Medication optimisation in hospitalised older people with polypharmacy and multimorbidity

Bastiaan Sallevelt

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Medication optimisation in hospitalised older people with polypharmacy and multimorbidity

Medicatie-optimalisatie bij klinisch opgenomen ouderen met polyfarmacie en multimorbiditeit
(met een samenvatting in het Nederlands)

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‘Diep peinsde hij, als in een diep water liet hij zich tot op de bodem van dit gevoel zakken, tot waar de oorzaken liggen, want weten wat de oorzaak is, zo kwam het hem voor, is denken, en daardoor alleen worden gevoelens tot kennis en gaan niet verloren, maar ze worden wezenlijk en beginnen uit te stralen wat ze in zich hebben.’

~ Uit: Siddhartha, een Indiase vertelling door Hermann Hesse (1922)

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Chapter 1

General introduction

Risk of drug-related harm in older people

Reducing drug-related harm is a continuous challenge for health care professionals who aim to maintain a positive benefit-risk balance of pharmacotherapy to treat patients [1–3]. Older age, multimorbidity and polypharmacy are important risk factors for negative health outcomes related to medication use, such as adverse drug events and drug-related hospital admissions (Figure 1) [1,4,5]. This thesis focuses on the applicability of tools for medication optimisation, the effectiveness of a medication review on clinical outcomes, and the evaluation of the medication review process in hospitalised older people with polypharmacy and multimorbidity.

Pharmacotherapy aims to optimise patients' health outcomes and quality of life and to minimise drug-related harm [6,7]. Risks are inherent to medication use and can be accepted as long as the benefit-risk balance is positive [8–10], requiring considering, monitoring and evaluating the risk-benefit balance of pharmacotherapy for and together with the individual patient.

In contrast, medication errors may cause potentially preventable patient harm and should be minimised. The report '*To Err Is Human: Building a Safer Health System*' by the American Institute of Medicine in 1999 refuelled the awareness that preventable medication errors are a serious problem in health care requiring efforts to improve patient safety [11]. Subsequent research has drawn attention to the population of older patients with multimorbidity and polypharmacy, who are particularly vulnerable to potentially preventable drug-related harm.

8.6 million
unplanned hospital admissions are caused by adverse drug events in Europe each year

50%
of drug-related hospital admissions in older people are potentially preventable

75%
of preventable drug-related hospital admission are from patients ≥ 65 years of age and on ≥ 5 drugs

Figure 1. Drug-related harm in Europe [1,4,5].

In 2008, two important Dutch observational studies on drug-related harm were published. A retrospective study (IPCI) found that 5% of all acute hospital admissions in adults (*n* = 2,238) were drug-related, which increased to almost 10% in the older population over 75 years of age [12]. In older patients, 40% of these hospitalisations were judged as potentially preventable compared to 16% in adults under 55 [12]. Similarly, the prospective Hospital Admissions Related to Medication (HARM) study concluded that 5.6% of the included 13,000 unplanned hospital admissions in adults were drug-related, of which about half were considered potentially preventable [4]. Older age, multimorbidity, polypharmacy, impaired cognition, dependent living situation, impaired renal function and non-adherence to medication regimens were identified as independent risk factors for drug-related hospital admissions [4].

These independent risk factors continue to cluster in the growing ageing population, explaining why older patients are particularly vulnerable to drug-related harm. In Europe, 20% of the total population is currently over 65 years of age, increasing to an estimated 30% by 2050 [13]. Life expectancy has risen by more than two years per decade since the 1960s. Improvements in the effectiveness of (pharmaco) therapy and healthcare coverage are key factors in these gained life-years [13–15]. However, with ageing, the susceptibility to developing chronic diseases and multimorbidity – the co-existence of multiple chronic diseases in an individual – increases [16–18]. Multimorbidity impacts the quality of life and frequently results in polypharmacy [19,20], usually defined as the concomitant use of five or more regularly prescribed medications [21,22]. In line with ageing population's demographic shift, polypharmacy's prevalence has increased over the past decades (Figure 2) [23].

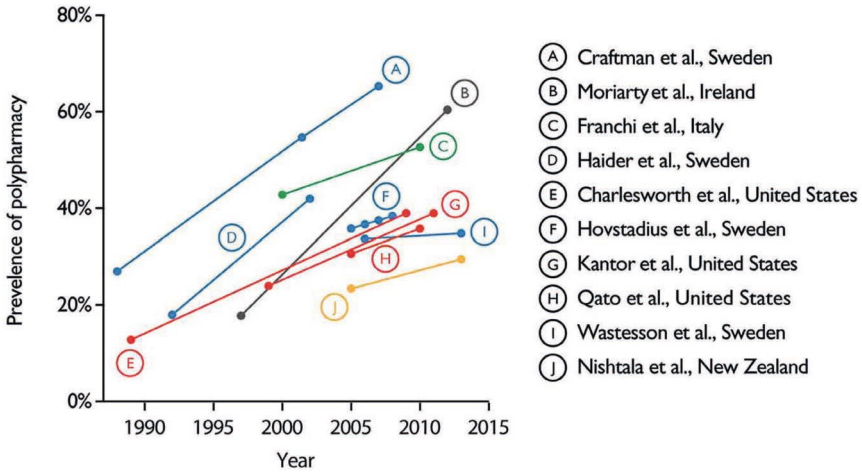

Figure 2. Trends in polypharmacy prevalence in older adults in the United States, Europe and New Zealand. Adopted from Wastesson et al. [23]

Although the combination of ageing, multimorbidity and polypharmacy are well-known important risk factors for drug-related harm, many other factors contribute to an increased vulnerability in this population. Frailty, age-related pharmacokinetic and pharmacodynamic changes, drug-disease interactions, drug-drug interactions, inadequate medication use and health care transitions (e.g. hospital admissions) are examples of such attributable risk factors (Figure 3) [24–26]. Therefore, reducing risk factors associated with drug-related harm requires a multidimensional approach on the levels of healthcare providers, patients, healthcare work environments and primary-secondary care interfaces, as addressed by the World Health Organization (WHO) [2,3,27]. Thus, complex interventions targeting multiple levels in healthcare are needed to enable the best possible outcomes and reduce healthcare expenditures in the growing older population with multimorbidity and polypharmacy.

In 2009, the Dutch Ministry of Health, Welfare and Sport initiated a multidisciplinary task force to develop specific recommendations for the reduction of potentially preventable drug-related hospital admissions, which resulted in the HARM-Wrestling report [28,29]. However, the absolute number of drug-related admissions increased from an estimated 39,000 in 2008 to 49,000 in 2013. Similar to the results in 2008, 10% of hospital admissions in older patients were drug-related, half of which were considered potentially preventable. These findings confirmed that implementing of medication optimisation strategies and the evaluation thereof in clinical practice requires continuous effort [30].

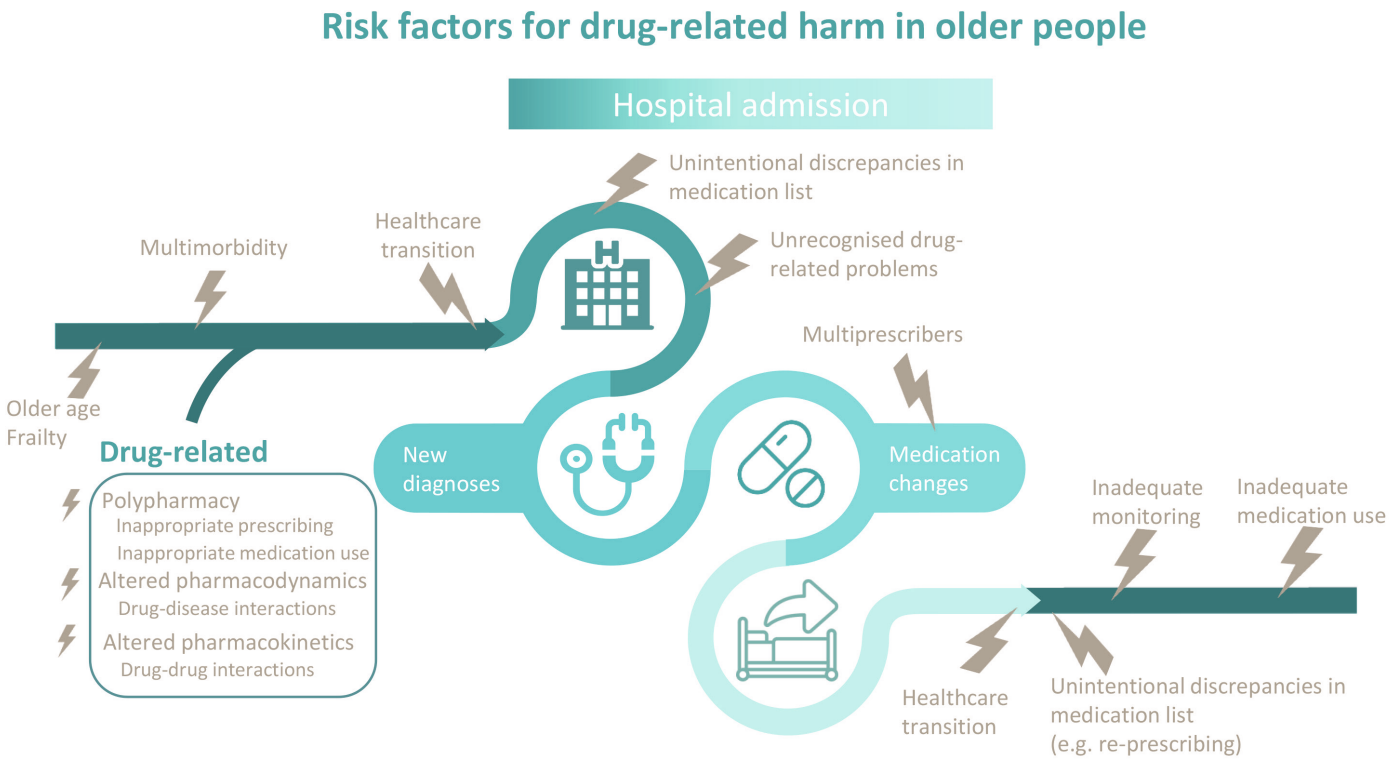

Figure 3. Examples of risk factors for drug-related harm in older people with polypharmacy and multimorbidity admitted to the hospital.

Prescribing in older people

Appropriate prescribing

Although polypharmacy is an independent and important risk factor for drug-related hospital admissions, the assumption that polypharmacy in itself is harmful to individual patients would be too simplistic. Indicated polypharmacy in multimorbid patients can also positively affect health outcomes, and withholding pharmacotherapy can have negative health consequences [31–33]. Under-prescribing (i.e. the lack of an indicated drug without a valid reason for not prescribing it) is remarkably common in older people, especially in patients with polypharmacy [33–35]. For example, cardiovascular drug underuse in older patients has been associated with hospital admissions due to heart failure exacerbation [32,36]. Therefore, increasing 'medication appropriateness' is critical, not just reducing the number of drugs.

Medication appropriateness is generally defined as the quality of prescribing pharmacotherapy related to the individual patient and refers to a continuous process of pharmacotherapeutic decision-making that maximises individual health gains [37,38]. The WHO six-step model is a validated method to promote appropriate prescribing (Figure 4) [39–41]. However, challenges in all steps of the prescribing process may be encountered in older patients with multimorbidity and polypharmacy compared to younger patients. For instance, the patient's problem may be less obvious in multimorbid patients, and the misinterpretation of adverse drug reactions can lead to prescribing cascades (i.e. prescription of a subsequent drug to treat a drug-induced adverse event) [42]. In addition, patient-specific therapeutic objectives may be different (e.g. life prolongation vs quality of life).

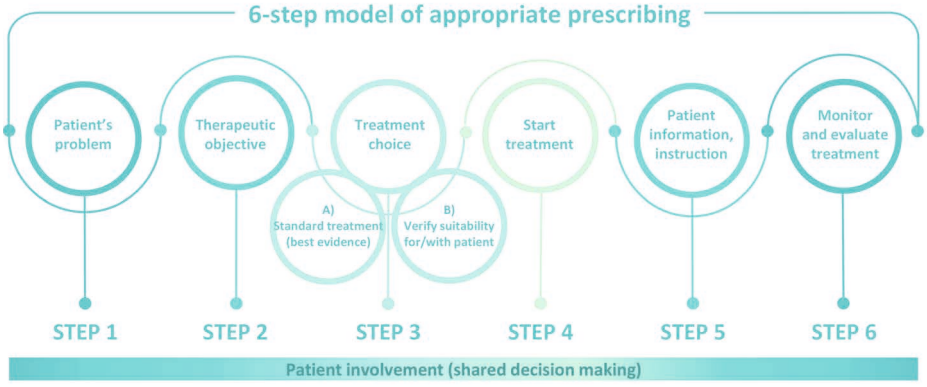

Figure 4. WHO 6-step model of appropriate prescribing [39–41].

Moreover, the risk-benefit balance in older multimorbid patients is often uncertain, which can complicate treatment choices [43,44]. Evidence-based guidelines for older patients with multimorbidity and polypharmacy are often lacking since they are largely underrepresented in clinical trials [45–48]. Although regulatory agencies are developing strategies to cover existing knowledge gaps in pharmaceutical patient care and drug product design for older people, the most currently available clinical practice guidelines are still single-disease oriented [45,49]. As a result, guideline recommendations are usually drawn from results in younger adults without multimorbidity or polypharmacy. In addition, difficulties may arise in communicating with older patients (e.g. due to cognitive impairment or hearing problems), impeding clear patient information, instruction for medication use and shared decision-making throughout the prescribing process. Lastly, frequent changes in medical conditions and co-medication make appropriate prescribing subject to highly dynamic factors in older patients over time, requiring close monitoring of pharmacotherapy. Monitoring is further compromised by involving multiple prescribers in patients with polypharmacy, which requires intensive collaboration between healthcare professionals to ensure adequate follow-up.

Explicit tools for appropriate prescribing in older patients

Due to the knowledge gap in single-disease-oriented clinical practice guidelines about optimal pharmacotherapy in older patients, several explicit tools have been developed to facilitate appropriate prescribing in this population [50]. Most explicit screening tools provide lists of drugs – often concerning concomitant diseases or medical conditions – frequently involved in drug-related harm in older people [51–53]. Although explicit screening tools are based on the best available evidence for the benefit-risk balance in older people, they do not consider individual patients' needs and preferences and require clinical consideration. Therefore, these drugs are often referred to as 'potentially' inappropriate in older people.

The Beers Criteria were the first list of explicit criteria developed to detect potential inappropriate prescribing in older people [54]. However, the Beers Criteria have several limitations that impede their use outside the United States [55]. For this reason, the **S**creening **T**ool of **O**lder **P**erson's **P**rescriptions (STOPP) and the **S**creening **T**ool to **A**lert to **R**ight **T**reatment (START) criteria were developed in Ireland (2008). This version was updated in 2015 by a European expert team resulting in STOPP/START version 2 comprising 114 explicit criteria [56,57]. In contrast to other explicit screening tools, STOPP/START also includes potential drug omissions to detect under-prescribing. Hence, the STOPP/START criteria are the most widely used and extensively studied explicit screening tool for older patients in Europe [58]. Applying the STOPP/START criteria has been shown to reduce potentially inappropriate prescribing and adverse drug reactions while lowering healthcare costs in older

patients in previous trials. However, their effects on other clinical outcomes, such as drug-related hospitalisations, remain to be established [56,59–62]. European geriatric clinical practice guidelines – including the Dutch geriatric guideline on polypharmacy – endorse considering using STOPP/START to facilitate medication reviews in older people [63,64].

Medication review in older people

A medication review can be defined as 'a structured, critical examination of a person's medicines with the objective of reaching an agreement with the person about treatment, optimising the impact of medicines, minimising the number of medicationrelated problems and reducing waste' [63]. A medication review aims to optimise a patient's existing pharmacotherapy to prevent worsening medical conditions or complications (related to pharmacotherapy) while individualising pharmacotherapy to a patient's needs to promote medication self-management. This purpose differs from regular medication safety monitoring, usually performed when preparing and dispensing (new) medication to ensure safe and effective pharmaceutical products related to co-medication or patient characteristics while limiting the likelihood of harm from the products' use [65].

The STRIP method for medication review

The Systematic Tool to Reduce Inappropriate Prescribing (STRIP) is a medication review method that combines implicit (judgement-based) questions with explicit screening tools (e.g. STOPP/START criteria) to increase appropriate prescribing in older people [64–67]. The STRIP method consists of five steps:

1. Medication reconciliation:
   Obtaining information about the patient's medication history and actual medication use while understanding wishes, experiences and beliefs about medications;

2. Pharmacotherapy analysis:
   Identifying potential drug-related problems (e.g. underuse, overuse, misuse, potential adverse drug reactions, drug-drug interactions, drug-disease interactions, practical intake issues);

3. Pharmaceutical care plan:
   Agreeing about therapeutic aims between the physician and pharmacist and how these aims could be achieved;

4. Shared decision-making:
   Collaborating between patients and healthcare professionals to jointly decide therapeutic aims and pharmacotherapy;

5. Follow-up and monitoring:
   Determining patient outcomes based on the desired goals of pharmacotherapy.

The steps of a medication review according to the STRIP method and tools to facilitate this process appear in Figure 5.

Medication reconciliation is the first step in the medication review process and aims to obtain and maintain a complete and accurate list of a patient's current medication use – both prescription and non-prescription drugs – particularly at care transitions [68]. The Structured History-taking of Medication (SHiM) tool was developed to reduce the number of unintentional medication discrepancies [69]. This implicit screening tool revealed unintentional discrepancies in medication lists of 92% of patients admitted to the geriatric ward, of which one-fifth had clinical consequences [69].

Unintentional discrepancies in medication lists at hospital discharge to the less controlled primary care environment pose an even higher risk for patient harm [70,71]. Van der Linden et al. found that more than a quarter (27%) of discontinued drugs during hospitalisation because of an adverse drug reaction were re-prescribed after discharge from geriatric wards [72]. Medication reconciliation effectively decreases admission and discharge order discrepancies, possibly reducing preventable medication harm [73,74]. Hence, the integration of medication reconciliation by pharmacy technicians at transitions of care has been implemented as a standard of care for several years in Dutch hospitals [75,76].

However, performing a complete medication review using the STRIP method is time-consuming. Therefore, computerised interventions have been suggested to increase the efficacy and quality of the medication review process in older people [55]. Explicit screening tools, such as STOPP/START, have the potential to be implemented as algorithms in clinical decision support systems (CDSS), thereby facilitating the pharmacotherapy analysis (step 2) of the medication review process [77].

The STRIP Assistant (STRIPA) is a Dutch software-based CDSS first developed in 2015 to assist healthcare professionals in performing a pharmacotherapy analysis during a medication review. This prototype of STRIPA included STOPP/START criteria version 1, intended for use in primary care [78]. Its performance was tested in a validation study among general practitioners and pharmacists. STRIPA increased correct decisions from 58% to 76% ($p < 0.01$) and reduced incorrect decisions

from 42% to 24% (P<0.01) compared to a pharmacotherapy analysis without clinical decision support [79]. However, unlike the aimed improvement in efficacy, participants spent more time using STRIPA attributed to the prototypical design of the software's user interface, and the users' unfamiliarity with the application. Further development of STRIPA aimed to improve usability, incorporate the updated STOPP/START criteria version 2 and make the tool suitable for application in a hospital setting [80].

Effectiveness of medication review on clinical outcomes

Although the aforementioned explicit screening tools have been shown to improve medication appropriateness in older people, the effect of medication reviews as a multicomponent intervention on clinical outcomes remains uncertain [81,82]. The low quality of currently available studies (e.g. short follow-up, small sample sizes, high risk of bias) impedes drawing firm conclusions [81,82]. In addition, heterogeneity in study designs, settings and outcomes also hamper comparing studies investigating the effectiveness of medication review [83,84].

Knowledge gap and thesis rationale

Although geriatric-specific clinical practice guidelines have been developed to guide safe and effective pharmacotherapy, drug-related adverse outcomes in older patients remain a major problem. Thus, healthcare professionals and older patients still need evidence-based strategies to reduce potentially preventable drug-related harm. The question arises whether the existing tools for medication optimisation recommended by clinical practice guidelines are suitable for implementation in clinical practice or how their applicability can be improved.

Hence, the uncertainty of the effectiveness of medication reviews in older people with polypharmacy and multimorbidity on clinical outcomes was the rationale to design a large, randomised controlled trial explicitly addressing the limitations of previous trials. The aim of the OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people (OPERAM) trial assessed the effectiveness of an in-hospital structured medication review compared to usual care on drug-related hospital admissions and other clinical outcomes, using a core outcome set previously developed by European healthcare professionals and patients [85,86]. A detailed evaluation of the different steps of this in-hospital medication review could provide relevant insights to optimise this complex process.

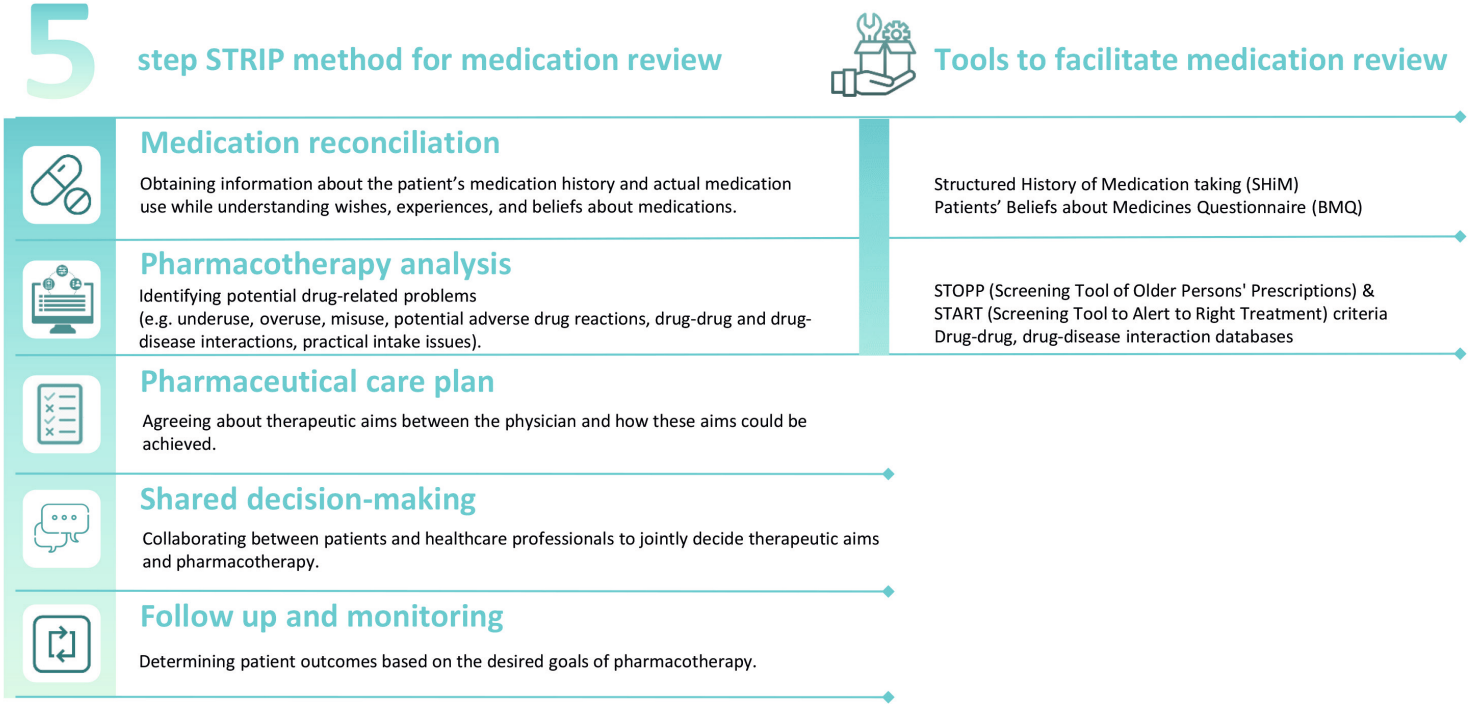

Figure 5. The five-step Systematic Tool to Reduce Inappropriate Prescribing (STRIP) method and tools to facilitate the medication review process.

Objectives of this thesis

The general aim of this thesis is to investigate strategies for medication optimisation in hospitalised older people with polypharmacy and multimorbidity. This aim was divided into the following objectives:

1. To evaluate the applicability of medication optimisation tools recommended by clinical practice guidelines;

2. To develop a process for in-hospital medication review using implicit and explicit medication optimisation tools;

3. To investigate the effect of an in-hospital medication review in older people with multimorbidity and polypharmacy on clinical outcomes;

4. To evaluate the process of the in-hospital medication review to formulate recommendations for future refinement of the medication review process.

Thesis outline

Chapter 2 describes the applicability of medication optimisation tools recommended by clinical practice guidelines. In Chapter 2.1, the performance of a trigger tool for detecting adverse drug reactions is evaluated. This ADR trigger tool has been recommended for use in all acutely admitted older patients with polypharmacy by the Dutch geriatric guideline on 'polypharmacy optimisation in hospitalised older people'. In Chapter 2.2, the clarity of STOPP/START version 2 as a clinical practice guideline for applicability in daily patient care is evaluated. The conversion of STOPP/START criteria version 2 into software algorithms to enable their incorporation into a CDSS is described in Chapter 2.3.

Chapter 3 focuses on the process development of a CDSS-assisted in-hospital medication review (Chapter 3.1) and its effect on clinical outcomes in hospitalised older people with multimorbidity and polypharmacy (Chapter 3.2). This research is part of the OPERAM trial, a European cluster-randomised controlled multicentre trial investigating the effect of a STOPP/START-based in-hospital medication review on drug-related readmissions in older (≥ 70 years) patients with multimorbidity (≥3 chronic conditions) and polypharmacy (≥5 regular medication use). Secondary outcomes are based on the aforementioned core outcome set [85]. The in-hospital medication review is performed according to the STRIP method supported by STRIPA software with incorporated STOPP/START version 2.

Chapter 4 evaluates the process of in-hospital medication reviews performed in the OPERAM trial on three levels. In Chapter 4.1, the clinical applicability of CDSS-generated STOPP/START signals in a hospital setting is evaluated. Second, the patients' and physicians' agreement with STOPP/START-based individualised medication optimisation recommendations are assessed in Chapter 4.2. In Chapter 4.3, the detectability of medication errors with the in-hospital medication review in the year prior to a potentially preventable drug-related hospital admission is assessed.

The thesis outline is graphically summarised in Figure 6.

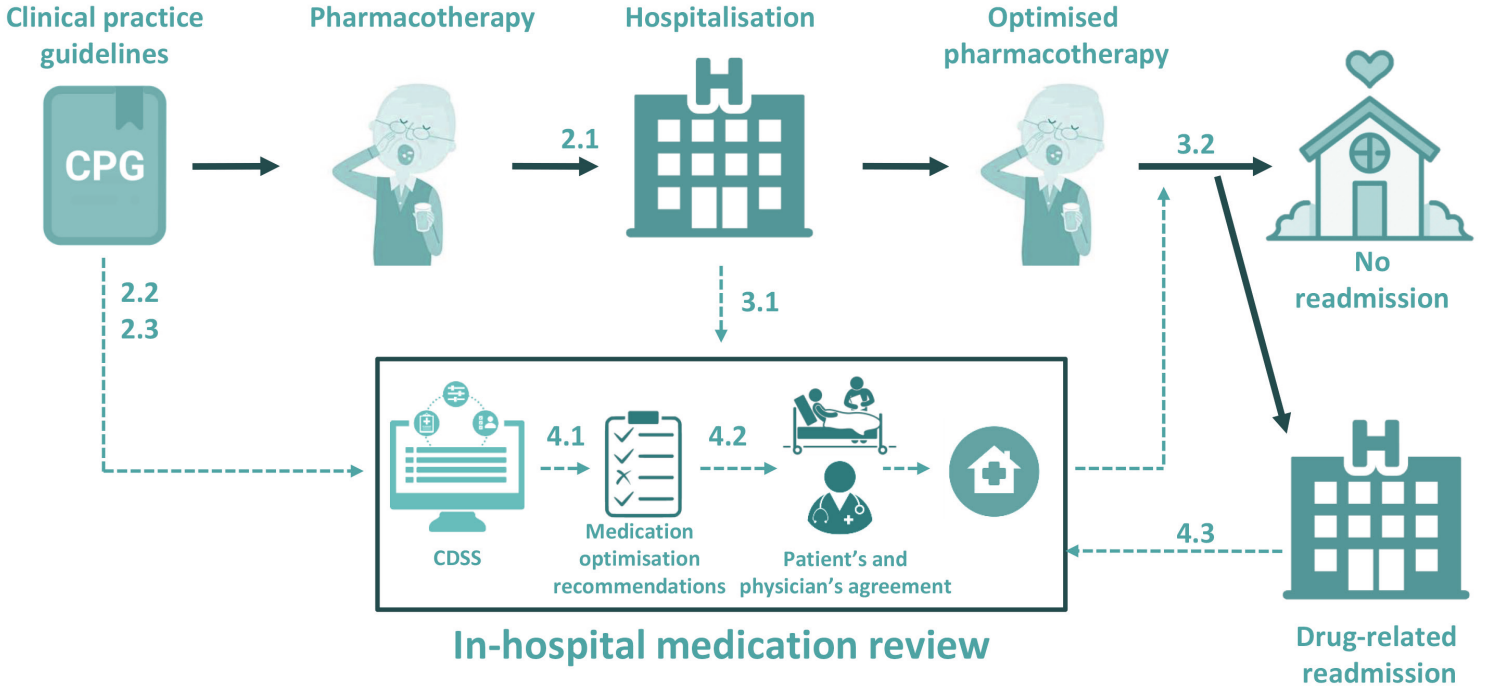

Figure 6. Graphical summary of the outline of this thesis.
CPG = clinical practice guidelines; *CDSS* = clinical decision support system.

Declarations

Authors' contributions

Bastiaan Sallevelt wrote the general introduction of this thesis. His supervisors Wilma Knol, Ingeborg Wilting, Eugène van Puijenbroek and Toine Egberts reviewed the manuscript critically for important intellectual content and approved the final version.

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Competing interests

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

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Chapter 2

Applicability of tools for medication optimisation in hospitalised older people

2.1

Chapter 2.1

Performance of a trigger tool for detecting adverse drug reactions in patients with polypharmacy acutely admitted to the geriatric ward

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Abstract

Introduction

Adverse drug reactions (ADRs) account for 10% of acute hospital admissions in older people, often under-recognised by physicians. The Dutch geriatric guideline recommends screening all acutely admitted older patients with polypharmacy with an ADR trigger tool comprising ten triggers and associated drugs frequently causing ADRs. This study investigated the performance of this tool and the recognition by usual care of ADRs detected with the tool.

Methods

A cross-sectional study was performed in patients ≥70 years with polypharmacy acutely admitted to the geriatric ward of the University Medical Centre Utrecht. Electronic health records (EHRs) were screened for trigger-drug combinations listed in the ADR trigger tool. Two independent appraisers assessed causal probability with the WHO-UMC algorithm and screened EHRs for recognition of ADRs by attending physicians. Performance of the tool was defined as the positive predictive value (PPV) for ADRs with a possible, probable or certain causal relation.

Results

In total, 941 trigger-drug combinations were present in 73% (n = 253/345) of the patients. The triggers fall, delirium, renal insufficiency and hyponatraemia covered 86% (n = 810/941) of all trigger-drug combinations. The overall PPV was 41.8% (n = 393/941), but the PPV for individual triggers was highly variable ranging from 0–100%. Usual care recognised the majority of ADRs (83.5%), increasing to 97.1% when restricted to possible and certain ADRs.

Conclusion

The ADR trigger tool has predictive value; however, its implementation is unlikely to improve the detection of unrecognised ADRs in older patients acutely admitted to our geriatric ward. Future research is needed to investigate the tool's clinical value when applied to older patients acutely admitted to non-geriatric wards.

Introduction

Older people are more susceptible to adverse drug reactions (ADRs) due to comorbidity, polypharmacy, frailty and age-related changes in pharmacokinetics and -dynamics [1–3]. It is estimated that ADRs account for approximately 10% of all acute hospital admissions in older people [4,5]. Despite this high frequency of hospital admissions due to ADRs in older people, studies show that drug related problems, including ADRs, are missed or misdiagnosed by physicians at the emergency department in approximately 40–60% of the cases [6–8]. Consequently, methods to improve detection and management of ADRs are needed [9].

Polypharmacy is one of the most important risk factors for developing ADRs [10]. It is known that a few commonly used drug classes account for the majority of ADRs leading to or developed during hospital admission in the older population [1,3–5,9]. A meta-analysis found that ADR-induced hospital admissions were most frequently related to nonsteroidal anti-inflammatory drugs (NSAIDs) causing upper gastrointestinal bleeding, hypertension, coronary events and renal failure. Other ADRs frequently associated with hospitalisations were hypotension due to beta-blockers, angiotensin-converting enzyme (ACE) inhibitors or calcium antagonists; hypoglycaemia due to oral antidiabetics; bleeding due to oral anticoagulants and bradycardia due to digoxin [4]. The use of a trigger tool focusing on clinical events and drugs frequently associated with such events may therefore reduce the problem of undiagnosed ADRs.

Several trigger tools have been developed to increase ADR detection in patient care. The most commonly known trigger tool is the Global Trigger Tool [11,12], but other trigger tools targeting ADR detection, especially in the older population, have been investigated [13–15]. These trigger tools have in common that they comprise lists of either clinical events (e.g. 'hypotension'), the use of specific drugs or antidotes (e.g. 'naloxone use') or abnormal drug or laboratory values (e.g. 'potassium <2.9 mEq/L', 'digoxin level >2 ng/L'). However, the positive predictive values (PPVs) of such triggers were generally low, which impedes their implementation in clinical practice to improve ADR detection in older people [12–15]. Consequently, no 'gold standard' to improve ADR detection in older people has yet been established.

The performance of trigger tools in detecting clinically relevant ADRs in older people may be improved by combining clinical events with drug classes frequently associated with such events. The Dutch national geriatric guideline on *'polypharmacy optimisation in hospitalised older people'* provides a consensus-based trigger tool listing combinations of certain clinical events and associated drugs that frequently result in ADR-related hospital admissions in older people [16]. The guideline strongly recommends screening each patient aged 70 years and older with polypharmacy (≥5

drugs) admitted to the emergency department for potential ADRs by using this ADR trigger tool. However, the recommendation has not been substantiated by evidence supporting the use of such a trigger tool in clinical practice. Hence, evaluation of the performance of the ADR trigger tool in the above-mentioned guideline is warranted.

This study aimed to investigate the performance of the ADR trigger tool recommended by the Dutch geriatric guideline and the recognition by usual care of ADRs detected with the tool in patients with polypharmacy acutely admitted to our geriatric ward.

Methods

Setting and study population

The study population consisted of patients aged 70 years and older with polypharmacy acutely admitted to the geriatric ward at a 1,000 bed tertiary university hospital in the Netherlands (University Medical Centre Utrecht). Admissions of patients to the geriatric ward through the emergency department (ED) in the period between 01-01-2011 and 01-08-2017 were extracted with SAS enterprise guide v7.1 from a pseudonymised hospital database. Based on the consecutive order of randomly assigned numbers for each patient, admission letters were manually screened to include approximately 350 patients aged ≥70 years with polypharmacy. Polypharmacy was defined as the chronic use of at least five prescription drugs excluding dermatological preparations at admission [16]. For patients with multiple hospital admissions during the study period, the first admission that met the inclusion criteria was selected. A patient's first admission was selected to minimise interference of consecutive hospital admissions with the study outcomes. Patients with an incomplete record (i.e. no admission or discharge letter available) were excluded.

Study procedures

Electronic health records (EHRs) from the ED on the day of admission were screened for trigger-drug combinations listed in the ADR trigger tool of the Dutch national geriatric guideline '*polypharmacy optimisation in hospitalised older people*' (first publication 2017, last revision 2020) [16]. This consensus-based trigger tool was developed in accordance with literature listing ten clinical events (i.e. triggers) and their associated drug classes frequently resulting in ADR-related admissions in older people [16–18]. Next, a causality assessment was performed for all detected trigger-drug combinations. The admission and discharge letters were also screened for ADR recognition by the attending physicians.

Screening for trigger-drug combinations

For this study, the original ADR trigger tool from the Dutch guideline was explicated to reduce undesirable variations in interpretation when applied to EHRs. Modifications to the original ADR trigger tool were implemented at three levels prior to screening for trigger-drug combinations:

1. Triggers were specified if they represented clinical events which could be linked to different drug classes (e.g. specification of 'disturbed serum glucose levels' into 'hypoglycaemia' and 'hyperglycaemia').

2. Drug classes were further specified following the ATC classification system (e.g. specification of 'diuretics' into 'thiazide diuretics', 'loop diuretics' and 'potassium sparing diuretics').

3. Triggers were merged for clinical events that are difficult to distinguish and are used interchangeably in clinical practice. For instance, 'fall' was merged with the triggers 'collapse / (orthostatic) hypotension / dizziness / syncope'. Especially in older patients, it is difficult to distinguish falls and syncope, because falls can be preceded by temporarily loss of consciousness due to cerebral hypoperfusion [19].

Modifications to the original ADR trigger tool were performed by two researchers with clinical experience in medical practice (WL, NN) and reviewed by a senior geriatrician/clinical pharmacologist (WK) with the intention to follow the original ADR trigger tool as closely as possible. Table 1 illustrates the original ADR trigger tool as published in the Dutch national geriatric guideline and the explicated ADR trigger tool used for this research.

Two researchers (WL, NN) screened EHRs for the presence of trigger-drug combination. The trigger had to be either documented as a symptom, or listed by the physician as a diagnosis or health problem. Trigger-drug combinations were regarded as discrete events if the prescribed drugs were related to different drug classes according to the explicated trigger tool. However, if multiple drugs from the same drug class were linked to the same trigger, this was counted as one trigger-drug combination. For example, oxycodone and morphine linked to constipation were considered as one trigger-drug combination (constipation-opioids), while hydrochlorothiazide (thiazide diuretics) and furosemide (loop diuretics) linked to hyponatraemia were considered as two separate trigger-drug combinations.

Table 1. The original ADR trigger tool as published in the Dutch national geriatric guideline *'polypharmacy optimisation in hospitalised older people'* and the explicated ADR trigger tool used for this research.

Original ADR trigger tool		Explicated ADR trigger tool	
Trigger	Associated drug	Trigger	Associated drug
1.Fracture / fall[a]	A. Steroids B. Psychotropic agents[a] C. Antihypertensive agents[a]	1. Fracture	A. Systemic corticosteroids
2. Collapse / hypotension / dizziness	A. Cardiac therapy (antihypertensive and antiarrhythmic agents) B. Psychotropic agents	2. Fall[a] / collapse / (orthostatic) hypotension / dizziness / syncope	A. Antihypertensive agents[a]: ACE-I, ARB, calcium antagonists, beta blockers, thiazide diuretics, loop diuretics, potassium sparing diuretics, alpha-1-blockers, long acting nitrates. Antiarrhythmic agents: digoxin, class I, II and III antiarrhythmics B. Psychotropic drugs[a]: benzodiazepines, antipsychotics, antidepressants (i.e. SSRI, TCA and miscellaneous: duloxetine, venlafaxine and mirtazapine)
3. Bleeding (mostly gastrointestinal) / INR above therapeutic range	A. Anticoagulants B. Thrombocyte aggregation inhibitors C. NSAIDs	3.1 Gastrointestinal bleeding3.2 Intracranial bleeding 3.3 Other bleedings	A. Vitamin K antagonists, DOACs, heparins, other anticoagulants B. Thrombocyte aggregation inhibitors C. NSAIDs
		3.4 Supratherapeutic INR	A. Vitamin K antagonists
4. Electrolyte disturbances / dehydration[b]	A. Diuretics B. ACE-I, ARB C. NSAIDs[b] D. Antidepressants	4.1 Hyponatraemia	A. Thiazide diuretics, loop diuretics, potassium sparing diuretics B. ACE-I, ARB C. Antidepressants (i.e. SSRI, TCA and miscellaneous: duloxetine, venlafaxine and mirtazapine)
		4.2. Hypokalaemia	A. Thiazide diuretics, loop diuretics
		4.3. Hyperkalaemia	A. Potassium sparing diuretics B. ACE-I, ARB

Table 1. Continued.

Original ADR trigger tool		Explicated ADR trigger tool	
Trigger	Associated drug	Trigger	Associated drug
5. Renal insufficiency	A. ACE-I, ARB B. NSAIDs	5. Renal insufficiency and/or dehydration[b]	A. ACE-I, ARB B. NSAIDs[b] C. Thiazide diuretics, loop diuretics, potassium sparing diuretics
6. Disturbed serum glucose levels	A. Blood glucose lowering agents B. Corticosteroids	6.1 Hypoglycaemia	A. Oral antidiabetics, insulin and analogues
		6.2 Hyperglycaemia	B. Systemic corticosteroids
7. Heart failure	A. NSAIDs	7. Acute heart failure	A. NSAIDs
8. Constipation / ileus	A. Opioids B. Calcium channel blockers	8. Constipation / ileus (based on constipation)	A. Opioids B. Calcium channel blockers
9. Vomiting / diarrhoea	A. Antibiotics	9. Vomiting / diarrhoea	A. Antibiotics
10. Delirium/ confusion/ drowsiness	A. Cardiac therapy B. Psychotropic agents C. Benzodiazepines D. Urinary antispasmodic agents	10. Delirium / confusion / drowsiness	Drugs with anticholinergic and sedative properties (*Supplementary Information SI1*), digoxin, anti-Parkinson drugs

[a]The trigger 'fall' and its associated drug classes 'psychotropic agents' and 'antihypertensive agents' were merged in the explicated version of the ADR trigger tool with the trigger 'collapse…'. [b]The trigger dehydration and its associated drug class 'NSAIDs' was merged in the explicated version of the ADR trigger tool with the trigger 'renal insufficiency'.
ACE-I = angiotensin converting enzyme inhibitors, *ARB* = angiotensin II receptor blockers, *SSRI* = selective serotonin reuptake inhibitor, *TCA* = tricyclic antidepressant, *DOAC* = direct oral anticoagulant, *NSAIDs* = nonsteroidal anti-inflammatory drugs.

Causality assessment

A causality assessment was performed to establish the likelihood of an ADR for all trigger-drug combinations detected with the ADR trigger tool. Data from the admission and discharge letters were taken into account, because both letters could contain relevant information for causality assessment (e.g. to establish a potential time-relationship). A geriatrician (NN) and a clinical pharmacist (BS) independently assessed all trigger-drug combinations. The WHO-UMC system was used for causality assessment, which differentiates between the categories certain, probable, possible, unlikely and unclassifiable [20,21]. Trigger-drug combinations with a causality score of certain, probable and possible were considered ADRs. Before the causality assessment, both appraisers trained with a previously published, Delphi-based chart review method developed to detect drug related admissions by Thevalin *et al* [22]. The level of agreement between the two appraisers was measured with the Cohen's kappa test statistic (poor: κ <0.00; slight: κ=0.00–0.20; fair: κ=0.21–0.40; moderate: κ=0.41–0.60; substantial: κ=0.61–0.80; almost perfect: κ=0.81–1.00) [23]. If ratings differed ≥1 WHO-UMC category for causality between the two appraisers, the appraisers discussed each case to reach consensus. The appraisers consulted a third expert (WK, senior geriatrician-clinical pharmacologist) for a final consensus round in case no consensus was reached.

ADR recognition by usual care

In addition to the causality assessment, EHRs were screened for recognition of ADRs by usual care. Recognition was defined as an explicit documented trigger-drug combination by the attending physician (i.e. a geriatric resident, supervised by a geriatrician) in the admission and/or discharge letter, implying that the trigger-drug combination was identified as an ADR. In addition, explicit documentation of the trigger combined with medication changes in associated drugs (i.e. withdrawal, discontinuation or a dose adjustment) was also considered as being recognised by usual care.

Outcomes

The performance of the ADR trigger tool was operationalised by calculating the overall PPV for detecting ADRs in general and for each trigger separately. The PPV was defined as the total number of detected trigger-drug combinations divided by the number of ADRs with a causality score of possible, probable or certain. The recognition by usual care was calculated for both ADRs with a causal relationship considered to be possible, probable or certain and for those with a probable or certain causal relationship.

Data analysis

Descriptive data analysis and Cohen's kappa test statistic was performed with IBM SPSS Statistics v.26.0.0.1.

Results

Study population

A random selection of 589 out of all 1366 patient admissions to the geriatric department through the ED between 01-01-2011 and 01-08-2017 was screened for eligibility. From this selection, 378 admissions met our inclusion criteria (i.e. age ≥70 and polypharmacy), of which 33 admissions were excluded because they were not a patient's first admission within the study period. The study population of 345 patients had a median age of 84 (IQR 79–88). The median number of drugs at admission was 10 (IQR 8–13), and 61% of the patients were female. Subsequently, admission letters of these patients were screened for the presence of trigger-drug combinations according to the ADR trigger tool. Out of 345 eligible patients, 253 (73%) had at least one trigger-drug combination present. In 52% (178/345) of the total study population, at least one ADR with a causal relationship considered possible, probable or certain was present.

Number of trigger-drug combinations

The total number of trigger-drug combinations was 941, with a median of 3 (IQR 2–5) and a maximum of 16 trigger-drug combinations per patient. Fall (32.4%), delirium (24.0%), renal insufficiency / dehydration (16.2%) and hyponatraemia (13.5%) were the most frequent clinical events and covered 86.3% of all identified trigger-drug combinations (Table 2).

Causality assessment and PPV

Of the 941 identified trigger-drug combinations, 41.8% (*n* = 393) were adjudicated as an ADR by the two appraisers in 178 patients. More than a quarter (27.0%) of all 941 trigger-drug combinations were considered as possible ADRs, 12.3% were adjudicated as probable ADRs, and 2.4% as certain ADRs. In 57.0% of the trigger-drug combinations, an ADR was considered as unlikely, and the other 1.3% of the combinations were unclassifiable (Table 2). Inter-rater agreement for causality assessment of ADRs was substantial (κ=0.61-0.80) with a Cohen's kappa of 0.76 [23]. In total, causality scores of 163/941 trigger-drug combinations differed between the adjudicators, with a difference of only one WHO-UMC category in 91.1% of the

cases (*n* = 149). The two appraisers reassessed and discussed all discrepancies and reached a consensus without consulting a third expert.

Overall, the PPV of the ADR trigger tool was 41.8%. The PPV varied considerably across triggers. The PPV related to the triggers fall (28.2%) and delirium (23.0%) were the lowest, whereas the mean number of drugs associated with these triggers was highest with a large range (fall: mean 3.1, min-max 1–8; delirium: mean 2.3, min-max 1–6). Although numbers were relatively small, the PPVs related to the triggers hypokalaemia (100%), supratherapeutic INR (100%) and vomiting/diarrhoea (88.9%) were highest (Table 2).

Drugs related to ADRs

More than half of the 941 trigger-drug combinations detected by the ADR trigger tool were associated with three drug classes: diuretics (25.4%), agents acting on the renin-angiotensin system (16.7%) and psychotropic agents (12.2%). The top three drug classes most frequently associated with the 393 ADRs were diuretics (35.4%), agents acting on the renin-angiotensin system (13.5%) and analgesics (11.2%), covering 60% of all drugs that caused an ADR.

ADR recognition by usual care

Usual care recognised 51.8% (481/929) of the trigger-drug combinations detected by the trigger tool and for which a causality classification could be determined. 42.3% (393/929) were considered ADRs with at least possible causality, of which 83.5% (328/393) were recognised by usual care according to information in the admission and discharge letters (Table 3). 16.5% (65/393) of ADRs were not recognised by usual care, of which 93.9% (*n* = 61) had a causal relationship considered to be possible. The majority of these possible ADRs not recognised by usual care were related to the top three most common events (fall, *n* = 29; delirium, *n* = 13; renal insufficiency, *n* = 10). Three probable ADRs were not recognised (furosemide – hyponatraemia; fentanyl – constipation; fentanyl – delirium) and one certain ADR was not recognised by usual care (bumetanide – renal insufficiency/dehydration). Recognition by usual care increased to 97.1% (135/139) when only ADRs considered to be probable or certain ADRs were included (Table 3).

In 75.6% of possible, probable or certain ADRs and in 85.6% of probable or certain ADRs, the suspected drug was discontinued, or the dosage was reduced by usual care. The top three most frequently discontinued drugs related to ADRs were thiazides, opioids and high-ceiling diuretics. Table 3 provides a detailed overview of the number of ADRs per trigger and their associated drug classes in relation to their recognition by usual care. ADRs were stratified for a causal relationship considered to be possible, probable or certain and for those considered to be probable or certain.

Table 2. Number of trigger-drug combinations per trigger, mean number of associated drugs and results of the causality assessment.

Trigger	Number of trigger-drug combinations, n (%)	Mean number of associated drugs per trigger (min-max)	Causality score, % (n)					PPVa, % (ADR / trigger-drug combinations)
			Unclassifiable	Unlikely	Possible	Probable	Certain	
Fall / collapse / (orthostatic) hypotension/ dizziness / syncope	305 (32.4)	3.1 (1–8)	0 (0)	71.8 (219)	23.6 (72)	4.6 (14)	0 (0)	28.2 (86/305)
Delirium / confusion / drowsiness	226 (24.0)	2.3 (1–6)	3.1 (7)	73.9 (167)	16.4 (37)	5.3 (12)	1.3 (3)	23.0 (52/226)
Renal insufficiency and/ or dehydration	152 (16.2)	1.8 (1–4)	0.7 (1)	37.5 (57)	43.4 (66)	17.8 (27)	0.7 (1)	61.8 (94/152)
Hyponatraemia	127 (13.5)	1.8 (1–4)	2.4 (3)	52.0 (66)	26.8 (34)	16.5 (21)	2.4 (3)	45.7 (58/127)
Constipation / ileus	35 (3.7)	1.3 (1–2)	2.9 (1)	28.6 (10)	31.4 (11)	20.0 (7)	17.1 (6)	68.6 (24/35)
Other bleedings	23 (2.4)	1.3 (1–2)	0 (0)	17.4 (4)	52.2 (12)	17.4 (4)	13.0 (3)	82.6 (19/23)
Hypoglycaemia	17 (1.8)	1.7 (1–2)	0 (0)	23.5 (4)	17.6 (3)	47.1 (8)	11.8 (2)	76.5 (13/17)
Hypokalaemia	14 (1.5)	1.0 (1–1)	0 (0)	0 (0)	64.3 (9)	28.6 (4)	7.1 (1)	100 (14/14)
Hyperkalaemia	13 (1.4)	1.3 (1–1)	0 (0)	30.8 (4)	46.2 (6)	23.1 (3)	0 (0)	69.2 (9/13)
Supratherapeutic INR	9 (1.0)	1.0 (1–1)	0 (0)	0 (0)	0 (0)	88.9 (8)	11.1 (1)	100 (9/9)
Vomiting / diarrhoea	9 (1.0)	1.0 (1–1)	0 (0)	11.1 (1)	22.2 (2)	44.4 (4)	22.2 (2)	88.9 (8/9)
Gastrointestinal bleeding	7 (0.7)	1.0 (1–1)	0 (0)	14.3 (1)	28.6 (2)	42.9 (3)	14.3 (1)	85.7 (6/7)
Hyperglycaemia	2 (0.2)	1.0 (1–2)	0 (0)	50.0 (1)	0 (0)	50.0 (1)	0 (0)	50.0 (1/2)
Fracture	1 (0.1)	1.0 (1–1)	0 (0)	100 (1)	0 (0)	0 (0)	0 (0)	0 (0/1)
Acute heart failure	1 (0.1)	1.0 (1–1)	0 (0)	100 (1)	0 (0)	0 (0)	0 (0)	0 (0/1)
Intracranial bleeding	0 (0.0)	N/A	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N/A
Total	**941 (100)**	**2.0 (1–8)**	**1.3 (12)**	**57.0 (536)**	**27.0 (254)**	**12.3 (116)**	**2.4 (23)**	**41.8 (393/941)**

[a]The PPV was defined as the number of ADRs divided by the number of all detected trigger-drug combinations per trigger.

Table 3. Number of ADRs per trigger and their associated drug classes, stratified for ADRs with a causal relationship considered to be possible, probable or certain, and for those considered to be probable or certain. *RAAS* = renin angiotensin aldosterone.

	ADR causality score: possible–probable–certain			ADR causality score: probable–certain		
Trigger	ADR, n (%)	Drugs related to ADR (n)	Recognition by usual care, %	ADR, n (%)	Drugs related to ADR (n)	Recognition by usual care, %
Fall / collapse / (orthostatic) hypotension/ dizziness / syncope	86 (21.9)	Diuretics (17) Beta blocking agents (17) Agents acting on RAAS (17) Other (35)	66.3	14 (10.1)	Diuretics (4) Psychoanaleptics (3) Beta blocking agents (2) Other (5)	100
Delirium / confusion / drowsiness	52 (13.2)	Analgesics (21) Psycholeptics (9) Psychoanaleptics (7) Other (15)	75.0	15 (10.8)	Analgesics (12) Antiepileptics (1) Anti-parkinson drugs (1) Cardiac therapy (1)	93.3
Renal insufficiency and/ or dehydration	94 (23.9)	Diuretics (59) Agents acting on RAAS (27) Antiinflammatory and –rheumatic drugs (8)	89.4	28 (20.1)	Diuretics (12) Agents acting on RAAS (9) Antiinflammatory and -rheumatic drugs (7)	96.4
Hyponatraemia	58 (14.8)	Diuretics (44) Psychoanaleptics (9) Agents acting on RAAS (5)	96.6	24 (17.3)	Diuretics (18) Psychoanaleptics (5) Agents acting on RAAS (1)	95.8
Constipation / ileus	24 (6.1)	Analgesics (23) Calcium channel blockers (1)	91.7	13 (9.4)	Analgesics (13)	92.3
Other bleedings	19 (4.8)	Antithrombotic agents (17) Antiinflammatory and antirheumatics (2)	73.7	7 (5.0)	Antithrombotic agents (7)	100
Hypoglycaemia	13 (3.3)	Drugs used in diabetes (13)	100	10 (7.2)	Drugs used in diabetes (10)	100
Hypokalaemia	14 (3.6)	Diuretics (14)	92.9	5 (3.6)	Diuretics (5)	100
Hyperkalaemia	9 (2.3)	Diuretics (5) Agents acting on RAAS (4)	88.9	3 (2.2)	Diuretics (2) Agents acting on RAAS (1)	100

Table 3. Continued.

	ADR causality score: possible–probable–certain			ADR causality score: probable–certain		
Trigger	ADR, n (%)	Drugs related to ADR (n)	Recognition by usual care, %	ADR, n (%)	Drugs related to ADR (n)	Recognition by usual care, %
Supratherapeutic INR	9 (2.3)	Antithrombotic agents (9)	100	9 (6.5)	Antithrombotic agents (9)	100
Vomiting / diarrhoea	8 (2.0)	Antibacterials for systemic use (8)	87.5	6 (4.3)	Antibacterials for systemic use (6)	100
Gastrointestinal bleeding	6 (1.5)	Antithrombotic agents (6)	83.3	4 (2.9)	Antithrombotic agents (4)	100
Hyperglycaemia	1 (0.3)	Corticosteroids for systemic use (1)	100	1 (0.7)	Corticosteroids for systemic use (1)	100
Fracture	0 (0)	N/A	N/A	0 (0)	N/A	N/A
Acute heart failure	0 (0)	N/A	N/A	0 (0)	N/A	N/A
Intracranial bleeding	0 (0)	N/A	N/A	0 (0)	N/A	N/A
Total	**393 (100)**	**Diuretics (139)Agents acting on RAAS (53) Analgesics (44) Other (157)**	**83.5**	**139 (100)**	**Diuretics (41) Analgesics (25) Antithrombotic agents (20) Other (53)**	**97.1**

Discussion

Main findings

ADRs were highly prevalent in older patients with polypharmacy acutely admitted to the geriatric ward. The ADR trigger tool detected one or more trigger-drug combinations at admission in almost three quarters (73%) of all screened patients, and more than half (52%) of these patients had at least one confirmed ADR after causality assessment. The overall PPV of the ADR trigger tool was 41.8%, indicating that less than half of the trigger-drug combinations were considered to be ADRs. Usual care recognised the majority of ADRs (83.5%), increasing to 97.1% when restricted to possible and certain ADRs.

Performance

The performance of the ADR trigger tool recommended by the Dutch geriatric guideline was not previously studied. Using an ADR trigger tool may be a helpful and efficient strategy to increase ADR detection in older people, especially in cases of low recognition by usual care. A high PPV is important for a positive balance between reviewing signals and detecting actual ADRs. Although there is no generally accepted definition to distinguish 'good' from 'poor' trigger tool performance – which also depends on its intended use – a PPV ≥20% is often considered good [23,24]. In our study, the PPV per trigger of the investigated ADR trigger tool was highly variable, ranging from 0–100%. However, if triggers with a frequency of only one were excluded, all triggers had a PPV ≥ 20%, of which the PPVs for the triggers 'fall/…/dizziness' (PPV 28%) and 'delirium/…/drowsiness' (PPV 23%) were lowest. These clinical events often have multiple possible causes related to comorbidity, drugs and drug combinations, impeding the confirmation of a clear causal relationship. The mean number of drugs related to these two events at a patient's level were highest. In contrast, trigger-drug combinations based on clinical events related to a single drug class (e.g. vitamin K antagonist – supratherapeutic INR) or for which a dechallenge usually results in a direct improvement (e.g. diuretics – hypokalaemia) were more likely considered to be ADRs.

The low PPV for triggers related to fall and delirium are in line with other findings. Carnevali et al. found a PPV for the triggers 'fall' and 'emergence of confused state' of 19% and 9%, respectively, in hospitalised adults [12]. In addition, a French retrospective cohort study in acutely admitted geriatric patients investigated the triggers 'fall' and 'delirium' from the Global Trigger Tool [11,25]. The mean number of suspected drugs per patient related to these clinical events was comparable with our results, as well as the PPV for delirium (21% vs 23%). However, the PPV for falls was much higher (54% vs. 28%), which is likely due to differences in the

ADR causality method used; the relationship between the suspected drug and the identified ADRs in this French study was uncertain in over 80%. Removing the triggers for falls and delirium from the ADR trigger tool will increase the overall PPV of the ADR trigger tool from 41.8% to 62.2% (*n* = 255/410, Table 2). Nevertheless, we would not recommend excluding falls and delirium as triggers because these clinical events are often associated with drug-related admissions in older patients with polypharmacy [24]. In addition, a large proportion of ADRs would be excluded (35%, *n* = 138/393), and recognition by usual care for these triggers was lowest for ADRs of at least possible causality (Table 3). To increase the PPV, we would rather suggest to explore strategies for excluding drugs with a relatively low risk on the clinical event. A recent observational study compared the association of potentially inappropriate medication on inpatient falls listed in the explicit screening tools STOPP v2, STOPP v2 section K, and STOPPFall [26–28] Although all screening tools were independently associated with falls, the strongest effect was identified for STOPP section K [28]. This is plausible because STOPP section K is the most restrictive tool, including only four drug classes with highest risk of falls (i.e. benzodiazepines, hyponotic z-drugs, vasodilator drugs, and neuroleptic drugs). For delirium, selecting drugs with the highest anticholinergic burden will likely increase the PPV. However, a disadvantage of excluding drugs from the ADR trigger tool is that less ADRs may be detected.

The difficulties in achieving a high PPV in ADR detection was illustrated in a systematic review on methods to detect drug-related problems. This systematic review identified 28 studies, three of which used a trigger tool to detect ADRs [29]. The PPVs of these ADR trigger tools ranged from 1.8%–32% [30–32]. The study with the lowest PPV (1.8%) was the only one performed in a geriatric population (rehabilitation ward) using a commercially available database grounded on potential ADRs extracted from a drug's product information [30]. The highest PPV was reported in patients (age 16–90 years) admitted to a gastroenterology department using a trigger tool solely based on laboratory signals [32]. The use of trigger tools appeared to be the most labour-efficient method; however, incident report review generally showed a higher specificity compared to other methods.

More recently, Zerah et al. evaluated the PPV of a trigger tool to detect adverse drug events (ADEs) and drug-related admissions (DRAs) in older people based on chart review [24]. The DRA trigger tool comprised 26 triggers and associated drugs frequently involved in ADEs. The DRA trigger tool was more comprehensive than the ADR trigger tool used in our study and included triggers to detect ADEs, including both ADRs and medication errors (i.e. underuse, overuse and misuse of drugs). The overall PPV for the detection of ADEs of the DRA trigger tool was 87% [24]. The better performance of the DRA trigger tool compared with the ADR trigger tool may be explained by the inclusion of medication errors, which had a large impact on the

PPV. For instance, 11.8% (*n* = 76) of all ADEs with a causal relationship were related to the trigger 'heart failure', with the majority of these ADEs being adjudicated as underuse of beta-blockers, ACE-inhibitors, and diuretics [24]. For this reason, the PPVs of these two tools are difficult to compare.

ADR recognition by usual care

In addition to aiming for a high PPV, an ADR trigger tool needs to be of clinical value to usual care and increase the detection of unrecognised ADRs. Previous studies reported that drug related problems are missed or misdiagnosed in approximately 40–60% of the cases by physicians at the ED; however, we found a much higher recognition by usual care of ADRs identified with the use of the ADR trigger tool [6–8]. There are several explanations for this discrepancy. First, we investigated a subset of most frequent and serious ADRs in older people targeted by the ADR trigger tool, which cannot be compared with the broader definition of 'drug-related problems' in previous studies. In addition, our study was performed in an academic, teaching hospital and all patients were under geriatric care. Compared to other specialists, geriatric residents are well trained in detecting drug-related problems in their patients under the direct supervision of experienced geriatricians [33]. The high recognition of ADRs found in our study was comparable with the results of Klopotowska et al., who found that 80% of ADRs of at least possible causality in older hospitalised patients admitted to an internal medicine ward were recognised by usual care during the hospital stay [34]. Similar to our results, the majority of unrecognised ADRs were those with a possible causality score [34].

Strengths and limitations

If implemented in daily practice, the PPV as a measure for performance is an important outcome to assess the relevance of triggers. The reported ADR recognition by usual care is highly relevant in deciding whether implementation of such a tool would add clinical value to usual patient care.

To ensure that ADR recognition by usual care was not biased, we selected patients who were admitted before publication of the tool in the national guideline. Two independent clinicians thoroughly and manually screened admission letters for trigger-drug combinations, followed by causality assessment by a geriatrician and a clinical pharmacist revealing substantial inter-rater agreement (κ=0.76).

There are, however, several limitations to this research. First, EHRs were only screened for trigger-drug combinations listed in the ADR trigger tool. Therefore, the negative predictive value, sensitivity or specificity of the tool could not be calculated. Second, retrospective studies based on chart review rely on documented

information by attending physicians. The introduction of information bias by physician's notes and actions cannot be fully ruled out. For instance, the screening of trigger-drug combinations was based on information documented in admission letters and laboratory results were not examined as a primary source of triggers. A mild hyponatraemia with concomitant use of diuretics could potentially have been missed as trigger-drug combination if it was not mentioned as a clinical problem by the attending physician. However, the triggers listed in the ADR trigger tool are serious and admission letters were comprehensive, which makes underreporting of these triggers unlikely.

Third, the definition of 'recognition by usual care' was not very specific since a documented event combined with discontinuation or a dose adjustment of the associated drug was also considered as being 'recognised' without explicit mention. However, this does not necessarily correspond with ADR recognition because drugs could be discontinued for other reasons (e.g. a lack of indication). In addition, the persistence of drug changes after hospital discharge was not evaluated in our study. A discontinuation or dose adjustment of the suspected drug was implemented by the attending physician in three quarters of ADRs, but previous research illustrated that a quarter of drugs discontinued because of an ADR were re-prescribed after admission [35].

In addition, this study was performed in a specific population of older patients with polypharmacy acutely admitted to a geriatric ward. The admission to a geriatric ward in an academic, teaching hospital could have biased the type and prevalence of certain trigger-drug combinations. For instance, patients presenting with fall and delirium are likely to be admitted to a geriatric ward; these clinical events were most prevalent in our population comprising more than half of all identified trigger-drug combinations. Consequently, these two triggers had the largest impact on the overall PPV of the ADR trigger tool. In contrast, the clinical event 'intracranial bleeding' was absent in our population and thus had no impact on the overall PPV. Acutely admitted patients with an intracranial bleeding are more likely to be admitted to a neurosurgical ward instead of a geriatric ward. Furthermore, geriatric residents and their supervisors in an academic, teaching hospital may be more focused on ADR recognition compared to other medical specialties. For these reasons, the generalisation of ADR prevalence and ADR recognition are limited. Lastly, the PPV was not stratified for different patient populations because the availability of baseline patient characteristics was limited.

