RESEARCH PAPER

Potentially inappropriate medications and their effect on falls during hospital admission

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Abstract

Objective: to investigate the effect of potentially inappropriate medications (PIMs) on inpatient falls and to identify whether PIMs as defined by STOPPFall or the designated section K for falls of STOPP v2 have a stronger association with inpatient falls when compared to the general tool STOPP v2.
Methods: a retrospective observational matching study using an electronic health records dataset of patients ($\geq$70 years) admitted to an academic hospital (2015–19), including free text to identify inpatient falls. PIMs were identified using the STOPP v2, section K of STOPP v2 and STOPPFall. We first matched admissions with PIMs to those without PIMs on confounding factors. We then applied multinomial logistic regression analysis and Cox proportional hazards analysis on the matched datasets to identify effects of PIMs on inpatient falls.
Results: the dataset included 16,678 hospital admissions, with a mean age of 77.2 years. Inpatient falls occurred during 446 (2.7%) admissions. Adjusted odds ratio (OR) (95% confidence interval (CI)) for the association between PIM exposure and falls were 7.9 (6.1–10.3) for STOPP section K, 2.2 (2.0–2.5) for STOPP and 1.4 (1.3–1.5) for STOPPFall. Adjusted hazard ratio (HR) (95% CI) for the effect on time to first fall were 2.8 (2.3–3.5) for STOPP section K, 1.5 (1.3–1.6) for STOPP and 1.3 (1.2–1.5) for STOPPFall.
Conclusions: we identified an independent association of PIMs on inpatient falls for all applied (de)prescribing tools. The strongest effect was identified for STOPP section K, which is restricted to high-risk medication for falls. Our results suggest that decreasing PIM exposure during hospital stay might benefit fall prevention, but intervention studies are warranted.

Keywords: hospital, inappropriate prescriptions, accidental falls, older people

Key Points

- Prevalences of potentially inappropriate medications (PIMs) were 56% for STOPP, 27% for STOPP section K and 85% for STOPPFall.
- Falls were found by searching the problem list and free text of an electronic health records cohort.
- Inpatient falls occurred in 446 (2.7%) of 16,678 hospital admissions.
- An independent association of PIMs on inpatient falls were identified using matching in observational data.
- The strongest effect (aOR: 7.9) on falls was found for PIMs according the designated section K for falls of STOPP.

Introduction

Falls during hospitalisation are common adverse events with multiple negative effects, including injuries, costs, prolonged hospital stay and fear of falling [1–3]. Fall incidence is estimated to be ~3.1% among all hospitalised patients and ~6.4% among hospitalised patients aged 70 and older [4, 5]. Occurrence of fall-related injury is frequent in a hospital setting, with 30–50% of the falls resulting in any injury and up to 8% resulting in moderate or severe injuries [3, 6]. A longitudinal national study from Denmark showed that incidence of major fall-related injuries increased over the years, with a 3.2% rise per year among patients aged 65–74 years [7]. Falls can result in a prolonged hospital stay. For example, in a study on patients with severe fall-related injuries, such as fractures, the length of stay more than doubled (from ~3.7 days in non-falling patients to ~10.9 days in patients with falls) [1].

Multiple risk factors for inpatient falls have been identified: i.e. age, use of certain medication types, history of falls and cognitive decline [8]. Fall risk during hospitalisation may be reduced by multifactorial interventions based on individual multifactorial risk assessment, including medication, mobility and the environment [8]. A medication review assessing appropriate prescribing should always be part of the in-hospital multifactorial falls assessment [9].

Multiple tools have been developed to identify potentially inappropriate prescribing in general, with and without specific sections for falls. These tools support (de)prescribing in terms of potentially inappropriate medications (PIMs) and potential prescribing omissions. Two systematic reviews identified 42 and 73 different (de)prescribing tools, respectively, for improving medication use for older patients [10, 11]. Of these tools, the STOPP/START criteria, Beers criteria, Drug Burden Index (DBI), Anticholinergic Risk Scale, Anticholinergic Drug Scale and Fit fOR The Aged (FORTA) have been shown to influence or to be associated with falls in trials or observational studies [10, 11]. Two studies showed that falls, related to PIMs using STOPP/START, contributed to hospitalisation in populations of 100 and 105 patients, respectively [12, 13]. However, studies with a larger study population and inpatient data are needed to identify the independent relationship of PIMs on inpatient falls.

