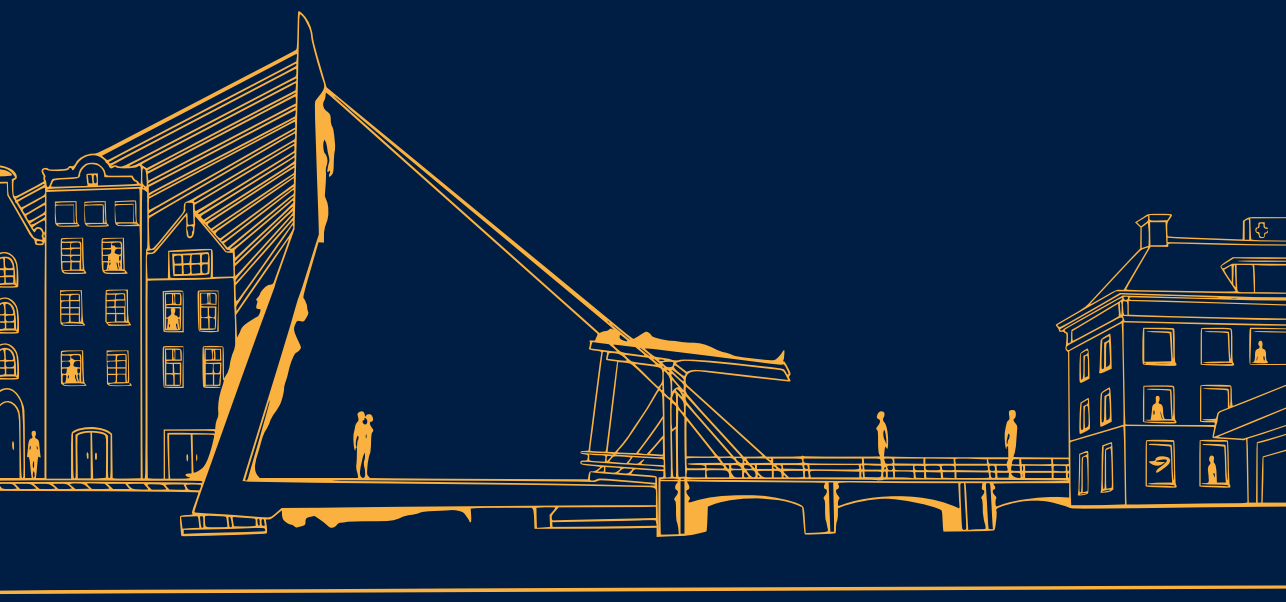
Bridging the gaps in transitional pharmaceutical care



Elien Uitvlugt

Bridging the gaps in transitional pharmaceutical care

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1

General Introduction

GENERAL INTRODUCTION

Medication-related harm after discharge

Today's healthcare system is a combination of processes, technologies and human interactions that bring significant benefits to patients (1). However, the complexity of this system also introduces the risk of iatrogenic patient harm. Iatrogenic harm (or adverse events) is defined as "harm due to unanticipated, unforeseen accidents which are a direct result of the care provided rather than the patient's underlying disease" (2). Certain processes of the complex healthcare system carry an especially high risk, such as all transitions in care. Prior studies have shown that suboptimal communication between inpatient and outpatient providers is common and can result in discontinuity of care and adverse events (3).

As medication is the most common therapeutic intervention, adverse events with medication frequently occur. This is shown in the systematic review by Parekh et al.: 17–51% of the older adults experience Adverse Drug Events (ADEs) within 30 days after discharge (4). ADEs are any injuries resulting from medication use, including physical harm, mental harm or loss of function (5). Adverse events that occur during or after hospital admission may result in unplanned readmissions (6). Several demographic factors, individual characteristics, comorbidities, and social and medical factors are associated with hospital readmissions, including polypharmacy (7-13).

There is a considerable methodological heterogeneity among studies investigating ADEs and readmissions due to ADEs, including the definition of ADEs, the methods of and sources for identification of ADEs, population characteristics, length of follow-up after discharge (10, 14-18). Therefore, a clear understanding of the epidemiology of ADEs after discharge and readmissions due to ADEs is lacking.

Causes of medication-related harm after discharge

Several circumstances may explain why ADEs frequently occur after discharge. First, the communication of medication-related information at discharge is often suboptimal. Medication-related information is not clearly documented and is not always exchanged. Today, pharmacists in the Netherlands are still using the fax machine to transfer medication-related information. Electronic exchange between healthcare settings is a challenge due to a lack of uniformity in language and technique together with a lack of an integrated approach to exchange data. This hampers the complete transfer of medication-related information after hospital discharge, leading to medication discrepancies, i.e. differences between the patient's actual medication use versus the medication listed in the medical patient record (3, 19). Fifty percent of patients is affected by one or more unintended medication discrepancies after discharge (20). This could result in discontinuity of care and difficulties with monitoring the patient's actual medication regimen.

Second, medication regimens changed during hospitalization are not always clear to the patient (21-23). The length of hospital stay in hospitals is decreasing. This decrease is partly due to the introduction of new treatments, such as minimally invasive surgery, the streamlining of care processes via clinical care pathways and the substitution of care from secondary to primary care (24). Providing adequate education of patients on the purpose of their medication, medication changes,

reasons for changes and side effects during such a short hospital stay proves to be a challenge (21).
In addition, during the hospital stay, patients have little control over their medication as it is administered by the nurse. This may result in the patient, for example, inadvertently using the pre-hospital medication regimen after discharge.
Third, the follow-up of the patient after discharge may be inadequate. The period immediately after discharge could be a stressful period for patients as they have to recover mentally and physically from the hospital admission, further increasing the risk of ADEs. A study performed in the UK showed that of the ADEs experienced within eight weeks after hospital discharge, 74% were attributable to medicines prescribed in the hospital setting and 28% due to medicines prescribed in the community after discharge (17). It is not always fully clear who is responsible for the follow-up of the patient and what needs to be monitored, but follow-up of patients is vital in order to recognize those ADEs (25-27).

Interventions to reduce medication-related harm after discharge

The urgency to improve medication safety at transitions of care is recognized worldwide. In 2017, the World Health Organization (WHO) launched its third Global Patient Safety Challenge: Medication Without Harm, with the goal to reduce severe, avoidable medication-related harm globally by 50% over the next five years (28) and medication safety at transitions of care is one of the three areas that has been prioritized for action (1).
In the Netherlands, initiatives have also been started to improve the medication safety at transitions of care (29-31). An electronic Nationwide Medication Record System (NMRS) has been available since 2011 in the Netherlands. The NMRS exchanges medication dispensing data from all pharmacies in the Netherlands, provided that the patient consents to exchanging information. The system is accessible 24-hour a day for physicians and pharmacists. The NMRS is used as a source for medication reconciliation, which is defined as the process of creating the most complete list of a patient's current medication (32). It includes: verification (comparing in-hospital prescribed medication with the medication used before admission); clarification (checking pharmacotherapy for appropriateness); reconciliation (documenting and discussing medication changes with the patient); and transmission (communicating the medication overview to the next healthcare provider). The transmission is essential to ensure that next healthcare providers have up-to-date information to continue the care.
In addition, other interventions are developed to ensure continuity and optimization of pharmacotherapy, including medication review (33) defined by the Pharmaceutical Care Network Europe (PCNE) as "a structured evaluation of a patient's medicines with the aim of optimising medicines use and improving health outcomes. This entails detecting medication-related problems and recommending interventions" (34). Other interventions include techniques to improve patient knowledge, such as the use of lay language, asking patients what they want to know regarding their medicines, providing written information, repeating information or using the "teach-back" method. Teach-back is a strategy in which patients are asked to restate information that has been presented to them (35). In addition, home-visits have been suggested to be useful, because performing medication-related interventions in the home setting may facilitate identification of ADEs that occur after hospital discharge,

and this may be a more suitable environment in which to provide medication advice and education (36).
Conflicting evidence exists on the effect of the interventions mentioned above. Studies have shown that medication reconciliation may reduce the number of medication discrepancies during transitions between different healthcare settings (37). However, the effect on clinically relevant outcomes (e.g., emergency department visits and readmission to hospital) is uncertain. Medication reviews may reduce emergency department visits, although no evidence exists that a medication review reduces mortality or hospital readmissions (38). The recent systematic review by Abbot et al. found no effect of a clinical pharmacist home visit on hospital admissions and mortality and consistent evidence of an effect on quality of life, medication adherence or knowledge was lacking (36). One potential explanation why no or little effect is found of the interventions described above may lie in the fact that those interventions are implemented most often as single component interventions in one setting, e.g. in- or out-of-hospital (39). Studies on transitional care interventions that support medication continuity show that interventions need to include both the hospital and primary care setting, so-called "bridging" and must involve multiple components (e.g. selfmanagement, telephone follow-up and medication reconciliation activities) to be effective (40, 41). Studies exploring the effect of multicomponent bridging transitional care interventions on ADEs post-discharge are rare (12, 42, 43). One study showed that medication-related multicomponent bridging care interventions reduce overall hospital readmission rates within 30 days of hospital discharge (39). This reduction is probably due to a reduction in ADEs, as medication-related interventions will especially affect ADEs. Further studies are necessary in order to explore the effect of these complex interventions.

OBJECTIVES OF THIS THESIS

The main objectives of this thesis are to study the prevalence and preventability of medication-related readmissions, to evaluate the transfer of medication-related information between secondary and primary care and to develop and explore a transitional care program to reduce medication-related harm after discharge.

OUTLINE

Part 1

The first part focuses on medication-related readmissions within 30 days after discharge. In *Chapter 2* the literature on the prevalence and preventability of medication-related readmissions is summarized. In *Chapter 3* an observational study is presented that aimed to determine the prevalence and preventability of medication-related readmissions in multiple departments in the Netherlands, and to identify risk factors, causes and types of medication involved in these preventable readmissions.
In *Chapter 4*, the patients' perspectives on the medication-relatedness and potential preventability of their readmissions are described and are compared with providers'

perspectives. Consensus between patients and providers with respect to the role of medication as a potential cause of readmissions is necessary to achieve optimal pharmacotherapy.

Part 2

In the second part of this thesis, the transfer of medication-related information between secondary and primary care is evaluated. In *Chapter 5* the adherence to a guideline for medication-related information in discharge letters is evaluated. As it is important to ensure a complete transfer of medication-related information in the healthcare continuum, the completeness of this information in both discharge letters and general practitioner overviews is determined in *Chapter 6*.

In the Netherlands, a Nationwide Medication Record System (NMRS) based on pharmacy dispensing data is used to obtain information on the patient's actual medication use. In *Chapter 7* the results of a study on the validity of medication dispensing records collected from the NMRS are reported.

Part 3

Finally, in part 3 (*Chapter 8*) the effect of a transitional care program, performed by both primary and secondary healthcare providers, on ADEs after discharge is explored.

In *Chapter 9* the results of the different studies are discussed in a broader context and recommendations for future research and for improving the medication-related care after discharge are provided. In *Chapter 10* a summary of this thesis is given.

REFERENCES

1. Medication Safety in Transitions of care. Technical Report. World Health Organisation 2019. https://apps.who.int/iris/bitstream/handle/10665/325453/WHO-UHC-SDS-2019.9-eng.pdf?ua=1. Accessed 10 december 2020.
2. Panagioti M, Khan K, Keers RN, Abuzour A, Phipps D, Kontopantelis E, et al. Prevalence, severity, and nature of preventable patient harm across medical care settings: systematic review and meta-analysis. BMJ. 2019;366:l4185.
3. Kripalani S, LeFevre F, Phillips CO, Williams MV, Basaviah P, Baker DW. Deficits in communication and information transfer between hospital-based and primary care physicians: implications for patient safety and continuity of care. JAMA. 2007;297(8):831-41.
4. Parekh N, Ali K, Page A, Roper T, Rajkumar C. Incidence of medication-related harm in older adults after hospital discharge: a systematic review. J Am Geriatr Soc. 2018;66(9):1812-22.
5. Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, et al. Incidence of adverse drug events and potential adverse drug events: implications for prevention. JAMA. 1995;274(1):29-34.
6. Basisset Medisch Specialistische Zorg. https://www.igj.nl/documenten/indicatorensets/2017/01/01/basisset-medisch-specialistische-zorg. Accessed 10 april 2020.
7. Ahmad A, Mast MR, Nijpels G, Elders PJ, Dekker JM, Hugtenburg JG. Identification of drug-related problems of elderly patients discharged from hospital. Patient Prefer Adherence. 2014;8:155.
8. Al Hamid A, Ghaleb M, Aljadhey H, Aslanpour Z. A systematic review of hospitalization resulting from medicine-related problems in adult patients. Br J Clin Pharmacol. 2014;78(2):202-17.
9. Calvillo–King L, Arnold D, Eubank KJ, Lo M, Yunyongying P, Stieglitz H, et al. Impact of social factors on risk of readmission or mortality in pneumonia and heart failure: systematic review. J Gen Intern Med.2013;28(2):269-82.
10. Garcia-Caballos M, Ramos-Diaz F, Jimenez-Moleon JJ, Bueno-Cavanillas A. Drug-related problems in older people after hospital discharge and interventions to reduce them. Age ageing. 2010;39(4):430-8.
11. García-Pérez L, Linertová R, Lorenzo-Riera A, Vázquez-Díaz J, Duque-González B, Sarría-Santamera A. Risk factors for hospital readmissions in elderly patients: a systematic review. QJM. 2011;104(8):639-51.
12. Kripalani S, Roumie CL, Dalal AK, Cawthon C, Businger A, Eden SK, et al. Effect of a pharmacist intervention on clinically important medication errors after hospital discharge: a randomized trial. Ann Intern Med. 2012;157(1):1-10.
13. Yam C, Wong E, Chan F, Wong F, Leung M, Yeoh E. Measuring and preventing potentially avoidable hospital readmissions: a review of the literature. Hong Kong Med J. 2010;16(5):383-9.
14. Frankl SE, Breeling JL, Goldman L. Preventability of emergent hospital readmission. Am J Med. 1991;90(6):667-74.
15. Davies EC, Green CF, Mottram DR, Rowe PH, Pirmohamed M. Emergency re-admissions to hospital due to adverse drug reactions within 1 year of the index admission. Br J Clin Pharmacol. 2010;70(5):749-55.
16. Bero LA, Lipton HL, Bird JA. Characterization of geriatric drug-related hospital readmissions. Med. Care. 1991:989-1003.
17. Parekh N, Ali K, Stevenson JM, Davies JG, Schiff R, Van der Cammen T, et al. Incidence and cost of medication harm in older adults following hospital discharge: a multicentre prospective study in the UK. Br J Clin Pharmacol. 2018;84(8):1789-97.
18. Ruiz B, García M, Aguirre U, Aguirre C. Factors predicting hospital readmissions related to adverse drug reactions. Eur J Clin Pharmacol. 2008;64(7):715-22.
19. Kattel S, Manning DM, Erwin PJ, Wood H, Kashiwagi DT, Murad MH. Information transfer at hospital discharge: a systematic review. J Patient Saf. 2020;16(1):e25-e33.
20. Alqenae FA, Steinke D, Keers RN. Prevalence and Nature of Medication Errors and Medication-Related Harm Following Discharge from Hospital to Community Settings: A Systematic Review. Drug Saf. 2020:1-21.
21. Eibergen L, Janssen MJA, Blom L, Karapinar-Carkit F. Informational needs and recall of

in-hospital medication changes of recently discharged patients. Res Social Adm Pharm. 2018;14(2):146-52.

22. Grimmsmann T, Schwabe U, Himmel W. The influence of hospitalisation on drug prescription in primary care–a large-scale follow-up study. Eur J Clin Pharmacol. 2007;63(8):783-90.

23. Knight DA, Thompson D, Mathie E, Dickinson A. 'Seamless care? Just a list would have helped!' Older people and their carer's experiences of support with medication on discharge home from hospital. Health Expect. 2013;16(3):277-91.

24. Cijfers en context Ziekenhuis zorg. https://www.volksgezondheidenzorg.info/onderwerp/ziekenhuiszorg/cijfers-context/trend-gebruik#node-trend-ligduur. Accessed 25 oktober 2020.

25. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. The incidence and severity of adverse events affecting patients after discharge from the hospital. Ann Intern Med. 2003;138(3):161-7.

26. Fylan B, Armitage G, Naylor D, Blenkinsopp A. A qualitative study of patient involvement in medicines management after hospital discharge: an under-recognised source of systems resilience. BMJ Qual Saf. 2018;27(7):539-46.

27. Fylan B, Marques I, Ismail H, Breen L, Gardner P, Armitage G, et al. Gaps, traps, bridges and props: a mixed-methods study of resilience in the medicines management system for patients with heart failure at hospital discharge. BMJ open. 2019;9(2):bmjopen-2018-023440.

28. World Health Organization. Action on Patient Safety – High 5s. https://www.who.int/patientsafety/topics/high-5s/en/. Accessed 10 april 2020.

29. Wetsvoorstel Elektronische gegevensuitwisseling in de zorg. https://www.rijksoverheid.nl/actueel/nieuws/2020/03/10/internetconsulatie-van-start-voor-het-wetsvoorstel-elektronische-gegevensuitwisseling-in-de-zorg. Accessed 26 oktober 2020.

30. Kwaliteitsstandaard Overdracht van medicatiegegevens in de keten. https://www.zorginzicht.nl/binaries/content/assets/zorginzicht/kwaliteitsinstrumenten/Kwaliteitsstandaard+Overdracht+van+medicatiegegevens+in+de+keten.pdf. Accessed 26 oktober 2020.

31. Informatiestandaarden Medicatieproces. https://www.nictiz.nl/standaardisatie/informatiestandaarden/medicatieproces. Accessed 26 oktober 2020.

