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ORIGINAL ARTICLE

Risk factors for and preventability of drug-related hospital revisits in older patients: A post-hoc analysis of a randomized clinical trial

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Aim: The aims of this study were (1) to identify older patients' risk factors for drug-related readmissions and (2) to assess the preventability of older patients' drug-related revisits.

Methods: Post hoc analysis of a randomized clinical trial with patients aged ≥65 years at eight wards within four hospitals in Sweden. (1) The primary outcome was risk factors for drug-related readmission within 12 months post-discharge. A Cox proportional hazards model was made with sociodemographic and clinical baseline characteristics. (2) Four hundred trial participants were randomly selected and their revisits (admissions and emergency department visits) were assessed to identify potentially preventable drug-related revisits, related diseases and causes.

Results: (1) Among 2637 patients (median age 81 years), 582 (22%) experienced a drug-related readmission within 12 months. Sixteen risk factors (hazard ratio >1, $P < 0.05$) related to age, previous hospital visits, medication use, multimorbidity and cardiovascular, liver, lung and peptic ulcer disease were identified. (2) The 400 patients experienced a total of 522 hospital revisits, of which 85 (16%) were potentially preventable drug-related revisits. The two most prevalent related diseases were heart failure (n = 24, 28%) and chronic obstructive pulmonary disease (n = 13,

The authors confirm that the Principal Investigator for this paper is Ulrika Gillespie and that she had direct clinical responsibility for patients.

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15%). The two most prevalent causes were inadequate treatment (n = 23, 27%) and insufficient or no follow-up (n = 22, 26%).

Conclusion: (1) Risk factors for drug-related readmissions in older hospitalized patients were age, previous hospital visits, medication use and multiple diseases. (2) Potentially preventable drug-related hospital revisits are common and might be prevented through adequate pharmacotherapy and continuity of care in older patients with cardiovascular or lung disease.

KEYWORDS

causality, drug therapy, drug-related side effects and adverse reactions, hospitalization, internal medicine, patient harm

1 | INTRODUCTION

Hospital admissions and emergency department (ED) visits due to problems related to pharmacotherapy remain a major healthcare concern despite efforts to improve medication prescribing and use in recent decades.[1–3] Two recent systematic reviews on drug-related admissions and readmissions to hospital report average prevalences of 15% and 21%.[2,3] There is large variation between studies due to heterogeneity in definitions and methods.[1–3] In this study, a drug-related admission or drug-related ED visit is defined as an unplanned hospital admission or ED visit where a drug-related problem (DRP) is either the main cause or a significantly contributing cause (ie, without the DRP, the visit would not have taken place).[4] DRPs are defined as "undesirable patient experiences that involve drug therapy and that actually or potentially interfere with desired patient outcomes".[5] These can involve not only adverse drug reactions to prescribed medication but also problems such as inappropriate prescribing and non-compliance. A drug-related readmission (or revisit) is a drug-related admission (or ED visit) within a certain period of time after a previous admission.[1] The literature on risk factors associated with drug-related hospital visits and revisits is extensive, but also characterized by heterogeneity. Common positively associated factors are age, functional disability or dependent living situation, previous hospital visits, length of previous hospital stay, number of medications in use and multimorbidity (eg, high Charlson Comorbidity Index score[6]).[1,2,7–9] There is little agreement between studies regarding specific diseases related to drug-related visits and revisits. Commonly associated drug classes are cardiovascular drugs, antibiotics, corticosteroids, opioids and psychotropic drugs.[1,2,9] The degree of preventability and the causes of drug-related visits have been less studied. Based on recent studies, at least a third of the drug-related admissions and readmissions seem potentially preventable.[2,3,10–13] A better understanding of preventable drug-related hospital visits is essential for developing targeted interventions to minimize drug-related harm.

One of the interventions proposed to prevent hospital visits in older patients is conducting a medication review.[14] In a recent multicentre randomized controlled trial (MedBridge) in Sweden, aiming to study the effects of comprehensive medication reviews with or without post-discharge follow-up, a total of 2637 hospitalized patients aged ≥65 years was included.[15] Patients were excluded if they were admitted for less than 24 h, had undergone a medication review by a clinical pharmacist within the preceding month, did not reside in the hospital county or were receiving palliative treatment. The trial interventions did not affect drug-related readmissions or all-cause readmissions within 12 months after discharge from index admission. Drug-related ED visits were not a study outcome, but all-cause ED visits within 12 months from index admission were increased in one of the intervention groups compared with usual care.[15] It is unclear whether drug-related revisits (readmissions or ED visits) could have been prevented or whether these revisits were caused by the trial interventions. There was a large variation in the trial population, with 2055 (78%) patients experiencing no drug-related readmission. It is

What is already known about this subject

- Drug-related hospital revisits—unplanned hospital revisits where a drug-related problem is either the main cause or a significantly contributing cause—are common.
- Multiple risk factors for such visits have been identified, but agreement on specific diseases is lacking.
- The degree of preventability is less studied and varies between studies, although at least a third of the visits seem preventable.

What this study adds

- In this study, disease-specific risk factors for drug-related hospital readmissions in older hospitalized patients were cardiovascular, liver, lung and peptic ulcer disease.
- Potentially preventable drug-related hospital revisits were common and might be prevented through adequate pharmacotherapy and continuity of care in older patients with cardiovascular or lung disease.