A position paper on fall-risk-increasing drugs (FRIDs) highlighted the need for higher quality research and more knowledge dissemination on medication-related falls in order to improve (de)prescribing and, in turn, to reduce fall incidents [14]. Although general tools, such as STOPP/START and Beers criteria, contain a specific designated section on falls, the paper also highlighted the need for a comprehensive tool regarding fall-risk-increasing medication [14]. Therefore, recently, STOPPFall was developed: an expert-based European consensus list and deprescribing tool containing all medication groups, with a possible effect on the risk of falling [15].

Additional research is needed to investigate whether a specific fall-risk-increasing medication (de)prescribing tool has a stronger relationship with falls when compared to general tools. Therefore, the aim of our current study was to assess the effect of PIMs on inpatient falls using a large electronic health record (EHR) cohort. The second aim was to identify whether PIMs, as defined by STOPPFall or the designated section K for falls of STOPP v2, have a stronger association with inpatient falls when compared to the general tool STOPP v2.

Methods

Study population and data collection

We conducted a retrospective observational matching study and used an EHR dataset of older patients admitted to a 1,002-bed university medical centre (Amsterdam, The Netherlands). Inclusion criteria were: admissions of patients aged ≥70 years with a minimum length of stay of 24 h in a time period of 4 years (November 2015–November 2019). Exclusion criteria were: patients admitted to non-clinical departments. The data included gender, admission/discharge dates, diagnoses, age, medication administrations, blood pressures, laboratory results, problem list, Delirium Observation Screening Score (DOSS), John Hopkins Fall Risk Assessment Tool (JHFRAT) and free text.

Ethics approval

The study plan was reviewed (reference number W18_027#18.043) by the Amsterdam UMC Medical Ethics Review Committee, which determined that approval was not required according to the Medical Research Involving Human Subjects Act (WMO).

PIMs

The technical translation of the Dutch STOPP criteria v2 has been described previously and was based on the consensus study of Huibers et al. [16, 17]. In total, 68 STOPP criteria were included, coded by B.A.-D.V. and checked by A.A.-H., D.S. and K.R. Of these 68 criteria, 4 belonged to the designated section K for falls of STOPP v2. STOPPFall contains 14 medication groups and was coded by K.R. and L.R. and checked by B.A.-D.V. by using the WHO ATC index and previous work on FRIDs [18, 19]. We used the PIM exposure in the statistical analysis. PIM exposure was calculated as the number of PIMs (sum of the unique PIMs each day) administered during hospital stay, divided by hospital length of stay in days.

Falls

Falls were identified by using the problem list and free-text data. We identified falls in the problem list of the EHR, with a regular expression, selecting all Dutch terms for 'fall', 'tripped' or other common synonyms and excluding all irrelevant terms, e.g. 'fall risk' and 'tendency to fall'. The

free-text search and regular expression to identify falls can be found in Supplementary Appendix S1 available in *Age and Ageing* online.

To search for inpatient falls in the free-text data, the program CTcue version 2.0.10 was used. We conducted two different search queries to identify patients with a fall in physician and nursing notes. The identified patients were manually reviewed by K.R. and D.S. and the first fall was extracted. The uncertain cases were also reviewed by B.A.D.-V. In determining if a text described a fall, we used the WHO definition for falls: *A fall is an event which results in a person coming to rest inadvertently on the ground or floor or other lower level* [20].

Statistical analysis

PIM prevalence was expressed as percentage of hospital admissions with at least one PIM according to STOPP v2, STOPP v2 section K and STOPPFall. Prevalence of inpatient falls was expressed as the percentage of admissions with a fall.

