controlegroep, namelijk 26.2% versus 3.4% voor onderbehandeling en 46,2% versus 15,3% voor overbehandeling. Hierbij was er geen verschil in postoperatieve mortaliteit na 3 maanden. Of dit verbeterde voorschrijven ook leidt tot betere uitkomsten voor de patiënten, zoals minder medicatie-gerelateerde problemen of ziekenhuisopnames, zal in grotere studies moeten worden onderzocht.

De complexe interventie, zoals die is uitgevoerd in de OPERAM studie, wordt in detail beschreven in **hoofdstuk 5**. Deze interventie bestond uit een aantal stappen volgens de STRIP methode, waarbij een gestructureerde medicatie anamnese werd afgenomen en er vervolgens een medicatiebeoordeling plaatsvond waarbij een beslis-ondersteunend instrument met geïntegreerde STOPP/START criteria werd gebruikt. Deze medicatiebeoordeling werd uitgevoerd door een arts en apotheker, die samen het farmacotherapieteam vormden (**Figuur 3**). De aanbevelingen met betrekking tot de farmacotherapie optimalisatie die het resultaat waren van deze medicatiebeoordeling werden vervolgens besproken met de betreffende patiënt en de zaalarts, waarbij keuzes werden gemaakt middels gezamenlijke besluitvorming. Als laatste werd er nog een overzicht gemaakt van alle aanbevelingen, inclusief de aanbevelingen die nog niet in het ziekenhuis waren doorgevoerd. Dit overzicht werd naar de huisarts van de patiënt gestuurd. Het effect van deze complexe interventie op medicatie-gerelateerde ziekenhuisopnames was de primaire uitkomst van de OPERAM studie.



Figuur 3: De verschillende stappen binnen de OPERAM interventie uitgevoerd door het farmacotherapie team.

Alle aanbevelingen die op basis van STOPP/START criteria door het beslis-ondersteunend instrument werden gegenereerd, zijn door het farmacotherapieteam beoordeeld op hun toepasbaarheid voor de individuele patiënt. Deze beoordeling leidde ertoe dat sommige aanbevelingen werden afgewezen, terwijl anderen werden geaccepteerd. De gegevens betreffende deze geaccepteerde en afgewezen aanbevelingen kunnen inzicht verschaffen in de toepasbaarheid van de STOPP/START criteria op individueel patiëntniveau. Dit resulteerde in **hoofdstuk 6**, waar we de frequentie van voorkomen en de acceptatie van de STOPP/START signalen, gegenereerd met behulp van een beslis-ondersteunend instrument, binnen de OPERAM studie hebben onderzocht. Bij vrijwel alle patiënten was tenminste één signaal van toepassing. In totaal werd 39% van deze signalen geaccepteerd door het farmacotherapieteam. Het meest voorkomende signaal betrof het stoppen van een medicijn waar geen duidelijke indicatie voor bestond. Dit signaal werd in 54% van de gevallen door het farmacotherapieteam geaccepteerd. De medicatiegroep die hierbij het meest voorkwam waren de middelen tegen maagzuur (protonpompremmers). Het bleek dat patiënt-gerelateerde factoren (zoals vallen, nierfunctie, aantal co-morbiditeiten) slechte voorspellers waren voor acceptatie van STOPP/START aanbevelingen. Op basis van deze resultaten is het dus lastig om een doelgroep aan te wijzen voor wie het toepassen van de START/STOPP criteria de grootste meerwaarde heeft binnen het ziekenhuis. Deze resultaten benadrukken wel het belang van kritische evaluatie van de door een beslis-ondersteund instrument gegenereerde farmacotherapie optimalisatie aanbevelingen door ervaren clinici, omdat meer dan 60% van de signalen na beoordeling uiteindelijk niet werd geaccepteerd door het farmacotherapieteam. Dit kan ook helpen om gezondheidsschade te voorkomen door niet zomaar alle aanbevelingen op te volgen zonder deze aan te passen op de situatie van de individuele patiënt.