32. Karapinar-Çarkit F, Borgsteede SD, Zoer J, Egberts TC, van den Bemt PM, Tulder Mv. Effect of medication reconciliation on medication costs after hospital discharge in relation to hospital pharmacy labor costs. Ann Pharmacother. 2012;46(3):329-38.

33. Bach QN, Peasah SK, Barber E. Review of the Role of the Pharmacist in Reducing Hospital Readmissions. J Pharm Pract. 2019;32(6):617-24.

34. Griese-Mammen N, Hersberger KE, Messerli M, Leikola S, Horvat N, van Mil JF, et al. PCNE definition of medication review: reaching agreement. Int J Clin Pharm. 2018;40(5):1199-208.

35. Schillinger D, Piette J, Grumbach K, Wang F, Wilson C, Daher C, et al. Closing the loop: physician communication with diabetic patients who have low health literacy. Arch Intern Med. 2003;163(1):83-90.

36. Abbott RA, Moore DA, Rogers M, Bethel A, Stein K, Coon JT. Effectiveness of pharmacist home visits for individuals at risk of medication-related problems: a systematic review and meta-analysis of randomised controlled trials. BMC Health Serv Res. 2020;20(1):39.

37. Redmond P, Grimes TC, McDonnell R, Boland F, Hughes C, Fahey T. Impact of medication reconciliation for improving transitions of care. Cochrane Database of Systematic Reviews. 2018(8).

38. Christensen M, Lundh A. Medication review in hospitalised patients to reduce morbidity and mortality. Cochrane database of Systematic Reviews. 2016(2).

39. Daliri S, Boujarfi S, el Mokaddam A, op Reimer WJS, ter Riet G, den Haan C, et al. Medication-related interventions delivered both in hospital and following discharge: a systematic review and meta-analysis. BMJ Qual Saf. 2020;30(2):146-56.

40. Hansen LO, Young RS, Hinami K, Leung A, Williams MV. Interventions to reduce 30-day rehospitalization: a systematic review. Ann Intern Med. 2011;155(8):520-8.

41. Tomlinson J, Cheong V-L, Fylan B, Silcock J, Smith H, Karban K, et al. Successful care transitions for older people: a systematic

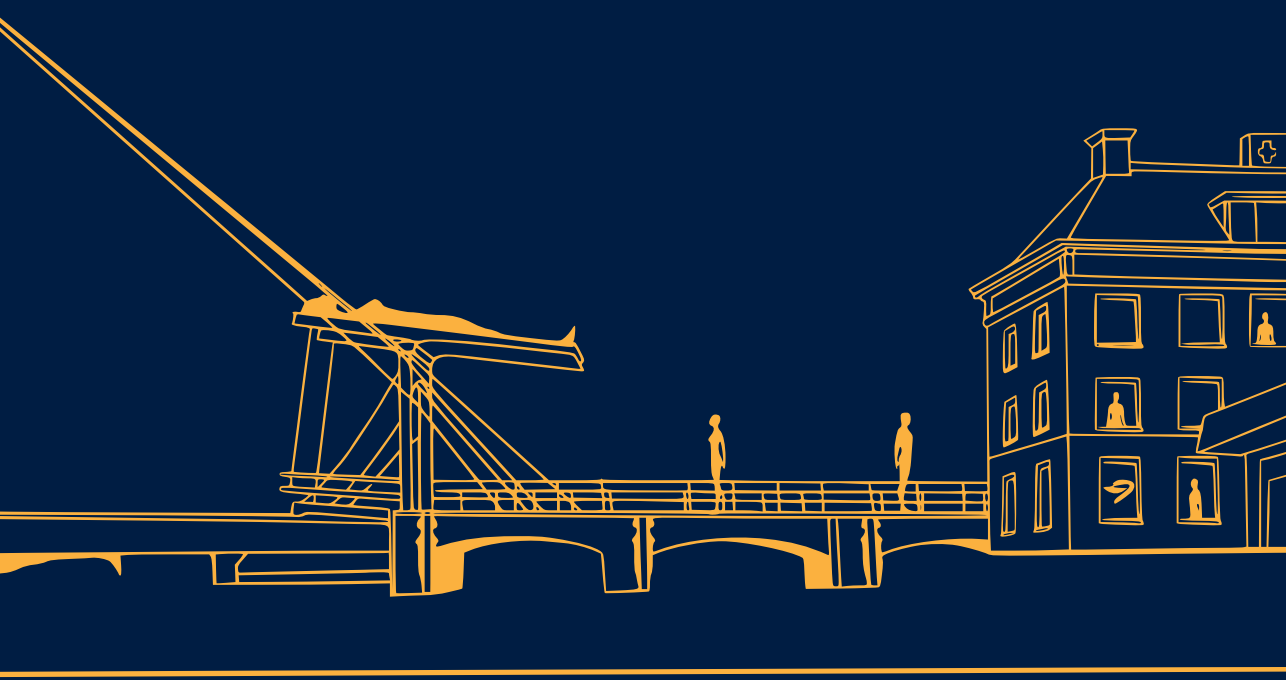
review and meta-analysis of the effects of interventions that support medication continuity. Age Ageing. 2020;49(4):558-69.

42. Daliri S, Hugtenburg JG, ter Riet G, van den Bemt BJ, Buurman BM, op Reimer WJS, et al. The effect of a pharmacy-led transitional care program on medication-related problems post-discharge: A before—After prospective study. PloS one. 2019;14(3).

43. Phatak A, Prusi R, Ward B, Hansen LO, Williams MV, Vetter E, et al. Impact of pharmacist involvement in the transitional care of high-risk patients through medication reconciliation, medication education, and postdischarge call-backs (IPITCH Study). J Hosp Med. 2016;11(1):39-44.

Part 1

Medication-related hospital readmissions



2

Prevalence and Preventability of Drug-Related Hospital Readmissions: A Systematic Review

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J Am Geriatr Soc. 2018 Mar;66(3):602-608

ABSTRACT

Objectives
To summarize the evidence on the prevalence and preventability of drug-related hospital readmissions.

Design
A systematic review was performed of studies that examined drug-related hospital readmissions. PubMed, EMBASE, and the Cochrane Library were searched from inception through August 2016. Reference lists and a citation analysis on Web of Science and Scopus were also consulted. Two reviewers extracted study data with dual assessment of risk of bias. Prevalence and preventability of readmission due to drugs were calculated. Data were qualitatively summarized according to outcome.

Results
Nineteen studies met the eligibility criteria. Nine measured readmissions due to drug-related problems, seven due to adverse drug reactions, two due to adverse drug events, and one due to drug-drug interactions. Rates of readmissions due to drugs varied from 3% to 64% (median 21%, interquartile range (IQR) 14–23%). Readmissions were deemed preventable in 5% to 87% of cases (median 69%, IQR 19–84%). Evidence regarding the risk factors for drug-related readmissions and drugs causing these readmissions was inconsistent.

Conclusion
Although studies show high variability in prevalence and preventability of drug-related hospital readmissions, readmissions due to drugs seem to occur often, especially in older adults. Further research is needed to specify the causes of preventable readmissions and implement effective interventions to reduce medication-related hospital admissions.

INTRODUCTION

Hospital readmissions pose a major burden for individuals and healthcare systems. Approximately 20% of Medicare beneficiaries experience a planned or unplanned hospital readmission within 30 days after discharge, and unplanned readmissions have an estimated annual cost of $17 billion in the United States (1, 2). The fact that hospital readmissions are increasingly used as a measure of healthcare quality emphasizes the effect of readmissions on outcomes and health expenditures (3, 4). This has led to several initiatives such as the Hospital Readmission Reduction Program, which was implemented in 2012 in the United States. This program includes payment penalties for hospitals with excessive readmissions for specific diagnoses such as heart failure and pneumonia. It is expected that the diagnosis list will continue to expand (5). Similar developments are seen in European hospitals (6).

There is broad discussion about the preventability of readmissions (7-9). A systematic review from 2011 estimated that 5% to 79% of hospital readmissions were preventable (median 27%) (10). Consequently, much research has been performed regarding the characteristics of these preventable readmissions to identify individuals at high risk of readmission and develop preventive measures. Several demographic factors, individual characteristics, comorbidities, and social and medical factors are associated with hospital readmissions (11-15), and polypharmacy is a frequently cited risk factor. Polypharmacy heightens the risk of drug-related problems (16-20). One review indicates that 18% to 38% of individuals report drug-related problems after hospital discharge (18), although the overall prevalence and preventability of drug-related readmission is unclear. Studies reported that 4.5 to 24% of hospital readmissions are drug-related; a limited number of studies have assessed the preventability of these readmissions (21-24). Because older age contributes to greater drug usage, it is reasonable to hypothesize that drug-related readmissions will occur especially in older adults, but insight into patterns of drug-related hospital readmissions and risk factors are needed to implement interventions that address problems in pharmacotherapy. Therefore, the aim of this study was to systematically review the evidence on the prevalence and preventability of drug-related hospital readmissions.

METHODS

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (25).

Data Sources and Searches

In collaboration with a medical librarian, a systematic search was conducted using Medical Subject Headings and relevant keywords in PubMed, EMBASE, and the Cochrane Library from the inception date of each database to August 2016 (Appendix S1). The search included terms for the prevalence and preventability of drug-related readmissions. The search strategy was validated by evaluating the extent to which the search retrieved previously obtained references. Additional literature was obtained by

hand-searching the reference lists of included studies and through a cited reference search performed on Web of Science and Scopus.

Definitions

An index admission is defined as a first hospital admission (26), and readmissions are admissions occurring within a specified period after the index admission (27). Drug-related hospital readmissions are defined as readmissions potentially due to pharmacotherapy, including readmissions due to a lack of appropriate drugs based on guidelines. Studies focus on different types of drug-related readmissions, including readmissions due to drug-related problems (DRPs), adverse drug events (ADEs), adverse drug reactions (ADRs), and medication errors (MEs). A summary of the definitions is provided in Figure 1.

Study Selection

Two reviewers (EU, NM) independently reviewed titles and abstracts for eligibility. Studies were included if they were published in English or Dutch and examined drug-related hospital readmissions in adults (aged ≥18). The authors of studies not published in English were contacted to explore whether an English version was available.

Studies were excluded if any of the following criteria applied: the readmission outcome could not be derived from the results after consulting the authors (e.g., reporting total readmission rate and mortality as one outcome), the method for identifying drug-related readmissions was unclear (e.g., drug-related readmissions were mentioned somewhere in the text without any specification of the detection method), the study focused on drug abuse or intentional drug overdose, the study focused on a specific drug group (e.g., readmissions due to statins only), or the study concerned a non-peer-reviewed article (e.g., abstracts, posters, presentations).

Full-text articles were obtained for studies that the two reviewers identified as potentially eligible and independently assessed for inclusion, and disagreements were resolved by consensus or a third reviewer (FK).

Data Extraction and Quality Assessment

A data extraction form was developed, tested, and refined. Two reviewers (NM and EU or MJ) extracted study data. Disagreements were resolved by consensus or a third reviewer (FK). Extracted data included study characteristics (e.g., study design, setting, study period), personal characteristics, definitions for drug-related readmissions, the applied methods to detect the drug related readmissions (e.g. interview with patient, database) and assess causality and preventability (e.g., Naranjo criteria, Schumock and Thornton) and the professionals that conducted the assessment and outcomes (e.g. medical specialist, pharmacist, nurse). Authors were contacted when further information was required or if information in the study was unclear. The Strengthening the Reporting of Observational Studies in Epidemiology statement checklist was used to assess the quality of the studies (28). The number of reviewers and information sources used for the identification of drug-related readmissions were also assessed. It was expected that having move reviewers and sources would increase the identification of drug-related readmissions. Finally, the data extractors specified whether clear definitions of outcomes were presented in the studies (how the causal association between the drug and the readmission and

the preventability of the readmission were assessed)

	Definition	Examples
DRP	Drug-related problem: an event or circumstance involving drug therapy that actually or potentially interferes with the desired health outcomes(29).	A patient with an adverse drug event, adverse drug reaction or medication error. See examples below.
ADE	Adverse drug event: any injuries resulting from medication use, including physical harm, mental harm, or loss of function. ADEs can result from adverse drug reactions (non-preventable) or medication errors (preventable)(30).	An allergic reaction in a patient with a penicillin allergy receiving amoxicillin (non-preventable if previously unknown), an allergic reaction in a patient with a known allergy receiving amoxicillin (preventable), a gastric bleeding in a patient with an NSAID an gastric ulcer in the history (preventable).
ADR	Adverse drug reaction: a response which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function(31).	Antibiotic-induced diarrhea, cough due to an ACE inhibitor.
ME	Medication error: errors in the process of prescribing, dispensing, or administering the medications that many cause or lead to inappropriate medication use or patient harm while the medication is the control of the health care professional, patient, or consumer(32, 33).	Administration of methotrexate daily instead of weekly causing patient harm (i.e. a preventable ADE). A wrong dose prescribed for a child but not causing harm either due to intercepting the error before reaching the child, or to the overdose not causing symptoms in the child (i.e. a potential ADE).

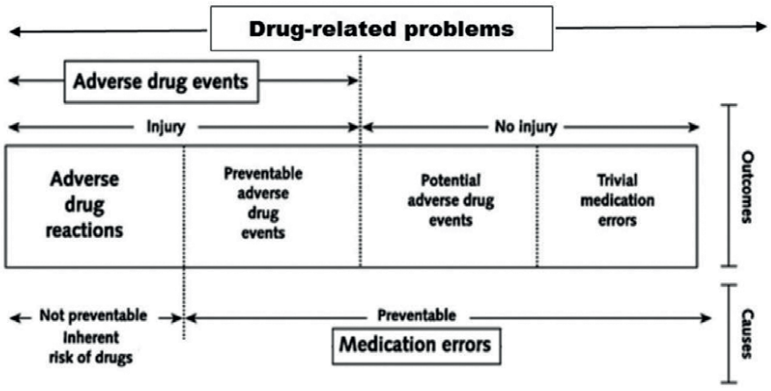

Figure 1. Association between drug-related problems, adverse drug events, adverse drug reactions, and medication errors. Adapted from Otero and Schmitt with permission(34).

Data Synthesis and Analysis

Meta-analysis was not conducted because of the substantial heterogeneity among the studies. Data were qualitatively summarized according to outcome. Articles were categorized according to the type of drug-related readmission reported (DRPs, ADEs, ADRs, MEs; Figure 1). Drugs associated with hospital readmissions were categorized according to the Anatomical Therapeutic Chemical Classification System of the World Health Organization (35).

The prevalence rates of drug-related hospital readmissions were calculated as the number of individuals with drug-related readmissions relative to the total number of individuals with readmissions. Likewise, preventability rates were calculated as the number of individuals with probable or definite preventable drug-related readmissions relative to the total number of individuals with drug-related readmissions. Prevalence and preventability rates were summarized using medians and their corresponding interquartile ranges (IQRs). Different median prevalence rates were compared according to type of drug-related readmission (DRP, ADE, ADR, ME) and study design (retrospective, prospective). In the case of intervention studies, prevalence and preventability rates were based on the control group. Because studies reported multiple risk factors, the risk factors were included in this review only if at least two studies reported them.

RESULTS

As shown in Figure 2, 1743 titles were screened and 1547 records were excluded. Of the 196 full-text articles that were screened, 19 were included. After exclusion of 175 studies, 19 were included. Good similarity was observed between the reviewers for screening (interrater agreement: $k = 0.78$). Of the 19 studies, 17 (89%) were observational, including 11 retrospective studies (21, 24, 36-44), 4 prospective studies (23, 45-47), and 2 case-control studies (22, 48). The remaining 2 studies were a randomized controlled trial (49) and a before-after study (50) (Appendix S2).

Of the 19 studies, 9 measured DRP-related readmissions (23, 24, 36, 40, 42, 45, 47, 49, 50), 7 measured ADRs (21, 22, 38, 41, 43, 44, 46), 2 measured ADEs (37, 48), and 1 measured readmissions due to drug-drug interactions (39). No study specifically examined readmissions due to MEs. The follow-up time between admission and readmission varied from 28 days to 4.2 years, but measurement of readmissions within 30 days of discharge was most common. Characteristics of the included studies are summarized in Table 1, with more-detailed descriptions provided in Appendices S2 and S3. The median age of the participant population was 76 (IQR 57–82).

The quality of reporting in studies varied; mainly, information on which departments were included and definitions for drug-related readmissions were missing. Forty-two percent of the studies did not define drug-related readmissions (Table 1). Studies mainly used 2 information sources (47%), with a maximum of 3 (21%), to detect drug-related readmissions. The most common information source was medical chart

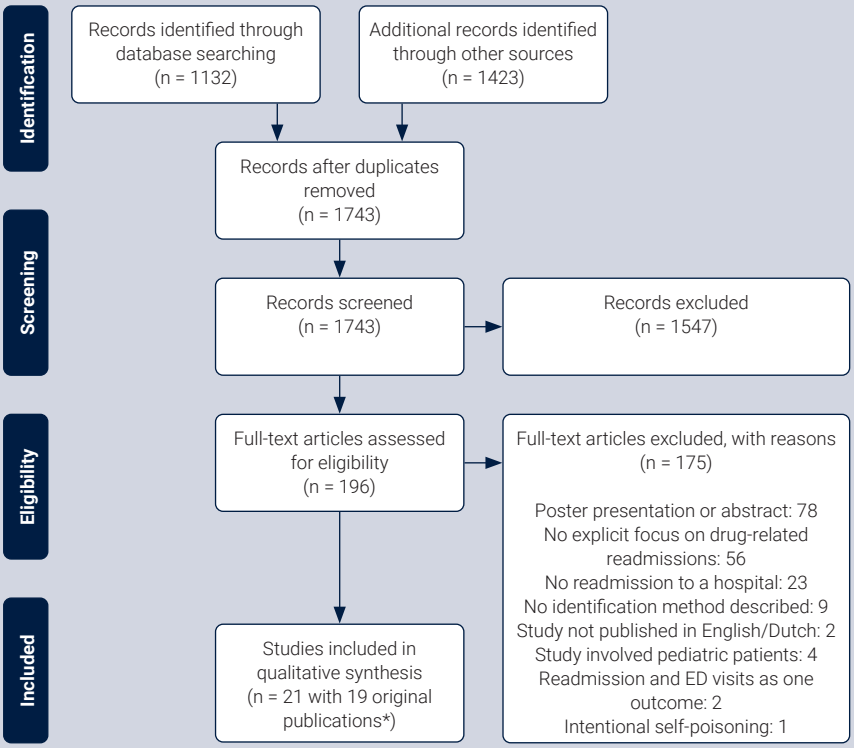

Figure 2. Flow diagram of inclusion process according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 guidelines. *There were 21 publications; one study concerned a double publication, and one study was a follow-up study to assess risk factors for medication-related readmissions.

review (84%). Studies often did not include information regarding laboratory values, participant adherence, and the individual's perspective on whether the readmission was drug-related. The assessment of readmissions mainly included medical specialists (63%) and pharmacists (53%) as reviewers. The inter-reviewer agreement was reported in 11% of the studies, and 1 study (24) described a training session for the reviewers to assess the readmissions.