The aim of our study was to assess effects between PIMs and falls. In observational data, 'treatment' and 'control' groups differ in co-variate distribution. Outcomes are therefore not directly comparable [21]. In randomised trials, 'treatment' is randomly assigned and the distribution of (un)observed co-variates are similar between treatment and control groups. This makes it possible to assess causal relationships [22, 23]. Matching attempts to mimic randomisation within matched pairs and gain groups with similar co-variate distributions in order to estimate a causal effect in observational data [21–24]. In current study, we matched each admission with ≥1 PIM(s) to an admission without PIMs. Matching was based on 12 potential confounders: age, gender, length of stay, number of medications, number of diagnoses, Charlson score, DOSS ≥ 3 (yes/no) and subcategories of the JHFRAT: fall history (yes/no), toilet demand (yes/no), patient care equipment (PCE) (yes/no), mobility impairment (yes/no) and cognitive impairment (yes/no). We used matching with replacement, so the best-fitting controls could be used multiple times to increase the quality of matching [22]. Matching weights were included in the regression analysis to account for possible dependence between controls due to controls being used multiple times [22]. The standardised mean difference (SMD) was used to identify the distribution of all potential confounders in the treatment and control groups [25]. A variable with an SMD > 0.2 was seen as serious imbalance. The variables with a SMD > 0.2 were used as co-variates in the doubly robust regression models of the outcome analysis to adjust for discrepancies in the co-variate distribution.

We conducted three analyses to assess the effect of PIMs on inpatient falls. We assumed that PIMs administered 24 h before the fall would mostly not have been eliminated at the time of the fall and therefore the fall could be ascribed to the PIM. As primary analysis, we conducted a multinomial logistic regression on the matched dataset, with each admission classified as having one of three possible outcomes: (i) fall <24 h after a PIM, (ii) fall >24 h after a PIM, or fall without a PIM or (iii) no fall. The association between PIM exposure and inpatient falls was expressed as adjusted OR (CI: 95%). In the first sensitivity analysis, we conducted a similar multinomial logistic regression analysis as in the primary analysis but now for 48 h. In the second sensitivity analysis, we conducted a Cox-proportional hazards analysis on the matched dataset to identify the effect of PIM exposure on time to first inpatient fall. The outcomes were expressed as adjusted HR (CI: 95%).

For this study, R version 3.6.1 was used with the following packages: readr, dplyr, stringr, Rcpp, rlang, DBI, odbc, tidyr, lubridate, ggplot2, TableOne, Matching, Nnet, Survival, Survminer and gtsummary. We considered a *P* value < 0.05 as significant.

Results

Characteristics

The data included 16,687 hospital admissions of older patients (≥ 70 years) involving 11,289 unique patients. The mean age of the included patients was 77.2 (SD = 5.8) years at time of hospital admission and 52.4% were male. Patient characteristics of the whole dataset (before matching) have been presented in Table 1.

PIMs

PIMs during hospital stay, from admission to discharge, showed a prevalence of 55.5% for admissions with ≥1 STOPP, 27.3% for ≥1 STOPP section K and 85.4% for ≥1 STOPPFalls. STOPP section K included 'benzodiazepines with history or risk of falls' (22.1%), 'neuroleptic drugs with history or risk of falls' (10.2%), 'hypnotic Z-drugs with history or risk of falling' (2.8%) and 'vasodilator drugs with orthostatic hypotension' (0.1%). Detailed prevalences of all STOPP/START v2 can be found in our previous paper [16]. Three of the five most common STOPPFalls administered in our population belonged to the STOPPFall group opioids. Prevalence of the medications related to STOPPFall can be found in Supplementary Appendix S2 available in *Age and Ageing* online.

Falls

In total, we identified 446 hospital admissions (2.7%) with an inpatient fall (Table 1). The problem list identified inpatient falls during 82 admissions and the free-text searches during 417 admissions. Of the 446 admissions with falls, 53 were found in both the problem list and the free text. The median time to first fall was 4.7 days (IQR = 1.9–12.0). In 67 of the 446 admissions, a fall was registered within the first 24 h of admission. In 12 of these 67 admissions, a STOPP was administered before the fall; in 6 admissions, a STOPP section K was administered and, in 26 admissions, a STOPPFall was administered.