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important to target patients at risk of drug-related readmission and to understand the underlying preventability and causes of drug-related revisits. This study was therefore divided into two parts, each with its own aim: (1) to identify older patients' risk factors for drug-related readmissions and (2) to assess the preventability of older patients' drug-related revisits (readmissions and ED visits within 12 months after discharge).

2 | METHODS

2.1 | Study design and population

The present study was a post hoc analysis of the MedBridge trial.[15,16] The trial was conducted from February 2017 until October 2018 at eight wards within four hospitals in Sweden: Uppsala University Hospital and the hospitals in Enköping, Gävle and Västerås. The wards differed in terms of medical specialty: internal medicine (three wards), stroke and neurology (two wards), acute internal medicine, diabetes and nephrology, and geriatrics. The trial population (n = 2637, median age 81 years, median number of medications was nine) was used to identify risk factors for drug-related readmissions (part 1). To assess preventability (part 2), Microsoft Excel was used to randomly select a sample of 400 patients from among all trial participants, stratified by county (hospital): 200 from Uppsala County (Uppsala and Enköping), 100 from Gävleborg County (Gävle) and 100 from Västmanland County (Västerås). We aimed for a representative sample, but no formal sample size calculation was performed.

2.2 | Outcomes, data collection and assessment

Part 1: Baseline (index admission) and outcome data were extracted from the patients' electronic health records (EHRs) and the counties' healthcare registries. The primary outcome for risk factor analysis was experiencing a possibly drug-related readmission within 12 months after hospital discharge from the index admission. Secondary outcomes were all-cause unplanned hospital readmissions and all-cause ED visits. In the MedBridge trial, all participants' unplanned hospital readmissions were assessed by a pair of final-year pharmacy students with a validated tool to identify readmissions that were possibly drug-related or unlikely to be drug-related (AT-HARM10[4]). The reason for readmission did not have to be related to the index admission other than that it occurred within 12 months after discharge. The assessments were based on information in the patients' EHRs: physicians' admission and discharge notes, medication list on admission and laboratory data during hospital stay. First, the students independently assessed each visit, classifying it as either unlikely or possibly drug-related. The students then discussed the visits they disagreed on to reach consensus. In case of doubt, an experienced clinical pharmacist was available to cast a deciding vote. In a validation study, the tool's inter-rater reliability was moderate to substantial (Cohen's kappa values within pairs were between 0.45 and 0.75 and Fleiss' kappa values between pairs were between 0.46 and 0.58[4]). Sensitivity, specificity, and positive and negative predictive values were between 70% and 86%. In the present study, all possibly drug-related readmissions were used as the primary outcome.

Part 2: The assessment of preventability of drug-related revisits followed a stepwise approach:

- Step 1: All ED visits of the 400 participants within 12 months were assessed with AT-HARM10 by a final-year pharmacy student (C.J.) and a clinical pharmacist (A.H.), in addition to the previously assessed hospital admissions (drug-related ED visits were not an outcome in the MedBridge trial and were therefore not previously assessed). ED visits that were followed by a hospital admission within 4 h were considered part of the admission and therefore not assessed separately.
- Step 2: All *possibly* drug-related revisits of the 400 participants were assessed by an expert panel of either an experienced clinical pharmacist and senior researcher (U.G.) and an experienced geriatrician (K.F.) or a second clinical pharmacist and researcher (T.K.). The expert panel had full access to the patients' EHRs, containing information from both hospital and primary care within each county, and applied the amended Hallas criteria for causality and the Hepler criteria for preventability, as proposed by Howard et al.[17] For a drug-related revisit to be classified as potentially preventable, its cause had to be identifiable with reasonable probability (probably or definitely for causality), reasonably foreseeable and controllable within the context and objectives of treatment (detailed description in Supporting Information S1). A one-sentence explanation of the cause was given by the expert panel.
- Step 3: Further data collection for all potentially preventable drug-related revisits was performed by a postgraduate clinical pharmacy student (M.E., Uppsala and Enköping) and one of two clinical pharmacists (A.H., Västerås, or J.S., Gävle) under the supervision of two researchers (U.G. and T.K.) with full access to the patients' EHRs. This data collection included (detailed description in Supporting Information S1) (1) the main disease related to the preventable revisit, (2) the cause, with a classification inspired by the five causes of drug-related morbidity proposed by Hepler and Strand[18] and adapted by the researchers to best reflect the identified cases, (3) the perceived origin of the cause (hospital care, primary care or patient/unclear) and (4) whether the revisit could reasonably have been prevented or was caused by actions related to the interventions (ie, medication reviews and follow-up calls) performed in the MedBridge trial.

2.3 | Statistical data analysis

Part 1: Categorical variables were summarized as frequencies and percentages. Numerical variables were summarized as mean, median, standard deviation and quartile. To investigate differences in baseline

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characteristics (potential risk factors) for each primary (drug-related readmission) and secondary outcome (all-cause readmission and all-cause ED visit), categorical baseline variables were compared using the χ^2 test and continuous variables using the Wilcoxon nonparametric test. Baseline characteristics included were sociodemographics, unplanned hospital visits within 12 months prior to admission, diagnoses in medical history, medication use, estimated glomerular filtration rate (eGFR) on admission, length of hospital stay and discharge diagnosis (full list of variables in Table 1). The choice of these baseline characteristics was based on the availability within the trial and each variable had to be a potential risk factor based on previous literature or the researchers' clinical judgement. To test for multicollinearity, the Cramer's V correlation and Point-Biserial correlation were calculated. Highly correlated variables were not used in the same model. A multivariate Cox proportional hazards model was developed for each primary and secondary outcome, with adjustment for the MedBridge trial treatment group. All baseline characteristics that were significant in the univariate test were initially included. All nonsignificant variables were then removed from the multivariate model in a stepwise way, starting with the least significant, until only significant characteristics remained. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. The underlying proportional hazards assumptions of the Cox proportional hazards models were verified by visual inspection of Schoenfeld residuals. Significance was specified as $P < 0.05$. To check the assumption that index hospital ward did not affect the results, a sensitivity analysis of the primary model was performed by adding index hospital ward as a random effect. All statistical analyses were performed with R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Part 2: For preventability of drug-related visits, descriptive statistics were analysed with Microsoft Excel.