Prevalence and Preventability

The prevalence of drug-related readmissions could be extracted in 12 of 19 studies that reported readmission rates at the individual level (21, 24, 37-42, 45-47, 50) (Appendix S3). Rates of readmission due to drugs varied between studies (range 3–64%, median 21%, IQR 14– 23%). Outliers did not significantly change the median and ranges. The highest prevalence rate originated from a study that interviewed patients. The studies mainly used the criteria from Naranjo and colleagues (33%) and author-defined criteria (33%) to assess causality between pharmacotherapy and readmission (Table 2).

Preventability rates were reported in 8 studies but could be extracted in 4 studies at the individual level (24, 38, 40, 42) (Appendix S3). Readmissions were deemed potentially preventable in 5% to 87% of all drug-related readmissions (median 69%, IQR 19–84%); if the outlier (study with 5%) was excluded, the median increased to 76% (IQR 61–87%). The most often used criteria to assess preventability were the Schumock and Thornton criteria (22%), Howard and colleagues criteria (22%), and author-defined criteria (22%) (Table 2). When stratifying the results according to type of drug-related readmission, a median prevalence rate of 22% (IQR 20–45%) was found for DRP-related readmissions (24, 40, 42, 45, 47, 50) with a median preventability rate of 76% (IQR 61–87%) (24, 40, 42). For ADR-related readmissions, the median prevalence rate was 20% (IQR 7–23%) (21, 38, 41, 46), and one study reported a preventability rate of 5% (38), although the literature states that ADRs are an inherent risk of drugs and therefore not preventable. An ADR can become preventable and would then be considered an ADE when it occurs for a second time (e.g., a known allergy) or when the individual's characteristics are not adequately evaluated (e.g., no dose adjustment based on poor kidney function).

For ADE-related readmissions, one study reported a prevalence of 13%, without information regarding preventability (37). One study specifically focused on readmissions due to drug-drug interactions and found a prevalence rate of 16% (39). No differences were observed for the prevalence of drug-related readmissions for studies that collected data retrospectively or prospectively, probably because of the small sample size. The prevalence did not differ at different readmission time intervals either.

Table 1. Summary of included studies

Study Description	Value
Publication year, median (IQR)	2010 (2007-2013)
Single-center studies, n (%)	13 (68%)
Studies that exclusively included university hospitals (reported for n = 14), n (%)	8 (57%)
Study population size, median (IQR)	344 (209-810)
Participants with readmissions (reported for n = 12), median (IQR)	158 (102-268)
Participant age (reported for n = 16), median (IQR)	76 (57-82)
Type of readmission	
Unplanned	10 (53%)
Not specified	5 (26%)
Unplanned and planned	4 (21%)
Definitions	
Drug-related problem (n = 9)	
Not specified	6 (67%)

Table 1. *Continued*

Study Description	Value
Author defined	2 (22%)
Adverse drug reaction (n = 7)	
World Health Organization	4 (57%)
Adverse drug event (n = 2)	
Nebeker et al.(52)	1 (50%)
Not specified	1 (50%)
Drug-drug interaction not reported (n = 1)	1 (100%)
Number of information sources used, n (%)	
1	6 (32%)
2	9 (47%)
3	4 (21%)
Information sources used, n (%)	
Medical chart review	16 (84%)
Patient adherence information	6 (32%)
Laboratory values	5 (26%)
Interview with individual or caregiver	5 (26%)
Database study	4 (21%)
Reviewers involved in the assessment, n (%)	
Medical specialist	12 (63%)
Pharmacist	9 (47%)
Not specified	3 (16%)
General practitioner	1 (5.3%)
Nurse	1 (5.3%)

All parameters reflect the total 19 included studies, unless otherwise stated.
IQR = interquartile range.

Table 2. Summary of Study Outcomes (n = 19)

Prevalence rates	
Drug-related readmissions (n = 12), median % (IQR)	21 (14-23)
Preventable drug-related readmissions (n = 4), median % (IQR)	69 (19-84)
Prevalence rates stratified on outcome measurements	
DRP-related readmissions (n = 6), median % (IQR)	22 (20-45)
Preventable DRP-related readmissions (n = 3), median % (IQR)	76 (61-87)
ADR-related readmissions (n = 4), median % (IQR)	20 (7-23)
Preventable ADR-related readmissions (n = 1), median %	5
Adverse drug event-related readmissions (n = 1), median %	13
Drug-drug interaction-related readmissions (n = 1), median %	3
Methodology of causality assessment (n = 12), n (%)	
Naranjo et al. criteria	4 (33%)
Author-defined method	4 (33%)
Howard et al. criteria	2 (17%)
World Health Organization	1 (8%)
Karch-Lassagna	1 (8%)
Methodology of preventability assessment (n = 9), n (%)	
Schumock and Thornton	2 (22%)
Howard et al. criteria	2 (22%)
Author defined method	2 (22%)
Hallas et al. criteria	1 (11%)
Oliviers scale	1 (11%)
Not reported	1 (11%)

IQR = interquartile range; DRP = drug-related problem; ADR = adverse drug reaction.

Risk Factors

Nine studies (21-23, 38, 43, 44, 47, 48, 53) identified risk factors for drug-related readmissions. Cancer and a higher Charlson Comorbidity Index score were identified as risk factors for drug-related readmissions in two studies (38, 44). Conflicting results were found for age. Three studies found that older age was a risk factor (21, 43, 47), whereas a fourth (38) found the opposite, and a fifth (48) found no association. The same was true for sex. Four studies found no association (21, 38, 43, 48), and one study reported that men were more likely to revisit a hospital for a pharmacotherapy-related problem (44).

Drug Classes

Ten studies reported on drug groups that caused hospital readmissions (21-23, 36-38, 41, 43, 49, 50). These studies showed the highest prevalence for antibiotics (21-23, 37, 38, 43, 49), diuretics (21-23, 38, 41, 49), vitamin K antagonists (21-23, 37, 38, 49) and opioids (21, 22, 36, 37, 41, 50). Antidiabetics (21, 23, 37, 38, 50), anticancer drugs (21-23, 37, 38), antihypertensives (21, 23, 36, 41, 49), digitalis glycosides (21-23, 49), corticosteroids (21, 36-38), and psychotropic drugs (36, 38, 43, 50) were also reported. Studies often failed to report the reason for readmission as drugs can have multiple side effects. Five studies (22, 23, 38, 40, 49) examined drugs causing preventable readmissions, with the most common being vitamin K antagonists (22, 23, 40), diuretics (22, 40, 49), heparins (22, 38), antihypertensives (22, 49), digitalis glycosides (23, 49), and antiplatelets (23, 40).

DISCUSSION

This is the first systematic review to summarize the evidence on the prevalence and preventability of specifically drug-related hospital readmissions. The findings of this review suggest that pharmacotherapy is an important cause of hospital readmissions. Rates of readmission due to drugs varied from 3% to 64% (median 21%, IQR 14–23%). The median proportion of these readmissions that were deemed to be preventable was 69% (IQR 19–84%). The high variability in rates makes it difficult to state how often drug-related readmissions could be expected to occur. Because only a limited number of studies have focused on preventability, an accurate estimate of the proportion of preventable drug-related readmissions is impossible.

Differences in the type of readmissions that were assessed, the population studied, the methods used to assess causality and preventability, and the sources used to assess readmissions can explain the differences in prevalence and preventability rates of readmission between the studies. The studied populations were mainly older adults (median age 76, IQR 57–82). Conflicting results were found for age as a risk factor for drug-related readmissions, but because a higher Charlson Comorbidity Index score was found as a risk factor, and older adults have more comorbidities, it is reasonable to expect that older adults are at higher risk of drug-related readmissions. A previous systematic review focused on all-cause readmissions and did not further specify the role of drug-related hospital readmissions. It found a median preventability rate of 27% (range 5–79%) (10). Based on the current systematic review, 20% of readmissions are due to drugs, and 69% of these readmissions are regarded as preventable, which is higher than reported in a previous systematic review (10) for all-cause readmissions. However, the studies in the current review, even the one focusing on the preventability of readmissions, do not provide insight into how the drug-related readmissions can be prevented (e.g., medication reconciliation, medication review, or focus on adherence).

A better understanding of the causes of readmissions is needed to implement effective interventions. For example, the included studies did not specify whether a drug-related readmission was causally related to the index admission. Therefore, it is

possible that these studies included readmissions that were the result of actions in the primary care setting and were beyond the control of the hospital. It is also important to understand how an individual handles medication. The individual's perspective was often lacking in the studies. Individual perspectives do not always align with those of healthcare providers and can provide new information that could influence the assessment of readmissions (54-56). Individuals can be a valuable information source because of their particular knowledge of the circumstances around their readmissions regarding recent medication changes, use of over-the-counter drugs, ADRs, and adherence to the therapy. The highest prevalence rate found in this review originated from a study that interviewed patients. Many studies failed to report the symptoms that a drug caused. For example, use of corticosteroids could result in a readmission because of bleeding, a fall (osteoporosis), or hyperglycemia. The intervention to prevent a readmission due to drugs may differ based on the reason for readmission.

The strengths of this review are the originality of its aim and the extensive validated search strategy, but this study also has some limitations that need to be considered when interpreting the findings. First, the interrater agreement (k = 0.78) was slightly below the benchmark of 0.8, although the search strategy was validated and built in collaboration with a medical librarian. We conducted an extensive search in multiple databases with reference list checks and therefore do not expect that we missed relevant articles. Nevertheless, publications could have been missed in the grey literature or due to language barriers. We contacted authors to explore whether an English version was available, but two studies were excluded because of language barriers. Given the number of studies included in our review, it is unlikely that the overall conclusions would change meaningfully if missed studies were included. Furthermore, these studies found drug-related readmission rates of 25% (57) and 36% (58), which are comparable with the prevalence rates reported in the included studies.

No meta-analysis could be performed because of the considerable heterogeneity among the studies, and therefore the data were analyzed in a qualitative manner using medians and corresponding IQRs to compare prevalence rates. The profound differences between the studies with respect to study characteristics, participant populations, definitions, and methods of identification of drug-related readmissions limit comparability. Most studies were single centered and moderately sized, limiting external generalizability. The prevalence of drug-related readmissions might be underestimated, because moderately sized studies mainly examined readmissions to the same hospital, and information from participants was not included.

Future studies should include larger sample sizes from multiple hospitals and multiple departments, and the process of identifying drug-related readmissions should be standardized. For example, a protocol that includes a preventability assessment and individuals' perspectives could be developed. Studies should also focus on causes of drug-related readmissions and possible interventions. An important knowledge gap remains regarding the risk factors for drug-related readmissions that should be addressed as part of future research.

In conclusion, this review demonstrated that the median prevalence of drug-related admissions was 21% (IQR 14–23%) with a preventability of 69% (IQR 19–84%). Drug-related readmissions seem to occur especially in older adults. It is likely that the wide variation in the prevalence and preventability rates was due to heterogeneity among the studies. Further research on drug-related readmissions is required to understand the causes of these readmissions. Such understanding will aid in the development and implementation of effective interventions.

REFERENCES

1. Allaudeen N, Vidyarthi A, Maselli J, Auerbach A. Redefining readmission risk factors for general medicine patients. J Hosp Med. 2011;6(2):54-60.
2. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. N Engl J Med. 2009;360(14):1418-28.
3. Benbassat J, Taragin M. Hospital readmissions as a measure of quality of health care: advantages and limitations. Arch Intern Med. 2000;160(8):1074-81.
4. Fischer C, Anema HA, Klazinga NS. The validity of indicators for assessing quality of care: a review of the European literature on hospital readmission rate. Eur J Public Health.. 2012;22(4):484-91.
5. Centers for Medicare and Medicaid Services. Readmission Reduction Program [online]. Available at https://www.cms.gov/medicare/medicare-feefor-service-payment/acuteinpatientpps/readmissions-reduction program.html Accessed April 20, 2016.
6. Kristensen SR, Bech M, Quentin W. A roadmap for comparing readmission policies with application to Denmark, England, Germany and the United States. Health policy. 2015;119(3):264-73.
7. Feigenbaum P, Neuwirth E, Trowbridge L, Teplitsky S, Barnes CA, Fireman E, et al. Factors contributing to all-cause 30-day readmissions: a structured case series across 18 hospitals. Med Care. 2012:599-605.
8. Donzé J, Aujesky D, Williams D, Schnipper JL. Potentially avoidable 30-day hospital readmissions in medical patients: derivation and validation of a prediction model. JAMA Intern Med. 2013;173(8):632-8.
9. Jackson AH, Fireman E, Feigenbaum P, Neuwirth E, Kipnis P, Bellows J. Manual and automated methods for identifying potentially preventable readmissions: a comparison in a large healthcare system. BMC Med Inform Decis Mak. 2014;14(1):28.
10. Van Walraven C, Bennett C, Jennings A, Austin PC, Forster AJ. Proportion of hospital readmissions deemed avoidable: a systematic review. CMAJ. 2011;183(7):E391-E402.
11. Calvillo–King L, Arnold D, Eubank KJ, Lo M, Yunyongying P, Stieglitz H, et al. Impact of social factors on risk of readmission or mortality in pneumonia and heart failure: systematic review. J Gen Intern Med. 2013;28(2):269-82.
12. Preyde M, Brassard K. Evidence-based risk factors for adverse health outcomes in older patients after discharge home and assessment tools: a systematic review. J Evid Based Soc Work. 2011;8(5):445-68.
13. Yam C, Wong E, Chan F, Wong F, Leung M, Yeoh E. Measuring and preventing potentially avoidable hospital readmissions: a review of the literature. Hong Kong Med J. 2010;16(5):383-9.
14. García-Pérez L, Linertová R, Lorenzo-Riera A, Vázquez-Díaz J, Duque-González B, Sarría-Santamera A. Risk factors for hospital readmissions in elderly patients: a systematic review. QJM. 2011;104(8):639-51.
15. Robinson S, Howie-Esquivel J, Vlahov D. Readmission risk factors after hospital discharge among the elderly. Popul Health Manag. 2012;15(6):338-51.
16. Kripalani S, Roumie CL, Dalal AK, Cawthon C, Businger A, Eden SK, et al. Effect of a pharmacist intervention on clinically important medication errors after hospital discharge: a randomized trial. Ann Intern Med. 2012;157(1):1-10.
17. Ahmad A, Mast MR, Nijpels G, Elders PJ, Dekker JM, Hugtenburg JG. Identification of drug-related problems of elderly patients discharged from hospital. Patient Prefer Adherence. 2014;8:155.
18. Garcia-Caballos M, Ramos-Diaz F, Jimenez-Moleon JJ, Bueno-Cavanillas A. Drug-related problems in older people after hospital discharge and interventions to reduce them. Age Ageing. 2010;39(4):430-8.
19. Ellitt GR, Engblom E, Aslani P, Westerlund T, Chen TF. Drug related problems after discharge from an Australian teaching hospital. Pharm World Sci. 2010;32(5):622-30.
20. Al Hamid A, Ghaleb M, Aljadhey H, Aslanpour Z. A systematic review of hospitalization resulting from medicine-related problems in adult patients. Br J Clin Pharmacol. 2014;78(2):202-17.
21. Davies EC, Green CF, Mottram DR, Rowe PH,

Pirmohamed M. Emergency re-admissions to hospital due to adverse drug reactions within 1 year of the index admission. Br J Clin Pharmacol. 2010;70(5):749-55.

22. Ruiz B, García M, Aguirre U, Aguirre C. Factors predicting hospital readmissions related to adverse drug reactions. Eur J Clin Pharmacol. 2008;64(7):715-22.

23. Frankl SE, Breeling JL, Goldman L. Preventability of emergent hospital readmission. Am J Med. 1991;90(6):667-74.

24. Bero LA, Lipton HL, Bird JA. Characterization of geriatric drug-related hospital readmissions. Med Care. 1991:989-1003.

25. Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. BMJ. 2009;339:b2535.

26. Maurer PP. Hospital readmissions-are they predictable and avoidable? Swiss Med Wkly. 2004;134(4142).

27. Halfon P, Eggli Y, van Melle G, Chevalier J, Wasserfallen J-B, Burnand B. Measuring potentially avoidable hospital readmissions. J Clin Epidemiol. 2002;55(6):573-87.

28. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg. 2014;12(12):1500-24.

29. Classification for Drug related problems: The PCNE Classification V 6.2. Pharmaceutical Care Network Europe [on-line]. Available at http://www.pc ne.org/upload/files/11_PCNE_classification_V6–2.pdf Accessed April 28, 2016.

30. Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, et al. Incidence of adverse drug events and potential adverse drug events: implications for prevention. JAMA. 1995;274(1):29-34.

31. Definitions. World Health Organization [on-line]. Available at http://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/defini tions.pdf Accessed May 19, 2016.

32. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med. 2008;168(17):1890-6.

33. National Coordinating Council for Medication Error Reporting and Prevention [on-line]. Available at http://www.nccmerp.org/sites/default/files/nccmerp_fact_sheet_2015–02-v91.pdf Accessed June 2, 2016.

34. Otero M-J, Schmitt E, Nebeker JR, Samore MH, Barach P. Clarifying terminology for adverse drug events. Ann Intern Med. 2005;142(1):77.

35. World Health Organization. Anatomical Therapeutic Chemical Classification System of the World Health Organization [on-line]. Available at http://www.whocc.no/atc_ddd_index Accessed April 10, 2016.

36. Bonnet-Zamponi D, d'Arailh L, Konrat C, Delpierre S, Lieberherr D, Lemaire A, et al. Drug-Related Readmissions to Medical Units of Older Adults Discharged from Acute Geriatric Units: Results of the Optimization of Medication in AGE d Multicenter Randomized Controlled Trial. J Am Geriatr Soc. 2013;61(1):113-21.

37. Guharoy R, Bradshaw J, Churmusi K, Baxter S, Smith A, Darko W, et al. Incidence of ADEs in patients readmitted within 30 days of discharge in a tertiary care teaching hospital. Formulary. 2007;42(12):691-3.

38. Hauviller L, Eyvrard F, Garnault V, Rousseau V, Molinier L, Montastruc JL, et al. Hospital re-admission associated with adverse drug reactions in patients over the age of 65 years. Eur J Clin Pharmacol. 2016;72(5):631-9.

39. Pasina L, Djade CD, Nobili A, Tettamanti M, Franchi C, Salerno F, et al. Drug–drug interactions in a cohort of hospitalized elderly patients. Pharmacoepidemiol Drug Saf. 2013;22(10):1054-60.

40. Rothwell M, Jukka C, Lum E, Mitchell C, Kyriakides P. Retrospective analysis of emergency readmissions to rural and regional hospitals. J Pharm Pract Res. 2011;41(4):290-4.

41. Teymoorian SS, Dutcher D, Woods M. Association between postdischarge adverse drug reactions and 30-day hospital readmission in patients aged 80 and older. J Am Geriatr Soc. 2011;59(5):948-9.

42. Witherington E, Pirzada O, Avery A. Communication gaps and readmissions to hospital for patients aged 75 years and older: observational study. Qual Saf Health Care. 2008;17(1):71-5.

43. Zhang M, Holman CDAJ, Preen DB, Brameld K. Repeat adverse drug reactions causing hospitalization in older Australians: a population-based longitudinal study 1980–2003. Br J Clin Pharmacol. 2007;63(2):163-70.

44. Zhang M, Holman CDAJ, Price SD, Sanfilippo FM, Preen DB, Bulsara MK. Comorbidity and repeat admission to hospital for adverse drug reactions in older adults: retrospective cohort study. BMJ. 2009;338:a2752.

45. Stowasser DA, Staatz CE, Stowasser M, Coombes JA, Collins DM. Identifying drug-related readmissions is there a better way of assessing the contribution of adverse medication events? Aust J Hosp Pharm. 2000;30(2):47-53.

46. Dormann H, Neubert A, Criegee-Rieck M, Egger T, Radespiel-Tröger M, Azaz-Livshits T, et al. Readmissions and adverse drug reactions in internal medicine: the economic impact. J Intern Med. 2004;255(6):653-63.

47. Thomas J, Coralic A, Ruegger M, Thompson-Moore N. Descriptive analysis of patient readmissions within 60 days due to medication-related events. Hosp Pharm. 2015;50(7):595-602.

48. Willson MN, Greer CL, Weeks DL. Medication regimen complexity and hospital readmission for an adverse drug event. Ann Pharmacother. 2014;48(1):26-32.

49. Gillespie U, Alassaad A, Henrohn D, Garmo H, Hammarlund-Udenaes M, Toss H, et al. A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: a randomized controlled trial. Arch Intern Med. 2009;169(9):894-900.

50. Hellström LM, Bondesson Å, Höglund P, et al. Impact of the Lund Integrated Medicines Management (LIMM) model on medication appropriateness and drug-related hospital revisits. Eur J Clin Pharmacol. 2011;6:741–752.

51. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356(9237):1255-9.

52. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. Ann Intern Med. 2004;140(10):795-801.

53. Gillespie U, Alassaad A, Hammarlund-Udenaes M, Mörlin C, Henrohn D, Bertilsson M, et al. Effects of pharmacists' interventions on appropriateness of prescribing and evaluation of the instruments'(MAI, STOPP and STARTs') ability to predict hospitalization–analyses from a randomized controlled trial. PLoS ONE. 2013;8(5).

54. Ahmad FS, Barg FK, Bowles KH, Alexander M, Goldberg LR, French B, et al. Comparing perspectives of patients, caregivers, and clinicians on heart failure management. J Card Fail. 2016;22(3):210-7.

55. Howard-Anderson J, Lonowski S, Vangala S, Tseng C-h, Busuttil A, Afsar-manesh N. Readmissions in the era of patient engagement. JAMA Intern Med. 2014;174(11):1870-2.

56. Toomey SL, Peltz A, Loren S, Tracy M, Williams K, Pengeroth L, et al. Potentially preventable 30-day hospital readmissions at a children's hospital. Pediatrics. 2016;138(2):e20154182.

57. Nikolaus T, Specht-Leible N, Kruse W, Oster P, Schlierf G. The early rehospitalization of elderly patients. Causes and prevention. Dtsch Med Wochenschr. 1992;117(11):403-7.

58. Chaye H, Bernard M, Tubery M, Rousseau V, Ecoiffier M, Montastruc J, et al. Hospital readmission induced by adverse drug reaction: a pilot study in a post-emergency unit of a French university hospital. Rev Med Intern. 2015;36(7):450-6.

APPENDIX S1 – Search Strategies

Embase

('hospital readmission'/exp OR readmission*:ab,ti OR 're admission*':ab,ti OR rehospitali*':ab,ti OR're-hospitali*':ab,ti) AND ('adverse drug reaction'/mj OR 'drug surveillance program'/exp OR 'medication error'/exp or adr:ab,ti OR ade:ab,ti OR prescribing next/1 error*:ab,ti OR prescription next/1 error*:ab,ti OR adverse next/1 drug*:ab,ti OR drug next/1 related*:ab,ti OR medication next/1 related :ab,ti OR medication next/1 error*:ab,ti)

PubMed

("Drug-Related Side Effects and Adverse Reactions"[Mesh] OR "Adverse Drug Reaction Reporting Systems"[Mesh] OR medication errors[MeSH Terms] OR drug-related*[tiab] OR medication-related[tiab] OR medication error*[tiab] OR prescribing error*[tiab] OR prescription error*[tiab] OR adverse drug*[tiab] OR ADE[tiab] OR ADR[tiab]) AND (Patient readmission[MeSH Terms] OR readmission*[tiab] OR re-admission*[tiab] OR rehospitali*[tiab] OR re-hospitali*[tiab])

Cochrane

(Drug-Related Side Effects and Adverse Reactions OR Adverse Drug Reaction Reporting Systems OR Medication Errors OR drug-related*:ti,ab,kw OR medication-related:ti,ab,kw OR medication error*:ti,ab,kw OR prescribing error*:ti,ab,kw OR prescription error*:ti,ab,kw OR adverse drug*:ti,ab,kw OR ADR:ti,ab,kw OR ADE:ti,ab,kw) AND (Patient Readmission OR readmission*:ti,ab,kw OR re-admission*:ti,ab,kw OR rehospitali*:ti,ab,kw OR re-hospitali*:ti,ab,kw)

APPENDIX S2 – Characteristics of the studies examining drug-related hospital readmissions

Hospital characteristics					Hospital characteristics			Patient characteristics	
Reference	**Country**	**Design**	**Study period**	**Sample size**	**N**	**Type (number beds)**	**Department**	**Mean age (years)**	**Male (%)**
Bero 1991[24]	US	RS	NR	706	1	Non-teaching, community (450)	NR	74	49
Bonnet-Z. 2013[36]	France	RS	April 2007-Oct 2008	665	6	5 University, 1 private clinic	Acute geriatric unit	86	34
Davies 2010[21]	UK	RS	NR	1000	1	University	9 Medical and 3 surgical wards	62**	47
Dormann 2004[46]	Germany	POS	NR	630	1	University	Internal medicine ward	57	NR
Frankl 1991[23]	US	POS	Nov 1986-March 1987	272	1	Teaching, tertiary care (720)	Medical service, not further specified	53	51
Gillespie 2009,2013* [49,53]	Sweden	RCT	Oct 2005-June 2006	368	1	University	2 Acute internal medicine wards	86	40
Guharoy 2007[37]	US	RS	Jan-June 2005	108	1	University	NR	58	NR
Hauviller 2016[38]	France	RS	Jan-Dec 2010	1000	1	University (2880)	All wards	78	49
Hellstrom 2011[50]	Sweden	BAS	Nov 2006-May 2008	210	1	University	3 Internal medicine wards	82	47
Pasina 2013[39]	Italy	RS	Jan-Dec 2008-Jan-Dec 2010	844	>1	NR	70 Internal medicine and geriatric wards	79	49
Rothwell 2011[40]	Australia	RS	March 2007-March 2008	170	3	1 Regional (323), 2 rural (57/44)	NR	79	NR
Ruiz 2008[22]	Spain	CCS	July 2001-April 2003	258	1	Tertiary (365)	Miscellaneous	NR	58

Stowasser 2000[45]	Australia	POS	Feb-Aug 1996	208	1	Teaching, tertiary care	13 Medical and surgical wards	62	54
Teymoorian 2011[41]	US	RS	Jan-Dec 2008	282	1	University, tertiary care	NR	86	41
Thomas 2015[47]	US	POS	Oct 2013-Jan 2014	100	1	Academic, tertiary care (824)	Acute medical unit	56	51
Willson 2014[48]	US	CCS	Sep 2009-July 2010	320	4	Urban, acute care	NR	50	42
Witherington 2008[42]	UK	RS	Jan-Feb 2004	108	1	Teaching	NR	80	54
Zhang 2007[43]	Australia	RS	1980-2003	37926	>1	All public/private hospitals in the region	NR	NR	44
Zhang 2009[44]	Australia	RS	1980-2003	28548	>1		NR	NR	44

Abbreviations are as follow: BAS= before after study, CCS= Case-control study, NR= not reported, POS= prospective observational study, RCT= randomized controlled trial, RS= retrospective study, UK= United Kingdom,
US= United States.
*This concerns an ancillary study on the randomized controlled trial of Gillespie 2009
**Median age

APPENDIX S3 – Assessment methods and prevalence of drug-related readmissions

	Measures	Definition*	Follow up (type of RA)	Identification method		Causality assessment; Preventability assessment	IA n	RA n (% of IA)	DRR n (% of IA; RA)	PDRR n (% of DRR)
				Sources used†	Persons involved‡					
Prospective studies										
Dormann 2004[46]	ADR	WHO	6m (U,P to same dept.)			Naranjo et al; -	630	214 (34)	9 (1.4;4.2)	-
Frankl 1991[23]	DRP	NR	30d (U)			Author defined;Author defined	2626#	318 (12)#	65 (2-20)#	9 (14)#
Gillespie 2009,2013*[49,53]	DRP	NR	12m (U)			-;-	440#	223 (61)#	45 (10-20)#	-
Ruiz 2008[22]	ADR	WHO	60d (U)			Karch-assagna;Schumock & Thornton	26559#	1802 (7)#	81 (0.3;4.5)#	28 (35)#
Stowasser 2000[45]	DRP	NR	30d (U,P)			Author defined;Author defined	208	46 (22)	9 (4.3;20)	Not computable
Thomas 2015[47]	DRP	PCNE	60d (U)			Author defined;-	NR	100	64 (-;64)	-
Retrospective studies										
Bero 1991[24]	DRP	Author defined	6m (NR)			Author defined;NR	684	224 (33)	45 (7;20)	34 (76)
Bonnet-Z. 2013[36]	DRP	NR	6m (U)			Naranjo et al;-	NR	94#	38 (-;40)#	-
Davies 2010[21]	ADR	Edwards & Aronson	12m (U)			Naranjo et al;Hallas et al.	955	28d:121 (13) 12m:403 (42)	23 (2.4;23) 73 (7.6;24)	Not computable
Guharoy 2007[37]	ADE	NR	30d (NR)			Naranjo et al;-	NR	108	14 (-;13)	-

Hauviller 2016[38]	ADR	Edwards & Aronson	12m (NR)			-; Olivier's scale	944	553 (59)	87 (9;16)	4 (5)
Hellstrom 2011[50]	DRP	NR	3m (U)			WHO;-	208	71 (34)	15 (7;21)	-
Pasina 2013[39]	DDI	NR	3m (NR)			-;-	844	145 (17)	5 (1;3)	-
Rothwell 2011[40]	DRP	Author defined	28d (U)			Howard et al;Howard et al	NR	170	39 (-;23)	34 (87)
Teymoorian 2011[41]	ADR	WHO	30d (U)			-;-	NR	282	66 (-;23)	-
Willson 2014[48]	ADE	Nebeker et al.	30d (NR)		NA	-;-	-	-	62 (-;-)	-
Witherington 2008[42]	DRP	NR	28d (U)			Howard et al;Howard et al	NR	108	41 (-;38)	25 (61)
Zhang 2007[43]	ADR	WHO	4.2y (U,P)		NA	-;-	37296	NR	6853 (18;-)	-
Zhang 2009[44]	ADR	Edwards & Aronson	3y (U,P)		NA	-;-	28548	NR	5056 (18;-)	-

Abbreviations are as follow: ADE= adverse drug event, ADR= adverse drug reaction, d=days, dept.=department, DDI= drug-drug interaction, DRP= drug-related problem, DRR= drug-related readmissions, IA=index admissions, m=month, NR= not reported, P=planned, PCNE= Pharmaceutical Care Network Europe, PDRR= preventable drug-related readmissions, RA=readmissions, WHO=World Health Organization, U=unplanned, y=years.

*The WHO definition for an ADR: a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function (31). The definition of an ADR according to Edwards and Aronson is as follows: any appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product (51).

† Each box uses the scheme at the right and represents the sources of information used in the assessment of the drug-relatedness of readmissions, A= patient adherence (n=6; 2 interview and 4 medical records), B= interview with patients and/or caregivers (n=5), C= database (n=4),
D= laboratory values (n=5), E= medical chart review (n=16)

‡ Each box uses the scheme at the right and represents the profession of the reviewers who were involved in the identification method of drug-related readmissions: A= specialist (n=12), B= general practitioner (n=1), C= nurse (n=1), D= not specified (n=2), E= pharmacist (n=9)

Prevalence reported with readmissions as denominator instead of patients

3

Medication-related hospital readmissions within 30 days of discharge: Prevalence, Preventability, Type of Medication Errors and Risk Factors

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ABSTRACT

Background
Hospital readmission rates are increasingly used as a measure of healthcare quality. Medicines are the most common therapeutic intervention but estimating the contribution of adverse drug events as a cause of readmissions is difficult.

Objectives
To assess the prevalence and preventability of medication-related readmissions within 30 days after hospital discharge and to describe the risk factors, type of medication errors and types of medication involved in these preventable readmissions.

Design
A cross-sectional observational study.

Setting
The study took place across the cardiology, gastroenterology, internal medicine, neurology, psychiatry, pulmonology and general surgery departments in the OLVG teaching hospital, The Netherlands.

Participants
Patients with an unplanned readmission within 30 days after discharge from an earlier hospitalization (index hospitalization: IH) were reviewed.

Measurements
The prevalence and preventability of medication-related readmissions were assessed by residents in multidisciplinary meetings. A senior internist and hospital pharmacist reassessed the prevalence and preventability of identified cases. Generalized estimating equation with logistic regression was performed to identify risk factors of potentially preventable medication-related readmissions.

Results
Of 1111 included readmissions, 181 (16%) were medication-related, of which 72 (40%) were potentially preventable. The number of medication changes at IH (Adjusted odds ratio [OR_{adj}]: 1.14; 95%CI: 1.05–1.24) and having ≥ three hospitalizations six months before IH (OR_{adj}: 2.11; 95%CI: 1.12–3.98) were risk factors of a preventable medication-related readmission. Of these preventable readmissions, 35% were due to prescribing errors, 35% by non-adherence and 30% by transition errors. Medications most frequently involved were diuretics and antidiabetics.

Conclusion
This study shows that 16% of readmissions are medication-related, of which 40% are potentially preventable. If the results are confirmed in larger multicentre studies, this may indicate that more attention should be paid to medication-related harm in order to lower the overall readmission rates.

