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ORIGINAL RESEARCH ARTICLE

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 hospital 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.

Objective 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 1 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 the 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

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(~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.

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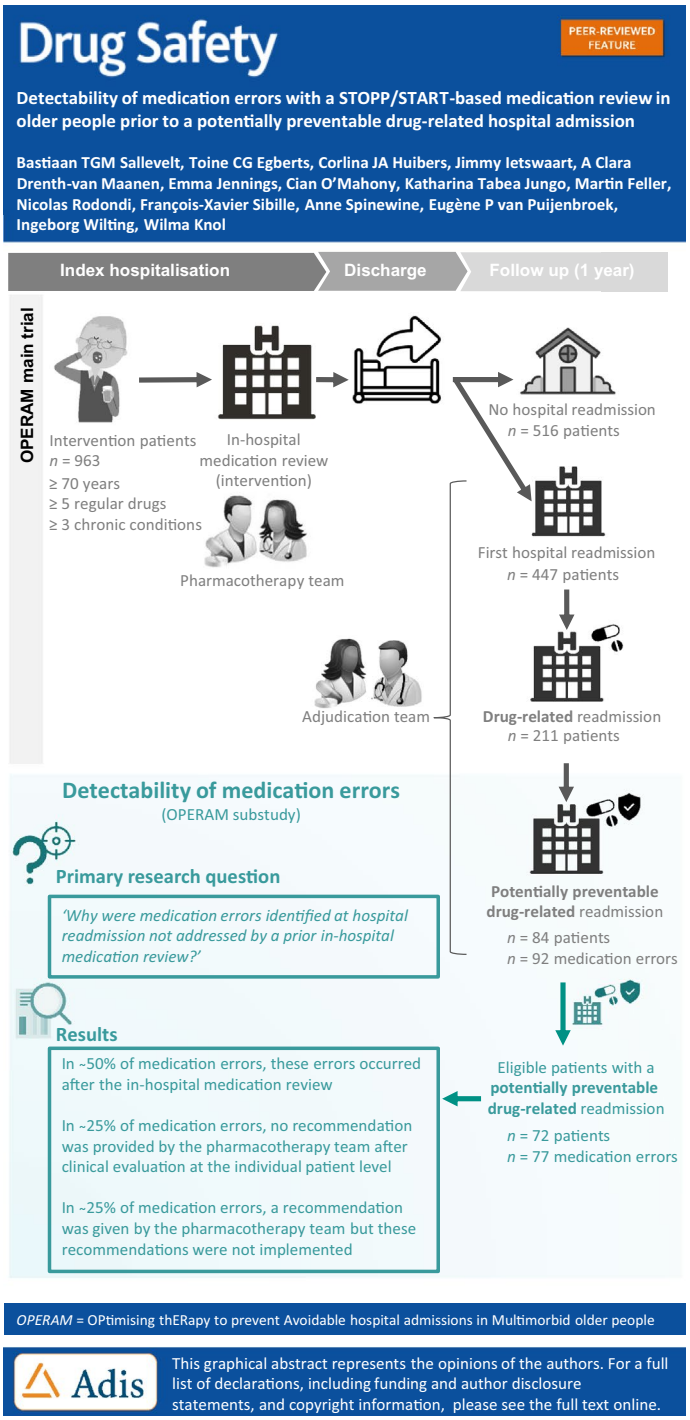
Graphical abstract



Key Points

Older people with polypharmacy and multimorbidity are at risk of medication errors that can lead to potentially preventable drug-related hospital admissions (DRAs).

A single, in-hospital medication review in the year prior to a potentially preventable DRA could not detect 50% of medication errors identified at readmission, because these medication errors occurred after the medication review.

In the other 50% of medication errors, no recommendation to change medication regimen was given after clinical evaluation at the individual patient level or recommendations to change medication regimen were not implemented.

1 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 1 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 with 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.

2 Methods

2.1 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 > 30 days prior to admission) [37, 38]. The two exclusion criteria were (i) patients admitted to palliative care within 24 hours after index hospitalisation and (ii) 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 1-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.

2.2 In-Hospital Medication Review at Index Hospitalisation

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 Electronic Supplementary Material 1 (ESM1).

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].

2.3 Drug-Related Hospital Admission (DRA) Adjudication Process at Readmission

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 ESM2. 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 and 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.