Table 1. Patient characteristics and inpatient falls per PIM group before matching

	Admissions with ≥1 STOPP n = 9205[a]	Admissions with ≥1 STOPP K n = 4491[a]	Admissions with ≥1 STOPPFall n = 14,202[a]	Overall N = 16,687
Gender, % (n)				
Female	49.0 (4506)	51.3 (2302)	48.3 (6860)	47.6 (7943)
Male	51.0 (4699)	48.7 (2189)	51.7 (7342)	52.4 (8744)
Age, mean (SD)	77.4 (5.8)	77.3 (5.8)	77.2 (5.8)	77.2 (5.8)
Length of stay, median (IQR)[a]	5.9 (2.9–10.9)	7.3 (4.1–14.2)	4.8 (2.1–8.8)	4.1 (2.0–8.0)
Number of medications, median (IQR)[a]	20.0 (13.0–28.0)	23.0 (16.0–33.0)	18.0 (12.0–25.0)	16.0 (10.0–23.0)
Number of diagnoses, median (IQR)	6.0 (4.0–9.0)	6.0 (4.0–9.0)	5.0 (3.0–8.0)	5.0 (3.0–7.0)
Charlson score, median (IQR)	2.0 (1.0–3.0)	2.0 (0.0–3.0)	2.0 (0.0–3.0)	1.0 (0.0–3.0)
High DOSS (score >2),[b] % (n)	3.3 (304)	4.8 (215)	2.7 (390)	2.6 (440)
JHFRAT—medium/high fall risk (score >5),[b] % (n)	34.6 (3185)	45.0 (2022)	29.0 (4118)	28.2 (4702)
JHFRAT—fall history,[b] % (n)	16.7 (1538)	22.9 (1030)	14.5 (2064)	14.2 (2375)
JHFRAT—mobility,[b] % (n)	26.4 (2431)	31.9 (1434)	23.0 (3265)	22.3 (3723)
JHFRAT—cognition,[b] % (n)	5.0 (463)	7.0 (316)	4.1 (576)	4.1 (690)
JHFRAT—toilet/incontinence,[b] % (n)	9.2 (846)	12.2 (546)	8.0 (1135)	7.7 (1289)
JHFRAT—PCE,[b] % (n)	19.6 (1801)	22.6 (1013)	17.5 (2479)	18.2 (3037)
1 PIM,[a] % (n)	49.2 (4525)	73.3 (3292)	20.3 (2884)	NA
2 PIMs,[a] % (n)	27.4 (2521)	25.1 (1129)	20.2 (2870)	NA
3 PIMs,[a] % (n)	13.1 (1207)	1.6 (70)	18.0 (2561)	NA
≥4 PIMs,[a] % (n)	10.3 (952)	0 (0)	41.5 (5887)	NA
Inpatient falls, % (n)	3.3 (301)	5.0 (224)	2.6 (364)	2.7 (446)
Fall <24 h of PIM	2.7 (249)	3.7 (167)	2.3 (329)	NA
Fall <48 h of PIM	2.9 (266)	4.2 (187)	2.4 (341)	NA

[a]includes (i) data from admission until discharge for admissions without a fall and (ii) data from admission until first fall for admissions with a fall. [b]First risk scores conducted in the first 48 h of admission.

Independent association between PIMs and inpatient falls

Supplementary Appendix S3 available in *Age and Ageing* online shows the co-variate balance in the datasets of STOPP, STOPP section K and STOPPFall before and after matching. Tables 2 and 3 display the estimated causal associations as adjusted ORs (95% CI) of PIM exposure on falls. Table 4 shows the effect of PIM exposure on time to inpatients' first fall as adjusted HRs (95% CI). Figure 1 shows a visualisation of the main analysis with the proportion of the three outcomes ((i) fall <24 h of PIM, (ii) fall not <24 h of PIM and (iii) no fall)) in admissions with an increasing PIM exposure.