INTRODUCTION

Unplanned hospital readmissions within 30 days are increasingly used as a measure of healthcare quality. Previous studies show that approximately 20% of patients discharged from hospital are readmitted within 30 days of discharge and 5–79% of those readmissions are estimated to be preventable (median: 27%) (1, 2). Medication, and more specifically polypharmacy, seems to be one of the causes for these readmissions (3, 4). It is estimated that 21% (range: 3–64%) of readmissions are due to medication and a median of 69% (range: 5–87%) of these readmissions were deemed preventable (5). However, previous studies on the impact of medication on (preventable) hospital readmissions have some methodological flaws (5). The wide range of point estimates found in previous studies may be due to the small sample size of the reviewed studies, the inclusion of only one department and the method to assess preventability (i.e. by either a pharmacist or physician, not both). Consequently, it is difficult to state how often medication-related readmissions occur. Only six studies have determined the preventability of medication-related readmissions and in only two of these was the preventability assessed by a multidisciplinary method (6, 7), despite the fact that a multidisciplinary review is recommended (8). Furthermore, the type of medication errors involved in preventable medication-related readmissions were unclear and there is a focus on prescribing errors, whereas other medication errors may also be important, such as non-adherence (5, 9). Thus, a clear understanding of the impact and risk factors for adverse drug events on readmissions is lacking. In order to develop interventions to lower overall readmission rates in hospitals it is important to understand the role that medication plays in patient readmissions because medication is the most common therapeutic intervention (10). Therefore, this study aims to assess the prevalence and preventability of medication-related readmissions within 30 days of discharge, Additionally, potential risk factors associated with preventable medication-related readmissions, the types of medication errors and the medications involved in those readmissions are assessed.

METHODS

Study design and participants

The data for this study were collected within the context of a larger study on all-cause readmissions (11). The all-cause study and the current study used the same inclusion criteria. The all-cause study assessed the extent to which the provided care during an earlier hospitalization, and the subsequent outpatient follow-up care provided by the hospital, was responsible for the readmission. The current study focused on readmissions due to adverse drug events, which are any injuries resulting from medication use, including physical harm, mental harm, or loss of function ((5), see for definitions supplementary material). Adverse drug events can result from (non-preventable) adverse drug reactions (defined as a response to a medicine that is noxious and unintended and occurs at doses normally used in man) (12) or (preventable) medication errors (defined as errors in the process of prescribing, dispensing or administering medication that may cause or lead to inappropriate

medication use or harm while the medication is in the control of the healthcare professional, patient or consumer) (13).

A cross-sectional single-centre observational study was conducted from 15 July 2016 until 28 February 2018 at seven clinical departments in the OLVG teaching hospital in Amsterdam, The Netherlands. All seven clinical departments and the hospital pharmacy assigned a resident to review readmissions. All residents received a group training prior to the start of the study regarding the assessment whether the readmission was caused by healthcare (i.e. causality) and the preventability of readmissions (11). In case of replacement of a resident, the new resident received the same training.
All the reviewers had full access to the hospital information system, including laboratory values, medication prescriptions and all notes (i.e. from nurses, physicians, pharmacy, etc.).
Inclusion criteria were: unplanned readmissions of adult patients (≥18 years) within 30 days after discharge from an earlier hospitalization (index hospitalization: IH) to one of the participating departments (cardiology, gastroenterology, internal medicine, neurology, psychiatry, pulmonology and general surgery). Those wards were chosen based on the highest readmission rates in previous years.
Exclusion criteria were: patients who were transferred to another hospital during IH, patients who left the hospital against medical advice during IH and if the readmission was due to attempted suicide. Furthermore, a readmission was excluded if it was deemed unrelated to the IH. This was initially assessed by the study coordinator (a medical doctor) and then double-checked by the resident of the department of IH. Any non-agreement between the two led to the case being discussed at a multidisciplinary meeting (see Figure 1).

The study was approved by the local review board of the hospital (Advies Commissie Wetenschappelijk Onderzoek Medische Ethische Commissie, ACWO-MEC; registration number 16-028). Patient data were obtained and handled in accordance with privacy regulations.

Usual care during index hospitalization
In the OLVG hospital, medication monitoring is performed by hospital pharmacists using a computerized system to check for the right dose and medication interactions. A Transitional Pharmaceutical Care (TPC)-program (14) was implemented gradually during the study.

On departments with this TPC-program, hospital pharmacy teams performed medication reconciliation upon hospital admission and discharge using the dispensing history of the community pharmacy and information from the patient/carer. Any discrepancies between a patient's actual medication use and the medication prescribed in hospital were discussed with the resident. No formal medication review was performed. However, obvious errors in pharmacotherapy were eliminated: for example, lack of a laxative when an opioid is prescribed or no indication for hypnotics upon discharge and/or addressing a stop date for antibiotics or opioids. The reason for medication changes was explained to the patient during discharge counseling and a written medication summary was provided. The pharmacy team compiled a

TPC-medication overview that the resident could upload into the discharge letter to the general practitioner.

On departments where the TPC-program was not yet implemented, residents and nurses were responsible for assessing the patient's actual medication use by interviewing patients/carers. If regarded as necessary, they could request the hospital pharmacy to obtain a dispensing history from the community pharmacy. At hospital discharge, the resident uploads information from the hospital's prescribing system or types information into the discharge letter to the general practitioner.

Assessment of causality, preventability and type of medication errors

Figure 1 shows the different steps in the assessment of causality, preventability and type of medication errors.

If medication was noted as a cause for readmissions by the residents, the readmission was included for a review by the resident of the hospital pharmacy. The resident of the hospital pharmacy assessed the causal relationship between the suspected medicine and the reason for readmission (i.e. causality), using an adjusted version of the algorithm of Kramer et al. ((15), see supplementary material). This algorithm has been used in a previous study to assess the causality of medication related admissions (16). This algorithm included three questions: whether the reason for admission is known to be an effect of the suspected medicine, whether alternative causes can explain the relationship between the suspected medicine and the readmission, and whether a plausible time relationship exists between the readmission and the start of medication administration (or the occurrence of the medication error). The subscores of the three questions were added to a total score, and classified as: possible, probable or unlikely causal. Readmissions classified as possible or probable causal were classified as medication-related and the preventability of those readmissions was assessed by the same pharmacist according to a modified version of the algorithm by Schumock and Thornton ((16-19), see supplementary material). The algorithm assessed dosing or therapeutic errors (e.g. type of medication inappropriate for the patient's clinical condition, inappropriate dose or frequency, medication contraindicated), inadequate monitoring of the therapy (e.g. therapeutic drug monitoring or other monitoring), lack of preventative measure (e.g. no laxative with opioid use) or incorrect medication use (e.g. non-adherence). A readmission was considered potentially preventable when a medication error caused the readmission. All potentially preventable readmissions were discussed in multidisciplinary meetings with all residents to reach consensus.

Hereafter all medication-related readmissions were reassessed by a senior internist and senior clinical pharmacologist/hospital pharmacist. The agreement between internist and hospital pharmacist for medication-relatedness's was $\kappa = 0.59$ (moderate) and for preventability $\kappa = 0.73$ (substantial). In case of disagreement, consensus was reached.

Finally, medication errors involved in potentially preventable readmissions were classified by the resident of the hospital pharmacy and the principal investigator/ hospital pharmacist into three mutually exclusive groups to determine where in the medication process the error has occurred. These groups included: prescribing errors (defined as dosing/therapeutic errors or inadequate monitoring); transition

errors (insufficient communication to the patient and/or next healthcare provider, e.g. regarding a medication change); and non-adherence (medication not used as prescribed by the patient), according to the van den Bemt and Egberts classification (13).

Data collection

Relevant information on included readmissions was collected from medical records and entered into a data processing program (Castor EDC). Potential risk factors were collected based on previous studies (2, 11, 21) (Table 1).
The updated Charlson comorbidity score (22) was derived from the hospital data system. Renal function was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. A cut-off of 50 ml/min/1.73m2 was chosen based on the Dutch guidelines for dose adjustments in renal impairment. The presence of a language barrier was determined based on notes from the resident or nurse in the electronic patient file (e.g. use of an interpreter, difficulties in asking the medical history). After completion of the data entry the data were visually checked with histograms and scatterplots to check extreme values and missing data.

Main outcome measures

The prevalence of medication-related readmissions (defined as the number of medication-related readmissions divided by the total number of unplanned readmissions) and the percentage of potentially preventable medication-related readmissions (defined as the number of potentially preventable medication-related readmissions divided by the total number of medication-related readmissions) were the main outcome measures. Additionally, the following measures for potentially preventable medication-related readmissions were assessed: potential risk factors (Table 1), type of medication and medication error that were involved.

Data analysis

Statistical analysis was performed in SPSS version 22.0 (IBM SPSS, Chicago, IL, USA). Categorical variables are reported as percentages. Normally and non-normally distributed continuous variables are reported as mean with standard deviation (SD) and median with interquartile range (IQR), respectively. To identify potential risk factors of potentially preventable medication-related readmissions and to adjust for patients with multiple readmissions, a univariate generalized estimating equation (GEE) with logistic regression was performed. Parameters with a p-value <0.10 in the univariate analysis were entered into a multivariable model (23). P-values lower than 0.05 were considered statistically significant. We checked for presence of collinearity (R>0.5) , reported unadjusted odds ratios (OR), adjusted odds ratios (OR_{adj}) and 95% confidence intervals (CI). No pairwise correlations were above 0.5.

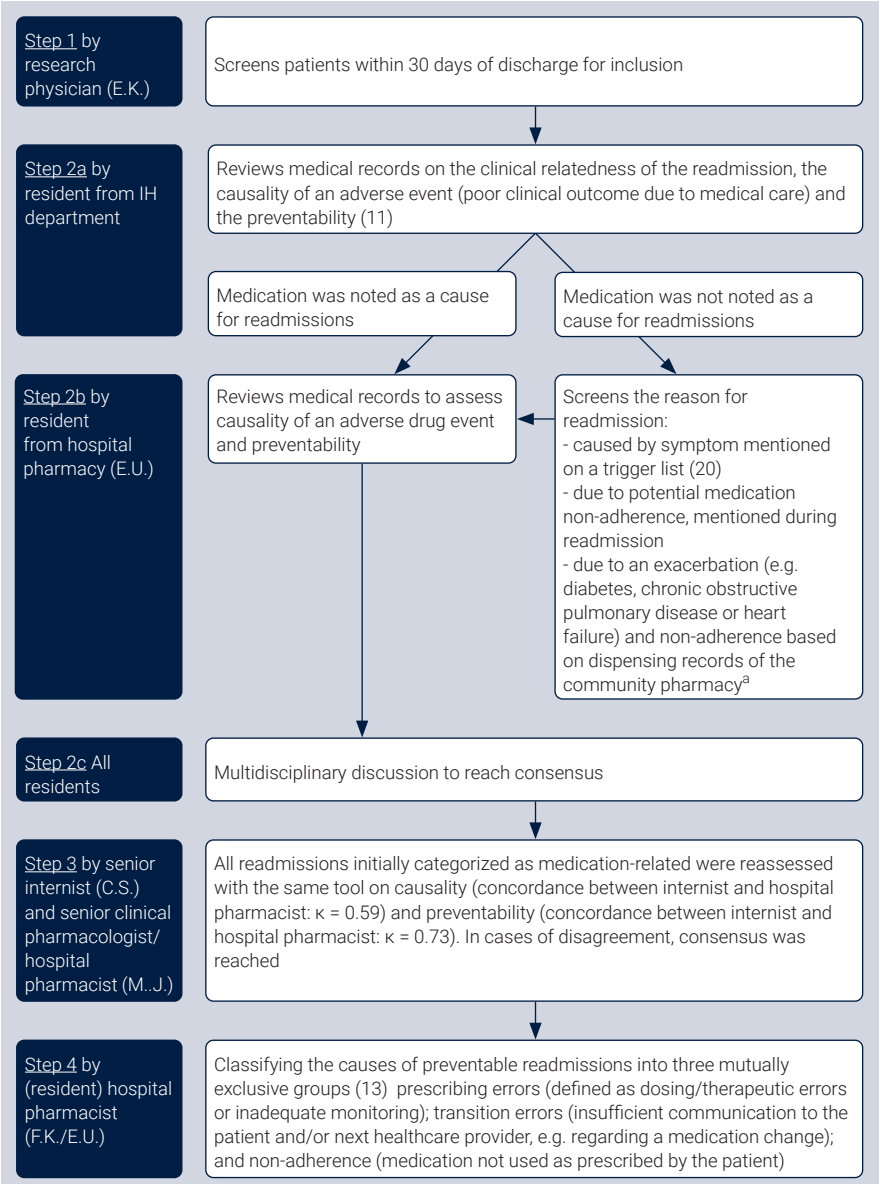

Figure 1 Assessment of causality, preventability and type of medication errors.
[a] Therapy adherence was defined as a refill rate higher than 0.8. The refill rate was defined as the number of daily doses dispensed (refill interval) divided by the total number of days between the first and last prescription in this period (we used a period of 8 months before readmission). If the refill rate could not be calculated but the doctor mentioned the patient as being therapy non-adherent, the patient was classified as such. Likewise, a refill rate above 0.8 can be overruled by a doctor classifying the patient as non-adherent.

RESULTS

Prevalence and preventability

Of the 1356 readmissions screened, 245 (18%) were excluded (see Figure 2). This resulted in the inclusion of 1111 readmissions for 873 unique patients: 699 patients had one readmission and 174 patients had two or more.

Initially, 210 readmissions were considered to be medication-related (step 2, Figure 1). After confirmation by a senior internist (C.S.) and senior clinical pharmacologist/hospital pharmacist (M.J.) (step 3, Figure 1), 181 of the 1111 readmissions (16%) were considered medication-related, of which 72 (40%) were assessed as potentially preventable (Figure 2).

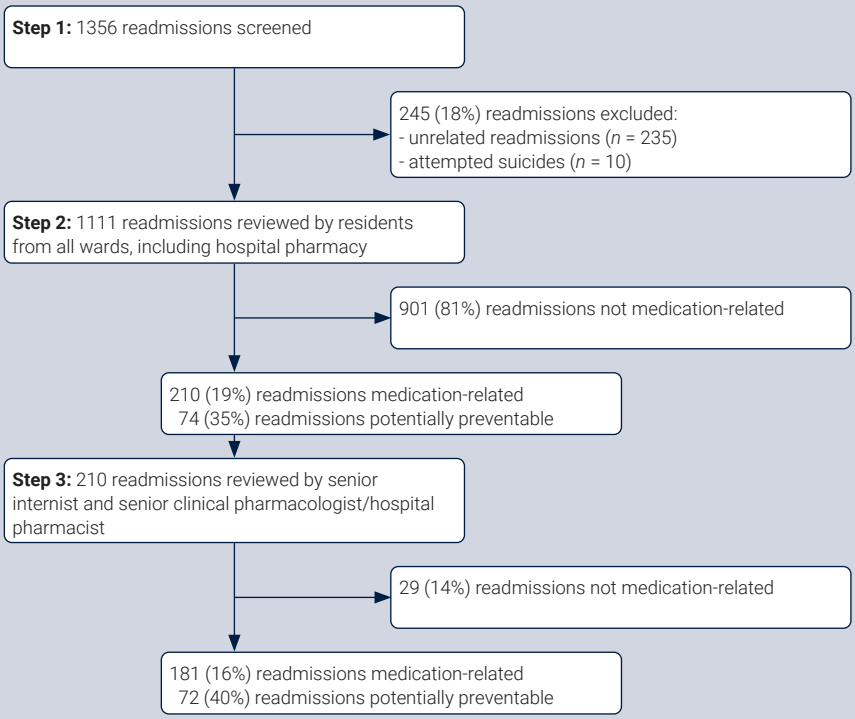

Figure 2 Study flow and main outcome

Table 1 Patient- and index hospitalization-related parameters and adjusted odds ratios and 95% confidence intervals from parameters significantly associated in the univariate analyses [a]

	Medication-related and potentially preventable N=72	Not medication-related N=930	OR (95%CI)	p-value	OR_{adj} (95%CI)	p-value
Patient related						
Male, n (%)	38 (52.8)	452 (48.6)	1.06 (0.53-2.14)	0.86		
Age in years, mean (SD)	69.5 (13.7)	63.4 (17.4)	1.02 (1.01-1.04)	0.01	1.02 (0.99-1.04)	0.15
Language barrier present, n (%)	25 (34.7)	170 (18.2)	1.75 (0.95-3.21)	0.08	1.76 (0.92-3.40)	0.09
Living situation, n (%)						
Living alone	24 (33.3)	278 (29.9)	1.13 (0.22-5.69)	0.89		
Living with partner/family	35 (48.6)	488 (52.5)	1.42 (0.24-8.53)	0.70		
Institution (rehabilitation centre or nursing home)	10 (13.8)	110 (11.8)		Ref.		
Number of medicines at discharge IH, mean (SD)	12.6 (5.4)	9.6 (5.7)	1.07 (1.04-1.12)	<0.01	1.02 (0.96-1.08)	0.57
Number of medication changes during IH, median + IQR	3 (2-6)	2 (1-4)	1.15 (1.03-1.29)	0.02	1.14 (1.05-1.24)	<0.01
0-1, n (%)	14 (19.4)	323 (34.7)				
2, n (%)	7 (9.7)	166 (17.8)				
3-4, n (%)	21 (29.2)	257(27.6)				
≥ 5, n (%)	29 (40.3)	173 (18.6)				
eGFR<50 ml/min/1.73m2, n (%)	24 (33.3)	166 (17.8)	1.32 (0.52-3.35)	0.56		
CCI score, median (IQR)	1 (0-3)	1 (0-2)	1.07 (0.95-1.21)	0.26		
0-1, n (%)	39 (54.1)	593 (63.7)				

Table 1 *Continued*

	Medication-related and potentially preventable N=72	Not medication-related N=930	OR (95%CI)	p-value	OR_{adj} (95%CI)	p-value
2-3, n (%)	16 (22.2)	206 (21.8)				
≥4 , n (%)	17 (23.6)	131 (14.1)				
IH related						
Unplanned IH, n (%)	60 (83.3)	751 (80.7)	1.02 (0.55-1.89)	0.94		
Duration of IH in days, median + IQR	7 (3-13)	5 (2-9)	1.01 (0.99-1.03)	0.43		
Time between IH and readmission in days, median + IQR	10.5 (4.3 – 18.9)	9 (4-17)	1.01 (0.97-1.06)	0.60		
Discharge on Saturday or Sunday, n (%)	11 (15.2)	143(15.4)	1.03 (0.44-2.37)	0.95		
Planned post-discharge outpatient visit, n (%)	61 (84.7)	792 (85.2)	1.66 (0.24-11.24)	0.61		
≥3 hospital hospitalizations 6 months before IH, n (%)	19 (26.4)	118 (12.7)	1.66 (0.94-2.95)	0.08	2.11 (1.12-3.98)	0.02
≥2 ED visits (without a hospitalization), 6 months before IH, n (%)	13 (18.1)	70 (7.5)	2.01 (1.05-3.86)	0.04	2.15 (1.00-4.65)	0.05
Discharge letter send to GP after discharge IH, n (%)	61 (84.7)	761 (81.8)	1.67 (0.83-3.34)	0.15		
Discharge letter send to GP ≤2 days after discharge IH, n (%)	22 (36.1)	222 (29.2)	1.52 (0.94-2.45)	0.09	1.37 (0.82-2.31)	0.23
Department, n (%)						
Internal medicine	17 (23.6)	190 (20.4)	-	Ref.		
Pulmonology	11 (15.3)	189 (20.3)	0.59 (0.09-3.72)	0.57		
Cardiology	17 (23.6)	113 (12.2)	1.12 (0.67-17.49)	0.94		

Surgery	12 (16.7)	264 (28.4)	0.45 (0.05-4.02)	0.48
Gastroenterology	13 (18.0)	125 (13.4)	0.52 (0.22-1.22)	0.13
Neurology [b]	2 (2.8)	42 (4.5)	-	-
Psychiatry [b]	0	7 (1)	-	-

GP: General Practitioner, IH: Index Hospitalization, IQR: Interquartile Range, ED: Emergency Department, eGFR: Estimated glomerular filtration rate
[a] Data were missing for: living situation (5.1%) and eGFR<50 ml/min/1.73m2 (0.8%).
[b] Too few cases to include in this analysis.