2.4 Detectability of Medication Errors (MEs)

The MEs identified at hospital readmission by the DRA adjudication teams were used as the 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:

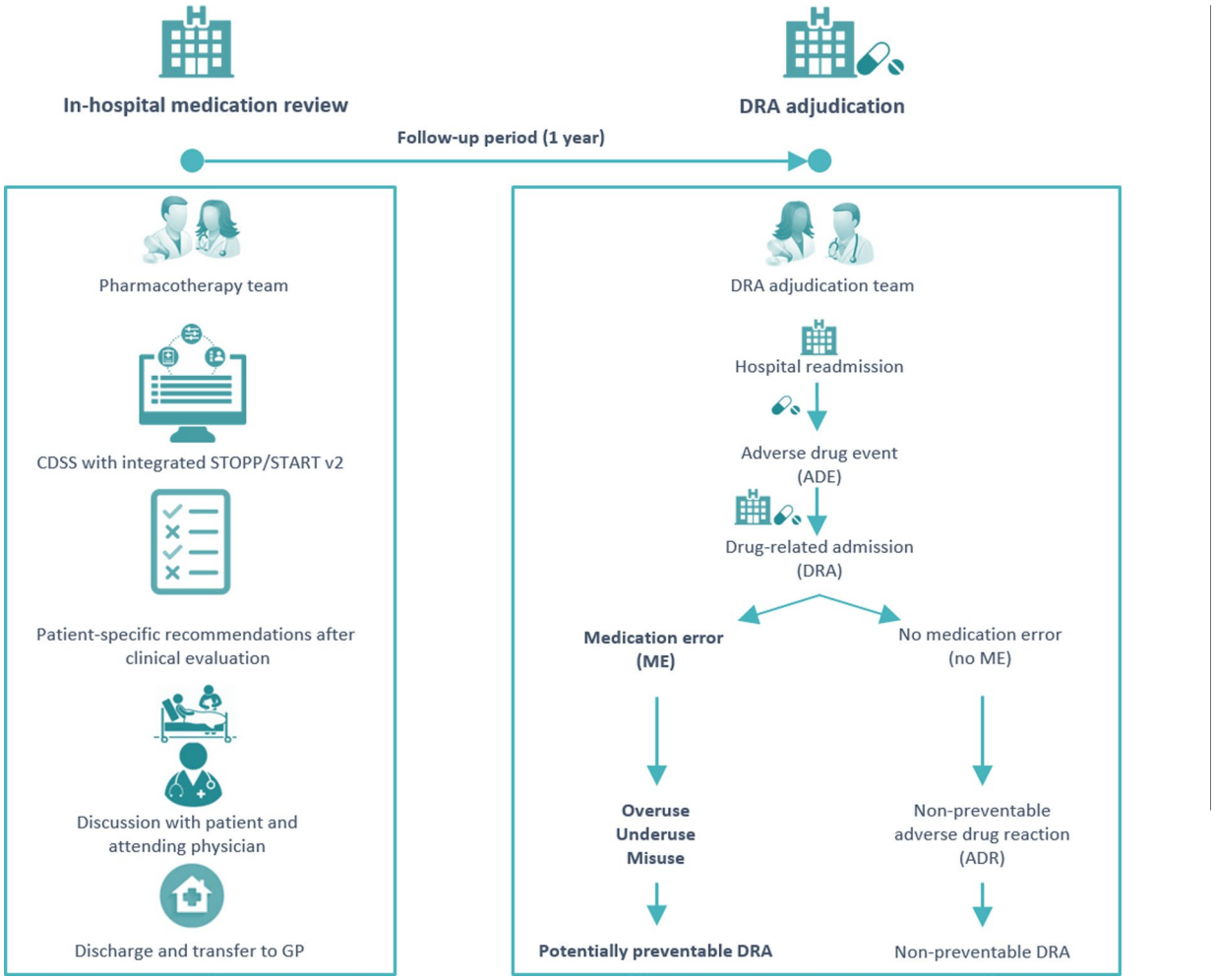


Fig. 1 Graphical illustration of the relationship between the in-hospital medication review at index hospitalisation and the adjudication process of hospital readmissions within 1 year after the in-hospital medication review. *CDSS* clinical decision support system, *DRA* drug-related hospital admission, *GP* general practitioner, *STOPP/START v2* Screening Tool of Older Person's Prescriptions / Screening Tool to Alert doctors to Right Treatment, version 2

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.

Text Box—Detectability of medication errors (MEs) during in-hsopital 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 teams (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 teams 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).