Implications

The ADR trigger tool detected ADRs in more than half (52%) of all patients with polypharmacy acutely admitted to the geriatric ward. Combining the ADR trigger

tool with ADR risk-prediction models may be a good future strategy to identify older patients at highest risk of ADRs, potentially increasing the predictive value of the tool. However, currently available ADR risk-prediction models for use in older people, such as the GerontoNet ADR risk scale and the Adverse Drug Reaction Risk in Older Persons (ADRROP) prediction scale, failed to predict ADRs well, and the most important risk factor for the occurrence of ADRs – polypharmacy – was already included in our study [10,36–38].

ADR recognition by geriatric residents/geriatricians was very high for ADRs detected with the trigger tool in the setting of a tertiary university teaching hospital. Therefore, implementation of this trigger tool is not likely to improve care for older patients acutely admitted to our geriatric ward. However, ADR recognition by physicians less experienced in ADR detection in older people may be lower. Future research could focus on the clinical value of the tool if used in older patients acutely admitted to non-geriatric wards. In addition, it would be interesting to investigate if the ADR trigger tool could decrease the time to ADR detection, for example, when integrated with electronic healthcare systems. The use of clinical decision support systems to improve in-hospital fall and delirium care (e.g. reminders for patient screening and support to review medication) was identified as a facilitator in a recent interview study among Dutch healthcare professionals [39]. However, the risk of alert fatigue was also addressed as a potential barrier for this strategy [39]. In view of our results, we highly recommend conducting performance and feasibility studies before recommending ADR trigger tools as a standard of care.

Conclusion

The ADR trigger tool has predictive value (PPV 41.8%), but implementation of this tool is not likely to improve ADR recognition in older patients acutely admitted to our geriatric ward because the majority of ADRs were recognised by usual care.

Declarations

Authors' contributions

Authorship eligibility is based on the four ICMJE authorship criteria. The authors certify that they have participated in the aspects conception and design (NN, WK), acquisition of data (NN, BS, WL), interpretation of data (NN, BS, TE, EvP, IW, WK), drafting the article (BS, NN) and revising it critically for important intellectual content (NN, BS, WL, TE, EvP, IW, WK). All authors have approved the final article. We have not received substantial contributions from non-authors. NN and BS are joint-first 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.

Ethics approval

The Research Ethics Committee of University Medical Centre Utrecht confrmed that the Medical Research Involving Human Subjects Act was not applicable to this study, and a waiver was granted (no. WAG/mb/17/024864)

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Trial registration

Not applicable.

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SUPPLEMENTARY INFORMATION SI1

Specification of drugs with anticholinergic and sedative properties, digoxin and anti-Parkinson drugs associated with the trigger for delirium/confusion/drowsiness. The list of drugs with anticholinergic and sedative properties available in the Netherlands was based on publications of Hilmer et al.[1] and Duran et al.[2]

Drugs	ATC code
Benzodiazepine agonists	
Diazepam	N05BA01
Oxazepam	N05BA04
Clorazepate	N05BA05
Temazepam	N05CD07
Alprazolam	N05BA12
Lorazepam	N05BA06
Zolpidem	N05CF02
Zopiclone	N05CF01
Bromazepam	N05BA08
Flurazepam	N05CD01
Prazepam	N05BA11
Nitrazepam	N05CD02
Lormetazepam	N05CD06
Brotizolam	N05CD09
Opiod analgesics	
Fentanyl	N02AB03
Morphine	N02AA01
Tramadol	N02AX02
Oxycodone	N02AA05
Codeine	N02AA59
Buprenorphine	N02AE01

Drugs	ATC code
Antidepressants	
Venlafaxine	N06AX16
Mirtazapine	N06AX11
Paroxetine	N06AB05
Sertraline	N06AB06
Citalopram	N06AB04
Escitalopram	N06AB10
Phenelzine	N06AF03
Amitryptiline	N06AA09
Clomipramine	N06AA04
Nortriptyline	N06AA10
Fluoxetine	N06AB03
Trazodone	N06AX05
Antipsychotics	
Risperidone	N05AX08
Quetiapine	N05AH04
Olanzapine	N05AH03
Haloperidol	N05AD01
Clozapine	N05AH02
Pipamperon	N05AD05
Zuclopenthixol	N05AF05

Drugs	ATC code
Anti-epileptics	
Phenytoin	N03AB02
Carbamazepine	N03AF01
Oxcarbazepine	N03AF02
Valproic acid	N03AG01
Gabapentin	N03AX12
Lamotrigine	N03AX09
Levetiracetam	N03AX14
Clonazepam	N03AE01
Pregabalin	N03AX16
Antihistamines	
Levocetirizine	R06AE09
Fexofenadine	R06AX26
Cinnarizine	N07CA02
Hydroxyzine	N05BB01
Cetirizine	R06AE07
Clemastine	R06AA04
Digoxin	C01AA05

Drugs	ATC code
Urinary antispasmodics	
Oxybutynin	G04BD04
Tolterodine	G04BD05
Darifenacine	G04BD10
Solifenacin	G04BD08
Fesoterodine	G04BD11
Anticholinergic bronchodilators	
Ipratropium	R03BB01
Tiotropium	R03BB04
Miscellaneous drugs	
Tamsulosin	G04CA02
Doxazosin	C02CA04
Disopyramide	C01BA03
Loperamide	A07DA03
Levomepromazine	N05AA02
Clonidine	C02AC01
Methyldopa	C02AB01
Anti-Parkinson drugs	N04

ATC = Anatomical therapeutic chemical classification.
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2.2

Chapter 2.2

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

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Abstract

Introduction

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 under- and overprescribing in this population, explicit drug optimization tools like STOPP/START have been developed. The aim of this quality appraisal study was to evaluate the clinical applicability of STOPP/START criteria in daily patient care by assessing the clarity of singular criteria.

Methods

For each of the 114 STOPP/START criteria version 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 & Evaluation (AGREE) Consortium.

The primary outcome measure was the clarity rating per element, categorized 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 were further classified into five descriptive components: disease, sign, symptom, laboratory finding and medication.

Results

STOPP recommendations had an average clarity rating of 65%, 60% and 67% 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.

Conclusion

Our results show that the clarity of the STOPP/START criteria can be improved. For future development of explicit drug optimization 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 (CPGs) 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 hospitalizations, 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 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 optimization 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 version 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 version 2 as published in November 2017 were used [18]. STOPP/START version 2 consists of a list of 80 Potentially Inappropriate Medications (PIMs, STOPP criteria) and 34 Potential Prescribing Omissions (PPOs, START criteria).

Clarity assessment

The AGREE II Instrument and 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 Appraisal of Guidelines for Research & Evaluation (AGREE) Consortium [19]. In addition to the AGREE II Instrument, AGREE developed a Guideline Implementability Decision Excellence Model (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 (CH) and a hospital pharmacist resident (BS), 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 post-graduate experience). The appraisers were trained with a rating guidance, developed and approved by senior clinicians (TE/EP/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 optimize '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 optimization 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 (EMA) 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 when a third appraiser was consulted. After scoring the elements, clarity ratings were categorized into low (<33.3%), moderate (33.3% – 67.7%) and high (>67.7%).

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). 44 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 to the average scores prior to consensus.

Average clarity ratings for STOPP recommendations were 65%, 60% and 67% 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 categorized 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 categorized 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 Supplementary Information SI1.

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.

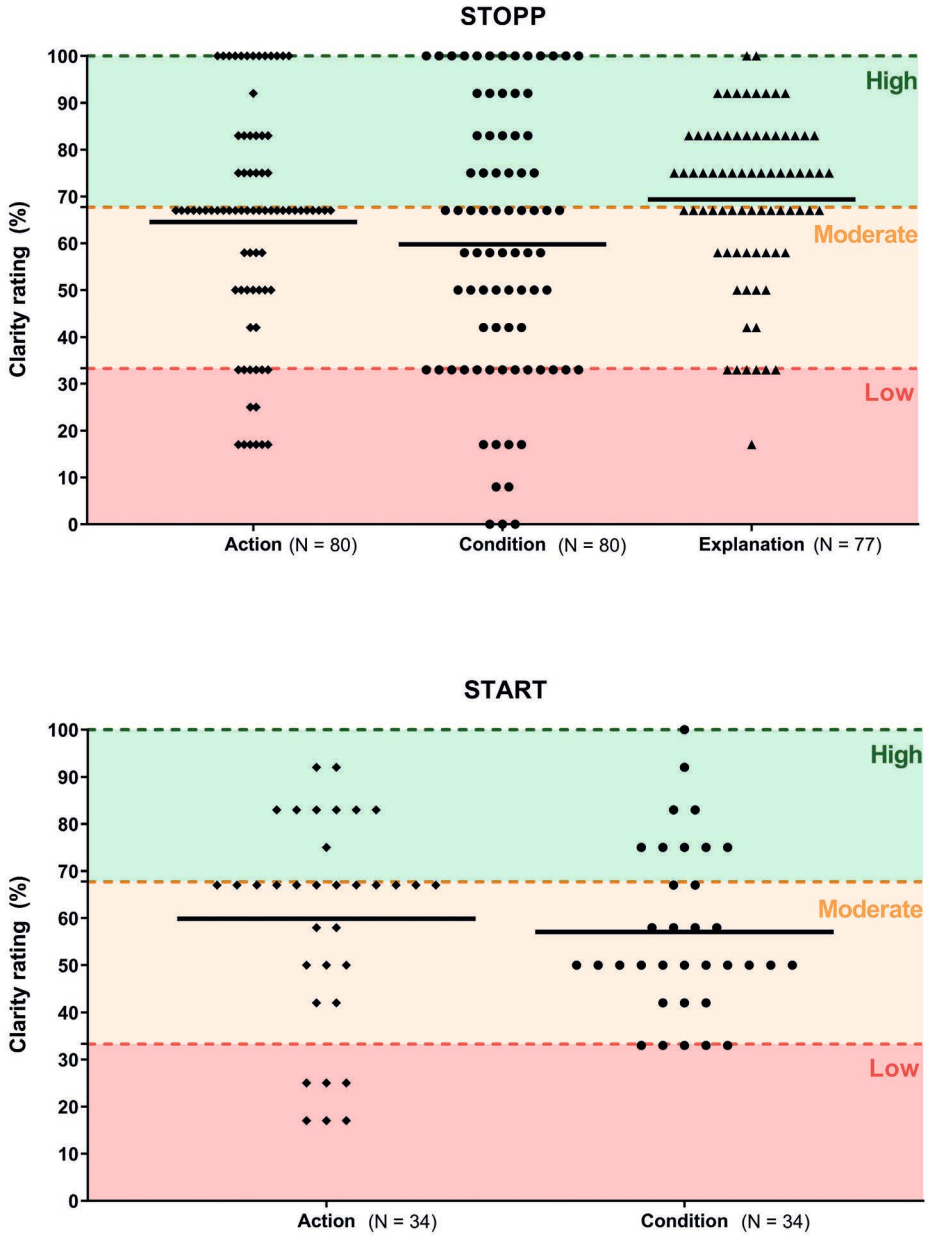

Figure 1. Distribution of clarity ratings for STOPP and START recommendations per element. Average clarity ratings for STOPP recommendations were 65%, 60% and 67% for actions, conditions and explanations, respectively. Average clarity ratings for START recommendations were 60% and 57% for actions and conditions, respectively.
STOPP = Screening Tool of Older Persons' Prescriptions;
START = 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 › In patients with potential omissions, warnings for important contra indications are lacking / not clearly defined	STOPP B5. …**as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias** (33%) 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 › Description of drug therapy (substance / dosage) not specific enough	STOPP D2. …**as first-line antidepressant treatment** (33%) 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.

Barriers	Example a (clarity rating, %)
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%)

Table 1. Continued.

Facilitators	Example [a] (clarity rating, %)
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%)
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 Information SI1.
eGFR = estimated glomerular filtration rate; *N/A* = not applicable; *pO2* = partial pressure of oxygen; *SaO2* = arterial oxygen saturation; *STOPP/START* = Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert to Right Treatment.

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%).

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 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 optimized 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

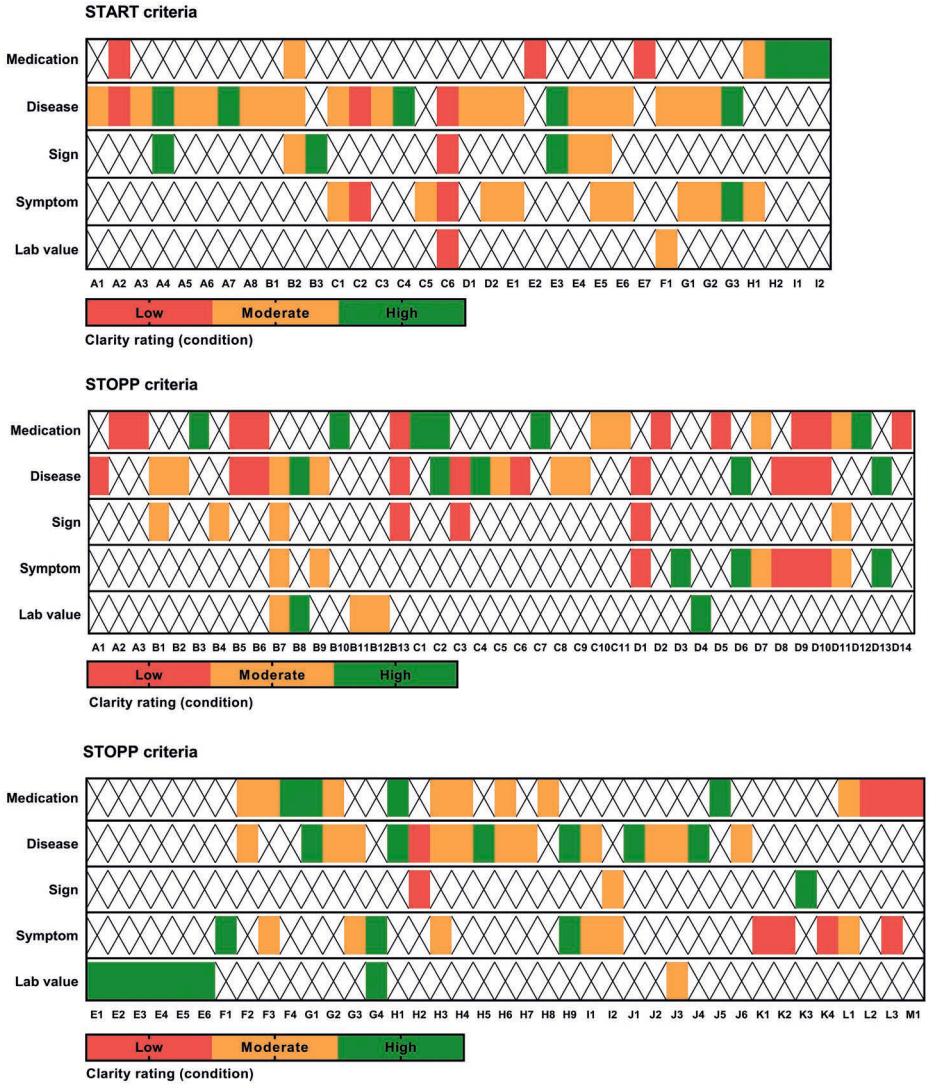

Figure 2. Clarity ratings of conditions for STOPP and START criteria related to five descriptive components. Green, orange and red colours correspond with high (>67.7%), moderate (33.3-67.7%) or low (<33.3%) clarity ratings of conditions.
STOPP = Screening Tool of Older Persons' Prescriptions;
START = Screening Tool to Alert to Right Treatment

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 developing 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, randomized 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 optimized 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, digital 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 to present 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

Authorship eligibility is based on the four ICMJE authorship criteria. All authors certify that they have participated sufficiently in the work to take public responsibility for the content. Study concept and design: BS, CH, WK, EP, TE, IW. Data acquisition: BS, CH, WK, IW. Analysis and/or interpretation of data: BS, CH, WK, EP, TE, IW. Drafting the manuscript: BS. Revising the manuscript critically for important intellectual content: BS, CH, WK, EP, TE, 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 Supplementary Information.

Ethics approval

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

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Informed consent

Not applicable.

Trial registration

Not applicable.

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SUPPLEMENTARY INFORMATION SI1

Clarity ratings per element for 80 STOPP and 34 START recommendations

Table SI1.1. Clarity rating for STOPP criteria.

STOPP	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
A						
A1	Any drug	100%	prescribed without an evidence-based clinical indication.	8%		N/A
A2	Any drug	100%	prescribed beyond the recommended duration, where treatment duration is well defined	8%		N/A
A3	Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants	33%	[*users with...duplicate drug class prescription*]	17%	(optimisation of monotherapy within a single drug class should be observed prior to considering a new agent).	33%
B						
B1	Digoxin	100%	for heart failure with normal systolic ventricular function	58%	(no clear evidence of benefit).	58%
B2	Verapamil or diltiazem	100%	with NYHA Class III or IV heart failure	58%	(may worsen heart failure).	75%
B3	Beta-blocker	67%	in combination with verapamil or diltiazem	92%	(risk of heart block).	75%
B4	Beta blocker	67%	with bradycardia (< 50/ min) , type II heart block or complete heart block	42%	(risk of profound hypotension, asystole).	75%

Table SI1.1. Continued.

STOPP	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
B5	Amiodarone	100%	as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias	33%	(higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem)	83%
B6	Loop diuretic	67%	as first-line treatment for hypertension	33%	(lack of outcome data for this indication; safer, more effective alternatives available).	33%
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	58%	(leg elevation and /or compression hosiery usually more appropriate)	75%
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	75%	(hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic).	83%
B9	Loop diuretic	67%	for treatment of hypertension with concurrent urinary incontinence	67%	(may exacerbate incontinence).	58%

Table SI1.1. Continued.

STOPP	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
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	75%	(centrally-active antihypertensives are generally less well tolerated by older people than younger people).	50%
B11	ACE inhibitors or Angiotensin Receptor Blockers	67%	in patients with hyperkalaemia.	50%		N/A
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	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%
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	33%	(risk of cardiovascular collapse).	67%
C						
C1	Long-term aspirin at doses greater than 160mg per day	83%		92%	(increased risk of bleeding, no evidence for increased efficacy).	75%
C2	Aspirin	92%	with a past history of peptic ulcer disease without concomitant PPI	100%	(risk of recurrent peptic ulcer).	83%

Table SI1.1. Continued.

STOPP	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
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	33%	(high risk of bleeding)..	58%
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	83%	(no evidence of added benefit over clopidogrel monotherapy) .	83%
C5	Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	100%	in patients with chronic atrial fibrillation	67%	(no added benefit from aspirin).	83%
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	33%	(no added benefit from dual therapy).	67%
C7	Ticlopidine	100%	in any circumstances	100%	(clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects)..	92%

Table SI1.1. Continued.

STOPP	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
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,	67%	(no proven added benefit).	83%
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	67%	(no proven added benefit).	83%
C10	NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%	in combination	67%	(risk of gastrointestinal bleeding).	67%
C11	NSAID	67%	with concurrent antiplatelet agent(s) without PPI prophylaxis	67%	(increased risk of peptic ulcer disease)	67%
D						
D1	Tricyclic Antidepressants (TCAs)	67%	with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention	33%	(risk of worsening these conditions).	50%

Table SI1.1. Continued.

STOPP	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
D2	Initiation of Tricyclic Antidepressants (TCAs)	67%	as first-line antidepressant treatment	33%	(higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).	42%
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	75%	(high risk of urinary retention).	92%
D4	Selective serotonin re-uptake inhibitors (SSRI's)	67%	with current or recent significant hyponatraemia i.e. serum Na+ < 130 mmol/l	75%	(risk of exacerbating or precipitating hyponatraemia).	92%
D5	Benzodiazepines	67%	for ≥ 4 weeks	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%
D6	Antipsychotics (i.e. other than quetiapine or clozapine)	75%	in those with parkinsonism or Lewy Body Disease	100%	(risk of severe extra-pyramidal symptoms)	83%

Table SI1.1. Continued.

STOPP	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
D7	Anticholinergics/antimuscarinics	17%	to treat extra-pyramidal side-effects of neuroleptic medications	50%	(risk of anticholinergic toxicity),	50%
D8	Anticholinergics/antimuscarinics	17%	in patients with delirium or dementia	33%	(risk of exacerbation of cognitive impairment).	75%
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	33%	(increased risk of stroke).	33%
D10	Neuroleptics	33%	as hypnotics, unless sleep disorder is due to psychosis or dementia	33%	(risk of confusion, hypotension, extra-pyramidal side effects, falls).	67%
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	50%	(risk of cardiac conduction failure, syncope and injury).	92%

Table SI1.1. Continued.

STOPP	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
D12	Phenothiazines	75%	as first-line treatment,	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%
D13	Levodopa or dopamine agonists	83%	for benign essential tremor	100%	(no evidence of efficacy)	83%
D14	First-generation antihistamines	17%	[*users of...first-generation antihistamines*]	33%	(safer, less toxic antihistamines now widely available).	75%
E						
E1	Digoxin at a long-term dose greater than 125µg/day	100%	if eGFR < 30 ml/min/1.73m2	83%	(risk of digoxin toxicity if plasma levels not measured).	67%
E2	Direct thrombin inhibitors (e.g. dabigatran)	58%	if eGFR < 30 ml/min/1.73m2	100%	(risk of bleeding)	67%
E3	Factor Xa inhibitors (e.g. rivaroxaban, apixaban)	58%	if eGFR < 15 ml/min/1.73m2	100%	(risk of bleeding)	67%
E4	NSAID's	42%	if eGFR < 50 ml/min/1.73m2	100%	(risk of deterioration in renal function).	75%

Table SI1.1. Continued.

STOPP	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
E5	Colchicine	100%	if eGFR < 10 ml/min/1.73m2	100%	(risk of colchicine toxicity).	83%
E6	Metformin	100%	if eGFR < 30 ml/min/1.73m2	100%	(risk of lactic acidosis).	83%
F						
F1	Prochlorperazine or metoclopramide	100%	with Parkinsonism	92%	(risk of exacerbating Parkinsonian symptoms).	92%
F2	PPI	58%	for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks	50%	(dose reduction or earlier discontinuation indicated).	33%
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	67%	(risk of exacerbation of constipation).	100%
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%		100%	(no evidence of enhanced iron absorption above these doses).	75%
G						
G1	Theophylline	100%	as monotherapy for COPD	75%	(safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).	75%

Table SI1.1. Continued.

STOPP	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
G2	Systemic corticosteroids	75%	instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD	67%	(unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available).	75%
G3	Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium)	50%	with a history of narrow angle glaucoma or bladder outflow obstruction	42%	(may cause urinary retention).	50%
G4	Benzodiazepines	67%	with acute or chronic respiratory failure i.e. pO2 < 8.0 kPa ± pCO2 > 6.5 kPa	92%	(risk of exacerbation of respiratory failure).	67%
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	100%	(risk of peptic ulcer relapse).	75%
H2	NSAID	67%	with severe hypertension or severe heart failure	33%	(risk of exacerbation of hypertension/heart failure)	67%
H3	Long-term use of NSAID (>3 months)	75%	for symptom relief of osteoarthritis pain where paracetamol has not been tried	58%	(simple analgesics preferable and usually as effective for pain relief)	42%

Table SI1.1. Continued.

STOPP	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
H4	Long-term corticosteroids (>3 months)	83%	as monotherapy for rheumatoid arthrtitis	67%	(risk of systemic corticosteroid side-effects).	58%
H5	Corticosteroids (other than periodic intra-articular injections for mono-articular pain)	83%	for osteoarthritis	100%	(risk of systemic corticosteroid side-effects).	58%
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	50%	(xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).	33%
H7	COX-2 selective NSAIDs	83%	with concurrent cardiovascular disease	42%	(increased risk of myocardial infarction and stroke).	75%
H8	NSAID	58%	with concurrent corticosteroids without PPI prophylaxis	58%	(increased risk of peptic ulcer disease).	75%
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	92%	(risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture)	83%

Table SI1.1. Continued.

STOPP	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
I						
I1	Antimuscarinic drugs	17%	with dementia, or chronic cognitive impairment or narrow-angle glaucoma or chronic prostatism	42%	(risk of increased confusion, agitation / risk of urinary retention).	67%
I2	Selective alpha-1 selective alpha blockers	67%	in those with symptomatic orthostatic hypotension or micturition syncope	50%	(risk of precipitating recurrent syncope).	75%
J						
J1	Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride)	50%	with type 2 diabetes mellitus	75%	(risk of prolonged hypoglycaemia).	75%
J2	Thiazolidenediones (e.g. rosiglitazone, pioglitazone)	50%	in patients with heart failure	58%	(risk of exacerbation of heart failure).	67%
J3	Beta-blockers	67%	in diabetes mellitus with frequent hypoglycaemic episodes	50%	(risk of suppressing hypoglycaemic symptoms).	83%
J4	Oestrogens	67%	with a history of breast cancer or venous thromboembolism	83%	(increased risk of recurrence).	67%
J5	Oral oestrogens	83%	without progestogen in patients with intact uterus	100%	(risk of endometrial cancer).	67%

Table SI1.1. Continued.

STOPP	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
J6	Androgens (male sex hormones)	67%	in the absence of primary or secondary hypogonadism	58%	(risk of androgen toxicity; no proven benefit outside of hypogonadism indication).	92%
K						
K1	Benzodiazepines	67%	[*falls*]	0%	(sedative, may cause reduced sensorium, impair balance).	58%
K2	Neuroleptic drugs	17%	[*falls*]	0%	(may cause gait dyspraxia, Parkinsonism).	58%
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	83%	(risk of syncope, falls).	75%
K4	Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon	50%	[*falls*]	0%	(may cause protracted daytime sedation, ataxia).	58%
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	50%	(WHO analgesic ladder not observed).	33%
L2	Use of regular (as distinct from PRN) opioids	67%	without concomitant laxative	17%	(risk of severe constipation).	83%
L3	Long-acting opioids	17%	without short-acting opioids for break-through pain	17%	(risk of non-control of severe pain)	67%

Table SI1.1. Continued.

STOPP	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
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*]	17%	(risk of increased antimuscarinic/anticholinergic toxicity)	17%

Table SI1.2. STOPP - Clarity rating of actions, from lowest to highest ranking.

STOPP	Action	Clarity rating
n=80		
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%

Table SI1.2. Continued.

STOPP	Action	Clarity rating
n=80		
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%
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%

Table SI1.2. Continued.

STOPP	Action	Clarity rating
n=80		
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%
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%

Table SI1.2. Continued.

STOPP	Action	Clarity rating
n=80		
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 SI1.3 STOPP - Clarity rating of conditions, from lowest to highest ranking.

STOPP	Condition	Clarity rating
n=80		
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%

Table SI1.3. Continued.

STOPP	Condition	Clarity rating
n=80		
D7	to treat extra-pyramidal side-effects of neuroleptic medications	50%
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 SI1.3. Continued.

STOPP	Condition	Clarity rating
n=80		
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 SI1.4 STOPP - Clarity rating of explanations, from lowest to highest ranking.

STOPP	Explanation	Clarity rating
n=77		
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%

Table SI1.4 Continued.

STOPP	Explanation	Clarity rating
n=77		
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%
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%

Table SI1.4 Continued.

STOPP	Explanation	Clarity rating
n=77		
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%
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 SI1.5 Clarity rating for START criteria.

START	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
A						
A1	Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors	67%	in the presence of chronic atrial fibrillation.	50%		N/A
A2	Aspirin (75 mg – 160 mg once daily)	92%	in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated.	33%		N/A
A3	Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor)	75%	with a documented history of coronary, cerebral or peripheral vascular disease.	58%		N/A
A4	Antihypertensive therapy	25%	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
A5	Statin therapy	67%	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
A6	Angiotensin Converting Enzyme (ACE) inhibitor	67%	with systolic heart failure and/or documented coronary artery disease.	58%		N/A
A7	Beta-blocker	67%	with ischaemic heart disease.	75%		N/A
A8	Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol)	83%	with stable systolic heart failure.	67%		N/A

Table SI1.5 Continued.

START	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
B						
B1	Regular inhaled B2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium)	58%	for mild to moderate asthma or COPD.	50%		N/A
B2	Regular inhaled corticosteroid	58%	for moderate-severe asthma or COPD, where FEV1 <50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.	50%		N/A
B3	Home continuous oxygen	83%	with documented chronic hypoxaemia (i.e. pO2 < 8.0 kPa or 60 mmHg or SaO2 < 89%)	92%		N/A
C						
C1	L-DOPA or a dopamine agonist	67%	in idiopathic Parkinson's disease with functional impairment and resultant disability.	50%		N/A
C2	Non-TCA antidepressant drug	25%	in the presence of persistent major depressive symptoms.	33%		N/A
C3	Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine)	50%	for mild-moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).	42%		N/A
C4	Topical prostaglandin, prostamide or beta-blocker	67%	for primary open-angle glaucoma.	100%		N/A
C5	Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated)	67%	for persistent severe anxiety that interferes with independent functioning.	50%		N/A
C6	Dopamine agonist (ropinirole or pramipexole or rotigotine)	83%	for Restless Legs Syndrome, once iron deficiency and severe renal failure have been excluded.	33%		N/A

Table SI1.5 Continued.

START	Action	Clarity rating	Condition	Clarity rating	Expla-nation	Clarity rating
D						
D1	Proton Pump Inhibitor	67%	with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation.	50%		N/A
D2	Fibre supplements (e.g. bran, ispaghula, methylcellulose, sterculia)	50%	for diverticulosis with a history of constipation.	58%		N/A
E						
E1	Disease-modifying anti-rheumatic drug (DMARD)	25%	with active, disabling rheumatoid disease.	42%		N/A
E2	Bisphosphonates and vitamin D and calcium	67%	in patients taking long-term systemic corticosteroid therapy.	33%		N/A
E3	Vitamin D and calcium supplement	17%	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
E4	Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab)	42%	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
E5	Vitamin D supplement	42%	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
E6	Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat)	50%	with a history of recurrent episodes of gout.	50%		N/A
E7	Folic acid supplement	92%	in patients taking methotexate.	33%		N/A

Table SI1.5 Continued.

START	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
F						
F1	ACE inhibitor or Angiotensin Receptor Blocker (if intolerant of ACE inhibitor)	67%	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
G						
G1	Alpha-1 receptor blocker	67%	with symptomatic prostatism, where prostatectomy is not considered necessary.	50%		N/A
G2	5-alpha reductase inhibitor	67%	with symptomatic prostatism, where prostatectomy is not considered necessary.	50%		N/A
G3	Topical vaginal oestrogen or vaginal oestrogen pessary	83%	for symptomatic atrophic vaginitis	75%		N/A
H						
H1	High-potency opioids	17%	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
H2	Laxatives	17%	in patients receiving opioids regularly.	75%		N/A
I						
I1	Seasonal trivalent influenza vaccine	83%	annually	83%		N/A
I2	Pneumococcal vaccine	83%	at least once after age 65 according to national guidelines	83%		N/A

Table SI1.6. START - Clarity rating of actions, from lowest to highest ranking.

START	Action	Clarity rating
n=34		
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 SI1.7. START - Clarity rating of conditions, from lowest to highest ranking.

START	Condition	Clarity rating
n=34		
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 S6.1.

START	Condition	Clarity rating
n=34		
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%

2.3

Chapter 2.3

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

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Abstract

Introduction

The rapid digitalization 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, modeled as inference rules in decision tables, are provided as Supplementary Information.

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 expliwcit (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 doctors 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) [10-8]. 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 PIM-Check compared to STOPP/START (4 vs 10 min) due to its electronic interface [18]. This emphasizes the need for digitalization 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-digitalized) 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 Center 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 procedure is shown in Figure 1.

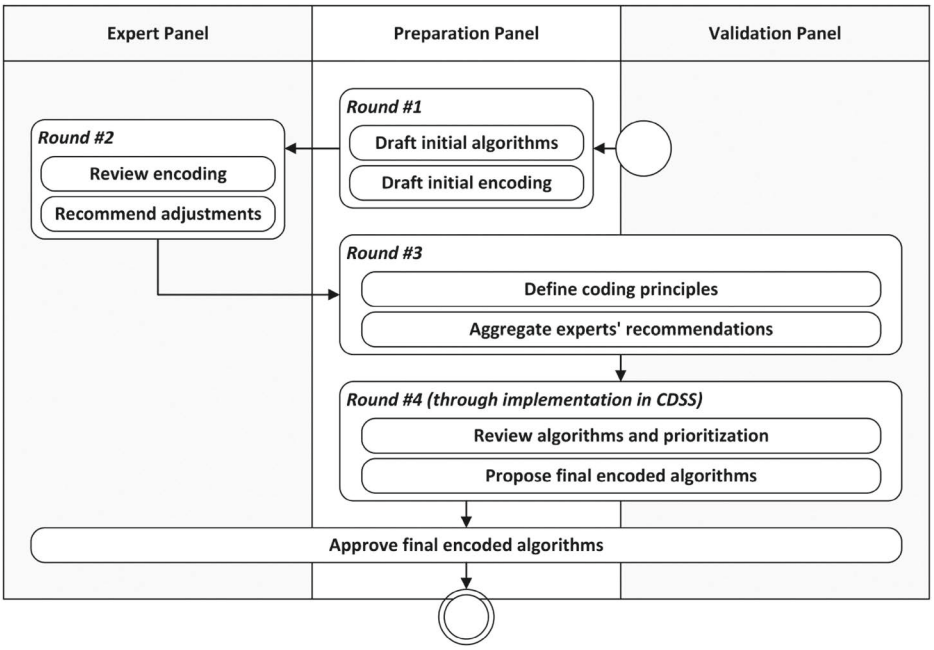

Figure 1. Flowchart illustrating the consensus procedure.

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 itemized 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.

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.

Table 1. Coding principles defined during the third round.

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	a. 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).
	b. 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 minimize 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).

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).

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.

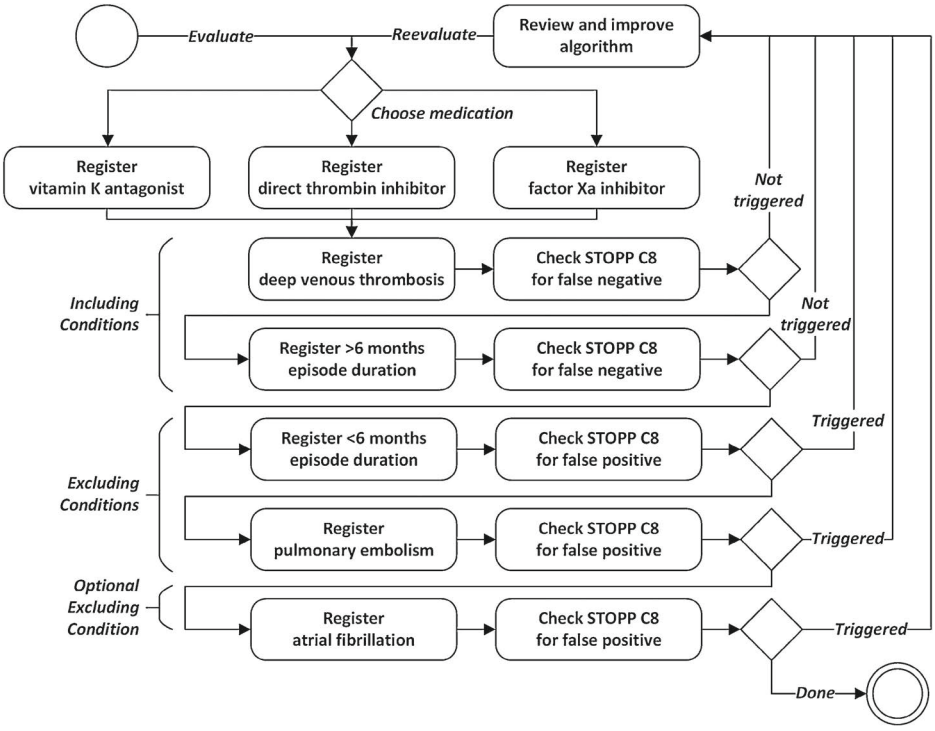

Figure 2. Flowchart illustrating the consensus procedure.
Schematic representation of STOPP criterion C8 *'Stop vitamin K antagonist, direct thrombin inhibitor* or *factor Xa inhibitors* for first *deep venous thrombosis* without continuing provoking risk factors (e.g. thrombophilia) for >6 months' illustrating 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 Information SI1. 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.

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

Coding principle	Examplesa	Solution based on ICD-10 coding
1	STOPP D1 'TCAs with dementia, narrow angle glaucoma, ***cardiac conduction abnormalities***…'	Not specified: Both **I44** *'Atrioventricular and left bundle-branch block'* and **I45**: *'Other conduction disorders'* including all sub categories are included.
	STOPP B11 'ACE inhibitors or Angiotensin Receptor Blockers in patients with ***hyperkalemia***'	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)
	START A1: 'Vitamin K antagonist…presence of ***chronic*** atrial fibrillation'	Exact match in ICD-10 **I48.2** '*Chronic atrial fibrillation*' exists and preferred over **I48:** '*atrial fibrillation and flutter*'
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)…'	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*'
3	START A3 '***Antiplatelet therapy*** (aspirin or clopidogrel or prasugrel or ticagrelor)…'	Specification of individual drugs: only these four were included in the algorithm.
	STOPP C6 '***Antiplatelet therapy*** with vitamin K antagonist…'	All antiplatelet agents registered under ATC **B01AC*** were included
4	START A6 'Angiotensin Converting Enzyme (ACE) inhibitor with a systolic heart failure and/or ***documented coronary artery disease***'	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

Table 2. Continued.

Coding principle	Examplesa	Solution based on ICD-10 coding
5	STOPP C8/C9 'Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitor for first deep venous thrombosis/pulmonary embolus…'	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.
	STOPP B6 Loop diuretic as first line treatment of hypertension'	Not applicable in case of concomitant heart failure. Heart failure (**I50**) added as an optional excluding condition for this rule.

[a]The examples are randomly selected from all coded criteria to illustrate the process of consensus, based on the coding principles. Similar decisions were made for several other criteria and codings. These decisions and their rationale are displayed below each corresponding STOPP/START criterion in Supplementary Information SI1.
*The asterisk indicates that all subcategories starting with the letter/number combinations prior to the asterisk are included.

Table 3. Criteria not coded.

STOPP criterion	Addressed disease/ diagnosis	Concerning-medication (-group)	Reason for the impossibility to code
A1, A2	-	Any drug without indication or beyond recommended duration	Not possible to specify and code
A3	-	Any duplicated drug class	Too comprehensive to code. Also, some duplicated drug classes are justified (e.g. concurrent use of aspirin and clopidogrel shortly after coronary stent)
L3	Break-through pain	Long-acting opioids without short acting opioids	Database related limitation. Long-acting and short-acting opioids cannot be distinguished, due to similar ATC codes.

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

Crite-rion	Original criterion text	Additional (excluding) condition	Justification
START			
E2	Bisphosphonates and vitamin D and calcium in patients taking ***long-term*** systemic corticosteroid therapy	Treatment duration >3 months for cortico-steroids (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.
G1, G2	Start alpha-1 receptor blocker and/or start 5-alpha reductase inhibitor with symptomatic prostatism, ***where prostatectomy is not considered necessary.***	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
STOPP			
B1	Stop digoxin for heart failure with normal systolic ventricular.	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.
B6	Loop diuretic as first-line treatment for hypertension.	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.
B7	Loop diuretic for dependent ankle edema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal 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.
B9	Loop diuretic for treatment of hypertension with concurrent urinary incontinence.	See explanation *STOPP B6*.	

Table 4. Continued.

Crite-rion	Original criterion text	Additional (excluding) condition	Justification
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.***	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.
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.	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
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.***	ICD-10 code F20*, F25* and 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.
D13	Stop levodopa or dopamine agonists for benign essential tremor.	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
H4	Stop long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis.	Additional excluding condition is concurrent use of a DMARD.	If DMARDs are used, corticosteroids are not used as monotherapy (monotherapy not codable otherwise)

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

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 reevaluated 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 Supplementary Information SI1. All ICPC 1, ICPC 2, ICD9-, ICD10- and ATC codes used to convert individual STOPP/START criteria are listed as a code dictionary in Supplementary Information SI2.

Technical aspects

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

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

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
5			Alzheimer's dementia	Lewy body dementia	acetylcholinesterase inhibitor
	START C3	1	G30*, F00*		N06DA*
		2		G31.8	N06DA03

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

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 prioritized 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.

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 prioritized 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.

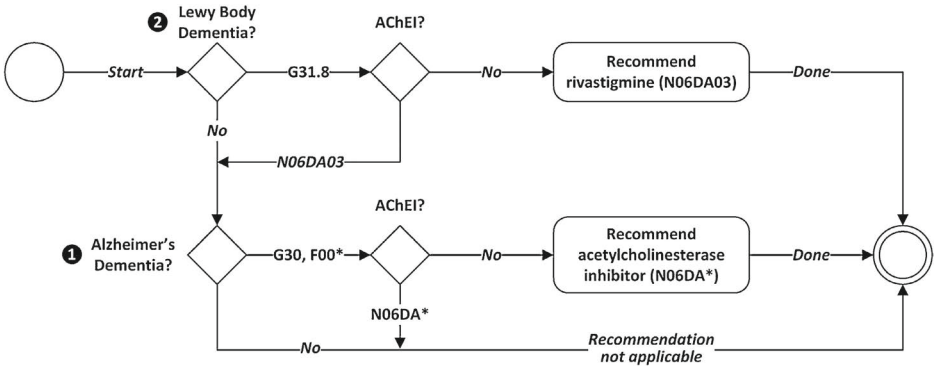

Figure 3. START criterion C3 as a flowchart.

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 minimize 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 hyperkalemia is addressed in several criteria, like STOPP B11: 'ACE inhibitor or Angiotensin Receptor Blockers in patients with hyperkalemia'. We defined hyperkalemia 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; Alpha1- receptor blocker/-5alpha 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 hyperkalemia this is contra-indicated 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 minimize 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 utilized 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 ‘hyperkalemia’ 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

Authorship eligibility is based on the four ICMJE authorship criteria. 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, CH, BS. Data acquisition, analysis and/or interpretation of data: DdG, CD, MM (preparation panel), MB, JvC, JH, AV, RvM (expert panel), BS, CH (validation panel). Drafting the manuscript: CH. Revising the manuscript critically for important intellectual content: 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

Not applicable.

Funding

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Informed consent

Not applicable.

Trial registration

Not applicable.

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SUPPLEMENTARY INFORMATION SI1

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 SI1.1. 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 SI1.1 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 SI1.2. 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 SI1.2 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 SI1.1 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.

Figure SI1.1. Diagram showing the relations between a criterion's inference rules, metadata, conditions, and actions, and their allowed values.

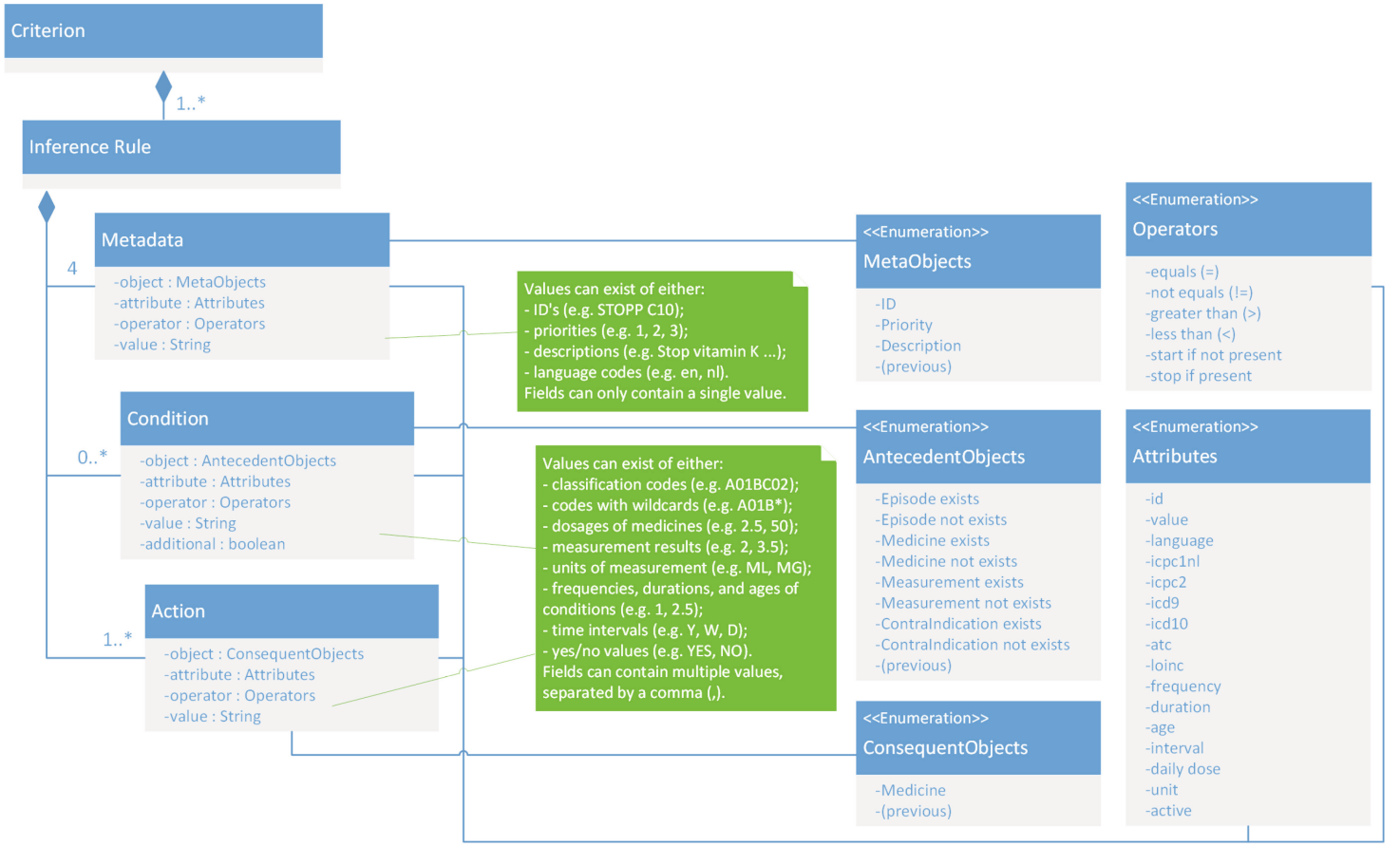

Table SI1.3. Metadata columns and their allowed objects, attributes, and operators.

#	Object	Attribute	Operator	Value Explanation
1	ID	value	equals (=)	Contains the STOPP- or START-criterion's key (e.g. STOPP C1).
	Contains the STOPP- or START-criterion's key (e.g. STOPP C1)			
2	Priority	value		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.
3	Description	value		Contains the STOPP- or START-criterion's English description (e.g. Stop vitamin K …).
4	(previous)	language		Contains the description's language; in all cases en.

Table SI1.4. Episode columns and their allowed objects, attributes, and operators.

#	Object	Attribute	Operator	Value Explanation
	Episode [not] exists	icpc1nl	equals (=), not equals (!=)	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*).
		icpc2		Contains one or more ICPC2 codes (e.g. *T90*), optionally with wildcards (e.g. *T90**), separated by commas (e.g. *T90, T91*).
		icd9		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*).
		icd10		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*).
		frequency	equals (=), not equals (!=), greater than (>), less than (<)	Contains a number indicating the frequency of the episode occurrence, for example for hypoglycaemic episodes (e.g. *1, 2*). Is always followed by *interval*.
		duration		Contains a number indicating how long the episode has been active (e.g. *1, 2*). Is always followed by *interval*.
		interval	equals (=)	Contains one of the following characters indicating a time interval: *Y (years), M (months), W (weeks)*. Always preceded by *frequency* or *duration*.
		active	equals (=), not equals (!=)	Contains a yes/no value indicating whether the episode is currently active or historical (i.e. *YES, NO*).

Table SI1.5. Medicine columns and their allowed objects, attributes, and operators.

#	Object	Attribute	Operator	Value Explanation
	Medicine [not] exists, Medicine	atc	equals (=), not equals (!=)	Contains one or more ATC codes (e.g. B01AC06), optionally with wildcards (e.g. B01A*), separated by commas (e.g. B01AC06, B01AC08).
		frequency	equals (=), not equals (!=), greater than (>), less than (<)	Contains a number indicating the frequency of the medicine prescription, for example for yearly vaccines (e.g. 1, 2). Is always followed by interval.
		duration		Contains a number indicating how long the medicine has been prescribed (e.g. 1, 2). Is always followed by interval.
		interval	equals (=)	Contains one of the following characters indicating a time interval: Y (years), M (months), W (weeks). Always preceded by frequency or duration.
		daily dose	equals (=), not equals (!=), greater than (>), less than (<)	Contains a number indicating the medicine's daily dosage (e.g. 2.5, 50). Is always followed by unit.
		unit	equals (=)	Contains one of the following abbreviations indicating a unit of measurement: G (gram), MG (milligram). Always preceded by daily dose.

Table SI1.6. Measurement columns and their allowed objects, attributes, and operators.

#	Object	Attribute	Operator	Value Explanation
	Measurement [not] exists	loinc	equals (=), not equals (!=)	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.
		value	equals (=), not equals (!=), greater than (>), less than (<)	Contains a number indicating the measurement's result (e.g. *60*).
		unit	equals (=)	Contains a unit of measurement (e.g. *mg/(24.h)*).
		age	equals (=), not equals (!=), greater than (>), less than (<)	Contains a number indicating the age of the measurement, for example for monthly repeated measurements (e.g. *1, 2*). Is always followed by *interval*.
		interval	equals (=)	Contains one of the following characters indicating a time interval: *Y (years), M (months), W (weeks)*. Always preceded by *age*.

Table SI1.7. STOPP/START criteria v2 encoded in ICPC1 (NL), ICPC2, ICD9, ICD10, ATC, AND LOINC.

START

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 (=) *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'*							

Table SI1.7. Continued.

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 (=) *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 (=) *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	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'*							

Table SI1.7. Continued.

STOPP

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	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)*							

value equals (=)	value equals (=)	value equals (=)	language equals (=)	loinc equals (=) *serum potassium*	value greater than (>) *greater than 5*	icd9 equals (=) *current hyperkalaemia*	icd10 equals (=) *current hyperkalaemia*	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*
STOPP C1	1	Stop long-term aspirin at doses greater than 160mg per day (increased risk of bleeding, no evidence	en	B01AC06	160	MG
	2			B01AC08	200	
Comments:	*'Long-term' not defined and therefore not coded. Equivalent dose of carbasalate calcium added.*					

Table SI1.7. Continued.

METADATA ID value equals (=)	METADATA Priority value equals (=)	METADATA Description value equals (=)	METADATA (previous) language equals (=)	ADDITIONAL CONDITION Episode not exists icd9 equals (=)	ADDITIONAL CONDITION Episode not exists icd10 equals (=)	ADDITIONAL CONDITION (previous) duration less than (<)	ADDITIONAL CONDITION (previous) interval equals (=)	CONDITION Medicine exists atc equals (=)	ACTION Medicine atc stop if present
				implant	*implant*		*12 months*	*Vit K antagonist, direct thrombin inhibitor or factor Xa inhibitors*	*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*					
	2				Z95.5	12	M	B01AA*, B01AE*, B01AF*	B01AC*
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	ACTION (previous) daily dose greater than (>)	ACTION (previous) unit equals (=)	ACTION (previous) duration greater than (>)	ACTION (previous) interval equals (=)
				PPI	*dosage*	*mg / day*	*duration*	*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.*							

The ten examples below were 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.

SUPPLEMENTARY INFORMATION SI2

Table SI2.1. Medical conditions in STOPP & START Criteria V2 Conversion.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Hypertension	Essential hypertension	401	I10	K86, K87	K86, K87	B6, H2	A4
Hypertension	Secondary hypertension	405	I15			B6, H2	A4
Hypertension	Elevated blood pressure			K85	K85	B6, H2	A4
Hypotension	Orthostatic hypotension	458	I95.1	K88	K88	I2, K3	
Hypotension	Chronische hypotensie	458,1	I95.8				
Hypotension	Iatrogene hypotensie	458,2	I95.2				
Hypotension	Other specified hypotension	458,8					
Hypotension	Unspecified hypotension	458,9	I95.9				
Hypotension	Idiopatic hypotension		I95.0				
Syncope	Syncope (excl. orthostatic hypotension)	780,2		A06	A06	D11, I2	
Syncope	Syncope/fainting (excl. micturition syncope)		R55				
Heart failure	Decompensatio cordis		I50	K77	K77	B1, B2, B6, B7 ,B9, B13, H2, J2	A6, A8
Heart failure	Decompensatio cordis	428				B1, B2, B6, B7 ,B9, B13, H2, J2	
Heart failure	Congestive heart failure, unspecified	428					
Heart failure	Left heart failure	428,1					
Heart failure	Systolic heart failure	428,2					A6, A8
Heart failure	Diastolic heart failure	428,3					
Heart failure	Combined systolic and diastolic heart failure	428,4					A6, A8
Heart failure	(Malignant) hypertensive heart disease with heart failure		I11.0			B1, B2, B6, B7, B9, B13, H2, J2	A6, A8

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Heart failure	(Malignant) hypertensive heart disease with heart failure	402,01				B1, B2, B6, B7, B9, B13, H2, J2	
Heart failure	Benign hypertensive heart disease with heart failure	402,11				B1, B2, B6, B7, B9, B13, H2, J2	
Heart failure	Unspecified hypertensive heart disease with heart failure	402,91				B1, B2, B6, B7, B9, B13, H2, J2	
Heart failure	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified	404,01				B1, B2, B6, B7, B9, B13, H2, J2	
Heart failure	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease	404,03				B1, B2, B6, B7, B9, B13, H2, J2	
Heart failure	Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified	404,11				B1, B2, B6, B7, B9, B13, H2, J2	
Heart failure	Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease	404,13				B1, B2, B6, B7, B9, B13, H2, J2	
Heart failure	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified	404,91				B1, B2, B6, B7, B9, B13, H2, J2	

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Heart failure	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease	404,93				B1, B2, B6, B7, B9, B13, H2, J2	
Heart failure	Hypertensive heart and renal disease with (congestive) heart failure		I13.0			B1, B2, B6, B7, B9, B13, H2, J2	A6, A8
Heart failure	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure		I13.2			B1, B2, B6, B7, B9, B13, H2, J2	A6, A8
Atrial fibrillation	Atrial fibrillation and flutter	427,3	I48	K78	K78	B1, B5, C8, C9	A3
Atrial fibrillation	Chronic atrial fibrillation	427,31	I48.2	K78	K78	C5	A1, A2
Atrial fibrillation	Sick sinus syndrome		I49.5	K80.03		B4, D11	
Atrial fibrillation	hartritmestoornissen nao				K80	B4, D11	
Atrial fibrillation	Other specified cardiac dysrhythmias (oa bradycardie en sick sinus syndrome)	427,8				B4, D11	
Atrial fibrillation	bradycardie		R00.1			B4, D11	
Atrial fibrillation	other heart disease (e.g. heart block)				K84	B4, D1, D11	
Atrial fibrillation	WPW syndrome			K84.01		D1	
Atrial fibrillation	Supraventricular tachyarrhytmias	427	I47.1	K79.01		B5	
Atrial fibrillation	Tachycardie				K79	B5	
Conduction disorders (major)	Conduction disorders	426				D1	
Conduction disorders (major)	Atrioventricular and left bundle-branch block		I44			D1	
Conduction disorders (major)	Other conduction disorders		I45			D1	

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Conduction disorders (minor)	Atrioventricular block, complete	426	I44.2			B4, D11	
Conduction disorders (minor)	Atrioventricular block, unspecified	426,1		K84.02		B4, D1, D11	
Conduction disorders (minor)	First degree atrioventricular block	426,11	I44.0				
Conduction disorders (minor)	Mobitz (type) II atrioventricular block	426,12	I44.1			B4, D11	
Conduction disorders (minor)	Other second degree atrioventricular block	426,13	I44.1			B4, D11	
Conduction disorders (minor)	Other heart block (oa sinoatrial block)	426,6	I45.5			B4, D11	
Conduction disorders (minor)	congenital heart block	746,86	Q24.6			B4, D11	
Conduction disorders (minor)	Other AV block		I44.3			B4, D11	
Conduction disorders (minor)	Conduction disorder specified (Heart block NOSStokes-Adams syndrome)	426,9	I45.9			B4, D11	
Conduction disorders (minor)	Long QT syndrome		I45.8	K84.07		D1	
Coronary artery disease	Acute myocardial infarction	410	I21	K75	K75	H7	A3, A5, A6, A7
Coronary artery disease	Subsequent myocardial infarction		I22			H7	A3, A5, A6, A7
Coronary artery disease	Old myocardial infarction	412	I25.2	K76.02		H7	A3, A5, A6, A7

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Coronary artery disease	Coronairsclerose			K76.01		H7	A3, A5, A6, A7
Coronary artery disease	Angina pectoris	413	I20	K74	K74	H7	A3, A5, A6, A7
Coronary artery disease	Other acute and subacute forms of ischemic heart disease	411	I24			H7	A3, A5, A6, A7
Coronary artery disease	Other forms of chronic ischemic heart disease	414	I25	K76	K76	H7	A3, A5, A6, A7
Coronary artery disease	Presence of aortocoronary bypass graft		Z95.1			H7	A3, A5, A6, A7
Coronary artery disease	Aortacoronary bypass status	V45.81				H7	A3, A5, A6, A7
Coronary artery disease	Bypass anastomosis for heart revascularisation	36,1				H7	A3, A5, A6, A7
Coronary artery disease	Presence of coronary angioplasty implant and graft		Z95.5			C4, H7	A3, A5, A6, A7
Coronary artery disease	Percutaneous transluminal coronary angioplasty status	V45.82				H7	A3, A5, A6, A7
Coronary artery disease	Insertion of coronary stent	36				C4, H7	A3, A5, A6, A7
Hemorrhagic CVA	Intracerebral hemorrhage	431	I61	K90.02		C3	
Hemorrhagic CVA	Other and unspecified intracranial hemorrhage	432				C3	
Hemorrhagic CVA	Other nontraumatic intracranial hemorrhage		I62			C3	
Hemorrhagic CVA	Subarachnoid haemorrhage	430	I60	K90.01		C3	
Ischaemic CVA	Cerebral infarction		I63	K90.03		C4	A3, A5

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Ischaemic CVA	Occlusion and stenosis of precerebral arteries (+/- infarction)	433				C4	A3, A5
Ischaemic CVA	Occlusion of cerebral arteries (+/- infarction)	434				C4	A3, A5
Unspecified CVA	Cerebrovascular accident (CVA)				K90	C3, C4	A3, A5
Unspecified CVA	Stroke, not specified as haemorrhage or infarction		I64			C3, C4	A3, A5
TIA	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction		I65				A3, A5
TIA	Occlusion of cerebral arteries, not resulting in cerebral infarction		I66				A3, A5
TIA	Transient cerebral ischemia	435	G45	K89	K89	C4	A3, A5
Peripheral vascular disease	Arterial embolism and thrombosis	444	I74				A3, A5
Peripheral vascular disease	Atheroembolism	445					A3, A5
Peripheral vascular disease	Peripheral vascular disease, unspecified (intermittent claudication)	443,9	I73.9	K92.01			A3, A5
Peripheral vascular disease	Aorta-iliac-femoral bypass	39,25	Z95.8				A3
Ankle oedema	Venous (peripheral) insufficiency, unspecified	459,81	I87.2			B7	
Ankle oedema	Oedema	782,3	R60			B7	
Ankle oedema	Ankle oedema			K07	K07	B7	
Gout	Gout	274	M10	T92	T92	B8, H6	E6
Lab Values	Hyperkaliemie	276,7	E87.5			B11	
Lab Values	Hypokaliemie	276,8	E87.6			B8	

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Lab Values	Hypercalciemie	275,42	E83.5			B8	
Lab Values	Hyponatriemie	276,1	E87.1			B8, D4	
Incontinence	Urine incontinence	788,3		U04	U04	B9	
Incontinence	Stress incontinence		N39.3			B9	
Incontinence	Other specified urinary incontinence (overflow/reflex/urge)		N39.4			B9	
Incontinence	Unspecified urinary incontinence		R32			B9	
Prostatism / urinary retention	Hypertrophy (benign) of prostate with urinary obstruction and other lower urinary tract symptoms	600,01					G1, G2
Prostatism / urinary retention	Nodular prostate with urinary obstruction	600,11					G1, G2
Prostatism / urinary retention	Benign localized hyperplasia of prostate with urinary obstruction and other lower urinary tract symptoms	600,21					G1, G2
Prostatism / urinary retention	Hyperplasia of prostate, unspecified, with urinary obstruction and other lower urinary symptoms	600,91					G1, G2
Prostatism / urinary retention	Hyperplasia of prostate	600	N40	Y85	Y85	D1, D3, G3, I1	G1, G2
Prostatism / urinary retention	Retention of urine	788,2	R33	U05.02	U08	D1, D3, G3, I1	G1, G2
Prostatism / urinary retention	Symptoms of prostate			Y06	Y06	G3, I1, D1, D3	G1, G2
Prostatectomy	Transurethral prostatectomy	60,2					G1, G2
Prostatectomy	Suprapubic prostatectomy	60,3					G1, G2

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Prostatectomy	Retropubic prostatectomy	60,4					G1, G2
Prostatectomy	Radical prostatectomy	60,5					G1, G2
Prostatectomy	Other prostatectomy	60,6					G1, G2
Risk of bleeding	Hereditary factor VIII deficiency	286	D66			C3	
Risk of bleeding	Hereditary factor IX deficiency	286,1	D67			C3	
Risk of bleeding	Von Willebrand's disease	286,4	D68.0			C3	
Risk of bleeding	Hemophilia A/B			B83.01		C3	
Risk of bleeding	Immune thrombocytopenic purpura	287,31	D69.3	B83.02		C3	
Risk of bleeding	Purpura				B83	C3	
Risk of bleeding	Bleeding NAO			A10	A10	C3	
Thrombosis	Phlebitis and thrombophlebitis	453,4		K94.01	K94	C8, C9, J4	
Thrombosis	Phlebitis and thrombophlebitis	451	I80				
Thrombosis	Phlebitis and thrombophlebitis of femoral vein		I80.1				
Thrombosis	Phlebitis and thrombophlebitis of other deep vessels of lower extremities (Deep vein thrombosis NOS)		I80.2			C8, C9, J4	
Thrombosis	Phlebitis and thrombophlebitis of lower extremities, unspecified (Embolism or thrombosis of lower extremity NOS)		I80.3				
Thrombosis	Phlebitis and thrombophlebitis of other sites		I80.8				
Thrombosis	Phlebitis and thrombophlebitis of unspecified site		I80.9				
Thrombosis	Other venous embolism and thrombosis		I82			J4	
Thrombosis	Embolism and thrombosis of vena cava	453,2	I82.2				
Thrombosis	Embolism and thrombosis of renal vein	453,3	I82.3				

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Thrombosis	Embolism and thrombosis of other specified veins		I82.8			C8, C9	
Thrombosis	Embolism and thrombosis of unspecified vein		I82.9			C8, C9	
Thrombosis	Other venous embolism and thrombosis	453				J4	
Thrombosis	Budd-chiari syndrome	453	I82.0				
Thrombosis	Chronic venous embolism and thrombosis of deep vessels of lower extremity	453,5					
Thrombosis	Chronic venous embolism and thrombosis of other specified vessels	453,7					
Thrombosis	Acute venous embolism and thrombosis of deep veins of upper extremity	453,82				C8, C9	
Thrombosis	Other venous embolism and thrombosis of unspecified site	453,9				C8, C9	
Thrombosis	Portal vein thrombosis	452	I81			J4	
Thrombosis	Phlebitis and thrombophlebitis of intracranial venous sinuses	325	G08				
Pulmonary embolism	Pulmonary embolism	415,1	I26	K93	K93	C8, C9, J4	
Peptic ulcer disease	Ulcer of esophagus	530,2	K22.1			C2, H1, H9	
Peptic ulcer disease	Gastric ulcer	531	K25			C2, H1, H9	
Peptic ulcer disease	Duodenal ulcer	532	K26	D85	D85	C2, H1, H9	
Peptic ulcer disease	Peptic ulcer site unspecified	533	K27	D86	D86	C2, H1, H9	
Peptic ulcer disease	Gastrojejunal ulcer	534	K28			C2, H1, H9	
GI blood loss	Haematemesis	578	K92.0	D14	D14	C3, H1, H9	
GI blood loss	Melaena	578,1	K92.1	D15	D15	C3, H1, H9	
GI blood loss	Gastrointestinal haemorrhage	578				H1, H9	
GI blood loss	Rectal bleeding			D16	D16	C3, H1	

