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

Thomas Kempen[1], Anton Hedman[2], Nermin Hadziosmanovic[3], Karl-Johan Lindner[4], Håkan Melhus[1], Elisabet Nielsen[1], Johanna Sulku[1], and Ulrika Gillespie[1]

[1]Uppsala University
[2]Linköping University Hospital
[3]Uppsala Clinical Research Center
[4]Region Västmanland

February 22, 2024

Abstract

Aim: To identify older patients' risk factors for drug-related readmissions and assess the preventability of older patients' drug-related revisits. **Methods:** Post-hoc analysis of a randomised clinical trial with patients aged [?] 65 years at eight wards within four hospitals in Sweden. The primary outcome used to identify risk factors was drug-related readmission within 12 months post-discharge. A Cox proportional hazards model was made with sociodemographic and clinical baseline characteristics. 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:** Among 2,637 patients (median age (interquartile range) 81 (74–87) 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. The 400 patients experienced a total of 522 hospital revisits, of which 85 (16%) were potentially preventable drug-related revisits. The two most prevalent diseases and causes related to preventable revisits were heart failure (n=24, 28%) and chronic obstructive pulmonary disease (n=13, 15%), and inadequate treatment (n=23, 27%) and insufficient or no follow-up (n=22, 26%). **Conclusion:** Risk factors for drug-related readmissions in older hospitalised patients were age, previous hospital visits, medication use and multiple diseases. Potentially preventable drug-related hospital revisits are common and might be prevented through adequate medication use and follow-up in older patients with cardiovascular or lung disease.

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 the last decades [1,2]. Two recent systematic reviews on drug-related readmissions to hospital report an average prevalence of 15% and 21%, of which at least a third seem preventable [3,4]. There is large variation between studies due to heterogeneity in definitions and methods [3,4]. In this study, a drug-related readmission or drug-related ED visit is defined as an unplanned hospital visit where a drug-related problem (DRP) is either the main cause or a significantly contributing cause (i.e., without the DRP, the visit would not have taken place). 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. The literature on risk factors associated with drug-related visits is extensive, but also characterised 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 (e.g., high Charlson Comorbidity Index score [6]) [1,3,7–9]. There is little agreement between studies regarding specific diseases related to drug-related visits. Commonly associated drug classes are cardiovascular drugs, antibiotics, corticosteroids, opioids and psychotropic drugs [1,3,9]. Studies often fail to report the degree of preventability and the causes of visits. A better understanding of preventable drug-related visits is essential for developing targeted interventions to minimise drug-related harm.

One of the interventions proposed to prevent hospital visits in older patients is conducting a medication review [10]. In a recent multicentre randomised controlled trial (MedBridge) in Sweden, aiming to study the effects of comprehensive medication reviews with or without post-discharge follow-up, a total of 2,637 hospitalised patients aged [?] 65 years was included [11]. Patients were excluded if they were admitted for less than 24 hours, 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. Drug-related ED visits were not a study outcome, but all-cause ED visits were increased in one of the intervention groups compared with in usual care [11]. It is unclear whether drug-related revisits could have been prevented or whether these visits were caused by the trial interventions. There was a large variation in the trial population, with 2,055 (78%) patients experiencing no drug-related readmission. It is important to target patients at risk of drug-related readmission and to understand the underlying preventability and causes of drug-related revisits. In this study, we therefore aimed to: 1) identify older patients' risk factors for drug-related readmissions and 2) assess the preventability of older patients' drug-related revisits (admissions and ED visits).

Methods

Study design and population

The present study was a post-hoc analysis of the MedBridge trial [11,12]. 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=2,637; median age 81 years; median number of medications 9) was used to identify risk factors for drug-related readmissions. To assess preventability, 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.

Outcomes, data collection and assessment

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. 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 possible drug-related or unlikely to be drug-related (AT-HARM10, [13]). 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 [13]). 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. Secondary outcomes were all-cause unplanned hospital readmissions and all-cause ED visits.

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 (CJ) and a clinical pharmacist (AH), 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 four hours 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 (UG for all hospitals) and an experienced geriatrician (KF for Uppsala, Enköping and Västerås) or a second clinical pharmacist and researcher (TK, Gävle). 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. [14]. 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 (ME, Uppsala and Enköping) and one of two clinical pharmacists (AH, Västerås, or JS, Gävle) under the supervision of two researchers (UG and TK) 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 [15] and reformulated based on the causes described by the expert panel; 3) the perceived origin of the cause in healthcare (hospital care or primary care); and 4) whether the revisit could reasonably have been prevented or was caused by actions related to the interventions (i.e., medication reviews and follow-up calls) performed in the MedBridge trial.