Deel III - Perspectieven van artsen en oudere patiënten op farmacotherapie optimalisatie in het ziekenhuis

Nadat de medicatiebeoordeling met behulp van het beslis-ondersteunend instrument was afgerond, werden alle farmacotherapie optimalisatie aanbevelingen besproken met de desbetreffende patiënt en zaalarts, zoals schematisch weergegeven in **Figuur 3**; stap 4. Tijdens dit proces van gezamenlijke besluitvorming konden zowel de patiënt als de voorschrijvend zaalarts het met de aanbevelingen eens of oneens zijn om verschillende redenen. In **hoofdstuk 7** zijn de resultaten van deze besluitvorming bij de Nederlandse OPERAM interventiegroep gepresenteerd. Hieruit bleek, dat ondanks dat alle besproken aanbevelingen relevant waren bevonden voor de individuele patiënt door het farmacotherapieteam, slechts 61% van de STOPP en START adviezen werd geaccepteerd. De hoogste acceptatie (74%) werd gevonden voor het starten van middelen tegen osteoporose en het stoppen van protonpompremmers. De belangrijkste reden om het advies niet op te volgen was weerstand van de patiënt tegen verandering van de medicatie (40%). Eén van de belangrijkste lessen die hieruit voortvloeit is het belang van betere voorlichting van patiënten en artsen over de mogelijke voordelen en risico's van farmacotherapie. Daarnaast bleek dat het medisch dossier van patiënten lang niet altijd compleet en up-to-date was, dit leidde tot veel irrelevante aanbevelingen (13%) die pas aan het licht kwamen tijdens de discussie met de patiënt.

Tenslotte worden in **hoofdstuk 8** de perspectieven van in het ziekenhuis werkzame arts-assistenten op farmacotherapie optimalisatie besproken. Dit hoofdstuk betreft een kwalitatieve studie waarbij arts-assistenten vanuit verschillende medische specialismen, zowel snijdend als beschouwend, zijn geïnterviewd over hun ervaringen met farmacotherapie optimalisatie bij oudere patiënten tijdens ziekenhuisopname. Hieruit kwam naar voren dat alle artsen, zowel snijdend als beschouwend, zich verantwoordelijk voelen voor de farmacotherapie van patiënten en dat zij zich bewust zijn van de mogelijke gevaren die gepaard gaan met het voorschrijven van ongeschikte medicatie aan deze kwetsbare patiëntengroep. Zij erkennen het belang van medicatiebeoordeling, maar ervaren verschillende barrières om dit tijdens een ziekenhuisopname uit te voeren. De belangrijkste belemmerende factoren die werden genoemd waren het gebrek aan tijd, veroorzaakt door de hoge werkdruk op de afdeling, andere prioriteiten tijdens een ziekenhuisopname, boven op een gebrek aan voldoende kennis en kunde om een medicatiebeoordeling uit te voeren. De snijdende arts-assistenten gaven daarbij nog aan dat zij het niet als de rol van de chirurg zien om farmacotherapie te optimaliseren. De belangrijkste bevorderende factoren die aan het licht kwamen waren de aanwezigheid van bepaalde 'triggers' voor het uitvoeren van een medicatiebeoordeling (bijvoorbeeld vermoeden op bijwerkingen, verminderde nierfunctie), supervisoren die hierin een

voorbeeldfunctie aannemen, meer onderwijs en training in adequaat voorschrijven en de mogelijkheid om een farmacotherapie optimalisatie team te kunnen raadplegen. Om het voorschrijfklimaat te veranderen zijn er interventies nodig die zich richten op artsen, patiënten, maar ook op het zorgsysteem als geheel.

Aanbevelingen

Met de belangrijkste lessen uit de onderzoeken in dit proefschrift in gedachten, rijst de vraag: hoe gaan we vanaf nu verder met farmacotherapie optimalisatie voor oudere patiënten met polyfarmacie?