2.5 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 (i) the proportion of MEs that were 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; (ii) the proportion of MEs that were detected by STOPP/START during the in-hospital medication review. The number of present MEs was used as the denominator; (iii) 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 a 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.

2.6 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 were 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 three 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.

3 Results

3.1 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 (Fig. 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) comorbidities and were prescribed a median of 10 (IQR 8–14) medications. Participants had a median estimated glomerular filtration rate (eGFR) of 51 mL/min/1.73m^2 (IQR 36–66). Other baseline characteristics of the study population at the time of the in-hospital medication review are illustrated in Table 1.

3.2 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

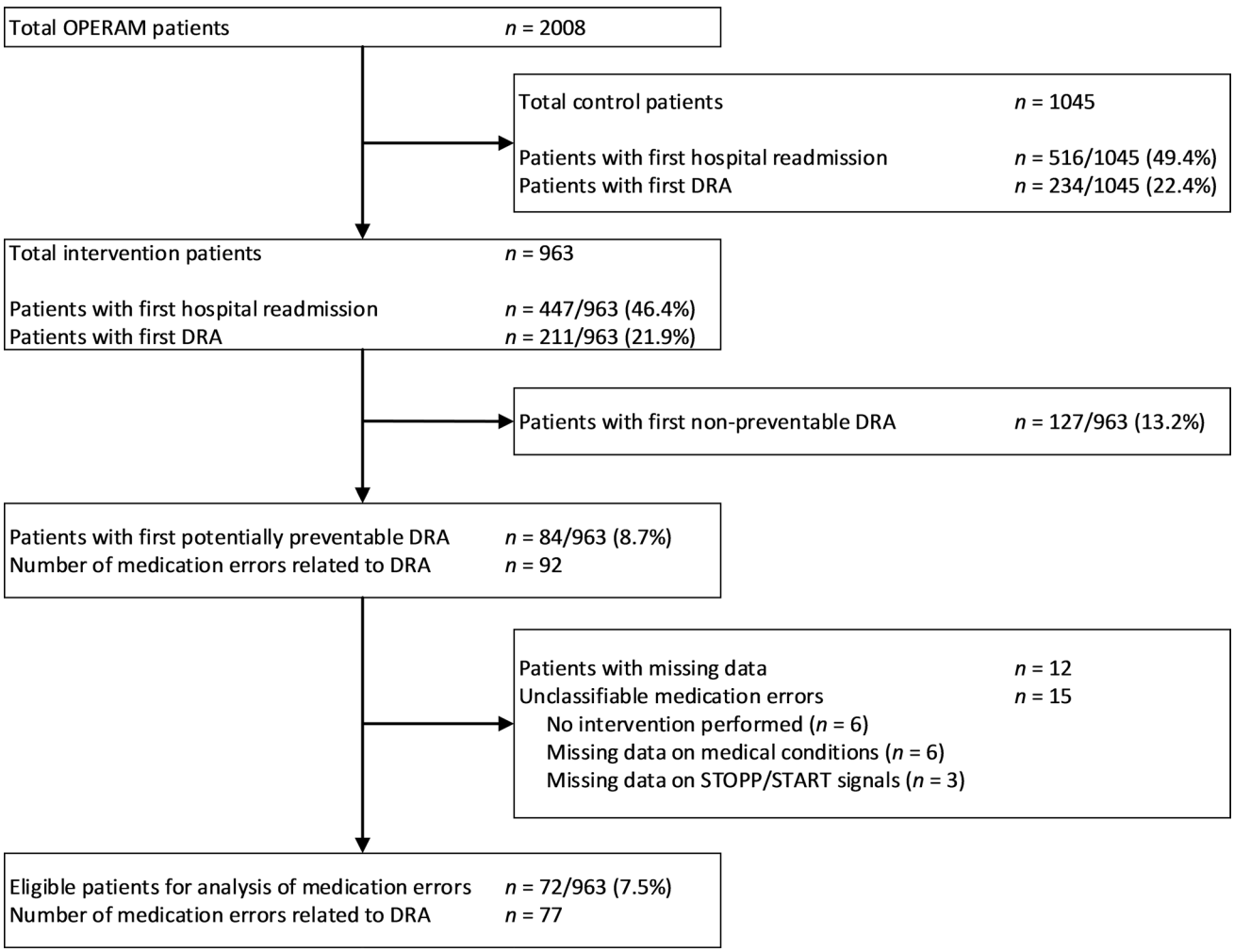


Fig. 2 Flowchart of the study population. DRAs were considered potentially preventable if medication errors were the main or contributory cause of the readmission. Non-preventable DRAs were caused by non-preventable adverse drug reactions. *DRA* drug-related hospital admission