Discussion

This study examined the effect between PIMs and inpatient falls in an EHR dataset of older hospitalised patients. To study this relationship, we matched admissions with PIMs to those without PIMs on the relevant confounding factors. In our population, PIMs were independently associated with inpatient falls for all applied (de)prescribing tools. Furthermore, we showed that PIMs according the designated section

Table 2. Main analysis: effect of exposure to PIM on inpatient falls showing the results of outcome 'fall <24h of PIM' (multinomial logistic regression)

	aOR (95% CI)	P value
STOPP	2.24 (2.01–2.49)[a]	<0.001
STOPP Section K	7.89 (6.06–10.26)[a]	<0.001
STOPPFall	1.42 (1.30–1.54)[b]	<0.001

[a]Doubly robust analysis, adjusted for poor match in variable 'number of medications'. [b]Doubly robust analysis, adjusted for poor match in variables 'number of medications' and 'length of stay/time to fall'.

K for falls of STOPP v2 had a stronger association with inpatient falls when compared to the general tool STOPP v2 and the comprehensive fall-risk medication tool STOPPFall.

A strength of our study is the use of a very large dataset derived from the hospital EHR, including all medication administrations with precise timing and free-text data to search for in-hospital falls. Furthermore, we used matching methods in observational data and therefore it was possible to estimate the effect between PIMs and falls. There was a significant association between PIM use and inpatient falls.

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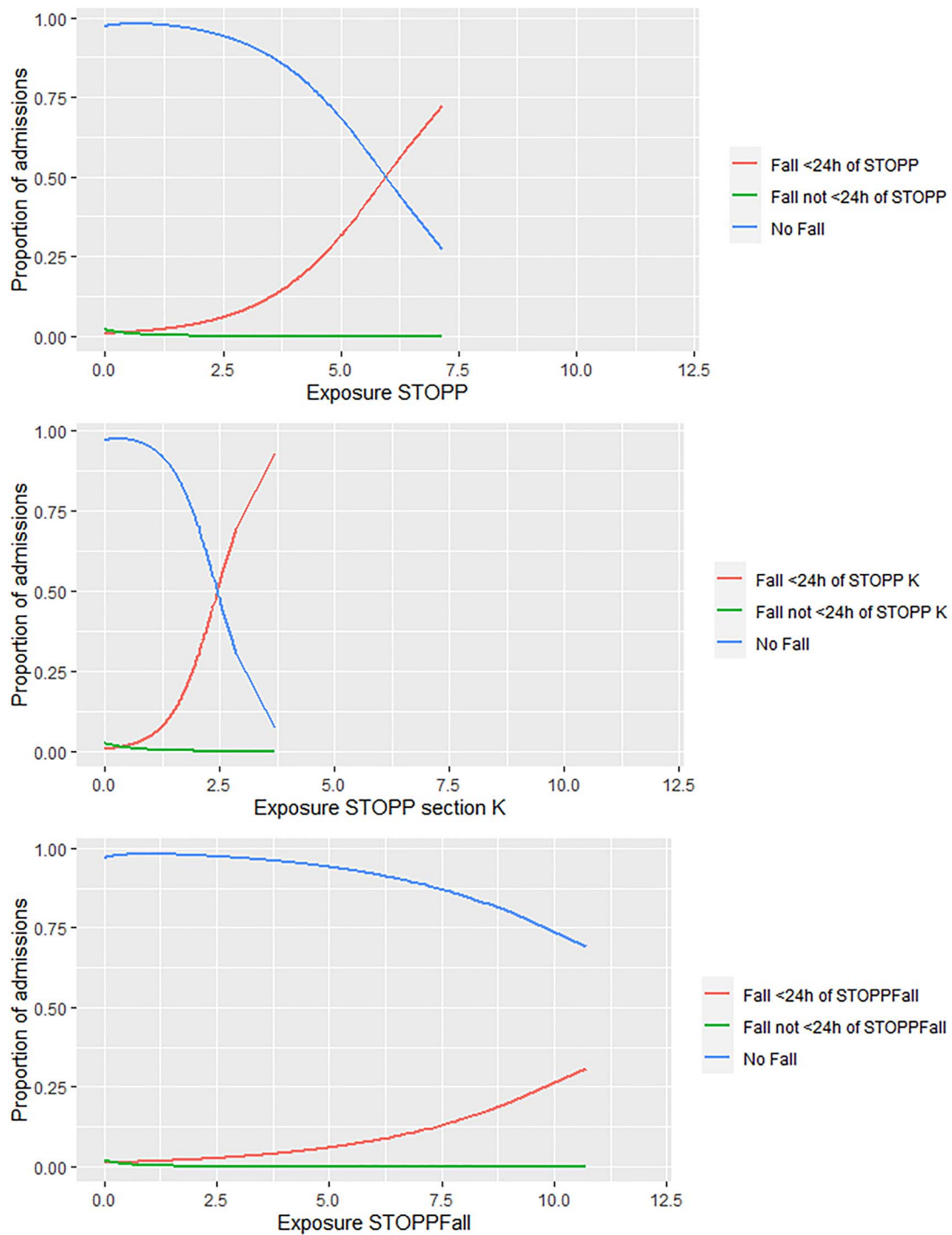