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
GI blood loss	Hemorrhage of gastrointestinal tract, unspecified	578,9	K92.2			C3, H1, H9	
Upper gastro-intestinal disease	Diseases of esophagus	530				H9	
Upper gastro-intestinal disease	Esophagitis	530,1	K20			H9	
Upper gastro-intestinal disease	Reflux esophagitis	530,11	K21.0	D84.03		H9	D1
Upper gastro-intestinal disease	Stricture and stenosis of esophagus	530,3	K22.2	D84.05		H9	D1
Upper gastro-intestinal disease	Perforation of esophagus	530,4	K22.3			H9	
Upper gastro-intestinal disease	(other) disease of oesophagus		K22		D84	H9	D1
Upper gastro-intestinal disease	Gastro-oesophageal reflux disease		K21			H9	D1
Upper gastro-intestinal disease	Esophageal reflux	530,81		D84.02		H9	D1
Upper gastro-intestinal disease	Barrett's esophagus	530,85	K22.7			H9	D1
Upper gastro-intestinal disease	Gastritis and duodenitis	535	K29	D87.01		H9	
Upper gastro-intestinal disease	Functional dyspepsia	536,8	K30	D87.02	D07	H9	
Upper gastro-intestinal disease	Disorders of function of stomach	536		D87	D87	H9	

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Upper gastro-intestinal disease	Other disorders of stomach and duodenum	537	K31			H9	
Upper gastro-intestinal disease	Gastrointestinal mucositis (ulcerative)	538				H9	
Upper gastro-intestinal disease	Dysphagia	787,2	R13	D21	D21	H9	
Upper gastro-intestinal disease	Heartburn	787,1	R12			H9	
Upper gastro-intestinal disease	Pain localized to upper abdomen (dyspepsia NOS, epigastric pain)		R10.1			H9	
Upper gastro-intestinal disease	Disorders of oesophagus in diseases classified elsewhere (e.g. tuberculous oesophagitis)		K23			H9	
Upper gastro-intestinal disease	Abdominal pain			D02	D02	H9	
Upper gastro-intestinal disease	Heartburn			D03	D03	H9	
Dementia	Dementias	290		P70	P70	D1, D8, D9, D10, I1	
Dementia	Alcohol-induced persisting amnestic disorder	291,1				D1, D8, D9, D10, I1	
Dementia	Alcohol-induced persisting dementia	291,2				D1, D8, D9, D10, I1	
Dementia	Drug induced persisting dementia	292,82				D1, D8, D9, D10, I1	

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Dementia	Dementia in conditions classified elsewhere	294,1	F02			D1, D8, D9, D10, I1	
Dementia	Dementia, unspecified	294,2	F03			D1, D8, D9, D10, I1	
Dementia	Alzheimer's disease	331	F00, G30	P70.01	(P70)	D1, D8, D9, D10, I1	C3
Dementia	Frontotemporal dementia	331,1				D1, D8, D9, D10, I1	
Dementia	Senile degeneration of brain (not elsewhere classified)	331,2	G31.1			D1, D8, D9, D10, I1	
Dementia	Dementia with lewy bodies	331,82				D1, D8, D9, D10, I1	C3
Dementia	Mild cognitive impairment	331,83				D1, D8, D9, D10, I1	
Dementia	Vascular dementia		F01			D1, D8, D9, D10, I1	
Dementia	Other specified degenerative diseases of nervous system (e.g. lewy bodies dementia/ disease)		G31.8			D1, D8, D9, D10, I1	C3
Dementia	Circumscribed brain atrophy (e.g. frontotemporal dementia)		G31.0			D1, D8, D9, D10, I1	
Dementia	amnestic/concentration/ orientation disorder			P20	P20	D1, D8, D9, D10, I1	
Psychotic disorders	Personality and behavioural disorders due to brain disease, damage and dysfunction		F07*			D9	

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Psychotic disorders	Delirium	293.0, 293.1	F05*	P71.04		D8	
Psychotic disorders	Organic psychosis other				P71	D8	
Psychotic disorders	psychotic disorder NOS	298,9	F29	P98	P98	D9, D10	
Psychotic disorders	schizophrenic disorders	295	F20, F25	P72	P72	D9, D10	
Glaucoma	Glaucoma	365	H40	F93	F93		
Glaucoma	Glaucoma in diseases classified elsewhere		H42				
Glaucoma	Glaucoma (unspecified)				F93	I1, G3	C4
Glaucoma	(primary) open-angle glaucoma	365,1	H40.1	F93.03			C4
Glaucoma	Primary angle-closure glaucoma	365,2	H40.2	F93.02		I1, G3	
Glaucoma	Borderline glaucoma	365					
Parkinson/ parkinsonism	Parkinson's disease	332	G20	N87.01	N87	D6, D13, F1	C1
Parkinson/ parkinsonism	Paralysis agitans	332				D6, D13, F1	C1
Parkinson/ parkinsonism	Secondary parkinsonism	332,1	G21	N87	N87	D6, D13, F1	
Parkinson/ parkinsonism	Corticobasal degeneration	331,6				D6, D13, F1	
Parkinson/ parkinsonism	Progressive supranuclear ophthalmoplegia [PSP]		G23.1			D6, D13, F1	
Parkinson/ parkinsonism	Multiple system atrophy, parkinsonian type [MSA-P]		G23.2			D6, D13, F1	
Parkinson/ parkinsonism	Dementia with lewy bodies (incl. dementia with parkinsonism)	331,82				D6, D13, F1	
Parkinson/ parkinsonism	other degenerative diseases of the basal ganglia (PSP/MSA)	333				D6, D13, F1	

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Parkinson/ parkinsonism	Other specified degenerative diseases of nervous system (e.g. lewy bodies dementia/ disease)		G31.8			D6, D13, F1	
Benign essential tremor	Abnormal involuntary movements	781			N08	D13	
Benign essential tremor	Essential tremor		G25.0			D13	
Benign essential tremor	Sensation disturbance other			N06		D13	
Renal failure	Acute kidney/renal failure	584	N17				
Renal failure	Chronic kidney disease	585	N18				
Renal failure	Renal failure, unspecified	586	N19				
Renal failure	Urinary disease, other				U99		
Renal failure	Renal failure			U99.01			
Renal failure	Chronic kidney disease stage III GFR 30-59	585,3	N18.3			E4	
Renal failure	Chronic kidney disease stage IV GFR <30	585,4	N18.4			E1, E2, E4, E6	
Renal failure	Chronic kidney disease stage V GFR < 15	585,5	N18.5			E1, E2, E3, E4, E5, E6	
Renal failure	End stage renal disease	585,6				E1, E2, E3, E4, E5, E6	
COPD	Bronchitis, not specified as acute or chronic	490	J40			G2	B1, B2
COPD	Chronic bronchitis	491	J42	R91.01		G2	B1, B2
COPD	Emphysema	492	J43			G2	B1, B2
COPD	Emphysema/COPD			R95		G2	B1, B2
COPD	Chronic bronchitis/ bronchiectasis			R91		G2	B1, B2
COPD	Chronic airway obstruction, not elsewhere classified	496				G2	B1, B2

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
COPD	Simple and mucopurulent chronic bronchitis		J41			G2	B1, B2
COPD	Other chronic obstructive pulmonary disease		J44		R95	G2	B1, B2
Asthma	Asthma	493	J45	R96	R96		B1, B2
Asthma	Status asthmaticus	493.01, 493.11, 493.21, 493.91	J46				B1, B2
Asthma / COPD exacerbations	Asthma with (acute) exacerbation	493.02, 493.12, 493.22, 493.92					B2
Asthma / COPD exacerbations	Chronic obstructive pulmonary disease with acute exacerbation	491.21, 491.22	J44.1				B2
Asthma / COPD exacerbations							
Pulmonary insufficiency	Pulmonary insufficiency following trauma and surgery (acute and chronic)	518,5				G4	B3
Pulmonary insufficiency	Other diseases of lung (acute and chronic respiratory failure)	518. 81/82 /83/84				G4	B3
Pulmonary insufficiency	Asphyxia (and hypoxemia)	799	R09.0			G4	B3
Pulmonary insufficiency	Postprocedural respiratory disorders, not elsewhere classified		J95			G4	
Pulmonary insufficiency	Postprocedural respiratory disorders, not elsewhere classified (acute and chronic pulmonary insufficiency)		J95.1 /2/3			G4	B3
Pulmonary insufficiency	Respiratory failure, not elsewhere classified (acute and chronic)		J96			G4	B3

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Diabetes mellitus	Diabetes mellitus	250		T90		J3	A4, F1
Diabetes mellitus	DM type 1		E10	T90.01		J3	A4, F1
Diabetes mellitus	DM type 2		E11	T90.02		J3	A4, F1
Diabetes mellitus	Insulin-dependent DM				T89	J3	A4, F1
Diabetes mellitus	Non-insulin-dependent DM				T90	J3	A4, F1
Diabetes mellitus	Hypoglycemia			T87	T87	J3	
Diabetes mellitus	Malnutrition-related diabetes mellitus		E12			J3	A4, F1
Diabetes mellitus	Other specified diabetes mellitus		E13			J3	A4, F1
Diabetes mellitus	Unspecified diabetes mellitus		E14			J3	A4, F1
Diabetes mellitus	Hypoglycemic coma	251				J3	
Diabetes mellitus	Other specified hypoglycemia	251,1				J3	
Diabetes mellitus	Hypoglycemia, unspecified	251,2	E16.2			J3	
Diabetes mellitus	Drug-induced hypglycemia without coma		E16.0			J3	
Diabetes mellitus	Other hypoglycaemia		E16.1			J3	
Diabetes with renal manifestations	Diabetes with renal manifestations	250,4	E10.2, E11.2, E12.2, E13.2, E14.2				F1
Diabetes with renal manifestations	Glomerular disorders in diabetes mellitus		N08.3				F1
Diabetes with renal manifestations	Proteinuria	791	R80	U98.01	U98		F1
Malignancy	Malignant neoplasm of female breast	174	C50	X76	X76	J4	
Malignancy	Carcinoma in situ of breast	233	D05			J4	
Hypogonadism	Postablative testicular hypofunction	257,1				J6	

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Hypogonadism	Other testicular hypofunction	257,2				J6	
Hypogonadism	Klinefelter's syndrome	758,7				J6	
Hypogonadism	Testicular hypofunction		E29.1			J6	
Hypogonadism	Postprocedural testicular hypofunction		E89.5			J6	
Hypogonadism	Klinefelter syndrome karyotype 47, XXY		Q98.0			J6	
Hypogonadism	Klinefelter syndrome, male with more than two X-chromosomes		Q98.1			J6	
Hypogonadism	Klinefelter syndrome, male with 46, XX karyotype		Q98.2			J6	
Hypogonadism	Klinefelter syndrome, unspecified		Q98.4			J6	
Depressive symptoms	Depression			P76	P76	D2	C2
Depressive symptoms	Major depressive disorder single episode	296,2				D2	C2
Depressive symptoms	Major depressive disorder recurrent episode	296,3				D2	C2
Depressive symptoms	Depressive episode		F32			D2	C2
Depressive symptoms	Recurrent depressive disorder		F33			D2	C2
Anxiety	Anxiety			P74	P74		C5
Anxiety	Anxiety states	300					C5
Anxiety	Other anxiety disorders		F41				C5
Anxiety	Phobia	300,2	F40				C5
Restless legs syndrome	Restless legs syndrome	333,94		N04	N04		C6
Restless legs syndrome	Other specified extrapyramidal and movement disorders (restless legs syndrome)		G25.8				C6
Obstipation	Constipation	564	K59.0	D12	D12	F3	D2
Diverticulosis	Diverticulosis/diverticulitis	562	K57	D92	D92		D2

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Rheumatoid arthritis	Rheumatoid arthritis	714		L88	L88	H4	E1
Rheumatoid arthritis	Other rheumatoid arthritis with visceral or systemic involvement	714,2				H4	E1
Rheumatoid arthritis	Felty's syndrome	714,1	M05.0			H4	E1
Rheumatoid arthritis	seropositive rheumatoid arthritis		M05			H4	E1
Rheumatoid arthritis	Other rheumatoid arthritis		M06			H4	E1
Osteopenia	Disorder of bone and cartilage, unspecified (osteopenia)	733,9					E5
Osteopenia	Osteopenia			L95.01			E5
Osteoporosis	Osteoporosis	733		L95.02	L95		E3, E4
Osteoporosis	Osteoporosis with pathological fracture		M80				E3, E4
Osteoporosis	osteoporosis without pathological fracture		M81				E3, E4
Possible osteoporotic fractures	Pathologic fracture	733,1					E3, E4
Possible osteoporotic fractures	Fractuur radius/ulna			L72	L72		E3, E4
Possible osteoporotic fractures	Fractuur tibia/fibula			L73	L73		E3, E4
Possible osteoporotic fractures	Fractuur hand/foot			L74	L74		E3, E4
Possible osteoporotic fractures	Fractuur colllum femoris			L75	L75		E3, E4
Possible osteoporotic fractures	Fractuur clavicula/humerus/rib/colon/pelvis/ patella			L76.03 - L76.08	L76		E3, E4

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Possible osteoporotic fractures	Fracture of spine and trunk	805-809					E3, E4
Possible osteoporotic fractures	Fracture of upper limb	810-819					E3, E4
Possible osteoporotic fractures	Fracture of lower limb	820-829					E3, E4
Possible osteoporotic fractures	Fracture of neck		S12				E3, E4
Possible osteoporotic fractures	fracture of rib(s), sternum and thoracic spine		S22				E3, E4
Possible osteoporotic fractures	fracture of lumbar spine and pelvis		S32				E3, E4
Possible osteoporotic fractures	fracture of shoulder and upper arm		S42				E3, E4
Possible osteoporotic fractures	fracture of forearm		S52				E3, E4
Possible osteoporotic fractures	fracture at wrist and handlevel		S62				E3, E4
Possible osteoporotic fractures	fracture of femur		S72				E3, E4
Possible osteoporotic fractures	fracture of lower leg, including ankle		S82				E3, E4
Possible osteoporotic fractures	fracture of foot except ankle		S92				E3, E4

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Possible osteoporotic fractures	fractures involving multiple body regions		T02				E3, E4
Possible osteoporotic fractures	fracture of spine, level unspecified		T08				E3, E4
Possible osteoporotic fractures	fracture of upper limb, level lunspecified		T10				E3, E4
Possible osteoporotic fractures	fracture of lower limb, level lunspecified		T12				E3, E4
Possible osteoporotic fractures	fracture of unspecified body region		T14.2				E3, E4
Falls	Trauma/injury			A80	A80		E5
Falls	Accidental fall on or from stairs or steps	E880					E5
Falls	Other accidental falls from one level to another	E884					E5
Falls	Fracture, cause unspecified	E887					E5
Falls	Other and unspecified fall	E888					E5
Falls	Tendency to fall, not elsewhere classified		R29.6				E5
Falls	Immobility		R26.3				E5
Falls	Fall on same level from slipping, tripping and stumbling		W01				E5
Falls	Fall involving wheelchair		W05				E5
Falls	Fall involving bed		W06				E5
Falls	Fall involving chair		W07				E5
Falls	Fall involving other furniture		W08				E5
Falls	Fall on and from stairs and steps		W10				E5

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Falls	Other fall on same level		W18				E5
Falls	Unspecified fall		W19				E5
Arthrosis	osteoarthrosis and allied disorders	715				H3, H5	
Arthrosis	artrosis spine			L84.01		H3, H5	
Arthrosis	coxartrosis		M16	L89	L89	H3, H5	
Arthrosis	gonartrosis		M17	L90	L90	H3, H5	
Arthrosis	other artrosis		M19	L91		H3, H5	
Arthrosis	polyarthrosis		M15			H3, H5	
Arthrosis	Arthrosis of first carpometacarpal join		M18			H3, H5	
Arthrosis	Spondylosis (incl: arthrosis of spine)		M47			H3, H5	
Arthrosis	Osteoarthrosis other				L91	H3, H5	
Vaginitis	atrofic vaginitis			X11.02			G3
Vaginitis	vaginitis/vulvitis nao			X84	X84		G3
Vaginitis	Postmenopausal atrophic vaginitis	627,3	N95.2				G3
Hysterectomy	Acquired absence of genital organs		Z90.7			J5	
Hysterectomy	Subtotal abdominal hysterectomy	68,3				J5	
Hysterectomy	Total abdominal hysterectomy	68,4				J5	
Hysterectomy	Radical abdominal hysterectomy	68,6				J5	
Hysterectomy	Radical vaginal hysterectomy	68,7				J5	
Hysterectomy	Other unspecified hysterectomy	68,9				J5	
Hysterectomy	Sleeping disorder			P06	P06	D9, D10	
Hysterectomy	Nonorganic sleep disorder, unspecified	307,4				D9, D10	
Hysterectomy	Transient disorder of initiating or maintaining sleep	307,41				D9, D10	

Table SI2.1. Continued.

Medical condition	Description	ICD9	ICD10	ICPC1	ICPC2	STOPP Criteria	START Criteria
Hysterectomy	Persistent disorder of initiating or maintaining sleep	307,42				D9, D10	
Hysterectomy	Organic disorders of initiating and maintaining sleep [organic insomnia]	327				D9, D10	
Hysterectomy	Disorders of initiating and maintaining sleep [insomnias]		G47.0			D9, D10	
Hysterectomy	Nonorganic insomnia		F51.0			D9, D10	
Pain	Pain, not elsewhere classified	338	R52				H1
Pain	Generalized pain	780,96		A01	A01		H1

Table SI2.2. Medications in STOPP & START Criteria V2 Conversion.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Antidepressants	N06AA	Non-selective monoamine reuptake inhibitors	N, D1, D2		
Antidepressants	N06AB	Selective serotonin reuptake inhibitors	A3, D2, D4	C2, C5	
Antidepressants	N06AF	Monoamine oxidase inhibitors, non-selective		C2	
Antidepressants	N06AG	Monoamine oxidase A inhibitors		C2	
Antidepressants	N06AX	Other antidepressants	D2	C2	
Antidepressants	N06AX16	venlafaxine		C5	
Psycholeptics and psychoanaleptics combinations	N06CA01	amitriptyline and Psycholeptics	D1, D2		
Psycholeptics and psychoanaleptics combinations	N06CA02	melitracen and Psycholeptics	D1, D2		
Psycholeptics and psychoanaleptics combinations	N06CA03	fluoxetine and Psycholeptics	A3, D2, D4	C2, C5	
Antidepressants	N06AX21	duloxetine		C5	
Other anti-epileptics	N03AX16	pregabaline		C5	
Antiinflammatory and antirheumatic products, non-steroids	M01A	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	A3, C10, C11, E4, H2, H3, H6, H8, L1	H1	
Antiinflammatory and antirheumatic products, non-steroids	M01AA	Butylpyrazolidines	H1	H1	

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Antiinflammatory and antirheumatic products, non-steroids	M01AB	Acetic acid derivatives and related substances	H1	H1	
Antiinflammatory and antirheumatic products, non-steroids	M01AC	Oxicams	H1	H1	
Antiinflammatory and antirheumatic products, non-steroids	M01AE	Propionic acid derivatives	H1	H1	
Antiinflammatory and antirheumatic products, non-steroids	M01AG	Fenamates	H1	H1	
Antiinflammatory and antirheumatic products, non-steroids	M01AH	Coxibs	H7	H1	
Antiinflammatory and antirheumatic products, non-steroids	M01AX	Other anti-inflammatory and antirheumatic agents, non-steroids	H1	H1	
Salicylic acid and derivatives	N02BA	OTHER ANALGESICS AND ANTIPYRETICS	A3, C10, C11, H1, H3, H6, H8, L1		
Salicylic acid and derivatives	N02BA01	acetylsalicylic acid	C2	H1	
Salicylic acid and derivatives	N02BA15	carbasalate calcium	C2	H1	
Salicylic acid and derivatives	N02BA51	acetylsalicylic acid, combinations excl. Psycholeptics	C2	H1	
Salicylic acid and derivatives	N02BA65	carbasalate calcium combinations excl. Psycholeptics	C2	H1	

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Salicylic acid and derivatives	N02BA71	acetylsalicylic acid, combinations with Psycholeptics	C2	H1	
Antiinflammatory and antirheumatic agents, combinations with steroids	M01BA	Antiinflammatory/ antirheumatic agents in combination with corticosteroids	A3, C10, C11, H1, H3, H5, H6, H8, L1		
Antiinflammatory and antirheumatic agents, combinations with steroids	M01BA01	phenylbutazone and corticosteroids	E4, H2		
Antiinflammatory and antirheumatic agents, combinations with steroids	M01BA02	dipyrocetyl and corticosteroids			
Antiinflammatory and antirheumatic agents, combinations with steroids	M01BA03	acetylsalicylic acid and corticosteroids	C2		
HMG CoA reductase inhibitors, combinations	C10BX01	simvastatin and acetylsalicylic acid	C2		
HMG CoA reductase inhibitors, combinations	C10BX02	pravastatin and acetylsalicylic acid	C2		
HMG CoA reductase inhibitors, combinations	C10BX04	simvastatin, acetylsalicylic acid and ramipril	C2		
HMG CoA reductase inhibitors, combinations	C10BX05	rosuvastatin and acetylsalicylic acid	C2		
HMG CoA reductase inhibitors, combinations	C10BX06	atorvastatin, acetylsalicylic acid and ramipril	C2		
HMG CoA reductase inhibitors, combinations	C10BX08	atorvastatin and acetylsalicylic acid	C2		
Anilides	N02BE01	paracetamol	H3, L1		

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Anilides	N02BE51	paracetamol, combinations excl. Psycholeptics	H3, L1		
Anilides	N02BE71	paracetamol, combinations with Psycholeptics	H3, L1		
Opioids	N02A	OPIOIDS	F3, L2	H2	
Opioids	N02AA01	morphine	L1	H1	
Opioids	N02AA51	morphine, combinations	L1	H1	
Opioids	N02AA03	hydromorphine		H1	
Opioids	N02AA04	nicomorphine		H1	
Opioids	N02AA05	oxycodone	L1	H1	
Opioids	N02AA08	dihydrocodeine		H1	
Opioids	N02AA58	dihydrocodeine, combinations		H1	
Opioids	N02AA59	codeine, combinations excl. Psycholeptics		H1	
Opioids	N02AA79	codeine, combinations with pyscholeptics		H1	
Opioids	N02AB02	pethidine	L1	H1	
Opioids	N02AB52	pethidine, combinations excl. Psycholeptics	L1	H1	
Opioids	N02AB72	pethidine, combinations incl. Psycholeptics	L1	H1	
Opioids	N02AG03	pethidine and antispasmodics	L1	H1	
Opioids	N02AB03	fentanyl	L1	H1	

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Opioids	N02AC52	methadone, combinations excl. Psycholeptics	L1	H1	
Opioids	N02AD01	pentazocine	L1	H1	
Opioids	N02AD02	phenazocine	L1	H1	
Opioids	N02AE01	buprenorphine	L1	H1	
Opioids	N02AG01	morphine and antispasmodics		H1	
Opioids	N02AG04	hydromorphone and antispasmodics		H1	
Opioids	N02AX01	tilidine		H1	
Opioids	N02AX02	tramadol	L1	H1	
Opioids	N07BC01	buprenorphine	F3, L2	H1, H2	
Opioids	N07BC02	methadone	F3, L1, L2	H1, H2	
Opioids	N07BC05	levomethadone	F3, L2	H1, H2	
Opioids	N07BC06	diamorphine	F3, L1, L2	H1, H2	
Opioids	R05DA04	codeine	F3, L2	H2	
Laxatives	A06A	DRUGS FOR CONSTIPATION	L2	H2	
Laxatives	A02AA04	magnesium hydroxide	L2	H2	
Laxatives	A06AC	Bulk-forming laxatives		D2	
Proton pump inhibitors	A02BC	proton pump inhibitors	C2, C11, H1, H8	D1	
Proton pump inhibitors	A02BC01	omeprazole	F2		
Proton pump inhibitors	A02BC02	pantoprazole	F2		
Proton pump inhibitors	A02BC03	lansoprazole	F2		

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Proton pump inhibitors	A02BC04	rabeprazole	F2		
Proton pump inhibitors	A02BC05	esomeprazole	F2		
Proton pump inhibitors	A02BC06	dexlansoprazole	F2		
H2 antagonist	A02BA	H2 antagonist	H1		
Antiadrenergic agents, centrally acting	C02AB	Methyldopa	B10		
Antiadrenergic agents, centrally acting	C02AC	Imidazoline receptor agonists	B10		
Antihypertensives and diuretics	C02LC	Imidazoline receptor agonists in combination with diuretics	B10		
Antihypertensives and diuretics	C02LB	Methyldopa and diuretics in combination	B10		
Thiazides	C03A	THIAZIDE DIURETICS	B8	A4	
Sulfonamides	C03BA	Sulfonamides, plain	B8		
Thiazide combinations	C03EA01	hydrochlorothiazide and potassium sparing agents	B8		
Thiazide combinations	C03EA02	trichlormethiazide and potassium sparing agents	B8		
Thiazide combinations	C03EA07	cyclopenthiazide and potassium sparing agents	B8		
Thiazide combinations	C03EA13	bendroflumethiazide and potassium sparing agents	B8		
Thiazide combinations	C09DX01	valsartan, amlodipine and hydrochlorothiazide	B8		
Thiazide combinations	C09DX03	olmesartan medoxomil, amlodipine and hydrochloorthiazide	B8		

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Thiazide combinations	C09XA52	aliskiren and hydrochlorothiazide	B8		
Thiazide combinations	C09XA54	aliskiren, amlodipine and hydrochlorothiazide	B8		
Thiazide combinations	C07B	Beta blocking agents and thiazides	B8		
Thiazide combinations	C07D	Beta blocking agents, thiazides and other diuretics	B8		
Thiazide combinations	C09BA01	captopril/hydrochlorothiazide			*Not included, as WHO specifies these ATC codes as 'and diuretics' and not specific thiazide diuretics. However, in the Netherlands, these combinations all contain hydrochlorothiazide.
Thiazide combinations	C09BA02	enalapril/hydrochlorothiazide			
Thiazide combinations	C09BA03	lisinopril/hydrochloorthiazide			
Thiazide combinations	C09BA05	ramipril/hydrochlorothiazide			
Thiazide combinations	C09BA06	quinapril/hydrochlorothiazide			
Thiazide combinations	C09BA09	fosinopril/hydrochlorothiazide			
Thiazide combinations	C09DA01	losartan/hydrochlorothiazide			
Thiazide combinations	C09DA02	eprosartan/ hydrochlorothiazide			
Thiazide combinations	C09DA03	valsartan/hydrochlorothiazide			
Thiazide combinations	C09DA04	irbesartan/hydrochlorothiazide			
Thiazide combinations	C09DA06	candesartan/ hydrochlorothiazide			
Thiazide combinations	C09DA07	telmisartan/ hydrochlorothiazide			
Thiazide combinations	C09DA08	olmesartan/ hydrochlorothiazide			

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Loop diuretics	C03C	HIGH-CEILING DIURETICS	A3, B6, B7, B9		
Loop diuretics	C03EB	High-ceiling diuretics and potassium-sparing agents	A3, B6, B7, B9		
Potassium-sparing agents	C03DA	Aldosterone antagonists	B12		
Potassium-sparing agents	C03DB	Other potassium-sparing agents	B12		
Diuretics and potassium-sparing agents	C03EA	Low-ceiling diuretics and potassium-sparing agents		A4	
Beta blocking agents	C07	BETA BLOCKING AGENTS	B3, B4, D11, J3	A4, A7	
Beta blocking agents	C07AA	Beta blocking agents, non-selective			
Beta blocking agents	C07AG	Alpha and beta blocking agents	K3		
Beta blocking agents	C07BA	Beta blocking agents, non-selective, and thiazides			
Beta blocking agents	C07BG	Alpha and beta blocking agents and thiazides	K3		
Beta blocking agents	C07CA	Beta blocking agents, non-selective, and other diuretics			
Beta blocking agents	C07CG	Alpha and beta blocking agents and other diuretics	K3		

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Beta blocking agents	C07DA	Beta blocking agents, non-selective, thiazides and other diuretics			
Beta blocking agents	C07EA	Beta blocking agents, non-selective, and vasodilators			
Beta blocking agents	C07FA	Beta blocking agents, non-selective, and other antihypertensives			
Beta blocking agents, selective	C07AB07	bisoprolol		A8	
Beta blocking agents and calcium channel blockers	C07FB07	bisoprolol and amlodipine		A8	
Beta blocking agents, selective, and thiazides	C07BB07	bisoprolol and thiazides		A8	
Beta blocking agents, selective	C07AB12	nebivolol		A8	
Beta blocking agents and calcium channel blockers	C07FB12	nebivolol and amlodipine		A8	
Beta blocking agents, selective, and thiazides	C07BB12	nebivolol and thiazides		A8	
Beta blocking agents, selective	C07AB02	metoprolol		A8	
Beta blocking agents and calcium channel blockers	C07FB02	metoprolol and felodipine		A8	
Beta blocking agents, selective, combinations	C07CB02	metoprolol and other diuretics		A8	
Beta blocking agents, selective, and thiazides	C07BB02	metoprolol and thiazides		A8	

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Beta blocking agents, selective, combinations	C07BB52	metoprolol and thiazides, combinations		A8	
Alpha and beta blocking agents	C07AG02	carvedilol		A8	
Calcium channel blockers	C08	CALCIUM CHANNEL BLOCKERS	K3	A4	
Selective calcium channel blockers	C08DB01	diltiazem	B2, B3, D11		
Selective calcium channel blockers	C08DA01	verapamil	B2, B3, D11, F3		
Selective calcium channel blockers combinations	C09BB10	trandolapril and verapamil	B2, B3, D11, F3		
Selective calcium channel blockers	C08DA51	verapamil, combinations	B2, B3, D11, F3		
ACE Inhibitors/AT II antagonists	C09	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	B11, B12, K3	A4, A6	
ACE Inhibitors/AT II antagonists	C09A	ACE INHIBITORS, PLAIN	A3	F1	
ACE Inhibitors/AT II antagonists	C09B	ACE INHIBITORS, COMBINATIONS	A3	F1	
ACE Inhibitors/AT II antagonists	C09C	ANGIOTENSIN II ANTAGONISTS, PLAIN		F1	
ACE Inhibitors/AT II antagonists	C09D	ANGIOTENSIN II ANTAGONISTS, COMBINATIONS		F1	

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
ACE Inhibitors/AT II antagonists	C09X	OTHER AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM			
Nitrates	C01DA	Organic nitrates	B13		
Antithrombotic agents	B01A	ANTITHROMBOTIC AGENTS			
Vitamin K antagonists	B01AA	Vitamin K antagonists	A3, C3, C5, C6, C8, C9, C10	A1, A2	
Heparin group	B01AB	Heparin group	A3		
Platelet aggregation inhibitors excl. heparin	B01AC	Platelet aggregation inhibitors excl. heparin	C3, C6, C11	A3	
Platelet aggregation inhibitors excl. heparin	B01AC04	clopidogrel	C4	A3	
Platelet aggregation inhibitors excl. heparin	B01AC05	Ticlopidine	C7		
Platelet aggregation inhibitors excl. heparin	B01AC06	acetylsalicylic acid	C1, C2, C4, C5	A2, A3	
Platelet aggregation inhibitors excl. heparin	B01AC07	dipyridamole			
Platelet aggregation inhibitors excl. heparin	B01AC08	carbasalate calcium	C1, C2, C4, C5	A2, A3	
Platelet aggregation inhibitors excl. heparin	B01AC22	Prasugrel		A3	
Platelet aggregation inhibitors excl. heparin	B01AC24	Ticagrelor		A3	
Platelet aggregation inhibitors excl. heparin	B01AC30	combinations	C4, C5		

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Platelet aggregation inhibitors excl. heparin	B01AC56	acetylsalicylic acid, combinations with proton pump inhibitors	C4, C5, C11	A2	
Direct thrombin inhibitors	B01AE	Direct thrombin inhibitors	A3, C3, C5, C6, C8, C9, C10, E2	A1, A2	
Direct factor Xa inhibitors	B01AF	Direct factor Xa inhibitors	A3, C3, C5, C6, C8, C9, C10, E3	A1, A2	
Other antithrombotic agents	B01AX	Other antithrombotic agents	A3		
Phosphodiesterase type 5 inhibitors	G04BE	Drugs used in erectile dysfunction			
Phosphodiesterase type 5 inhibitors	G04BE03	Sildenafil	B13		
Phosphodiesterase type 5 inhibitors	G04BE08	Tadalafil	B13		
Phosphodiesterase type 5 inhibitors	G04BE09	Vardenafil	B13		
Phosphodiesterase type 5 inhibitors	G04BE10	Avanafil	B13		
Cardiac glycosides	C01AA05	digoxin	B1, D11, E1		
Antigout preparations	M04AC01	colchicine	E5, H6		
Antipsychotics	N05AB04	prochlorperazine	F1		
Drugs for functional gastrointestinal disorders	A03FA01	metoclopramide	F1		
Antiarrhythmics class III	C01BD01	amiodarone	B5		

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Psycholeptics	N05AF01	flupenthixol	D3		Psycholeptics with moderate-marked antimuscarinic/ anticholinergic effects (as in STOPP D3)
Psycholeptics	N05AH02	clozapine	D3		
Psycholeptics	N05AA01	chlorpromazine	D3		
Psycholeptics	N05AB02	fluphenazine	D3		
Psycholeptics	N05AC04	pipothiazine	D3		
Psycholeptics	N05AA03	promazine	D3		
Psycholeptics	N05AF05	zuclopenthixol	D3		
Psycholeptics	N05A	ANTIPSYCHOTICS	D6, D7, D9, D10, K2		
Psycholeptics	N05AA	Phenothiazines with aliphatic side-chain	D12		
Psycholeptics	N05AB	Phenothiazines with piperazine structure	D12		
Psycholeptics	N05AC	Phenothiazines with piperidine structure	D12		
Psycholeptics	N05AX07	prothipendyl	D12		
Psycholeptics	N05AH04	quetiapine	D6		
Psycholeptics	N05AH02	clozapine	D6		
Psycholeptics	N05AN	lithium	D6, D7, D9, D10, K2		
Benzodiazepines	N05BA	Benzodiazepine derivatives	D5, G4, K1		
Benzodiazepines	N05CD	Benzodiazepine derivatives	D5, G4, K1		

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Benzodiazepines	N05CF	Benzodiazepine related drugs (Z-drugs)	D5, G4, K4		
Benzodiazepines	N03AE	Benzodiazepine derivatives	D5, G4, K1		
Anti-dementia drugs	N06DA	Anticholinesterases	D11	C3	
Dopaminergic agents	N04B	DOPAMINERGIC AGENTS	D13	C1	
Dopamine agonist	N04BC04	ropinirole		C6	
Dopamine agonist	N04BC05	pramipexole		C6	
Dopamine agonist	N04BC09	rotigotine		C6	
Anticholinergic agents	N04A	anticholinergic anti-parkinson drugs	D7		
Blood glucose lowering drugs, excl. insulins	A10BA02	Metformin	E6		
Blood glucose lowering drugs, excl. insulins	A10BD02	metformin and sulfonylureas	E6		
Blood glucose lowering drugs, excl. insulins	A10BD03	metformin and rosiglitazone	E6		
Blood glucose lowering drugs, excl. insulins	A10BD05	metformin and pioglitazone	E6		
Blood glucose lowering drugs, excl. insulins	A10BD07	metformin and sitagliptin	E6		
Blood glucose lowering drugs, excl. insulins	A10BD08	metformin and vildagliptin	E6		
Blood glucose lowering drugs, excl. insulins	A10BD10	metformin and saxagliptin	E6		
Blood glucose lowering drugs, excl. insulins	A10BD11	metformin and linagliptin	E6		
Blood glucose lowering drugs, excl. insulins	A10BD13	metformin and alogliptin	E6		
Blood glucose lowering drugs, excl. insulins	A10BD14	metformin and repaglinide	E6		
Blood glucose lowering drugs, excl. insulins	A10BD15	metformin and dapagliflozin	E6		
Blood glucose lowering drugs, excl. insulins	A10BD16	metformin and canagliflozin	E6		

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Blood glucose lowering drugs, excl. insulins	A10BD17	metformin and acarbose	E6		
Blood glucose lowering drugs, excl. insulins	A10BD18	metformin and gemigliptin	E6		
Blood glucose lowering drugs, excl. insulins	A10BD22	metformin and evogliptin	E6		
Sulfonylureas (with a long duration of action)	A10BB01	glibenclamide	J1		
Sulfonylureas (with a long duration of action)	A10BB02	chlorpropamide	J1		
Sulfonylureas (with a long duration of action)	A10BB12	glimepiride	J1		
Sulfonylureas (with a long duration of action)	A10BD06	glimepiride + pioglitazone	J1		
Sulfonylureas (with a long duration of action)	A10BD04	glimepiride + rosiglitazone	J1		
Drugs for obstructive airway diseases	R03A	ADRENERGICS, INHALANTS	G1		
Drugs for obstructive airway diseases	R03BA	Glucocorticoids (inhalants)	G1, G2	B2	
Drugs for obstructive airway diseases	R03BB	Anticholinergics (inhalants)	G1, G3	B1	
Drugs for obstructive airway diseases	R03DA04	theophylline	G1		
Drugs for obstructive airway diseases	R03AC	Selective beta 2 adrenoreceptor agonist.		B1	
Anticholinergics (inhalants)	R03BB01	ipratropium bromide			
Anticholinergics (inhalants)	R03BB04	tiotropium bromide			
Anticholinergics (inhalants)	R03BB54	tiotropium bromide, combinations			
adrenergics (inhalants) in combination with other drugs, excl. anticholinergics	R03AK04	salbutamol and sodium cromoglicate		B1	
adrenergics (inhalants) in combination with other drugs, excl. anticholinergics	R03AK05	reproterol and sodium cromoglicate		B1	

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
adrenergics (inhalants) in combination with corticosteroids or other drugs, excl. anticholinergics	R03AK06	salmeterol and fluticasone		B1, B2	Only combinations with adrenergics, combinations with 'epinephrine' and 'isoprenaline' excluded
adrenergics (inhalants) in combination with corticosteroids or other drugs, excl. anticholinergics	R03AK07	formoterol and budesonide		B1, B2	
adrenergics (inhalants) in combination with corticosteroids or other drugs, excl. anticholinergics	R03AK08	formoterol and beclometasone		B1, B2	
adrenergics (inhalants) in combination with corticosteroids or other drugs, excl. anticholinergics	R03AK09	formoterol and mometasone		B1, B2	
adrenergics (inhalants) in combination with corticosteroids or other drugs, excl. anticholinergics	R03AK10	vilanterol and fluticasone furoate		B1, B2	
adrenergics (inhalants) in combination with corticosteroids or other drugs, excl. anticholinergics	R03AK11	formoterol and fluticasone		B1, B2	
adrenergics (inhalants) in combination with corticosteroids or other drugs, excl. anticholinergics	R03AK12	salmeterol and budesonide		B1, B2	

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
adrenergics (inhalants) in combination with corticosteroids or other drugs, excl. anticholinergics	R03AK13	salbutamol and beclometasone		B1, B2	
Drugs for obstructive airway diseases	R03AL	adrenergics (inhalants) in combination with anticholinergics		B1	
Corticosteroids (systemic)	H02A	corticosteroids for systemic use, plain	H8		
Corticosteroids (systemic)	H02B	corticosteroids for systemic use, combinations	H8		
Corticosteroids (systemic)	N02CB01	flumedroxone (antimigraine preparation/corticosteroid derivative)	H8		
Corticosteroids (systemic)	H02AB	glucocorticoids for systemic use	H4, H5, H8	E2	
Corticosteroids (systemic)	H02BX01	methylprednisolone, combinations	H4, H5, H8, G2		
Corticosteroids (systemic)	H02AB01	betamethasone	G2		
Corticosteroids (systemic)	H02AB02	dexamethasone	G2		
Corticosteroids (systemic)	H02AB04	methyl-prednisolone	G2		
Corticosteroids (systemic)	H02AB06	prednisolone	G2		
Corticosteroids (systemic)	H02AB07	prednisone	G2		
Corticosteroids (systemic)	H02AB08	triamcinolone	G2		

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Corticosteroids (systemic)	H02AB09	hydrocortisone	G2		
Antiglaucoma preparations	S01EE	Prostaglandin analogues		C4	
Antiglaucoma preparations	S01ED	Betablocking agents		C4	
Antiglaucoma preparations	S01ED01	timolol			
Antiglaucoma preparations	S01ED51	timolol combinations			
Antiglaucoma preparations	S01ED05	carteolol			
Antiglaucoma preparations	S01ED55	carteolol combinations			
Antiglaucoma preparations	S01ED03	levobunolol			
Antiglaucoma preparations	S01ED04	metipranolol			
Antiglaucoma preparations	S01ED54	metipranolol combinations			
Antiglaucoma preparations	S01ED06	befunolol			
Bisphosphonates	M05BA	BISPHOSHONATES		E2	
Bisphosphonates	M05BA01	Etidronic acid	H9		*can be either oral or parenteral
Bisphosphonates	M05BA02	clodronic acid	H9		*can be either oral or parenteral
Bisphosphonates	M05BA04	alendronic acid	H9		
Bisphosphonates	M05BA05	tiludronic acid	H9		
Bisphosphonates	M05BA06	ibandronic acid	H9		*can be either oral or parenteral
Bisphosphonates	M05BA07	risedronic acid	H9		
Bisphosphonates, combinations	M05BB	Bisphoshonates, combinations	H9	E2	

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Bisphosphonates, combinations	M05BB01	etidronic acid and calcium, sequential		E2, E3	
Bisphosphonates, combinations	M05BB02	risedronic acid and calcium, sequential		E2, E3	
Bisphosphonates, combinations	M05BB03	alendronic acid and colecalciferol		E2, E3, E5	
Bisphosphonates, combinations	M05BB04	risedronic acid, calcium and colecalciferol, sequential		E2, E3, E5	
Bisphosphonates, combinations	M05BB05	alendronic acid, calcium and colecalciferol, sequential		E2, E3, E5	
Bisphosphonates, combinations	M05BB06	alendronic acid and alfacalcidol, sequential		E2, E3, E5	
Bisphosphonates, combinations	M05BB07	risedronic acid and colecalciferol		E2, E3, E5	
Bisphosphonates, combinations	M05BB08	zoledronic acid, calcium and colecalciferol, sequential		E2, E3, E5	
Drugs affecting bone structure and mineralization	M05B	Drugs affecting bone structure and mineralization		E4	
Drugs affecting bone structure and mineralization	H05AA02	Teriparatide		E4	
Drugs used in benign prostatic hypertrophy	G04CA	alpha-adrenoreceptor antagonists	I2, K3	G1	
Antiadrenergic agents, peripherally acting	C02CA	alpha-adrenoreceptor antagonists	I2, K3		

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Alpha-adrenoreceptor antagonists and diuretics	C02LE01	prazosin and diuretics	I2, K3		
Thiazolidenediones	A10BG	Thiazolidinediones	J2		
Thiazolidenediones (and combinations)	A10BD04	glimepiride + rosiglitazone	J2		
Thiazolidenediones (and combinations)	A10BD03	metformin + rosiglitazone	J2		
Thiazolidenediones (and combinations)	A10BD06	glimepiride + pioglitazone	J2		
Thiazolidenediones (and combinations)	A10BD05	metformin + pioglitazone	J2		
Thiazolidenediones (and combinations)	A10BD09	pioglitazone + alogliptin	J2		
Thiazolidenediones (and combinations)	A10BD12	pioglitazone + sitagliptin	J2		
Sex hormones and modulators of genital system	G03AA	progestogens and estrogens, fixed combinations	J4		
Sex hormones and modulators of genital system	G03AB	progestogens and estrogens, sequential preparations	J4		
Sex hormones and modulators of genital system	G03C	estrogens	J4, J5		
Sex hormones and modulators of genital system	G03CA03	estradiol	J4	G3	
Sex hormones and modulators of genital system	G03CA04	estriol	J4	G3	
Sex hormones and modulators of genital system	G03EA	androgens and estrogens	J4, J5		
Sex hormones and modulators of genital system	G03EB	androgens, progestogen and estrogen in combination	J4		

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Sex hormones and modulators of genital system	G03F	progestogens and estrogens in combination	J4		
Sex hormones and modulators of genital system	G03HB	antiandrogens and estrogens	J4, J5		
Sex hormones and modulators of genital system	G03XC	selective estrogen receptor modulators	J4, J5		
Hormones and related agents	L02AA	estrogens (endocrine therapy: hormones and related agents)	J4, J5		
Contraceptives for topical use	G02BB	vaginal ring with progestogen and estrogen	J4		
Sex hormones and modulators of genital system	G03AC	progestogens (hormonal contraceptives for systemic use)	J5		
Sex hormones and modulators of genital system	G03D	progestogens	J5		
Hormones and related agents	L02AB	progestogens (endocrine therapy: hormones and related agents)	J5		
Sex hormones and modulators of genital system	G03B	androgens	J6		
Lipid modifying agents	C10AA	HMG CoA reductase inhibitors		A5	
Lipid modifying agents	C10B	lipid modifying agents, combinations		A5	
Oxygen	V03AN01	Oxygen		B3	

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Immunosuppressants	L04AX01	azathioprine	H4	E1	
Immunosuppressants	L04AX03	methotrexate	H4	E1, E7	
Immunosuppressants	L04AA13	leflunomide	H4	E1	
Immunosuppressants	L04AD01	ciclosporin	H4	E1	
Intestinal antiinflammatory agents	A07EC01	sulfasalazine	H4	E1	
Antimalarials	P01BA	aminoquinolines	H4	E1	
Specific antirheumatic agents	M01CB	gold preparations	H4	E1	
Specific antirheumatic agents	M01CC	penicillaminen	H4	E1	
Multivitamins, combinations	A11AA02	multivitamins and calcium		E2, E3	
Vitamin A and D	A11CB	Vit A en Vit D in combination		E2, E3, E5	
Vitamin D	A11CC	Vit D and analogues		E2, E3, E5	
Ascorbic acid, combinations	A11GB01	Ascorbic acid and vit C		E2, E3	
Mineral supplements	A12AA	calcium		E2, E3	
Mineral supplements	A12AX	calcium combination with Vit D.		E2, E3, E5	
Preparations inhibiting uric acid production	M04AA	Xanthine-oxidase inhibitors		E6	
Folic acid, derivatives	B03BB	Folic acid and combinations		E7	
Iron preparations	B03AD	Iron in combination with folic acid		E7	

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Iron preparations	B03AE02	iron, multivitamins and folic acid		E7	
Iron preparations	B03AE01	iron, vitamin B12 and folic acid		E7	
Testosterone-5-alpha reductase inhibitors	G04CB01	Finasteride		G2	
Testosterone-5-alpha reductase inhibitors	G04CB02	Dutasteride		G2	
Vaccines (viral)	J07BB	Influenza vaccin		I1	
Vaccines (bacterial)	J07AL	Pneumococcal vaccines		I2	
Iron preparations	B03AA	Oral preparations (bivalent)	F3		
Iron preparations	B03AB	Oral preparations (trivalent)	F3		
Iron preparations	B03AD	Combinations with folic acid	F3		
Iron preparations	B03AE	Combinations with folic acid, vitamin B12, multivitamins	F3		
Iron bivalent, oral preparations	B03AA02	ferrous fumarate	F4		
Iron bivalent, oral preparations	B03AA07	ferrous sulphate	F4		
Iron bivalent, oral preparations	B03AA03	ferrous gluconate	F4		
Antacids	A02AB	aluminium antacids	F3		
Aminoalkyl ethers	R06AA	Aminoalkyl ethers	D8, D14, F3, M		
Substituted alkylamines	R06AB	Substituted alkylamines	D8, D14, F3, M		
Substituted ethylene diamines	R06AC	Substituted ethylene diamines	D8, D14, F3, M		
Phenothiazine derivatives	R06AD	Phenothiazine derivatives	D8, D14, F3, M		
Piperazine derivatives	R06AE01	buclizine	D8, D14, F3, M		
Piperazine derivatives	R06AE03	cyclizine	D8, D14, F3, M		

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Piperazine derivatives	R06AE04	chlorcyclizine	D8, D14, F3, M		
Piperazine derivatives	R06AE05	meclozine	D8, D14, F3, M		
Piperazine derivatives	R06AE06	oxatomide	D8, D14, F3, M		
Piperazine derivatives	R06AE51	buclizine, combinations	D8, D14, F3, M		
Piperazine derivatives	R06AE53	cyclizine, combinations	D8, D14, F3, M		
Piperazine derivatives	R06AE55	meclozine, combinations	D8, D14, F3, M		
Other antihistamines for systemic use	R06AX01	bamipine	D8, D14, F3, M		
Other antihistamines for systemic use	R06AX02	cyproheptadine	D8, D14, F3, M		
Other antihistamines for systemic use	R06AX03	thenalidine	D8, D14, F3, M		
Other antihistamines for systemic use	R06AX04	phenindamine	D8, D14, F3, M		
Other antihistamines for systemic use	R06AX05	antazoline	D8, D14, F3, M		
Other antihistamines for systemic use	R06AX08	pyrrobutamine	D8, D14, F3, M		
Other antihistamines for systemic use	R06AX09	azatadine	D8, D14, F3, M		
Other antihistamines for systemic use	R06AX15	mebhydrolin	D8, D14, F3, M		
Other antihistamines for systemic use	R06AX16	deptropine	D8, D14, F3, M		
Other antihistamines for systemic use	R06AX17	ketotifen	D8, D14, F3, M		
Other antihistamines for systemic use	R06AX23	pimethixene	D8, D14, F3, M		
Other antihistamines for systemic use	R06AX53	thenalidine, combinations	D8, D14, F3, M		
Other antihistamines for systemic use	R06AX58	pyrrobutamine, combinations	D8, D14, F3, M		
Diphenylmethane derivatives	N05BB01	hydroxyzine	D8, D14, F3, M		
Diphenylmethane derivatives	N05BB51	hydroxyzine + combinations	D8, D14, F3, M		

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Antivertigo preparations	N07CA02	cinnarizine	D8, D14, F3, M		
Antivertigo preparations	N07CA52	cinnarizine + combinations			
Drugs for urinary frequency and incontinence	G04BD01	emepronium	D8, F3, I1, M		
Drugs for urinary frequency and incontinence	G04BD02	flavoxate	D8, F3, I1, M		
Drugs for urinary frequency and incontinence	G04BD03	meladrazine	D8, F3, I1, M		
Drugs for urinary frequency and incontinence	G04BD04	oxybutynin	D8, F3, I1, M		
Drugs for urinary frequency and incontinence	G04BD05	terodiline	D8, F3, I1, M		
Drugs for urinary frequency and incontinence	G04BD06	propiverine	D8, F3, I1, M		
Drugs for urinary frequency and incontinence	G04BD07	tolterodine	D8, F3, I1, M		
Drugs for urinary frequency and incontinence	G04BD08	solifenacin	D8, F3, I1, M		
Drugs for urinary frequency and incontinence	G04BD09	trospium	D8, F3, I1, M		
Drugs for urinary frequency and incontinence	G04BD10	darifenacin	D8, F3, I1, M		

Table SI2.2. Continued.

Drug Class (ATC)	ATC Code	Description (ATC)	STOPP Criteria	START Criteria	Comments
Drugs for urinary frequency and incontinence	G04BD11	fesoterodine	D8, F3, I1, M		
Non-selective monoamine reuptake inhibitors	N06AA	Non-selective monoamine reuptake inhibitors	D8, F3, M		
Drugs for functional gastrointestinal disorders	A03B	Belladonna derivatives	D8, F3, M		
Drugs for functional gastrointestinal disorders	A03AA	Synthetic anticholinergics, esters with tertiary amino group	D8, F3, M		
Drugs for functional gastrointestinal disorders	A03AB	Synthetic anticholinergics, quaternary ammonium compounds	D8, F3, M		
Other antiemetics	A04AD01	Scopolamine (hyoscine)	D8, F3, M		
Muscle relaxants, centrally acting agents	M03BX02	tizanidine	D8, F3, M		
Anti-parkinson drugs	N04A	Anticholinergic agents	D8, F3, M		
Phenothiazines with aliphatic side-chain	N05AA01	Chlorpromazine	D8, F3, M		*High potency anticholinergic antipsychotics derived from Duran et al. Eur J Clin Pharmacol (2013) 69:1485-1496
Diazepines, oxazepines, thiazepines and oxepines	N05AH02	Clozapine	D8, F3, M		
Phenothiazines with piperazine structure	N05AB02	Fluphenazine	D8, F3, M		
Phenothiazines with aliphatic side-chain	N05AA02	Levomepromazine	D8, F3, M		
Phenothiazines with piperidine structure	N05AC02	Thioridazine	D8, F3, M		
Phenothiazines with aliphatic side-chain	N05AA04	Acepromazine	D8, F3, M		
Thioxanthene derivatives	N05AF04	Thiothixene	D8, F3, M		

Chapter 3

Process development and clinical outcomes of in-hospital medication reviews

3.1

Chapter 3.1

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

Introduction

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.

Conclusion

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, randomized 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.

Introduction

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 Multi-morbid 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 multi-centre OPERAM trial, the STRIPA software was translated into four languages; English, German, French and Dutch.

Integration of STOPP/START criteria into a stand-alone web-based clinical decision support system (CDSS) could improve the detection of inappropriate prescribing. A recent review has demonstrated that computerised 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, multi-component intervention and compare it with the approach in the comparator arm (see Figure 1). This protocol has been written in line with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) recommendations.

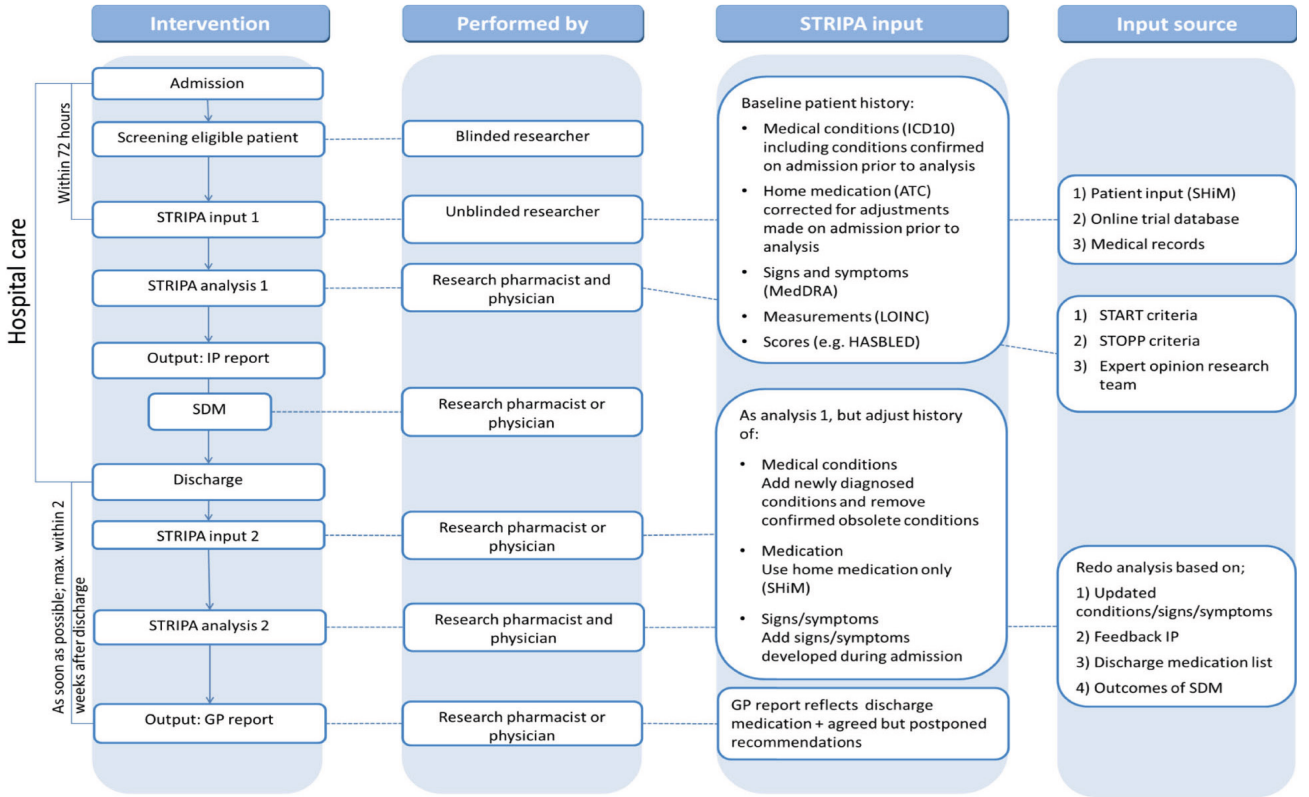


Figure 1. Flowchart of STRIP and STRIPA intervention process.
STRIPA = Systematic Tool to Reduce Inappropriate Prescribing Assistant; *SDM* = shared decision making; *IP* = internal physician; *ICD-10* = International Statistical Classification of Disease and related Health Problems, 10th revision; *ATC* = Anatomical Therapeutic Chemical; *LOINC* = Logical Observation Identifiers Names and Codes; *SHiM* = structured history-taking of medication; *GP* = general practitioner

Methods

Intervention arm

The STRIP intervention as 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). 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.

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 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:

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.

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.

1. 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.

2. 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.

3. 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.

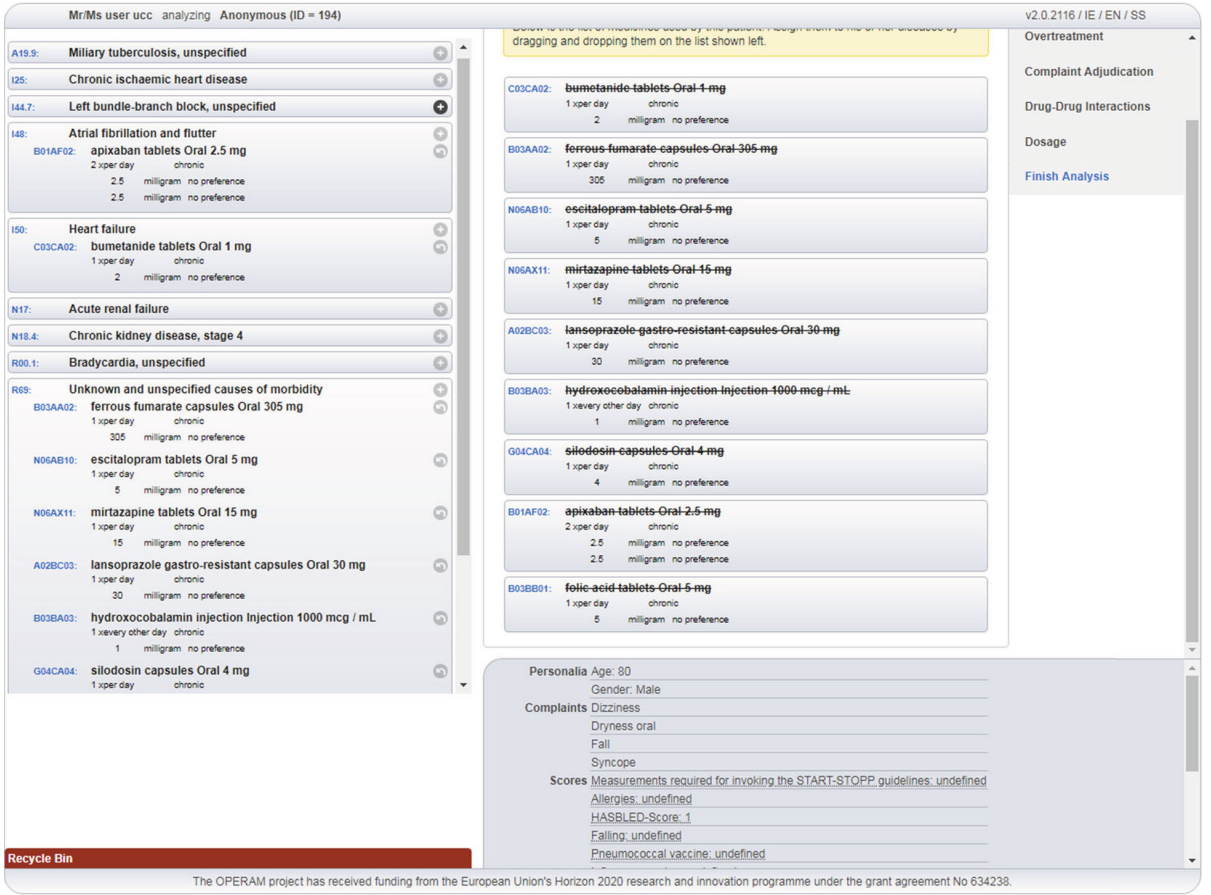


Figure 2. Screenshot of STRIPA process during which medications are assigned to relevant medical conditions.

STRIPA analysis

The pharmaceutical analysis consists of six steps, according to the Prescribing Optimization 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 ICD10- codes representing the patient's medical conditions (see Figure 2). 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 ICD10-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 Fig. 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.

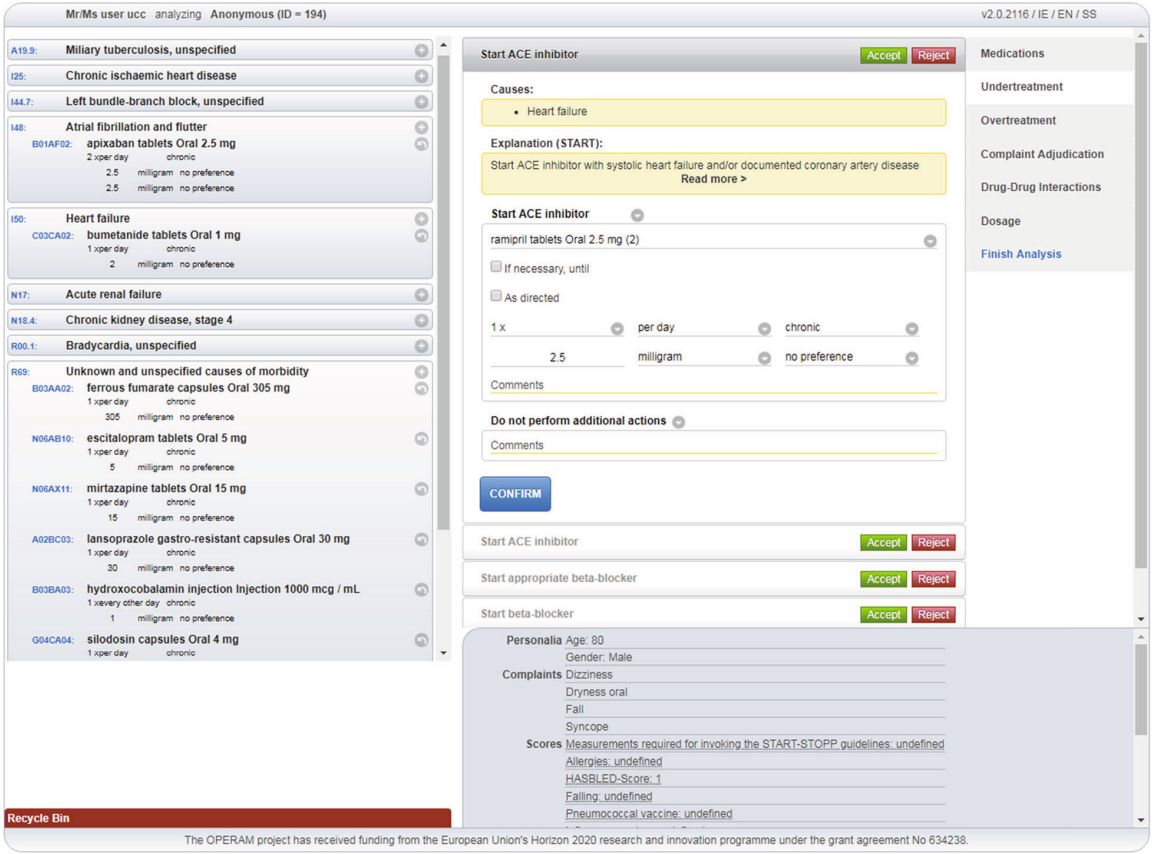


Figure 3. Screenshot of triggered START criteria.

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).