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	35 (48.6)
Number of falls in the previous year	0 (0–1)
Patients with one or more hospital admission in the previous year	38 (52.8)
Number of hospital admissions in the previous year	1 (0–2)
Length of hospital stay (days)	8 (5–11)
Admission type	
Elective	13 (18.1)
Non-elective	59 (81.9)
Ward	
Medical	58 (80.6)
Surgical	14 (19.4)
Country of inclusion[c]	
Switzerland	36 (50.0)
Belgium	12 (16.7)
Ireland	9 (12.5)
The Netherlands	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

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.

3.3 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 (Fig. 3).

3.4 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 (Fig. 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).

3.5 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 (Fig. 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) (Fig. 3). Overall, the pharmacotherapy team recommended a change in medication regimen in 50% ($n = 20/40$) of present MEs (Fig. 3).

3.6 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 Fig. 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.

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) B-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) β 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)	Anticoagulation[e] (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									
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)
Hyponatraemia	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)	Antihyperglycaemics (2)	0.0 (0)	N/A	0.0 (0)	N/A	100.0 (2/2)	0.0 (0/2)
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)	β-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)

Table 2 (continued)

[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 ESM2

[b]Omitted in systolic heart failure

[c]Including three cases of noncompliance

[d]Omitted in insulin-dependent type II diabetes mellitus with poor glycaemic control

[e]Omitted with concomitant atrial fibrillation

[f]Subtherapeutic dosage of apixaban

[g]Overuse in end-stage renal disease (Stage 5)

[h]Supratherapeutic dosage in relation to decreased renal function

[i]Drug–drug interaction with diuretics

ACE-I angiotensin-converting enzyme inhibitor, *ME* medication error, *NSAID* non-steroid anti-inflammatory drug, *PPI* proton pump inhibitor, *START* Screening Tool to Alert doctors to Right Treatment, *STOPP* Screening Tool of Older Person's Prescriptions