Een belangrijke boodschap van de geïnterviewde arts-assistenten (**Hoofdstuk 8**) was dat zij zich onvoldoende bekwaam voelen in het (zelfstandig) uitvoeren van een medicatiebeoordeling. Het is daarom belangrijk om alle toekomstige artsen voldoende voor te bereiden tijdens hun geneeskundeopleiding, zodat de farmacotherapie basiskennis van alle voorschrijvers voldoende is. Daarnaast is het ook belangrijk om tijdens hun vervolgopleidingen hier voldoende aandacht aan te besteden om deze kennis bij te houden en toe te passen. Het is hierbij niet het streven om alle artsen complexe medicatiebeoordelingen uit te laten voeren en farmacotherapie te optimaliseren, maar vooral het voorkomen van medicatie-gerelateerde problemen door adequaat voorschrijven te stimuleren. Het is namelijk niet realistisch om van alle voorschrijvers te verwachten dat zij de farmacotherapie van oudere patiënten optimaliseren. Niet alleen vanwege het gebrek aan tijd, maar ook omdat het een vaardigheid is die specifieke kennis en expertise vereist. Chirurgen zijn immers opgeleid om te opereren, dus dat is waar ze goed in zijn en wat ze vooral moeten doen. Het is echter wel belangrijk om chirurgen en andere voorschrijvers te helpen bij het opsporen van patiënten met een hoog risico op medicatie-gerelateerde problemen en hen te stimuleren om te overleggen met andere zorgverleners die kunnen helpen bij het optimaliseren van farmacotherapie, in het bijzonder als het gaat om ouderen met polyfarmacie.

Dit is waar beslis-ondersteunende instrumenten voor kunnen worden ingezet. Als een beslis-ondersteunend instrument met geïntegreerde screeningsinstrumenten, zoals de STOPP/START criteria, wordt geïmplementeerd in de elektronische voorschrijfsystemen van de ziekenhuizen en de huisartsenpraktijken, kan dit voorschrijvers attenderen op hoog-risico patiënten voor ongeschikt medicatiegebruik en medicatie-gerelateerde problemen. Het is daarbij natuurlijk wel van belang dat de medische dossiers van patiënten volledig en up-to-date zijn en gelinkt aan dit beslis-ondersteunend instrument. Daarnaast kunnen artsen dan tijdens het voorschrijven van medicatie door het systeem gewaarschuwd worden als zij op het punt staan om een potentieel ongeschikt geneesmiddel voor te schrijven en kunnen veiligere alternatieven worden

voorgesteld. Als het middel desondanks toch wordt voorgeschreven kan het systeem adviezen geven over hoe en wanneer monitoring zou moeten plaatsvinden. Uiteindelijk is preventie waarschijnlijk de meest effectieve methode om onjuist medicatiegebruik te verminderen. Het blijkt namelijk lastig om potentieel ongewenste medicatie te stoppen (zoals bijvoorbeeld in het geval van benzodiazepines) als deze eenmaal chronisch in gebruik zijn. Om die reden moet het voorschrijven van deze middelen direct ontmoedigd worden. Het is daarbij wel belangrijk dat het beslis-ondersteunend instrument uitleg en toelichting geeft op de reden van ongeschiktheid en de risico's als het middel toch wordt voorgeschreven. Deze uitleg kan vervolgens ook weer worden gebruikt in de gezamenlijke besluitvorming met de patiënt. Het is belangrijk om de patiënt al vroeg in dit proces te betrekken. De interventies om medicatie-gerelateerde (her)opnames te voorkomen lijken namelijk het meest effectief als deze zijn gericht op empowerment van patiënten, vergeleken met alle andere interventies.

Om onjuist medicatiegebruik effectief te verminderen en patiënt-gerelateerde uitkomsten te verbeteren is het cruciaal om goede afspraken te maken en samen te werken met alle zorgverleners die betrokken zijn bij de zorg voor de patiënt. Dit betekent ook een goede overdracht naar de eerstelijn voor ouderen met polyfarmacie als zij uit het ziekenhuis worden ontslagen. Wijzigingen in de medicatie van oudere patiënten die in het ziekenhuis zijn doorgevoerd, moeten in de thuissituatie vervolgd en gemonitord worden. Dit kan worden gedaan door de huisarts, maar deze patiënten kunnen ook worden verwezen naar speciaal ingerichte polyfarmacie poliklinieken, vaak een samenwerking tussen klinisch geriaters en ziekenhuisapothekers. Het is waarschijnlijk effectiever om de follow-up en monitoring van medicatiewijzigingen te laten uitvoeren door dezelfde personen die de wijzigingen hebben voorgesteld en dit ook met patiënten hebben besproken bij de gezamenlijke besluitvorming tijdens de ziekenhuisopname. Ook hebben huisartsen vaak niet de tijd om dit te coördineren en bezitten zij ook niet altijd de kennis en expertise om alle medicatiewijzigingen te monitoren en te handelen als de patiënt problemen ervaart.