3 | RESULTS

The trial population (n = 2637), of whom 1355 (51%) were female, had a median age of 81 years (interquartile range 74-87 years) and a median of nine (interquartile range five to 13) medications prescribed (Table 1). The total study population and the 400 randomly selected patients were similar in terms of baseline characteristics.

3.1 | Part 1: Risk factors for drug-related revisits

In the trial population, 582 (22%) patients experienced one or more drug-related readmission within 12 months after hospital discharge. Sixteen risk factors (HR > 1) and three protecting factors (HR < 1) for experiencing a drug-related readmission were identified (Figure 1). Risk factors were related to age, previous hospital visits, cardiovascular, liver, lung and peptic ulcer disease in medical history, multimorbidity (ie, higher Charlson Comorbidity Index score), number of medications on admission and cardiovascular or lung disease as discharge diagnosis. The individual risk factors with the highest HRs were previous liver disease (HR 2.46, 95% CI 1.15-5.24), ischaemic heart disease as discharge diagnosis (HR 2.06, 95% CI 1.32-3.21) and previous peptic ulcer disease (HR 1.86, 95% CI 1.10-3.14). Protecting factors were previous dementia diagnosis (HR 0.55, 95% CI 0.39-0.78) and urinary tract infection (HR 0.60, 95% CI 0.39-0.92) and injuries, intoxications and other complications of external factors (HR 0.50, 95% CI 0.31-0.83) as discharge diagnosis. Twelve risk factors and two protecting factors were associated with all-cause readmissions (Supporting Information S2, Figure A). The risk factor with the highest HR was tumour as discharge diagnosis (HR 2.33, 95% CI 1.69-3.22). In the sensitivity analysis, the index hospital ward did not affect these results. Five risk factors for experiencing an all-cause ED visit were identified, with one or more ED visits 12 months prior to admission having the highest HR (1.71, 95% CI 1.51-1.94; Supporting Information S2, Figure B).

3.2 | Part 2: Preventability of drug-related revisits

The random sample of 400 participants experienced a total of 522 unplanned hospital revisits during follow-up (338 hospital admissions and 184 ED visits), of which 181 (35%) were possibly drug-related visits: 128 (38%) possibly drug-related readmissions and 53 (29%) possibly drug-related ED visits (Figure 2). In total, 85 (47% of all possibly drug-related visits and 16% of all unplanned visits) visits were potentially preventable: 68 preventable drug-related readmissions (20% of all unplanned readmissions) and 17 preventable drug-related ED visits (9.4% of all unplanned ED visits). Of all potentially preventable drug-related revisits (n = 85), 56 (44 readmissions and 12 ED visits) were preceded by a hospital-based medication review in the MedBridge trial (Figure 2). Of these visits, 22 (39%) could potentially have been prevented by that intervention. None of the visits seemed to have been caused by the medication review.

The diseases most often related to potentially preventable drug-related revisits were heart failure (n = 24, 28%), chronic obstructive pulmonary disease (COPD; n = 13, 15%), atrial fibrillation (n = 7, 8.2%) and gastrointestinal bleeding or ulcer (n = 7, 8.2%; Table 2).

Five main causes of potentially preventable drug-related revisits were identified (Table 3): inadequate treatment (n = 23, 27%), insufficient or no follow-up (n = 22, 26%), noncompliance (n = 21, 25%), lack of investigation or diagnostics (n = 10, 12%) and inappropriate treatment (n = 9, 11%). The origin of the cause of these visits within healthcare was more often hospital care (n = 49, 58%) than primary care (n = 27, 32%). In nine (11%) cases, the origin of the cause was either unclear or the visit seemed to be caused by the patient.

Five patient cases are described in Table 4 to exemplify the diseases related to and causes of preventable drug-related revisits, their origin in healthcare and whether the revisits could have been prevented by the medication review performed during the MedBridge trial.

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TABLE 1 Study population baseline (index admission) characteristics for risk factor analysis population (trial population, n = 2637) and preventability assessment population (random sample, n = 400)