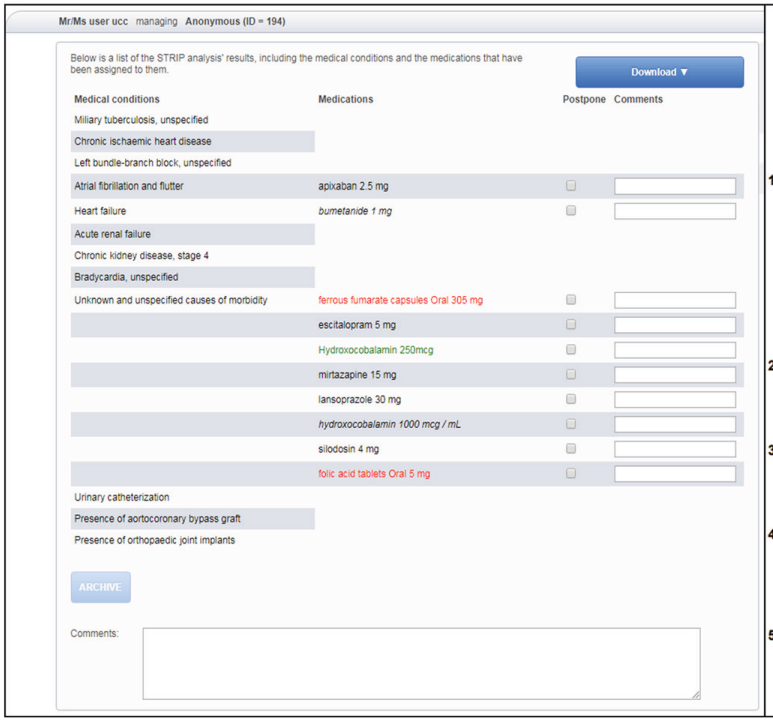
4. Medication-Disease Interactions (ADEs): this step encompasses the adjudication of clinical signs or symptoms entered which are based on the predefined list of symptoms and signs that may be attributable to medications or medical conditions. The software user, based on expert opinion, can assign symptoms 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 4a**.** The internal physician report: (A) final screen in the STRIPA process, and (B) completed report). This will not affect the underlying ATC and ICD10- 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 Figure 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

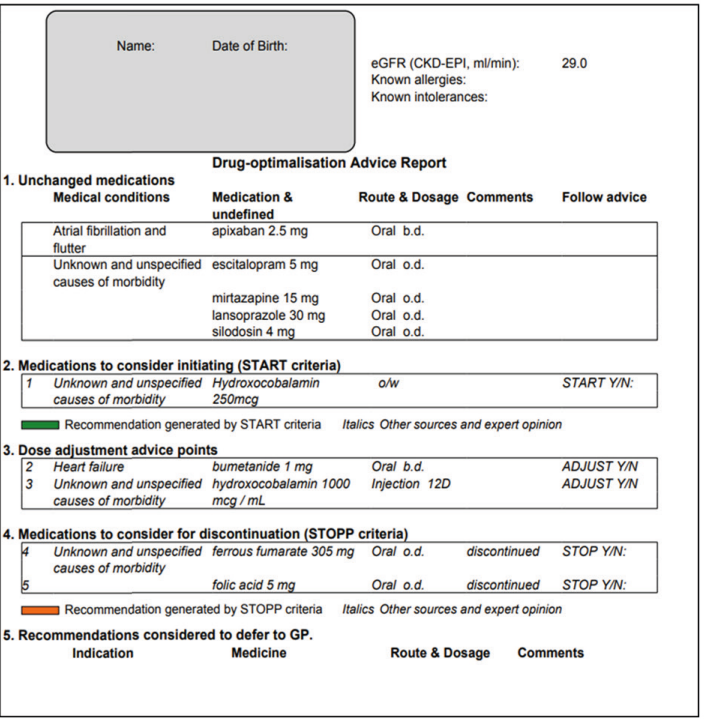


Figure 4. The internal physician report: (a) final screen in the STRIPA process, and (b) completed report

- **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 [42–40].

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 [45] as an "*Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance. 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 24 h to the software developers, who then assess whether the problem in question is a possible device deficiency. They will then report back within 72 h 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 48 h.

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 [45]. 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 multi-disciplinary 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

MS, BB, AS, OD, IW, WK, NR, SB, and DOM made substantial contributions to the conception and design of the intervention. 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, 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 Saint-Luc 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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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).

Abbreviations

ACE	Angiotensin-converting enzyme
ADE	Adverse drug event
ADR	Adverse drug reaction
ATC	Anatomical therapeutic chemical
CDSS	Clinical decision support systems
CKD-EPI	Chronic kidney disease epidemiology collaboration
DRA	Drug-related admissions
DRP	Drug-related problem
eGFR	Estimated glomerular filtration rate
GP	General practitioner
ICD-10	International Statistical Classification of Disease and related Health Problems, 10th revision
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
KNMP	Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (Royal Dutch Pharmacists Association)
LOINC	Logical observation identifiers names and codes
MEDDEV	European Medical Device Vigilance System
MedDRA	Medical Dictionary for Regulatory Activities
MMAS-8	8-item Moriskey Medication Adherence Scale questionnaire
OPERAM	Optimising thERapy to prevent Avoidable hospital admission in the Multi-morbid elderly
PIP	Potentially inappropriate prescribing
PPO	Potential prescribing omissions
QoL	Quality of life
RCT	Randomised controlled trials
SDM	Shared decision making
SHiM	Structured history taking of medication
START	Screening tool to alert to right treatment
STOPP	Screening tool of older persons' prescriptions
STRIP	Systemic tool to reduce inappropriate prescribing
STRIPA	STRIP Assistant

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3.2

Chapter 3.2

Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Patients: The OPERAM Cluster Randomized Clinical Trial

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Abstract

Objective

To examine the effect of optimising drug treatment on drug related hospital admissions in older adults with multimorbidity and polypharmacy admitted to hospital.

Design

Cluster randomised controlled trial.

Setting

110 clusters of inpatient wards within university based hospitals in four European countries (Switzerland, Netherlands, Belgium, and Republic of Ireland) defined by attending hospital doctors.

Participants

2008 older adults (≥70 years) with multimorbidity (≥3 chronic conditions) and polypharmacy (≥5 drugs used long term).

Intervention

Clinical staff clusters were randomised to usual care or a structured pharmacotherapy optimisation intervention performed at the individual level jointly by a doctor and a pharmacist, with the support of a clinical decision software system deploying the screening tool of older person's prescriptions and screening tool to alert to the right treatment (STOPP/START) criteria to identify potentially inappropriate prescribing.

Main outcome measure

Primary outcome was first drug related hospital admission within 12 months.

Results

2008 older adults (median nine drugs) were randomised and enrolled in 54 intervention clusters (963 participants) and 56 control clusters (1045 participants) receiving usual care. In the intervention arm, 86.1% of participants (n=789) had inappropriate prescribing, with a mean of 2.75 (SD 2.24) STOPP/START recommendations for each participant. 62.2% (n=491) had ≥1 recommendation

successfully implemented at two months, predominantly discontinuation of potentially inappropriate drugs. In the intervention group, 211 participants (21.9%) experienced a first drug related hospital admission compared with 234 (22.4%) in the control group. In the intention-to-treat analysis censored for death as competing event (n=375, 18.7%), the hazard ratio for first drug related hospital admission was 0.95 (95% confidence interval 0.77 to 1.17). In the per protocol analysis, the hazard ratio for a drug related hospital admission was 0.91 (0.69 to 1.19). The hazard ratio for first fall was 0.96 (0.79 to 1.15; 237 *v* 263 first falls) and for death was 0.71) 0.90 to 172 ;1.13 *v* 203 deaths).

Conclusions

Inappropriate prescribing was common in older adults with multimorbidity and polypharmacy admitted to hospital and was reduced through an intervention to optimise pharmacotherapy, but without effect on drug related hospital admissions. Additional efforts are needed to identify pharmacotherapy optimisation interventions that reduce inappropriate prescribing and improve patient outcomes.

Introduction

Multimorbidity defined as ≥ 2 chronic medical conditions increases with age, with an estimated prevalence of ≥70% in older populations, and is accompanied by increased mortality, healthcare utilization, hospital admissions and increased prescription rates of long-term medications [1–4]. This commonly results in polypharmacy, often defined as prescription of ≥ 5 long-term daily drugs [5]. While polypharmacy may be indicated and beneficial in many multimorbid patients, it also increases the risk of inappropriate prescribing [6,7]. Inappropriate prescribing may take the form of drug overuse (drug prescribing without an evidence-based indication), drug underuse (omission of drug prescribing despite an evidence-based indication), or drug misuse (such as inappropriate combinations with risk for drug-drug interactions, and inappropriate dosing) [8–11]. Inappropriate prescribing is highly prevalent among older people, with reported prevalence varying from 30% to 60% [10,12], and may lead to important adverse outcomes [6] Studies have reported increased risks of drug-drug interactions and adverse drug reactions [13], drug-related hospital admissions, falls, mortality, and decreased quality of life arising from inappropriate prescribing in the context of polypharmacy [6,7,14,15]. Up to 30% of all hospital admissions in older people are drug-related, half of which are potentially preventable [15–18].

A wide variety of interventions have been designed to optimize pharmacotherapy in patients with polypharmacy, with the aim of improving medication appropriateness and lowering the risk of adverse drug reactions [7]. Most of these structured interventions consist of multifaceted interventions delivered by pharmacists [7], but more recently, software systems have been developed to support pharmacotherapy optimization [19,20]. While most computerized decision support systems focus on a single aspect, such as detecting drug-drug or drug-disease interactions, or potentially inappropriate medications [21], the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) facilitated by the web-based STRIP Assistant (STRIPA) can perform multiple tasks intrinsic to pharmacotherapy optimisation simultaneously. It combines the Screening Tool of Older Person's Prescriptions and Screening Tool to Alert to the Right Treatment (STOPP/START) criteria [22] with a more global evaluation of drug appropriateness and shared decision-making with the patient [23]. However, it remains uncertain whether these structured pharmacotherapy optimization interventions result in improved clinical outcomes. A Cochrane systematic review of interventions designed to improve the appropriate use of polypharmacy in older people found few studies investigating important clinical outcomes, such as hospital admissions or quality of life, with inconsistent results. While some prospective non-randomised studies have indicated a reduction in hospital admissions with multi-faceted interventions of pharmaceutical care [24,25], and two small single-centre randomized clinical trials (RCTs) showed a

reduction in hospital admissions [16,26], other RCTs failed to demonstrate any relevant benefit on clinical outcomes [7,27]. However, the certainty of the evidence was deemed to be very low because of limitations in the study design, including risk of bias (e.g. contamination bias due to non-cluster randomization, outcome assessment bias due to non-adjudicated outcomes), lack of statistical power (small sample size), short follow-up, or being single-site studies [7]. Adequately powered high-quality trials are therefore needed to assess the potential clinical benefit of pharmacotherapy optimization; if effective, optimization of pharmacotherapy could lead to major improvements in the care of the growing population of older multimorbid individuals with polypharmacy. Improving medication appropriateness is particularly important among inpatients, given that hospitalization is a risk factor for drug-related adverse events and inappropriate prescribing [16].

Aiming to overcome the limitations of previous pharmacotherapy optimization studies [7], we conducted a large-scale multicentre cluster-RCT assessing the effect of a multidisciplinary optimization of pharmacotherapy, supported by a software-based clinical decision-support tool on adjudicated drug-related hospital admissions and other clinical outcomes in older multimorbid patients with polypharmacy, compared to usual care.

Methods

Trial design

The rationale and design of the OPERAM trial have been published previously [28]. We conducted a multi-centre, partially-blinded cluster-RCT among older multimorbid patients with polypharmacy, who were admitted to hospital. The trial assessed the effects of a structured pharmacotherapy optimization intervention on drug-related hospital admission and was conducted in four university-based hospitals located in four European countries (Bern, Switzerland; Utrecht, The Netherlands; Louvain, Belgium; Cork, Ireland). Written informed consent was obtained from patients or legal representatives before enrolment.

Patients

Patients aged ≥70 years with multimorbidity (≥3 chronic medical conditions defined by ICD-10 codes with an estimated duration of ≥6 months or based on a clinical decision) and polypharmacy (≥5 daily long-term drugs for >30 days prior to eligibility assessment) who were admitted to a participating hospital ward were eligible for inclusion if their expected minimal length of stay within the cluster was sufficient to apply the intervention. Both medical and surgical admissions, as well as both

elective and emergency admissions were included if the patient was ultimately hospitalized. To increase external validity [29], we applied few exclusion criteria: 1) planned transfer to palliative care ≤24 hours after admission, 2) patients with report of any structured medication review performed by a clinician ≤2 months prior to enrolment, 3) inability to provide written informed consent or to obtain written informed consent from a proxy.

Randomization and blinding

The clusters were defined at the level of attending hospital physicians. No specific eligibility criteria were defined for physicians other than sufficient enrolment potential. Physicians were sequentially enrolled over 21 months and allocated in a 1:1 ratio to the intervention or control arms. To ensure intervention safety and to enable shared decision-making with the patients, the trial was partially blinded. The intervention team consisted of a physician and a pharmacist; neither was blinded in order to have direct interactions with both the attending hospital physicians and the patients. Patients, hospital physicians, and general practitioners (GPs) were partially blinded and received only general trial information without specific details about the intervention. Each cluster-defining hospital physician signed a discretion contract to keep trial arm allocations confidential and not to share information with colleagues. In addition, cluster-defining hospital physicians worked on separate hospital units and were autonomous in their treatment decisions, further minimizing between-cluster contamination. To limit selection bias [30], the recruitment team, the teams conducting follow-up calls, and the adjudication teams consisting of pharmacists and physicians were fully blinded.

Trial procedures

The trial protocol describing the intervention used in OPERAM has been previously published [31]. The intervention was performed on the individual patient level and consisted of a structured medication review using STRIP, a process developed to support pharmacotherapy optimization in older patients. STRIP combines the STOPP/START criteria [22] to detect medication overuse and underuse with implicit drug appropriateness assessment methods, such as structured questions on medication history, therapy adherence, adverse drug reactions, and shared decision-making with the patient on proposed medication changes [23]. Detailed description of the intervention is available in Methods appendix. This process was supported by the web-based STRIPA (see Methods appendix), a decision-support system that takes into account clinically relevant interactions, dose adjustment according to renal function, and predictable adverse drug effects [23,32,33].

Pre-admission medication was assessed using the Structured History taking of Medication (SHiM) questionnaire [34] (see Methods appendix), and entered into STRIPA along with the patient's current diagnoses and relevant laboratory values. A trained research physician and pharmacist jointly performed the STRIP medication review, and generated patient-specific prescribing recommendations based on STOPP/START criteria, with possible adaptations after discussion with the attending hospital physician and the patient to take patient preferences into account. After considering additional in-hospital clinical information (e.g. new diagnoses, adverse drug reaction history), a final report was sent to the patient's GP with further recommendations that could not be implemented during the index hospitalization.

The control group received usual care that could include unstructured medication review by the attending hospital physicians, which was not specifically encouraged or discussed. Usual care was performed according to site-specific standards of care that did not include application of STOPP/START criteria or STRIP. To mimic the intervention for blinding purposes of the patients and blinded team members, a sham intervention was administered to all patients by the intervention team through completion of the Morisky Medication Adherence Measure Questionnaire (©MMAS-8) [35–37].

Follow-up and outcome data were collected by blinded team members through telephone interviews with the patients or their proxies at 2, 6 and 12 months post-randomization. When a hospital admission (at the index hospital or any other hospital) was identified, a second unblinded team gathered hospitalization data and concealed all information identifying the intervention allocation before sending it to the adjudication team.

Outcomes

The primary outcome was the first confirmed drug-related hospital admission after discharge following the index hospitalization within 12 months of enrolment. An independent blinded adjudication committee at each trial site, consisting of physicians and pharmacists, consecutively adjudicated all hospital admissions (both medical and surgical) for drug relatedness according to a previously published standardized adjudication guideline [38]. Briefly, potential adverse drug events were identified with the aid of triggers (linked to both causative drugs and potential causes for underuse) and screening questions, based on review of medical records and medication lists. If goals of care or patient preferences were documented in the medical record, these were also taken into account by the adjudication team. Confirmed adverse drug events were then adjudicated by the blinded adjudication committee for relatedness to the hospital admission. When adverse drug events were judged to be the main or a significant contributory reason, the admission

was identified as a drug-related hospital admission. Hospitalizations leading to death were also adjudicated for drug-related hospital admission, but not those for diagnostic/elective procedures for pre-existing conditions, or outpatient or emergency department visits, as the documentation of such visits is often too incomplete for adjudication of drug-relatedness. During trial conduct, but before enrolment ended and without looking at the data, non-substantial clarifications of the primary outcome definition were introduced: 1) clarification that the effect measure was a hazard ratio (HR), and 2) shorter description of what constitutes a "hospitalization" in clinicaltrials.gov.

Secondary outcomes within 12 months of enrolment included all-cause mortality, cancer mortality (negative control outcome to assess selection bias and blinding [39], as it was not expected to be influenced by the intervention), incident falls, and quality of life (visual analogue scale of the European Quality of Life 5 Dimensions (EQ-5D) questionnaire [40]). Other outcomes were selected according to a core outcome set for trials of medication review in multimorbid older patients with polypharmacy [41] and included pain/discomfort score (EQ-5D questionnaire), number of long-term prescription drugs, activities of daily living (Barthel Index of Activities of Daily Living [42]) and drug compliance (©MMAS-8 [35]), with month 12 as the main outcome month.

Secondary outcomes within 2 months after enrolment included the presence of drug overuse and misuse (based on STOPP criteria [22]), drug underuse (defined by START criteria [22]), and clinically significant drug-drug interactions [43] (see Methods appendix for details). As a process measure for intervention patients, we calculated the number of STOPP/START recommendations made to attending hospital physicians and the number of implemented recommendations at 2 months.

We also added two post-hoc outcomes: 1) first confirmed preventable drug-related hospital admission, considering admissions to be preventable when deemed potentially related to inappropriate prescribing (drug overuse, underuse or misuse as evaluated by the adjudication committee); 2) first drug-related hospital admission in a subpopulation restricting the intervention group to patients with ≥1 STOPP recommendation implemented after 2 months.

Statistical analysis

We based the sample size estimation of 80 clusters with 2,000 patients for the primary outcome on an estimated 1-year event rate of ≥1 drug-related hospital admission in 20% of the control group [17,44], 1-year mortality of 20% [45], assumed 1-year drop-out rate of 6%, 80% power to detect a 30% relative risk reduction in the intervention group at a two-sided type-1 error level of 0.05, an assumed intra-

cluster correlation coefficient (ICC) of 0.02 [46], and variable cluster sizes from 12 to 38 (mean 25) patients [28,47]. The 30% relative risk reduction was based on assessment of the effect that we did not want to miss [48].

The primary analysis was performed according to intention-to-treat, including all clusters and patients in the allocated groups. The between-group difference for the primary outcome was analysed using a mixed-effects Cox proportional hazards model with a fixed effect for the intervention group and random effects for site and attending hospital physician [49,50]. Patients were censored at death to calculate cause-specific HRs. An additional analysis used extensions of the Fine-Gray proportional hazards model that accounts for clustering in competing risk settings, treating death as the competing event to calculate subdistribution HRs [49]. Statistics were reported with their respective 95% confidence intervals (CIs) and p-values. All-cause deaths, cancer deaths, all-cause hospitalizations, falls and preventable drug-related hospital admissions were analysed similarly.

Between-group differences for in-hospital death, drug-drug interaction, and drug overuse/underuse/misuse were analysed using mixed-effects logistic regression with fixed and random effects as above. Between-group differences for continuous outcomes were analysed using mixed-effects linear regression models with fixed and random effects as above, and adjustment for baseline values.

Pre-specified subgroup analyses considered sex, age (<80 years vs. ≥80 years), home accommodation (independently living versus non-independently living), presence of dementia, number of drugs (<10 per day versus ≥10 per day), number of comorbidities (<median versus ≥median), cluster specialty (medical versus surgical) and trial site.

Pre-specified sensitivity analyses adjusted for baseline characteristics and investigated time variation of the intervention effect [51]. A post-hoc added sensitivity analysis only considered data collected in interviews conducted within protocol-specified time windows.

Per-protocol analyses were performed for time-to-first-event outcomes, omitting attending hospital physicians and patients with pre-defined protocol deviations (allocated intervention not received, cluster size <5 patients, violated inclusion or exclusion criteria) and intervention group patients for whom none of the STOPP/START recommendations were implemented at month 2 [52].

The detailed statistical analysis plan is described in a supplement. All analyses were performed using R version 3.6.0. software [53].

This study was registered with ClinicalTrials.gov, NCT02986425. The trial results are reported in line with the CONSORT extension for Cluster Trials [54].

Patient and public involvement

As part of the OPERAM project, patients and family caregivers, healthcare professionals and experts were involved in interviews and an international Delphi survey to develop an international core outcome set for clinical trials of medication review in multimorbid older patients with polypharmacy [41]; this core outcome set was added to the OPERAM trial outcomes. The contribution of patients and family caregivers was pivotal to the choice of the core outcome set, particularly for the final inclusion of 'pain relief' as one of the seven outcomes retained in this set [41].

Results

Between December 1, 2016 and October 31, 2018, 2,008 patients (median age 79 years [interquartile range, IQR, 74 to 84 years]; 898 [44.7%] female) provided consent and were enrolled in 54 intervention clusters (963 patients) and 56 control clusters (1,045 patients) (Figure 1, Figure SI1.1). During follow-up, ten (0.5%) patients were lost to follow-up, 118 (5.9%) withdrew from the trial, and 385 (19.2%) died.

Cluster size, specialty type and time interval between first and final patient recruitment were similar between groups (Table 1). Patient characteristics, number of comorbidities, number of daily medications and length of stay during index hospitalization were also similar between groups. The patients had a median number of 9 medications and 11 comorbidities at baseline. Medications were similar between groups (Table SI1.1). The average per-patient time spent on the full intervention, including data recording and discussion with the patient, was 97 minutes.

Of 916 patients who received the intervention (Figure 1), 789 (86.1%) had ≥1 STOPP/START recommendation provided to their attending hospital physician, with a mean (SD) of 2.75 (2.24) recommendations per patient (Table 2). Implicit STOPP criteria, such as STOPP A1 and A3 criteria, were common (Table 3). After 2 months, ≥1 of these recommendations were successfully implemented in 491 patients (62.2% of all patients in the intervention group with ≥1 recommendation), with a mean of 1.16 implemented recommendations per patient, primarily discontinuation of potentially inappropriate medications (Table 3).

Primary outcome

The number of patients with a first confirmed drug-related hospital admission was 211 (21.9%) in the intervention group, and 234 (22.4%) in the control group (Table 4, Figure SI1.2). Table SI1.2 lists the medication classes implicated in drug-related hospital admissions. In the intention-to-treat analysis, applying censoring for death at time of death, the HR for drug-related hospital admission was 0.95 (95%CI=0.77 to 1.17). In the per-protocol analysis, HR was 0.91 (95%CI=0.69 to 1.19, Table SI1.3, Figure SI1.3), with similar results in sensitivity analyses of competing risk of death, adjusting for baseline characteristics, and assessing varying intervention effect across time (Tables SI1.4-1.6). In post-hoc analyses, HR for first preventable drug-related hospital admission (41% of first confirmed drug-related hospital admissions) was 0.89 (95%CI=0.63 to 1.25), and HR was 0.88 (95%CI=0.65 to 1.19) for first drug-related hospital admission in patients with ≥1 STOPP recommendation implemented after 2 months (N=398 in the intervention group, N=875 in the control group still in the trial after 2 months). The intervention effect on drug-related hospital admissions did not differ in pre-specified subgroup analyses, except for trial site (Louvain HR 0.50, 95%CI=0.30 to 0.85, p for interaction=0.05) and dementia diagnosis (p for interaction=0.04) (Figure SI1.4).

Secondary outcomes

The event rates for falls were 0.49 and 0.59 per person-year in the intervention and control groups respectively, with a HR for first fall was 0.96 (95%CI=0.79 to 1.15) among intervention patients. The HR for death was 0.90 (95%CI=0.71 to 1.13, Table 4, Figure SI1.5). Pain, activities of daily living status, drug adherence and drug-related outcomes did not differ significantly between groups, except for quality of life at 12 months which was better in the intervention group (between-group adjusted mean difference: 2.29 [95%CI=0.31 to 4.26], Table 5). Results were similar in per-protocol analyses, as well as in sensitivity analyses of competing risk of death, adjusting for baseline characteristics, time-varying intervention effect, and exclusion of interviews outside pre-specified time windows (Tables SI1.3-1.7). Subgroup analyses of all-cause mortality showed potential benefits for men, patients aged ≥ 80 years, and those randomized in Louvain (p values for interaction = 0.004, 0.01 and 0.02, respectively; Figure SI1.6). The ICCs for the main outcomes were in the expected range (Table SI1.8).

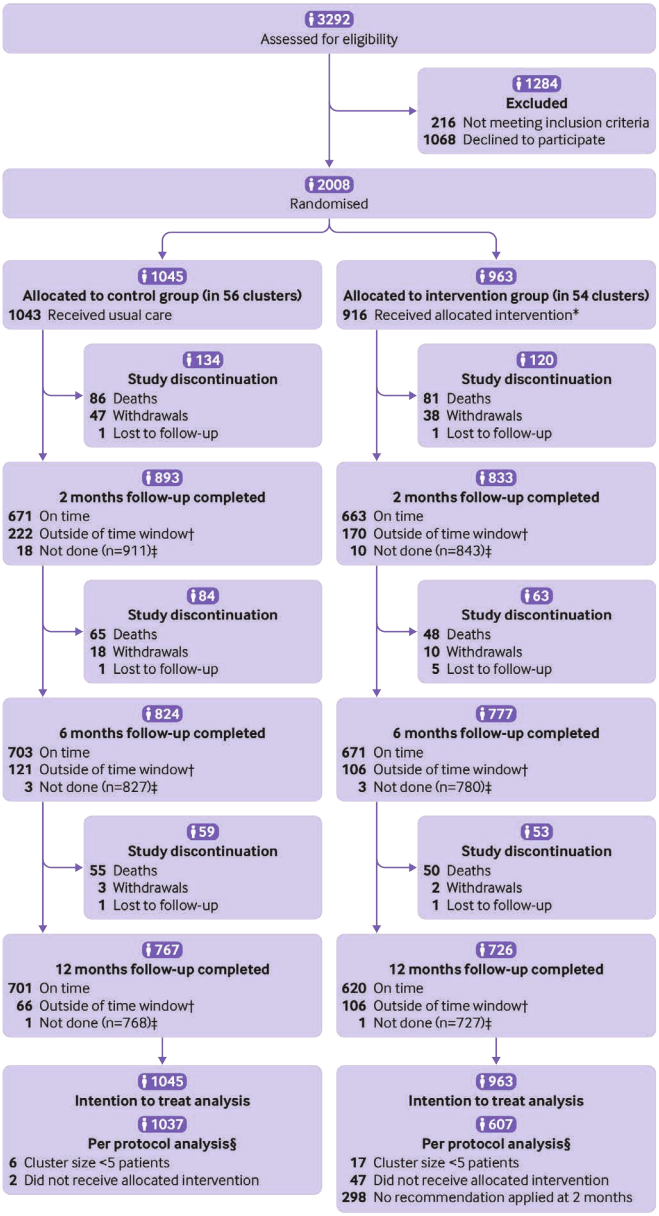

Figure 1. Flow of participants through study.
*Reasons for not receiving intervention in intervention group: discharge or transfer from hospital before intervention could be applied (n=25), patient died before intervention could be applied (n=7), withdrawal from study before intervention could be applied (n=6), and other or unknown (n=9). †Time windows for follow-up interviews: ±14 days at two months; ±30 days at six months; ±30 days at 12 months. ‡Participants or their proxies could not be reached for interview but excludes reasons for study discontinuation. §Reasons listed for exclusion in the per protocol analysis are not mutually exclusive.

Table 1. Baseline characteristics of clusters and patients.

	Control	Intervention
CLUSTERS, N	**56**	**54**
Cluster size	16.0 (11.8 - 25.2)	16.5 (10.0 - 23.8)
Cluster specialty type		
Medical	42 (75%)	43 (80%)
Surgical	14 (25%)	11 (20%)
Time between first and last recruitment, weeks	24.6 (15.2 - 37.3)	23.9 (11 - 35.9)
PATIENTS, N	**1,045**	**963**
Cluster specialty type [1]		
Medical	825 (78.9%)	764 (79.3%)
Surgical	220 (21.1%)	199 (20.7%)
Age, years	79 (74 - 84)	79 (74 - 84)
< 80 years	557 (53%)	521 (54%)
≥ 80 years	488 (47%)	442 (46%)
Female	453 (43%)	445 (46%)
Trial site		
Bern, Switzerland	376 (36%)	446 (46%)
Cork, Ireland	208 (20%)	138 (14%)
Louvain, Belgium	238 (23%)	150 (16%)
Utrecht, The Netherlands	223 (21%)	229 (24%)
Number of comorbidities	10 (8 - 15)	11 (8 - 16)
Number of medications	9 (7 - 12)	10 (7 - 13)
Non-independently living [2]	216 (21%)	168 (17%)
Dementia	49 (5%)	51 (5%)
Any fall during the last year	405 (39%)	364 (38%)
Number of falls during the last year	0 (0 - 1)	0 (0 - 1)
Any hospitalization during the last year	533 (51%)	486 (51%)
Number of hospitalizations during the last year	1 (0 - 1)	1 (0 - 1)
BMI, kg/m2	26.5 (23.7 - 30.1)	26 (23.2 - 29.6)
Current smoking	81 (8%)	77 (8%)
EQ-5D VAS [3]	60 (45 - 72)	60 (50 - 73)
Pain/discomfort score (EQ-5D) [4]	1 (0 - 2.00)	1 (0 - 2.00)
Barthel Index of ADL [5]	90 (80 - 100)	95 (75 - 100)
©MMAS-8 [6]	7 (6 - 7)	7 (6 - 7)
Length of stay during index hospitalization	9 (6 - 14)	8 (6 - 13)

Cluster and patient characteristics are presented as number and percentage (based on all -missing and non-missing- data) or median and interquartile range for categorical and continuous variables, respectively.
Missing data: Number of comorbidities at baseline: 3 (0.1%); number of medication at baseline: 3 (0.1%); number of falls during the last year: 19 (0.9%); number of hospitalizations during the last year: 12 (0.6%); BMI: 163 (8.1%); EQ5D VAS: 92 (4.6%); pain/discomfort score (EQ-5D) at baseline: 20 (1%); Barthel Index of ADL at baseline: 45 (2.2%); ©MMAS-8 at baseline: 99 (4.9%); Length of stay during index hospitalization: 28 (1.4%).

[1] The clusters refer to the randomization unit, i.e., the attending hospital physician responsible for a ward, which could be either from medical type (e.g., general internal medicine, pneumology) or surgical type (e.g., orthopedics, cardiovascular surgery). [2] Non-independently living was defined as living in a nursing home (at least 3 months in the 6 months before the index admission) or being housebound. [3] QoL/EQ-VAS: Quality of life as measured by the visual analogue scale that is the second part of the European Quality of Life-5 Dimensions questionnaire (EQ-VAS). Values ranged from 0 to 100. Higher values indicate higher quality of life. [4] Pain/discomfort score (EQ-5D): Pain/discomfort as measured in the 5-level version of the European Quality of Life-5 Dimensions questionnaire. Values ranged from 0 to 4. Higher values indicate higher level of pain or discomfort. [5] ADL: Basic Activities of Daily Living, as measured by the Barthel Index. Values ranged from 0 to 100. Higher values indicate higher functional independence. [6] ©MMAS-8: Drug compliance, measured by Medication Adherence Questionnaire (©MMAS-8) developed by Morisky (35–37). Values ranged from 0 to 8. Higher scores indicate higher levels of adherence. Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E. Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA Fielding School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772, dmorisky@ucla.edu. ©MMAS-8 questionnaire was applied a total of 4,805 times (1,913 at baseline, 1,519 at 2 months, 1,373 at 12 months).
Abbreviations: N, number

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Table 2. STRIP recommendations per patient.

Overall (N = 916)	Mean (SD)	Min - Max	N (%)
RECOMMENDATIONS BY THE STRIP METHOD			
Number of recommendations per patient	2.75 (2.24)	0 - 19	
Number of patients with at least one recommendation			789 (86.1%)
Number of STOPP recommendations per patient	1.79 (1.89)	0 - 18	
Number of patients with at least one STOPP recommendation			665 (72.6%)
Number of START recommendations per patient	0.95 (1.17)	0 - 7	
Number of patients with at least one START recommendation			497 (54.3%)
RECOMMENDATIONS IMPLEMENTED AT 2 MONTHS			
Number of implemented recommendations per patient	1.16 (1.48)	0 - 12	
Number of patients with at least one implemented recommendation			491 (62.2%)[1]
Number of implemented STOPP recommendations per patient	0.93 (1.35)	0 - 12	
Number of implemented START recommendations per patient	0.22 (0.54)	0 - 4	

The Systematic Tool to Reduce Inappropriate Prescribing (STRIP) is an optimization process for drug review that implements STOPP/START (Screening Tool of older People's Prescriptions/ Screening Tool to Alert to right treatment) criteria and implicit drug appropriateness assessment methods to increase appropriate prescribing for older people. This table presents the number of the accepted STRIP recommendations and accepted START criteria and STOPP criteria recommendations per patient as well as their implementation at 2 months (i.e. 61 days) after enrolment. In case of death, loss to follow-up or withdrawal before 61 days, information on the implementation of the recommendation was judged as missing. In total, 2,331 recommendations were made, of which 1,524 (65.4%) were STOPP recommendations, and 807 (34.6%) were START recommendations.

[1] The denominator is 789 patients with at least one recommendation, excluding the patients without recommendations.

Missing data: Number of implemented recommendations per patient: 57 (6.2%); number of patient with at least one implemented recommendation: 57 (6.2%); number of implemented STOPP recommendations per patient: 47 (5.1%); number of implemented START recommendations per patient: 38 (4.1%)

Abbreviations: Max, maximum; Min, minimum; N, number; SD, standard deviation

Table 3. Most commonly identified STOPP/START recommendations and implementation at 2 months.

STOPP/ START	Description	Count in intervention group, N (%)	Imple-mented, N (%)	Not imple-mented, N (%)
STOPP				
STOPP A1[1]	Any drug prescribed without an evidence-based clinical indication	828 (35.5)	428 (51.7)	400 (48.3)
STOPP A3	Any duplicate drug class prescription	147 (6.3)	95 (64.6)	52 (35.4)
STOPP D5	Benzodiazepines for ≥ 4 weeks	115 (4.9)	45 (39.1)	70 (60.9)
START				
START E3	Vitamin D supplement in patients with known osteoporosis and previous fragility fracture(s) and/or Bone Mineral Density T-scores more than -2.0 in multiple sites	96 (4.1)	22 (22.9)	74 (77.1)
START H2	Laxatives in patients receiving opioids regularly	82 (3.5)	12 (14.6)	70 (85.4)
START A6	Angiotensin Converting Enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease	80 (3.4)	19 (23.8)	61 (76.3)
START E5	Vitamin D supplement 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)	80 (3.4)	31 (38.8)	49 (61.3)
START E2	Bisphosphonates and vitamin D and calcium in patients taking long-term systemic corticosteroid therapy	74 (3.2)	21 (28.4)	53 (71.6)
START E4	Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab) 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)	71 (3.0)	9 (12.7)	62 (87.3)

Table 3. Continued.

STOPP/ START	Description	Count in intervention group, N (%)	Imple-mented, N (%)	Not imple-mented, N (%)
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	62 (2.7)	14 (22.6)	48 (77.4)

This table presents the 10 most commonly identified STOPP/START criteria (22) of the overall 2,331 recommendations made. Implemented vs. not implemented refers to whether recommendations were implemented at month 2 after enrolment. START I1 and I2 criteria and some STRIPA generated signals that could not be interpreted as recommendations were omitted from the analysis.

[1] The ten most commonly identified drug classes with no evidence-based indication were in descending order of frequency: antacids, mineral supplements, psychoanaleptics, lipid modifying agents, psychotropics, antithrombotics, vitamin, analgesics including opioids, drugs for constipation, and drugs for obstructive airway diseases.

Abbreviations: NSAID, non-steroidal anti-inflammatory drugs; STOPP/START, Screening Tool of older People's Prescriptions/ Screening Tool to Alert to right treatment.

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Table 4. Clinical outcomes.

	Events (%)			
Outcome	**Control (N=1,045)**	**Intervention (N=963)**	**HR (95% CI)** [1]	**P value**
First drug-related hospital admission	234 (22.4%)	211 (21.9%)	0.95 (0.77 to 1.17)	0.62
Death	203 (19.4%)	172 (17.9%)	0.90 (0.71 to 1.13)	0.37
Death from cancer	55 (5.3%)	43 (4.5%)	0.76 (0.47 to 1.23)	0.27
First hospitalization	516 (49.4%)	447 (46.4%)	0.87 (0.75 to 1.02)	0.08
First fall	263 (25.2%)	237 (24.6%)	0.96 (0.79 to 1.15)	0.64
First preventable drug-related hospital admission [2]	100 (9.6%)	84 (8.7%)	0.89 (0.63 to 1.25)	0.49
First drug-related hospital admission in patients with ≥1 STOPP recommendation implemented [2,3]	156 (17.8%)	64 (16.1%)	0.88 (0.65 to 1.19)	0.41
			OR (95% CI) [1]	
In hospital death within 2 months	54 (5.2%)	41 (4.3%)	0.81 (0.51 to 1.29)	0.38

[1] HR <1 and OR <1 indicate less events in the intervention group; [2] Post hoc analysis; [3] For drug-related hospital admissions occurring after 2 months from enrolment (N=398 in the intervention group, N=875 in the control group still in the trial after 2 months with available STRIPA data). Note that this analysis of a subset of intervention patients may be biased from unequal distribution of confounding factors and should be regarded as exploratory.
For time-to-event outcomes, between-group differences were first analysed using a random-effects Cox proportional hazards model; for the first drug-related hospital admission, first hospitalization, first fall, first preventable drug-related hospital admission, and death by cancer, we then used an extension of the Fine-Gray proportional model to account for the competing risk of death (results are presented in the appendix). Drug-related hospital admission was considered preventable when deemed by the adjudication committee as potentially related to a drug overuse, underuse or misuse (i.e. drug with an indication, but error in prescribing, dispensing, administering or monitoring the drug).
Abbreviations: CI, confidence interval; HR, hazard ratio; N, number; OR, odds ratio

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Table 5. Medication-related and patient-reported outcomes.

Outcome	Follow-up (month)	Control		Intervention			P value
Medication-related outcomes		N [1]	Events (%)	N [1]	Events (%)	OR (95% CI) [2]	
Clinically significant drug-drug interaction	2	893	521 (58.3%)	832	462 (55.5%)	0.87 (0.67 to 1.14)	0.31
Drug misuse [3]	2	893	378 (42.3%)	832	355 (42.7%)	0.99 (0.81 to 1.20)	0.92
Drug overuse [3]	2	893	376 (42.1%)	832	348 (41.8%)	0.99 (0.82 to 1.20)	0.91
Drug underuse [3]	2	893	638 (71.4%)	832	583 (70.1%)	0.91 (0.70 to 1.17)	0.45
		N [1]	***Mean (SD)***	***N*** [1]	***Mean (SD)***	***Adjusted difference (95% CI)*** [4]	
Number of long-term medications [5]	2	893	11.0 (4.27)	833	11.2 (4.54)	-0.13 (-0.49 to 0.22)	0.47
	6	824	11.5 (4.81)	777	11.9 (5.04)	-0.10 (-0.46 to 0.26)	0.60
	12	767	10.7 (4.57)	726	10.7 (4.54)	-0.20 (-0.56 to 0.17)	0.29
Patient-reported outcomes		***N*** [1]	***Mean (SD)***	***N*** [1]	***Mean (SD)***	***Adjusted difference (95% CI)*** [4]	
QoL/EQ-VAS [6]	2	828	64.0 (20.1)	764	65.0 (19.4)	0.63 (-1.24 to 2.50)	0.51
	6	763	65.6 (18.8)	727	67.1 (17.0)	1.34 (-0.58 to 3.25)	0.17
	12	703	65.1 (19.1)	657	67.1 (17.8)	2.29 (0.31 to 4.26)	0.02
Pain/discomfort score [7]	2	850	1.16 (1.20)	787	1.09 (1.12)	-0.04 (-0.16 to 0.07)	0.43
	6	777	1.17 (1.18)	741	1.08 (1.16)	-0.07 (-0.19 to 0.04)	0.20
	12	722	1.15 (1.20)	673	1.02 (1.11)	-0.11 (-0.23 to 0.01)	0.06

Table 5. Continued.

Outcome	Follow-up (month)	Control		Intervention			P value
Medication-related outcomes		N [1]	Events (%)	N [1]	Events (%)	OR (95% CI) [2]	
ADL [8]	2	833	86.0 (21.4)	780	87.8 (19.7)	0.53 (-1.71 to 2.78)	0.64
	6	767	87.7 (19.2)	735	88.6 (19.1)	0.49 (-1.78 to 2.76)	0.67
	12	713	86.9 (20.3)	665	89.0 (18.4)	1.60 (-0.70 to 3.89)	0.17
©MMAS-8 [9]	2	793	6.52 (0.834)	725	6.55 (0.819)	0.02 (-0.06 to 0.10)	0.68
	12	707	6.57 (0.815)	666	6.60 (0.759)	0.03 (-0.05 to 0.12)	0.46

[1] Numbers of participants differ for each outcome at different time points, as they were based on available data at months 2, 6, and 12 for medication-related outcomes and for patient-reported outcomes, and non-available data at 12 months were mainly due to death (see Figure 1, N of deaths until month 2, 6, 12: 167, 280, 385). [2] OR <1 indicates less events in the intervention group. [3] Drug misuse: drugs with an indication, but error in prescribing, dispensing, administering or monitoring the medication. For the detailed definitions of clinically significant drug-drug interactions, drug overuse and underuse see Methods appendix. [4] Adjusted difference: Adjusted for the baseline value of the outcome. Positive values indicate higher values in the intervention group. [5] Long-term medications are defined as use of a drug for >30 days. [6] QoL/EQ-VAS: Quality of life as measured by the visual analogue scale that is the second part of the European Quality of Life-5 Dimensions questionnaire. Values ranged from 0 to 100. Higher values indicate higher quality of life. [7] Pain/discomfort score (EQ-5D): Pain/discomfort as measured in the 5-level version of the European Quality of Life-5 Dimensions questionnaire (EQ-VAS). Values ranged from 0 to 4. Higher values indicate higher level of pain or discomfort. [8] ADL: Basic Activities of Daily Living, as measured by the Barthel Index. Values ranged from 0 to 100. Higher values indicate higher functional independence. [9] ©MMAS-8: Drug compliance, measured by Medication Adherence Questionnaire (©MMAS-8) developed by Morisky (35–37). Values ranged from 0 to 8. Higher scores indicate higher levels of adherence.
Abbreviations: CI, confidence interval; N, number; OR, odds ratio; SD, standard deviation

Discussion

Principal findings

In this cluster-RCT, evaluating the effect of a structured pharmacotherapy optimization intervention, five out of six multimorbid older patients experienced inappropriate prescribing. On average, 2.75 STOPP/START recommendations per patient were provided in the intervention group, and 62% of intervention patients had ≥1 recommendation implemented at 2 months, mostly discontinuation of drug overuse. Reduction of potentially inappropriate medication led to no detriment to patient outcomes, but drug-related hospital admissions were not significantly reduced during a 12-month follow-up, compared to usual care, despite providing evidence-based recommendations to hospital physicians, patients and their GPs.

Comparison with other evidence

Few RCTs have assessed the impact of reducing inappropriate prescribing on clinical outcomes. A previous Cochrane review of pharmacotherapy optimization interventions in older people identified nine RCTs reporting hospital admissions as outcomes, seven of which found no significant difference between intervention and control groups [7]. However, the primary endpoint of these studies was often non-clinical and measurement methods varied considerably across these studies. The review judged the risk of bias for this outcome as very high, due to risk of contamination between groups, insufficient blinding, selective reporting, lack of adjudication of clinical outcomes, short follow-up and/or small sample size. In addition, only four of these RCTs were conducted in hospitalized patients. Hospitalizations and emergency department visits were reduced in one small RCT (N=110) whose setting however differed substantially from ours in that it included only patients undergoing first-time transfer to a long-term care facility, was single-blinded (primary outcome assessors blinded), and the intervention was performed by a pharmacist transition coordinator [26]. Another RCT of 368 hospitalized patients aged ≥80 years (with and without polypharmacy) compared medication review performed by ward-based pharmacists to usual care, and found an 80% (95%CI 59-90%) subsequent reduction in drug-related hospital readmissions [16]. However, outcomes were not independently adjudicated, and generalizability of the results was limited due to the single centre design. Other RCTs had additional limitations such as short follow-up, single-centre design, and insufficient power to identify a difference in hospital admissions [7].

More recently, the SENATOR RCT of 1,537 hospitalized multimorbid older patients with polypharmacy compared software-guided medication optimization advice provided to attending physicians versus standard care, and found no between-

group difference for adverse drug reactions and neither for the secondary endpoints of rehospitalization or death [19]. Implementation of medication advice was very low (approximately 15%), blinding was limited, and contamination risk was not completely eliminated due to individual-level instead of cluster randomization. Another cluster-RCT of 3,904 older adults with polypharmacy in general practices compared an electronic decision support tool for comprehensive medication review designed to de-prescribe inappropriate medications versus standard care [55]. After 24 months, there was no between-group difference for the composite endpoint of unplanned hospital admissions or death, although the per-protocol analysis favoured the intervention (OR 0.82, 95%CI=0.68 to 0.98). However, patients, physicians and research staff were not blinded, and outcomes were not independently adjudicated. In contrast to these two RCTs, OPERAM combined software-based pharmacotherapy optimization with direct contact between research physicians/pharmacists and hospital physicians. This may have contributed to greater implementation of recommendations compared to SENATOR and allowed the consideration of individual patient needs and preferences.

Potential explanations for the lack of effect on drug-related hospital admission

Although pharmacotherapy optimization reduced potentially inappropriate medication and led to no detriment to patient outcomes, there are several possible explanations for the lack of effect on drug-related hospital admissions in OPERAM. Firstly, the impact of a single timepoint pharmacotherapy optimization may not persist over a 1-year follow-up, during which multiple physician contacts may occur. Although we provided evidence-based recommendations on inappropriate prescribing to patients' GPs, including reasons for stopping or starting drugs, the contacts with other physicians (e.g., specialists) over 1 year may have resulted in new potentially inappropriate medications or discontinuation of appropriate medications, which may have negated an intervention effect. Nevertheless, our point estimates are reassuring for a lack of detrimental effect on patient outcomes from primarily stopping inappropriate medications and showed a pattern favouring the intervention which may indicate that the effect was as intended, albeit weak. Secondly, the high mortality rate of the population approaching 20% at 12 months may have diluted benefits from pharmacotherapy optimization. Thirdly, implementation of recommendations (i.e., medication changes recommended by STRIP) at two months was suboptimal, although implementation of complex interventions is often lower in multi-centre trials (approximately 15% to 42%) [19,55] compared to some single centre trials (93%) [27]. The moderate implementation level in OPERAM was likely multifactorial. Multiple prescribers' barriers to minimizing inappropriate prescribing have been identified [56]. Our intervention could address some of these barriers among attending hospital physicians and GPs; it improved prescriber awareness

by providing evidence-based recommendations, it filled physicians' knowledge gaps, and it provided the resources required for pharmacotherapy optimisation. However, it may have been less successful in addressing these barriers among GPs who received a written report of the recommendations but had no direct contact with the intervention team, and who may not have implemented recommendations or reverted medication changes. In a recent RCT involving 1,499 hospitalized Danish patients with polypharmacy, the intervention incorporated close contact with the patient and an outpatient follow-up setting with motivational patient interviews and follow-up phone calls with outpatient providers. Reduced all-cause hospital readmission rate (HR 0.75, 95%CI=0.62 to 0.90) within 180 days was observed in the extended intervention group compared to usual care [57]. However, drug-related hospital admissions were not significantly reduced (HR 0.80, 95%CI=0.59 to 1.08), although this study was not powered to detect an effect on drug-related hospital admissions. This study was not multinational and had risk of contamination bias due to lack of cluster-randomization [30]. OPERAM implemented direct interaction of physicians and pharmacists with the attending hospital physicians and patients with shared decision-making. However, several recommendations could not be implemented during the index hospitalization, as some patients wished to discuss them with their GPs at a future appointment, when there may have been additional barriers to implementation. For example, the priority may have switched to issues other than inappropriate prescribing (e.g., because of a new health problem or worsening of a chronic condition). Furthermore, similar to previous studies [58,59], there was a low implementation rate of START recommendations that are known to reduce drug-related hospital admissions such as angiotensin converting enzyme inhibitors for systolic heart failure or statins for secondary cardiovascular prevention; this was possibly due to the already high drug burden in this population with polypharmacy (Table 3). Finally, some common STRIP recommendations included common drugs that are unlikely to contribute relevantly to drug-related hospital admissions, such as regular laxatives for patients on opioids (Table 3).

Implications for future research

Future pharmacotherapy optimization trials will need to enforce prescribing advice implementation with greater involvement of the outpatient setting and to address more effectively physicians' and patients' perceived barriers to pharmacotherapy optimization. In addition, future trials might benefit from focusing on specific drug classes (e.g. benzodiazepines) to develop specific interventions combining explicit and implicit approaches with individual and patient-centred decisions, accounting for barriers/enablers that may differ between drug classes [60], or prioritizing medications that are more likely to be associated with drug-related hospital admissions. Finally, future research needs to explore when, where and with whom pharmacotherapy optimization conversations should be taking place to best engage

patients. Future trials should also assess implementation of pharmacotherapy optimization in outpatient settings, such as by GPs or in pharmacies.

Strengths and limitations of this study

OPERAM has several strengths. Firstly, it enrolled multimorbid patients with minimal exclusion criteria, heightening the generalizability of the results. Secondly, few patients were lost to follow-up and death was the main reason for study discontinuation. Thirdly, OPERAM's study design addressed many of the limitations of previous trials: its cluster-randomization design limited allocation contamination, blinding was maximized, hospital admissions were adjudicated by a blinded adjudication committee and statistical power was sufficient with an adequate follow-up length for clinical outcomes.

OPERAM has some limitations. Although complete blinding was not possible, we sought to maximize blinding and to lower the risk of related bias – in contrast with previous trials [7] – by recruiting staff and adjudicators/outcome assessors who were fully blinded; patients were partially blinded and received a sham intervention in the control group. In addition, the risk of death from cancer was included as a negative control outcome and did not point to strong selection bias. Cluster-randomization was at the physician-level and not at the hospital-level, and the potential for contamination in control clusters cannot be completely ruled out. However, physicians were independent in the treatment decisions on their units and had signed a discretion contract not to share information with their physician or pharmacist colleagues. STRIP was not applied in the control group and whether medication changes in the control group met STOPP/START criteria was not assessed. Therefore, we cannot rule out the possibility that some medication changes in the control group similar to the intervention recommendations may have been made, which might have led to results closer towards no between-group difference. Frailty was not assessed at baseline, and we cannot therefore determine whether the intervention effect depended on frailty status. Relying on retrospective chart review for identifying drug-related hospital admissions is the gold standard [38], but it depends on the quality of documentation in the medical record, particularly for assessment of potential underuse; e.g. adherence and patient preferences are often not documented in the medical charts. Finally, one could argue that the lower limit of the confidence interval does not exclude the effect observed in a previous trial with a different follow-up period [57] However, the lower limit is very close to this effect, which still makes it unlikely that any replication of OPERAM would find such an effect. Moreover, the rate of the primary outcome in the control group was even higher than expected in the original sample size calculation, resulting in a sufficiently powered trial for the targeted effect.

Conclusion

In this cluster-RCT of older multimorbid patients with polypharmacy who were admitted to hospital, a mean of 2.75 STOPP/START recommendations per patient were provided in the intervention group and 62% of patients had ≥1 recommendation implemented at 2 months, mostly discontinuation of inappropriate medication. Drug-related hospital admissions were not significantly reduced in the intervention group compared to the control group despite providing evidence-based recommendations to physicians and patients. However, the intervention caused no detriment to patient outcomes.

Declarations

Authors' contributions

MR and ST had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. NR, ST, DOM, AS, WK, and MS conceived and designed the study. All authors contributed to data acquisition, analysis, and interpretation. MR and ST performed the statistical analyses. MRB and NR drafted the manuscript. All authors revised the manuscript for important intellectual content. NR, DOM, AS, WK, MS, and MS obtained funding. NR, DOM, AS, WK, NS, and MS were responsible for administrative, technical, and material support. NR, ST, DOM, AS, and WK supervised the study. NR is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Use of Morisky medication adherence measure questionnaire is protected by US copyright laws. Permission for use is required. A license agreement is available from Donald E Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA Fielding School of Public Health, 650 Charles E Young Drive South, Los Angeles, CA 90095-1772, USA (ude.alcu@yksiromd). The questionnaire was applied 4805 times (1913 at baseline, 1519 at 2 months, 1373 at 12 months). The European quality of life-5 dimensions instrument is used by permission of the EuroQol Group.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: Financial support from grants from Swiss State Secretariat for Education, Research, and Innovation (NR, MSch), EU Horizon 2020 (LG), Gottfried and Julia Bangerter Rhyner Stiftung (LA), European Commission (ST, MR), during the conduct of the study. ST and MR are affiliated with CTU Bern, University of Bern, which has a staff policy of not accepting honorariums or consultancy fees. However, CTU Bern is involved in design, conduct, or analysis of clinical studies funded by not-for-profit and for profit organisations. In particular,

pharmaceutical and medical device companies provide direct funding to some of these studies or an up-to-date list of CTU Bern's conflicts of interest see https://www.ctu.unibe.ch/research/declaration_of_interest/index_eng.html. 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.

The lead author (NR) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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. Data and documentation will be made available through a secure file exchange platform after approval of proposal and a data transfer agreement is signed (which defines obligations that the data requester must adhere to with regard to privacy and data handling). Partially deidentified participant data limited to the data used for this work will be made available, along with a data dictionary and annotated case report forms. For data access, please contact the corresponding author.

Dissemination to participants and related patient and public communities

The results of the Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Patients (OPERAM) trial are published in a peer reviewed journal. In addition, we will disseminate results at local meetings in each country, through lay press and media releases and newsletters to the trial participants, as well as through the World Health Organisation Patients for Patient Safety (PFPS) Advocate Group (Margaret Murphy, member of the OPERAM advisory board).

Ethics approval

This study was approved by the independent research ethics committees at each 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-Luc-UCL: 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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Trial registration

ClinicalTrials.gov NCT02986425.

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SUPPLEMENTARY INFORMATION SI

SI1 - Figures and tables

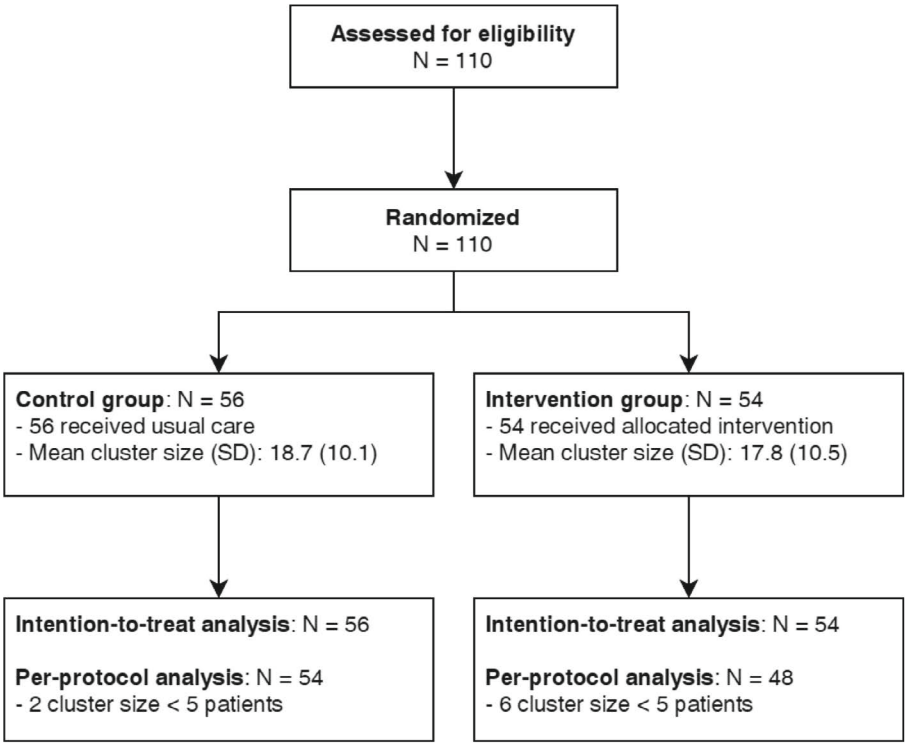
SI2 - Methods appendix

- STRIPA
- Structured History of Medication (SHiM)
- Definations of underuse, overuse and misuse in Table 5

References supplementary information

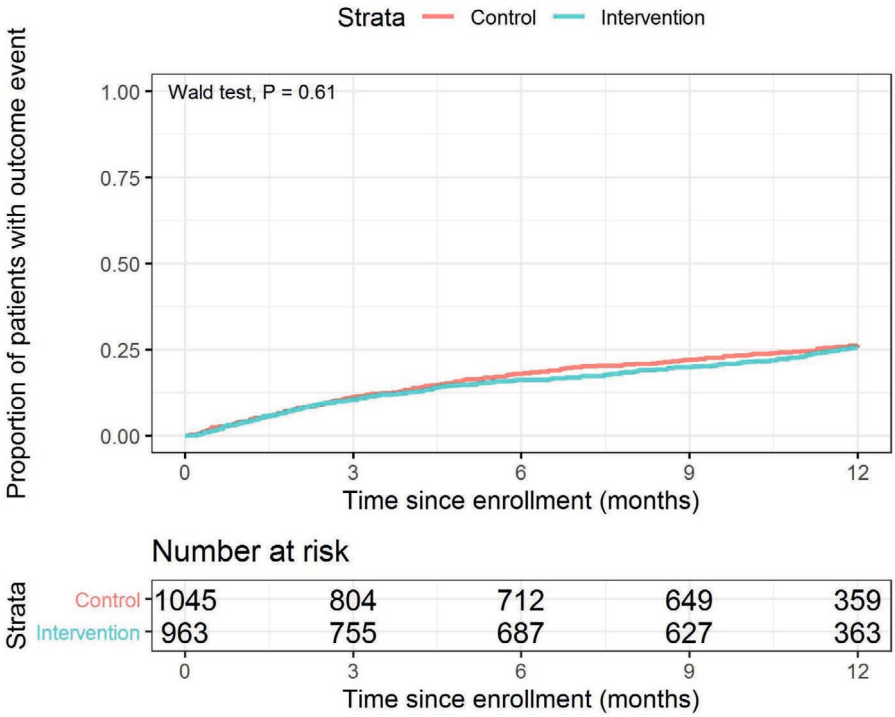
SI1 - Figures and tables

Figure SI1.1. Cluster flow chart.



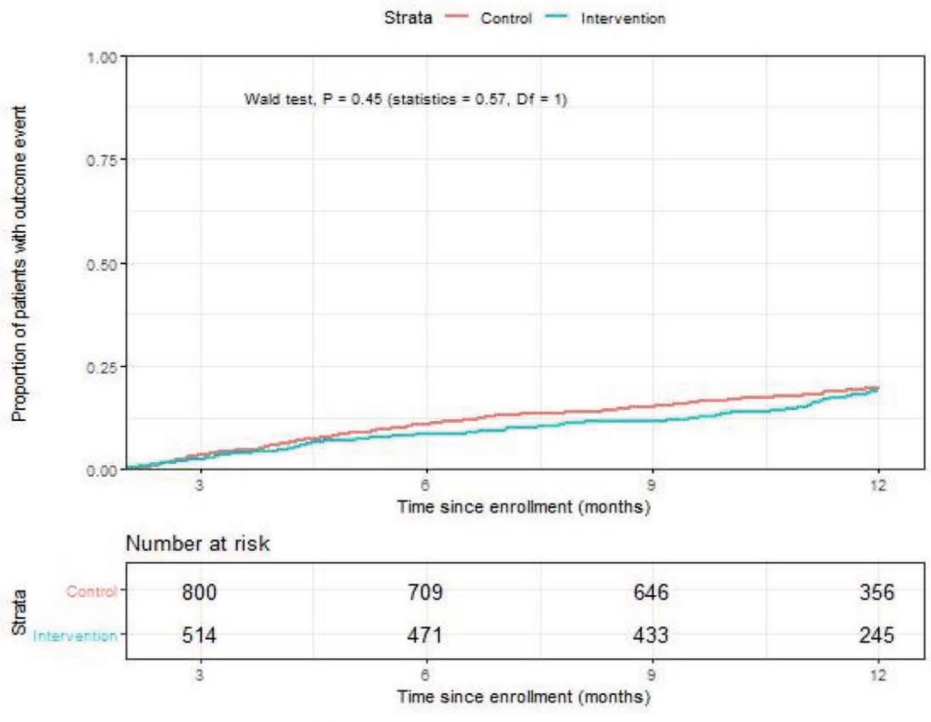
Abbreviations: N, number; SD, standard deviation

Figure SI1.2. Time to first drug-related hospital admission.



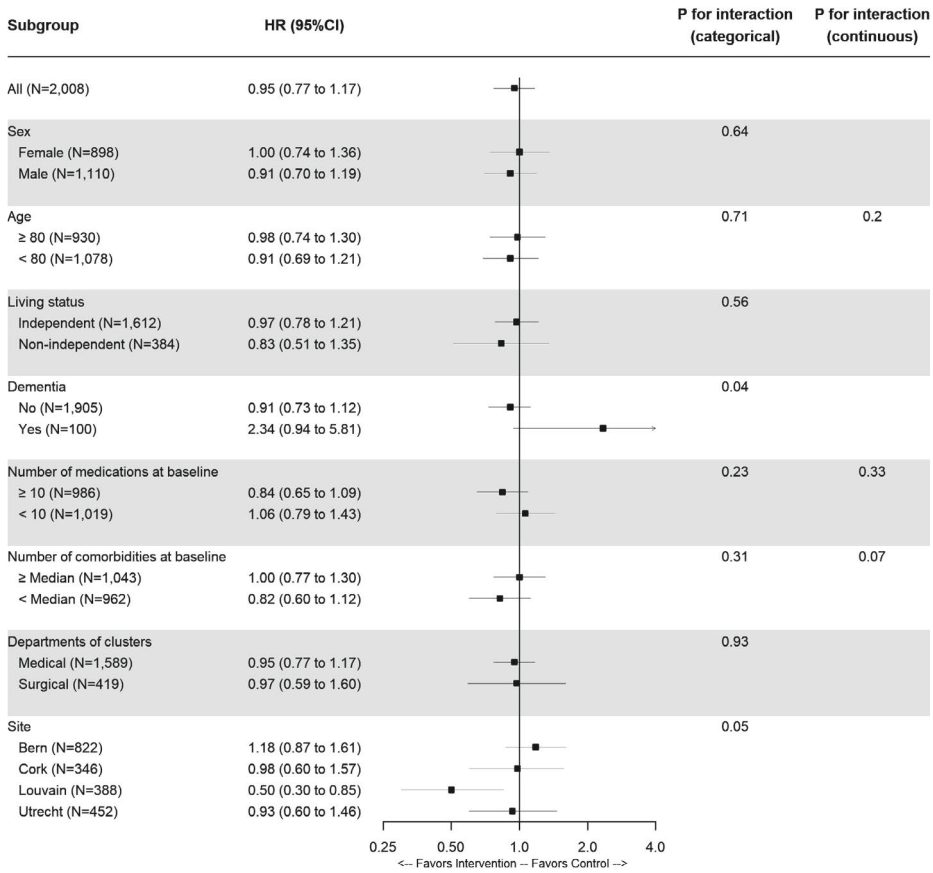
Curve truncated at 365 days. Statistics = 0.26, Df = 1.

Figure SI1.3. Per-protocol analysis for time to first drug-related hospital admission.