Statistical data analysis

Categorical variables were summarised as frequencies and percentages. Numerical variables were summarised as mean, median, standard deviation and quartile. To investigate differences in baseline 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 non-parametric 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) upon admission, length of hospital stay and discharge diagnosis (full list of variables in Supporting Information S2). In order to a 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 MedBridge trial treatment group. All baseline characteristics that were significant in the univariate test were initially included. All non-significant 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 $p < 0.05$. All statistical analyses were performed with R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). For preventability of drug-related visits, descriptive statistics were analysed with Microsoft Excel.

Results

The trial population (n=2,637), of which 1,355 (51%) were female, had a median age of 81 years (interquartile range, 74–87 years) and a median of 9 (interquartile range, 5 to 13) medications prescribed (Table 1). The total study population and the 400 randomly selected patients were similar in terms of baseline characteristics (full list of baseline characteristics for total study population and random selection in Supporting Information S2).

[Insert Table 1 here]

Risk factors for drug-related readmissions

In the trial population, 582 (22%) patients experienced one or more drug-related readmissions 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 (i.e., higher Charlson Comorbidity Index score), number of medications upon 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 S3, Figure A). The risk factor with the highest HR was tumour as discharge diagnosis (HR 2.33, 95% CI 1.69–3.22). 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 S3, Figure B).

[Insert Figure 1 here]

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).

[Insert Figure 2 here]

[Insert Table 2 here]

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%), non-compliance (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.

[Insert Table 3 here]

4

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.

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.

[Insert Table 4 here]

Discussion

This post-hoc analysis of a randomised controlled trial (MedBridge) in older patients identified multiple risk factors and protecting factors for drug-related readmissions within 12 months after hospital discharge. 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-related readmissions were previous dementia diagnosis, and urinary tract infection and injuries, intoxications and other complications of external factors as discharge diagnosis. Sixteen percent of the hospital revisits assessed in this study were potentially preventable drug-related revisits. 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 [1,3]. Although there is little agreement on specific diseases that affect drug-related visits in the literature, cardiovascular disease and its treatment are often reported as risk factors for drug-related (re)admissions [1,3,4]. Previous liver disease and peptic ulcer disease were the risk factors with the highest HRs, but are not commonly identified risk factors in other studies. 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 [16,17]. Hence, it seems plausible that inappropriate pharmacotherapy for patients with existing liver disease may cause hospital admissions. 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 were associated with an increased risk of readmission in older patients [18]. Furthermore, medications that may cause gastroduodenal bleeding (e.g., antiplatelets and anticoagulants) are often identified as risk factors for drug-related readmissions [1,3] 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 [18]. 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 [19,20]. 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' (i.e., 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 [4] and 15% of all-cause readmissions based on four studies [3]). 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 [21–24]. Gastroprotective proton pump inhibitor 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 proton pump inhibitor treatment may have led to the restrictive use of gastroprotection in older patients [25–27].

The three main causes (inadequate treatment, insufficient or no follow-up and non-compliance) that accounted for 78% of all preventable revisits in our study indicate the potential for improvement through better treatment guideline adherence and patient involvement and education [28,29]. Further, 39% of the potentially preventable drug-related revisits could have been prevented by the medication review in the MedBridge trial, if the review 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 upon discharge by the pharmacist in more than half of the patients [30]. Improving these shortcomings could make medication review an effective strategy to prevent hospital revisits. However, our results indicated that an estimated 6% reduction in hospital revisits within 12 months (39% of the 16% potentially preventable drug-related revisits) might be the maximum achievable by a hospital-based pharmacotherapy intervention, making 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 general internal medicine or internal medicine subspecialty wards were included, which limits generalisability to a broader group. We excluded one-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 under- 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 [1,3]. For risk factor analysis, we lacked data about medications upon discharge, although we included the number of medications upon admission. 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 (e.g., 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.

Conclusion

Risk factors for drug-related readmissions in older hospitalised 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 follow-up 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, the 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 treatment follow-up, and through better patient education and involvement.

Ethical approval

This study was part of the MedBridge project, which has received ethical approval from the Swedish Central Ethical Review Board (CEPN; registration number: Ö21-2016).

Acknowledgements

Competing interests

There are no competing interests to declare.

Contributors

Concept and design: Kempen, Hedman, Lindner, Melhus, Nielsen, Sulku, Gillespie.

Obtained funding: Kempen, Melhus, Nielsen, Sulku, Gillespie.

Acquisition, analysis, or interpretation of data: All authors.

Statistical analysis: Kempen, Hedman, Hadziosmanovic.