Variable group	Baseline (index admission) variable[a]	Risk factor population (n = 2637)	Preventability population (n = 400)
Sociodemographics	Age, median, years (IQR)	81 (74-87)	82 (74-87)
	Sex, female	1355 (51.4%)	206 (51.5%)
	Home care	679 (25.7%)	117 (29.3%)
	Residential home	322 (12.2%)	50 (12.5%)
Unplanned visits within 12 months prior to admission	ED visits (one or more)	895 (33.9%)	124 (31.0%)
	Unplanned hospital admissions (one or more)	1015 (38.5%)	142 (35.5%)
Medical history	Diagnosis in medical history[b]		
	Hypertension	1826 (69.2%)	276 (69%)
	Diabetes mellitus (with or without complication)	747 (28.3%)	107 (26.8%)
	Atrial fibrillation and flutter	725 (27.5%)	110 (27.5%)
	Heart failure (congestive)	721 (27.3%)	114 (28.5%)
	COPD	362 (13.7%)	51 (12.8%)
	Ischaemic heart disease	355 (13.5%)	52 (13.0%)
	Any malignancy including lymphoma and leukaemia and metastatic solid tumour	348 (13.2%)	55 (13.8%)
	Myocardial infarction	332 (12.6%)	43 (10.8%)
	Renal disease	310 (11.8%)	51 (12.8%)
	Cerebrovascular disease	284 (10.8%)	41 (10.3%)
	Dementia	244 (9.3%)	42 (10.5%)
	Asthma	194 (7.4%)	27 (6.8%)
	Peripheral vascular disease	163 (6.2%)	27 (6.8%)
	Rheumatic disease	160 (6.1%)	19 (4.8%)
	Hemiplegia or paraplegia	58 (2.2%)	14 (3.5%)
	Chronic pulmonary disease excluding COPD and asthma	46 (1.7%)	4 (1%)
	Peptic ulcer disease	37 (1.4%)	4 (1%)
	Liver disease (mild, moderate, or severe)	16 (0.6%)	0 (0%)
	Charlson Comorbidity Index score, median (IQR)	1 (0-3)	1 (0-3)
Medication use	Automated drug dispensing in home setting	678 (25.7%)	97 (24.3%)
	Number of medications upon admission		
	0-4	500 (19%)	68 (17%)
	5-9	976 (37%)	164 (41%)
	10+	1161 (44%)	168 (42%)
eGFR on admission (mL/min/1.73 m^2)[c]	<15	112 (4.2%)	20 (5%)
	15-29	365 (13.8%)	49 (12.3%)
	30-59	1111 (42.1%)	173 (43.3%)
	60-89	963 (36.5%)	149 (37.3%)
	≥90	77 (2.9%)	7 (1.8%)
Length of hospital stay, median, days (IQR)		8 (5 to 14)	8 (5 to 15)
Discharge diagnosis at index admission (ICD-10 code)[d]	Diseases in the cerebrovascular system (I6*)	385 (14.6%)	51 (12.8%)
	Respiratory tract infections (J1*-J0*)	257 (9.7%)	47 (11.8%)

(Continues)

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TABLE 1 (Continued)

Variable group	Baseline (index admission) variable[a]	Risk factor population (n = 2637)	Preventability population (n = 400)
	Heart failure (I50*)	213 (8.1%)	26 (6.5%)
	Urinary tract infections (N3*, N109)	149 (5.7%)	20 (5.0%)
	Other infections and parasite diseases (A*, B*)	138 (5.2%)	27 (6.8%)
	Injuries, intoxications and certain other complications of external factors (S*, T*)	124 (4.7%)	26 (6.5%)
	Other conditions of the circulatory system (I*, except I20*-I26*, I48*, I50*, I6*)	107 (4.1%)	12 (3.0%)
	Transient neurological diseases (G4*)	98 (3.7%)	16 (4.0%)
	Chronic diseases of the lower respiratory tract (J4*)	85 (3.2%)	14 (3.5%)
	Atrial fibrillation and flutter (I48*)	72 (2.7%)	10 (2.5%)
	Tumours (C*, D00*-D48*)	67 (2.5%)	13 (3.3%)
	Diabetes mellitus (E10*-E14*)	67 (2.5%)	7 (1.8%)
	Other diseases of the urinary system and genitals (N*, except for N3*, N109)	66 (2.5%)	6 (1.5%)
	Pulmonary embolism (I26*)	62 (2.4%)	8 (2.0%)
	Other diseases of the respiratory system (J*, except J0*-J1*, J4*)	61 (2.3%)	14 (3.5%)
	Diseases of the digestive organs (K*)	57 (2.2%)	11 (2.8%)
	Ischaemic heart diseases (I20*-I25*)	53 (2.0%)	4 (1.0%)
	Metabolic disorders (E8*)	47 (1.8%)	8 (2.0%)
	Diseases of the musculoskeletal system and connective tissue (M*)	47 (1.8%)	5 (1.3%)
	Diseases of the blood and blood-forming organs (D5*-D9*)	44 (1.7%)	4 (1.0%)
	Other diseases of the nervous system (G*, except G4*)	43 (1.6%)	7 (1.8%)
	Diseases of the ear and mastoid process (H6*-H9*)	21 (0.8%)	4 (1.0%)
	Diseases of the skin and subcutaneous tissue (L*)	21 (0.8%)	4 (1.0%)
	Diseases of the eye and adnexa (H0*-H5*)	14 (0.5%)	4 (1.0%)
	Mental and behavioural disorders (F*)	11 (0.4%)	2 (0.5%)
	Other endocrine, nutritional and metabolic diseases (E*, except E10*-E14*, E8*)	8 (0.3%)	1 (0.3%)

Abbreviations: COPD, chronic obstructive pulmonary disease; ED, emergency department; eGFR, estimated glomerular filtration rate; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision; IQR, interquartile range.

[a]Unless otherwise indicated, data are numbers (%) of patients.

[b]Based on registered Charlson Comorbidity Index[6] diagnosis codes up to 2 years before index admission, classified in accordance with Quan et al,[19] with the following additions: hypertension (I10*-I15*) and atrial fibrillation and flutter (I48*).

[c]Patients with missing eGFR values (n = 9) were excluded from this calculation.

[d]All ICD-10 groups were included except R*, W* and Z* because of the heterogenous and unclear nature of these diagnosis groups.