Een ander veelbelovend alternatief zou zijn om een apotheker-farmacotherapeut deze rol te laten vervullen. Deze kan bijvoorbeeld werken vanuit de huisartsenpraktijk, zodat kwetsbare oudere patiënten niet op en neer hoeven naar het ziekenhuis. Ook is mogelijk om bij patiënten op huisbezoek te gaan als zij niet in staat zijn zelfstandig te reizen. De apotheker-farmacotherapeut werkt nauw samen met de huisarts en de openbaar apotheker en kan naast follow-up van medicatiewijzigingen na ziekenhuisopname ook zelf medicatiebeoordelingen uitvoeren bij thuiswonende ouderen. Op deze manier kunnen zij een belangrijke rol vervullen als het gaat om de primaire preventie van medicatie-gerelateerde ziekenhuisopnames, zoals recent is onderzocht in de POINT-studie.

Conclusie

Het optimaliseren van farmacotherapie voor ouderen met polyfarmacie blijft een grote uitdaging, vooral in de dynamische ziekenhuis setting. De resultaten van de onderzoeken die in dit proefschrift zijn beschreven verschaffen inzicht in hoe met sommige van deze uitdagingen kan worden omgegaan, zowel in de klinische praktijk als in toekomstige onderzoeken op dit gebied. Goede ketenzorg is belangrijk om in het ziekenhuis doorgevoerde medicatiewijzingen op te volgen na ontslag van de patiënt. Nauwe samenwerking tussen alle zorgverleners die betrokken zijn bij de zorg voor één patiënt met polyfarmacie en multimorbiditeit, inclusief de huisarts en de openbaar apotheker, is onmisbaar als het gaat om het verbeteren van patiënt-gerelateerde uitkomsten en het verminderen van medicatie-gerelateerde gezondheidsschade. Daarnaast is patiënt voorlichting en empowerment, door actieve betrokkenheid in gezamenlijke besluitvorming, cruciaal om therapietrouw te bevorderen en de algehele patiënt tevredenheid te verbeteren.

PART V

APPENDICES

LIST OF PUBLICATIONS
LIST OF CO-AUTHORS

"One never notices what has been done;
one can only see what remains to be done."

- Marie Curie

LIST OF PUBLICATIONS
PART OF THIS THESIS

Conversion of STOPP/START version 2 into coded algorithms for software implementation: A multidisciplinary consensus procedure.
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"Coming together is a beginning,
staying together is progress,
and working together is success."

– Henry Ford

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DANKWOORD
ABOUT THE AUTHOR

"Life is like riding a bicycle.
To keep your balance
you must keep moving."

- Albert Einstein

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Bastiaan Sallevelt. Lieve Sally, samen hebben we het hele OPERAM avontuur doorlopen. En wat een avontuurlijke reis is het geweest! Ik ben heel blij en dankbaar dat ik dit samen met jou mocht doen. We hadden vanaf de eerste dag een goede klik en ook als 'farmacotherapieteam' vulden we elkaar goed aan. Het was hard werken en ondanks de veelal technische obstakels ("STRIPA says no..." en "data not saved...") hadden we er ook veel plezier in. Ons gezamenlijke chronotype maakte dat we niet altijd stipt om 9.00u in het UMC waren als dat niet hoefde. We schuwden het echter niet om vervolgens tot in de avond door te werken om de uurtjes in te halen. Naast hard werken hebben we ook ontzettend veel lol gehad samen en zijn de beste ideeën soms ontstaan tijdens onze 'werkbesprekingen' in The Basket, onder het genot van LaChouffe van de tap. Behalve een goede samenwerking hebben we ook een mooie vriendschap opgebouwd in de afgelopen jaren. Ondanks dat we elkaar niet meer dagelijks zien of spreken, kunnen we nog steeds uren kletsen en lachen. En ook al hebben we inmiddels allebei een nieuwe stap in onze carrière gezet, waarbij we waarschijnlijk geen collega's meer zullen worden, hoop ik dat onze vriendschap en 'werkbesprekingen' blijven bestaan!