Readmission characteristics and risk factors

Table 1 shows the patient-related and IH-related characteristics of the potentially preventable medication-related readmissions (*n* = 72) versus non-medication-related readmissions (*n* = 930). Mean age in the potentially preventable group was 69.5 years, 52.8% were men and the average number of medicines at discharge of the IH was 12.6.

Parameters independently associated with potentially preventable readmissions were number of medication changes during IH (OR_{adj}: 1.14; 95%CI: 1.05–1.24) and three or more hospitalizations six months before IH (OR_{adj}: 2.11; 95%CI: 1.12–3.98) (Table 1).

Types of medication and reasons for potentially preventable readmissions

The top five medications associated with potentially preventable medication-related readmissions were antidiabetics (15%), diuretics (15%), laxatives (14%), antithrombotic agents (10%) and medications for asthma/chronic obstructive pulmonary disease (COPD) (8%).

The most common reason for readmissions was cardiovascular symptoms (32%). Other reasons were poor glycemic control (15%), liver diseases (14%), gastrointestinal tract symptoms (6%), coagulation disorders (10%), respiratory symptoms (10%), central nervous system diseases (6%), electrolyte disturbances (6%) and infections (3%) (Table 2).

Medication errors involved in potentially preventable readmissions

Table 3 shows the type of medication errors of the 72 potentially preventable medication-related readmissions. Prescribing errors (35%) and non-adherence (35%) were the most common medication errors. Underprescribing (40%), wrong dosage (24%) and inadequate monitoring (20%) were the most common sub-types of the prescribing errors.

Table 2 Reasons for potentially preventable medication-related readmissions and the associated medication[a]

Clinical presentation at readmission	Preventable readmissions (n = 72, 100%)	Associated medications (no. of readmissions)
Circulatory		
Cardiovascular symptoms (e.g. heart failure, dysrhythmias, hyper- or hypotension)	23 (32%)	Diuretics (10), calcium antagonists (4), beta-blockers (3), medication affecting RAAS (3), cardiac glycosides (2), organic nitrates (1), theophylline (1), alpha-blocker (1)
Endocrine system		
Hypoglycemia or hyperglycemia	11 (15%)	Insulin (7), oral antidiabetics (3), corticosteroids (1)
Gastrointestinal system		
Hepatic encephalopathy/liver failure Gastrointestinal symptoms (diarrhea, constipation)	10 (14%) 4 (6%)	Laxatives (9), acetaminophen (1) Laxatives (1), loperamide (1), oral antidiabetics (1), antiemetics (1)
Blood		
Coagulation disorders (e.g. bleeding, anemia, embolism)	7 (10%)	Anticoagulants (7)
Respiratory system		
Respiratory symptoms (e.g. dyspnoea)	6 (8%)	Respiratory medication (5), opioids (1)
Central nervous system		
Epileptic seizure, pain, dysregulation of Parkinson's disease	4 (6%)	Opioids (1), antiepileptics (2), anti-Parkinson medication (1)
Electrolytes		
Electrolyte disturbance (e.g. hyper- or hypokalemia)	4 (6%)	Mineral supplements (2), medication for treatment of hyperkalemia (1), diuretics (1)
Immune system		
Infection	2 (3%)	Antibiotics (2)
Other		
Headache	1 (1%)	Infliximab (1)

[a] More than one medicine per readmission is possible. RAAS, renin–angiotensin–aldosterone system.

Table 3 Type and subtype of medication errors involved in potentially preventable medication-related readmissions

Type of error	Subtype of error	n (%)
Prescribing		**25 (35)**
	Underprescribing	10 (40)
	Dosage	6 (24)
	Inadequate monitoring	5 (20)
	No indication	3 (12)
	Contraindication	1(4)
Across settings	Transition errors	**22 (30)**
Medication use	Non-adherence	**25 (35)**

DISCUSSION

This study shows that 16% of the readmissions are caused by medication and that 40% of these are potentially preventable. Most of the medication errors involved in the potentially preventable readmissions were classified as non-adherence (35%) and prescribing errors (35%), followed by transition errors (30%).

The frequency of 16% found in the current study is comparable to the median of 21% found in a systematic review of medication-related readmissions (5). Of the medication-related readmissions 40% were considered potentially preventable and the systematic review found that a median of 69% were preventable. The difference in preventability between studies could be caused by the case-mix of studies (e.g. including only geriatric patients versus adult patients) and how preventability was assessed (e.g. monodisciplinary or multidisciplinary).

The finding that 40% of the medication-related readmissions were considered to be potentially preventable indicates that improvements may be possible. A total of 35% of the potentially preventable readmissions were due to prescribing errors, with underprescribing, wrong dosage and inadequate monitoring being the most common. To address underprescribing, a clinical medication review is needed to recognize the undertreated symptoms. To address inadequate monitoring, the clinical medication review should include a monitoring plan as well, describing when and how the effects of medication changes are evaluated and defining the responsibilities of the different care providers involved. Another 35% of the potentially preventable readmissions were due to medication non-adherence. Most of the previous studies investigating readmissions did not describe this relevant cause (5, 24). Rosen et al. show that patients with low or intermediate medication adherence had more than 2.5-fold greater odds of being readmitted within 30 days (25). However, non-adherence is a multifaceted problem (26). The question is whether medication adherence is a modifiable predictor of hospital readmissions or a measure for underlying causes, such as socioeconomic, condition- or therapy-related factors, which are the true

causes for readmission (27). This is an important issue for future research. The final 30% of the potentially preventable readmissions were due to transition errors, including failure to communicate medication changes to the patient and/or the next healthcare providers. It remains a challenge to communicate medication changes after discharge, despite the efforts made in recent years to improve the transfer of medication-related information, including the implementation of medication reconciliation (28). Interventions across the settings are needed, with specific recommendations to the patient and the next healthcare provider on what should be done after discharge. The study by Ravn-Nielsen et al. showed that a transitional pharmacist intervention, based on medication review, medication reconciliation, motivational interviews and follow-up after discharge, resulted in a significant reduction in the number of patients readmitted within 30 days (29). The intensity of this intervention could explain its effectiveness. To implement such labor-intensive interventions in an effective way, a focus on patients at risk of adverse drug events is needed. The potential risk factors identified in this study might help to select these patients. A higher number of medication changes during IH and three or more hospital hospitalizations six months before IH were associated with potentially preventable medication-related readmissions within 30 days.

It would be interesting to explore the association between the clinical presentation during previous hospitalizations and this presentation during the preventable medication-related readmission. Possibly, adverse drug events were already present during the previous hospitalizations and index admission, but not recognized by the caregivers. As also described by Ravn-Nielsen et al. some Emergency Department visits or (re)admissions are not obviously medication-related (29). If patients present themselves at the Emergency Department due to non-adherence, this will typically manifest itself as a worsening of his or her underlying disease and only if the patient indicates to be non-adherent this will be recognized as an adverse drug event. Apparently, in most cases the patient will be discharged without solving the adverse drug event, which could result in (re)admissions. Antidiabetics, diuretics, laxatives, antithrombotic agents and medications for asthma/COPD were most frequently involved. These agents correspond to medicines associated with medication-related admissions (16).

Although this is the first study to describe an extensive assessment of the prevalence and preventability of unplanned medication-related readmissions, it does have some limitations. First, this was a single-centre study and only the wards with the highest readmission rates in previous years were included, limiting the generalizability. However, reviewing files of readmitted patients is resource-intensive and so the selection of high-risk departments increased the focus of reviewers. Second, we used a two-step approach (resident review and confirmation by senior internist and hospital pharmacist) to assess the prevalence and preventability of medication-related readmissions. Some medication-related readmissions could have been missed if they were not recognized in the first step by the residents. However, our approach is likely to result in high specificity, which increases the reliability of the results. Third, during this study a TPC-program was implemented. As this program tends to improve the transfer of medication-related information to the patient and next healthcare providers, it is possible that it resulted in less medication-related

readmissions. Finally, the preventability of medication-related readmissions was assessed using information from medical records and adherence information based on the medication history. Relevant information from the patient or primary care providers not documented in the medical records could have been missed: for example, non-adherence due to practical problems or adverse drug reactions, leading to a higher preventability in reality. Furthermore, we examined non-adherence based on refill rates, which does not establish whether a patient actually uses his medication. However, the value of using refill rates in clinical research has been shown (30).

In summary, this study shows that 16% of the readmissions are caused by medication, of which 40% are potentially preventable. If the results are confirmed in larger multicentre studies, this may indicate that more attention should be paid to medication-related harm as a cause of readmissions in order to lower the overall readmission rates.

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REFERENCES

1. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. N Engl J Med. 2009;360(14):1418-28.
2. Van Walraven C, Bennett C, Jennings A, Austin PC, Forster AJ. Proportion of hospital readmissions deemed avoidable: a systematic review. CMAJ. 2011;183(7):E391-E402.
3. Ahmad A, Mast MR, Nijpels G, Elders PJ, Dekker JM, Hugtenburg JG. Identification of drug-related problems of elderly patients discharged from hospital. Patient Prefer Adherence. 2014;8:155.
4. Garcia-Caballos M, Ramos-Diaz F, Jimenez-Moleon JJ, Bueno-Cavanillas A. Drug-related problems in older people after hospital discharge and interventions to reduce them. Age Ageing. 2010;39(4):430-8.
5. El Morabet N, Uitvlugt EB, van den Bemt BJF, van den Bemt P, Janssen MJA, Karapinar-Carkit F. Prevalence and Preventability of Drug-Related Hospital Readmissions: A Systematic Review. J Am Geriatr Soc. 2018;66(3):602-8.
6. Rothwell M, Jukka C, Lum E, Mitchell C, Kyriakides P. Retrospective analysis of emergency readmissions to rural and regional hospitals. J Pharm Pract Res. 2011;41(4):290-4.
7. Ruiz B, García M, Aguirre U, Aguirre C. Factors predicting hospital readmissions related to adverse drug reactions. Eur J Clin Pharmacol. 2008;64(7):715-22.
8. van Doormaal JE, Mol PG, van den Bemt PM, Zaal RJ, Egberts AC, Kosterink JG, et al. Reliability of the assessment of preventable adverse drug events in daily clinical practice. Pharmacoepidemiol. Drug Saf. 2008;17(7):645-54.
9. Parekh N, Ali K, Page A, Roper T, Rajkumar C. Incidence of medication-related harm in older adults after hospital discharge: a systematic review. J Am Geriatr Soc. 2018;66(9):1812-22.
10. Medication Safety in Transitions of care. Technical Report. World Health Organisation 2019. Available at: https://apps.who.int/iris/bitstream/handle/10665/325453/WHO-UHC-SDS-2019.9-eng.pdf?ua=1. Accessed december 2020.
11. van der Does AM, Kneepkens EL, Uitvlugt EB, Jansen SL, Schilder L, Tokmaji G, et al. Preventability of unplanned readmissions within 30 days of discharge. A cross-sectional, single-center study. PloS one. 2020;15(4):e0229940.
12. Definitions. World Health Organization. (online) Available from: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf Accessed 27 November 2019.
13. van den Bemt PM, Egberts A. Drug related problems: definitions and classification. EJHP Practice. 2007;2007(13):62-4.
14. Karapinar-Çarkit F, Borgsteede SD, Zoer J, Egberts TC, van den Bemt PM, Tulder Mv. Effect of medication reconciliation on medication costs after hospital discharge in relation to hospital pharmacy labor costs. Ann Pharmacother. 2012;46(3):329-38.
15. Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions: I. Background, description, and instructions for use. JAMA. 1979;242(7):623-32.
16. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med. 2008;168(17):1890-6.
17. Lau PM, Stewart K, Dooley MJ. Comment: hospital admissions resulting from preventable adverse drug reactions. Annals of Pharmacotherapy. 2003;37(2):303-4.
18. Schumock G, Thornton J. Focusing on the preventability of adverse drug reactions. Hospital pharmacy. 1992;27(6):538.
19. McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother. 2002;36(9):1331-6.
20. Warlé-van Herwaarden MF, Valkhoff VE, Herings RM, Engelkes M, van Blijderveen JC, Rodenburg EM, et al. Quick assessment of drug-related admissions over time (QUADRAT study). Pharmacoepidemiol. Drug Saf. 2015;24(5):495-503.
21. Feigenbaum P, Neuwirth E, Trowbridge L, Teplitsky S, Barnes CA, Fireman E, et al. Factors

contributing to all-cause 30-day readmissions: a structured case series across 18 hospitals. Med Care. 2012;50(7):599-605.

22. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am. J. Epidemiol. 2011;173(6):676-82.

23. Steyenberg EW. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating (Statistics for Biology and Health). 2009th Edition.

24. Reynolds M, Hickson M, Jacklin A, Franklin BD. A descriptive exploratory study of how admissions caused by medication-related harm are documented within inpatients' medical records. BMC Health Serv. Res. 2014;14(1):257.

25. Rosen OZ, Fridman R, Rosen BT, Shane R, Pevnick JM. Medication adherence as a predictor of 30-day hospital readmissions. Patient Prefer Adherence. 2017;11:801.

26. Kardas P, Lewek P, Matyjaszczyk M. Determinants of patient adherence: a review of systematic reviews. Front. Pharmacol. 2013;4:91.

27. Sabaté, E. Adherence to long-term therapies: evidence for action. World Health Organization. Available from: https://apps.who.int/iris/bitstream/handle/10665/42682/9241545992.pdf Accessed November 27, 2019.

28. Mueller SK, Sponsler KC, Kripalani S, Schnipper JL. Hospital-based medication reconciliation practices: a systematic review. Arch Intern Med. 2012;172(14):1057-69.

29. Ravn-Nielsen LV, Duckert M-L, Lund ML, Henriksen JP, Nielsen ML, Eriksen CS, et al. Effect of an in-hospital multifaceted clinical pharmacist intervention on the risk of readmission: a randomized clinical trial. JAMA Intern. Med.. 2018;178(3):375-82.

30. Arnet I, Kooij MJ, Messerli M, Hersberger KE, Heerdink ER, Bouvy M. Proposal of standardization to assess adherence with medication records: methodology matters. Ann Pharmacother. 2016;50(5):360-8.

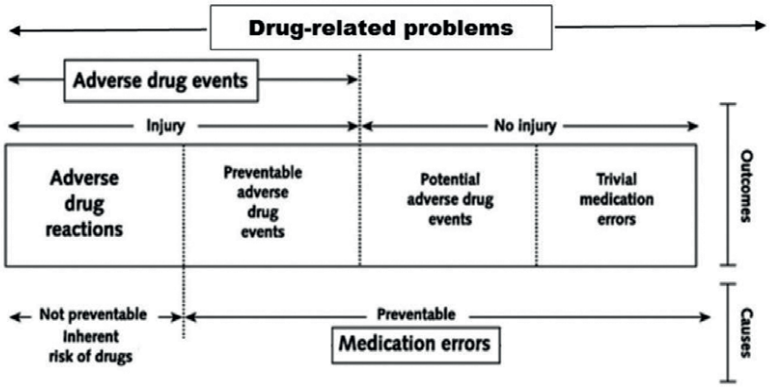
31. Otero M-J, Schmitt E, Nebeker JR, Samore MH, Barach P. Clarifying terminology for adverse drug events. Ann Intern Med. 2005;142(1):77.

32. Classification for Drug related problems: The PCNE Classification V 6.2. Pharmaceutical Care Network Europe [on-line]. Available at http://www.pcne.org/upload/files/11_PCNE_classification_V6–2.pdf Accessed April 28, 2016.

33. Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, et al. Incidence of adverse drug events and potential adverse drug events: implications for prevention. JAMA. 1995;274(1):29-34.

Supplementary Table 1 Association between drug-related problems, adverse drug events, adverse drug reactions, and medication errors. Adapted from Otero and Schmitt (5, 31).