*Any additional number within the presented ICD-10 group.

4 | DISCUSSION

This post hoc analysis of a randomized controlled trial (MedBridge) in older patients identified multiple risk factors and protecting factors for drug-related readmissions within 12 months after hospital discharge (part 1). Sixteen risk factors related to age, previous hospital visits, medication use, multimorbidity and cardiovascular, liver, lung and peptic ulcer disease were identified. Protecting factors for drug-

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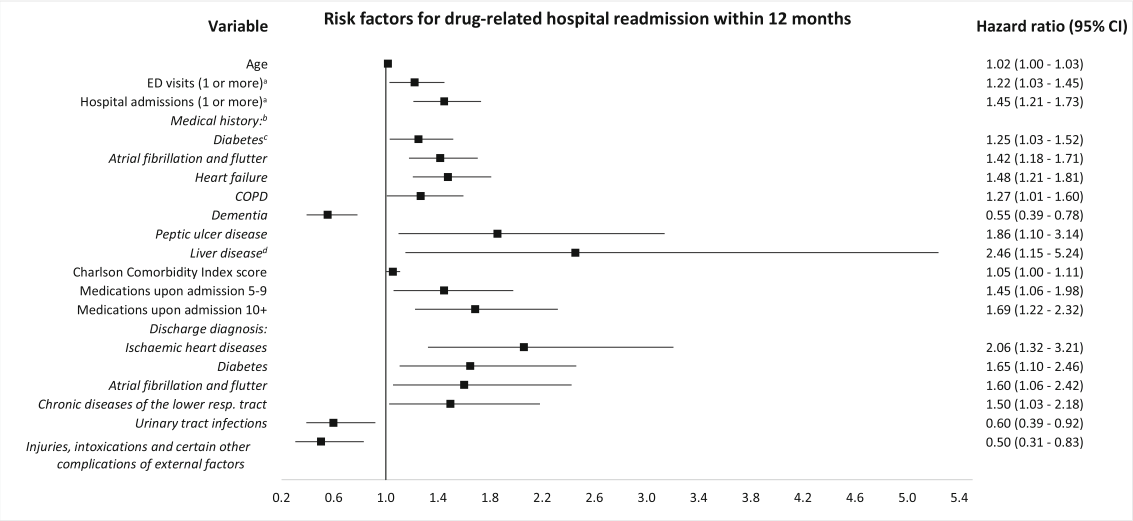

FIGURE 1 Risk factors (hazard ratio >1) and protecting factors (hazard ratio <1) associated with experiencing a possibly drug-related hospital readmission within 12 months after hospital discharge, adjusted for MedBridge trial treatment group. Detailed information about each variable (factor) is provided in Table 1. CI, confidence interval; COPD, chronic obstructive pulmonary disease; ED, emergency department; resp., respiratory.[a]1 or more in the previous 12 months.[b] Based on registered Charlson Comorbidity Index[6] diagnosis codes up to 2 years before index admission, classified in accordance with Quan et al,[19] with the following additions: hypertension (I10*-I15*) and atrial fibrillation and flutter (I48*).[c] Diabetes mellitus with or without complications.[d] Mild, moderate or severe liver disease

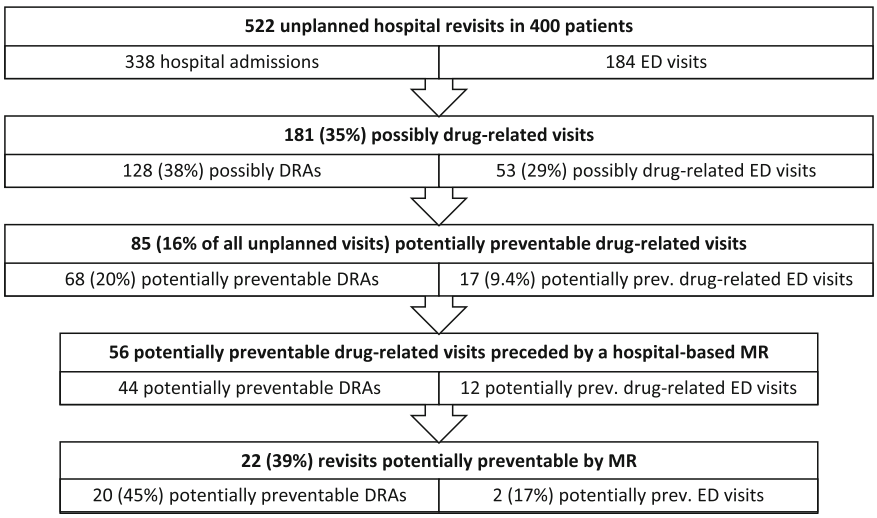

FIGURE 2 Flowchart of hospital revisits assessed for preventability. DRA, drug-related admission; ED, emergency department; prev., preventable; MR, medication review

related readmissions were previous dementia diagnosis and urinary tract infection and injuries, intoxications and other complications of external factors as discharge diagnosis. Sixteen per cent of the hospital revisits assessed in this study were potentially preventable drug-related revisits (part 2). The two most prevalent diseases and causes related to preventable revisits were heart failure and COPD, and inadequate treatment and insufficient or no follow-up, respectively.