Supervision: Melhus, Nielsen, Gillespie.

Administrative, technical, or material support: Lindner, Sulku, Gillespie.

Drafting of the manuscript: Kempen, Hedman.

Critical revision of the manuscript: Hadziosmanovic, Lindner, Melhus, Nielsen, Sulku, Gillespie.

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.

References

1. Linkens AEMJH, Milosevic V, van der Kuy PHM, et al. Medication-related hospital admissions and readmissions in older patients: an overview of literature. Int J Clin Pharm. 2020;42(5):1243–51; https://doi.org/10.1007/s11096-020-01040-1.

2. Wallerstedt SM, Hoffmann M, Lönnbro J. Methodological issues in research on drug-related admissions: A meta-epidemiological review with focus on causality assessments. Br J Clin Pharmacol. 2022 Feb 1;88(2):541–50; https://doi.org/10.1111/bcp.15012.

3. El Morabet N, Uitvlugt EB, van den Bemt BJF, et al. Prevalence and Preventability of Drug-Related Hospital Readmissions: A Systematic Review. J Am Geriatr Soc. 2018 Mar 1;66(3):602–8; https://doi.org/10.1111/jgs.15244.

4. Ayalew MB, Tegegn HG, Abdela O. Drug Related Hospital Admissions; A Systematic Review of the Recent Literatures. Bull Emerg Trauma. 2019;7(4):339–46; https://doi.org/10.29252/beat-070401.

5. PCNE. PCNE Classification for Drug-Related Problems V9.1 [Internet]. Pharmaceutical Care Network Europe Association. 2020 [cited 2022 Jan 7]. p. 10. Available from: https://www.pcne.org/working-groups/2/drug-related-problem-classification

6. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83; https://doi.org/10.1016/0021-9681(87)90171-8.

7. García-Pérez L, Linertová R, Lorenzo-Riera A, et al. Risk factors for hospital readmissions in elderly patients: a systematic review. QJM An Int J Med. 2011 Aug 1;104(8):639–51; https://doi.org/10.1093/qjmed/hcr070.

8. Lea M, Mowe M, Mathiesen L, et al. Prevalence and risk factors of drug-related hospitalizations in multimorbid patients admitted to an internal medicine ward. PLoS One. 2019 Jul 22;14(7):e0220071; https://doi.org/10.1371/journal.pone.0220071.

9. Nymoen LD, Björk M, Flatebø TE, et al. Drug-related emergency department visits: prevalence and risk factors. Intern Emerg Med. 2022; https://doi.org/10.1007/s11739-022-02935-9.

10. Christensen M, Lundh A. Medication review in hospitalised patients to reduce morbidity and mortality. Cochrane Database Syst Rev. 2016;CD008986; https://doi.org/10.1002/14651858.CD008986.pub3.

11. Kempen TGH, Bertilsson M, Hadziosmanovic N, et al. Effects of Hospital-Based Comprehensive Medication Reviews Including Postdischarge Follow-up on Older Patients' Use of Health Care: A Cluster Randomized Clinical Trial. JAMA Netw Open. 2021 Apr 30;4(4):e216303–e216303; https://doi.org/10.1001/jamanetworkopen.2021.6303.

12. Kempen TGH, Bertilsson M, Lindner K-J, et al. Medication Reviews Bridging Healthcare (MedBridge): Study protocol for a pragmatic cluster-randomised crossover trial. Contemp Clin Trials. 2017 Oct;61:126–32; https://doi.org/10.1016/j.cct.2017.07.019.

13. Kempen TGH, Hedström M, Olsson H, et al. Assessment tool for hospital admissions related to medications: development and validation in older patients. Int J Clin Pharm. 2019;41(1); https://doi.org/10.1007/s11096-018-0768-8.

14. Howard RL, Avery AJ, Howard PD, et al. Investigation into the reasons for preventable drug related admissions to a medical admissions unit: observational study. Qual Saf Heal Care. 2003 Aug;12(4):280–5; https://doi.org/10.1136/qhc.12.4.280.

15. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. Am J Hosp Pharm. 1990 Mar;47(3):533–43.

8

16. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018;69(2):406–60; https://doi.org/10.1016/j.jhep.2018.03.024.

17. Weersink RA, Burger DM, Hayward KL, et al. Safe use of medication in patients with cirrhosis: pharmacokinetic and pharmacodynamic considerations. Expert Opin Drug Metab Toxicol. 2020 Jan 2;16(1):45–57; https://doi.org/10.1080/17425255.2020.1702022.