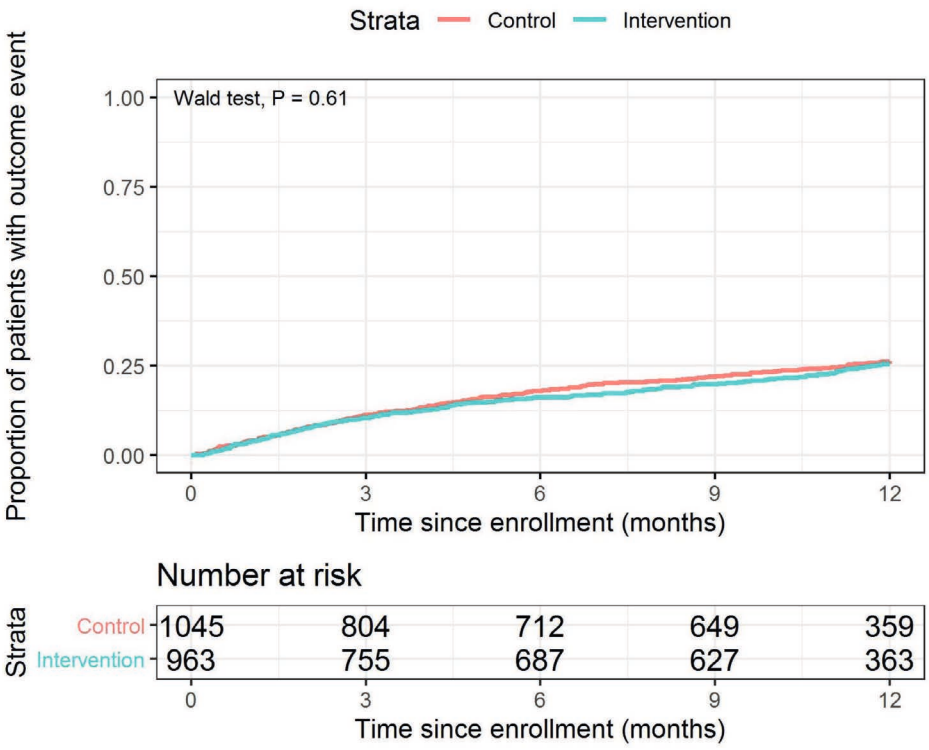
Curve truncated at 365 days. Statistics = 0.57, Df = 1.

Figure SI1.4. Subgroup analysis for first drug-related hospital admission.



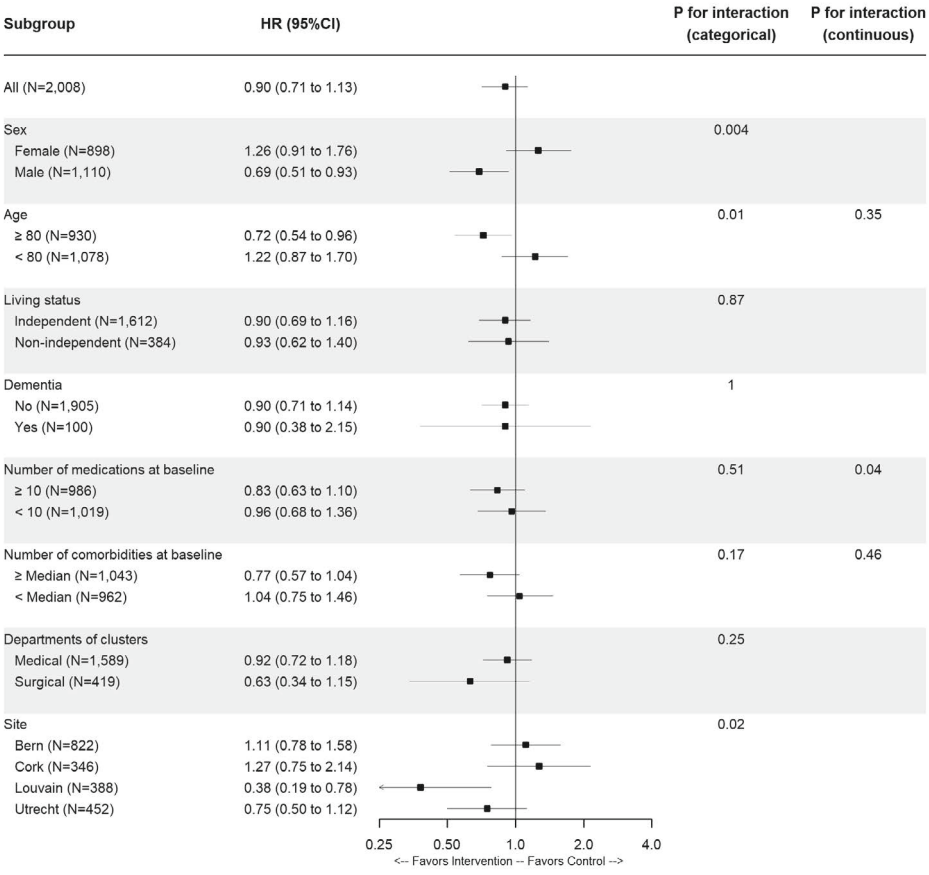
Non-independently living was defined as living in a nursing home (at least 3 months in the 6 months before the index admission) or being housebound.
Abbreviations: CI, confidence interval; HR, hazard ratio; N, number; P, P value.

Figure SI1.5. Kaplan-Meier curve for all-cause death.



Curve truncated at 365 days. Statistics = 0.79, Df = 1.

Figure SI1.6. Subgroup analysis for all-cause death.



Non-independently living was defined as living in a nursing home (at least 3 months in the 6 months before the index admission) or being housebound.
Abbreviations: CI, confidence interval; HR, hazard ratio; N, number; P, P value.

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Table SI1.1. Baseline medications grouped by ATC drug class and study group.

ATC code	ATC group name	Intervention group N (%)	Control group N (%)
B01	Antithrombotic agents	862 (8.6)	971 (9.3)
C03	Diuretics	644 (6.5)	685 (6.5)
A02	Drugs for acid related disorders	631 (6.3)	656 (6.3)
C10	Lipid modifying agents	570 (5.7)	651 (6.2)
R03	Adrenergics, inhalants	613 (6.1)	586 (5.6)
C09	Agents acting on the renin-angiotensin system	559 (5.6)	618 (5.9)
C07	Beta blocking agents	537 (5.4)	576 (5.5)
N02	Analgesics	547 (5.5)	526 (5.0)
A11	Vitamins	516 (5.2)	472 (4.5)
A10	Drugs used in diabetes	434 (4.4)	531 (5.1)
N05	Psychotropics	344 (3.5)	368 (3.5)
A12	Mineral supplements	344 (3.5)	339 (3.2)
N06	Psychoanaleptics	301 (3.0)	321 (3.1)
C08	Calcium channel blockers	276 (2.8)	287 (2.7)
G04	Urologicals	230 (2.3)	306 (2.9)
A06	Drugs for constipation	251 (2.5)	262 (2.5)
C01	Cardiac therapy	242 (2.4)	232 (2.2)
S01	Ophthalmologicals	202 (2.0)	179 (1.7)
B03	Antianemic preparations	170 (1.7)	205 (2.0)
N03	Antiepileptics	137 (1.4)	195 (1.9)
H03	Thyroid therapy	157 (1.6)	145 (1.4)
H02	Corticosteroids for systemic use	139 (1.4)	127 (1.2)
M04	Antigout preparations	110 (1.1)	156 (1.5)
Total		9,970	10,479

Note: Drug classes with <1% prevalence were omitted from this table for readability.

Table SI1.2. Involved or omitted medication classes in adjudicated drug-related hospital admissions.

ATC group code	ATC group name	N (%)
C03	Diuretics	130 (14%)
B01	Antithrombotics	116 (13%)
C09	Agents acting on the renin-angiotensin system	87 (10%)
N02	Analgesics	69 (8%)
C07	Beta blocking agents	66 (7%)
N05	Psychotropics	60 (7%)
N06	Psychoanaleptics	54 (6%)
Lxx	Antineoplastic and immunomodulating agents	41 (5%)
H02	Corticosteroids for systemic use	39 (4%)
A02	Drugs for acid related disorders	33 (4%)
Jxx	Antiinfectives for systemic use	23 (3%)
C01	Cardiac therapy	21 (2%)
A10	Drugs used in diabetes	20 (2%)
N03	Antiepileptics	20 (2%)
C10	Lipid modifying agents	16 (2%)
G04	Urologicals	16 (2%)
C08	Calcium channel blockers	14 (2%)
R03	Drugs for obstructive airway diseases	14 (2%)
A06	Drugs for constipation	12 (1%)

Note: Medication groups with ≤10 counts were omitted from this table for readability.

Table SI1.3. Per protocol analysis for time to first event outcomes.

	Events (%)			
Outcome	Control	Intervention	HR (95% CI) [1]	P value
Regression on cause-specific hazards				
First drug-related hospital admission	156/871 (17.9%)	93/556 (16.7%)	0.91 (0.69 to 1.19)	0.49
Death by cancer	37/943 (3.9%)	21/599 (3.5%)	0.87 (0.46 to 1.64)	0.66
First hospitalization	308/751 (41.0%)	182/491 (37.1%)	0.85 (0.70 to 1.04)	0.11
First fall	177/861 (20.6%)	115/548 (21.0%)	1.03 (0.81 to 1.31)	0.80
Death	125/943 (13.3%)	67/599 (11.2%)	0.85 (0.61 to 1.17)	0.32
First preventable drug-related hospital admission [2]	65/871 (7.5%)	38/556 (6.8%)	0.89 (0.58 to 1.37)	0.60
Regression on sub hazards (taking into account the competing risk of death)				
First drug-related hospital admission	156/871 (17.9%)	93/556 (16.7%)	0.91 (0.70 to 1.19)	0.51
Death by cancer	37/943 (3.9%)	21/599 (3.5%)	0.87 (0.46 to 1.65)	0.66
First hospitalization	308/751 (41.0%)	182/491 (37.1%)	0.85 (0.70 to 1.04)	0.11
First fall	177/861 (20.6%)	115/548 (21.0%)	1.03 (0.81 to 1.31)	0.79
First preventable drug-related hospital admission[2]	65/871 (7.5%)	38/556 (6.8%)	0.90 (0.59 to 1.37)	0.62

[1] HR<1 indicates fewer events in the intervention group; [2] Post hoc analysis.drug-related hospital admission was considered preventable when deemed by the adjudication committee as potentially related to a drug overuse, underuse or misuse (i.e. drug with an indication, but error in prescribing, dispensing, administering or monitoring the medication).
Abbreviations: CI, confidence interval; HR, hazard ratio

Table SI1.4. Time-to-event analysis taking into account competing risks (regression on sub-hazards).

	Events (%)			
Outcome	Control	Intervention	HR (95% CI) [1]	P value
First drug-related hospital admission	234 (22.4%)	211 (21.9%)	0.96 (0.79 to 1.18)	0.71
Death by cancer	55 (5.3%)	43 (4.5%)	0.76 (0.47 to 1.23)	0.27
First hospitalization	516 (49.4%)	447 (46.4%)	0.89 (0.77 to 1.03)	0.12
First fall	263 (25.2%)	237 (24.6%)	0.96 (0.81 to 1.16)	0.70
First preventable drug-related hospital admission [2]	100 (9.6%)	84 (8.7%)	0.91 (0.65 to 1.27)	0.58

[1] HR<1 indicates fewer events in the intervention group; [2] Post hoc analysis.
For the first drug-related hospital admission, first hospitalization and first fall, the analysis takes into account the competing risk of death. For death by cancer, the analysis takes into account the competing risk of other type of death. For first preventable drug-related hospital admission, the competing risk of other types of drug-related hospital admission were taken into account. Drug-related hospital admission was considered preventable when deemed by the adjudication committee as potentially related to a drug overuse, underuse or misuse (i.e. drug with an indication, but error in prescribing, dispensing, administering or monitoring the medication).
Abbreviations: CI, confidence interval; HR, hazard ratio.

Table SI1.5. Analysis adjusted for baseline characteristics.

Outcome	Control		Intervention		HR (95% CI)[1]	P value
	N	Events (%)	N	Events (%)		
First drug-related hospital admission	1,045	234 (22.4%)	963	211 (21.9%)	0.94 (0.76 to 1.16)	0.57
Death	1,045	203 (19.4%)	963	172 (17.9%)	0.89 (0.71 to 1.12)	0.33
	N [2]	Mean (SD)	N [2]	Mean (SD)	Adjusted difference (95% CI) [3]	
Number of long-term medications 2 months after enrolment [4]	893	11.0 (4.27)	833	11.2 (4.54)	-0.21 (-0.53 to 0.10)	0.18
Number of long-term medications 12 months after enrolment [4]	767	10.7 (4.57)	726	10.7 (4.54)	-0.39 (-0.73 to -0.04)	0.03

[1] HR<1 indicates fewer events in the intervention group; [2] Numbers of participants differ from those for clinical outcomes, as they were based on available data at months 2, 6, and 12 for medication-related outcomes, and non-available data at 12 months were mainly due to death (N of deaths until month 2, 6, 12: 167, 280, 385). [3] Adjusted difference: Adjusted for the baseline value of the outcome. Positive values indicate higher values in the intervention group. [3] Long-term medications are defined as use of a drug for >30 days.
Analysis further adjusted for baseline characteristics (i.e., site, departments of clusters, sex, non-independently living, age, number of medications at baseline, number of comorbidities at baseline, dementia).
Abbreviations: CI, confidence interval; HR, hazard ratio; N, number; SD, standard deviation.

Table SI1.6. Variation of the intervention effect across time.

Outcome		N	HR (95% CI) [1]	P value	P for interaction
First drug-related hospital admission	Before 2 months	2,008	0.98 (0.70 to 1.37)	0.91	0.80
	After 2 months	1,685	0.93 (0.73 to 1.19)	0.57	
Death by cancer	Before 2 months	2,008	0.71 (0.35 to 1.46)	0.35	0.82
	After 2 months	1,822	0.79 (0.47 to 1.33)	0.38	
First hospitalization	Before 2 months	2,008	0.91 (0.74 to 1.11)	0.34	0.76
	After 2 months	1,454	0.86 (0.71 to 1.03)	0.11	
First fall	Before 2 months	2,008	0.98 (0.72 to 1.33)	0.89	0.86
	After 2 months	1,660	0.94 (0.76 to 1.18)	0.61	
Death	Before 2 months	2,008	0.93 (0.64 to 1.35)	0.71	0.88
	After 2 months	1,822	0.88 (0.68 to 1.14)	0.33	

[1] HR<1 indicates less events in the intervention group.
Abbreviations: CI, confidence interval; HR, hazard ratio; N, number

Table SI1.7. Patient-reported outcomes, considering only interviews within the pre-specified time window.

		Control		Intervention			
Outcome	Follow-up (month) [1]	N	Mean (SD)	N	Mean (SD)	Adjusted difference (95% CI) [2]	P value
QoL/EQ-VAS [3]	2	625	64.6 (20.3)	614	65.7 (19.6)	0.56 (-1.50 to 2.63)	0.59
	6	657	65.6 (19.0)	631	67.0 (17.4)	0.98 (-1.06 to 3.02)	0.35
	12	648	64.8 (19.4)	568	67.0 (18.0)	2.26 (0.18 to 4.34)	0.03
Pain/discomfort score (EQ-5D) [4]	2	643	1.13 (1.19)	631	1.07 (1.11)	-0.05 (-0.17 to 0.07)	0.45
	6	670	1.19 (1.19)	644	1.05 (1.15)	-0.11 (-0.23 to 0.01)	0.08
	12	666	1.15 (1.21)	582	1.02 (1.11)	-0.12 (-0.25 to -0.00)	0.048
ADL [5]	2	631	86.9 (20.5)	627	88.6 (19.4)	0.94 (-1.29 to 3.17)	0.41
	6	660	88.0 (18.8)	638	89.4 (18.6)	0.73 (-1.49 to 2.96)	0.52
	12	658	87.0 (20.2)	575	88.6 (18.9)	1.60 (-0.64 to 3.83)	0.16
©MMAS-8 [6]	2	599	6.54 (0.804)	593	6.56 (0.788)	0.02 (-0.07 to 0.11)	0.67
	12	653	6.58 (0.811)	576	6.61 (0.746)	0.04 (-0.05 to 0.12)	0.41

[1] Time windows: ±14 days at the 2-month interview; ±30 days at the 6-month interview; ±30 days at the 12-month interview. [2] Adjusted difference: Adjusted for the baseline value of the outcome. Positive values indicate higher values in the intervention group. [3] QoL/EQ-VAS: Quality of life as measured by the visual analogue scale that is the second part of the 5-level version of the European Quality of Life-5 Dimensions questionnaire (EQ-VAS). Values ranged from 0 to 100. Higher values indicate higher quality of life. [4] Pain/discomfort score (EQ-5D): Pain/discomfort as measured in the 5-level version of the European Quality of Life-5 Dimensions questionnaire (EQ-VAS). Values ranged from 0 to 4. Higher values indicate higher level of pain or discomfort. [5] ADL: Basic Activities of Daily Living, as measured by the Barthel Index. Values ranged from 0 to 100. Higher values indicate higher functional independence. [6] ©MMAS-8: Drug compliance, measured by Medication Adherence Questionnaire (©MMAS-8) developed by Morisky [1–3]. Values ranged from 0 to 8. Higher scores indicate higher levels of adherence.
Abbreviations: CI, confidence interval; N, number; OR, odds ratio; SD, standard deviation

Table SI1.8. Intracluster correlation for main outcomes.

Outcome	ICC (95% CI)
First drug-related hospital admission	0.0103 (0 to 0.0763)
Death	0.0198 (0 to 0.1424)
First preventable drug-related hospital admission	0.0170 (0 to 0.1692)

The intracluster correlation calculations were made using the analysis of variance estimate of ICC and the associated CI calculated using modified Wald test (ICCbin package V1.1.1). Clusters with less than 2 patients were ignored.
Abbreviations: CI, confidence interval; ICC, intra-cluster correlation coefficient

SI2 Methods appendix

The multi-component intervention used in OPERAM was performed on the individual patient level, in several steps. The intervention protocol has been previously published [4]. The intervention was designed to identify the most relevant drug-related problems and optimize treatment during the index hospitalization and was based on the structured medication review using the systemic tool to reduce inappropriate prescribing (STRIP) method [5].

The STRIP method was developed to support pharmacotherapy optimization in older patients. This method combines the STOPP/START criteria [6] to detect medication overuse and underuse with patient-centered implicit methods, such as the Structured History taking of Medication (SHiM, see form below), therapy adherence, adverse drug reactions and shared decision making on proposed medication changes and includes shared decision-making with the patient [5,7].

Pharmacotherapeutic analysis is based on START/STOPP criteria, START/STOPP criteria version 2, with 114 criteria, reflect more complete and up-to-date sets of potentially inappropriate medications and potential prescribing omissions - explicit criteria - in comparison to version 1 in 2008. In addition, version 2 includes three implicit prescribing criteria (STOPP A1, A2, A3).

Newly admitted patients were screened, usually on the day of admission to the inpatient ward. Pre-admission medication was assessed using the SHiM questionnaire [7] with the patients or their proxies. In addition, at least one other information source was consulted (pharmacy, general practitioner) to improve the accuracy of the medication list.

Next, a trained research physician and pharmacist jointly performed the medication review using the STRIP method [5]. The pharmaceutical analysis was performed

using the web-based STRIP Assistant (STRIPA), a decision-support system (see details below). Via the software, based on STRIP recommendations and their own complementary expertise, the physician and the pharmacist generated a first report with prescribing recommendations to discontinue, initiate or modify medications, accompanied by detailed evidence-based explanations.

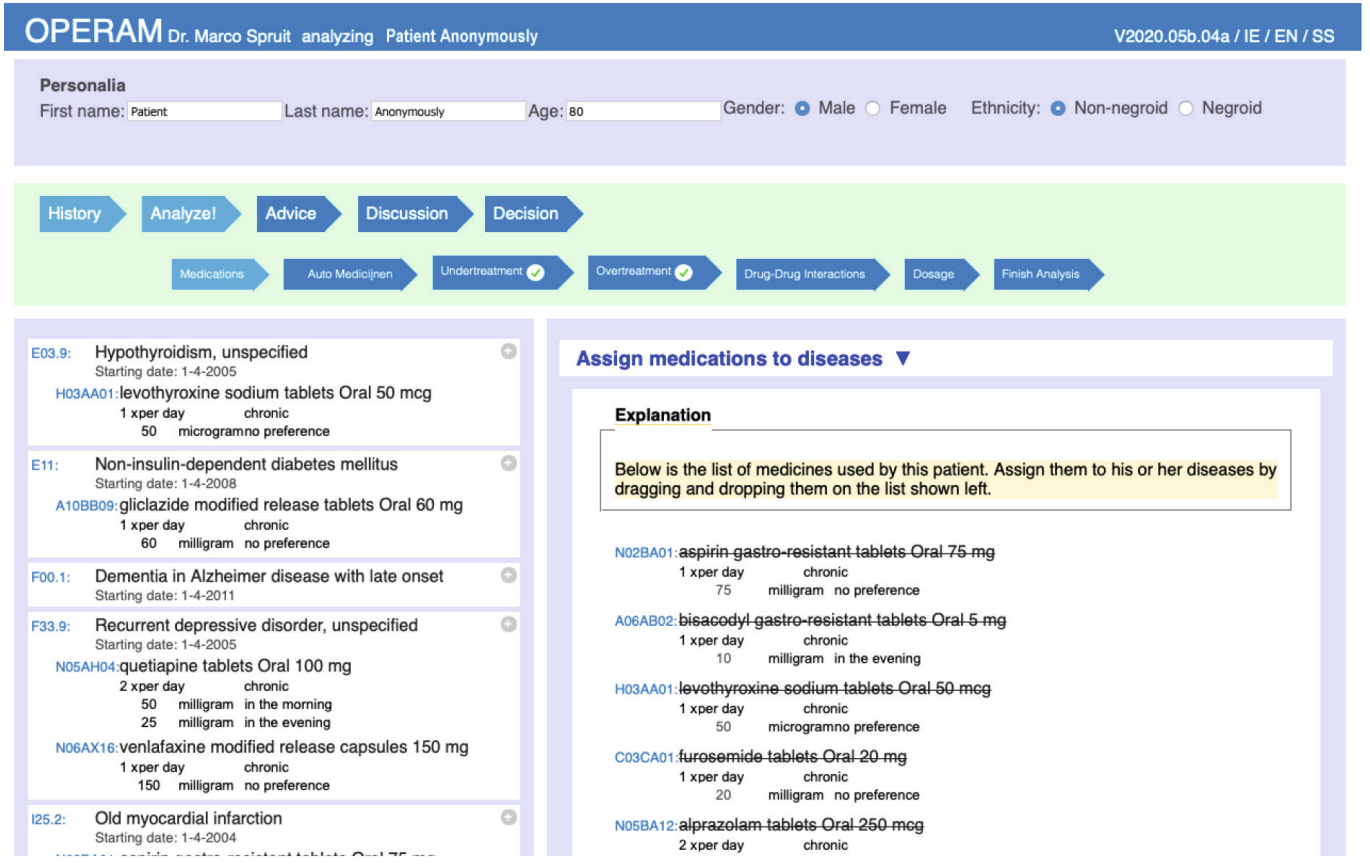
In the third step, this report was discussed with the attending hospital physician to reach a consensus about the recommendations. In addition, to promote patient engagement and to take patient preferences into account, a shared decision-making process with the patient or proxy took place. The researchers, treating hospital physicians and the patient agreed on the final medication changes. The research team was trained to each step of the intervention and standard operating procedures supported the process.

Lastly, after considering additional in-hospital clinical information (e.g. new diagnoses, adverse drug reactions), a final report was sent to the patient's GP to inform about in-hospital medication changes and all recommendations, including those that could not be implemented during the index hospitalization. All recommendations provided evidence-based reasons for changes.

STRIPA

The STRIP Assistant (STRIPA) version 2.0 is a stand-alone, web-based software tool that was used to perform a pharmaceutical analysis, an important step of the STRIP process. Data on diagnoses and current drug use (collected via SHiM and the actual medical record), recent measurements and laboratory values (e.g. renal function, blood pressure) and possible adverse drug reactions, as listed in the patient's medical record and according to patient information (SHiM) were entered in STRIPA. The assignment of drugs to diseases has been implemented through a drag and drop mechanism (see Methods appendix Figure). START A1 and START A2 were merged to one and STOPP A2 could not be converted into an algorithm, leaving a total of 79 STOPP and 33 START algorithms implemented into the clinical decision support system. Based on these data, pharmacotherapy optimization signals were generated by the clinical decision support software and evaluated for appropriateness on the individual patient level by the research physician and pharmacist.

Figure SI2.1. Screenshot Methods appendix – Figure. Screenshot of STRIPA process during which medications are assigned to relevant medical conditions.



Structured History Taking of Medication (SHIM)

Questions asked per drug on the medication list, provided by the community pharmacist

Drug no.: _____ Drug Name: _____

1. Are you using this drug as prescribed (dosage, dose frequency, dosage form)? Yes/No [Specify]
2. Are you experiencing any side effects? Yes [specify]/No
3. What is the reason for deviating (from the dosage, dose frequency, or dosage form) or not taking a drug at all? *(Please tick the box that applies)*

Side effects	☐
Inconvenient	☐
Forgot	☐
Too expensive	☐
Difficult to swallow	☐
Unpleasant taste	☐
Other, ...	☐

4. Are you using any other prescription drugs that are not mentioned on this list? (view medication containers) Yes [specify]/No
5. Are you using nonprescription drugs? Yes [specify]/No
6. Are you using homeopathic drugs or herbal medicines (eg. St. Johns wort)? Yes [specify]/No
7. Are you using drugs that belong to family members or friends? Yes [specify]/ No
8. Are you using any “as needed” drugs? Yes [specify]/ No
9. Are you using drugs that are no longer prescribed? Yes [specify]/ No

Questions concerning the use of medicines

10. Are you taking your medication independently? Yes/No
11. Are you using a dosage system? Yes/No
12. Are you experiencing problems taking your medication? Yes [specify]/No
13. In case of inhalation therapy: What kind of inhalation system are you using? Are you experiencing any problems using this system?
14. In case of eye drops: Are you experiencing any difficulties using the eye drops?
15. Do you ever forget to take your medication? No/Yes. If so,

which medication	☐
why	☐
what do you do?	☐

16. Would you like to comment on or ask a question about your medication?
17. Do you have any drug allergies? Yes/No
    b. If yes, specify which drugs/drug classes
    c. If yes, specify the symptoms of the allergy

Rash	☐
Swelling/angio-oedema	☐
Collapse	☐
Hypotension	☐
Bronchospasm	☐
Other symptom,	☐

18. Do you have any drug intolerances? Yes/ No
    b. If yes, specify which drugs/drug classes
    c. If yes, specify the symptoms of the drug intolerance

For study team member to answer and enter in the eCRF:

Did the SHIM led to any change in the medication list? *(Please tick the correct box)*

Yes	☐
No	☐

If yes, specify which drug, dosage, dose frequency or dosage form.
Was medicine reconciliation done?

Yes	☐
No	☐

Definitions of underuse, overuse and misuse in Table 5

Underuse, overuse and misuse were based on START and STOPP criteria version 2, and using an algorithm run on the trial database. The START criteria were used to detect drug underuse (i.e., potential prescribing omissions); each STOPP criterion was categorized as either measuring overuse or measuring misuse (i.e., potentially inappropriate medication). In total, 30 of 34 START criteria and 65 or 80 STOPP criteria were included and measured, as some criteria required data that were not available (mainly (i) laboratory measurements that were not available at two months in this pragmatic RCT, and (ii) the implicit STOPP criteria A1, A2, and A3 that require evaluation at patient-level by a trained clinician. We developed and validated an algorithm for the measurement of the following outcomes: drug underuse, drug overuse, drug misuse. The algorithm was developed from previous experience and reports from our team related to the automated detection of STOPP and START criteria [8,9]. Research Team statisticians and programmers (Prof. Dimitris Mavridis and Mr Agapios Panos, University of Ioannina, Greece) developed an R package that provided automated evaluation for each criterion (https://github.com/agapiospanos/StartStopp). In summary, detection was performed by using a validated algorithm (that was applied to the research database), based on the STOPP and START criteria.

Drug-drug interactions were assessed using a validated consensus-based list of 66 drug-drug-interaction criteria that we have recently published [10]. Once again, research team statisticians and programmers developed an R package that evaluated patient data for drug-drug interactions based on these criteria, using ATC coded medication lists (https://github.com/agapiospanos/DDI). This algorithm identifies combinations of ATC codes and was pilot tested in several rounds to check for accuracy in the detection.

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Chapter 4

Evaluation of the in-hospital medication review process

4.1

Chapter 4.1

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

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Drugs Aging. 2022;39:59-73.

Abstract

Introduction

The STOPP/START instrument is a screening tool to evaluate the appropriateness of medication in older people. 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. The objective of this study was to determine the frequency of CDSS-generated STOPP/START signals and subsequent acceptance by a pharmacotherapy team in a hospital setting.

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) 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 one or more hospital admissions (+ 7.9; 95% confidence interval [CI] 1.6–14.1) or one or more 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 (– 11.0%; 95% CI – 19.4 to – 2.6) signals for patients

with more than nine and between seven and nine co-morbidities, respectively. For setting-related determinants, the acceptance differed significantly between the participating trial sites. Compared with Switzerland, the acceptance was higher in Ireland (STOPP: + 26.8%; 95% CI 16.8–36.7; START: + 31.1%; 95% CI 18.2–44.0) and in the Netherlands (STOPP: + 14.7%; 95% CI 7.8–21.7). Admission to a surgical ward was positively associated with acceptance of STOPP signals (+ 10.3%; 95% CI 3.8–16.8).

Conclusion

An expert team's involvement 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 provide further insights for implementation in clinical practice.

Introduction

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) 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 comprising 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.

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].

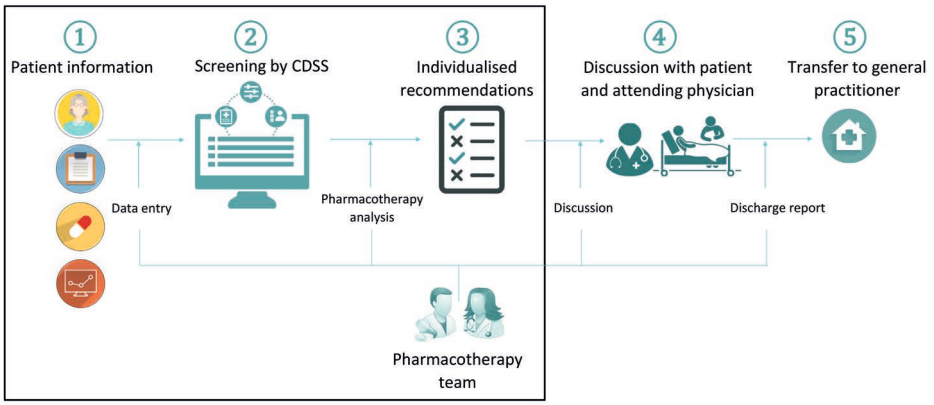

Figure 1. Summary of all consecutive steps (1–5) of the medication review within the OPERAM trial and the focus of this study: the acceptance of CDSS-generated STOPP/START signals by the pharmacotherapy team (steps 1–3) prior to discussion with the attending hospital physician and the patient.
CDSS =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

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 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).

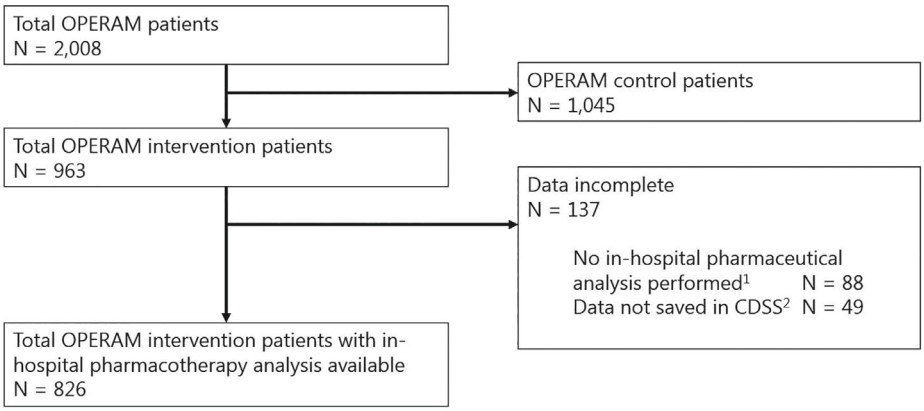

Figure 2. Flowchart of the study population.
[1]Reasons why no in-hospital pharmacotherapy analysis was performed in 88 (9%) of the OPERAM intervention patients were not collected on patient level but included: patient was discharged or transferred from ward, patient died, patient withdrew from study, 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).

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.

In total, 68 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. The team accepted 40.1% (*n*=1,390) STOPP signals 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. The team accepted 37.2% (*n*=600) START signals resulting in a recommendation to initiate a drug (median 0; IQR 0–1).

In general, there was 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 drug class most often recommended for discontinuation based on STOPP A1 (22.5%) followed by mineral supplements (calcium) (8.0%) and psychoanaleptics (7.3%). Figure 3 shows the drug classes recommended for discontinuation based on STOPP A1.

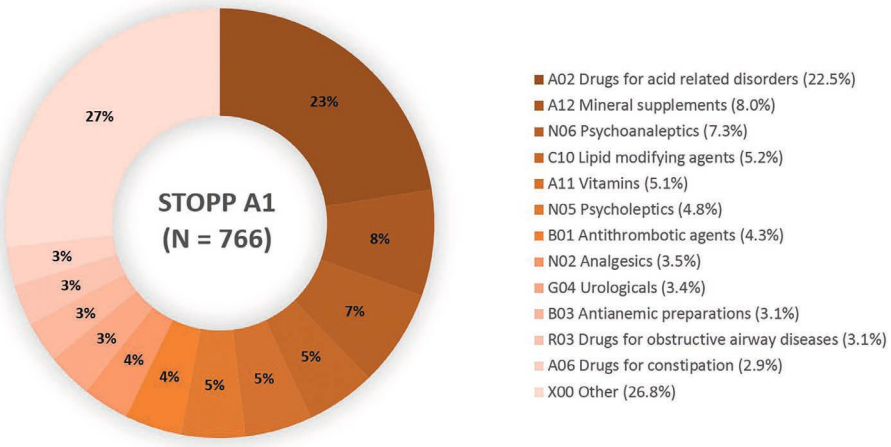

Figure 2. Distribution of drugs on ATC-2 level that were recommended for discontinuation because of a lack of an evidence-based clinical indication (STOPP A1).
Drugs that resulted in a recommendation <20 times were categorized as 'X00 Other'. 766 out of 1412 generated STOPP A1 signals were accepted by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

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.

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).

Determinants

There was no difference in mean acceptance of STOPP versus START signals (+2.1 [95% CI, -1.5; +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 more co-morbidities (>9: -11.8% [95% CI, -19.2; -4.5%], Table 3). Admission to a surgical ward was positively associated with acceptance (+10.3% [95% CI, 3.8; 16.8]). In Ireland (+26.8% [95% CI, 16.8; 36.7]) and the Netherlands (+14.7 [95% CI, 7.8; 21.7]) a higher acceptance was found compared with Switzerland as reference country.

For START signals, mean acceptance significantly decreased by -11.0% [95% CI, -19.4; -2.6] for patients with 7–9 co-morbidities after multivariate analysis. One or more falls

(+7.1% [95% CI, 0.7; 13.4]) and one or more 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 was only found in Ireland (+31.1% [95% CI, 18.2; 44.0]).

Table 3 shows all results of univariate and multivariate linear regression analysis of patient- and setting-related determinants on mean acceptance of STOPP and START signals.

Table 1. Baseline characteristics of the study population.

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

Data are presented as % (n) for categorical variables or median (interquartile range) 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%)
ADL activities of daily living, *CKD-EPI* chronic kidney disease epidemiology collaboration equation
[1]ADL as measured by the Barthel Index. Values ranged from 0 to 100. Higher values indicate higher functional independence.[18]

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.	1412	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%
Other STOPP criteria	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

Table 2. Continued.

Top 10 most frequently generated STOPP signals	Frequency, N	Acceptance, %
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
STOPP M1 – Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties	0	N/A
Total	**3465**	**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%

Table 2. Continued.

Top 10 most frequently generated START signals	Frequency, N	Acceptance, %
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%
Other START criteria	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	**1615**	**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. 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.

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

Determinant	STOPP			START		
	Patients *N*	Univariate % [95% CI]	Multivariate % [95% CI]	Patients *N*	Univariate % [95% CI]	Multivariate % [95% CI]
Patient-related						
Gender						
Male	421	37.7	Reference	374	37.0	Reference
Female	370	**+5.5 [1.0; 9.9]***	+2.8 [-1.9; 7.5]	307	+2.5 [-3.4; 8.3]	-0.8 [-7.1; 5.5]
Age (years)						
<75	226	38.6	Reference	193	37.2	Reference
75-80	249	+0.9 [-4.8; 6.7]	+1.0 [-4.8; 6.9]	211	+0.7 [-6.8; 8.3]	+0.9 [-7.0; 8.8]
>80	316	+3.3 [-2.1; 8.8]	+2.7 [-3.1; 8.5]	277	+1.9 [-5.2; 9.0]	+1.9 [-5.8; 9.7]
Number of co-morbidities						
<7	282	48.7	Reference	234	42.6	Reference
7-9	257	**-7.5 [-12.7; -2.2]***	-5.4 [-11.6; 0.8]	224	**-7.1 [-14.1; -0.04]***	**-11.0 [-19.4; -2.6]***
>9	252	**-19.0 [-24.3; -13.7]***	**-11.8 [-19.2; -4.5]***	223	-6.5 [-13.6; 0.5]	-7.1 [-17.2; 3.0]
Number of medications						
<9	287	39.3	Reference	252	38.7	Reference
9-12	275	+2.9 [-2.4; 8.2]	+2.7 [-2.9; 8.3]	239	-0.4 [-7.2; 6.4]	-2.9 [-10.3; 4.6]
>12	229	-0.4 [-6.0; 5.1]	+5.2 [-0.9; 11.2]	190	-1.5 [-8.8; 5.8]	-2.1 [-10.2; 6.1]
Number of falls in the previous year						
0	480	41.1	Reference	403	35.8	Reference
1	302	-1.7 [-6.4; 2.9]	+0.2 [-4.6; 4.9]	269	+5.0 [-0.9; 10.9]	**+7.1 [0.7; 13.4]***

Table 3. Continued.

Determinant	STOPP			START		
	Patients *N*	Univariate % [95% CI]	Multivariate % [95% CI]	Patients *N*	Univariate % [95% CI]	Multivariate % [95% CI]
Number of hospital admissions in the previous year						
0	386	43.4	Reference	319	34.2	Reference
1	402	-5.9 [-10.4; -1.5]*	-3.5 [-8.1; 1.2]	359	**+7.2 [1.4; 13.0]***	**+7.9 [1.6; 14.1]***
Housebound						
No	687	40.0	Reference	589	36.8	Reference
Yes	102	+1.2 [-5.5; 7.9]	-4.9 [-12.5; 2.7]	90	+9.1 [0.6; 17.6]	-0.0 [-10.0; 10.0]
Renal function (eGFR;CKD-EPI; ml/min/1.73m2)						
>50	477	39.4	Reference	407	36.6	Reference
30-50	169	-1.6 [-7.2; 4.0]	-2.0 [-7.6; 3.6]	149	+2.5 [-4.7; 9.7]	+2.1 [-5.5; 9.6]
<30	76	0.2 [-7.5; 8.0]	+1.6 [-6.0; 9.3]	69	-1.0 [-10.7; 8.8]	-1.0 [-11.1; 9.1]
Systolic blood pressure (mmHg)						
120-140	298	39.8	Reference	261	37.2	Reference
<120	243	-2.8 [-8.1; 2.7]	-0.0 [-5.5; 5.5]	209	-0.3 [-7.3; 6.7]	-1.1 [-8.4; 6.2]
>140	235	+3.9 [-1.6; 9.4]	+3.0 [-2.6; 8.6]	199	+3.3 [-3.8; 10.4]	+4.7 [-2.9; 12.2]
Setting-related						
Ward						
Medical	618	38.6	Reference	535	38.1	Reference
Surgical	173	**+7.2 [1.8;12.6]***	**+10.3 [3.8; 16.8]***	146	+0.2 [-6.9; 7.3]	-1.8 [-10.5; 6.9]
Admission type						
Elective	198	39.1	Reference	163	38.6	Reference
Non-elective	589	+1.5 [-3.7; 6.7]	+4.8 [-1.2; 10.8]	514	-0.4 [-7.2; 6.4]	+1.4 [-6.8; 9.7]

Table 3. Continued.

Determinant	STOPP			START		
	Patients *N*	Univariate % [95% CI]	Multivariate % [95% CI]	Patients *N*	Univariate % [95% CI]	Multivariate % [95% CI]
Length of hospital stay (days)						
– <6	194	38.6	Reference	151	35.9	Reference
– 6-10	332	+2.2 [-3.5; 7.9]	-1.5 [-7.4; 4.4]	385	+1.4 [-6.2; 9.0]	-0.8 [-8.9; 7.3]
– >10	263	+2.2 [-3.8; 8.2]	-3.8 [-10.2; 2.5]	244	+4.8 [-3.0; 12.6]	+3.9 [-4.6; 12.4]
Country of inclusion						
– Switzerland	392	30.7	Reference	320	31.3	Reference
– Belgium	122	**+9.6 [3.5; 15.8]***	+4.2 [-4.4; 12.8]	107	**+11.6 [3.4; 19.9]***	+8.8 [-2.7; 20.2]
– Ireland	88	**+27.7 [20.7; 34.7]***	**+26.8 [16.8; 36.7]***	78	**+26.2 [16.9; 35.5]***	**+31.1 [18.2; 44.0]***
– The Netherlands	189	**+20.8 [15.6; 26.1]***	**+14.7 [7.8; 21.7]***	176	**+7.8 [0.9; 14.8]***	-2.3 [-7.1; 11.6]

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 (*).

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 in in-hospital multimorbid older patients [21]. The frequency of generated START signals (1.8 vs 2 per patient) was similar to that in 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 rate of signal acceptance by the pharmacotherapy team 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 with 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 now widely used across Europe, and the pharmacotherapy teams were trained according to standardised operating procedures before 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. Investigation of patient-related factors revealed a negative association between an increased number of co-morbidities and the acceptance of STOPP and START signals. 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 inpatient patient population for whom the application of STOPP/START would be of lower or higher value from a clinical perspective.

CDSS-related restrictions

To incorporate guideline recommendations into the CDSS, STOPP/START criteria were converted into algorithms; however, many lacked 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, but decisions to accept or reject STOPP/START signals may be different in other clinical settings as well as the willingness of patients and phycians to change long-term medication use. 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 in retrospective studies, essential factors, such as life expectancy, drug exposure length and time until benefit, were considered by the pharmacotherapy team. Carvalho et al. 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 [31]. Consequently, applying STOPP/START using medical databases without clinical evaluation is hampered compared with 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 reasons, 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, in this substudy, the study population and the term 'recommendations' were defined differently than in the OPERAM main trial (see SI3).

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 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 in which 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

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

Authorship eligibility is based on the ICMJE authorship criteria. The authors certify that they have participated in the aspects conception and design (BS, CH, TE, EvP, DOM, AS, NR, IW, WK), acquisition and interpretation of data (BS, CH, JoH, IS, TE, EvP, IW, WK, NR, AS, DOM), drafting the article (BS, CH) 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-Luc-UCL: 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

Abbreviations

ATC	Anatomical Therapeutic Chemical Classification System
CDSS	Clinical Decision Support System
OPERAM	OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people
SHiM	Structured History taking of Medication use
START	Screening tool to alert to right treatment
STOPP	Screening tool of older persons' prescriptions
STRIP	Systematic Tool to Reduce Inappropriate Prescribing
STRIPA	STRIP Assistant

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SUPPLEMENTARY INFORMATION SI1

Table SI1.1. Frequency and acceptance of CDSS-generated STOPP/START signals in total and per country.

STOPP criteria (n=79)	All countries		Belgium (BE)		Switzerland (CH)		Ireland (IE)		The Netherlands (NL)	
	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)
TOTAL	**3465**	**40.1%**	**423**	**39.7%**	**2025**	**34.7%**	**384**	**57.6%**	**633**	**47.2%**
A 1. Any drug prescribed without an evidence-based clinical indication.	1412	54.2%	156	53.8%	846	46.8%	171	76.6%	239	64.9%
A 3. Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants	503	26.0%	54	31.5%	293	27.0%	51	25.5%	105	21.0%
D 5. Benzodiazepines for ≥ 4 weeks	181	64.1%	54	59.3%	71	60.6%	11	90.9%	45	68.9%
F 2. PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks	146	34.9%	13	38.5%	81	28.4%	28	46.4%	24	41.7%
B 6. Loop diuretic as first-line treatment for hypertension .	101	22.8%	8	0%	71	18.3%	8	25.0%	14	57.1%
C 3. Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, 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%	2	0%	71	4.2%	2	0%	0	0%
F 3. Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids) in patients with chronic constipation where non-constipating alternatives are available	75	20.0%	6	16.7%	38	7.9%	13	30.8%	18	38.9%

Table SI1.1. Continued.

STOPP criteria (n=79)	All countries		Belgium (BE)		Switzerland (CH)		Ireland (IE)		The Netherlands (NL)	
	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)
G 2. Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD	63	6.3%	2	0%	28	7.1%	4	50.0%	29	0%
C 5. Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic atrial fibrillation	60	31.7%	9	44.4%	43	23.3%	2	100%	6	50.0%
L 2. Use of regular (as distinct from PRN) opioids without concomitant laxative	56	12.5%	20	0%	19	10.5%	0	N/A	17	29.4%
C 6. Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease .	51	17.6%	3	0%	42	14.3%	2	100%	4	25.0%
B 7. Loop diuretic for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure	48	25.0%	3	33.3%	33	12.1%	4	25.0%	8	75.0%
L 1. Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine) as first line therapy for mild pain	47	10.6%	8	0.0%	32	12.5%	1	0%	6	16.7%
B 5. Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias	46	32.6%	9	11.1%	25	36.0%	6	66.7%	6	16.7%

Table SI1.1. Continued.

STOPP criteria (n=79)	All countries		Belgium (BE)		Switzerland (CH)		Ireland (IE)		The Netherlands (NL)	
	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)
H 2. NSAID with severe hypertension (risk of exacerbation of hypertension) or severe heart failure	40	57.5%	8	50.0%	28	53.6%	1	100%	3	100%
C 9. Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmonary embolus without continuing provoking risk factor s (e.g. thrombophilia) for > 12 months	37	2.7%	3	0%	24	4.2%	4	0%	6	0%
G 3. Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium) with a history of narrow angle glaucoma or bladder outflow obstruction	35	17.1%	3	0%	21	9.5%	0	N/A	11	36.4%
H 5. Corticosteroids (other than periodic intra-articular injections for mono-articular pain) for osteoarthritis	32	15.6%	6	16.7%	13	30.8%	5	0%	8	0%
G 4. Benzodiazepines with acute or chronic respiratory failure i.e. $pO2 < 8.0$ kPa ± $pCO2 > 6.5$ kPa	31	58.1%	4	50.0%	18	61.1%	0	N/A	9	55.6%
B 4. Beta blocker with bradycardia (< 50/min) , type II heart block or complete heart block	28	10.7%	1	0%	25	12.0%	1	0%	1	0.0%
K 1. Benzodiazepines (in patients with risk of falls)	27	74.1%	2	50.0%	9	44.4%	6	83.3%	10	100%
B 8. Thiazide diuretic 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	22	54.5%	2	50.0%	13	46.2%	2	50.0%	5	80.0%

Table SI1.1. Continued.

STOPP criteria (n=79)	All countries		Belgium (BE)		Switzerland (CH)		Ireland (IE)		The Netherlands (NL)	
	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)
E 3. Factor Xa inhibitors (e.g. rivaroxaban, apixaban) if eGFR < 15 ml/min/1.73m2	21	9.5%	0	N/A	18	5.6%	2	50.0%	1	0.0%
C 10. NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination	20	45.0%	0	N/A	15	26.7%	5	100%	0	N/A
E 6. Metformin if eGFR < 30 ml/min/1.73m2	18	50.0%	3	33.3%	10	60.0%	1	0%	4	50.0%
B 11. ACE inhibitors or Angiotensin Receptor Blockers in patients with hyperkalaemia.	17	35.3%	2	0%	6	33.3%	9	44.4%	0	N/A
K 2. Neuroleptic drugs (in patients with risk of falls)	17	47.1%	1	100%	11	36.4%	3	66.7%	2	50.0%
B 9. Loop diuretic for treatment of hypertension with concurrent urinary incontinence.	15	6.7%	0	N/A	12	0%	1	100%	2	0%
H 9. Oral bisphosphonates 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	15	0%	8	0%	0	N/A	7	0%	0	N/A
D 9. Neuroleptic antipsychotic in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed	14	42.9%	0	N/A	9	33.3%	4	75.0%	1	0%

Table SI1.1. Continued.

STOPP criteria (n=79)	All countries		Belgium (BE)		Switzerland (CH)		Ireland (IE)		The Netherlands (NL)	
	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)
K 3. Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers,) with persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥ 20mmHg (in patients with risk of falls)	14	14.3%	0	N/A	9	11.1%	5	20.0%	0	N/A
B 10. Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine), unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives	13	46.2%	9	44.4%	3	66.7%	0	N/A	1	0%
J 1. Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride) with type 2 diabetes mellitus	12	50.0%	3	100.0%	4	50.0%	0	N/A	5	20.0%
C 8. 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,	10	0%	1	0.0%	7	0%	0	N/A	2	0%
D 14. First-generation antihistamines	10	40.0%	0	N/A	6	16.7%	2	100.0%	2	50.0%
H 4. Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthrtitis	9	22.2%	0	N/A	3	0%	5	40.0%	1	0%

Table SI1.1. Continued.

STOPP criteria (n=79)	All countries		Belgium (BE)		Switzerland (CH)		Ireland (IE)		The Netherlands (NL)	
	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)
H 6. Long-term NSAID or colchicine (>3 months) for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor (e.g. allopurinol, febuxostat)	9	11.1%	1	0%	2	0%	2	0%	4	25.0%
K 4. Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon (in patients with risk of falls)	9	88.9%	0	N/A	4	75.0%	3	100%	2	100%
D 1. Tricyclic Antidepressants (TCAs) with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention	8	87.5%	0	N/A	4	100%	1	100%	3	66.7%
E 4. NSAID's if eGFR < 50 ml/min/1.73m2	8	75.0%	1	0.0%	7	85.7%	0	N/A	0	N/A
H 3. Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried	8	37.5%	1	100%	3	33.3%	4	25.0%	0	N/A
H 7. COX-2 selective NSAIDs with concurrent cardiovascular disease	8	100%	0	N/A	2	100%	0	N/A	6	100%
I 2. Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope	8	50.0%	0	N/A	3	0.0%	1	100%	4	75.0%

Table SI1.1. Continued.

STOPP criteria (n=79)	All countries		Belgium (BE)		Switzerland (CH)		Ireland (IE)		The Netherlands (NL)	
	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)
D 11. Acetylcholinesterase inhibitors 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	6	50.0%	0	N/A	5	40.0%	1	100%	0	0%
F 4. 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)	6	16.7%	0	N/A	0	N/A	1	0.0%	5	20.0%
J 5. Oral oestrogens without progestogen in patients with intact uterus	6	16.7%	2	0%	4	25.0%	0	N/A	0	N/A
C 11. NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis	5	80.0%	0	N/A	5	80.0%	0	N/A	0	N/A
D 2. Initiation of Tricyclic Antidepressants (TCAs) as first-line antidepressant treatment	5	40.0%	1	0%	2	100%	0	N/A	2	0%
D 4. Selective serotonin re-uptake inhibitors (SSRI's) with current or recent significant hyponatraemia i.e. serum Na+ < 130 mmol/l	5	20.0%	1	0%	4	25.0%	0	N/A	0	N/A
L 3. Long-acting opioids without short-acting opioids for break-through pain	5	0%	1	0%	2	0%	2	0%	0	N/A
B 1. Digoxin for heart failure with normal systolic ventricular function	4	25.0%	2	0%	2	50.0%	0	N/A	0	N/A

Table SI1.1. Continued.

STOPP criteria (n=79)	All countries		Belgium (BE)		Switzerland (CH)		Ireland (IE)		The Netherlands (NL)	
	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)
B 3. Beta-blocker in combination with verapamil or diltiazem	4	50.0%	1	100%	2	50.0%	0	N/A	1	0%
B 13. Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) in severe heart failure characterised by hypotension i.e. systolic BP < 90 mmHg, or concurrent nitrate therapy for angina.	4	25.0%	0	N/A	2	50.0%	0	N/A	2	0.0%
C 1. Long-term aspirin at doses greater than 160mg per day	4	50.0%	1	100%	3	33.3%	0	N/A	0	N/A
C 2. Aspirin with a past history of peptic ulcer disease without concomitant PPI.	4	0%	2	0%	2	0%	0	N/A	0	N/A
E 2. Direct thrombin inhibitors (e.g. dabigatran) if eGFR < 30 ml/min/1.73m2	4	75.0%	2	100%	2	50.0%	0	N/A	0	N/A
D 8. Anticholinergics/antimuscarinics in patients with delirium or dementia	3	66.7%	0	N/A	0	N/A	1	100%	2	50.0%
I 1. Antimuscarinic drugs with dementia, or chronic cognitive impairment (risk of increased confusion, agitation) or narrow-angle glaucoma or chronic prostatism	3	33.3%	0	N/A	1	0%	0	0%	2	50.0%
J 3. Beta-blockers in diabetes mellitus with frequent hypoglycaemic episodes	3	33.3%	1	0%	0	N/A	1	100%	1	0%

Table SI1.1. Continued.

STOPP criteria (n=79)	All countries		Belgium (BE)		Switzerland (CH)		Ireland (IE)		The Netherlands (NL)	
	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)
B 2. Verapamil or diltiazem with NYHA Class III or IV heart failure	2	50.0%	0	N/A	0	N/A	0	N/A	2	50.0%
B 12. Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene) without monitoring of serum potassium	2	0%	0	N/A	2	0%	0	N/A	0	N/A
C 4. Aspirin plus clopidogrel 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 .	2	0%	0	N/A	0	N/A	1	0%	1	0%
D 10. Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia	2	50.0%	1	0%	1	100%	0	N/A	0	N/A
D 12. Phenothiazines as first-line treatment, since safer and more efficacious alternatives exist	2	0%	1	0%	0	N/A	0	N/A	1	0.0%
J 6. Androgens (male sex hormones) in the absence of primary or secondary hypogonadism	2	0%	0	N/A	2	0%	0	N/A	0	N/A
D 13. Levodopa or dopamine agonists for benign essential tremor	1	100%	0	N/A	1	100%	0	N/A	0	N/A
E 1. Digoxin at a long-term dose greater than 125µg/day if eGFR < 30 ml/min/1.73m2	1	0%	1	0%	0	N/A	0	N/A	0	N/A

Table SI1.1. Continued.

STOPP criteria (n=79)	All countries		Belgium (BE)		Switzerland (CH)		Ireland (IE)		The Netherlands (NL)	
	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)
H 8. NSAID with concurrent corticosteroids without PPI prophylaxis	1	0%	0	N/A	1	0%	0	N/A	0	N/A
C 7. Ticlopidine in any circumstances.	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
D 3. Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol) with a history of prostatism or previous urinary retention	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
D 6. Antipsychotics (i.e. other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Disease	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
D 7. Anticholinergics/ antimuscarinics to treat extra-pyramidal side-effects of neuroleptic medications	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
E 5. Colchicine if eGFR < 10 ml/min/1.73m2	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
F 1. Prochlorperazine or metoclopramide with Parkinsonism	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
G 1. Theophylline as monotherapy for COPD	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
H 1. Non-steroidal anti-inflammatory drug (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	0	N/A	0	N/A	0	N/A	0	N/A

Table SI1.1. Continued.

STOPP criteria (n=79)	All countries		Belgium (BE)		Switzerland (CH)		Ireland (IE)		The Netherlands (NL)	
	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)
J 2. Thiazolidenediones (e.g. rosiglitazone, pioglitazone) in patients with heart failure	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
J 4. Oestrogens with a history of breast cancer or venous thromboembolism	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
M 1. Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines)	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A

Table SI1.2. Frequency and acceptance of CDSS-generated START signals in total and per country

START criteria (n=31)	All countries		Belgium (BE)		Switzerland (CH)		Ireland (IE)		The Netherlands (NL)	
	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)
TOTAL	**1615**	**37.2%**	**236**	**43.2%**	**761**	**30.5%**	**192**	**55.7%**	**426**	**36.9%**
H 1. 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%	25	4.0%	88	0%	28	0%	21	14.3%
A 6. Angiotensin Converting Enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease.	133	51.1%	11	54.5%	48	64.6%	18	61.1%	56	35.7%
E 4. Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab) 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).	118	43.2%	20	55.0%	59	32.2%	11	81.8%	28	42.9%
H 2. Laxatives in patients receiving opioids regularly.	115	47.8%	41	51.2%	39	38.5%	10	90.0%	25	40.0%
E 3. 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%	22	59.1%	49	42.9%	14	78.6%	25	88.0%

Table SI1.2. Continued

START criteria (n=31)	All countries		Belgium (BE)		Switzerland (CH)		Ireland (IE)		The Netherlands (NL)	
	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)
E 5. Vitamin D supplement 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).	99	75.8%	4	50.0%	46	76.1%	13	61.5%	36	83.3%
A 5. 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%	10	80.0%	38	50.0%	5	60.0%	27	74.1%
G 2. 5-alpha reductase inhibitor with symptomatic prostatism, where prostatectomy is not considered necessary.	79	15.2%	16	31.3%	46	13.0%	1	0.0%	16	6.3%
D 2. Fibre supplements (e.g. bran, ispaghula, methylcellulose, sterculia) for diverticulosis with a history of constipation.	76	18.4%	6	16.7%	38	0%	15	73.3%	17	11.8%
A 1/A 2. Start vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation. If oral anticoagulants are contra-indicated, start aspirin instead.	72	50.0%	17	17.6%	31	58.1%	12	83.3%	12	41.7%
A 7. Beta-blocker with ischaemic heart disease.	69	34.8%	4	75.0%	35	31.4%	6	66.7%	24	25.0%

Table SI1.2. Continued

START criteria (n=31)	All countries		Belgium (BE)		Switzerland (CH)		Ireland (IE)		The Nether-lands (NL)	
	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)
E 2. Bisphosphonates and vitamin D and calcium in patients taking long-term systemic corticosteroid therapy.	69	52.2%	12	75.0%	25	48.0%	10	80.0%	22	31.8%
A 3. Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease.	59	37.3%	4	50.0%	35	22.9%	8	50.0%	12	66.7%
A 8. Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol) with stable systolic heart failure.	58	22.4%	4	25.0%	24	25.0%	6	83.3%	24	4.2%
G 1. Alpha-1 receptor blocker with symptomatic prostatism, where prostatectomy is not considered necessary.	53	24.5%	4	25.0%	35	31.4%	1	0%	13	7.7%
B 3. Home continuous oxygen with documented chronic hypoxaemia (i.e. pO2 < 8.0 kPa or 60 mmHg or SaO2 < 89%)	52	0%	1	0%	42	0%	7	0%	2	0.0%
A 4. Antihypertensive therapy 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.	49	24.5%	11	36.4%	10	20.0%	5	60.0%	23	13.0%

Table SI1.2. Continued

START criteria (n=31)	All countries		Belgium (BE)		Switzerland (CH)		Ireland (IE)		The Netherlands (NL)	
	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)
E 6. Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat) with a history of recurrent episodes of gout.	35	37.1%	3	33.3%	10	60.0%	5	60.0%	17	17.6%
F 1. ACE inhibitor or Angiotensin Receptor Blocker (if intolerant of ACE inhibitor) in diabetes with evidence of renal disease i.e. dipstick proteinuria or microalbuminuria (>30mg/24 hours) with or without serum biochemical renal impairment.	22	59.1%	4	75.0%	6	66.7%	5	80.0%	7	28.6%
B 1. Regular inhaled B2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium) for mild to moderate asthma or COPD.	21	0%	5	0%	11	0%	1	0%	4	0%
C 2. Non-TCA antidepressant drug in the presence of persistent major depressive symptoms.	18	27.8%	2	100%	10	30.0%	3	0%	3	0%
C 5. Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated) for persistent severe anxiety that interferes with independent functioning.	14	28.6%	6	33.3%	5	40.0%	1	0%	2	0%

Table SI1.2. Continued

START criteria (n=31)	All countries		Belgium (BE)		Switzerland (CH)		Ireland (IE)		The Nether-lands (NL)	
	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)
E 1. Disease-modifying anti-rheumatic drug (DMARD) with active, disabling rheumatoid disease.	14	28.6%	1	0%	5	40.0%	4	50.0%	4	0%
C 6. Dopamine agonist (ropinirole or pramipexole or rotigotine) for Restless Legs Syndrome, once iron deficiency and severe renal failure have been excluded.	9	11.1%	1	100%	7	0%	0	N/A	1	0%
B 2. Regular inhaled corticosteroid for moderate-severe asthma or COPD, where FEV1 <50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.	8	25.0%	0	N/A	7	14.3%	0	N/A	1	100%
C 3. Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine) for mild-moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).	8	12.5%	0	N/A	4	0%	1	100%	3	0%
D 1. Proton Pump Inhibitor with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation.	8	37.5%	1	100%	5	20.0%	1	100%	1	0%
C 1. L-DOPA or a dopamine agonist in idiopathic Parkinson's disease with functional impairment and resultant disability.	3	0%	0	N/A	2	0%	1	0%	0	N/A

Table SI1.2. Continued

START criteria (n=31)	All countries		Belgium (BE)		Switzerland (CH)		Ireland (IE)		The Netherlands (NL)	
	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)	Frequency (N)	Acceptance (%)
E 7. Folic acid supplement in patients taking methotrexate.	2	100%	1	100%	1	100%	0	N/A	0	N/A
C 4. Topical prostaglandin, prostamide or beta-blocker for primary open-angle glaucoma.	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
G 3. Topical vaginal oestrogen or vaginal oestrogen pessary for symptomatic atrophic vaginitis.	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A

Data was ordered from highest to lowest frequency of generated signals. STOPP criteria C7, D3, D6, D7, E5, F1, G1, H1, J2, J4 and M1 and START criteria C4 and G3 were in no case generated. STOPP A2 *("Any drug prescribed beyond the recommended duration, where treatment duration is well defined")* could not be coded and was therefore not incorporated in the CDSS. START A1 *("Vitamin K antagonists, direct thrombin inhibitors or factor Xa in the presence of chronic atrial fibrillation")* and START A2 *("Aspirin 75-160 mg once daily in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated")* were merged into one algorithm (START A1/2). START I1 *("Seasonal trivalent influenza vaccine annually)* and I2 *("Pneumococcal vaccine at least once after age 65 according to national guidelines")* were excluded from analysis.

SUPPLEMENTARY INFORMATION SI2

Table SI2.1. List of recommended drug changes based on accepted STOPP/START signal

Drug class	ATC-2	Total	STOPP	START
Drugs for acid related disorders	A02	235	232	3
Antipsychotics	N05	232	232	0
Vitamins (e.g. vitamin D)	A11	148	50	98
Antithrombotic agents	B01	125	69	56
Mineral supplements (e.g. calcium)	A12	121	61	60
Agents acting on the renin-angiotensin system	C09	105	16	89
Drugs for constipation	A06	102	33	69
Antidepressants	N06	91	81	10
Lipid modifying agents	C10	90	40	50
Analgesics (e.g. opioids, high dose salicylic acid excl. NSAID)	N02	77	71	6
Drugs for treatment of bone diseases	M05	73	2	71
Diuretics	C03	61	61	0
Urologicals	G04	59	34	25
Antiinflammatory and antirheumatic products (e.g. NSAID)	M01	58	58	0
Drugs for obstructive airway diseases	R03	51	49	2
Beta blocking agents	C07	47	10	37
Cardiac therapy (e.g. antiarrhythmics, nitrates)	C01	34	34	0
Antianemic preparations	B03	27	25	2
Cough and cold preparations	R05	27	27	0
Drugs used in diabetes	A10	19	19	0
Antigout preparations	M04	19	6	13
Antihistamines for systemic use	R06	19	19	0
Topical products for joint and muscular pain	M02	15	15	0
Corticosteroids for systemic use	H02	14	14	0
Drugs for functional gastrointestinal disorders	A03	13	13	0
Opthalmologicals	S01	13	13	0
Calcium channel blockers	C08	12	8	4
Nasal preparations	R01	12	12	0
Antiepileptics	N03	10	10	0
General nutrients	V06	9	9	0
Antidiarrheals, intestinal antiinflammatory/infective agents	A07	8	7	1
Other nervous system drugs	N07	8	8	0
Antihypertensives	C02	7	7	0
Vasoprotectives	C05	5	5	0
Sex hormones and modulators of the genital system	G03	5	5	0
Other (<5)		39	35	4
Total		**1,990**	**1,390**	**600**

Data was ordered from highest to lowest numbers of accepted STOPP/START-signals by the pharmacotherapy teams. Drug class was based on ATC classification level 2.
ATC Classification = Anatomical Therapeutic Chemical Classification

SUPPLEMENTARY INFORMATION SI3

OPERAM trial results in relation to this substudy

In this Supplementary Information, differences in results provided in the main OPERAM trial paper [1] and this substudy will be elaborated. Different choices were made in the substudy to define the study population and to define the term 'recommendations' compared to the OPERAM main trial.