The identified risk factors in this study confirm results of previous studies showing that age, previous hospital visits, number of medications and comorbidity were positively associated with drug-related readmissions.[1,2] Specific diseases that are associated with drug-related visits have been less studied and there is little agreement in current literature. Still, cardiovascular disease including diabetes mellitus and its treatment are often reported as risk factors for drug-related (re)admissions.[1–3,10,13,20] Previous liver disease and peptic ulcer disease were the risk factors with the highest HRs. These diseases are not commonly identified risk factors in other studies, perhaps because not all studies register these specific diagnoses. Pharmacotherapy for management of severe liver disease and adjustment of pharmacotherapy based on changes in pharmacokinetics and pharmacodynamics due to liver disease are challenging for clinicians.[21,22] Hence, it seems plausible that inappropriate pharmacotherapy for patients with existing liver disease may cause hospital admissions. In a study by Parekh et al, post-discharge drug-related harm was often related to

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TABLE 2 Main disease related to potentially preventable drug-related revisits (n = 85) and the distribution of readmissions (n = 68) and emergency department visits (n = 17)

Main disease (based on ICD-10)	Number of potentially preventable drug-related revisits (%)		
	Readmissions	ED visits	Total
Heart failure	20 (29)	4 (24)	24 (28)
COPD	10 (15)	3 (18)	13 (15)
Atrial fibrillation	7 (10)		7 (8)
Gastrointestinal bleeding or ulcer	6 (9)	1 (6)	7 (8)
Ischaemic heart disease	4 (6)	2 (12)	6 (7)
CVA or TIA	5 (7)		5 (6)
Respiratory infections	4 (6)	1 (6)	5 (6)
Diabetes mellitus type 2	3 (4)		3 (4)
Depression	2 (3)	1 (6)	3 (4)
Epilepsy	2 (3)		2 (2)
Other (<2 cases per disease)	5 (7)	5 (29)	10 (12)
Total	68	17	85

Abbreviations: COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; ED, emergency department; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision; TIA, transient ischemic attack.

TABLE 3 Causes of potentially preventable drug-related revisits (n = 85) and the origin of the cause in healthcare

Main cause of potentially preventable drug-related revisit (short explanation, for detailed description see Supporting information S1, Table B)	Origin of cause of potentially preventable drug-related revisit			
	Hospital care	Primary care	Patient or unclear	Total (%)
Inadequate treatment (lack of treatment, undertreatment, too low dose)	13	9	1	23 (27)
Insufficient or no follow-up (or monitoring)	14	8		22 (26)
Noncompliance (intentional and nonintentional)	8	5	8	21 (25)
Lack of investigation or diagnostics	7	3		10 (12)
Inappropriate treatment (wrong or unnecessary treatment)	7	2		9 (11)
Total (%)	49 (58)	27 (32)	9 (11)	85 (100)

gastrointestinal problems.[12] A previous study by our research group at Uppsala University Hospital, one of the current study sites, found that medications prescribed for peptic ulcer or gastroesophageal reflux disease (eg, proton pump inhibitors [PPIs]) were associated with an increased risk of readmission in older patients.[23] Furthermore, medications that may cause gastroduodenal bleeding (eg, antiplatelets and anticoagulants) are often identified as risk factors for drug-related readmissions,[1,2] and this risk may be higher in patients with previous peptic ulcer disease. However, our results on previous liver and peptic ulcer disease should be interpreted with caution, as the prevalence rates of these diseases in medical histories were low (n = 16, 0.6%, and n = 37, 1.4%, respectively) and no related revisits of patients with these diseases were identified in our random sample of 400 participants. Lung disease (mainly COPD) in the medical history and as discharge diagnosis were risk factors in our study, confirming the results of our previous study at Uppsala University Hospital showing that asthma and COPD were associated with an increased risk of readmission.[23] A review on risk factors for adverse health outcomes after discharge (ie, unplanned readmission or adverse drug event after discharge) that are potentially modifiable by pharmacist interventions found COPD to be one of the most frequently reported modifiable risk factors.[24] Interestingly, previous dementia diagnosis was a protecting factor for drug-related readmissions in our study, in contrast to other studies that have identified cognitive impairment or dementia as risk factors for drug-related (re)admissions.[25,26] A possible explanation may be that dementia generally occurs in more complex patients and that their readmissions may frequently be classified as "caused by progression of the disease" (ie, unlikely to be drug-related), rather than being caused by a DRP. This is supported by dementia not appearing as a protecting factor for all-cause readmission in our secondary analysis. The other protecting factors in our study (urinary tract infections and injuries, intoxications and other external factors as discharge diagnosis) may be explained by their relative unrelatedness to pharmacotherapy, in contrast to other discharge diagnoses.

The prevalence of potentially preventable drug-related revisits in our study (47% of all possibly drug-related visits and 16% of all unplanned visits) confirms the average prevalence in recent systematic reviews (43% of drug-related readmissions based on six studies[3]

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TABLE 4 Five patient case descriptions of potentially preventable drug-related revisits with corresponding results of the preventability assessment in terms of ICD-10 diagnosis, cause(s), origin and possible prevention by MR in the MedBridge trial