	Definition	Examples
DRP	Drug-related problem: an event or circumstance involving drug therapy that actually or potentially interferes with the desired health outcomes (32).	A patient with an adverse drug event, adverse drug reaction or medication error. See examples below.
ADE	Adverse drug event: any injuries resulting from medication use, including physical harm, mental harm, or loss of function. ADEs can result from adverse drug reactions (non-preventable) or medication errors (preventable) (33).	An allergic reaction in a patient with a penicillin allergy receiving amoxicillin (non-preventable if previously unknown), an allergic reaction in a patient with a known allergy receiving amoxicillin (preventable), a gastric bleeding in a patient with an NSAID an gastric ulcer in the history (preventable).
ADR	Adverse drug reaction: a response which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function (12).	Antibiotic-induced diarrhea, cough due to an ACE inhibitor.
ME	Medication error: errors in the process of prescribing, dispensing, or administering the medications that many cause or lead to inappropriate medication use or patient harm while the medication is the control of the health care professional, patient, or consumer (13, 16).	Administration of methotrexate daily instead of weekly causing patient harm (i.e. a preventable ADE). A wrong dose prescribed for a child but not causing harm either due to intercepting the error before reaching the child, or to the overdose not causing symptoms in the child (i.e. a potential ADE).



Supplementary Table 2 Causality assessment: i.e. whether the readmission is due to medication (15, 16).

Question			
1. Is the reason of (re) admission known to be an adverse event of the suspected medication?	Reason of (re) admission is known to be an adverse event of the medication **Score:** +1	Reason of (re) admission is unknown to be an adverse event of new medication (<5 year registered in Europe) **Score:** 0	Reason of (re) admission is unknown to be an adverse event of well known medication (>5 year registered in Europe) **Score:** -1
2. Are there alternative causes that can explain the adverse event?	a) No alternative causes can explain the adverse event **Score:** +2	Alternative causes are present, but unlikely **Score:** 0	Possible other causes are present **Score:** -1
	b) Inexplicable exacerbation or comeback underlying condition **Score:** +1		
3. Does a plausible time relationship exist between the adverse event and start of medication administration (or the occurrence of the medication error)?	Time relationship as expected **Score:** +1	Time relationship is unclear **Score:** 0	Time relationship is not appropriate **Score:** -2

The subscores of the three questions are added to a total score, and classified as following:

Possible causal: total score +4
Probable causal: total score 0 till 3
Unlikely causal: total score -4 tm -1

Supplementary Table 3 Preventability assessment: i.e. a medication error caused the readmission (16-19)

Section A/ Section B

1. Answering YES to one or more of the following implies that an ADE is potentially preventable.
2. Was there a history of allergy, previous reactions or contra-indication to the drug?
3. Was the drug involved inappropriate for the patient´s clinical condition (e,g. renal function, liver function, pregnancy)?
4. Was the dose, route, or frequency of administration inappropriate for the patient´s age, weight or disease state?
   a. Was required therapeutic drug monitoring or other necessary laboratory tests not performed?
   b. If required therapeutic drug monitoring or other necessary laboratory tests were performed, insufficient actions has been taken?
5. Was a documented drug interaction involved in the ADE?
6. Was incorrect use of the drug involved in the ADE? (e.g. non-adherence)
   a. Was a preventative measure not administrated to the patient?
   b. If a preventative measure was administrated, was it inadequate, and/or inappropriate?

If answers are all negative to the above, then proceed to Section C.

Section C

The ADE is NOT preventable.

4

Patients' and providers' perspectives on medication relatedness and potential preventability of hospital readmissions within 30 days of discharge

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ABSTRACT

Background
Hospital readmissions are increasingly used as an indicator of quality in health care. One potential risk factor of readmissions is polypharmacy. No studies have explored the patients' perspectives on the medication relatedness and potential preventability of their readmissions.

Objective
To compare the patients' perspectives on the medication relatedness and potential preventability of their readmissions with the providers' perspectives.

Methods
Patients unplanned readmitted within 30 days after discharge at one of the participating departments of OLVG Hospital in Amsterdam were interviewed during their readmission. Patients' perspectives regarding medication relatedness of their readmissions, the potential preventability, possible preventable interventions, and satisfaction with medication information were examined. Healthcare providers also reviewed files of these readmitted patients. Primary outcome was the percentage of medication-related and potentially preventable readmissions according to the patient vs. the provider. Descriptive data analysis was used.

Results
According to patients, 36 of 172 (21%) readmissions were medication-related, and of these, 21 (58%) were potentially preventable. According to providers, 26 (15%) readmissions were medication-related and 6 (23%) of these were potentially preventable. Patients and providers agreed on the medication relatedness in 11 of the 172 readmissions, and in two of these, agreement on the potential preventability existed. According to patients, preventive interventions belonged mostly to the hospital level, followed by the primary care level and patient level.

Conclusion
Patients and providers differ substantially on their perspectives regarding the medication relatedness and preventability of readmissions. Patients were more likely to view medication-related readmissions as preventable.

INTRODUCTION

Unplanned hospital readmissions within 30 days are increasingly used as an indicator of quality and safety in health care (1-3). This assumed that readmissions are preventable. Measuring the preventability of readmissions is a challenge, because uniform factors related to preventable readmissions and a clear definition of 'preventability' have not been established (4-7). Feigenbaum et al. (8) found that on average, 8.7 factors contributed to each potentially preventable readmission. Those factors frequently occurred during follow-up care and were related to transition care planning and care coordination. Medication management was a factor in more than a quarter of readmissions, including medication errors during or after index admission and inadequate patient and caregiver understanding of medication management. The existing literature on medication-related readmissions shows that a median of 21% of readmissions are due to medication and 5%-87% (median 69%) of these readmissions were deemed preventable (9). The risk for medication-related problems increases with polypharmacy. A review indicates that 18%-38% of patients report medication-related problems after hospital discharge (10).

As the patient is the only constant factor in the care continuum, information from the patient is needed to get insight into medication-related problems occurring between discharge from hospital and readmission. Kari et al show that patient involvement is essential in detecting medication-related problems, because otherwise poor therapy control, non-optimal medication use, or intentional or unintentional non-adherence might be missed (11).

However, studies investigating patients' perspectives on medication relatedness and preventability of these readmissions are lacking. Consensus between patients and providers with respect to the role of medication as a potential cause of readmissions is necessary to achieve optimal pharmacotherapy (12). If a readmission is caused by medication according to the patient without being aware that his provider is not convinced of a causal association, a patient could stop independently with the suspicious medication resulting in non-adherence. On the other hand, if a provider believes the readmission is caused by medication but the patient is unaware of the provider's perspective, medication could still be taken by the patient resulting in a repeated readmission.

First, the aim of this study is to describe patients' perspectives on the medication relatedness and potential preventability of their readmissions and compare these with providers' perspectives. Secondly, we describe the patients' perspectives regarding interventions that could have prevented medication-related readmissions and the patients' satisfaction with information about medication during the index admission.

METHODS

Design and setting

The data for this cross-sectional observational study were collected within the context of a larger study on all-cause readmissions. This current study however focuses on medication-related readmissions. The study was performed at OLVG, a

general teaching hospital in Amsterdam, the Netherlands, from July 2016 until May 2017. A list with readmissions within 30 days of discharge was generated within the hospital information system and daily screened by the research coordinator for eligibility.

Patients ≥18 years readmitted within 30 days after an index admission (first admission) to one of the departments of cardiology, gastro-enterology, internal medicine, neurology, psychiatry, pulmonology and surgery were interviewed during their readmission. Patients were excluded if they were transferred to another hospital or self-discharged, or when it was not the first readmission of the patient and if the readmission was due to attempted suicide or when the patient did not use any medication at all. Furthermore, a readmission was excluded if it was scored by providers (see below) as unrelated to the index admission. This was done to exclude 30-day readmissions that occurred coincidentally. For example, a patient admitted with pneumonia discharged in a good clinical condition and readmitted within 30 days due to a traffic accident. Finally, providers had access to the interviews and registered whether they had used the interview in their review to assess the preventability of a readmission. If a patient interview was used by providers, this interview was excluded as well. The study was approved by the local review board of the hospital (ACWO-MEC, registration number: 16-028). Patient data were obtained and handled in accordance with privacy regulations.

Pharmaceutical care during the index admission

In the OLVG Hospital, two different processes are carried out to improve continuity of pharmaceutical care (13).

- On the departments of cardiology, pulmonology, internal medicine, gastroenterology and neurology, our hospital has implemented a Transitional Pharmaceutical Care (TPC)-program (14). In short, hospital pharmacy teams perform medication reconciliation at hospital admission and discharge using the dispensing history of the community pharmacy and information from the patient/carer himself. Any discrepancies between a patient's actual medication use and the medication prescribed in hospital are discussed with the resident. No formal medication review is performed. However, obvious errors in the pharmacotherapy are eliminated, for example lack of a laxative when an opioid is prescribed or no indication for hypnotics at discharge, addressing a stop date for antibiotics or opioids. The reason for medication changes is explained to the patient during discharge counselling, and a written medication summary is provided. The pharmacy team makes a TPC-medication overview that the resident could upload into the discharge letter.
- On the departments of psychiatry and surgery, residents and nurses are responsible for assessing a patient's actual medication use by interviewing patients/carers. If regarded necessary, they can request the hospital pharmacy to obtain a dispensing history from the community pharmacy. At hospital discharge, the resident uploads information from the hospital's prescribing system or types information into the discharge letter to the general practitioner.

Patients' perspectives

Patients were interviewed during their readmission, or three attempts were made by phone in case the patient was already discharged or when a caregiver (family member or partner) needed to be approached, or in case of a language barrier or when the patient was unable to answer the questions. A structured interview guide was developed based on previous studies on readmissions and expert opinion (15-20). For the purpose of this study, the following main topics were included: patients' perspectives on medication relatedness, patients' perspectives on potential preventability and preventive interventions, and patients' perspectives on medication-related information received during index admission (File S1). Additionally, the following socio-demographic factors were asked: nationality, living situation, educational level and self-experienced health status. Format of the questions included multiple-choice, yes/no and free text. Interviews were conducted by medical students who received the interview guide and were trained for this. Interviews lasted approximately 30 minutes. During the entire interview period, students were supervised by the coordinating physician-researcher. Interviewers manually recorded responses on data extraction sheets in Access 2010 (Microsoft).

Providers' perspectives

Healthcare providers who reviewed the readmissions were residents of the participating departments and a pharmacist. First, providers reviewed complete medical records of the readmitted patients to assess whether the readmissions were clinically related to the index admissions. If it was clinically related, the medication relatedness, using the algorithm of Kramer et al (21), and the preventability, using a modified algorithm of Schumock et al, were assessed (22). Readmissions that were assessed as potentially preventable by the providers or raised questions after the research coordinator's check were included to be discussed once a month, during a multidisciplinary meeting with the research coordinator, residents and a pharmacist. All readmissions assessed as medication-related by the residents and pharmacist have been reassessed by a senior physician (CS) and a clinical pharmacologist (MJ) to validate the findings.

Outcomes

Primary outcome was the percentage of medication-related and potentially preventable readmissions according to the patient vs the provider. Secondary outcomes were patients' perspectives regarding interventions that could have potentially prevented the readmission and percentage of patients who were satisfied with information about medication during their index admission.

Data analysis

Quantitative analysis was performed in SPSS version 21.0 (IBM SPSS). Data from interviews were analysed in MS Excel 2010 (Microsoft). For each question, frequency tables were made. The content of the open questions was qualitatively (inductively) independently coded by EU and AL. The codes were compared and discussed until consensus was reached. Hereafter, both researchers placed the codes into categories, which were also discussed until consensus was reached. Each answer was classified in one of these categories and presented in frequency tables in MS Excel. Patients' and providers' perspectives on medication relatedness and potential preventability were compared descriptively.

RESULTS

Of 646 readmissions that were screened, 427 (66%) readmissions met the inclusion criteria, and 227 interviews were conducted, of which 172 (76%) were included in the final data analysis (Figure 1). Main reasons that the interview was not conducted were as follows: failed attempts to get into contact (n = 50), unwillingness to participate (n = 39) and cognitive/physical problems (n = 34). One hundred fifty interviews (87%) were conducted with patients, 4 (2%) with patients and caregivers and 18 (10%) with caregivers. The mean age of the included patients was 62 years (SD 18), 47% were male, and the mean number of the medications at discharge of index admission was 9.2 (SD 5.9) (Table 1).

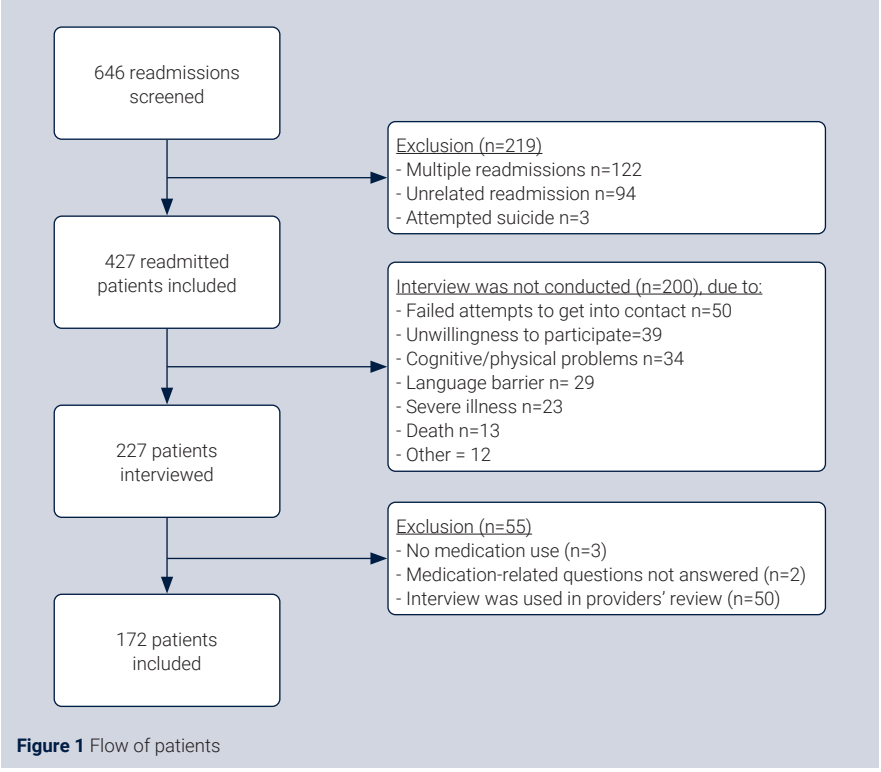

Figure 1 Flow of patients

Patients' and providers' perspectives on medication relatedness and potential preventability

Table 2 shows patients' and providers' perspectives on medication relatedness and potential preventability in 172 readmissions. According to patients' perspectives, 36 (21%) readmissions were medication-related, of which 21 (58%) were potentially preventable (File S2). The causes (n = 23) of the potentially preventable readmissions according to patients were as follows: issues with dosage (n = 8, 35%), for example antibiotic discontinued too soon or too high dosage prescribed; change in medication (n = 6, 26%), for example medication changes that were unclear to the patient; a medication interaction (n = 1, 4%); costs (n = 1, 4%); or adherence (n = 1, 4%). In six readmissions (26%), the patient described an adverse drug reaction as a cause, but in most of those cases, the patient could not pinpoint which medication exactly was responsible for the side-effects. According to providers' perspectives, 26 (15%) readmissions were medication-related, of which 6 (23%) were potentially preventable. In 11 of the 172 readmissions, patients and providers agreed on the medication relatedness, and in two of these, agreement on the potential preventability existed (File S2).

Patients' perspectives on preventive interventions

Of the readmissions that were medication-related and potentially preventable according to the patient (n = 21), patients reported 23 preventative interventions. Hospital-based interventions were 18 times reported, including performing more diagnostics (33%), improving medication-related information (17%), providing a longer hospital stay (17%), treating symptoms/complaints (17%), providing better aftercare (11%) or reacting faster (6%) (Table 3). In two cases, patients reported that general practitioner–based interventions could have prevented the readmission, by reacting faster. Two patients reported that he or she could have prevented the readmission by being adherent to therapy.

Patients' satisfaction on medication-related information

Table 4 shows patients' satisfaction on medication-related information. In readmissions that were medication-related but not preventable according to patients' perspectives (n = 15), patients reported in 93% (n = 14) that they had received as much information as they needed about medicines compared with 67% (n = 14) in readmissions deemed potentially preventable (n = 21). Also, information about side-effects of medicines was more often scored as 'as much information as I needed' in readmissions not preventable according to patients' perspectives compared with potentially preventable readmissions, 87% (n = 13) vs 43% (n = 9), respectively. In 73% (n = 11) of the readmissions scored as not preventable, patients received written instructions, compared with 57% (n = 12) in readmissions scored as potentially preventable.