OPERAM trial

In the OPERAM trial paper, intervention patients were eligible for analysis when they 'received the allocated intervention' (n=916, Fig 1, Table 2) [1] which was defined by:

1) Having received an in-hospital pharmacotherapy (=first) analysis prior to discussion with the attending hospital physician and the patient
   AND/OR
2) Having received a second pharmacotherapy analysis to generate a discharge report for the general practitioner (GP)

Substudy

In this substudy, the aim was to determine the frequency of CDSS generated STOPP/START signals and subsequent acceptance by a pharmacotherapy team for in-hospital use, prior to discussion with the attending hospital physician and patient. Therefore, patients (n=826) from the OPERAM intervention group were selected for whom:

1) An in-hospital pharmacotherapy (=first) analysis was performed prior to discussion with the attending hospital physician and the patient
   AND
2) Data of the in-hospital pharmacotherapy analysis was available in the CDSS

SI3 - Figure SI3.1 shows a visual presentation of the definition for the term 'recommendations' used in de OPERAM trial paper and this substudy in relation to the OPERAM intervention.

Reference

1. Blum MR, Sallevelt BTGM, Spinewine A, Mahony DO, Feller M, Baumgartner C, et al. Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults (OPERAM): cluster randomised controlled trial. BMJ 2021;374:n1585. https://doi.org/10.1136/bmj.n1585.

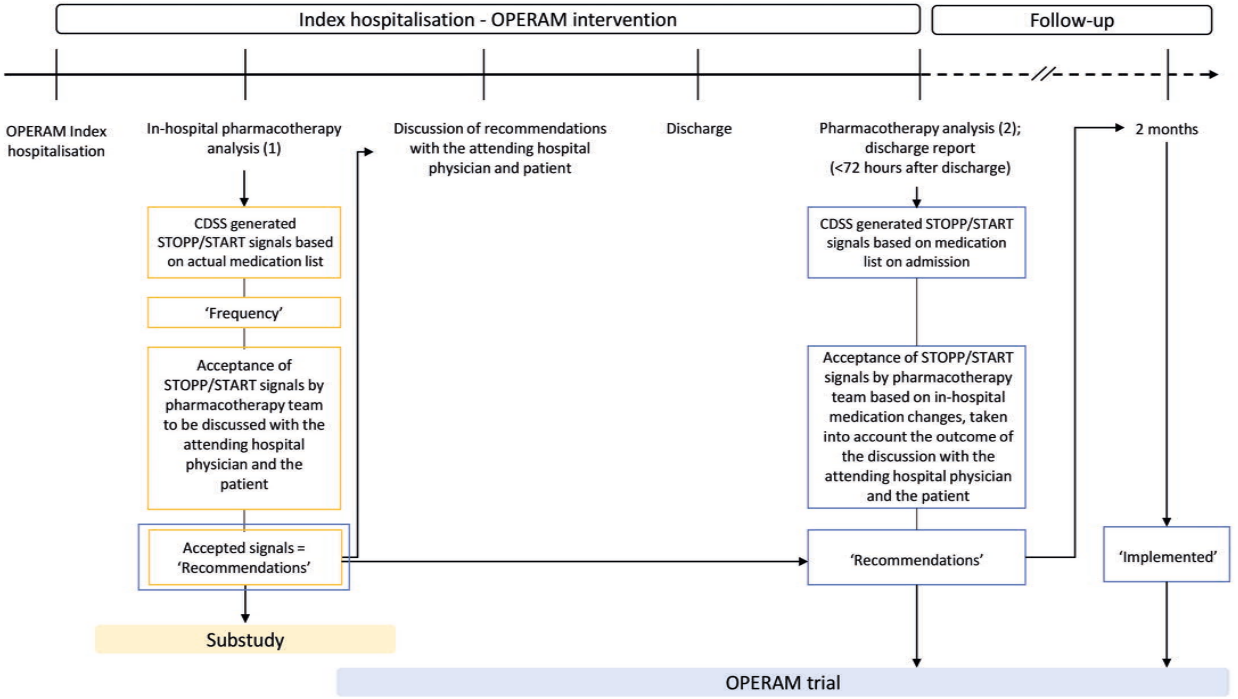

Figure SI3.1. Visual presentation of the definition 'recommendations' in de main OPERAM trial paper and this substudy in relation to the OPERAM intervention.

In the OPERAM trial (Chapter 3.2 - Table 3) [1] 'recommendations' included both accepted STOPP/START signals from the in-hospital pharmacotherapy analysis and the second analysis for the discharge report sent to the GP (n=2,331). Duplicates were removed as well as conflicting recommendations (e.g. both a recommendation to initiate and to discontinue a drug), which could occur due to changes in medication and conditions in the timeframe between first and second pharmacotherapy analysis. Dose reductions based on STOPP criteria were excluded from analysis. Frequencies of CDSS-generated signals are not provided in the main OPERAM trial paper.

In this substudy, 'recommendations' included only accepted STOPP/START signals from the in-hospital pharmacotherapy analysis (n=1,990).

4.2

Chapter 4.2

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

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Abstract

Introduction

Multimorbidity and polypharmacy remain challenging in the context of rapidly ageing populations globally. Periodic evaluation of the individual patient's pharmacotherapy by medication review is important to ensure an optimised balance between therapeutic and preventive benefits and potential harms of treatment. The aim of this study was to evaluate 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 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 i.e. 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.

Introduction

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) [1–3]. 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 [4–6].

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 [11–13]. 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) digitalized 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).

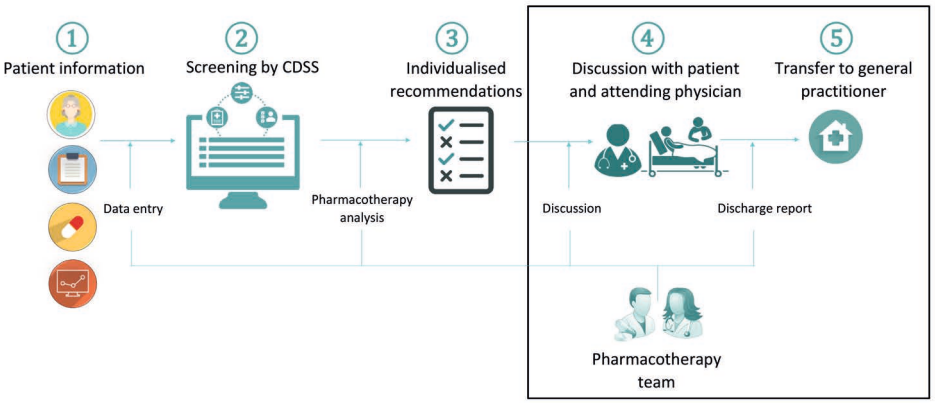

Figure 1. Summary of all consecutive steps (1-5) of the intervention within the OPERAM trial and the focus of this study highlighted: the agreement of recommendations by patients and attending physicians after discussion with the pharmacotherapy team (step 4).

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.

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.

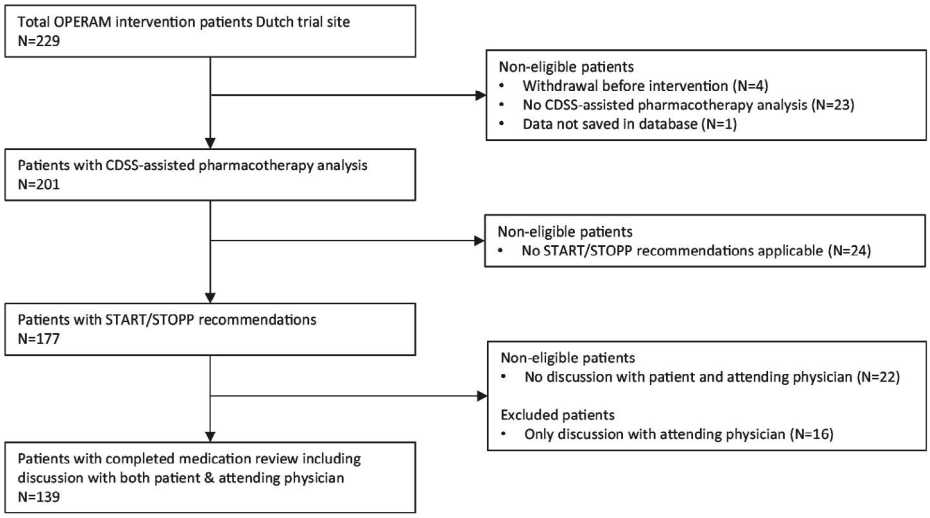

Figure 2. Study population flowchart. Non-eligible patients did not fulfil the inclusion criteria of this OPERAM substudy i.e. discussion of recommendations with patient and attending physician in order to determine agreement with recommendations.

Table 1. Baseline characteristics of study population.

Characteristics	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/1.73m2) 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.

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.

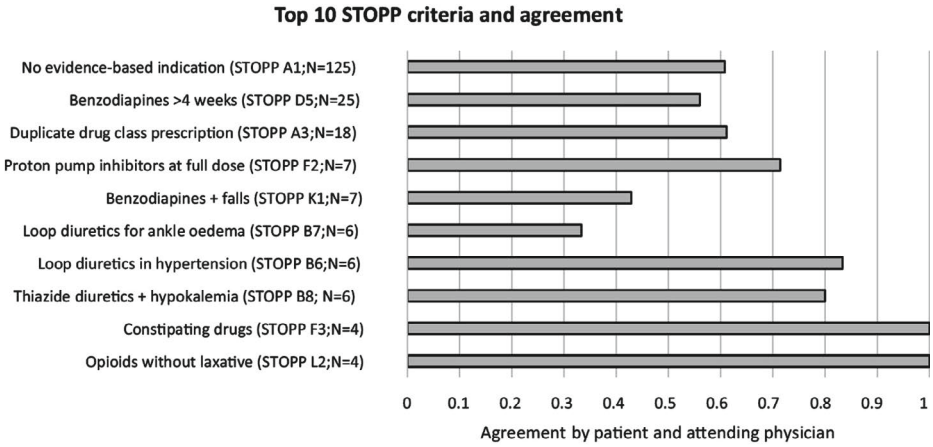

Figure 3. Top 10 STOPP recommendations and corresponding agreement by patient and attending physician after discussion with PT.
STOPP A1: 'No evidence-based clinical indication' contains stop recommendations for multiple medications with 'drugs for acid related disorders' being the most prevalent (43.2%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

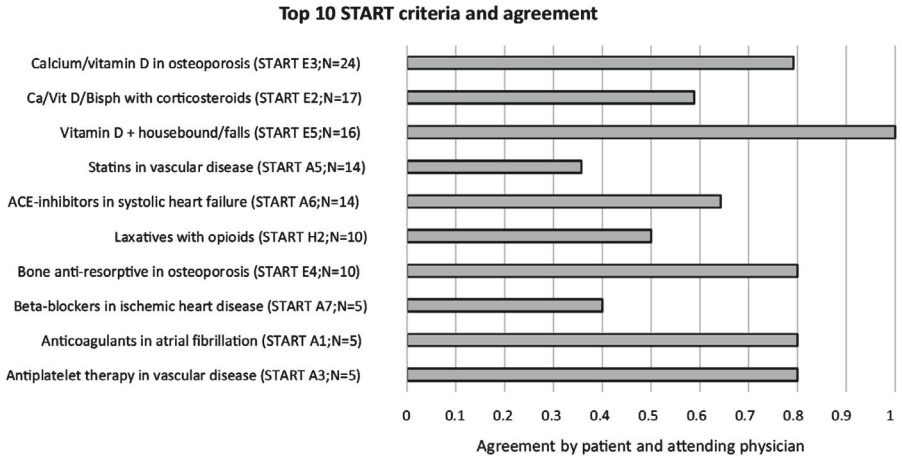

Figure 4. Top 10 START recommendations and corresponding agreement by patient and attending physician after discussion with PT.
START E3 consist of recommendations for both calcium and/or vitamin D. START E2 consist of recommendations for calcium, vitamin D and/or bisphosphonates (i.e. Ca/Vit D/Bisph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

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).

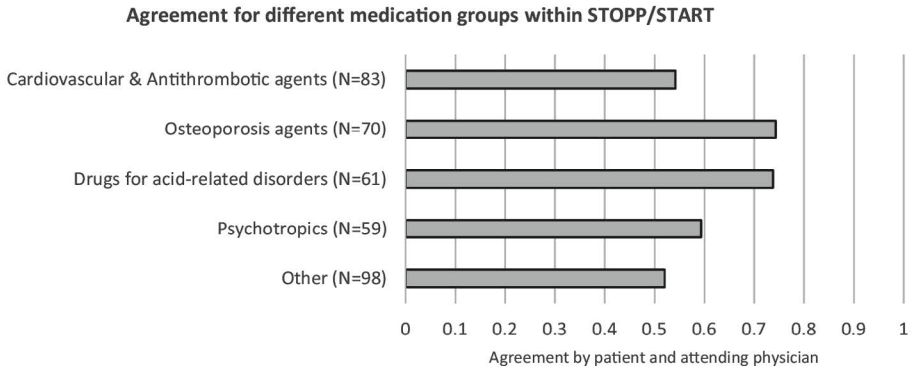

Figure 5. Categorisation of individual STOPP/START recommendations (N=371) into 5 medication groups and subsequent agreement after discussion with patient and attending physician. Note: Groups 'psychotropics' and 'drugs for acid related disorders' contain only STOPP recommendations, 'osteoporosis agents' 3 STOPP and 67 START, 'cardiovascular & antithrombotic agents' 35 STOPP and 48 START and the group 'other' contained 79 STOPP and 19 START recommendations.

Table 2. Statistical analysis of determinants of agreement.

Determinant	Patients (N)	Mean agreement (%)	Linear regression (% [95%-CI])	
Patient related determinants			**Univariate**	**Multivariate**
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]
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/1.73m2)				
>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			**Univariate**	**Multivariate**
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.

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

Authorship eligibility is based on the ICMJE authorship criteria. The authors certify that they have participated in the aspects conception and design (CH, BS, TE, RvM, DOM, OD,NR, IW, WK), acquisition and interpretation of data (CH, BS, JOH, TE, IW, WK, RvM, NR, OD, DOM), drafting the article (CH) 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-Luc-UCL: 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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views of the EC and the Swiss government. The funder of the study had no role in the study design; data collection, analysis and interpretation or writing of the report.

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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4.3

Chapter 4.3

Detectability of medication errors with a STOPP/START-based medication review in older people prior to a potentially preventable drug-related hospital admission

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Abstract

Introduction

Multimorbidity and polypharmacy are risk factors for drug-related admissions (DRAs) in the ageing population. DRAs caused by medication errors (MEs) are considered potentially preventable. The STOPP/START criteria were developed to detect potential MEs in older people. The aim of this study was to assess the detectability of MEs with a STOPP/START-based in-hospital medication review in older people with polypharmacy and multimorbidity prior to a potentially preventable DRA.

Methods

Hospitalised older patients (*n* = 963) with polypharmacy and multimorbidity from the intervention-arm of the OPERAM-trial received a STOPP/START-based in-hospital medication review by a pharmacotherapy team. Readmissions within one year after the in-hospital medication review were adjudicated for drug-relatedness. A retrospective assessment was performed to determine whether MEs identified at the first DRA were detectable during the in-hospital medication review.

Results

In total, 84 of 963 OPERAM intervention patients (8.7%) were readmitted with a potentially preventable DRA, of which 72 patients (*n* = 77 MEs) were eligible for analysis. About half (48%, *n*=37/77) of MEs were not present during the in-hospital medication review and therefore were not detectable at that time. The pharmacotherapy team recommended a change in medication regimen in 50% (*n*=20/40) of present MEs, which corresponds to 26% (*n* = 20/77) of the total identified MEs at readmission. However, these recommendations were not implemented.

Conclusion

MEs identified at readmission were not addressed by a prior single in-hospital medication review because either these MEs occurred after the medication review (~50%), or no recommendation was given during the medication review (~25%), or the recommendation was not implemented (~25%). Future research should focus on optimisation of the timing and frequency of medication review and the implementation of proposed medication recommendations.

Introduction

Reducing drug-related harm is a continuous challenge for health care professionals who aim to maintain a positive benefit-risk balance of pharmacotherapy to treat patients [1–3]. With ageing, the susceptibility to develop chronic diseases and multimorbidity – the co-existence of multiple chronic diseases in an individual – increases [4–6]. Multimorbidity impacts the quality of life and frequently results in polypharmacy [7,8], usually defined as the concomitant use of five or more regularly prescribed medications [9,10]. Multimorbidity and polypharmacy are both important risk factors for drug-related hospital admissions (DRAs) [11,12]. A DRA is defined as 'a hospitalisation due to an adverse drug event (ADE); harm due to an adverse drug reaction (ADR) or a medication error (ME) related to overuse, underuse, or misuse of prescription and non-prescription medications and which is the main reason for or contributes to hospital admission of a patient' [13]. DRAs caused by MEs are of particular interest, because they are potentially preventable [14–17].

Older people are four times more likely to be admitted due to drug-related problems than younger adults [18,19]. It is estimated that DRAs account for 10–30% of all acute hospital admissions in older people, and about half of these are considered potentially preventable [19–25]. Similarly, the risk of drug-related readmissions is high in older people with an estimated incidence of 21% (IQR 14–23), although reported incidences vary greatly among studies due to heterogeneity in definitions and study populations [11,12,26]. Hence, effective strategies to reduce preventable DRAs in this population are urgently needed.

Several explicit screening tools have been developed to facilitate the detection of potential MEs in medication review in older people [27]. The Screening Tool of Older Person's Prescriptions and the Screening Tool to Alert doctors to Right Treatment (STOPP/START) criteria are the most widely used explicit screening tools in Europe, and their use in older patients has proven to decrease potential medication overuse, underuse and misuse [27–31]. In addition, the use of clinical decision support systems (CDSS) demonstrated a reduction in potentially inappropriate medication in hospitalised older adults [32,33]. A CDSS-assisted structured medication review with integrated STOPP/START algorithms may contribute to reducing MEs that lead to potentially preventable DRAs [34]. Hence, the STOPP/START criteria version 2 were converted to software algorithms to enable their incorporation into a CDSS [35,36].

The effect of a CDSS-assisted STOPP/START-based medication review in hospitalised older people with polypharmacy and multimorbidity was recently investigated in the OPtimising thERapy to Prevent Avoidable Hospital Admissions in the Multimorbid Elderly (OPERAM) trial [37,38]. The primary outcome of this multicentre randomised controlled trial was the occurrence of a first DRA within one year after receiving

an in-hospital medication review. Although pharmacotherapy optimisation reduced potentially inappropriate prescribing, the intervention did not significantly affect the primary outcome DRA nor was it detrimental to patient outcomes compared to usual care [38]. The presumed effect of reducing overuse, underuse, and misuse with an in-hospital structured medication review on preventing DRAs in older people with multimorbidity and polypharmacy was not confirmed. A better understanding of the relationship between the occurrence of potentially preventable DRAs and the detectability of MEs linked to these DRAs during a single, in-hospital medication review may provide guidance on ways to improve the medication review process.

The aim of the present study was to assess the detectability of MEs with a STOPP/START-based in-hospital medication review in older people with polypharmacy and multimorbidity prior to a potentially preventable DRA.

Methods

Setting, design and study population

This study was embedded within the OPERAM trial [37,38]. OPERAM was a large (n = 2008) cluster-randomised controlled trial intended to investigate the effect of a structured medication review on the occurrence of DRAs in older people with multimorbidity and polypharmacy. In-hospital patients were recruited from four hospitals in Switzerland, Belgium, Ireland, and the Netherlands. Inclusion criteria were older age (≥70 years), multimorbidity (defined as ≥3 chronic conditions), and polypharmacy (defined as the use of ≥5 regular medications for more than 30 days prior to admission) [37,38]. The two exclusion criteria were (1) patients admitted to palliative care within 24 hours after index hospitalisation and (2) patients undergoing a structured medication review other than the trial intervention or having received a medication review in the 2 months preceding the index hospitalisation to reduce the risk of contamination bias.

Patients included in the OPERAM trial were randomised at index hospitalisation to receive usual pharmaceutical care (control group, n = 1045) or a structured in-hospital medication review (intervention group, n = 963). Readmissions occurring after discharge from the index hospitalisation were adjudicated for drug-relatedness consecutively until a first DRA was confirmed or until the one year follow up period ended [37,38]. This substudy relies on data available from the in-hospital medication review in OPERAM intervention patients with a first potentially preventable DRA. The OPERAM trial was approved by the participating hospitals' medical ethics committees and registered under trial registration number NCT02986425.

In-hospital medication review

The in-hospital structured medication review was assisted by a CDSS with integrated STOPP/START criteria (version 2) [35,36]. In addition to the detection of potential drug overuse, underuse, and misuse based on STOPP/START algorithms, the CDSS generated signals for potential ADRs, clinically relevant drug-drug interactions, and dose adjustments based on a patient's renal function [39]. A detailed description of the CDSS used in the OPERAM trial and its interface can be found in the Supplementary Information SI1.

A pharmacotherapy team consisting of a trained physician and a trained pharmacist for each trial site performed the in-hospital medication review according to the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) method [40]. The pharmacotherapy teams had full access to the patient's medical record and evaluated all CDSS-generated signals for clinical applicability based on the patient's actual medical status. Pharmacotherapy optimisation recommendations were presented in a patient-specific feedback report, and the pharmacotherapy teams discussed the report contents with the attending physician and the patient. A second report of in-hospital medication changes and deferred recommendations (e.g. tapering off the use of benzodiazepines) was sent to the GP after discharge. A detailed description of the OPERAM intervention has been previously published [39].

DRA adjudication process

All OPERAM patients received follow-up calls at 2, 6, and 12 months after enrolment. The patients or their proxies were asked to report any hospital readmissions since discharge from the index hospitalisation [37]. In case of a hospital readmission, all relevant medical information (e.g. admission and discharge letters, laboratory values, recent medication lists) were obtained from the hospital of readmission and anonymised prior to the DRA adjudication process. Data on readmissions and outcomes of the DRA adjudication process were recorded in an electronic case report form (eCRF).

Within the OPERAM trial, all hospital readmissions were screened for potential ADEs through a standardised adjudication process, previously published by Thevelin et al. [14], to establish the primary endpoint (DRA). The DRA adjudication guide can be found in Supplementary Information SI2. DRA adjudication was performed by blinded adjudication teams consisting of senior physician-pharmacist pairs per trial site. DRAs related to MEs (i.e., overuse, underuse, or misuse of drugs) were considered potentially preventable as opposed to DRAs caused by non-preventable ADRs. The DRA adjudication process allowed for identifying multiple MEs per patient. Overuse was defined as the use of a prescribed drug without a

clinical indication, the use of double medication, or the use of a drug beyond the recommended duration. Underuse was defined as the lack of use of an indicated drug according to evidence-based clinical guidelines, adherence issues, or the discontinuation of a drug before the recommended prescription period was completed (e.g. antibiotics). Misuse included inappropriate dosing, inadequate therapy monitoring, the presence of clinically relevant drug-disease, or drug-drug interactions of indicated drugs [14]. Figure 1 presents a graphical illustration of the relationship between the in-hospital medication review at index hospitalisation and the DRA adjudication process at readmission.

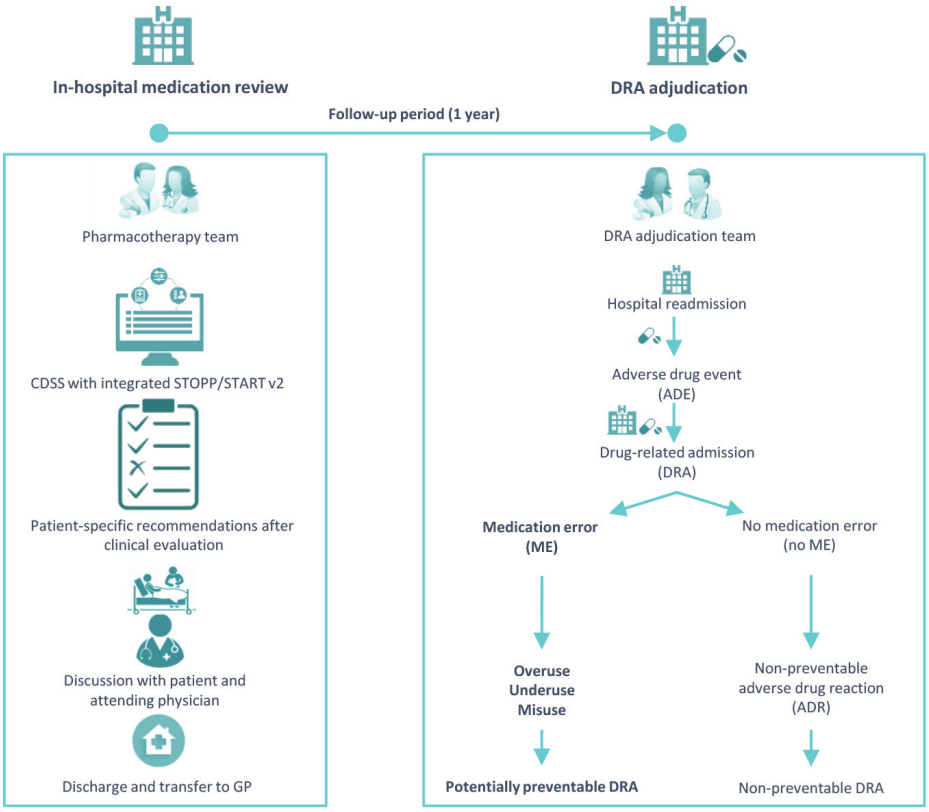

Figure 1. Graphical illustration of the relationship between the in-hospital medication review and the adjudication process of drug-related admissions.
DRA = Drug-related hospital admission; *CDSS* = Clinical decision support system; *STOPP/START v2* = Screening Tool of Older Person's Prescriptions / Screening Tool to Alert doctors to Right Treatment, version 2; *GP* = General practitioner.

Detectability of medication errors

The MEs identified at hospital readmission by the DRA adjudication teams were used as primary source for conducting this substudy. The relationship between the identified MEs and the detectability of these MEs at the time of the in-hospital medication review during index hospitalisation was retrospectively explored based on three screening questions:

1. Was the ME present at the time of the in-hospital medication review?

MEs were considered present if the inappropriate prescription (i.e., a drug omission identified as underuse or a prescribed drug identified as overuse/misuse) and the medical condition related to the ME were both present during the in-hospital medication review. MEs that were not present during the in-hospital medication review were considered not detectable.

2. Was the ME detected by STOPP/START?

MEs were considered detected if a STOPP/START signal was generated by the CDSS during the in-hospital medication review, regardless of whether this signal resulted in a change in medication regimen recommended by the pharmacotherapy teams.

3. Was a change in medication regimen recommended by the pharmacotherapy teams?

Recommendations for changes in medication regimen by the pharmacotherapy teams were based on the acceptance of STOPP/START signals; if no STOPP/START signal was generated, such recommendations were based on expert opinion (i.e., non-STOPP/START-based recommendation).

Three theoretical examples of ME detectability at the time of the in-hospital medication review are outlined in the Text Box.

Outcomes

The primary outcome of this study was the detectability of MEs identified at readmission with a STOPP/START-based in-hospital medication review at the time of the index hospitalisation prior to a potentially preventable DRA. The outcome included; 1) the proportion of MEs that was present and therefore detectable during the in-hospital medication review. The total number of MEs was used as the denominator. The total number of MEs identified at readmission was defined by the DRA adjudication teams; 2) the proportion of MEs that was detected by STOPP/START during the in-hospital medication review. The number of present

MEs was used as the denominator; 3) the proportion of MEs that resulted in a recommendation by the pharmacotherapy team to change medication regimen. The number of present MEs was used as the denominator. The numerator included both STOPP/START-based and non-STOPP/START-based recommendations.

As secondary outcome, the time between the occurrence of a first potentially preventable DRA and the presence of MEs during the in-hospital medication review was evaluated.

Data collection and analysis

Baseline patient characteristics (e.g. age, gender, number of co-morbidities, number of medications, renal function) were prospectively collected at index hospitalisation for all OPERAM intervention patients and captured in an eCRF. Data on CDSS-generated signals and changes in medication regimens recommended by the pharmacotherapy teams were saved within the CDSS and available for analysis. Data on medical conditions was captured at index hospitalisation and at readmission. This data included diagnoses, laboratory values (e.g. renal function, sodium/potassium levels), measurements (e.g. blood pressure) and patient-reported information (e.g. pain score measured by EQ-VAS [41], drug adherence measured by MMAS-8 [42]). Data on drug use was initially registered at index hospitalisation and updated during follow-up calls within the OPERAM trial. The results of the DRA adjudication process at readmission were extracted from the eCRF for all OPERAM intervention patients.

Patient data from the index hospitalisation on medical conditions, drug use, CDSS-generated signals and pharmacotherapy teams' recommendations were registered in an electronic data capture tool (Castor v.2021.5.5) and initially reviewed by a researcher (JI, final year pharmacy master student). Subsequently, all data and the proposed answers to the screening questions were again reviewed and validated by a second researcher (BS, hospital pharmacist, clinical pharmacologist). If MEs identified at rehospitalisation needed additional information for detectability assessment, the physician from the DRA adjudication team who had initially identified the ME was consulted to provide this information. For instance, the ME 'underuse of analgesics in uncontrolled pain' required additional information on the type and dosage of the underused analgesic drug. The additional information was provided using the same documents that were available at DRA adjudication.

Descriptive data analysis on baseline characteristics and MEs was performed using IBM SPSS Statistics v.26.0.0.1. The time between the occurrence of a potentially preventable DRA and the presence of MEs during the in-hospital medication review was visualised using GraphPad Prism 9.

TEXT BOX
Detectability of medication errors (MEs) during in-hospital medication review: three theoretical examples.

- **Example 1 – ME not present**

A patient was admitted with electrolyte disturbances, which were adjudicated as overuse of furosemide for ankle oedema (wrong indication). At the time of the in-hospital medication review, no loop diuretics were present. Consequently, this ME could not have been detected during the in-hospital medication review.

- **Example 2 – ME present, detected by STOPP/START**

A patient was admitted with an exacerbation of systolic heart failure, adjudicated as being secondary to the underuse of an ACE inhibitor. At the time of the in-hospital medication review, a START signal to initiate an ACE inhibitor for systolic heart failure was generated (START A6). Either this signal was considered not applicable by the pharmacotherapy team (e.g. considered contraindicated due to persistent hypotension) or a recommendation to initiate an ACE inhibitor was not implemented.

- **Example 3 – ME present, not detected by STOPP/START**

A patient with atrial fibrillation was admitted with gastrointestinal bleeding, which was adjudicated as misuse of a direct oral anticoagulant in supratherapeutic (unadjusted) dosage with concomitant decreased renal function. At the time of the in-hospital medication review, renal function was 40 ml/min/1.73m2, and no STOPP signal was generated. The pharmacotherapy team recommended a dose adjustment (i.e., non-STOPP/START-based recommendation). However, either this recommendation was not implemented by the attending physician (either intentionally because renal function recovered to >50 ml/min/1.73m2 or unintentionally) or the implemented dose adjustment did not persist (i.e., the dosage prior to admission was re-prescribed after discharge).

Results

Study population

One fifth of OPERAM intervention patients (n = 211, 21.9%, N = 963) experienced their first DRA within the year following the in-hospital medication review. A total of 84 DRAs in 963 intervention patients (8.7%) were adjudicated as potentially preventable and were related to 92 MEs.

Fifteen MEs in twelve OPERAM intervention patients were excluded from analysis of this substudy due to missing data (no intervention performed, n = 6; missing data on medical conditions at the time of the in-hospital medication review, n = 6; missing data on generated STOPP/START signals, n = 3). A total of 77 MEs occurring in 72

patients experiencing their first potentially preventable DRA were analysed (Figure 2). In 22 of these 77 MEs (28.7%), a DRA adjudication member was consulted by the primary researchers for further specification of the ME to finalise the assessment of ME detectability at the time of the in-hospital medication review.

The median age of participants was 80 years (interquartile range [IQR] 76–86) at the time of the in-hospital medication review. Participants had a median of 14 (IQR 9–19) co-morbidities and were prescribed a median of 10 (IQR 8–14) medications. Participants had a median eGFR of 51 ml/min/1.73m2 (IQR 36–66). Other baseline characteristics of the study population at the time of the in-hospital medication review are illustrated in Table 1.

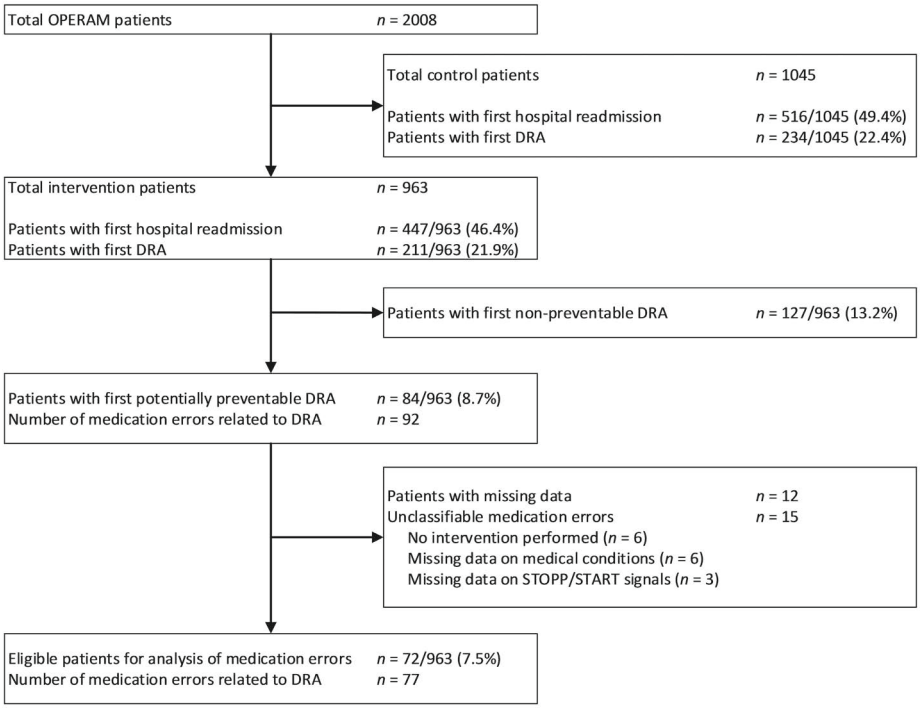

Figure 2. Flowchart of the study population.
DRAs were considered potentially preventable if medication errors were the main or contributory cause of the readmission. Non-preventable DRAs were caused by non-preventable adverse drug reactions.
DRA = Drug related admission

Table 1. Baseline characteristics of the study population.

Characteristics	n = 72
Age, years	80 (76–86)[a]
Sex, female	36 (50.0)[a]
Number of co-morbidities	14 (9–19)
Number of medications	10 (8–14)
Renal function, CKD-EPI; ml/min/1.73m^2	51 (36–66)
Nursing home residents	6 (8.3)
Housebound	9 (12.5)
Barthel Index for activities of daily living[b]	90 (70–100)
Patients with one or more fall(s) in the previous year Number of falls in the previous year	35 (48.6) 0 (0–1)
Patients with one or more hospital admission in the previous year Number of hospital admissions in the previous year	38 (52.8) 1 (0–2)
Length of hospital stay (days)	8 (5–11)
Admission type - Elective - Non-elective	 13 (18.1) 59 (81.9)
Ward - Medical - Surgical	 58 (80.6) 14 (19.4)
Country of inclusion[c] - Switzerland - Belgium - Ireland - The Netherlands	 36 (50.0) 12 (16.7) 9 (12.5) 15 (20.8)

[a]Data are presented as median (interquartile range) for continuous variables or numbers (percentages) for categorical variables.
[b]Values ranged from 0–100. Higher values indicate higher functional independence [43].
[c]The distribution of the total enrolled intervention patients in the OPERAM trial (n = 963) differed between the four participating countries; Switzerland: n = 446 (46%), Belgium: n = 150 (16%), Ireland: n = 138 (14%), The Netherlands: n = 229 (24%) [38].

Missing data: renal function: n = 8 (11.1%). Data were collected at the time of the in-hospital medication review at index hospitalisation.
CKD-EPI = Chronic kidney disease epidemiology collaboration equation.

Frequency and type of medication errors identified at readmission

Potentially preventable DRAs were caused by one ME in 68 out of 72 patients (94.4%), two MEs in three patients (4.2%), and three MEs in one patient (1.4%). MEs were adjudicated as the main cause for admission in 68.8% of cases and as a contributory cause in 31.2% of cases. Underuse was the most frequently identified ME type (49.3%), followed by overuse (36.4%), and misuse (14.3%). The top three clinical presentations of potentially preventable DRAs were heart failure exacerbation (26.0%), fall or fracture (20.8%), and bleeding (10.4%). A detailed overview of the frequency, type, and detectability of MEs is provided in Table 2.

Detectability of MEs at index hospitalisation (screening question 1)

Over half of the total identified MEs at readmission (52.0%, n = 40/77) were present at the time of the in-hospital medication review at index hospitalisation. In the remaining 48.0% (n = 37/77) of cases, the ME was not present and therefore not detectable during the in-hospital medication review; in these cases, either the inappropriate prescription (51.4%, n = 19/37) or the medical condition (48.6%, n=18/37) related to the ME were not present (Figure 3).

Detection of present MEs by STOPP/START (screening question 2)

The STOPP/START tool detected 60.0% (*n* = 24/40) of MEs that were present during the in-hospital medication review (Figure 3). Present MEs related to non-neuropathic pain (*n* = 2), acute renal impairment (*n* = 2), hyperglycaemia (*n* = 2) and tremor (*n*=2) were in no case detected by the STOPP/START tool (Table 2).

Recommendations by the pharmacotherapy team (screening question 3)

In 54.2% (n = 13/24) of MEs detected by STOPP/START, the signal resulted in a recommendation to change the patient's medication regimen. In the other 45.8% (n = 11/24), the pharmacotherapy team decided that a change in medication regimen was not clinically applicable based on the patient's medical status at the time of the in-hospital medication review (Figure 3). These rejected signals did not result in a recommendation to be discussed with the attending physician and patient or deferred to the GP. The pharmacotherapy team recommended a change in medication in 43.7% (n = 7/16) of present MEs that were not detected by STOPP/START (i.e., non-STOPP/START recommendation) (Figure 3). Overall, the pharmacotherapy team recommended a change in medication regimen in 50% (n = 20/40) of present MEs (Figure 3).

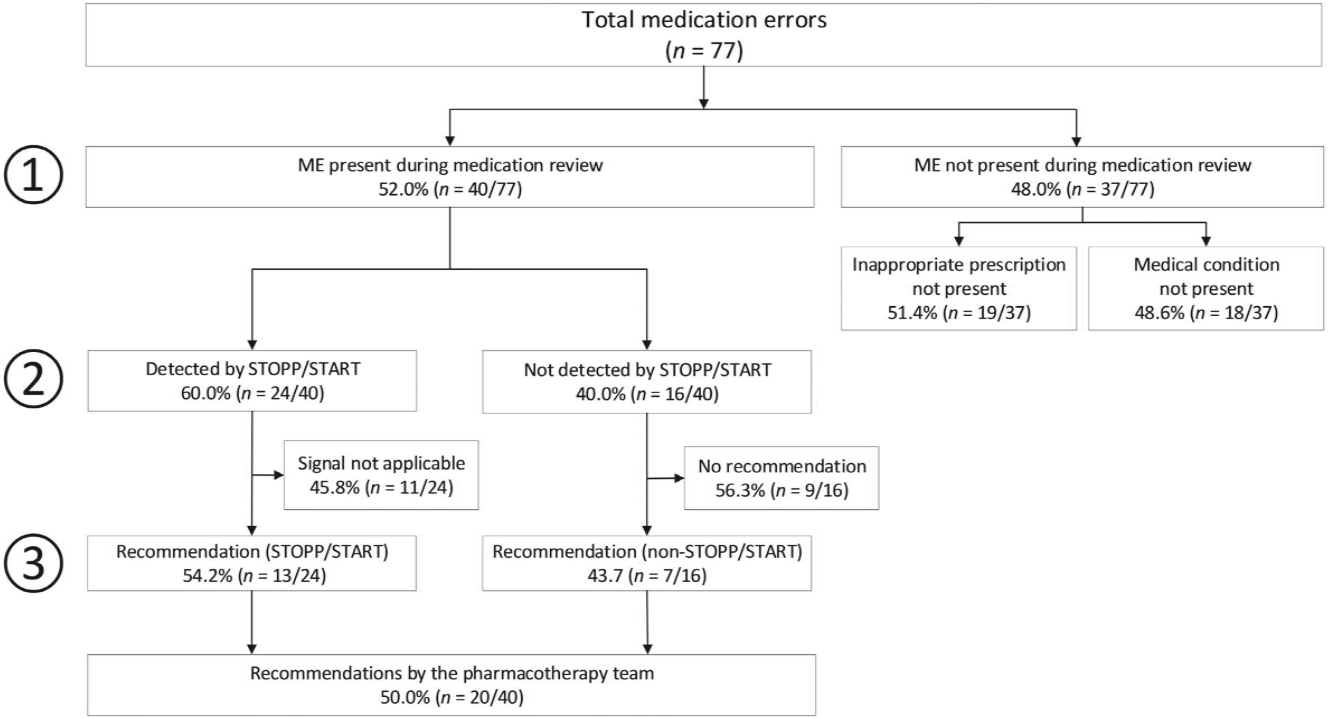

Figure 3. Flowchart of the detectability of medication errors (MEs) at the time of the in-hospital medication review, based on the three screening questions used for detectability assessment. STOPP = Screening Tool of Older Person's Prescriptions; START = Screening Tool to Alert doctors to Right Treatment.

Table 2. Frequency, type, and detectability of medication errors (MEs) per adverse drug event.

Adverse drug event	Total MEs	Underuse		Overuse		Misuse		ME detectability	
	n (% total)	% (n)	Drug (n)	% (n)	Drug (n)	% (n)	Drug (n)	% MEs present during medication review (n)	% present MEs detected by STOPP/ START, (n)
Based on explicit trigger tool[a] [14]									
Heart failure exacerbation	20 (26.0)	90.0 (18)	ACE-I[b] (8) Beta blocker[b] (3) Diuretics[c] (7)	5.0 (1)	NSAID (1)	5.0 (1)	Sotalol[g] (1)	45.0 (9/20)	66.7 (6/9)
Fall/fracture	16 (20.8)	25.0 (4)	Calcium and/or vitamin D (2) Bisphosphonates (1) Metformin[d] (1)	68.8 (11)	Antidepressants (3) Urinary antispasmodics (2) Benzodiazepines (2) Beta blockers (1) Nitrates (1) Dopamine agonist (1) PPI (1)	6.3 (1)	Ciprofloxacin[g] (1)	56.3 (9/16)	66.7 (6/9)
Bleeding	8 (10.4)	0.0 (0)	N/A	87.5 (7)	Antiplatelet therapy (5) Anticoagulation (2)	12.5 (1)	Antiplatelet therapy (1)	50.0 (5/8)	80.0 (4/5)
Myocardial infarction or ischemic disease	5 (6.5)	100.0 (5)	Anticoagulatione (1) ACE-I (2) Antiplatelet therapy (1) Statin (1)	0.0 (0)	N/A	0.0 (0)	N/A	40.0 (3/5)	66.7 (2/3)
Uncontrolled pain									

Table 2. Continued.

Adverse drug event	Total MEs	Underuse		Overuse		Misuse		ME detectability	
	n (% total)	% (n)	Drug (n)	% (n)	Drug (n)	% (n)	Drug (n)	% MEs present during medication review (n)	% present MEs detected by STOPP/ START, (n)
Non-neuropathic	4 (5.2)	75.0 (3)	Analgesics (3)	0.0 (0)	N/A	25.0 (1)	Analgesics (1)	50.0 (2/4)	0.0 (0/2)
Neuropathic	1 (1.3)	100.0 (1)	Gabapentin (1)	0.0 (0)	N/A	0.0 (0)	N/A	0.0 (0/1)	N/A
Acute renal impairment	4 (5.2)	0.0 (0)	N/A	75.0 (3)	Diuretics (2) ACE-I[g] (1)	25.0 (1)	NSAID (1)	50.0 (2/4)	0.0 (0/2)
Major constipation or faecal impaction	3 (3.9)	66.7 (2)	Laxative (2)	33.3 (1)	Opioid (1)	0.0 (0)	N/A	33.3 (1/3)	100.0 (1/1)
COPD exacerbation	2 (2.6)	50.0 (1)	Inhalation corticosteroid (1)	50.0 (1)	Opioid (1)	0.0 (0)	N/A	50.0 (1/2)	100.0 (1/1)
Stroke	2 (2.6)	100.0 (2)	Anticoagulation[f] (1) Antiplatelet therapy (1)	0.0 (0)	N/A	0.0 (0)	N/A	0.0 (0/2)	N/A
Dehydration	2 (2.6)	0.0 (0)	N/A	50.0 (1)	Diuretic (1)	50.0 (1)	Diuretic (1)	50.0 (1/2)	100.0 (1/1)
Hyponatremia	2 (2.6)	0.0 (0)	N/A	100.0 (2)	Thiazide (1) Diuretic (1)	0.0 (0)	N/A	50.0 (1/2)	100.0 (1/1)
Hyperglycaemia	2 (2.6)	100.0 (2)	Antihyper-glycaemics (2)	0.0 (0)	N/A	0.0 (0)	N/A	100.0 (2/2)	0.0 (0/2)

Table 2. Continued.

Adverse drug event	Total MEs	Underuse		Overuse		Misuse		ME detectability	
	n (% total)	% (n)	Drug (n)	% (n)	Drug (n)	% (n)	Drug (n)	% MEs present during medication review (n)	% present MEs detected by STOPP/ START, (n)
Confusion/ delirium	1 (1.3)	0.0 (0)	N/A	0.0 (0)	N/A	100.0 (1)	Baclofen (1)	0.0 (0/1)	N/A
Based on implicit screening questions[a] [14]									
Tremor	2 (2.6)	0.0 (0)	N/A	0.0 (0)	N/A	100.0 (2)	Pregabalin[h] (1) Lithium[i] (1)	100.0 (2/2)	0.0 (0/2)
Bradycardia	1 (1.3)	0.0 (0)	N/A	100.0 (1)	Beta-blocker (1)	0.0 (0)	N/A	100.0 (1/1)	100.0 (1/1)
Pancreatitis	1 (1.3)	0.0 (0)	N/A	0.0 (0)	N/A	100.0 (1)	Statin (1)	0.0 (0/1)	N/A
Anaemia	1 (1.3)	0.0 (0)	N/A	0.0 (0)	N/A	100.0 (1)	Acetylsalicylic acid (1)	100.0 (1/1)	100.0 (1/1)
Total	77 (100.0)	49.3 (38)		36.4 (28)		14.3 (11)		52.0 (40/77)	60.0 (24/40)

[a]The complete list of 26 explicit and two implicit screening questions of the DRA adjudication guideline from Thevelin et al. can be found in SI2.
[b]Omitted in systolic heart failure; cIncluding three cases of noncompliance; dOmitted in insulin-dependent Type II diabetes mellitus with poor glycaemic control; eOmitted with concomitant atrial fibrillation; fSubtherapeutic dosage of apixaban; gOveruse in end-stage renal disease (Stage 5); hSupratherapeutic dosage in relation to decreased renal function; iDrug-drug interaction with diuretics.
ME = medication error; STOPP = Screening Tool of Older Person's Prescriptions; START = Screening Tool to Alert doctors to Right Treatment; *ACE-I* = Angiotensin-converting enzyme inhibitor; *NSAID* = non-steroid anti-inflammatory drug.

Time to first potentially preventable DRA

Of 72 first potentially preventable DRAs, 33.3% (*n* = 24) occurred in the period between discharge and 2 months, whereas 29.2% (*n* = 21) occurred 2–6 months after the in-hospital medication review and 37.5% (*n* = 27) occurred 6–12 months after the in-hospital medication review. The cumulative incidence of MEs over time stratified for present and not present MEs during the in-hospital medication review is shown in Figure 4. No clear time relationship was observed between the occurrence of a potentially preventable DRA and the presence of MEs during the in-hospital medication review.

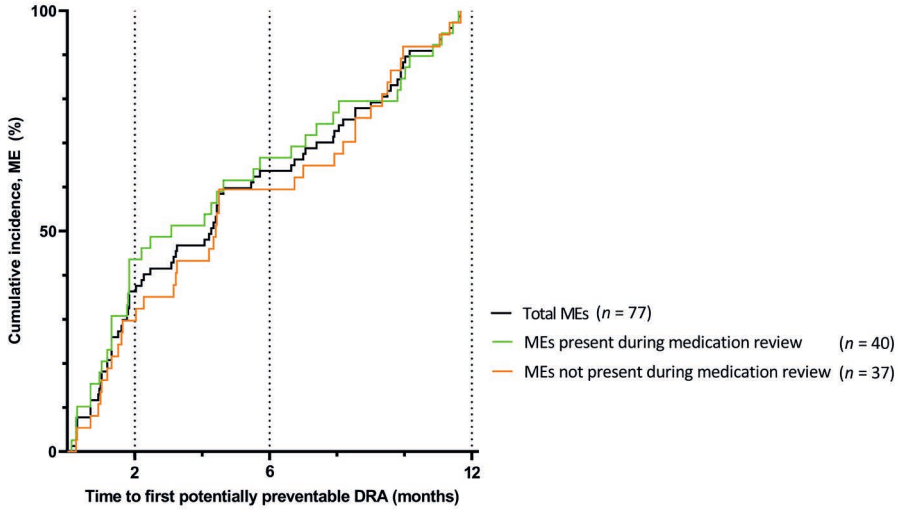

Figure 4. Cumulative incidence (%) of MEs over time stratified for total, present, and not present MEs during the in-hospital medication review.

Discussion

Main findings

About half of MEs (48%) were not present during an in-hospital medication review in the year prior to potentially preventable DRA and were therefore not detectable at that time. Of the MEs that were present during the in-hospital medication review, 60% were detected by CDSS-generated STOPP/START signals, however, only about half of these signals (54%) were considered clinically applicable and resulted in a recommendation. Overall, the pharmacotherapy teams recommended a change in medication regimen in 50% of present MEs; however, these proposed recommendations were not implemented. Underuse was the most frequently identified ME type (49%), followed by overuse (36%) and misuse (14%) of drugs.

Uitvlugt *et al.* investigated the prevalence, preventability, and type of MEs in adults (≥18 years) readmitted to a Dutch non-academic hospital [44]. One in six readmissions (16%, *N* = 1,111) were drug-related of which 40% were considered potentially preventable. Although the study population significantly differed from the OPERAM population (e.g. adult patients vs patients ≥70 years in OPERAM), the proportion of DRAs that were considered potentially preventable was similar (OPERAM intervention patients: 39.8%, *n* = 84/211; OPERAM control patients, 42.7%, *n* = 100/234) [38,44]. In both studies, underuse was the most frequently reported ME type, and cardiovascular events and diuretics were most frequently associated with MEs.

Based on the results of the current study's sub-analysis of OPERAM intervention patients, three strategies were identified that may improve DRA prevention in older people with multimorbidity and polypharmacy.

Timing of medication review

The finding that about half of MEs were not present during the in-hospital medication review provides evidence that the detection of MEs is highly time dependent. Multimorbid older people with polypharmacy are susceptible to changes in (the severity of) medical conditions and pharmacotherapy over time [45]. The effect of a single medication review over a one-year period is therefore difficult to measure. A longitudinal approach to medication review is likely to be more effective than a single, cross-sectional intervention. This theory is supported by the finding that there was no difference between MEs present and not present during in-hospital medication review and the occurrence of potentially preventable DRAs over time (Figure 4). One third of all potentially preventable DRAs occurred within the 2 months after hospital discharge. The cumulative incidence of newly developed MEs was also highest during this period. Previous studies have confirmed that medication errors frequently occur in transition from hospital to primary care, often due to unintentional medication discrepancies [46,47]. Performing a medication review shortly after hospital discharge could therefore have a high impact on reducing MEs [11,12,26].

In about half (*n* = 11/24) of present MEs, the pharmacotherapy teams decided that a medication change based on STOPP/START criteria was not applicable at the moment of the in-hospital medication review. Explicit screening tools, such as STOPP/START, provide population-based criteria to assist with medication review in older people. However, additional clinical consideration by health care professionals is necessary. A previous sub-analysis of OPERAM intervention patients found that about 40% of CDSS generated STOPP/START signals are of clinical relevance in a hospital setting according to the pharmacotherapy teams [48,49]. Although

recommendations to change medication regimen could also be deferred to the GP, the decision to accept or ignore STOPP/START signals during an in-hospital medication review is likely to be influenced by a patient's acute condition. This further highlights the need for regular medication review across healthcare settings.

ME detection by STOPP/START

CDSS-generated STOPP/START signals detected 60% of present MEs during medication review. STOPP/START version 2 lists 114 explicit criteria and is not definitive in detecting all MEs that may occur in older people [17,50]; many other explicit screening tools have been developed to facilitate the detection of potentially inappropriate drug use in older people with limited overlap between the tools [51,52]. However, the STOPP/START criteria are unique among validated explicit screening tools in targeting underuse, which was the most prevalent ME type in our study. The goal of explicit screening tool development is to achieve a high sensitivity and specificity in detecting MEs associated with negative clinical outcomes in older patients. Refining the STOPP/START criteria may further improve the performance of the tool when applied to clinical practice [48].

One approach to improve detection of MEs by software-based STOPP/START signals could be to clarify textual definitions in the current version of STOPP/START. Lack of clarity of essential elements has made it challenging to convert these explicit criteria into algorithms suitable for software implementation [35,53]. For example, two MEs not detected by STOPP/START were related to the underuse of analgesics in uncontrolled pain. The START criteria for pain management include ambiguous elements that are difficult to translate into algorithms (e.g. 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'*). Making the essential elements of the criteria as specific as possible (e.g. replacing the term *'moderate-severe pain'* with *'a VAS-score ≥5'*) could potentially enhance detection of MEs by software-generated STOPP/START signals [53].

Finally, some MEs require an implicit screening approach. For example, MEs related to noncompliance are difficult to identify using explicit screening tools, especially in hospital settings where long-term dispensing data from community pharmacies are not readily available. Although noncompliance was identified by the DRA adjudication teams in only three cases (all related to underuse of diuretics in heart failure exacerbation), the aforementioned study by Uitvlugt *et al.* reported that one third of all potentially preventable DRAs were related to non-adherence [44] emphasising the relevance of adherence monitoring in older patients to avoid harm.

Implementation of recommendations

A change in medication regimen was recommended by the pharmacotherapy teams in one half of present MEs; however, these proposed recommendations were not implemented. Recommendations can be either intentionally or unintentionally non-implemented and many factors affect actual implementation. Reasons for intentional non-implementation of recommendations was studied in the Dutch cohort of OPERAM intervention patients, which revealed that around 40% of all recommendations provided by the pharmacotherapy teams were disagreed upon by either the attending physician, the patient or both [54]. The main reason for disagreement was patients' reluctance to discontinue or initiate medication. Trusting patient-physician relationships are one of the key facilitators for successful shared decision-making, as found in another multicentre mixed-methods interview study among OPERAM patients (n = 48) [55]. Therefore, whether the acute hospital setting is the most appropriate setting to conduct medication reviews from a patient's perspective could be questioned. Future improvements in the shared decision-making process may result in a higher uptake of pharmacotherapy optimisation recommendations disagreed upon by the patient [56,57]. Physician-related factors also contributed to non-implementation, including attending physicians' reluctance to take responsibility for suggested medication changes that were beyond their area of expertise [54]. Another study found that the attending physician's implementation of STOPP/START-recommendations were significantly higher if the recommendation was discussed by a physician rather than a pharmacist [58]. Although the pharmacotherapy analysis within OPERAM was performed jointly by a pharmacist and a physician, the discussion of recommendations with attending physicians and patients was not always conducted by both professionals of the pharmacotherapy teams.

In addition to initial non-implementation of proposed recommendations, the persistence of medication changes across health settings could be an issue as well. For example, Van der Linden *et al.* found that more than one-quarter of drugs that were discontinued due to an ADR in hospitalised older patients were re-prescribed after hospital discharge [59]. Another study found that about 20% of medications that were discontinued based on STOPP criteria were re-prescribed within six months after discharge from geriatric units; more than half of those resumptions occurred within a month after discharge [60]. Improvements in medication reconciliation across healthcare settings could address these unintentional re-prescriptions [61,62]. Data to distinguish between non-implementation and non-persistence of recommended drug changes were not available within the OPERAM trial.

Strengths and limitations

This study was embedded within a large European multicentre trial, which contributes to the external validity of the study [38]. However, despite OPERAM having few exclusion

criteria, it should be noted that the population included in this substudy was relatively functionally independent with a considerably high Barthel Index (median 90; IQR 70–100), which was comparable to the baseline characteristics of participants in the main OPERAM trial. In addition, only a small proportion of nursing home residents were included. Hence, our findings may not be generalisable to frailer populations. Although DRA adjudication remains partially subjective and variability between teams of adjudicators cannot be completely ruled out, the adjudication process was performed by skilled senior clinicians (blinded for the allocation group) using a standardised DRA adjudication guide that has proven to effectively identify DRAs in older people [14,63]. The presence of MEs during in-hospital medication review was retrospectively assessed for those MEs identified by the DRA adjudication teams at readmission. However, information on drug use, laboratory values, medical conditions, and acceptance of STOPP/START signals was prospectively collected at the time of the in-hospital medication review. Therefore, this information can be considered of high quality.

This study has several limitations. First, the sample of MEs described in the study was rather small and heterogeneous which impedes the drawing of firm conclusions. Second, data to assess ME detectability were not available for OPERAM control patients with a potentially preventable DRA, because no in-hospital medication review was performed. Therefore, the study results could not be compared with a control group. Third, the reasons for not recommending medication changes by the pharmacotherapy teams for MEs present at the time of medication review were not available. However, decisions of the pharmacotherapy teams were made after careful evaluation of a patient's medical record at the time of the medication review and therefore considered appropriate. Re-evaluation of these decisions would introduce information bias. Nonetheless, it is possible that present MEs not detected by STOPP/START and in which no medication change was recommended, were missed by the pharmacotherapy teams during the in-hospital medication review. Finally, a relatively large proportion of MEs were excluded from analysis due to missing data, but the reasons for the missing data were unrelated to the study outcome. Therefore, these omissions are unlikely to have affected the findings.

Conclusion

Overall, MEs identified at readmission were not addressed by a prior single in-hospital medication review because either these MEs occurred after the medication review (~50%), or no recommendation was given during the medication review (~25%), or the recommendation was not implemented (~25%). Future research should focus on optimisation of the timing and frequency of medication review and the implementation of proposed medication recommendations.

Declarations

Authors' contributions

Authorship eligibility is based on the ICMJE authorship criteria. The authors certify that they have participated in the aspects of conception and design (BS, CH, TE, EvP, IW, WK), acquisition and interpretation of data (all authors), drafting the article (BS, JI, TE, EvP, IW, WK) and revising it critically for important intellectual content (all authors). All authors have approved the final article.

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

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-Luc-UCL: 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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Commission and the Swiss government. The funder of the study had no role in the study design; data collection, analysis, and interpretation; or writing of the report.

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

Abbreviations

ADE	Adverse drug event
ADR	Adverse drug reaction
DRA	Drug-related hospital admission
ME	Medication error, comprising overuse, underuse and misuse
CDSS	Clinical Decision Support System
OPERAM	OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people
START	Screening tool to alert to right treatment
STOPP	Screening tool of older persons' prescriptions
STRIP	Systematic Tool to Reduce Inappropriate Prescribing
GP	General practicioner
EQ-5D	European Quality of Life-5 Dimensions questionnaire

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SUPPLEMENTARY INFORMATION SI1

Detailed description of the STRIP Assistant 2.0

The STRIP Assistant (STRIPA) version 2.0 is a stand-alone, web-based clinical decision support system (CDSS) with integrated STOPP/START version 2 algorithms [1,2]. STRIPA was used to assist the structured medication review according to the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) method within the OPERAM trial [3–5]. Actual medical information at index hospitalisation - from the patient's electronic health record (EHR) and from the individual patient interview according to the Structured History of Medication taking method (SHiM)-method [6] - were entered into STRIPA by the pharmacotherapy team. This information included diagnoses, current drug use, recent measurements (e.g. blood pressure), laboratory values (e.g. renal function) and suspected adverse drug reactions (i.e. 'complaints'). Pharmacotherapy optimisation signals, including those based on STOPP/START v2, were generated by STRIPA and evaluated for appropriateness on the individual patient level by the trained physician-pharmacist pair. Table SI1.1 provides a detailed overview the medical information entered in STRIPA, their sources and the databases used alerts. Figure SI1.1 shows an example of STRIPA's interface for generating a STOPP signal for potential overuse. A detailed description of the OPERAM intervention has been published previously [3].

Table SI1.1. Components of the clinical decision-support tool STRIPA v2.0 used for pharmacotherapy analysis in OPERAM intervention patients.

Component	Source	Database
Data entry		
Diagnoses	EHR	WHO ICD-10 v2016 [7]
Drugs	SHiM and EHR	WHO ATC codes v2016 [8]
Measurements and laboratory values	EHR	LOINC [9]
Potential adverse drug reactions	SHiM and EHR	MedDRA v2013 [10]
Pharmaceutical analysis		
Check for indications of current drugs	Evidence Based Clinical guidelines + Expert opinion*	N/A If no clinical indication was found, the drug was linked to dummy code 'unknown and unspecified causes of morbidity' which generated STOPP A1 ('Any drug prescribed without an evidence-based clinical indication')

Table SI1.1. Continued.

Component	Source	Database
Underuse	START criteria v2 [1] + Expert opinion*	34 original START v2 criteria were converted into 33 algorithms. START A1 and A2 were merged into: '*Start vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation (START A1) or start aspirin instead if a vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitor is contraindicated (START A2)*'.
Overuse, misuse	STOPP criteria v2 [1] + Expert opinion*	80 original STOPP v2 criteria were converted into 79 algorithms STOPP A2 *('any drug prescribed beyond the recommended duration')* could not be coded
Double medication	Royal Dutch Society for the Advancement of Pharmacy (KNMP) database	KNMP G-Standard was used to code STOPP A3 *('any duplicate drug class prescription')* [11]
Adverse drug reactions	Expert opinion*	SIDER v4 [12]
Drug-drug interactions	National interaction databases	Switzerland – INDEX [13] Ireland – Safescript [14] Belgium – Delphi-Care [15] The Netherlands – KNMP G-Standard [11]
Dose adjustments based on renal function	Royal Dutch Society for the Advancement of Pharmacy (KNMP) database	KNMP G-Standard [11]

*i.e. expert opinion of a trained physician-pharmacist pair performing the pharmaceutical analysis. *EHR* = Electronic health record; *SHiM* = Structured History taking of Medication use.