No.	Case description of potentially preventable drug-related revisit[a]	Results of preventability assessment: • Readmission or ED visit • ICD-10 diagnosis • Main cause (other causes) • Origin • Could have been prevented by MR (explanation)?
1	88-year-old patient with a.o.t. heart failure with midrange ejection fraction, chronic atrial fibrillation and orthostatism in medical history, admitted to hospital (index) because of dizziness, dyspnoea and chest pain. Unclear aetiology of symptoms (blood pressure 130/70, no abnormal cardiac biomarker test results, no changes compared with previous echocardiogram, chest radiograph normal). Ward physician suspected adverse drug effects due to complex pharmacotherapy and adjusted treatment: oral furosemide 20 mg once daily, metoprolol 25 mg once daily and simvastatin 20 mg once daily were stopped, enalapril was reduced from 10 mg to 5 mg once daily, felodipine 5 mg was started and an antacid was given during hospital stay. Patient symptoms decreased and the patient was discharged 2 days after pharmacotherapy adjustments. Referral for follow-up was sent to the GP. One and a half weeks later (before GP follow-up took place), the patient presented at the ED with dyspnoea and enalapril was increased to 7.5 mg once daily.	• ED visit • I509 heart failure • Insufficient or no follow-up (inappropriate treatment, felodipine instead of metoprolol and decreased enalapril dose) • Hospital • Yes (ward pharmacist cautioned about a relatively large number of pharmacotherapeutic changes during hospital stay, but no clear action/follow-up was proposed)
2	74-year-old patient with a.o.t. diabetes mellitus type 1, hypertension, heart failure with preserved ejection fraction (diastolic heart failure), pulmonary hypertension and paroxysmal atrial fibrillation in medical history, admitted to hospital (index) because of dyspnoea due to newly diagnosed COPD stage 2. COPD exacerbation was treated with 5-day course of amoxicillin and prednisolone, and the patient was prescribed tiotropium and terbutaline inhalers on discharge. Previous treatment with carvedilol (nonselective beta-blocker) 25 mg twice daily for heart failure was continued. Three days later, the patient was readmitted due to worsening dyspnoea. Patient had not been taking the inhalers because no inhalation instruction had been provided. During readmission, the patient received inhaler training and carvedilol was replaced with bisoprolol (selective beta-blocker).	• Readmission • J441 COPD with acute exacerbation • Noncompliance (inappropriate treatment, nonselective beta-blocker in heart failure) • Hospital • Yes (ward pharmacist tested patient's inhalation technique and recommended prescribing specific inhalers during hospital stay, but there was a lack of medication reconciliation and inhaler instructions upon discharge)
3	87-year-old patient with a.o.t. diastolic heart failure and persistent atrial fibrillation, admitted to hospital (index) because of dyspnoea and lower back pain due to pneumonia and lung oedema and collapsed vertebra due to osteoporosis, respectively. During hospital stay, enalapril/hydrochlorothiazide 20/12.5 mg was replaced by losartan 50 mg once daily because of high age and dry cough (adverse drug effect of enalapril). Oral furosemide 40 mg once daily was started, but the patient developed hypokalaemia and received potassium supplementation during hospital stay. Previously prescribed bisoprolol 10 mg and felodipine 5 mg once daily were continued. Patient discharged to nursing home with referral to GP for follow-up. After 2 weeks, hospital readmission due to dyspnoea and new-onset tachycardia (heart rate 130-160 beats/min) with normokalaemia. Bisoprolol dosage was increased to 15 mg once daily and felodipine was stopped. Furosemide was increased to 40 mg in the morning and at noon.	• Readmission • I489 atrial fibrillation • Inadequate treatment (insufficient or no follow-up) • Hospital • Not applicable (no MR, control group)
4	70-year-old patient with a.o.t. persistent atrial fibrillation in medical history, admitted to hospital (index) because of diarrhoea, vomiting and iron-deficiency anaemia, probably due to gastrointestinal bleeding (no clear source of bleeding identified through gastroscopy and colonoscopy). Apixaban was temporarily paused and replaced with dalteparin awaiting capsule endoscopy. During 6-week post-discharge follow-up, the physician and patient discussed the potential restart of apixaban if haemoglobin levels are recovered and stabilized, followed by close monitoring of haemoglobin. Two	• Readmission • K922 gastrointestinal haemorrhage • Noncompliance (insufficient or no follow-up) • Hospital • Not applicable (no MR, control group)

(Continues)

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TABLE 4 (Continued)

No.	Case description of potentially preventable drug-related revisit[a]	Results of preventability assessment: • Readmission or ED visit • ICD-10 diagnosis • Main cause (other causes) • Origin • Could have been prevented by MR (explanation)?
	weeks later, no identification of bleeding source through capsule endoscopy, although some parts of the endoscopy results were unclear. Follow-up visit planned by hospital, but did not take place (reason unclear) and no reminder to patient. Three months later, readmission with iron-deficiency anaemia. Patient had switched back from dalteparin to apixaban on his own initiative, having misunderstood the physician as stating that apixaban could be restarted.	
5	68-year-old patient with a.o.t. dysuria with haematuria due to suspected thickening of bladder wall and enlarged prostate in medical history, admitted to hospital (index) because of fever and weakness due to endocarditis. Decrease in renal function (eGFR from 58 to 31 mL/min/1.73 m^2) during hospital stay, probably due to antibiotic treatment. Discharged to nursing home with antibiotic treatment adapted to renal function and follow-up by hospital. Ten months later, the patient presented to GP with sleep problems, nocturia, constipation and an 'unpleasant feeling in the stomach'. GP prescribed mirtazapine 15 mg once daily in the evening and hyoscyamine sulphate (anticholinergic) 0.4 mg twice daily without any laboratory tests or notes regarding previous renal and urinary problems. Three days later, the patient presented at the ED with acute urinary retention for which he received a urinary catheter.	• ED visit • R33 retention of urine • Inappropriate treatment, anticholinergic in patient with previous dysuria • Primary care • No (cause originated after MR)

Abbreviations: a.o.t., among other things; COPD, chronic obstructive pulmonary disease; ED, emergency department; GP, general practitioner; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision; LVEF, left ventricular ejection fraction; MR, medication review.