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Jody Op Heij. Beste Jody, ik weet nog goed dat Wilma kwam vertellen dat ze een wetenschapsstudent had die ons wel op weg kon helpen met het analyseren van de STRIPA data. En oh ja, je was ook apotheker, dus met die medicatiekennis zat het ook wel goed. Wat ik me op dat moment nog niet realiseerde was dat jij een ontzettend gemotiveerde en ambitieuze wetenschapsstudent was en dat je tijdens jouw stage de basis hebt gelegd voor uiteindelijk 3 artikelen in dit proefschrift. Eén onderwerp was voor jou niet genoeg, je wilde ook graag meehelpen met het afnemen en analyseren van de interviews. Je hebt mij voor een deel wegwijs gemaakt in NVivo en mij veel werk uit handen genomen. Je hebt er een mooi verslag van geschreven en uiteindelijk mag je jezelf coauteur noemen van 3 wetenschappelijke publicaties. Dankjewel voor al jouw hulp en inzet (en geduld). Ik wens je veel succes met jouw verdere carrière!

Kamergenoten van 'de leukste kamer van het UMC' en mede-promovendi, Namiko, Esther, Nienke, Evelien, Jurre en Lauren. Met de meeste van jullie heb ik heel wat uren doorgebracht op 'onze' kamer. Soms in stilte en hard aan het werk, maar gelukkig ook vaak verwikkeld in discussies over onderzoek of persoonlijke onderwerpen. We gingen gezamenlijk lunchen, een rondje lopen of een ijsje eten buiten bij mooi weer. Mede dankzij jullie ben ik al die jaren met veel plezier naar het UMC gekomen en had ik veel aan jullie luisterend oor of (on)gevraagd advies. Bedankt daarvoor! En ik hoop dat we ook in de toekomst nog eens af en toe een bijpraat-etentje organiseren!

Namiko Goto. Lieve Namiko, jou wil ik graag nog even persoonlijk bedanken. Samen hebben we een groot deel van onze onderzoekstijd doorgebracht op dezelfde kamer in het UMC. Naast dat we het heel gezellig hebben gehad en er een mooie vriendschap aan over hebben gehouden, hebben we natuurlijk ook veel lief en leed gedeeld m.b.t. onze promotie-trajecten. Al in 2019 mocht ik jou als paranimf bijstaan tijdens jouw verdediging. Nu zijn de rollen omgedraaid en ben ik blij dat jij op deze belangrijke dag aan mijn zijde staat! Dankjewel voor jouw steun en gezelligheid gedurende dit hele traject en hopelijk nog heel lang daarna!

Nikki Noorda. Lieve Nikki, dankzij jouw ambitie om klinisch farmacoloog te worden en mijn ambitie om te promoveren zijn wij met elkaar in contact gekomen. Een half jaar lang zaten we bijna dagelijks in dezelfde kamer, wat niet altijd zorgde voor efficiënt werken....

Wel was het altijd gezellig en hebben we heel wat koffie gedronken en geluncht. Ik ben blij dat we aan deze periode een mooie vriendschap en een 2-mans intervisiegroepje hebben overgehouden, waarin we al onze belevenissen als klinisch geriater, klinisch farmacoloog en onderzoeker met elkaar delen. Dankjewel voor je positiviteit en energie, die kon ik vaak goed gebruiken en wakkerde mijn relativeringsvermogen meestal wel weer aan. Ik hoop dat we deze vriendschap blijven koesteren en elkaar nog regelmatig spreken tijdens onze woon-werkverkeer telefoontjes!