18. Alassaad A, Melhus H, Hammarlund-Udenaes M, et al. A tool for prediction of risk of rehospitalisation and mortality in the hospitalised elderly: secondary analysis of clinical trial data. BMJ Open. 2015 Feb 1;5(2):e007259; https://doi.org/10.1136/bmjopen-2014-007259.

19. Leendertse AJ, Egberts ACG, Stoker LJ, et al. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med. 2008 Sep;168(17):1890–6; https://doi.org/10.1001/archinternmed.2008.3.

20. Wimmer BC, Dent E, Bell JS, et al. Medication Regimen Complexity and Unplanned Hospital Readmissions in Older People. Ann Pharmacother. 2014 May 27;48(9):1120–8; https://doi.org/10.1177/1060028014537469.

21. Tsuyuki RT, McKelvie RS, Arnold JMO, et al. Acute Precipitants of Congestive Heart Failure Exacerbations. Arch Intern Med. 2001 Oct 22;161(19):2337–42; https://doi.org/10.1001/archinte.161.19.2337.

22. Goyal P, Kneifati-Hayek J, Archambault A, et al. Prescribing Patterns of Heart Failure-Exacerbating Medications Following a Heart Failure Hospitalization. JACC Hear Fail. 2020;8(1):25–34; https://doi.org/10.1016/j.jchf.2019.08.007.

23. Katzenberg G, Deacon A, Aigbirior J, et al. Management of chronic obstructive pulmonary disease. Br J Hosp Med. 2021 Jul 2;82(7):1–10; https://doi.org/10.12968/hmed.2020.0561.

24. Molimard M, Raherison C, Lignot S, et al. Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients. Eur Respir J. 2017 Feb 1;49(2):1601794; https://doi.org/10.1183/13993003.01794-2016.

25. Klatte DCF, Gasparini A, Xu H, et al. Association Between Proton Pump Inhibitor Use and Risk of Progression of Chronic Kidney Disease. Gastroenterology. 2017;153(3):702–10; https://doi.org/10.1053/j.gastro.2017.05.046.

26. Brusselaers N, Wahlin K, Engstrand L, et al. Maintenance therapy with proton pump inhibitors and risk of gastric cancer: a nationwide population-based cohort study in Sweden. BMJ Open. 2017 Oct 1;7(10):e017739; https://doi.org/10.1136/bmjopen-2017-017739.

27. Brusselaers N, Engstrand L, Lagergren J. Maintenance proton pump inhibition therapy and risk of oesophageal cancer. Cancer Epidemiol. 2018;53:172–7; https://doi.org/10.1016/j.canep.2018.02.004.

28. Verhestraeten C, Heggermont WA, Maris M. Clinical inertia in the treatment of heart failure: a major issue to tackle. Heart Fail Rev. 2021;26(6):1359–70; https://doi.org/10.1007/s10741-020-09979-z.

29. Cooke CE, Sidel M, Belletti DA, et al. Review: clinical inertia in the management of chronic obstructive pulmonary disease. COPD. 2012 Feb;9(1):73–80; https://doi.org/10.3109/15412555.2011.631957.

30. Kempen TGH, Cam H, Kälvemark A, et al. Intervention fidelity and process outcomes of medication reviews including post-discharge follow-up in older hospitalized patients: process evaluation of the MedBridge trial. J Clin Pharm Ther. 2020 Mar 14; https://doi.org/10.1111/jcpt.13128.

Tables

Table 1. Total study population baseline (index admission) characteristics.

Variable group	Baseline (index admission) variable[a]	Trial population (n=2,637)
Sociodemographics	Age, median, years (IQR)	81 (74–87)
	Sex, female	1,355 (51%)
	Home care	679 (26%)
	Residential home	322 (12%)
Unplanned visits within 12 months prior to admission	ED visits (1 or more)	895 (34%)
	Hospital admissions (1 or more)	1,015 (39%)
Medical history	Diagnosis in medical history:[b]	1,826 (69%) 747 (28%) 725 (28%)
	Hypertension	721 (27%) 362 (14%) 244 (9.3%)
	Diabetes mellitus	37 (1.4%) 16 (0.6%)
	Atrial fibrillation and flutter	
	Heart failure	
	COPD	
	Dementia	
	Peptic ulcer disease	
	Liver disease	
	Charlson Comorbidity Index score, median (IQR)	1 (0–3)
Medication use	Automated drug dispensing in home setting	678 (26%)
	Number of medications upon admission: 0–4	500 (19%) 976 (37%) 1,161 (44%)
	5–9	
	10+	
eGFR upon admission (mL/min/1.73 m^2)[c]	< 15	112 (4.2%) 365 (14%) 1,111 (42%)
	15–29	963 (37%) 77 (2.9%)
	30–59	
	60–89	
	?90	
Length of hospital stay, median, days (IQR)	Length of hospital stay, median, days (IQR)	8 (5–14)