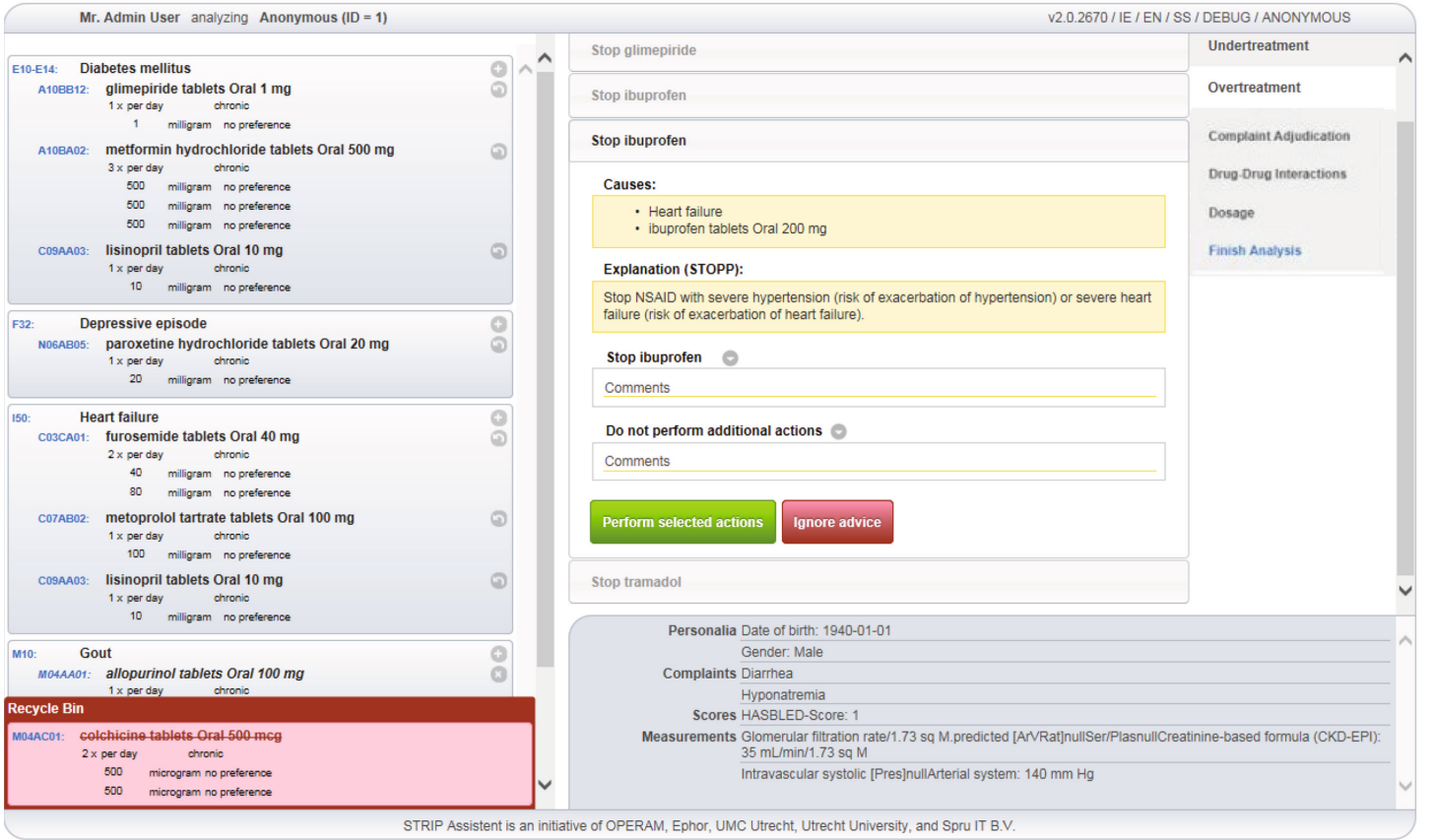

Figure SI1.1. STRIPA 2.0 interface. Example: STOPP-signal for potential overuse of ibuprofen with concomitant heart failure.

References SI1

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SUPPLEMENTARY INFORMATION SI2

Adjudication guide for drug-related hospital admissions

A standardized chart review method previously published by Thevelin *et al*. was used for the adjudication of drug-related hospital admissions (DRAs) and related medication errors within the OPERAM trial [1-2]. The three-step approach for identifying DRAs (Figure SI2.1) and the trigger tool with 26 explicit screening questions and 2 implicit screening questions (Table SI2.1) are reprinted with permission of Thevelin *et al*. [1]

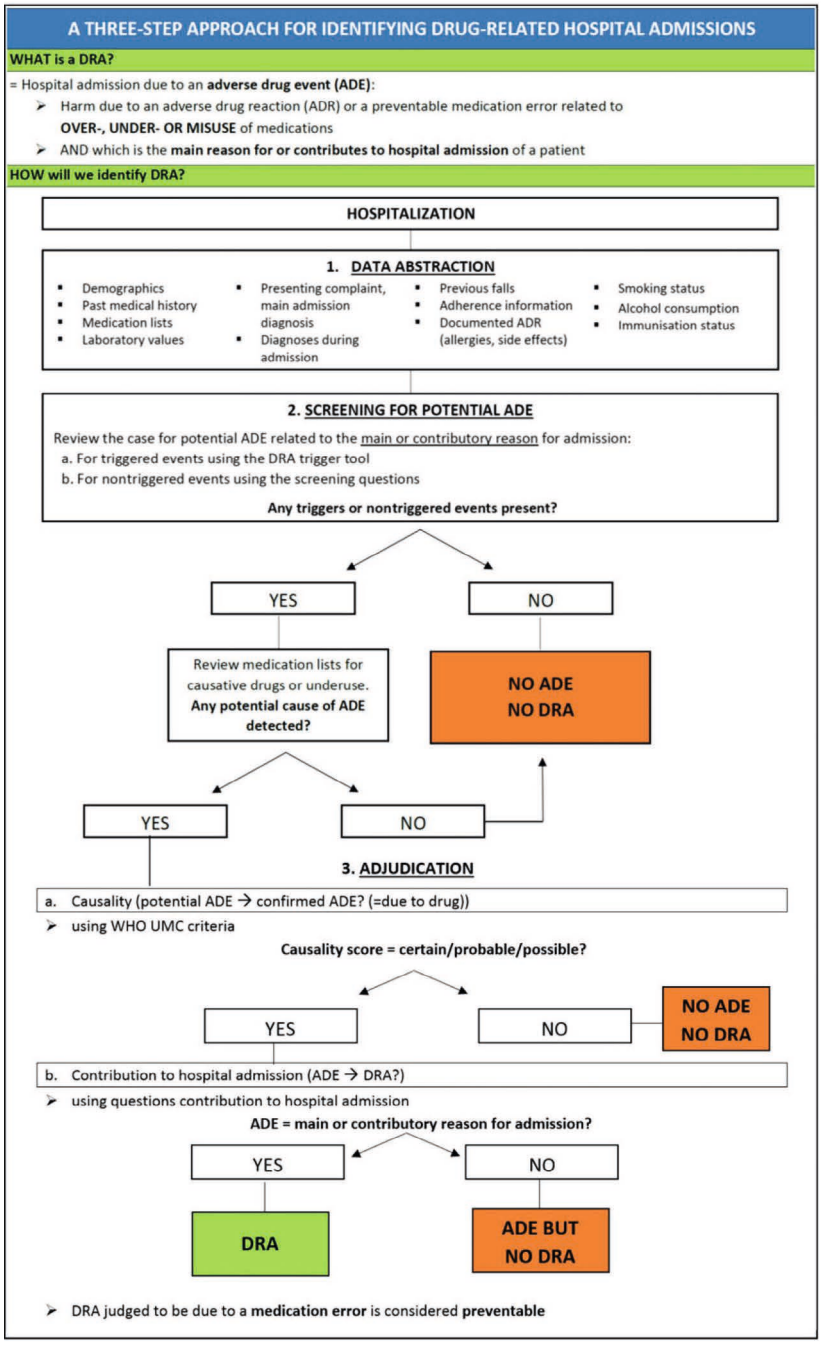

Figure SI2.1. Three-step approach for identifying DRAs [1].
ADE = adverse drug event; *DRA* = drug-related hospital admission.

Table SI2.1. Trigger tool for identifying DRAs in older persons [1].

TRIGGER TOOL TO SCREEN FOR DRUG-RELATED HOSPITAL ADMISSIONS IN OLDER PERSONS	
Trigger on admission up to 48h of admission	**Suspected causative drugs or causes for underuse**
Diagnoses	
Fall and/or fracture	**Use** of any of the following drugs? ☐ Benzodiazepines ☐ Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem ☐ Antipsychotics ☐ Antidepressants ☐ Sedating antihistamines ☐ Opioids ☐ Anticholinergic drugs[a] ☐ Other (*Please specify*):
	Use of any drugs causing orthostatic hypotension? ☐ Calcium channel blockers ☐ Diuretics ☐ α1-receptor blockers ☐ Nitrates ☐ β-blockers ☐ ACE-inhibitors ☐ Angiotensin receptor blockers ☐ Direct renin inhibitors (e.g. aliskiren) ☐ Anti-Parkinson drugs ☐ Antidepressants (mainly tricyclic) ☐ Antipsychotics ☐ Gliflozines (SGLT2-inhibitors) ☐ Other (*Please specify*):
	If a fall is caused by hypoglycaemia, look for **use** of drugs contributing to hypoglycaemia (check trigger hypoglycaemia)
	Underuse of any of the following drugs in patients with known osteoporosis and/or history of fragility fracture(s) and/or Bone Mineral Density T-scores of -2.5 or lower in multiple sites? ☐ 800 IU Vitamin D/day (+ 1000-1200 mg calcium/day if dietary intake is <1200-1000mg/day) ☐ Bone anti-resorptive therapy (e.g. bisphosphonates, strontiumranelate,teriparatide, denosumab)
	Underuse of any of the following drugs in patients on corticosteroid therapy ≥ 3 months? ☐ 800 IU Vitamin D/day (+ 1000-1200 mg calcium/day if dietary intake is <1200-1000mg/day) ☐ Bisphosphonates
	Underuse of vitamin D in patients who are housebound and/or experiencing falls or with osteopenia with Bone Mineral Density T-score between -1 and -2.5 in multiple sites?
Confusion/delirium[b]	**Use** of any of the following drugs? ☐ Benzodiazepines ☐ Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem ☐ Antipsychotics ☐ Anti-epileptics ☐ Antihistamines (H1- and H2-receptor blockers) ☐ Antidepressants ☐ Opioids ☐ Dopaminergic agonists ☐ Digoxin ☐ Fluoroquinolones *(dose adjustment in renal impairment required)* ☐ Acetylcholinesterase-inhibitors (new onset confusion in patients with dementia) ☐ Other anticholinergic drugs[a] (*Please specify*):
	Abrupt discontinuation/rapid dose reduction of any of the following drugs? ☐ Benzodiazepines ☐ Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem ☐ Corticosteroids ☐ Dopaminergic agonists ☐ Antidepressants ☐ Opioids ☐ Lithium ☐ Antipsychotics ☐ Other (*Please specify*):
Acute renal impairment[b]	**Use** of any of the following drugs? ☐ Non-steroidal anti-inflammatory drugs ☐ ACE-inhibitors ☐ Angiotensin receptor blockers ☐ Diuretics ☐ Sulphonamides ☐ Cephalosporins ☐ Quinolones (ciprofloxacin) ☐ Aminoglycosides ☐ Vancomycin ☐ Pentamidine ☐ Rifampicin ☐ Acyclovir, valacyclovir, gancyclovir, valgancyclovir, foscarnet, cidofovir ☐ Lithium ☐ Calcineurin Inhibitors (e.g. cyclosporine, tacrolimus) ☐ Cisplatin ☐ Radiology contrast medium ☐ Amphotericin ☐ Bisphosphonates ☐ Other nephrotoxic drugs (*Please specify*):
Dehydration	Use of any of the following drugs? ☐ Diuretics ☐ Gliflozines (SGLT2-inhibitors) ☐ Laxatives ☐ Any drugs causing vomiting ☐ Any drugs causing diarrhoea ☐ Other (*Please specify*):
Bleeding[b]	Use of any of the following drugs? ☐ Antiplatelets ☐ Vitamin K antagonists ☐ Direct oral anticoagulants ☐ Unfractionated heparin ☐ Low molecular weight heparins ☐ Selective serotonin reuptake inhibitors ☐ Non-steroidal anti-inflammatory drugs ☐ Other (*Please specify*):
	☐ **Underuse** of proton pump inhibitors prophylaxis while - NSAIDs monotherapy (≥ 70 years old) or on concurrent NSAIDs and/or antiplatelets and/or corticosteroids - NSAIDs or antiplatelet or corticosteroids monotherapy with a history of peptic ulcer disease/gastrointestinal bleeding while on these drugs
Stroke	**Underuse** of any of the following drugs in patients with known chronic atrial fibrillation? ☐ Vitamin K antagonists ☐ Direct oral anticoagulants (except valvular atrial fibrillation)
	Underuse of adequate antihypertensive therapy? * *Note*: Adequate antihypertensive therapy is defined according to the recommendations for older patients in the 2013 European ESH/ESC guidelines for the management of arterial hypertension.
	Underuse of any of the following drugs in patients with history of coronary, cerebral or peripheral vascular disease? ☐ Antiplatelets ☐ Statins** (unless end-of-life or > 85 years old) **Note*: Evidence for statin treatment above the age of 80-85 years is limited and clinical judgement should guide decisions in the very old, taking into account life expectancy, serious adverse events, possible drug interactions. Low to moderate intensity statin regimens are recommended. (**low**: simvastatin 10mg, pravastatin 10-20mg, fluvastatin 20-40 **moderate**: atorvastatin 10-20mg, Rosuvastatin 5-10mg, Simvastatin 20-40mg, pravastatin 40-80 mg, Fluvastatin 80 mg, Fluvastatin 40 mg BID)

Table SI2.1. Continued.

Thromboembolic event (DVT or PE)	**Underuse** of adequate anticoagulation? ☐ Unfractionated heparin ☐ Low molecular weight heparins ☐ Direct oral anticoagulants ☐ Vitamin K antagonists
(Recurrent) myocardial infarction or ischaemic disease	**Underuse** of cardiovascular secondary prevention? ☐ Antiplatelets (unless already anticoagulated) ☐ Statins** (unless end-of-life or > 85 years old) ☐ β-blocker/ACE-inhibitor or angiotensin receptor blocker /adequate anti-anginal therapy in case of ischaemic disease **Underuse** of adequate antihypertensive therapy? *
Heart failure exacerbation	**Use** of any drugs that could precipitate heart failure exacerbation? ☐ Non-steroidal anti-inflammatory drugs ☐ Corticosteroids ☐ Thiazolidinediones (glitazones) ☐ Non-dihydropyridine calcium channel blockers (verapamil, diltiazem) ☐ Sodium-containing formulations (effervescent, dispersible and soluble medications) ☐ Other (*Please specify*): **Underuse** of any of the following drugs? ☐ β-blockers¥ ☐ ACE-inhibitors¥ ☐ Diuretics *Note:* ¥ β-blocker and ACE-inhibitors in heart failure due to left ventricular dysfunction
COPD exacerbation	**Use** of any drugs that could precipitate COPD exacerbation? ☐ Benzodiazepines with acute or chronic respiratory failure ☐ Opioids ☐ Other (*Please specify*): **Underuse** of any of the following drugs? ☐ Single or dual inhaled bronchodilator therapy i.e. a β2 agonist and/or anticholinergic bronchodilator according to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) grade
Uncontrolled (non-neuropathic) pain	**Underuse** of adequate pain treatment (according to the WHO analgesic ladder)? ☐ A strong opioid in moderate to severe pain if paracetamol, NSAIDs or weak opioids are not appropriate (e.g. because of insufficient pain relief) ☐ Short-acting opioids for break-through pain during treatment with long acting opioids ☐ Other (*Please specify*):
Gastrointestinal disorders (severe diarrhoea, vomiting)	**Use** of any of the following drugs? ☐ Antibiotics ☐ Laxatives ☐ Selective serotonin reuptake inhibitors ☐ Digoxin ☐ Cholinesterase-inhibitors ☐ Opioids ☐ Non-steroidal anti-inflammatory drugs ☐ Chemotherapy (*Please specify*): ☐ Other (*Please specify*):
Major constipation or faecal impaction	**Use** of any of the following drugs? ☐ Chronic (stimulant) laxative use ☐ Opioids (look for **underuse of laxatives** with regular opioid use) ☐ Calcium antagonists (Mainly verapamil) ☐ Calcium ☐ Oral iron ☐ Aluminium antacids ☐ Atypical antipsychotics ☐ Tricyclic antidepressants ☐ Bladder antimuscarinics ☐ Other anticholinergic drugs[a] ☐ Other (*Please specify*):
Laboratory values	
INR > 5	Look for evidence of bleeding (see trigger) to determine if an adverse drug event (ADE) has occurred. A raised INR in itself is not an ADE.
Digoxin level > 2ng/ml	Look for signs or symptoms of digoxin toxicity (bradycardia, nausea, diarrhoea, confusion) to determine if a potential ADE has occurred. Not all levels above normal will result in an ADE.
Hypoglycaemia (blood glucose < 4 mmol/L or 72 mg/dl)	Look for symptoms such as lethargy, tremor, confusion, faintness or administration of intravenous or oral glucose. **Use** of any of the following drugs? ☐ Insulin ☐ Oral hypoglycaemic agents (except metformin in monotherapy) ☐ MAO – inhibitors ☐ β-blockers (masking symptoms of hypoglycaemia)
Hyperglycaemia (blood glucose > 11 mmol/L or 198 mg/dl)	**Use** of any drugs that may cause or worsen hyperglycaemia? ☐ Corticosteroids ☐ Atypical antipsychotics (mainly olanzapine & clozapine) ☐ Thiazide diuretics *less frequent* ☐ β-blockers (except carvedilol and nebivolol) *less frequent* ☐ Protease-inhibitors ☐ Calcineurin Inhibitors (cyclosporine, sirolimus, tacrolimus) ☐ Other (*Please specify*): In case hyperglycaemia is part of diabetic ketoacidosis or hyperosmolar hyperglycaemic state in a patient, review for **underuse** of insulin or oral hypoglycaemic agents.
Hyperkalaemia (K^+ > 5.5 mmol/L)	**Use** of any the following drugs? ☐ Intravenous or oral potassium ☐ Potassium-sparing diuretics ☐ ACE-inhibitors ☐ Angiotensin receptor blockers ☐ Direct renin inhibitors (e.g. aliskiren) ☐ Non-steroidal anti-inflammatory drugs ☐ Heparins (seldom, mainly when treated > 7days and concomitant other risk factors) ☐ Trimethoprim-sulfamethoxazole ☐ Cyclosporine ☐ Tacrolimus ☐ Other (*Please specify*):
Hypokalaemia (K^+ < 3 mmol/L)	**Use** of any of the following drugs? ☐ Loop diuretics ☐ Thiazide and thiazide-like diuretics ☐ Corticosteroids ☐ Laxatives ☐ Salbutamol (IV or aerosol) ☐ Theophylline ☐ Other (*Please specify*):

Table SI2.1. Continued.

Hyponatraemia (Na^+ < 130 mmol/L)	**Use** of any of the following drugs? ☐ Diuretics ☐ Selective serotonin reuptake inhibitors ☐ Tricyclic antidepressants ☐ ACE-inhibitors ☐ Angiotensin receptor blockers ☐ Carbamazepine & oxcarbazepine ☐ High dose cyclophosphamide ☐ Other (*Please specify*):
White blood cells < 3000 /mm^3 or < 3 x 10^9/µL	**Use** of any of the following drugs? ☐ Carbamazepine & oxcarbazepine ☐ Antipsychotics (mainly clozapine) ☐ Thyreostatics ☐ Ganciclovir ☐ Immunosuppressants ☐ Chemotherapy (*Please specify):* ☐ Mirtazapine (first 6 weeks of treatment) ☐ Voriconazole ☐ Other (*Please specify*):
Platelet count < 50000 /mm^3 or < 50 x 10^3/µL	**Use** of any of the following drugs? ☐ Carbamazepine & oxcarbazepine ☐ Ganciclovir ☐ Unfractionated heparin ☐ Low molecular weight heparins ☐ Immunosuppressants ☐ Thienopyridines (mainly ticlopidine) ☐ Quinine sulfate ☐ Sulfamides *Less frequent* ☐ Chemotherapy (*Please specify):* ☐ Other (*Please specify*):
Neutrophils < 1400/mm^3 or < 1.4 x 10^3/µL	**Use** of any of the following drugs? ☐ Ganciclovir ☐ Antipsychotics (mainly clozapine) ☐ Thyreostatics ☐ Thienopyridines (mainly ticlopidine) ☐ Chemotherapy (*Please specify):* ☐ Other (*Please specify*):
Other	
Antidote use or treatments that suggest a potential ADE	Use of any of the following drugs on the day of admission? ☐ Flumazenil in a patient on benzodiazepines ☐ Naloxone in a patient on opioids ☐ Phytonadione (vitamin K) in a patient on VKA ☐ Protamine sulphate in a patient on heparins ☐ Oral or intravenous glucose or glucagon in a patient taking hypoglycaemic drugs ☐ Potassium supplements in case of hypokalaemia ☐ Sodium polystyrene (Kayexalate) in case of hyperkalaemia ☐ Adrenaline, antihistamines and corticosteroids (general drug allergy) ☐ Acetylcysteine (paracetamol overdose) ☐ Digoxin antibodies in a patient with supratherapeutic digoxin levels ☐ Oral metronidazole or vancomycin in a patient who has recently been treated with an antibiotic that may cause *Clostridium difficile* associated diarrhoea
Mention of a (potential) ADE in the medical record	Assess causality using the WHO-UMC criteria
Abrupt medication stop within 24h of admission	When medications are stopped or withheld as compared to medications taken at home, look for reasons why this was done. Abruptly stopping medications is a trigger requiring further investigation for cause. A sudden change in patient condition requiring adjustment of medications is often related to an ADE.

ADE, adverse drug event; ADR, adverse drug reaction; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; FEV_1, forced expiratory volume in 1 second; ESH/ESC, European Society of Hypertension/European Society of Cardiology; INR, international normalised ratio, NSAIDS, non-steroidal anti-inflammatory drugs; PE, pulmonary embolism; VKA, Vitamin K antagonists
[a]A list of medications with clinically relevant anticholinergic properties is available in the DRA adjudication guide; [b]Detailed definition of trigger available in the DRA adjudication guide

SCREENING QUESTIONS FOR NON-TRIGGERED, SPONTANEOUSLY DETECTED EVENTS	
1. Could the main or contributory reason for admission be related to a drug or recent change in medications?	
☐ Adverse drug reaction (non-preventable side effect, first allergic reaction) ☐ Overuse of medication(s) (drug without an indication, too long duration of therapy, therapeutic duplication) ☐ Inappropriate discontinuation (removal or dosage decrease) leading to physiological withdrawal signs/symptoms or return of the underlying disease signs/symptoms	☐ Wrong drug ☐ Wrong dose (supratherapeutic or subtherapeutic) ☐ Clinically significant drug-drug or drug-food interactions ☐ Inappropriate monitoring ☐ Other (e.g. drug not correctly dispensed/prepared/administered)
2. Could the main or contributory reason for admission be related to underuse?	
☐ Omission of an indicated drug ☐ Too short duration of medication therapy	☐ Suspected adherence concerns

References SI2

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2. Blum MR, Sallevelt BTGM, Spinewine A, Mahony DO, Feller M, Baumgartner C, et al. Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults (OPERAM): cluster randomised controlled trial. BMJ 2021;374:n1585. https://doi.org/10.1136/bmj.n1585.

Chapter 5

General Discussion

Introduction

The prevalence of multimorbidity and polypharmacy is increasing in the ageing population. Multimorbidity and polypharmacy are important risk factors for drug-related harm including drug-related hospital admissions. Previous studies have reported that 10%–30% of all hospital admissions in older people are drug-related, half of which are potentially preventable [1–4]. Consequently, healthcare professionals and patients require effective strategies to reduce drug-related harm [5,6].

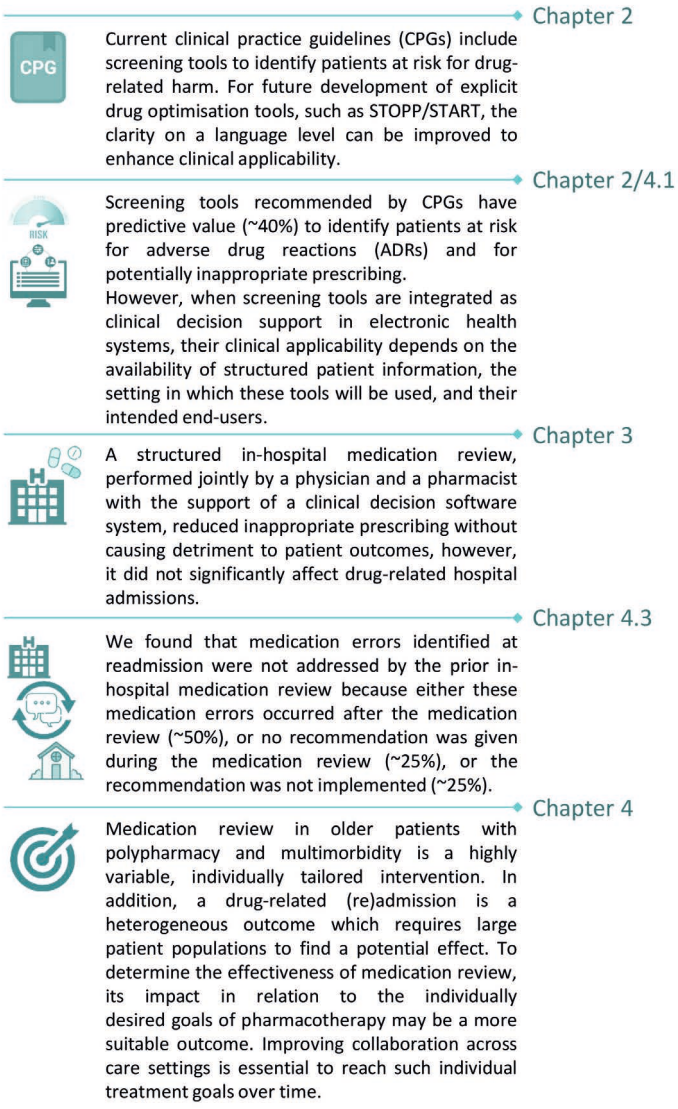
Clinical practice guidelines (CPGs) focusing on medication optimisation in older people have been developed to guide prescribers in safe and effective pharmacotherapy. In European guidelines, the Screening Tool of Older Person's Prescriptions (STOPP) and the Screening Tool to Alert to Right Treatment (START) have been recommended to detect potentially inappropriate prescribing during medication reviews. STOPP/START has been shown to effectively reduce potentially inappropriate prescribing, adverse drug reactions (ADRs) and lower healthcare costs in single-centre clinical trials [7–11]. However, the effect on other clinical outcomes, such as drug-related hospitalisations, remains to be established. In addition, the effectiveness of a structured medication review as a multicomponent intervention is uncertain [12,13].

This rationale was used to develop a structured, clinical decision support system (CDSS)-assisted medication review process integrating expert opinions, shared decision-making and evidence-based medication optimisation tools, such as STOPP/START (Chapter 3.1) [14]. The effect of this in-hospital medication review on drug-related hospital readmissions and other clinical outcomes was investigated in the multicentre OPtimising thERapy to prevent avoidable hospital Admissions in the Multimorbid elderly (OPERAM) randomised controlled trial [15,16]. OPERAM was thoroughly designed in terms of scientific standards to maximise high-quality evidence by explicitly addressing the limitations of previous trials (e.g. short follow-up times, being underpowered, high risk of bias) [12,13]. The in-hospital medication review decreased potentially inappropriate prescribing in older people with multimorbidity and polypharmacy with no detriment to patient outcomes. However, it did not significantly alter the primary outcome of 'drug-related hospital readmissions' within one year after the intervention compared to usual care (Chapter 3.2) [16].

Therefore, the hypothesis that an in-hospital medication review would prevent drug-related hospital readmissions in this vulnerable population could not be established. However, drawing conclusions about the effectiveness of medication reviews based on population-based clinical outcomes poses a risk of rejecting worthwhile interventions without critically appraising the process in which these strategies have been embedded. For instance, interventions might have failed at the level of implementation. This concern was also addressed in a recent review investigating

the effect of deprescribing interventions in older people on emergency department visits and hospitalisations [17]. Hence, a detailed understanding and evaluation of the factors underlying the study outcomes of OPERAM could aid putting the results into perspective.

This general discussion reflects how strategies for medication optimisation can be improved in future clinical practice and research. The main conclusions of this thesis are:



Based on these lessons learned, we elaborate on the following main topics:
1. The applicability of screening tools for medication optimisation
2. The process of in-hospital medication reviews
3. Outcome measures of medication reviews
4. Medication reviews in older people – who, when, where and how?

1. The applicability of screening tools for medication optimisation

Previous research has demonstrated that most drug-related harm in the older population is caused by a few commonly used drug classes [18–22]. Consequently, screening tools targeting these drugs have emerged in geriatric CPGs. To identify older people at risk for inappropriate pharmacotherapy, the ADR trigger tool recommended by the Dutch geriatric guideline and the more widely used STOPP/START criteria are examples of explicit screening tools based on drugs frequently associated with drug-related harm.

We showed that both screening tools had predictive value for detecting ADRs and potentially inappropriate prescribing in a hospital setting. The positive predictive value (PPV) of the ADR trigger tool was 42% (Chapter 2.1) when applied to acutely admitted older people, and the acceptance of software-generated STOPP/START signals by a pharmacotherapy team was 39% (Chapter 4.1) when applied as clinical decision support [23]. Therefore, these tools could contribute to identifying patients at risk for ADRs and potentially inappropriate prescribing.

Moreover, we found that the prevalence of potentially inappropriate prescribing by screening older people with multimorbidity and polypharmacy using STOPP/START was very high; in 99% of OPERAM intervention patients at least one STOPP/START signal was generated by a CDSS with a median of 6 (IQR 4–8) generated signals per patient. After evaluation of these signals by a pharmacotherapy team in the clinical context of the individual patient, a median of 2 (IQR 1–3) recommendations per patient was discussed with the attending physician and the patient (Chapter 4.1) [23]. These results implied that potentially inappropriate prescribing among older people is still remarkably common, thereby highlighting the gap between CPGs and prescribing behaviours in clinical practice, including the potential for interventions to improve appropriate pharmacotherapy.

The next paragraphs reflect on 1) improving the applicability of screening tools by increasing the clarity of CPGs 2) integrating screening tools in CDSS and 3) improving the applicability by increasing the availability of structured electronic patient data.

1.1. Improving applicability by increasing the clarity of clinical practice guidelines

Clinical decision-making on (in)appropriate prescribing in older people is a highly complex process. It depends on the healthcare provider's ability to structure and obtain all relevant patient information, relate this information to evidence-based guidelines and decide on the most appropriate treatment for and with patients. Specific and unambiguous wording in guideline recommendations is important to change prescribing behaviour and may facilitate adherence to evidence-based recommendations [24,25]. We found that the clarity of both investigated screening tools could be improved. In Chapter 2.1, we explicated the original ADR trigger tool as presented in the Dutch geriatric guideline to reduce undesirable variations in interpretation when applied to electronic health records (EHRs; e.g. specifying 'psychotropic agents'). Then, in Chapter 2.2, we identified that refinements in the STOPP/START criteria might enhance applicability in clinical practice [26].

Thus, guideline developers should inquire whether recommendations are tailored for their intended end-users to maximise the applicability of CPGs. Explicit screening tools on polypharmacy optimisation, like STOPP/START, are likely to be developed to reach a variety of healthcare professionals since all prescribers treat older patients with polypharmacy. Clinicians less experienced with pharmacotherapy optimisation in older people will likely require more specific guidance than the current version of the STOPP/START criteria [26]. Improvements in the content clarity of STOPP/START could be made to the level of individual criteria and the level of coherence between the criteria, which in some cases contradict. Merging recommendations could increase guideline uptake and prevent potential patient harm by overlooking relevant contra-indications.

For example, assessing of the indications for mono, double and triple antithrombotic therapy, the preferred type of therapy, and the recommended duration of the therapy is complex. Detailed but relevant information for this assessment is currently scattered across single-disease (cardiovascular) guidelines [27]. Integrating this information into one clinical decision model may be more effective than presenting 11 single-sentence individual STOPP criteria (version 2, section C) to alert for potential risks in antithrombotic therapy [28]. In a time where almost all evidence-based CPGs are electronically requested, additional information that can improve the clarity of recommendations (e.g. electronic linkage to deprescribing tools or referral to more in-depth information on benefits/risks in specific populations) may further increase guideline uptake in clinical practice without making the recommendations too extensive.

1.2. Integration of screening tools in clinical decision support systems

The lack of clarity of some STOPP/START criteria makes their conversion into algorithms for use in CDSSs challenging [29]. In Chapter 2.3, we described that multiple consensus rounds were necessary to make the current version of STOPP/START (version 2) suitable for software systems [30]. Therefore, in the process of future guideline development, the collaboration of medical experts and experts in medical informatics could be valuable to avoid ambiguous wording in formulating guideline recommendations, possibly easing the integration of such recommendations in software systems.

The introduction of electronic health systems provides opportunities to integrate CPG recommendations as screening tools to identify patients at risk of potentially inappropriate prescribing and assist healthcare professionals in clinical decision-making, thereby reducing unintentional guideline deviations [24,25]. Although the software cannot replace decision-making by healthcare professionals and patients, it can effectively translate knowledge acquired by CPGs, education and clinical experience into actions (the 'knowing-doing' gap) [31–33]. In addition, the screening on potentially inappropriate prescribing may be used to select patients who may benefit from a full medication review considering the number and type of signals.

A disadvantage of implementing the investigated tools as clinical decision support in electronic health systems is that they will likely result in false-positive signals in approximately 60% of cases, posing a risk of alert fatigue. In contrast, an observational study on regular drug safety alerts, including drug-drug interactions, overdosing and double medications, found that 91% of signals were overridden by prescribers [34]. Thus, a predictive value of the ADR trigger tool and STOPP/START signals at approximately 40% may be acceptable.

However, notably, the acceptance of STOPP/START signals by a pharmacotherapy team was performed by physician-pharmacist pairs specialised in medication optimisation in older people, and the actual implementation of STOPP/START-based recommended actions was lower (Chapter 3.2). Therefore, it is important to consider the context in which such signals will be presented, with special attention to the healthcare setting and the healthcare professional receiving such signals. For instance, a recent study investigated the impact of CDSS-assisted alerts to discontinue benzodiazepines in patients ≥ 65 years when integrated into primary care EHRs. Prescribers ignored or overrode over 99% of alerts. The authors concluded that a CDSS-generated signal to alert for benzodiazepine use is insufficient to create behaviour change in clinicians [35]. Thus, better support in handling these signals may be more successful in turning detection into action.

The predictive value of CDSS-generated STOPP/START signals may be increased by identifying patients at the highest risk for a 'true' inappropriate prescription. In Chapter 4.1, we investigated several potential determinants that might positively or negatively affect the acceptance of STOPP and START signals. Unfortunately, the investigated patient-related potential determinants were poor predictors of acceptance [23]. Thus, it would be interesting for future research to explore whether the PPV could be increased by selecting patients by, for instance, co-morbidity (e.g. excluding an alert for benzodiazepine use in patients with psychiatric illness) or by settings (e.g. primary care, in-hospital, or long-term care facility).

1.3. Improving applicability by increasing the availability of structured electronic patient data

The use of software to reduce prescribing errors has already been suggested to add as an additional step to the original six-step WHO model for appropriate prescribing [36,37]. Most evidence for the benefits of software assistance in healthcare has been demonstrated for computerised physician/prescriber order entry (CPOE) combined with clinical decision support, which has been shown to reduce prescribing errors by about 50% [38]. Although electronic prescribing of drugs is a common practice, in most European countries, a more advanced approach (i.e. not exclusively based on a patient's medication list) is necessary to alert for potentially inappropriate prescribing. The STOPP/START considers various patient data (e.g. clinical conditions, problems, diseases, laboratory values and measurements), requiring the structurally coded documentation of all relevant data.

In OPERAM, we used a stand-alone CDSS to manually document a patient's medical history, while clinical conditions are often registered in free-text in EHRs. Developments in software techniques (e.g. natural language processing) will likely facilitate converting unstructured clinical context into coded information shortly, as a source for clinical decision support [39]. Recent research has demonstrated that contextualised drug-drug interaction management had a greater clinical utility than basic drug-drug interaction management in hospitalised patients by suppressing irrelevant alerts based on clinical context [40]. Thus, further improvements in such techniques may allow for the automated linkage of drugs to clinical conditions, thereby facilitating the efficient software detection of potentially unindicated drug use; the first step of the pharmacotherapy analysis of the medication review process [41]. This feature would be critical in screening for potentially inappropriate prescribing, given that the most frequently generated signal and recommended action in OPERAM was to discontinue a drug without a clear indication (STOPP A1), which is in fact an implicit criterion.

2. The process of in-hospital medication review

A medication review can be defined as 'a structured, critical examination of **a person's medicines** with the objective of reaching an **agreement with the person** about treatment, optimising the impact of medicines, minimising the number of medication-related problems and reducing waste [author's emphasis]' [42]. By definition, a medication review is an individually tailored intervention involving many healthcare professionals considering different treatment options that should be separately weighed with the patient. Older people with polypharmacy and multimorbidity are, in particular, a diverse patient population, with patient-specific treatment goals, patient preferences, contra-indications and drug-drug interactions that affect treatment decisions and, therefore, the medication review outcome.

This variability is contrary to the relative homogeneity of ideal study designs where all potential factors that might affect the outcome are minimised, except for the usually highly standardised investigated intervention. The randomised controlled trial is still considered the gold standard in the hierarchy of evidence-based medicine [43]. Although the cluster randomisation design of the OPERAM trial limited allocation contamination and balanced general baseline characteristics of the study population between intervention and control patients, polypharmacy optimisation in each older person with multimorbidity could be considered as an $n = 1$ experiment, with each medication review, or even each recommendation for a medication change as an $n = 1$ intervention. Thus, it is challenging to establish a causal relationship between reducing inappropriate prescribing with a cross-sectional medication review and outcomes over a predefined time window.

The process of in-hospital medication review as investigated in the OPERAM trial was evaluated in detail in three descriptive substudies in Chapter 4. The studies aimed to better understand the decisions made during the in-hospital medication review process and the consequences of these decisions. To elucidate our findings presented in Chapter 4, we introduced two illustrative examples for potentially inappropriate prescribing in the same polypharmacy patient using a benzodiazepine (Boxes 1–3, Example 1) and a direct anticoagulant (DOAC) combined with acetylsalicylic acid (Boxes 1–3, Example 2).

In the next paragraphs, we reflect on 1) the implementation of medication optimisation recommendations (within the OPERAM trial) and 2) perspectives on improving the implementation of medication optimisation recommendations.

2.1. Implementation of medication optimisation recommendations

The variability of a medication review intervention started with high variability in the applicability of CDSS-generated signals after evaluating the clinical context at the individual patient level. In the OPERAM trial, this evaluation was performed by a pharmacotherapy team consisting of a physician-pharmacist pair based on additional EHR information. The acceptance of STOPP/START signals ranged from 2.5% (i.e. initiate high-potency opioids in moderate-severe pain) to 75.8% (i.e. initiate vitamin D) for the top ten most frequently generated STOPP and START signals (Chapter 4.1) [23]. Consequently, some signals were more likely to be discussed with the attending physician and the patient than others (Box 1). Strategies to improve the predictive value of CDSS-assisted screening were reflected in the previous section about the 'applicability of screening tools for medication optimisation'.

BOX 1 **Two examples to illustrate the variability in frequency and acceptance of CDSS-generated signals for medication optimisation**

Example 1 **Benzodiazepine (BZD) use and increased risk of falls**

Approximately 5% of STOPP signals concerned the potentially inappropriate long-term use of BZDs (STOPP D5). Pharmacotherapy teams accepted almost two-thirds of these signals, but one-third were considered not appropriate after evaluating the individual patient level and, therefore, did not result in a recommendation for benzodiazepine discontinuation [23].

Example 2 **Unindicated acetylsalicylic acid (ASA) and increased risk of (gastro-intestinal) bleeding**

Approximately 2% of STOPP signals concerned the discontinuation of unindicated ASA combined with an oral anticoagulant for atrial fibrillation (STOPP C5). One-third of signals were considered appropriate after evaluation at the individual patient level, while in two-thirds, ASA was still indicated and was therefore not recommended to be discontinued [23].

After detecting potentially inappropriate prescribing, the next step in the medication review process was implementing proposed medication changes in agreement with patients and their attending physicians (Chapter 4.2). Overall, 62% of OPERAM intervention patients with at least one recommendation had one or more

recommendations implemented at two months, with a mean of 1.16 (*SD* = 1.48) implemented recommendations per patient, mostly discontinuing inappropriate prescribing (Chapter 3.2).

Reasons for intentional non-implementation of recommendations provided by the pharmacotherapy team were studied in the Dutch cohort of OPERAM intervention patients, revealing that approximately 40% of all recommendations were disagreed upon by either the attending physician, the patient or both (Chapter 4.2). Our results showed that, in addition to the aforementioned variability in the acceptance of CDSS-generated signals, the subsequent implementation of recommendations was also highly susceptible to variability, thereby impacting the effectiveness of the medication review on clinical outcomes. The level of agreement between the attending physician and the patient depended on the type of recommendation (Chapter 4.2, Box 2) which likely required different strategies to increase implementation [44].

In Box 2, Example 1 (discontinuation of benzodiazepines), strategies primarily focusing on *patients' barriers* to deprescribe a benzodiazepine might increase successful implementation. We found that 90% of disagreed recommendations to discontinue a benzodiazepine were due to patient reluctance. A systematic review of primary care interventions to deprescribe benzodiazepines emphasised the importance of shared decision-making between health care professionals and patients [45], finding that patient education combined with tapering recommendations resulted in discontinuation rates varying from 27% to 36%, while pharmacological substitution or tapering recommendations combined with psychological support resulted in discontinuation rates between 65% and 80% [45]. These results highlighted how to overcome patient barriers and question the feasibility of successfully deprescribing of long-term benzodiazepine use in the acute hospital setting, given the importance of intensive patient follow-up and monitoring.

In Box 2, Example 2 (discontinuation of unindicated acetylsalicylic acid), strategies primarily focused on *prescriber's barriers* and the adequate transfer of medication changes across care settings might increase the implementation of this recommendation. A recent multicentre non-controlled intervention study in Dutch hospitals investigated unintentional guideline deviations in hospitalised patients with two or more antithrombotic agents. An algorithm prospectively selected patients based on antithrombotic prescriptions. In 42% of patients (median age 74; IQR 69–81]), an unintentional guideline deviation was observed and 70% were related to anticoagulation therapy combined with the use of unindicated antiplatelet therapy [46]. Admission to a non-cardiology ward was significantly associated with a higher risk of unintentional guideline deviations (OR 4.25 [95% confidence interval (CI); 3.07–5.88]). The overall proportion of patients with an unintentional deviation was reduced to 2.2% after a hospital pharmacist's intervention, with

an overall in-hospital implementation of 97% [46]. This study demonstrated the feasibility of discontinuing unindicated ASA in a hospital setting. In OPERAM, the implementation rate of presumed unindicated ASA at two months was lower (67%).

Box 2 **Two examples to illustrate the variability in physician's and patient's agreement with medication optimisation recommendations**

Example 1 **Benzodiazepine (BZD) use and increased risk of falls**

Only a quarter of CDSS-generated STOPP signals to discontinue long-term BZD use (STOPP D5) was implemented at two months after the in-hospital medication review (64% of signals were accepted by the pharmacotherapy team, of which 39% were implemented). In the Dutch cohort of OPERAM intervention patients, approximately 50% of recommendations to discontinue a BZD were not agreed upon and, therefore, intentionally not implemented, which in 90% of disagreed recommendations was due to patient reluctance to discontinue BZDs [44].

Example 2 **Unindicated acetylsalicylic acid (ASA) and increased risk of (gastro-intestinal) bleeding**

One-fifth of CDSS-generated STOPP signals to discontinue ASA combined with an oral anticoagulant for atrial fibrillation (STOPP C5) were implemented at two months after the in-hospital medication review (32% of signals were accepted, of which 67% were implemented). Although reasons for non-implementation were not studied for this recommendation, intentional non-implementation of ASA was unlikely if ASA was considered unindicated. In contrast to the discontinuation of BZD use, the decision to continue or discontinue anticoagulation therapy predominantly relied on a clinician's decision based on CPGs rather than patient preferences.

The implementation of medication optimisation recommendations to reduce potentially inappropriate prescribing remains challenging, especially in large multicentre clinical trials. Before OPERAM, a European randomised controlled trial (SENATOR) investigated ADR occurrence in hospitalised older people with multimorbidity and polypharmacy within two weeks of an in-hospital intervention [47]. CDSS-generated medication optimisation signals in intervention patients were directly presented to attending clinicians on a feedback report at a single time point within 60 hours after hospital admission, and no difference between the intervention

and control group was found in the occurrence of ADRs (24.5% vs 24.8%; OR 0.98; 95% CI 0.77–1.24; p = 0.88) [47]. The results of this SENATOR trial were attributed to the poor implementation of CDSS-generated STOPP/START signals, approximately 15%, while a retrospective examination of signals found that 39% of all presented signals were deemed clinically relevant [48]. The results of this large, multicentre trial contrasted with the results of a smaller single-center cluster randomised controlled trial, in which a significant effect on ADR incidence and medication costs was found after applying STOPP/START criteria in admitted older adults [11]. However, the implementation rates of STOPP and START recommendations in single-centre trials were much higher (STOPP: 81%; START: 87%) [10].

In contrast to the SENATOR trial, CDSS-generated signals for OPERAM intervention patients were first reviewed for clinical applicability by a pharmacotherapy team before discussing with the attending physician and patient. Nevertheless, pharmacotherapy team's recommended drug changes were moderate, with an overall implementation rate of recommendations of 42% at two months after the in-hospital medication review. Again, there was high variability in implementing recommendations for different drug classes, ranging from 13% to 65% for the top ten most prevalent recommended drug changes (Chapter 3.2) [16].

2.2. Perspectives on how to improve the implementation of medication optimisation recommendations

The reasons for the non-implementation of proposed recommendations were investigated in Chapter 4.2 [44]. Barriers to changing medication differed between prescribers and patients and varied per drug class. An important factor significantly impacting patient's and prescriber's barriers to implementation is the clinical setting in which these recommendations are presented. The OPERAM trial was performed in a hospital setting, while decisions to accept or reject STOPP/START signals might have been different in other healthcare settings, as well as the willingness of patients and attending physicians to change long-term medication use. For instance, 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 by a research pharmacist were implemented by the attending physician [49].

Another important condition for implementing medication changes is trusting relationships, on the patient-physician level and among healthcare professionals [50]. For instance, previous research found that attending physicians' implementations of STOPP/START recommendations were significantly higher if the recommendations were discussed by a physician rather than a pharmacist [51]. In addition, a multicentre mixed-methods interview study among OPERAM patients (n = 48) found that trusting

patient-physician relationships are one of the facilitators for successful shared decision-making [50]. Thus, insufficient, long-term trustful relationships may negatively influence the implementation of medication optimisation recommendations, which may also explain lower implementation rates usually found in multicentre clinical trials compared to single-centre trials.

While the OPERAM trial was ongoing, the results of a European large randomised controlled study were published investigating the effectiveness of a CDSS-assisted deprescribing tool used in older adults (≥75 years) with polypharmacy (≥8 chronic drugs) in a primary care setting versus usual care. After 24 months, no between-group difference was found according to the intention-to-treat analysis for the composite endpoint of unplanned hospital admissions or death. However, the per-protocol analysis restricted to patients who fully followed the trial protocol favoured the intervention (odds ratio 0.82, 95% CI 0.68–0.98), possibly indicating that the non-implementation of the intervention affected trial results significantly [52]. This tool resulted in a reduction of 0.42 drugs per patient. In line with the results from OPERAM, it appears to be safe to withdraw drugs in older people, which is a positive result in itself by reducing the treatment burden and prescribing costs.

Furthermore, unintentional non-implementation can occur at any stage during a follow-up period, and many possible factors can impede the actual and persistent implementation of agreed recommendations. For example, unintentional medication discrepancies at the transition of care are common, posing an increased risk of avoidable patient harm [53–55]. Canadian research found that almost half (44%) of all included patients (n = 2,655; mean age 69.5 years [SD = 14.7]) were not adherent to some or all changes made to their medications after hospital discharge. Patients who were not adherent to any medication changes had a significantly higher risk (35%) of adverse events compared than those who were adherent to all medication changes [56].

Unfortunately, no data was available in the OPERAM study to distinguish between the intentional and unintentional non-implementation of recommendations. Thus, concise documentation and the transfer of reasons for medication changes will likely prevent unintentional (dis)continuation of medication across care settings and will be an informative source for future research.

3. Outcome measures in medication review

The previous section discussed the causes of the high variability in the medication review process impacting potential outcomes. The next paragraphs reflect on 1) the risk of drug-related hospital readmissions (the primary outcome of the OPERAM trial) and 2) how to measure the impact of medication review.

3.1. The risk of a drug-related hospital readmission

The primary outcome of the OPERAM trial was a patient's first hospital readmission that was considered a drug-related admission (DRA), within one year after inclusion. A DRA was defined as a 'hospitalisation due to an adverse drug event; harm due to an adverse drug reaction or a medication error related to overuse, underuse, or misuse of prescription and non-prescription medications and which is the main reason for or contributes to hospital admission of a patient' [57]. DRAs were not significantly reduced in the intervention group compared to the control group, and no between-group difference was found for any hospital readmissions or potentially preventable DRAs. A first hospital readmission occurred in 46.4% (*n* = 447/963) of total intervention patients compared to 49.4% (n = 516/1045) of total control patients. In patients who were readmitted, 47.2% (*n* = 211/447) of intervention patients and 45.3% (*n* = 234/516) of control patients had a drug-related readmission. The preventability of drug-related readmissions was defined as readmissions related to potential medication errors (i.e. drug overuse, underuse, or misuse). A DRA was considered preventable in 39.8% (84/211) of intervention patients and in 42.7% (*n* = 100/234) of control patients. A summary of the results of the OPERAM trial (Chapter 3.1) and of the different steps in the medication review process (Chapters 4.1–4.3) appear in Figure 1.

The outcome of a DRA requires clinical consideration, including a causality assessment. Thus, a DRA remains a partially subjective outcome as it relies on the quality of documented information available for adjudication. Unsurprisingly, reported incidences of DRAs have varied greatly in the literature due to differences in definitions, study populations and assessment methods [58]. Thus, the intervention and outcome variability further complicates establishing a causal relationship between a medication review and the outcome of a DRA. Therefore, the adjudication process in OPERAM was performed by skilled senior clinician pairs who were blinded for patient allocation using a standardised adjudication guide to maximise reliability of this outcome [59,60]. Hence, difficulties that may have arisen in the adjudication process were similar for OPERAM intervention and control patients and would not likely have affected the primary outcome.

However, a DRA remains a broadly defined outcome measure that can occur in any patient using medication over time. Although observational studies identified certain drugs (or a lack of indicated drugs) posing an increased risk of DRAs in older people, this outcome remains open to multiple interpretations of risk factors associated with each drug therapy related to individual patient characteristics at a certain moment in time. Inappropriate prescribing may increase the risk of a DRA but does not necessarily result in a DRA. Conversely, interventions to optimise drug therapy may positively affect the risk of drug-related harm, but the risk of a DRA can remain substantial in a patient with polypharmacy and multimorbidity, as explained by combining Examples 1 and 2 (Box 3).

BOX 3 **The risk of a DRA**

Examples 1 and 2 combined

As a result of the variability in screening and implementation, each signal for potentially inappropriate prescribing can result in at least eight possible outcomes, as shown in Figures 2.1 and 2.2. A medication review might only prevent a DRA if the signal for potentially inappropriate prescribing was accepted after clinical evaluation at the individual patient level, followed by implementing the recommended medication change (1 of 8 possible outcomes).

If unindicated ASA was successfully discontinued in the example patient, bleeding might have been prevented. However, the number needed to harm (NNH) of unindicated use of ASA combined with a DOAC is 24 over a mean period of 21 months according to literature [61]. Hence, 24 patients with unindicated ASA should be discontinued to prevent one bleeding. In OPERAM, unindicated ASA was discontinued in only 18 patients.

In addition, if ASA was discontinued, but the use of a BZD in the same patient was not (e.g. due to patient disagreement or re-prescription at discharge), the patient was still at risk for a DRA (i.e. a fall related to benzodiazepine use). This risk of falls with BZD use could either result in an actual fall during the follow-up period of a clinical trial or may not (yet) have occurred. In either case, continued inappropriate prescribing would be unfavourable because the BZD would still contribute to an increased risk of falls (OR 1.6) [62].

The two decision trees presented in Figure 2.1 and 2.2 illustrate how the variability in decisions during the medication review process can impact the outcome ‘DRA’, based on the aforementioned examples (Boxes 1–3).

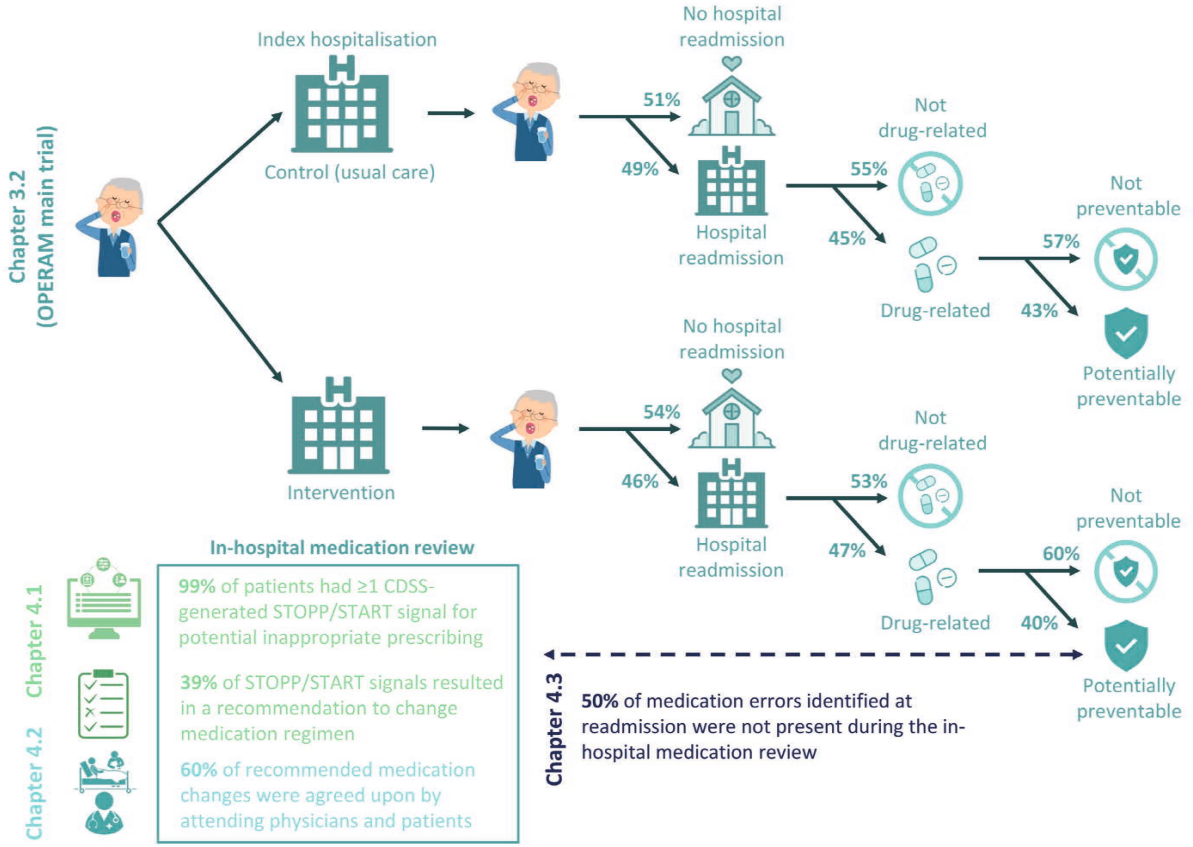


Figure 1. Flowchart of the OPERAM randomised controlled trial results (Chapter 3.2 [16]) and results of the detailed evaluation of the in-hospital medication review process (Chapter 4.1–4.3 [23,44])

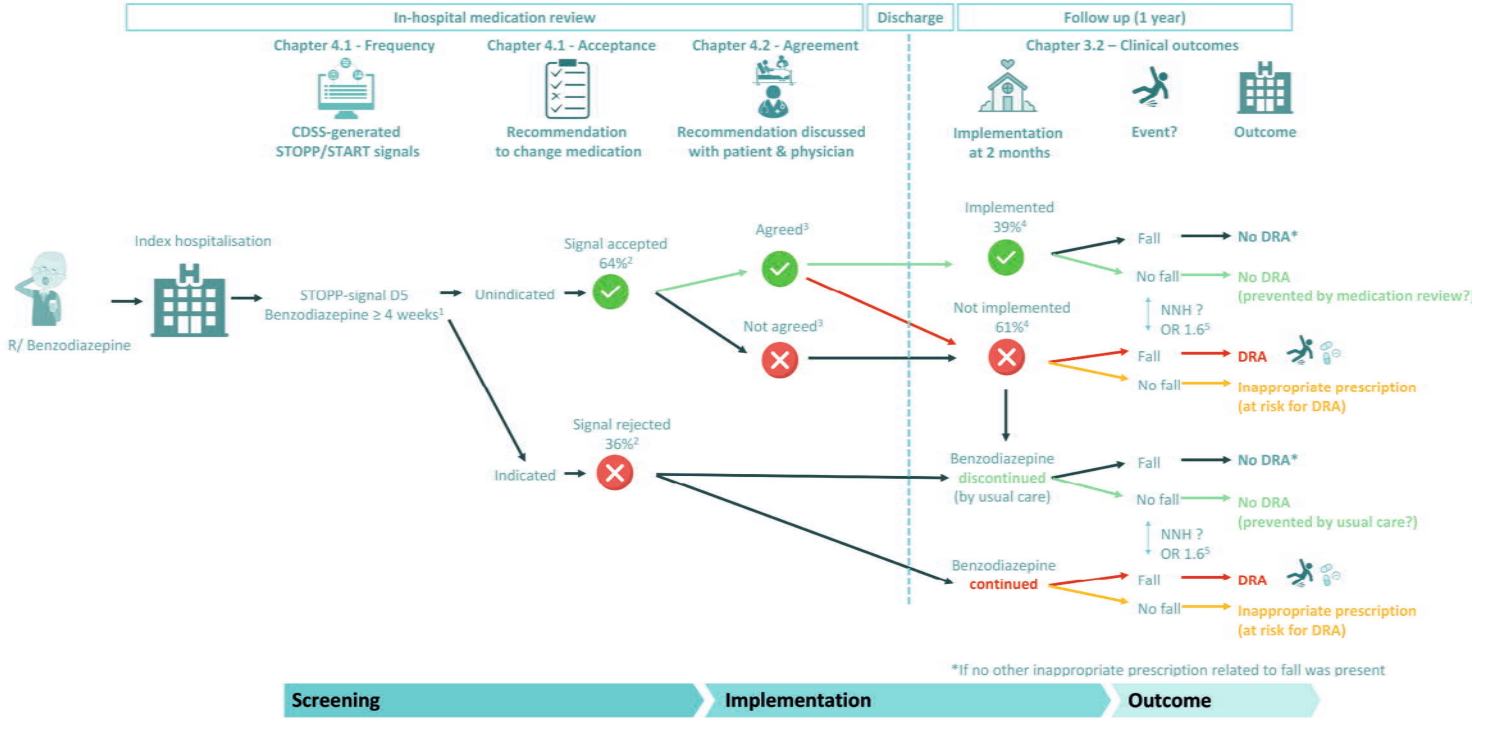


Figure 2.1, Example 1. Decision tree of a STOPP-signal (STOPP D5) to discontinue long-term benzodiazepine use related to the potential outcomes of these decisions.

Figure 2.1. Continued.
[1]STOPP D5 comprised 5.2% (*n* = 181/3465) of all generated STOPP signals in all OPERAM trial sites (Switzerland, Belgium, Ireland and the Netherlands).
[2]Percentage of accepted signals by the pharmacotherapy team with the number of generated STOPP D5 signals (*n* = 181) as the denominator in all OPERAM trial sites
[3]A subanalysis in Dutch OPERAM patients revealed that 44% of recommendations to discontinue long-term use of a benzodiazepine based on STOPP D5 were not agreed upon, primarily due to patient reluctance [44].
[4]The implementation of STOPP/START-based recommendations was calculated at two months after discharge with the number of recommendations based on STOPP D5 as the denominator.
[5]Based on results from Woolcott et al (2009) [62]. The Bayesian unadjusted odds ratio OR) estimate for benzodiazepine use on falls was 1.57 (95% CI, 1.43–1.72) and the adjusted OR was 1.41 (95% CI, 1.20–1.71) in patients >60 years.
DRA = drug related hospital admission; *NNH* = number needed to harm; *OR* = odds ratio.

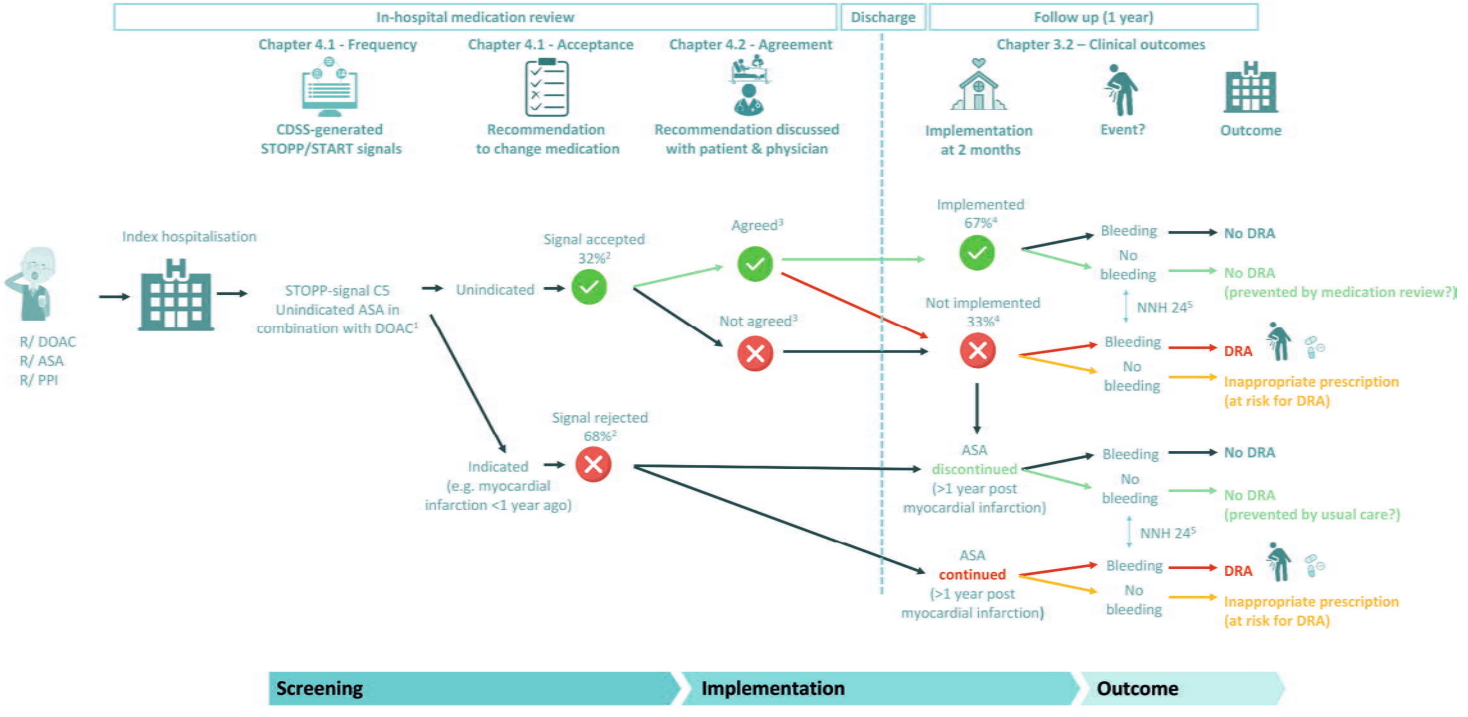


Figure 2.2, Example 2. Decision tree of a STOPP-signal (STOPP C5) to discontinue unindicated ASA in combination with DOAC use related to the potential outcomes of these decisions.

Figure 2.2. Continued.
[1]STOPP C5 comprised 1.7% (*n* = 60/3465) of all generated STOPP signals in all OPERAM trial sites (Switzerland, Belgium, Ireland and the Netherlands).
[2]Percentage of accepted signals by the pharmacotherapy team with the number of generated STOPP C5 signals (*n* = 60) as the denominator in all OPERAM trial sites.
[3]No data on agreement after discussion with patient and physician was available for recommendations related to STOPP C5.
[4]The implementation of STOPP/START-based recommendations was calculated at two months after discharge with the number of recommendations based on STOPP C5 as the denominator.
[5]Based on results from Schaefer et al (2021) [61]. Patients taking DOAC and ASA (without indication) experienced more bleeding events compared with DOAC monotherapy (26.0 bleeds vs 31.6 bleeds per 100 patient years, P = 0.01). This equals a NNH of 24 patients (i.e. unindicated aspirin needs to be discontinued in 24 DOAC users to prevent one bleeding).
DOAC = direct oral antigoaculant; *ASA* = acetylsalicylic acid; *PPI* = proton pump inhibitor; *DRA* = drug related hospital admission; *NNH* = number needed to harm.