Tergooi-vriendinnen. Lieve Mariska, Anouschka, Dineke, Esther, Mirjam, Inez en Tineke. Het is inmiddels alweer 10 jaar geleden dat we samen als ANIOS werkte bij de geriatrie in Tergooi. Meer dan de helft van ons is nog steeds werkzaam binnen de geriatrie, dat is een goede score! Ik weet nog dat ik tijdens een gezellig etentje bij Inez vertelde dat ik was benaderd voor een promotietraject en dat we samen alle voors en tegens op een rij hebben gezet. In de jaren daarna was het altijd fijn om de voortgang (of gebrek daaraan) van mijn promotietraject met jullie te bespreken en jullie waren altijd geïnteresseerd. Inmiddels is Esther zelf al gepromoveerd en is Anouschka ook druk bezig, dus onze kruisbestuiving blijft bestaan. Ik ben blij dat we nog steeds goed contact hebben en ik hoop dat dat in de toekomst zo blijft!

Anouschka Pronk. Lieve Anouschka, ook jou wil ik graag persoonlijk bedanken. Ik ben blij dat jij mijn paranimf wil zijn en mij tijdens dit laatste stukje naar mijn promotie wil ondersteunen. Sinds onze gezamenlijke baan in Tergooi zijn we bevriend en hebben we al heel wat samen meegemaakt. We gingen regelmatig samen stappen in Utrecht en zijn ook samen op vakantie geweest. Inmiddels doen we het allebei wat rustiger aan, maar spreken nog steeds regelmatig af voor een wijntje en/of spelletje. Binnenkort is het jouw beurt om te promoveren en ik help je graag om ook jouw promotietraject tot een mooi einde te brengen!

Vriendinnengroep 'Oudenrijn is fijn'. Lieve Tessa, Eva, Ellen, Dieuwke, Larissa, Wanda en Marloes, het is alweer ruim 12 jaar geleden dat wij onze eerste meters als jonge (bewust onbekwame) artsen 'beschouwende specialismen' samen hebben afgelegd. Sindsdien is er heel wat veranderd, ons ziekenhuis Oudenrijn bestaat niet meer, er zijn heel wat carrière moves geweest en de meesten van ons hebben Utrecht inmiddels verlaten. Desalniettemin proberen we ondanks ieders drukke agenda's af en toe een moment te vinden om bij te kletsen. De laatste jaren is dit veelal een dagje in de sauna, waarbij we vooral uren in het restaurant doorbrengen (in de sauna mag je immers niet praten…). Ik geniet hier altijd erg van en hoop dat we dat de komende jaren vooral blijven doen. Bedankt voor jullie support en betrokkenheid tijdens mijn opleiding tot klinisch geriater en ook tijdens dit promotietraject!

Miriam Alebregtse. Lieve Miriam, wij kennen elkaar sinds ons eerste jaar als geneeskundestudent in 2004 en zijn inmiddels al ruim 15 jaar goede vriendinnen. In al die jaren hebben we heel wat lief en leed gedeeld en ook elkaars carrière op de voet gevolgd. Het was al vrij snel duidelijk dat jij huisarts wilde worden en ik in het ziekenhuis wilde werken. Ondanks jouw verhuizing naar Rotterdam bleven we goed bevriend. We zagen elkaar weliswaar minder vaak, maar onze band is in de loop der jaren alleen maar sterker geworden. Het was altijd fijn om mijn hart bij jou te luchten, zowel als het privé even wat minder goed ging als tijdens stressvolle perioden van werk en onderzoek. Bedankt voor al jouw advies en de nodige afleiding die ik mocht ontvangen de afgelopen jaren. Nu ik weer meer vrije tijd heb weet ik zeker dat wij elkaar weer vaker gaan zien. Dus, maak maar vast ruimte in huis voor al onze toekomstige klus- en knutselprojecten!