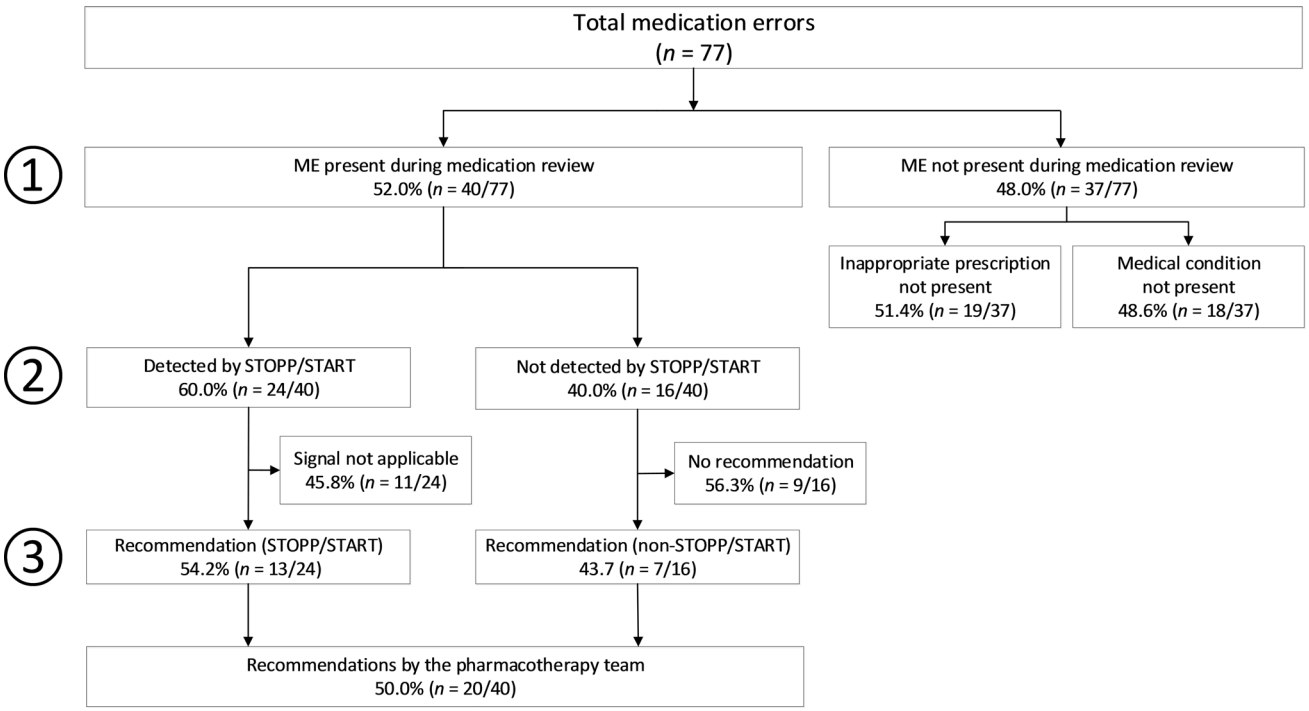


Fig. 3 Flowchart of the detectability of medication errors (MEs) at the time of the in-hospital medication review, based on the three screening questions used for detectability assessment. *START* Screening Tool to Alert doctors to Right Treatment, *STOPP* Screening Tool of Older Person's Prescriptions

4 Discussion

4.1 Main Findings

About half of MEs (48%) were not present during an in-hospital medication review in the year prior to a 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%, $N = 1111$) 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 aged ≥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.

4.2 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 1-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 (Fig. 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 MEs 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 large 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 health care settings.

4.3 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

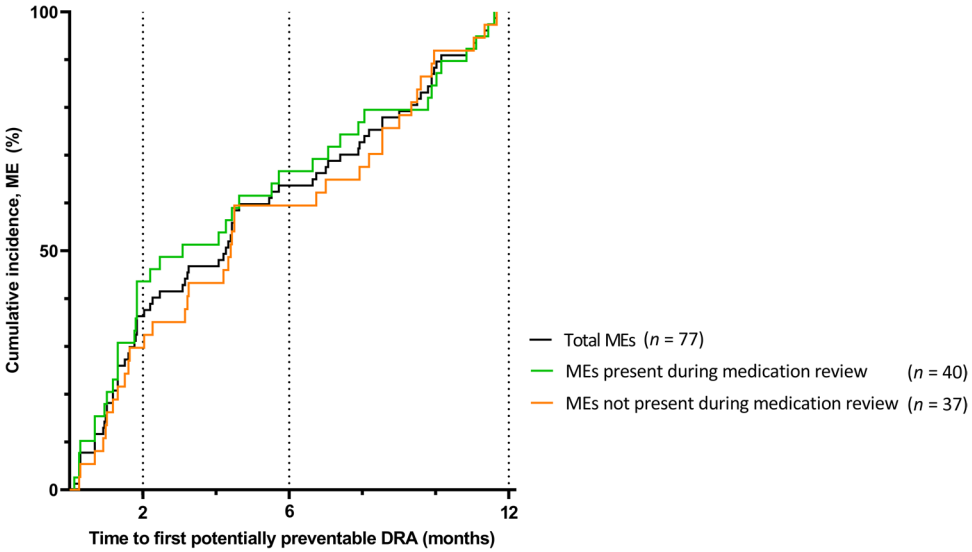


Fig. 4 Cumulative incidence (%) of medication errors (MEs) over time stratified for total, present and not present MEs during the in-hospital medication review

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.

4.4 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. Trusted 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 team.

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 6 months after discharge from geriatric units; more than half of those resumptions occurred within a month after discharge [60]. Improvements in medication reconciliation across health care 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.

4.5 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 the 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.

5 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.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40264-022-01237-5.

Declarations

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Competing interests Bastiaan T.G.M. Sallevelt, Toine C.G. Egberts, Corlina J.A. Huibers, Jimmy Ietswaart, A. Clara Drenth-van Maanen, Emma Jennings, Cian O'Mahony, Katharina Tabea Jungo, Martin Feller, Nicolas Rodondi, François-Xavier Sibille, Anne Spinewine, Eugène van Puijenbroek, Ingeborg Wilting and Wilma Knol have no conflicts of interest related to the content of this article.

Ethical 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 the responsible regulatory authority.

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

Consent for publication Not applicable.

Availability of data and material 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.

Code availability statement The codes used to convert the Screening Tool of Older Person's Prescriptions (STOPP) / Screening Tool to Alert doctors to Right Treatment (START) criteria version 2 into algorithms for use in clinical decision support systems have been previously published by Huibers CJA, Sallevelt BTGM, de Groot DA, et al [35]. The code that supports the findings of this study will be made available for scientific purposes for researchers whose proposed use of the data has been approved by a publication committee.

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.

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