[a]For data protection reasons, the patients' age in these examples is fictive (indicative of the actual age).

and 15% of all-cause readmissions based on four studies[2]). The diseases most often related to these preventable visits were cardiovascular disease (mainly heart failure, 28%) and COPD (13%), followed by gastrointestinal bleeding or ulcer (8.2%). These results seem in line with the identified risk factors for drug-related readmissions in this study. For both heart failure and COPD, inadequate use of medications is associated with poor clinical outcomes and exacerbations are often avoidable through better prescribing by clinicians and clearer instructions for patients.[27–30] Multidisciplinary transitional care interventions can reduce readmissions in patients with heart failure and COPD[31–33] and in older patients in general.[34,35] Gastroprotective PPI treatment is an evidence-based strategy to prevent gastrointestinal bleeding or ulcers. However, recent Swedish studies focusing on the potential harmful effects of long-term PPI treatment,[36–38] and our previous identified association between PPI use and readmission in older patients,[23] may have led to the restrictive use of gastroprotection in older patients.

The three main causes (inadequate treatment, insufficient or no follow-up and noncompliance) that accounted for 78% of all preventable revisits in our study indicate the potential for improvement through better treatment guideline adherence, continuity of care, and patient involvement and education.[34,35,39,40] Not all revisits could be attributed to shortcomings within healthcare, as some seemed to be caused by the patients themselves. Furthermore, 39% of the potentially preventable drug-related revisits could have been prevented by the medication review (and/or medication reconciliation) in the MedBridge trial, if the intervention had been performed optimally. A previous process evaluation of the trial found a lack of integration of medication reviews into the daily workflow at the ward, inadequate time allotted for follow-up on treatment changes and no medication reconciliation on discharge by the pharmacist in more than half of the patients.[41] Improving these shortcomings could make medication review and medication reconciliation at care transitions effective strategies to prevent hospital revisits.[34,35,42] However, our results indicated that an estimated 6% reduction in hospital revisits within 12 months (ie, 39% of the 16% preventable drug-related revisits were potentially preventable by a medication review) might be the limit for what is achievable by a hospital-based pharmacotherapy intervention in our setting, assuming that medication reviews only affect drug-related revisits. This would make it challenging to conduct adequately powered clinical trials.

This study has several strengths. The large study population with long and complete post-discharge follow-up and the use of a validated method to identify drug-related revisits increase the reliability of the results. There are also some limitations to the study. Only patients who had been admitted to a limited number of medical specialty

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wards were included, which limits the generalisability to any hospital population. We excluded 1-day admissions, patients who had recently undergone a medication review and patients receiving palliative treatment, which may have led to the exclusion of patients with both relatively mild and severe health conditions. All analyses and assessments were based solely on electronic data from the regional health registries and the hospitals' general EHR systems, which could lead to potential underestimation or overestimation of study outcomes. Cytostatic treatment is often prescribed in a separate system that was not accessible to the researchers. Hence, cancer was a risk factor for all-cause readmissions in our study, but not drug-related readmissions. Anticancer drugs have been associated with readmissions in previous studies.[1,2] In general, this study was limited to the availability of EHR data that were collected during the MedBridge trial. For risk factor analysis, we lacked data about medications on discharge, although we included the number of medications on admission. Several other previously identified risk factors for drug-related revisits were not available for our risk factor analysis, such as functional dependency, previous adverse drug events, medication changes and electrolyte imbalances during index admission, and living alone after discharge.[1,3,11,43] For the preventability assessment, we chose not to include which medications were involved in each drug-related visit because of the generally complex pharmacotherapy and multiple medications involved (eg, inadequate heart failure treatment often involves [the lack of] four different drug substances). We could have reported all therapeutic drug classes that were potentially involved, but the reliability of such results would have been questionable. Lastly, at one of the four hospitals, the preventability assessments were performed by two pharmacists instead of a geriatrician being involved. This may decrease the reliability of the results[44,45] although we did not see notable differences in the results between the hospitals.

5 | CONCLUSION

Risk factors for drug-related readmissions in older hospitalized patients were age, previous hospital visits, multimorbidity, medication use and cardiovascular, liver, lung and peptic ulcer disease. Potentially preventable drug-related hospital revisits are common and might be prevented through adequate medication use and continuity of care in older patients with cardiovascular or lung disease. Interventions to reduce drug-related hospital visits are generally conducted in older patients with multiple medications in use. In addition, this study suggests focusing on patients with multiple previous visits and those with heart failure or COPD. Hospital revisits in these patients may be prevented through better treatment guideline adherence concerning adequate pharmacotherapy and continuity of care, and through better patient education and involvement.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

T.G.H.K., A.N.H., K.-J.L., H.M., E.I.N., J.S. and U.G contributed to the study concept and design. T.G.H.K., H.M., E.I.N., J.S. and U.G obtained funding. All authors contributed to acquisition, analysis and interpretation of data. T.G.H.K., A.N.H. and N.H. conducted the statistical analysis. H.M., E.I.N. and U.G supervised the study. K.-J.L., J.S. and U.G provided administrative, technical and material support. T.G.H.K. and A.N.H. drafted the manuscript. N.H., K.-J.L., H.M., E.I.N., J.S. and U.G revised the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. All proposals requesting data access will need to specify an analysis plan and have approval from the MedBridge trial research group before data release.

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SUPPORTING INFORMATION

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