Figure 1. Visualisation of the main analyses: the proportion of the three outcomes ((i) fall <24 h of PIM, (ii) fall not <24 h of PIM and (iii) no fall) of the multinomial logistic regression in patients with an (increasing) exposure to PIMs (STOPP, STOPP section K and STOPPFall). Exposure PIM = number of PIMs (sum of the unique PIMs each day) administered during hospital and divided by hospital length of stay in days.

Until now, published literature did not show convincing results for the effect of PIMs on falls in a hospital setting. A pilot RCT studying an intervention to improve appropriate prescribing using the FORTA criteria found a significant difference between the groups for in-hospital falls (3.4 versus 21.4%), but it included only 114 patients and was underpowered to assess a causal effect between PIMs and falls [26]. In the RCT following this pilot RCT, the intervention with FORTA criteria showed a significant reduction in adverse drug reactions overall but not specifically for falls [27].

Table 3. Sensitivity analysis: effect of exposure to PIM on inpatient falls showing the results of outcome 'fall <48h of PIM' (multinomial logistic regression)

	aOR (95% CI)	*P* value
STOPP	2.14 (1.93–2.37)[a]	<0.001
STOPP Section K	6.76 (5.27–8.67)[a]	<0.001
STOPPFall	1.39 (1.28–1.50)[b]	<0.001

[a]Doubly robust analysis, adjusted for poor match in variable 'number of medications'. [b]Doubly robust analysis, adjusted for poor match in variables 'number of medications' and 'length of stay/time to fall'.

Table 4. Sensitivity analysis: effect of exposure to PIM on time to first fall (cox-proportional hazards analysis)

	aHR (95% CI)	*P* value
STOPP	1.46 (1.32–1.61)[a]	<0.001
STOPP Section K	2.84 (2.32–3.48)[a]	<0.001
STOPPFall	1.34 (1.24–1.46)[a]	<0.001

[a]Doubly robust analysis, adjusted for poor match in variable 'number of medications'.

Another RCT in a hospital setting studied an intervention with STOPP/START v1 and did not show a significant difference in prevalence of patients with ≥1 fall in a 6-month follow-up period (5.8 versus 8.4%). This RCT was also not powered to assess an effect on falls [28]. Our study differed from these previously published studies in design (RCT versus observational study), sample size (114 and 382 versus 16,687) and PIM tools used.

We calculated a prevalence of 56% for admissions with ≥1 STOPP, 27% for ≥1 STOPP section K and 85% for ≥1 STOPPFall. The prevalence of STOPP v2 was similar to prevalences reported in other studies [29]. The STOPPFall tool was just recently published and, for now, we cannot compare the prevalence to other studies. However, a systematic review on FRIDs found a prevalence of 65–93% in older patients, with a fall-related injury, admitted to the emergency department of hospital [30]. In our study, three opioids, sufentanil (35%), oxycodone (30%) and morphine (30%), were in the top-five most common STOPPFall administrations, and our expectation is that these percentages will be different in a non-hospital setting. Therefore, future studies need to explore the prevalence of STOPPFall in other settings.