Another issue that complicates measuring the effectiveness of cross-sectional medication optimisation on long-term clinical outcomes, is that multimorbid older people with polypharmacy are in a rather dynamic health condition involving changes in (the severity of) medical conditions and pharmacotherapy over time [63]. These changes and subsequent actions by usual care interfere with clinical outcomes measuring drug-related harm. In Chapter 4.3, we found that the prior in-hospital medication review did not address medication errors identified at readmission because either these medication errors occurred after the medication review (~50%), no recommendation was given during the medication review (~25%) or the recommendation was not implemented (~25%). Thus, the relationship between reducing potentially inappropriate prescribing by a medication review (intervention) and the occurrence of a 'DRA' (outcome) over time is indirect and, therefore, difficult to measure. The type of medication optimisation recommendations and their implementation can highly affect treatment outcomes, given that each treatment has a unique benefit-risk balance. In addition, outcome measures in older people with polypharmacy and multimorbidity are highly affected by changes in medical conditions, pharmacotherapy and treatment goals over time, inadequately addressed by a single, cross-sectional in-hospital medication review.

3.2. How to measure the impact of medication review

Prior to the initiation of the OPERAM trial, Beuscart et al. developed a core outcome set containing seven outcomes to be included in future trials of medication reviews in multimorbid older patients with polypharmacy: 1) drug-related hospital admissions; 2) drug overuse; 3) drug underuse; 4) potentially inappropriate medications; 5) clinically significant drug-drug interactions; 6) health-related quality of life and 7) pain relief [64]. Similarly, Rankin et al. developed a core outcome set including 16 outcomes to be considered in effectiveness studies aimed at improving the appropriateness of polypharmacy in older people in primary care. This core outcome set included endpoints in several domains: medication-related outcomes (e.g. adherence, medication appropriateness, medication errors, medication complexity), patient-related outcomes (e.g. cognitive functioning, quality of life, patient perception of treatment burden), patient's knowledge about treatment and disease, healthcare utilisation and clinical (adverse) outcomes (e.g. severe drug-related harm, mortality).

These core outcome sets were thoroughly developed by Delphi consensus procedures and included the relevant outcomes that we attempted to improve via a medication review. However, given the highly individual medication review process, we learned from OPERAM and similar large clinical trials that it is challenging to measure the effect of a medication review on serious clinical adverse outcomes

[16,52,65]. In addition, the low implementation of the investigated, complex interventions impeded drawing firm conclusions about their potential effectiveness.

Therefore, investigating the effectiveness of domains that more directly relate to medication review interventions may be more suitable as outcomes in clinical trials, along with efforts to ensure actual implementation of interventions. Examples of domains from the aforementioned core outcome sets that may be more directly related to the medication review process are measurements of medication-related outcomes, patient-related outcomes and patient knowledge about treatment. Previous research has observed that a medication review focused on patient's personal preferences and goals in older patients (> 70 years) with polypharmacy (≥ 7 chronic drugs) in a primary care setting improved older persons' self-reported quality of life measured with EQ-VAS (but not with EQ-5D) and decreased the number of health problems impacting daily life [66]. Such 'step-by-step' results are highly relevant to gaining knowledge for the future development of the medication review process. The impact of a deprescribing intervention on older patients' priorities and goals is currently being investigated in a Canadian RCT conducted in a primary care setting [67]. If such interventions demonstrate effectiveness on several medication-related and patient-related outcomes and implementation is feasible and scalable, we can further explore their potential benefits in reducing 'hard' clinical (adverse) outcomes.

4. Medication optimisation in older people – who, when, where and how?

Given the vulnerable sustainability of our current healthcare system by increasing healthcare expenditures, making choices in healthcare (and research) is unavoidable [68]. Delivering the right care to the right patient at the right time is more important than ever.

In the next section, we will reflect on 1) selecting patients with the highest risk of drug-related harm (the who) and 2) when, where and how to perform medication optimisation interventions.

4.1. Selecting patients with the highest risk of drug-related harm (the who)

Risk prediction models and screening tools based on high-risk medications could support the triage of patients with the highest risk of drug-related harm and, therefore, may benefit most from a structured medication review (Figure 3). The applicability of the STOPP/START criteria and the ADR trigger tool have predictive

value in a hospital setting (~40%), considerably high compared to other risk-prediction models for drug-related harm or regular drug safety monitoring [69–75]. Similarly, the adjudication guide used within OPERAM for DRA assessment had a PPV of 42% [60]. Therefore, these tools may be valuable screening tools to select older patients at risk for potential drug-related harm. However, increasing the availability of structured, electronic patient data (e.g. medical conditions) is necessary before clinical practice implementation.

The increased use of digital health combined with the rapidly evolving science of machine learning allows exploring new methods for developing more sophisticated predictive models. For instance, a recent systematic review concluded that prediction models using EHR data perform better than administrative data [75]. Another study demonstrated that artificial intelligence could identify patients at high risk of heart failure or death after myocardial infarction [76]. Thus, the availability of large, real-time patient data combined with computer sciences is a promising strategy for future differentiation between older people at high or lower risk for drug-related harm, thereby increasing the PPV of existing screening tools based on medication use. Until then, an integrated approach based on known high-risk factors (e.g. polypharmacy, multimorbidity, older age, high-risk medication), expert opinions (including frailty assessment) and patient preferences remain the next best option to select patients who are at the highest risk for drug-related harm (Figure 3) [6].

4.2. When, where and how to perform medication optimisation interventions

We focused on medication optimisation in a hospital setting for older people with multimorbidity and polypharmacy. Our choice to study an in-hospital intervention is understandable given the association between inappropriate prescribing and the increased risk of drug-related hospital admissions. In addition, the hospital is a high-risk environment prone to medication errors, including those resulting from care transitions. However, preventing medication-related harm is better than cure. In addition, the average hospital stay of patients ≥70 years is only five to seven days in the Netherlands, the shortest among European countries, impeding long-term monitoring and follow-up [77]. Therefore, whether the acute hospital setting is the most appropriate setting to conduct medication reviews could be questioned. Nevertheless, the hospital environment facilitates specific geriatric and non-geriatric expertise (e.g. cardiovascular, pain management) with easy access to diagnostics, laboratory values and therapeutic drug monitoring. For example, a comprehensive geriatric assessment (CGA) has proven benefits in a clinical setting, while the benefits of CGA in primary care remain uncertain [78,79].

Although advanced software-assisted screening may contribute to the increased detection of patients at risk of drug-related harm, not all prescribers have expertise in medication optimisation in older people, possibly impeding the safe and successful uptake of software-generated signals, especially in a hospital setting with various experts. We found that postponed recommendations to primary care were frequently associated with attending physicians feeling ill-equipped to take responsibility for suggested medication changes beyond their area of expertise (Chapter 4.2) [44]. In addition, not all drug-related problems in older people are detectable by screening EHRs. For instance, detecting non-adherence or medication use problems and determining individual patient preferences require an implicit approach and discussion with patients by skilled professionals.

Introducing a multidisciplinary geriatric pharmacotherapy team or 'geriatric stewardship' may be a solution to overcome patients' and prescribers' barriers in the transition of care and may assist the process of medication review in high-risk patients (Figure 3) [80]. Although the transfer of care is already a known risk factor for drug-related harm, our findings confirmed that one-third of all potentially preventable DRAs identified in OPERAM intervention patients occurred within two months after hospital discharge (Chapter 4.3).

The role of geriatric stewardship was recently studied in older people (≥ 65 years) with polypharmacy (≥ 5 chronic drugs) and a frailty risk factor admitted to surgical and orthopaedic wards in a Dutch non-academic hospital. Patient-reported drug-related problems were reduced compared to usual care (2.8 versus 3.3 per patient), although this reduction was not significant, which may have been caused by the small sample size (n = 127 patients) [81]. The study also showed that one-in-three initial recommendations based on EHRs were altered after input from the primary care provider and the patient. Therefore, the authors highlighted that in-hospital medication reviews require transmural collaboration and patient participation to ensure continuity of patient care.

The evidence suggests that interventions designed to improve the care transition from hospital to home are effective and can reduce hospital readmission in adults, as concluded by a systematic review [82]. Such interventions preferably start in the hospital and continue after discharge rather than starting after discharge. Patient empowerment and shared decision-making, as with motivational interviewing, are key factors in the effectiveness of discharge interventions in reducing readmissions [82]. The exchange of individual treatment goals across care settings may assist all healthcare professionals in shared decision-making to meet an older patient's needs [50]. In addition, it will likely positively affect patients' attitudes towards medication optimisation [50].

A recent network meta-analysis concluded that medication review in older people combined with 1) medication reconciliation and patient education and 2) medication reconciliation, patient education, professional education and transitional care were associated with a lower risk of all-cause hospital readmission compared to usual care (risk ratio (RR) 0.45, 95% CI 0.26–0.80; RR 0.64, 95% CI 0.49–0.84, respectively) [83]. These results substantiated the hypothesis that a medication review is likely more effective when integrated into a more continuous medication optimisation process following a patient's journey across care settings, underlining the importance of patient and professional involvement.

In the United States, the transmural approach for delivering older persons' care has resulted in several restructured care models [84]. For example, the comprehensive care physician (CCP) model paired a patient with a trained hospital physician responsible for providing inpatient and outpatient care. Key factors in this programme were an integrated approach to care, a trusted physician-patient relationship, ready access to outpatient care, and a proactive interdisciplinary team tailored to patient needs. The preliminary findings based on patient-reported outcomes suggested significant improvements in patient experience and mental health status, with a 15%–20% decrease in hospitalisation, implying savings of $3000–$4000 per patient annually [85,86].

Thus, the introduction of a geriatric stewardship seems to be a promising strategy to improve care for older patients across care settings. However, a recent Swedish cluster randomised crossover trial in older (median age 81; IQR 74–87) hospitalised patients (n = 2,637) did not find a significant effect of an in-hospital medication review combined with a postdischarge follow-up on the incidence of unplanned hospital visits compared to usual care [87]. A process evaluation suggested that the follow-up was suboptimal, again highlighting the importance of successfully implementing investigated strategies to draw reliable conclusions. The authors also concluded that patient-reported outcomes, such as the health-related quality of life, might have been more suitable for capturing the potential effects of treatment changes than the primary outcome of unplanned hospital visits.

One explanation for these conflicting results may be that the success or failure of these care models highly depends on the healthcare systems in which they are embedded, as addressed in the Medication Safety in Polypharmacy report by the WHO [6]. It is not unlikely that current medication optimisation strategies can be effective but first require a change in existing healthcare structures and organisational cultures. A rigorous change of healthcare structure is often unfeasible in a clinical trial setting requiring the active involvement of many stakeholders, such as policy-makers, health care professionals, managers, patients, families and caregivers.

The proportion of drug-related hospital admissions (10%) in the Netherlands did not change over five years after the appearance of the HARM-Wrestling report in 2009. However, the absolute number has increased over the past years [88,89]. Therefore, we wonder if we should continue to search for scientific proof of effective medication optimisation strategies, or rethink our current delivery of care systems.

Future research perspectives

Although this thesis adds valuable insights to better understand the complexity of medication optimisation interventions in older people and measuring the effectiveness on clinical outcomes, some questions remain unanswered. The limited availability of risk prediction models, interventions with proven effectiveness based on current scientific standards, and the ongoing search for appropriate outcome measures highlight many opportunities for future research in medication optimisation in older people at risk of medication-related harm [90].

The application of a STOPP/START-based CDSS-assisted medication review – similarly to the applied intervention in OPERAM but in a primary care setting – is currently under investigation in the Optimising PharmacoTherapy In the multimorbid elderly in primary CAre (OPTICA) trial and may provide insights whether primary care is a more appropriate setting for conducting structured medication reviews in older people. In the Netherlands, the recently initiated cluster randomised controlled trial 'Less Is More: Optimised pharmacotherapy with improved coNtinuity of CarE in hospitaLised oLder peOple (LIMONCELLO)' [91] will focus on transitional multidisciplinary pharmacotherapeutic care consisting of four steps: a structured medication review, a transitional multidisciplinary discussion, a pharmacotherapeutic care discharge interview and discussion with the patient and a pharmacotherapeutic care plan incorporated in the discharge note. The primary outcome will be the proportion of patients with drug-related hospital readmissions in the first month after discharge, and secondary outcomes will include a cost-effectiveness analysis.

Several limitations of the OPERAM study will be addressed in the design of this clinical trial. For instance, the pharmacotherapy optimisation process will be better integrated into the usual care process, focusing on transitional care instead of a cross-sectional in-hospital medication review within 72 hours of admission as investigated in OPERAM. However, the short-term follow-up time in LIMONCELLO will impede measuring the advantages of long-term outcomes of medication optimisation in underuse and overuse of preventative, chronic medications. Another potentially important difference compared to OPERAM is that LIMONCELLO only includes Dutch hospitals, eliminating differences between countries. OPERAM

confirmed this variability could be significant: the effect on drug-related hospital admissions did not differ in prespecified subgroup analyses, except for the site of inclusion (Louvain, Belgium: hazard ratio 0.50, 95% CI 0.30–0.85, $p = 0.05$ for interaction) and dementia diagnosis ($p = 0.04$ for interaction).

The current paradigm of gaining high-quality evidence by conducting RCTs may not be the most suitable model for research in older people nor for the medication review process due to variability in medication optimisation interventions and outcomes. Focusing on the effectiveness of medication optimisation related to patient-reported treatment goals may be a more suitable outcome for highly individually tailored interventions ('$n = 1$'). In addition, choosing severe drug-related adverse outcomes as the primary outcome implies that such studies require large populations to reach sufficient statistical power, necessitating costly multicentre clinical trials.

Indeed, sharing knowledge about failed initiatives with special attention to enablers and implementation barriers could bridge the gap between research outcomes and translating these outcomes to real-world practice [92]. In the era of electronic healthcare, using large real-world health data to obtain real-world evidence would be an interesting method to build and evaluate effective medication optimisation strategies in older people [93,94]. One condition to using real-time patient data so that feedback and learning can occur is that such data should allow for 'following' a patient's journey and sharing outcomes of interest, necessitating connecting inpatient and outpatient care systems (Figure 3). Only then can the future use of real-world big data discover patterns that cannot be identified with RCTs due to sample size restrictions.

Concluding remarks

Medication optimisation in older people with polypharmacy and multimorbidity needs ongoing effort. Addressing appropriate prescribing and medication use in this vulnerable population should be embedded as part of a continuous process, with specific attention at the initiation, change and discontinuation of drugs, during medication review, care transitions and at changes in patients' medical conditions. Successful implementation of medication optimisation strategies is essential to draw reliable conclusions about their (in)effectiveness. The prevention of drug-related harm on a structural basis (i.e. not only at the level of individual patients but at a population level) likely requires a system approach. This approach would involve patients, healthcare professionals, medical education developers, software developers, health care organisations, policy-makers and regulators jointly collaborating on this mutual goal.

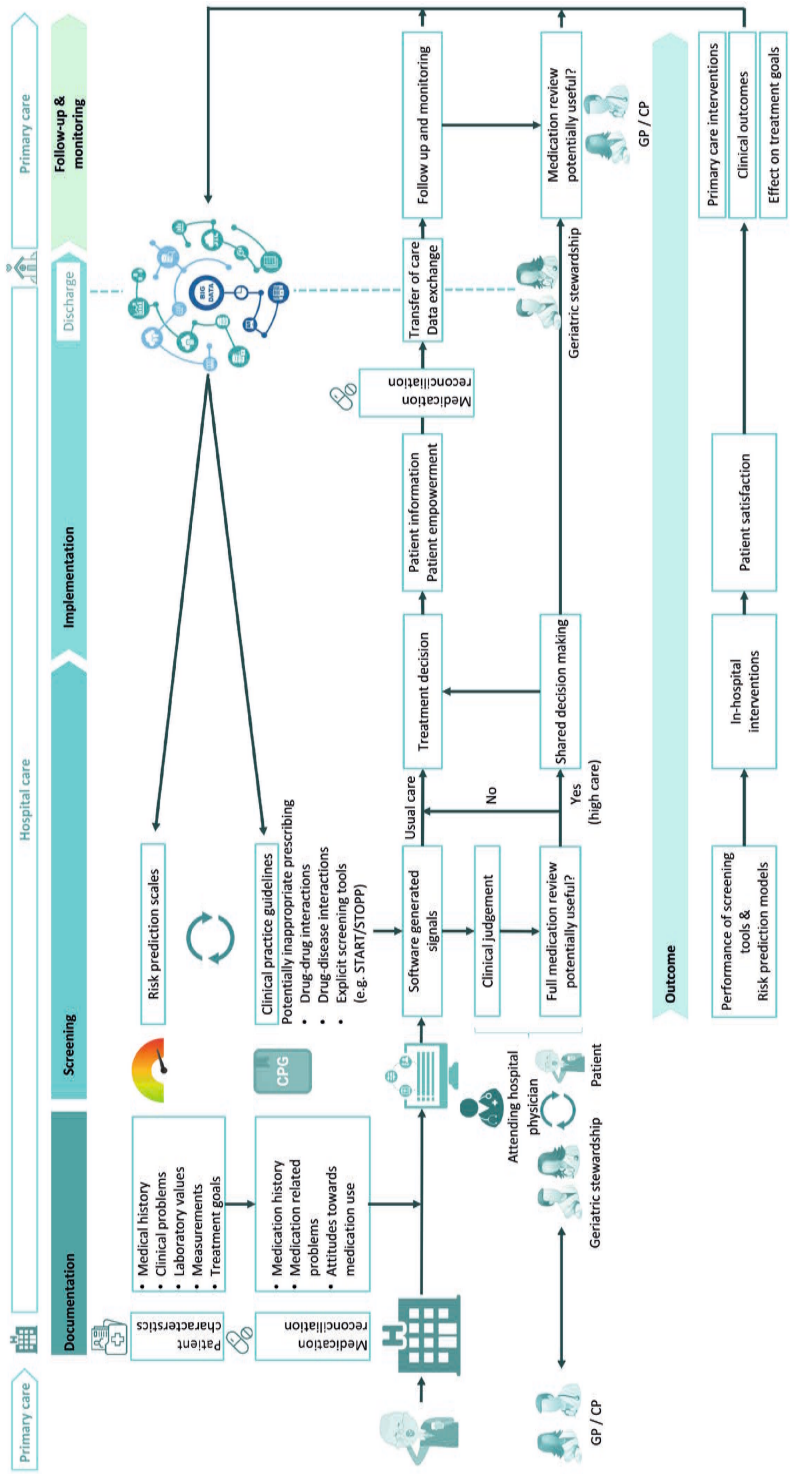


Figure 3. Flow chart of future projections on improving care for older people in transitional care.
GP = general practitioner; *CP* = community pharmacist; *CPG* = clinical practice guideline.

Declarations

Authors' contributions

Bastiaan Sallevelt wrote the general introduction of this thesis. His supervisors Wilma Knol, Ingeborg Wilting, Eugène van Puijenbroek and Toine Egberts reviewed the manuscript critically for important intellectual content and approved the final version.

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Competing interests

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

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Chapter 6

Summary

SUMMARY

Background

The prevalence of multimorbidity and polypharmacy is increasing in the ageing population, and both are important risk factors for drug-related harm, such as drug-related hospital admissions. Previous studies have reported that 10%–30% of all hospital admissions in older people are drug-related, half of which are potentially preventable.

Several tools, such as the Screening Tool of Older Person's Prescriptions (STOPP) and the Screening Tool to Alert to the Right Treatment (START) criteria, have been developed to detect potentially inappropriate prescribing in multimorbid older people to improve medication appropriateness and prevent adverse outcomes. To incorporate such tools into daily clinical practice, the application of software assistance has gained attention in facilitating medication optimisation. However, previous studies investigating pharmacotherapy optimisation interventions in older people reported inconsistent results on improved clinical outcomes.

In this thesis, we focus on strategies for medication optimisation in hospitalised, multimorbid older people with polypharmacy and evaluate the effectiveness of a software-assisted in-hospital medication review on clinical outcomes.

Applicability of tools for medication optimisation in hospitalised older people

In **Chapter 2**, the applicability of medication optimisation tools recommended by clinical practice guidelines was investigated. The performance of a trigger tool recommended by the Dutch geriatric guideline for detecting adverse drug reactions (ADRs) was evaluated in a cross-sectional study in **Chapter 2.1**. This trigger tool lists combinations of clinical events and drugs frequently associated with drug-related hospital admissions in older people. In 73% (n = 253/345) of patients with polypharmacy acutely admitted to the geriatric ward, 941 trigger-drug combinations listed in the ADR trigger tool were present. The fall, delirium, renal insufficiency and hyponatraemia triggers covered 86% (n = 810/941) of all trigger-drug combinations. After causality assessment based on the WHO-UMC criteria, 393 of 941 trigger-drug combinations were considered ADRs with at least possible causality, resulting in an overall positive predictive value (PPV) of 42%.

However, the PPV for individual triggers was highly variable, ranging from 0% to 100%. Usual care at the geriatric ward recognised the majority of ADRs (84%), increasing to 97% when restricted to ADRs with a 'probable' or 'certain' causality score.

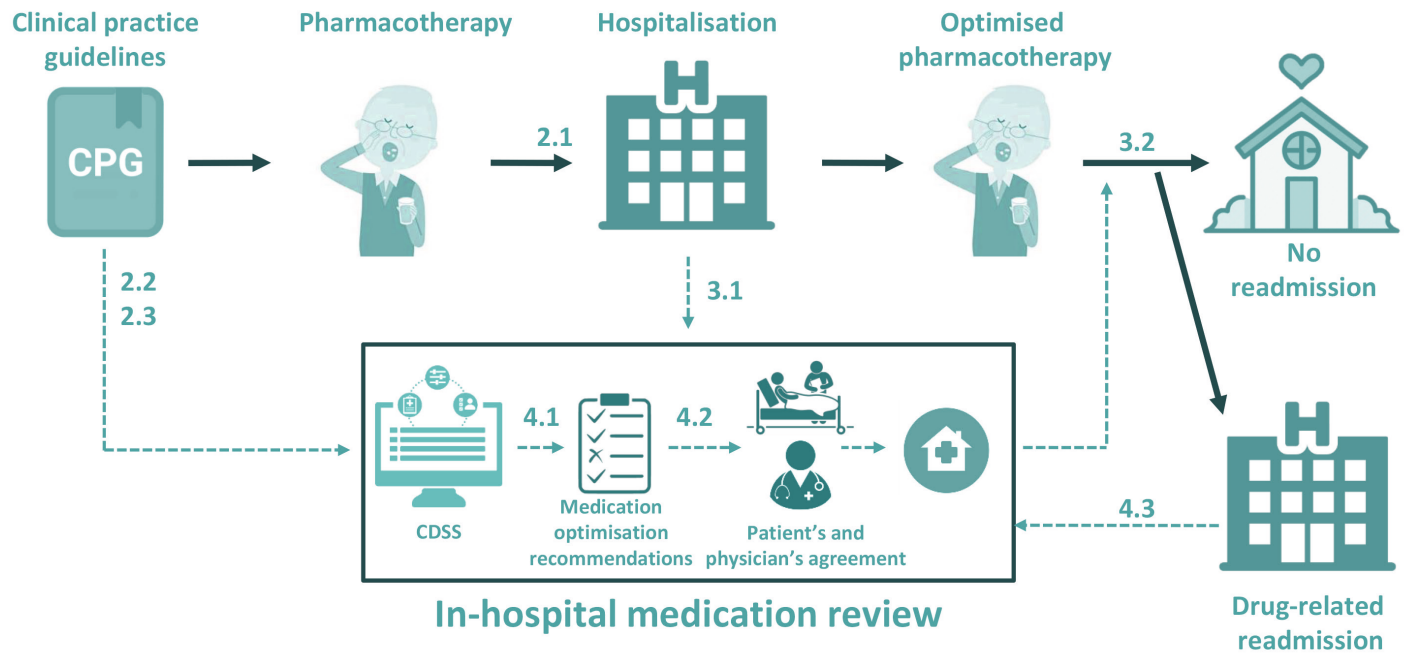

Figure 1. Graphical summary of this thesis.
CPG = Clinical practice guidelines; *CDSS* = Clinical decision support system.

For this reason, we concluded that implementing the ADR trigger tool at admission is unlikely to improve the detection of unrecognised ADRs in older patients acutely admitted to our geriatric ward. However, future research is needed to investigate the tool's clinical value when applied to older patients acutely admitted to non-geriatric wards.

In Europe, geriatric clinical practice guidelines endorse considering the use of the STOPP/START criteria to detect potentially inappropriate prescribing in older patients. The aim of the quality appraisal study performed in **Chapter 2.2** was to evaluate the clarity of recommendations of this explicit screening tool for use in daily patient care. Clarity of the action (what/how to do), condition (when to do) and explanation (why to do) of the individual STOPP/START criteria were rated on a 7-point Likert scale using tools provided by the Appraisal of Guidelines for Research & Evaluation (AGREE) Consortium. Our results showed that the clarity of the STOPP/START criteria could be improved, with an average clarity ranging between 57%–67%. For the future development of explicit medication optimisation tools, such as STOPP/START, our findings identified facilitators (high clarity) and barriers (low clarity) to improve the clarity of clinical practice guidelines (CPGs) on a language level and therefore enhance clinical applicability.

The lack of clarity of some STOPP/START criteria also made their conversion to algorithms for use in software systems challenging, as described in **Chapter 2.3**. Multiple multidisciplinary expert rounds were necessary to reach a consensus on how to interpret ambiguous wordings. A consensus was reached for all 34 START criteria and 76 of 80 STOPP criteria. The resulting 110 algorithms, modelled as inference rules in decision tables, were published as a template for integrating STOPP/START criteria version 2 to any software application.

Process development and clinical outcomes of in-hospital medication reviews

In **Chapter 3.1**, we developed a protocol for a medication review intervention, integrating single interventions that had demonstrated effectiveness in addressing drug-related problems in older patients. The developed intervention consisted of the following steps: a structured history-taking of medication (SHiM), a pharmacotherapy analysis according to the Systemic Tool to Reduce Inappropriate Prescribing (STRIP) method, assisted by a clinical decision support system (CDSS) with integrated STOPP/START criteria (developed in Chapter 2.3), followed by shared decision-making with the patient and the attending physician, and lastly, sending an information letter on in-hospital medication changes to inform the general practitioner. The method integrated patient input, patient data, involvement from other healthcare

professionals and CDSS-assistance into one structured medication review intervention, and was investigated in the OPtimising thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly (OPERAM) trial.

The OPERAM trial (**Chapter 3.2**) was a cluster randomised controlled multicentre trial investigating the effect of an in-hospital medication review performed jointly by a physician and a pharmacist (i.e. pharmacotherapy team) on drug-related readmissions in older (≥70 years) patients with multimorbidity (≥3 chronic conditions) and polypharmacy (≥5 regular medication use). The primary endpoint of OPERAM was the first drug-related hospital admission within one year after inclusion. Eligible patients were randomised in clusters on the level of the attending physician in four European hospitals (Switzerland, Belgium, the Netherlands, and Ireland). In total, 2,008 older adults (median = 9 drugs) were enrolled in 54 intervention clusters (963 participants) and 56 control clusters (1,045 participants) receiving usual care. In the intervention arm, 86% of participants (n = 789) had inappropriate prescribing, with a mean of 2.75 (SD = 2.24) STOPP/START recommendations for each participant.

Notably, 62% (n = 491) of intervention patients had ≥1 STOPP/START recommendation successfully implemented at two months, predominantly discontinuing their medication. In the intervention group, 211 participants (21.9%) experienced a first drug-related hospital admission compared with 234 (22.4%) in the control group. In the intention-to-treat analysis censored for death as a competing event (n = 375, 18.7%), the hazard ratio for first drug-related hospital admission was 0.95 (95% confidence interval [CI] 0.77–1.17). Although the structured CDSS-assisted medication review designed in Chapter 3.1 reduced inappropriate prescribing, it did not significantly affect drug-related hospital admissions.

Evaluation of the in-hospital medication review process

In **Chapter 4**, the process of in-hospital medication review as investigated in the OPERAM trial was evaluated in three studies.

First, the frequency of CDSS-generated STOPP/START signals and the subsequent acceptance of these signals by a pharmacotherapy team in a hospital setting were determined in **Chapter 4.1**. In 99% of OPERAM intervention patients, at least one STOPP/START signal was generated during the pharmacotherapy analysis with a median of 6 (IQR 4–8) signals per patient using a set of 110 STOPP/START algorithms. Overall, the pharmacotherapy team accepted 39% of the 5,080 signals after evaluating clinical applicability to the individual patient. These accepted signals resulted in medication optimisation recommendations to be discussed with the attending physician and the patient. The signal to discontinue a drug without a clinical

indication (STOPP A1) was most frequently generated (28%), with over half of these signals accepted (54%). The acceptance of signals was highly variable, ranging from 2.5% to 75.8% for the ten most frequently generated STOPP and START signals. These findings emphasised the importance of an expert team's involvement in translating population-based CDSS-generated STOPP/START signals to individual patients, as more than half the signals for potential overuse, underuse and misuse were not deemed clinically appropriate in a hospital setting. In addition, we found that country of the participating trial site was the strongest predictor of signal acceptance, while patient-related characteristics were poor predictors of acceptance.

Second, the patients' and physicians' agreement with STOPP/START-based individualised medication optimisation recommendations were assessed in **Chapter 4.2**. For this study, only data from the Dutch intervention arm of the OPERAM trial were used. In total, 371 recommendations for 139 patients were discussed with patients and attending physicians. The overall agreement was 62% for STOPP and 61% for START recommendations. The highest agreement was found for initiating osteoporosis agents and discontinuing proton pump inhibitors (both 74%). Factors associated with higher agreement in multivariate analysis were female gender (+17% [95% CI 3.7–30.4]), ≥1 falls in the past year (+15% [95% CI 1.5– 28.5]) and renal impairment (i.e. eGFR 30–50 ml/min/1.73 m2; +18% [95% CI 2.0–34.0]). The main disagreement (40%) was patients' reluctance to discontinue or initiate medication. Moreover, the reasons for disagreement differed per drug class.

For instance, the disagreement to discontinue benzodiazepines or z-drugs was mostly (91%) due to patient reluctance because of self-reported dependence or because patients argued that side effects (falls or sleepiness) were absent. In contrast, the most important reason for cardiovascular drugs was 'physician does not agree or does not feel qualified to advise' in 30% of cases of disagreement. Therefore, we concluded that better patient and physician education regarding pharmacotherapy's benefit/risk balance, with more precise and up-to-date medical records to avoid irrelevant recommendations, would likely result in higher adherence to future pharmacotherapy optimisation recommendations.

In **Chapter 4.3**, the detectability of medication errors with the in-hospital medication review in the year prior to a potentially preventable drug-related hospital admission was assessed. In total, 84 of 963 OPERAM intervention patients (8.7%) were readmitted within one year after the medication review with a potentially preventable drug-related admission, of which 72 patients (*n*=77 medication errors) were eligible for analysis. We found that the prior in-hospital medication review did not address medication errors identified at readmission because either these MEs occurred after the medication review (~50%), no recommendation was given during the medication review (~25%) or the recommendation was not implemented (~25%).

Conclusion and future perspectives

The investigated screening tools recommended by geriatric CPGs have predictive value in detecting potential drug-related risks in hospitalised older people with polypharmacy (ADR trigger tool, PPV: 42%; STOPP/START, signal acceptance: 39%). Therefore, these tools could contribute to identifying patients at risk for inappropriate prescribing. However, they also pose a risk of alert fatigue if implemented as clinical decision support in electronic health records. For future guideline development, it is important to formulate specific recommendations that ease integration in software systems and may contribute to increased guideline adherence. In addition, to bridge the potential gap between guideline recommendations and clinical practice, it is important to evaluate the performance of clinical decision support if implemented in electronic healthcare systems. These results obtained from clinical practice could be used to further develop and specify CPGs, for instance, to identify patients and settings in which interventions are most successful.

However, even with optimal software assistance, the interaction between attending physicians, patients and healthcare professionals with expertise in geriatric care remains essential in translating evidence-based signals for potentially inappropriate prescribing to the most appropriate pharmacotherapy at the individual patient level. The barriers to the non-implementation of proposed recommendations differed between prescribers and patients and varied per drug class. Thus, more research is necessary to identify the most effective strategies to overcome these barriers.

The results of the OPERAM trial showed that a single, structured in-hospital medication review reduced potentially inappropriate prescribing in older people with no detriment to patient outcomes. However, it did not significantly reduce drug-related hospital readmissions. To explain these results, we found that the prior single in-hospital medication review did not address medication errors identified at readmission because either these errors occurred after the medication review, no recommendation was given during the medication review or the recommendation was not implemented. Therefore, future research should focus on optimising the medication review timing, setting and frequency and implementing of proposed medication recommendations across health care settings.

Overall, we learned that the association between a patient-specific medication review and the clinical outcome ‘drug-related hospital admission’ is difficult to establish with a randomised controlled trial because both the intervention and outcome are highly variable. Thus, to further explore the potential clinical benefits of medication optimisation interventions in older people, we recommend exploring research designs based on large, real-world data rather than randomised clinical trials.

Chapter 7

Nederlandse samenvatting

SAMENVATTING

Achtergrond

Het behandelen of voorkomen van ziekten en aandoeningen met geneesmiddelen, ofwel farmacotherapie, heeft als doel om gezondheid en welzijn van patiënten te verbeteren. In de afgelopen decennia is de levensverwachting in Europa sterk toegenomen en farmacotherapie heeft hier een belangrijke positieve bijdrage aan geleverd. De toegenomen levensverwachting in combinatie met een dalend geboortecijfer leidt tot vergrijzing in Europa, waarbij het huidige percentage ouderen in Europa van 20% naar schatting zal toenemen naar 30% in 2050. In lijn met deze stijging, neemt ook het aantal mensen met meerdere chronische aandoeningen, ofwel multimorbiditeit, toe. Veel kwetsbare ouderen gebruiken meerdere verschillende geneesmiddelen. Doorgaans wordt het dagelijks gebruik van vijf of meer verschillende geneesmiddelen polyfarmacie genoemd.

Naast de positieve effecten van farmacotherapie, kunnen geneesmiddelen ook gezondheidsschade toebrengen. Het is daarom bij elke patiënt belangrijk om de potentiële voordelen van een geneesmiddel vanaf het moment van voorschrijven regelmatig zorgvuldig af te wegen tegen de potentiële risico's. Uit eerdere onderzoeken is naar voren gekomen dat oudere patiënten met multimorbiditeit en polyfarmacie een verhoogd risico hebben op medicatie-gerelateerde problemen met aanzienlijke negatieve consequenties voor patiënt en maatschappij. Zo is naar schatting 10% tot 30% van de ziekenhuisopnames bij ouderen geneesmiddel-gerelateerd, waarvan ongeveer de helft potentieel vermijdbaar is. In Nederland is het aantal geneesmiddel-gerelateerde ziekenhuisopnames in absolute aantallen over de periode 2008 tot 2013 gestegen van 39.000 naar 49.000.

Om geneesmiddel-gerelateerde schade bij ouderen te voorkomen en veilig gebruik van medicatie te bevorderen, zijn diverse richtlijnen ontwikkeld. Nationale en internationale richtlijnen bevelen aan om bij ouderen met polyfarmacie periodiek een gestructureerde medicatiebeoordeling uit te voeren. Tijdens een medicatiebeoordeling wordt de effectiviteit en veiligheid van de op dat moment gebruikte medicatie op individueel patiëntniveau en in samenspraak met de patiënt beoordeeld door een arts en een apotheker. Er wordt bijvoorbeeld voor elk voorgeschreven geneesmiddel nagegaan of er nog een actuele indicatie voor dit geneesmiddel is, met als doel overbehandeling op te sporen, en of de medicatie goed wordt verdragen. Ook wordt beoordeeld of alle aandoeningen van de patiënt zo optimaal mogelijk behandeld worden of dat er sprake is van onderbehandeling. Eventuele medicatie-gerelateerde problemen en de wensen van de patiënt worden

in kaart gebracht, resulterend in een behandelplan of behandeladvies om de farmacotherapie te optimaliseren.

Er zijn diverse screening-instrumenten ontwikkeld die als hulpmiddel tijdens een medicatiebeoordeling kunnen worden ingezet om farmacotherapie bij ouderen te optimaliseren. In Europa is de Screening Tool of Older Person's Prescriptions (STOPP) en de Screening Tool to Alert to the Right Treatment (START) het meest gebruikte screening-instrument om potentiële onder- en overbehandeling bij ouderen te detecteren. Eerder onderzoek heeft aangetoond dat de toepassing van de STOPP/START criteria geneesmiddelbijwerkingen en medicatiefouten kan verminderen.

Studies naar het effect van een medicatiebeoordeling bij ouderen laten geen eenduidige resultaten zien op het voorkómen van ernstige geneesmiddel-gerelateerde schade, zoals ziekenhuisopnames, en kennen beperkingen in de studieopzet. Centraal in dit proefschrift staat de vraag welke strategieën en interventies kunnen bijdragen aan het verminderen van onjuiste farmacotherapie bij ouderen met multimorbiditeit en polyfarmacie die opgenomen zijn in het ziekenhuis. Onderdeel hiervan is de ontwikkeling en effectiviteitsevaluatie van een beslisondersteunend instrument in de optimalisatie van farmacotherapie bij ouderen. In de internationale OPERAM-studie (acroniem voor 'OPtimising thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly') is de effectiviteit van een gestructureerde medicatiebeoordeling in het ziekenhuis bij patiënten met multimorbiditeit en polyfarmacie onderzocht met als doel om geneesmiddel-gerelateerde heropnames te voorkomen.

Figuur 1. Grafische sammenvatting van dit proefschrift. CPG = 'clinical practice guidelines' (medische richtlijnen)

Toepasbaarheid van screeningsinstrumenten voor medicatie-optimalisatie in het ziekenhuis

In **hoofdstuk 2** wordt de toepasbaarheid van screeningsinstrumenten onderzocht die momenteel worden aanbevolen voor het detecteren van ongeschikt medicatiegebruik in de Nederlandse richtlijn Polyfarmacie bij ouderen. Zo adviseert de richtlijn om voor iedere patiënt van 70 jaar en ouder die zich presenteert op de spoedeisende hulp te evalueren of de opname mogelijk gerelateerd is aan het medicatiegebruik op basis van een triggerlijst. Deze lijst is gebaseerd op de meest voorkomende medicatie-gerelateerde problemen bij ouderen en bevat 10 klinische problemen (triggers) met daarnaast een overzicht van geneesmiddelen die volgens literatuur vaak geassocieerd zijn met het probleem (bijvoorbeeld obstipatie bij opiaatgebruik). In **hoofdstuk 2.1** werd een retrospectief, dwarsdoorsnede-onderzoek uitgevoerd naar de meerwaarde van deze triggerlijst. Geïncludeerd werden patiënten van 70 jaar en ouder met polyfarmacie die via de spoedeisende hulp opgenomen werden op de afdeling geriatrie. In totaal werden 941 trigger-geneesmiddelcombinaties geïdentificeerd bij driekwart (73%, n = 253/345) van de geïncludeerde patiënten. De triggers voor vallen, delier, nierinsufficiëntie en hyponatriëmie kwamen het vaakst voor. Vervolgens werd op basis van het patiëntdossier een causaliteitsbeoordeling uitgevoerd volgens de WHO-UMC criteria, om te onderzoeken welke trigger-geneesmiddelcombinaties vermoedelijk ook als bijwerking konden worden aangemerkt. Dit bleek in 42% (positief voorspellende waarde, n = 393/941) van alle gevonden trigger-geneesmiddelcombinaties het geval te zijn. De positief voorspellende waarde voor het detecteren van bijwerkingen liep echter sterk uiteen voor de verschillende triggers (0%-100%). Daarnaast werd het overgrote deel (84%-97%) van de vermoedelijke bijwerkingen al herkend tijdens de ziekenhuisopname door de zaalarts op de afdeling geriatrie, zonder gebruik van de triggerlijst. Het implementeren van de triggerlijst zal daarom nauwelijks bijdragen aan het detecteren van niet-herkende bijwerkingen bij patiënten onder behandeling van de geriatrie. Vervolgonderzoek zal moeten uitwijzen of een dergelijke triggerlijst van toegevoegde waarde is voor het detecteren van bijwerkingen bij ouderen die op andere afdelingen dan de geriatrie worden opgenomen.

Een ander screeningsinstrument voor medicatie-optimalisatie bij ouderen zijn de eerdergenoemde STOPP/START-criteria. De STOPP/START-criteria vormen een expliciete screeningslijst met 80 STOPP-criteria voor het signaleren van potentiële overbehandeling en 34 START-criteria voor het signaleren van potentiële omissies (onderbehandeling). Het is belangrijk dat aanbevelingen voor medicatie-optimalisatie, zoals de STOPP/START-criteria, duidelijk zijn geformuleerd om enerzijds implementatie in de praktijk te bevorderen en anderzijds zorgprofessionals te ondersteunen in het maken van een weloverwogen afweging met betrekking tot de toepasbaarheid van de aanbeveling voor de individuele patiënt. In **hoofdstuk 2.2**

werd daarom de duidelijkheid in tekstuele formulering van de 114 STOPP/START-criteria geëvalueerd.

Per criterium werd de eenduidigheid van de aanbevolen actie (welke actie dient te worden ondernomen?), de voorwaarde (onder welke omstandigheden of voor wie is het criterium van toepassing?) en de toelichting op de aanbeveling (waarom is dit criterium van toepassing?) beoordeeld. De gemiddelde score op de drie onderdelen varieerde tussen de 57% en 67%. Deze resultaten laten zien dat er nog ruimte voor verbetering is om de STOPP/START criteria verder te verduidelijken op tekstueel niveau, met als doel de klinische toepasbaarheid te vergroten. Het onderzoek geeft daartoe handvatten door elementen met een hoge en lage mate van eenduidigheid te identificeren.

Hoofdstuk 2.3 beschrijft het proces waarin de STOPP/START-criteria zijn omgezet naar algoritmes geschikt voor toepassing in softwaresystemen, bijvoorbeeld als medisch-farmaceutische beslisregels. Voor de omzetting van de 114 STOPP/START-criteria naar coderingen waren meerdere consensusrondes noodzakelijk met een multidisciplinair team van experts. Dit resultaat sluit aan op de bevindingen uit hoofdstuk 2.2 en nodigt uit om screeningsinstrumenten zo eenduidig mogelijk te formuleren, zodat ze geschikter zijn voor software-implementatie. Consensus werd bereikt voor alle 34 START-criteria en 76 van de 80 STOPP-criteria resulterend in 110 STOPP/START algoritmes.

Procesontwikkeling en klinische uitkomsten van een medicatiebeoordeling in het ziekenhuis

In **hoofdstuk 3.1** wordt de procesontwikkeling van een interventie beschreven voor het uitvoeren van een gestructureerde medicatiebeoordeling in het ziekenhuis. De interventie werd gebaseerd op wetenschappelijk bewezen effectieve methoden in het detecteren en reduceren van medicatie-gerelateerde problemen, onderbehandeling en overbehandeling bij ouderen. Als methode voor het uitvoeren van een gestructureerde medicatiebeoordeling werd gekozen voor de 'Systemic Tool to Reduce Inappropriate Prescribing' (STRIP)-methode. Deze methode bestaat uit vijf processtappen die zijn beschreven in hoofdstuk 1. De beoordeling van de farmacotherapie werd uitgevoerd door een farmacotherapieteam bestaande uit een arts en een apotheker met behulp van een beslisondersteunend systeem, de STRIP Assistent. De STOPP/START-criteria zoals ontwikkeld in hoofdstuk 2.3 werden geïntegreerd in het beslisondersteunend systeem in de vorm van medisch-farmaceutische beslisregels. Vervolgens werden adviezen voor medicatie-optimalisatie door het farmacotherapieteam besproken met de zaalarts en de patiënt. Tot slot werd een medicatie-rapport opgesteld ter overdracht aan de huisarts. Deze methode voor

het uitvoeren van een gestructureerde medicatiebeoordeling werd toegepast in de interventie-groep van de OPERAM-studie.

Het effect van de gestructureerde medicatiebeoordeling – toegepast als interventie in het ziekenhuis – werd onderzocht in de OPERAM-studie (**hoofdstuk 3.2**). Ouderen (≥ 70 jaar) met multimorbiditeit (≥ 3 chronische aandoeningen) en polyfarmacie (≥ 5 chronisch gebruikte geneesmiddelen) werden op het niveau van de behandelend zaalarts in clusters gerandomiseerd naar reguliere zorg of interventie in vier Europese ziekenhuizen (Zwitserland, België, Ierland en Nederland). Het primaire eindpunt was de eerste geneesmiddel-gerelateerde heropname in het ziekenhuis binnen 1 jaar na deelname. In totaal werden 2008 patiënten die gemiddeld 9 geneesmiddelen gebruikten gerandomiseerd naar 54 interventieclusters (n = 963 patiënten) en 56 controleclusters (n = 1045 patiënten). In de interventiegroep werd bij 86% (n = 789) van de patiënten ongeschikt geneesmiddelgebruik gesignaleerd door het farmacotherapieteam, wat resulteerde in gemiddeld bijna 3 STOPP/START adviezen per patiënt die werden voorgelegd aan de zaalarts en de patiënt.

In de interventiegroep was bij 62% (n = 491) ten minste 1 STOPP/START advies succesvol geïmplementeerd in de twee maanden na de medicatiebeoordeling. Dit betrof voornamelijk het staken van medicatie op basis van STOPP-adviezen. Een geneesmiddel-gerelateerde heropname trad op bij 211 (21,9%) patiënten in de interventiegroep tegenover 234 (22,4%) in de controlegroep. Hoewel het uitvoeren van een gestructureerde medicatiebeoordeling bij ouderen opgenomen in het ziekenhuis resulteerde in een reductie van ongeschikt medicatiegebruik, werd geen significant effect aangetoond op geneesmiddel-gerelateerde heropnames (‘intention-to-treat’-analyse; hazard-ratio: 0,95; 95%-betrouwbaarheidsinterval: 0,77-1,17). Er werd ook geen verschil gevonden van het risico op potentieel vermijdbare geneesmiddel-gerelateerde ziekenhuisopnames, vallen en overlijden.

Procesevaluatie van een medicatiebeoordeling in het ziekenhuis

In **hoofdstuk 4** zijn de diverse processtappen van de medicatiebeoordeling in het ziekenhuis, zoals uitgevoerd in de OPERAM-studie, nader geëvalueerd. In **hoofdstuk 4.1** werd de frequentie van STOPP/START-signalen, gegenereerd door het beslisondersteunend instrument tijdens de medicatiebeoordeling, onderzocht. Tevens werd gekeken hoeveel signalen geaccepteerd werden door het farmacotherapieteam na evaluatie van de toepasbaarheid van het signaal voor de individuele patiënt. Bij 99% van de patiënten werd tenminste één STOPP/START-signaal gegenereerd met een mediaan van 6 (interkwartielafstand 4–6) signalen per patiënt. In totaal werden 5080 signalen gegenereerd, waarvan minder dan

de helft (39%) werd geaccepteerd door het farmacotherapieteam. Het signaal om een geneesmiddel zonder indicatie te stoppen (STOPP A1) kwam het meest frequent voor (28% van alle signalen), waarvan meer dan de helft (54%) resulteerde in een advies om medicatie te staken. De acceptatie door het farmacotherapieteam van STOPP/START-signalen varieerde sterk (2.5%–75.8%) voor de top 10 meest frequent gegeneerde signalen. Dit resultaat benadrukt dat een vertaalslag van STOPP/START-signalen door een farmacotherapieteam naar concrete adviezen voor de individuele patiënt essentieel is. Veel van de door beslisondersteuning gegenereerde signalen bleken namelijk niet toepasbaar te zijn voor patiënten opgenomen in het ziekenhuis. Tot slot is in dit onderzoek gekeken naar eventuele voorspellers voor acceptatie van de STOPP/START-signalen middels een multivariate regressieanalyse. Het grootste verschil in acceptatie werd veroorzaakt door het land waar de medicatiebeoordeling werd uitgevoerd, terwijl de onderzochte patiënt-kenmerken geen goede voorspellers voor acceptatie waren.

In **hoofdstuk 4.2** werd onderzocht in hoeverre zaalarts en patiënt het eens waren met de voorgestelde medicatie-optimalisatie adviezen van het farmacotherapieteam. Dit onderzoek werd uitgevoerd met gegevens van Nederlandse OPERAM-patiënten die een medicatiebeoordeling in het ziekenhuis hadden gehad. In totaal werden 371 adviezen bij 139 patiënten voorgelegd aan zowel de zaalarts als de patiënt. De zaalarts en de patiënt waren het eens met 62% van de adviezen om medicatie te staken (STOPP-adviezen) en met 61% van de adviezen om medicatie te starten (START-adviezen). Consensus met de zaalarts en patiënt werd het vaakst bereikt voor het starten van medicatie ter preventie van osteoporose en voor het advies om maagzuurremmers te staken (beide 74%). Met multivariate analyse is gekeken naar voorspellende factoren voor het overnemen van de medicatie-optimalisatie adviezen door de zaalarts en de patiënt. De patiënt-factoren vrouwelijk geslacht, ≥ 1 val in het afgelopen jaar en verminderde nierfunctie waren voorspellers om adviezen over te nemen. De belangrijkste reden om adviezen niet over te nemen (in 40% van alle adviezen) was dat de patiënt er niet voor open stond om medicatie te wijzigen.

De redenen van zaalarts en patiënt om adviezen van het farmacotherapieteam niet te implementeren liepen sterk uiteen per type geneesmiddel. Het advies om benzodiazepines, zopiclon of zolpidem te staken werd in 91% niet doorgevoerd omdat de patiënt aangaf van deze medicatie afhankelijk te zijn of geen last te hebben van mogelijke bijwerkingen (zoals vallen of sufheid). Anderzijds lag de belangrijkste oorzaak om cardiovasculaire medicatie niet te wijzigen voornamelijk bij de arts, waarvan in 30% van deze adviezen de zaalarts aangaf zich niet bekwaam te voelen om deze medicatie te wijzigen. Om een hogere implementatiegraad van adviezen te realiseren, zou betere educatie voor zowel patiënt als voorschrijver over farmacotherapie mogelijk positief kunnen bijdragen.

In **hoofdstuk 4.3** lag de focus op de vraag waarom medicatiefouten niet waren opgemerkt tijdens de medicatiebeoordeling voor patiënten die werden heropgenomen met een potentieel vermijdbare geneesmiddel-gerelateerde ziekenhuisopname. In totaal werden 84 van de 963 patiënten (8.7%) – bij wie in het kader van de OPERAM-studie een medicatiebeoordeling plaatsvond – heropgenomen met een potentieel vermijdbare ziekenhuisopname veroorzaakt door een medicatiefout. Een medicatiefout was gedefinieerd als 1) het onjuist gebruik van medicatie (bijvoorbeeld een te hoge dosering op basis van een verminderde nierfunctie), 2) het ontbreken van farmacotherapie terwijl hier wel een indicatie voor was (onderbehandeling) of 3) het gebruik van niet-geïndiceerde farmacotherapie (overbehandeling). Van de 84 patiënten met een potentieel vermijdbare geneesmiddel-gerelateerde heropname waren 72 patiënten geschikt voor analyse, waarbij de heropnames gelinkt werden aan 77 medicatiefouten. In de helft van alle medicatiefouten geïdentificeerd tijdens de heropname, was de medicatiefout nog niet aanwezig tijdens de medicatiebeoordeling. In 25% van de medicatiefouten werd een wijziging in farmacotherapie geadviseerd door het farmacotherapieteam, maar werd de aanbeveling niet geïmplementeerd. De overige medicatiefouten (25%) werden niet ondervangen omdat er, na zorgvuldige afweging van de individuele situatie van de patiënt op het moment van de medicatiebeoordeling, geen aanbeveling voor wijziging van medicatie werd gegeven door het farmacotherapieteam.

Conclusie en aanbevelingen

De toepassing van de onderzochte screeningsinstrumenten in het ziekenhuis kan bijdragen aan het identificeren van onjuist medicatiegebruik bij ouderen met polyfarmacie en multimorbiditeit (positief voorspellende waarde triggerlijst: 42%; acceptatie van STOPP/START-signalen door een farmacotherapieteam: 39%). Het duidelijker formuleren van richtlijnadviezen voor medicatie-optimalisatie zou kunnen bijdragen aan betere implementatie in de klinische praktijk en tegelijkertijd de integratie met beslisonderseunende systemen kunnen bevorderen. De toepassing van de huidige screeningsinstrumenten kan echter ook resulteren in ‘signaalmoeheid’ indien geïmplementeerd als beslisondersteuning in bijvoorbeeld elektronische voorschrijfsystemen. Toekomstig onderzoek moet uitwijzen of de balans tussen relevante en niet-relevante signalen voor medicatie-optimalisatie voor kwetsbare oudere patiënten met multimorbiditeit en polyfarmacie verder geoptimaliseerd kan worden.

Het streven naar optimale beslisondersteuning om potentieel ongeschikte medicatie op te sporen is echter zeker niet de belangrijkste boodschap van dit proefschrift in het streven naar optimale farmacotherapie voor elke oudere patiënt. De interactie

tussen het netwerk aan zorgverleners – betrokken bij het evalueren en aanpassen van farmacotherapie – en de wensen van de patiënt zijn essentieel in het succes om voor elke individuele patiënt de juiste afweging te maken voor optimale farmacotherapie. Zo laat ons onderzoek zien dat de redenen om adviezen voor medicatie-optimalisatie niet te implementeren sterk verschilt tussen arts, patiënt en type medicatie. Meer onderzoek is noodzakelijk om interventies te ontwikkelen die de barrières voor het wijzigen van medicatie vanuit zowel de voorschrijver als patiënt effectief kunnen overbruggen.

Hoewel het uitvoeren van een gestructureerde medicatiebeoordeling in het ziekenhuis resulteerde in een afname van ongeschikt medicatiegebruik, laten de resultaten van de OPERAM-studie zien dat een eenmalige medicatiebeoordeling in het ziekenhuis onvoldoende effectief is om geneesmiddel-gerelateerde heropnames te voorkomen. Er zijn diverse verklaringen voor het niet aangetoonde effect van een gestructureerde medicatiebeoordeling, die ondersteund worden door de onderzoeken in dit proefschrift. Door tussentijdse wijzigingen in zowel de farmacotherapie als de conditie van de patiënt was de helft van de medicatiefouten resulterend in een heropname niet te detecteren tijdens een eenmalige gestructureerde medicatiebeoordeling in het ziekenhuis (**hoofdstuk 4.3**). Tevens was de implementatie van de medicatie-optimalisatie adviezen laag, met een grote spreiding per type advies. Door zowel patiënten als alle behandelende zorgverleners (in zowel de eerste lijn als in het ziekenhuis) optimaal te betrekken, kan mogelijk een hogere implementatiegraad van de adviezen gerealiseerd worden. Daarnaast is er sprake van een grote variatie in zowel de adviezen die voortkomen uit een medicatiebeoordeling als in de uitkomstmaat 'geneesmiddel-gerelateerde ziekenhuisopname'. Mogelijk is een positief effect van medicatie-optimalisatie eenvoudiger aan te tonen voor interventies die specifiek gericht zijn op geneesmiddelklassen met een bewezen negatieve invloed op een gezondheidsuitkomst – bijvoorbeeld benzodiazepines en vallen – of bij vooraf geïdentificeerde hoog-risico patiënten. Tevens kan de follow-up periode van 1 jaar te kort zijn geweest om een positief effect aan te tonen van preventieve medicatie waar de patiënten mee gestart waren.

De onderzoeken in dit proefschrift hebben ons inzicht gegeven dat het effect van een medicatiebeoordeling voor de individuele patiënt lastig aan te tonen is op groepsniveau in een klinische studie, vanwege de grote variatie in de interventie, de studiepopulatie en de uitkomstmaat. Mogelijk biedt het gebruik van real world big data kansen voor vervolgonderzoek om eventuele trends in positieve effecten van medicatie-optimalisatie te ontdekken, omdat de studiepopulatie daarmee vergroot kan worden. Toekomstig onderzoek moet uitwijzen hoe medicatie-optimalisatie interventies bij ouderen met het hoogste risico op geneesmiddel-gerelateerde schade zo effectief mogelijk ingezet kunnen worden, en welke

strategieën de implementatiegraad van adviezen kunnen vergroten. Het is daarvoor belangrijk te achterhalen wat het meest geschikte moment, de frequentie en de setting (ziekenhuis, de eerste lijn, of beide) is voor het uitvoeren van een medicatiebeoordeling.

Chapter 8

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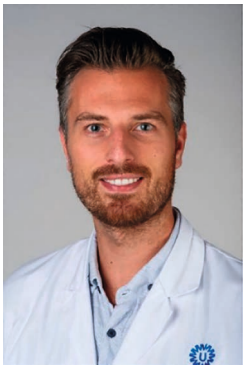

About the author

Bastiaan Sallevelt was born on the 31st of March 1991 in Boxmeer, the Netherlands, as the youngest of three children. In 2009, he graduated cum laude from the secondary school (Gymnasium) at the Elzendaalcollege, Boxmeer. He obtained both his bachelor's (2012) and master's degree (2016) in Pharmacy at the Utrecht University. Because of his broad interests, he combined his bachelor with a 2-year during interdisciplinary honours course (Descartes College) which enabled academic thinking from different perspectives. During his master's degree he attended several interdisciplinary courses on ethics, social sciences and psychology.

His master thesis focused on medication optimisation for people living with HIV, with special attention to polypharmacy and multimorbidity in this population (supervisors drs. Maaike van Aarle, prof. dr. Toine Egberts). This research project highly motivated him to combine research and clinical practice to optimise pharmaceutical care for vulnerable patients across healthcare settings.

In 2016, he joined the European OPtimising thERapy to prevent avoidable hospital Admissions in the Multimorbid elderly (OPERAM) consortium (Dutch Principal Investigator: dr. Wilma Knol). This was the start of his PhD research project under the supervision of dr. Ingeborg Wilting, dr. Wilma Knol, prof. dr. Eugène van Puijenbroek and prof. dr. Toine Egberts. From 2017 to 2020, he combined his PhD research with a hospital pharmacy residency at the UMC Utrecht and St. Antonius Hospital Utrecht/ Nieuwegein (supervisors dr. Ingeborg Wilting, dr. Karin Rademaker, dr. Ewoudt van de Garde). In 2021 he obtained his degree as a clinical pharmacologist at the UMC Utrecht, where he currently works as a hospital pharmacist.

Besides his involvement in patient care and research, he is also passionate about educating, which already started during primary and secondary school being a tutor. During his residency, he participated in several teaching courses and was involved as a teacher in non-academic, academic and post-academic education. He is currently applying for a Basic Teaching Qualification (BKO).

In his future career, Bastiaan strives to combine patient care, research and education, as these pillars are strongly connected in the continuous cycle of healthcare improvement.

Chapter 9

Dankwoord

DANKWOORD

Het dankwoord van dit proefschrift vormt het einde van een reis van meer dan zes jaar op weg naar '*hora est*'. Het was een fantastische leerzame reis waar op sommige momenten ook veel veerkracht voor nodig was, zeker in combinatie met de opleiding tot ziekenhuisapotheker. Ook in letterlijke zin zijn vele kilometers afgelegd om de Europese OPERAM-studie zo goed mogelijk te laten verlopen tijdens internationale bijeenkomsten, en daarnaast om onze onderzoeksresultaten te delen tijdens diverse congressen.

Het uitvoeren van onderzoek is een reis vol uitdagingen. Vaak leiden verrassende momenten tot nieuwe inzichten en te bewandelen routes. Hobbels op de weg zijn echter onoverkomelijk tijdens het doen van onderzoek. Tegenslagen zijn de meest leerzame momenten, ook voor persoonlijke groei. Ik heb me altijd proberen te focussen op factoren waar ik wèl zelf invloed op kon uitoefenen, en het beste te maken van factoren waar ik geen invloed op had. Zo heb ik tijdens de coronapandemie de lockdown goed kunnen benutten om meters te maken met het schrijven van dit proefschrift. Dat roept haast het klassieke beeld op van een promovendus die zich afzondert om onderzoek uit te voeren, maar niets is minder waar; ik heb me gedurende het hele traject altijd sterk verbonden en gesteund gevoeld door alle mensen om mij heen, zowel op professioneel vlak als privé. Graag maak ik dan ook van deze gelegenheid gebruik om een aantal personen te bedanken.

Allereerst wil ik alle deelnemende patiënten bedanken. Door jullie bijdrage aan de onderzoeken in dit proefschrift zijn we tot belangrijke inzichten gekomen om de geneesmiddelzorg voor ouderen verder te optimaliseren.

Mijn promotie*team*, Toine, Eugene, Wilma en Ingeborg, jullie hebben laten zien waar *team* in deze term voor staat. Jullie waren complementaire en unieke mentoren voor mij. Jullie inhoudelijke kennis, de (aanstekelijke) passie voor het onderzoek, en de interesse in mij als persoon zorgden ervoor dat ik me altijd gesteund heb gevoeld tijdens dit intensieve traject. Een opvallende gelijkenis was jullie immer snelle en zorgvuldige respons; wanneer ik stukken met jullie deelden (dikwijls in de nachtelijke uurtjes) stond jullie feedback vaak de volgende ochtend al in mijn mailbox te wachten. Hierdoor kon ik meteen weer aan de slag en dit heeft mij erg geholpen om de schaarse tijd goed te benutten. Ik had me geen fijner promotieteam kunnen wensen.

Beste Toine, als mijn eerste promotor was je een grote inspiratiebron voor mij. Jij hebt ons altijd op koers gehouden, waarbij je de voortgang van het onderzoek en de ontwikkeling van mij als promovendus nauwkeurig hebt bewaakt. Minstens zo belangrijk als de stip op de horizon is de weg ernaartoe en dat heb je goed over

weten te brengen met jouw coachende begeleiding. Promoveren is een werkwoord dat veel meer omvat dan enkel het eindproduct van een proefschrift. Jouw rol als director van de *Graduate School of Life Science* is dan ook op je lijf geschreven als je het mij vraagt. Hoewel mijn traject in het algemeen soepel is verlopen, kan ik me het moment nog goed herinneren dat het wat kritisch werd of ik de deadline voor mijn registratieonderzoek zou halen vanwege externe vertragingen. Je heb mij laten zien dat je pal naast me ging staan op een cruciaal moment, en deze back-up heb ik erg gewaardeerd. Toen we eenmaal de beschikking hadden over de data, hebben we ons samen een dag opgesloten voor dataverwerking met als resultaat dat de deadline gehaald werd. Bijzonder vind ik ook hoe jij moeiteloos kunt schakelen tussen denken in grote lijnen (conceptontwikkeling) en detail; niets ontsnapt aan jouw oplettend oog.

Beste Eugène, als mijn tweede promotor met enige afstand tot de OPERAM-studie en het UMC Utrecht, was jij een enorm waardevolle toevoeging in ons team. Jouw bedachtzame en scherpzinnige opmerkingen leerden mij OMdenken. Hoewel ons promotie-overleg op vrijdagochtend zo nu en dan conflicteerde met verplichtingen in Groningen, was je altijd aanwezig om waardevolle input te leveren ongeacht de plaats (fysiek, online, tijdens forensen, of op een hotelkamer). Dit weerspiegelt jouw grote betrokkenheid tijdens mijn promotietraject.

Beste Wilma, als mijn co-promotor en de 'principal investigator' van de OPERAM-studie heb jij onze rol binnen het OPERAM-consortium gewaarborgd. Ik heb enorm veel van je geleerd, zowel hoe een grote klinische trial werkt, als ook softskills, waaronder het onderhouden van (internationale) contacten. Ik besef me dat ik kansen heb gekregen en ervaringen heb opgedaan die niet voor iedere promovendus vanzelfsprekend zijn. Tijdens al die jaren van intensieve samenwerking hebben we diverse mooie momenten beleefd, zoals de tour met de Nederlandse OPERAM-delegatie met een busje door de bergen van Bern en diverse gezellige etentjes, zoals op congres in Athene of de geriatriedagen, waar niet zelden uiteindelijk de voetjes van de vloer gingen. Dank dat je het vertrouwen in mij had om de apotheek te vertegenwoordigen binnen OPERAM. Ik kijk ernaar uit om ook in de toekomst de samenwerking op te zoeken.

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en leerden we elkaar ook op persoonlijk vlak steeds beter kennen waardoor een vriendschap ontstond. We hebben onze krachten gebundeld, wat leidde tot een symbiose op medisch-inhoudelijk vlak (als 'farmacotherapieteam' voor Nederland) en op het gebied van onderzoek. Ik weet nog goed hoe wij in jouw groene bolide richting het Antonius ziekenhuis scheurden om de OPERAM-patiënten te spreken voordat ze alweer met ontslag zouden gaan. Hoewel ik je helaas niet altijd kon vergezellen tijdens deze patiëntgesprekken vanwege mijn opleidingsverplichtingen, leerde ik van jou om informatie af te stemmen op de patiënt. Onze tripjes naar Zwitserland, Polen en London waren de kersen op de taart van onze internationale samenwerking. Jouw zin '*dat boekje komt er wel*' staat nog altijd geschreven op mijn whiteboard in de keuken, en niets is minder waar. Jij bent binnenkort aan de beurt om te promoveren en ik wens je alle succes met het afronden van de laatste loodjes!

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