007-vrienden. Beste aardwetenschappers, mijn bonus-vriendengroep, zolang ik jullie ken ben ik al bezig met dit promotietraject en kreeg ik bij elk vriendenweekend, etentje of fietsvakantie wel de vraag: hoe is het met je proefschrift? Een kort antwoord was hierop meestal niet mogelijk, maar jullie waren altijd geïnteresseerd en meedenkend. Niet in de laatste plaats omdat velen van jullie deze reis zelf ook hebben afgelegd. Vaak op een mooie plek in het buitenland. Ik wil jullie danken voor alle gezelligheid, sportiviteit en afleiding die ik de afgelopen jaren zo goed kon gebruiken. En ik hoop dat er nog vele 007-weekenden, fietsvakanties en kerstwandelingen zullen volgen! Aan mijn vrije tijd zal het niet liggen!

Collega's van de vakgroep geriatrie van het Spaarne Gasthuis. Beste Kees, Bob, Gerrit Jan, Lieke, Hester, Hilje, Drieske, Irene, Jorien en Ralph. Mede dankzij dit promotietraject mocht ik onderdeel worden van de vakgroep, om in de toekomst een bijdrage te kunnen leveren aan het onderzoek binnen de geriatrie van het Spaarne Gasthuis. Ik wil jullie bedanken voor de fijne en gezellige sfeer, op de werkvloer en daarbuiten, en voor jullie steun en geduld bij het afronden van dit proefschrift. Ik ga elke dag met plezier naar mijn werk en zonder de achtergrondstress van een proefschrift dat nog afgemaakt moet worden, kan dat alleen maar beter worden!

Als laatste mijn ouders. Lieve pa en ma, vanaf mijn eerste dag als geneeskundestudent hebben jullie mij gesteund en aan iedereen die het wilde horen verteld dat ik arts (of dokter) zou worden. Nu, bijna 20 jaar later, ben ik niet alleen dokter, maar mag ik mezelf ook doctor noemen en daar ben ik zelf ook best trots op. Ondanks dat jullie inhoudelijk niet altijd alles mee krijgen van wat mijn werk en onderzoek precies omvat, waren jullie altijd geïnteresseerd en begripvol en was de hele familie op de hoogte van mijn ontwikkelingen. Dank daarvoor! Ik hoop dat oma na vandaag ook weet dat ik nu echt met alles klaar ben en ik geen antwoord meer hoef te geven op de vraag: "Hoe is het met je studie?"

"Declare the past,
diagnose the present,
foretell the future."

- Hippocrates

ABOUT THE AUTHOR

Lianne Huibers was born on October 24th 1985 in Veenendaal, the Netherlands. She atteded high school at the Christelijk Lyceum Veenendaal, from which she graduated in 2004. That same year she moved to Utrecht where she started medical school at Utrecht University.

In 2010 she finished her training and obatined her medical degree. First, she worked as a resident internal medicine at the Antonius Hospital, Nieuwegein and Utrecht.

She decided to explore the field of geriatric medicine and started working as a geriatric resident in Tergooi Ziekenhuizen in 2012. This is where her ambition to become a geriatrician was born. She started her training in geriatric medicine in September 2013 at the UMC Utrecht, where she also started an extra specialisation in clinical pharmacology. In 2014 she returned to the Antonius Hospital to complete her preliminary training in internal medicine.

At that point she was approached by one of her former supervisors from the UMC to apply for a PhD project in the field of pharmacotherapy and she interrupted her residency in June 2016 for nearly 3 years to participate in the OPERAM project. During this research period she operated and cooperated internationally to develop the intervention of the trial and she conducted all the medication reviews in the Dutch intervention group, as part of the pharmacotherapy team. As part of her PhD project she conducted interviews with hospital residents and developed skills in qualitative research as well.

After completion of the inclusion and follow-up within the OPERAM trial, Lianne resumed her geriatric residency in 2019. She returned to the UMC Utrecht and completed 9 months of psychiatry training at Altrecht in Zeist. She finished her training and became a geriatrician in May 2021. In the meanwhile she continued her PhD in her spare time. On June 15th 2023, exactly 8 years after she began her journey as a PhD student, she will defend her thesis.

Lianne started her career as a geriatrician at Gelre Ziekenhuizen Apeldoorn in July 2021. In August 2022 she started working in her current position at the Spaarne Gasthuis Haarlem where she will combine patient care as a geriatrician with clinical pharmacology and research acitivities.