Variable group	Baseline (index admission) variable[a]	Trial population (n=2,637)
Discharge diagnosis	Discharge diagnosis at index admission:[b] Diseases in the cerebrovascular system Respiratory tract infections Heart failure Urinary tract infections Other infections and parasite diseases Injuries, intoxications and certain other complications of external factors Chronic diseases of the lower respiratory tract Atrial fibrillation and flutter Diabetes mellitus Ischaemic heart diseases	385 (15%) 257 (9.7%) 213 (8.1%) 149 (5.7%) 138 (5.2%) 124 (4.7%) 85 (3.2%) 72 (2.7%) 67 (2.5%) 53 (2.0%)

Abbreviations: COPD, chronic obstructive pulmonary disease; ED, emergency department; eGFR, estimated glomerular filtration rate; IQR, interquartile range.[a] Unless otherwise indicated, data are numbers (%) of patients.[b] Five most prevalent diagnoses plus those present in final Cox proportional hazards model (Figure 1).[c] Patients with missing eGFR values (n=9) were excluded from this calculation.

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 (%)	Number of
	Readmissions	ED visits
Heart failure	20 (29)	4 (24)
COPD	10 (15)	3 (18)
Atrial fibrillation	7 (10)	
Gastrointestinal bleeding or ulcer	6 (9)	1 (6)
Ischaemic heart disease	4 (6)	2 (12)
CVA or TIA	5 (7)	
Respiratory infections	4 (6)	1 (6)
Diabetes mellitus type 2	3 (4)	
Depression	2 (3)	1 (6)
Epilepsy	2 (3)	
Other (< 2 cases per disease)	5 (7)	5 (29)
Total	68	17

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 Supportin
Inadequate treatment (lack of treatment, undertreatment, too low dose)
Insufficient or no follow-up (or monitoring)
Non-compliance (intentional and non-intentional)
Lack of investigation or diagnostics
Inappropriate treatment (wrong or unnecessary treatment)
Total (%)

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	Results of preventability assessment: Readmission or ED visit ICD-10 diagnosis Main cause (other causes) Origin Could have been prevented by MR (explanation)?
1	87-year-old man 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 two 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) Hospital Yes (ward pharmacist cautioned about a relatively large number of pharmacotherapeutic changes during hospital stay, but no clear action/follow-up was proposed)

13

No.	Case description of potentially preventable drug-related revisit	Results of preventability assessment: Readmission or ED visit ICD-10 diagnosis Main cause (other causes) Origin Could have been prevented by MR (explanation)?
2	75-year-old woman 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 upon discharge. Previous treatment with carvedilol (non-selective 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 Non-compliance (inappropriate treatment) 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)

14

No.	Case description of potentially preventable drug-related revisit	Results of preventability assessment: Readmission or ED visit ICD-10 diagnosis Main cause (other causes) Origin Could have been prevented by MR (explanation)?
3	88-year-old woman with a.o.t. diastolic heart failure and chronic 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 two weeks, hospital readmission due to dyspnoea and tachycardia (heart rate 130–160 beats/minute) 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, inappropriate treatment) Hospital Not applicable (no MR, control group)

15

No.	Case description of potentially preventable drug-related revisit	Results of preventability assessment: Readmission or ED visit ICD-10 diagnosis Main cause (other causes) Origin Could have been prevented by MR (explanation)?
4	69-year-old man 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 stabilised, followed by close monitoring of haemoglobin. Two 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.	Readmission K922 Gastrointestinal haemorrhage Non-compliance (insufficient or no follow-up) Hospital Not applicable (no MR, control group)

No.	Case description of potentially preventable drug-related revisit	Results of preventability assessment: Readmission or ED visit ICD-10 diagnosis Main cause (other causes) Origin Could have been prevented by MR (explanation)?
5	69-year-old man 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 lab 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 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.

Figure legends

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. Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ED, emergency department; resp., respiratory.

Figure 2. Flowchart of hospital revisits assessed for preventability. Abbreviations: DRR, drug-related admission; ED, emergency department; prev., preventable; MR, medication review.

Supporting information files

Supporting Information S1: Methods for the assessment of preventability of drug-related revisits.

Supporting Information S2: Baseline characteristics for risk factor analysis and preventability assessment.

Supporting Information S3: Risk factors and protecting factors associated with experiencing an unplanned hospital revisit (all causes) within 12 months.