The prevalence of STOPPFall is higher than the prevalence of section K for falls of STOPP v2. Furthermore, the independent association with inpatient falls is stronger for STOPP section K when compared to STOPPFall. Both results are reasonable as section K is restricted to high-risk medications. The STOPPFall is more comprehensive, covering medium- and high-risk medications. The STOPP section K admissions had a higher prevalence of inpatient falls, compared to the STOPPFall admissions, but included less inpatient falls (5.0%, 224/4491 versus 2.6%, 364/14,202). The prevalence of inpatient falls was even slightly lower in the

STOPPFall admissions, compared to the total population (2.6% versus 2.7%), but 42% of the STOPPFall admissions had ≥4 PIMs with an inpatient fall prevalence of 3.2%. Our results suggest that STOPPFall covers more potential falls and may support a comprehensive fall-related medication review. The STOPP section K may support fall prevention in situations with high work-loads and might be more efficient. However, future intervention studies should demonstrate added value to clinical practice and look whether these (de)prescribing tools actually lower inpatient falls.

We found a prevalence of 2.7% for admissions with ≥1 fall. This percentage of falls is lower than the 5.9–6.4% observed in other studies with older inpatients [5, 31]. An explanation for this lower prevalence could be that we used real-world EHR data in which possibly not all falls were recorded and/or our free-text search did not identify all fall incidents. More than 85% of the admissions with a fall were identified using free text and 30% were identified using the problem list. This percentage identifying falls in free text is high when compared to Baus *et al*. in which 34% of all falls were identified using free text [32]. This difference with our results is probably due different settings (primary care in Baus *et al*. versus university medical centre) and a different system for free-text search [32]. However, our percentage of free-text falls is lower than in the study of Toyabe *et al*., which found 100% of the falls in free text by using natural language processing in a hospital setting [33]. The difference with this study can be explained by a difference in country (Japan versus The Netherlands), sample size (80 versus 440 fall events) and system for free-text search. Our findings highlight the importance of free-text searches for identifying falls during hospital stay. Fall incident reports underestimate falls in a hospital setting and multiple sources, such as text data, should be used to detect falls [33, 34].

Our study has some limitations. Falls were detected using the program CTcue, which supports identification of patients but not the extraction of data. Therefore, we manually extracted data about falls (date and time). Another limitation was that we did not know whether patients were able to mobilise, and therefore, we could not include this information as adjustment in the analyses. Due the study design and data collection, we could not estimate whether clinicians prescribed PIMs for clinical reasons. We did not have information on the use of medication before admission, and therefore, we could not identify all PIMs that were potentially relevant to falls that occurred in the first 24 h of admission. The dataset did not include the reason for hospital admission, and therefore, we did not know whether patients were admitted as a result of a fall. Furthermore, we did not correct for repeated admissions of patients and treated each admission as a 'new' patient. However, we corrected for admissions used multiple times during matching. Future studies can look at the possibility of including elimination time and dosages per single medication and changes in medication use during hospital stay in evaluating the relationship between PIMs and inpatient falls. An observational study with 337 patients

showed that an increase in DBI exposure during hospital stay was associated with an increased risk of falls when compared to a stable or decreasing DBI exposure [31].

Our results increase knowledge on medication-related falls, indicate that fall prevention might benefit from decreasing PIM exposure during hospital stay and show differences in effect between the (de)prescribing tools. However, to demonstrate the added value of these tools on inpatient falls in clinical practice, intervention studies are warranted. With the aim to support and study fall-related (de)prescribing in a hospital setting, we are currently developing a clinical decision support system for older hospitalised patients [35].

Conclusion

In a dataset with observational EHR data of older hospitalised patients, we identified an effect of PIMs on inpatient falls using matching methods. Two fall-risk-specific and a general (de)prescribing tool were all independently associated with inpatient falls. The strongest effect was identified for the designated section K for falls of STOPP, which is restricted to high-risk medication for falls.

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