Table 1 Patient and admission characteristics

Patient Characteristics	n=172
Interviewee	
Patient, n (%)	150 (87)
Patient and caregiver, n (%)	4 (2)
Caregiver, n (%)	18 (10)
Age, mean years (SD)	62 (18)
Male, n (%)	81 (47)
Native Dutch, n (%)	110 (64)
Living situation alone, n (%)	77 (45)
Help with medication use, yes (%)	64 (37)
Education level	
Primary (0-8 years education), n (%)	33 (19)
Secondary (9-12 years education), n(%)	88 (51)
Higher (>12 years education), n (%)	49 (28)
Unknown, n (%)	2 (1)
Experienced health status	
Moderate/bad, n (%)	63 (37)
Good, n (%)	106 (62)
Missing, n (%)	3 (2)
Number of medicine at discharge (index admission), mean (SD)	9 (6)
Admissions Characteristics	
Length of stay, days, mean (SD)	6 (7)
Time between discharge and readmission, mean (SD)	12 (8)
Unplanned index admission, n (%)	139 (80)
Discharge department, n (%)	
Surgery	42 (24)
Pulmonology	36 (21)
Internal Medicine	32 (19)
Cardiology	30 (17)
Gastroenterology	17 (10)
Neurology	15 (9)
Psychiatry	0 (0)

Table 2 Patients' and providers' perspectives on medication relatedness and potential preventability

Providers' perspectives			Patients' perspectives		
	Total readmissions n=172		Not medication-related (n=136)	**Medication-related (n=36)**	
				Not preventable (n=15)	Potentially preventable (n=21)
	Not medication-related (n=146)		121	9	16
	Medication-related (n=26)	Not preventable (n=20)	12	**5**	**3**
		Potentially preventable (n=6)	3	**1**	2

Table 3 Patients' reported interventions for preventable medication-related readmissions (n=21). Patients could mention more than one intervention

Question	Yes, n (%)
All interventions	23
Hospital based:	**18 (78)**
More diagnostics	6 (33)
Example patient's answer *"I did not get enough medicines to get an adequate INR. I asked to monitor my blood, however this was not done. I got discharged with an INR of 1.2."*	
Improving medication related information	3 (17)
Example patient's answer *"I was confused about my diuretics, one was started and one was stopped. I would get some diuretics upon discharge, however at discharge there was a lot of confusion and I did not get them. Not taking the diuretics could contribute to my rehospitalisation".*	
Longer hospital stay	3 (17)
Example patient's answer *"My father was discharged too early. The neurologist could not find anything and he thought it was something with the heart. However, the cardiologist refused to examine my father, so there was no follow-up. We thought something was wrong with the medication, but they did not listen to us. Now he is readmitted due to a way too low blood pressure."*	
Treating symptoms/ complaints	3 (17)
Example patient's answer *"The anti-inflammatory medicines should have been given longer, then the shortness of breath might not have come back."*	
Better aftercare	2 (11)
Example patient's answer *"I read in the package leaflet that ciprofloxacin could cause pain in the Achilles tendon; I needed home care because I could not walk anymore because of the pain."*	

Table 3 *Continued*

Question	Yes, n (%)
React faster	1 (6)
Example patient's answer: *"I should have gotten a higher dose of dexamethasone earlier, then my readmission might have been prevented."*	
General practitioner based:	**2 (9)**
React faster	2 (100)
Example patient's answer: *"My general practitioner should have arranged home care, because I needed help with daily self-care activities."*	
Patient based:	**2 (9)**
Therapy compliance	2 (100)
Example patient's answer: *"I have mixed up Oxynorm® and Oxycontin®."*	
Other:	**1 (4)**
Unclassifiable due to lack of clear information	1 (100)

Table 4 Patients' satisfaction of medication-related information during index admission

	Not medication-related according to patients' perspectives (n=136) n, (%)	Medication-related according to patients' perspectives (n=36) n, (%)	
		Not preventable (n=15)	Potentially preventable (n=21)
How much information did you receive during hospitalization about medicines you had to take at home?			
- No information or some information, but not enough.	19 (14)	1 (7)	7 (33)
- As much information as I needed	117 (86)	14 (93)	14 (67)
How much information did you receive during hospitalization about side effects of medicines you had to take at home?			
- No information or some information, but not enough	58 (42)	2 (13)	12 (57)
- As much information as I needed	78 (58)	13 (87)	9 (43)
Did you receive written instructions at discharge about medicines you had to take at home?			
- No	59 (43)	4 (27)	9 (43)
- Yes	77 (56)	11 (73)	12 (57)

DISCUSSION

This study shows that according to patients, readmissions are more often medication-related (21% of readmissions in patients vs 15% in providers) and are more often potentially preventable (patients 58% vs providers 23%) compared to providers. Patients and providers agreed on the medication relatedness in 11 of the 172 readmissions, and in two of these, agreement on the potential preventability existed. Patients reported most often that actions in the hospital were needed to potentially prevent readmissions. Patients who stated that their readmission was preventable more often reported that they lacked information regarding medicines and about side-effects and written instructions.

To our knowledge, this is the first study showing the perspectives of patients and providers on the role of medication in readmissions. Previous studies have described the perspectives of patients and providers on the preventability of all-cause readmissions (8, 23-28). A recent European study investigated the opinions of all-cause readmitted patients, their carers, nurses and physicians on predictability and preventability (27). They found that consensus on predictability and preventability of all-cause readmissions was poor, especially between patients and professionals (kappa values ranged from 0.105 to 0.173). This is in line with our study, where patients reported more often that the readmissions were preventable compared to providers. Also, Smeraglio et al. found that patients often felt more could have been done at discharge to prevent readmissions compared to providers (24). Interestingly, they found that nurse case managers more often agreed with the patients' perspectives compared to physicians. They hypothesized that fundamentally, physicians place more onus on patients to self-advocate for care, while nurse case managers emphasize the system providing support. This suggests that including the perspectives of the nurse case managers could be useful to assess the preventability from a broader perspective, including the help that the care system could have offered.

Several explanations can be given for the disparities in perspectives of patients and providers. First, this can be related to the differences in pharmacological knowledge between patients and providers. When providers review the readmission, they may recognize a complication or contraindication from a medication responsible for the readmission which the majority of patients would be unaware of. For example, if a patient is readmitted because of symptoms of a digoxin intoxication, a patient could think this is because of worsening of the underlying disease, where a provider will relate this to digoxin. Secondly, providers used the information available in the hospital to review readmissions and lack information about what happened after discharge. Therefore, medication-related problems and compliance issues after discharge could be missed. Consequently, providers could relate the readmission to worsening of the underlying disease and patients could indicate that this is caused by medication-related problems. Lastly, patients and providers differed in the perspective of the care that was needed. Some patients were dissatisfied at discharge because of different expectations of their admission and the continuation of care after discharge, while according to the providers, adequate standard of care has been provided. All in all, more studies are needed to identify the exact reasons for the gap between patients' and providers' perspectives. Given the preventive interventions cited by the patients

in this study: diagnostics, longer hospital stay, treating symptoms and improving medication-related information, the patients seem to feel not ready for discharge. Van Galen et al. showed that the patient reporting not feeling ready for discharge was strongly associated with predictability and preventability (27). Also, patients in our study who stated that their readmission was preventable were less satisfied about the information regarding medicines. Nowadays, patients are discharged as early as possible. As a consequence, it is a challenge to provide adequate patient education about their disease, medication purpose, medication changes, reason for changes and side-effects during short hospital stays.

This suggests that more patient engagement is needed not only during hospitalization, but also in the discharge process and the period after hospitalization, especially for pharmaceutical care. This could be achieved by several methods, such as the use of lay language, asking patients what they want to know regarding their medicines, providing written information, repeating information or using the 'teach-back' method, which is a strategy in which patients are asked to restate information that has been presented to them (29). As previous studies have shown that patients' needs can increase after discharge, also a follow-up phone call after discharge could be helpful to identify and to prevent medication-related problems (30-32). Further research should find out how these interventions could help to reduce medication-related readmissions.

The strength of this study is the description and comparison of the medication relatedness and potential preventability of readmissions according to perspectives of both patients and providers from several hospital departments. However, some limitations need to be discussed. This study is conducted in one hospital, which limits the generalizability. Another limitation is that patients were interviewed about the index admissions during readmission, which could lead to subjectivity and hindsight bias. However, in this way we could obtain information of the period after discharge of the index admission. Some patients could not be interviewed due to severe illness or unwillingness to participate. This could lead to selection bias as healthier or more satisfied patients were more often interviewed, which may have resulted in lower reporting of medication relatedness and preventability.

Conclusion

Patients and providers differ substantially on their perspectives regarding medication relatedness and potential preventability of hospital readmissions. According to patients, medication-related readmissions occur more often and are more often potentially preventable compared with providers' perspectives. Patients reported most often that actions on the hospital level were possible to potentially prevent the readmission. Further studies need to explore the reasons for the gap between patients' and providers' perspectives.

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REFERENCES

1. Ashton CM, Del Junco DJ, Souchek J, Wray NP, Mansyur CL. The association between the quality of inpatient care and early readmission: a meta-analysis of the evidence. Med Care. 1997:1044-59.
2. Fischer C, Anema HA, Klazinga NS. The validity of indicators for assessing quality of care: a review of the European literature on hospital readmission rate. Eur J Public Health. 2012;22(4):484-91.
3. Kristensen SR, Bech M, Quentin W. A roadmap for comparing readmission policies with application to Denmark, England, Germany and the United States. Health Policy. 2015;119(3):264-73.
4. Kneepkens E-L, Brouwers C, Singotani RG, de Bruijne MC, Karapinar-Çarkit F. How do studies assess the preventability of readmissions? A systematic review with narrative synthesis. BMC Med Res Methodol. 2019;19(1):128.
5. Van Walraven C, Bennett C, Jennings A, Austin PC, Forster AJ. Proportion of hospital readmissions deemed avoidable: a systematic review. CMAJ. 2011;183(7):E391-E402.
6. Yam C, Wong E, Chan F, Wong F, Leung M, Yeoh E. Measuring and preventing potentially avoidable hospital readmissions: a review of the literature. Hong Kong Med J. 2010;16(5):383-9.
7. van Walraven C, Jennings A, Forster AJ. A meta-analysis of hospital 30-day avoidable readmission rates. J Eval Clin Pract. 2012;18(6):1211-8.
8. Feigenbaum P, Neuwirth E, Trowbridge L, Teplitsky S, Barnes CA, Fireman E, et al. Factors contributing to all-cause 30-day readmissions: a structured case series across 18 hospitals. Med Care. 2012:599-605.
9. El Morabet N, Uitvlugt EB, van den Bemt BJ, van den Bemt PM, Janssen MJ, Karapinar-Çarkit F. Prevalence and preventability of drug-related hospital readmissions: a systematic review. J Am Geriatr Soc. 2018;66(3):602-8.
10. Garcia-Caballos M, Ramos-Diaz F, Jimenez-Moleon JJ, Bueno-Cavanillas A. Drug-related problems in older people after hospital discharge and interventions to reduce them. Age Ageing. 2010;39(4):430-8.
11. Kari H, Kortejärvi H, Airaksinen M, Laaksonen R. Patient involvement is essential in identifying drug-related problems. Br J Clin Pharmacol. 2018;84(9):2048-58.
12. Mullen PD. Compliance becomes concordance: making a change in terminology produce a change in behaviour. BMJ. 1997;314(7082):691-692.
13. Uitvlugt EB, Suijker R, Janssen MJ, Siegert CE, Karapinar-Çarkit F. Quality of medication related information in discharge letters: a prospective cohort study. Eur J Intern Med. 2017;46:e23-e5.
14. Karapinar-Çarkit F, Borgsteede SD, Zoer J, Egberts TC, van den Bemt PM, Tulder Mv. Effect of medication reconciliation on medication costs after hospital discharge in relation to hospital pharmacy labor costs. Ann Pharmacother. 2012;46(3):329-38.
15. Chew LD, Bradley KA, Boyko EJ. Brief questions to identify patients with inadequate health literacy. Fam Med. 2004;36(8):588-594.
16. Graumlich JF, Novotny NL, Aldag JC. Brief scale measuring patient preparedness for hospital discharge to home: Psychometric properties. Hosp Med. 2008;3(6):446-54.
17. Fransen M, Van Schaik T, Twickler T, Essink-Bot M. Applicability of internationally available health literacy measures in the Netherlands. J Health Commun. 2011;16(sup3):134-49.
18. Schroeder K, Fahey T, Hay AD, Montgomery A, Peters TJ. Adherence to antihypertensive medication assessed by self-report was associated with electronic monitoring compliance. J Clin Epidemiol. 2006;59(6):650-1.
19. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens. 2008;10(5):348-54.
20. RAND. 36-item health survey. https ://www.rand.org/health-care/ surve ys_tools/ mos/36-item-short-form.html. Visited on 16 August 2019.
21. Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions: I. Background, description, and instructions for use. JAMA. 1979;242(7):623-32.
22. Leendertse AJ, Egberts AC, Stoker LJ, van den

Bemt PM, Group HS. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med. 2008;168(17):1890-6.

23. Auerbach AD, Kripalani S, Vasilevskis EE, Sehgal N, Lindenauer PK, Metlay JP, et al. Preventability and causes of readmissions in a national cohort of general medicine patients. JAMA Intern Med. 2016;176(4):484-93.

24. Smeraglio A, Heidenreich PA, Krishnan G, Hopkins J, Chen J, Shieh L. Patient vs provider perspectives of 30-day hospital readmissions. BMJ Open Qual. 2019;8(1):e000264.

25. Stein J, Ossman P, Viera A, Moore C, Brubaker BA, French J, et al. Was This Readmission Preventable? Qualitative Study of Patient and Provider Perceptions of Readmissions. South Med J. 2016;109(6):383-9.

26. Sutherland T, David-Kasdan JA, Beloff J, Mueller A, Whang EE, Bleday R, et al. Patient and provider-identified factors contributing to surgical readmission after colorectal surgery. J Invest Surg. 2016;29(4):195-201.

27. van Galen LS, Brabrand M, Cooksley T, van de Ven PM, Merten H, So RK, et al. Patients' and providers' perceptions of the preventability of hospital readmission: a prospective, observational study in four European countries. BMJ Qual Saf. 2017;26(12):958-69.

28. Carter J, Ward C, Wexler D, Donelan K. The association between patient experience factors and likelihood of 30-day readmission: a prospective cohort study. BMJ Qual Saf. 2018;27(9):683-90.

29. Eibergen L, Janssen MJ, Blom L, Karapinar-Çarkit F. Informational needs and recall of in-hospital medication changes of recently discharged patients. Res Social Adm Pharm. 2018;14(2):146-52.

30. Anthony MK, Hudson-Barr D. A patient-centered model of care for hospital discharge. Clinical nursing research. 2004;13(2):117-36.

31. Cawthon C, Walia S, Osborn CY, Niesner KJ, Schnipper JL, Kripalani S. Improving care transitions: the patient perspective. Clin Nurs Res. 2012;17(sup3):312-24.

32. Grimmer K, Moss J. The development, validity and application of a new instrument to assess the quality of discharge planning activities from the community perspective. Int J Qual Health Care. 2001;13(2):109-16.

Supplementary file 1 - Interview

Admission number:_____
Date of interview:_____
Name of interviewer:_____

Questions for the patient:

1. You were admitted to the hospital from _____ to _____ Why were you admitted to the hospital?

   _____

2. What do you think that the reason is that you are readmitted?

   _____

Interviewer: I would like to discuss your experiences about your previous hospitalization from _____ to _____

3. How much information did you receive during hospitalization on medicines you had to take at home?
   a. No information
   b. Some information, but not enough
   c. As much information as I needed
   d. Not applicable (I don't take medication)

4. How much information did you receive during hospitalization on side effects of medicines you had to take at home?
   a. No information
   b. Some information, but not enough
   c. As much information as I needed
   d. Not applicable (I don't take medication)

5. Did you receive written instructions upon discharge on medicines you had to take at home? If so, did anyone take the time to explain the written instructions?
   a. I have not received written instructions
   b. Yes, I have received written instructions but nobody has taken the time to explain them
   c. Yes, I have received written instructions and yes, someone has taken the time to explain them
   d. Not applicable (I don't take medication)

Interviewer: I would like to discuss your experiences about the period between your previous and your current hospitalization

6. How many different medicines do you use at home?

   _____

7. Do you also use medicines that you buy without a prescription at a drugstore, pharmacy or health food store? (e.g. vitamins, anti-pain agents, soothing agents, herbs, homeopathic remedies, purchased online)
   o No o Yes, namely _____

8. Are you receiving any help with your medication at home?
   o Yes, home care
   o Yes, family member or _____
   o Yes, week box / multi dose drug dispensing system
   o No
   o Not applicable (I don't take medication)

9. Do you think your medication contributed to having to go to the hospital again? (e.g. side effect, too many medicines)
   o No o Yes, namely _____
   o Not applicable (I don't take medication)

10. If you look back at your last admission, is there something that your doctor, the hospital, your family or yourself could have done differently so that you would not have been admitted to the hospital again?
    o No o Yes, namely
    o General practitioner _____
    o Hospital _____
    o Family _____
    o Self _____
    o Other _____

Interviewer: I would like to ask you some general questions.

11. What is your living situation at the moment?
    o I live alone o I live together

12. In which country were you born?
    o The Netherlands o Suriname o NL Antilles o Turkey o Morocco o Other, namely: _____

13. In which country was your mother born?
    o The Netherlands o Suriname o NL Antilles o Turkey o Morocco o Other, namely: _____

14. In which country was your father born?
    o The Netherlands o Suriname o NL Antilles o Turkey o Morocco o Other, namely: _____

15. What is your highest completed education?
    o No training completed
    o Primary school
    o Secondary general education (such as MAVO, (M) ULO)
    o (Lower) vocational education (such as LTS, MBO, MTS, MEAO, MHNO, INAS)
    o Higher general secondary education (such as HAVO, VWO, HBS, MMS)
    o Higher professional education (such as HBO, HTS, HEAO, PABO)
    o University
    o Other, namely _____

16. In general, would you say your health is:
    a. Excellent
    b. Very good
    c. Good
    d. Fair
    e. Poor

To be completed by the Interviewer:
The questionnaire was completed with:
    o Patient himself o Patient / caregiver o Caregiver

Have you experienced a language barrier with the patient / caregiver:
    o No o Yes, namely _____

How long did the interview last in minutes: _____

Remarks / details / notes
    o No o Yes, namely _____

Supplementary file 2 - Patient's and providers' explanations

	Patient			Provider			
	Patient's reason for readmission	**Patient's explanation that medication caused a potentially preventable readmission**	**Classification**	**Providers' reason for readmission**	**Providers' medication related**	**Providers' potentially preventable**	**Providers' explanation**
1	CVA	Dosage of blood pressure pill too high already mentioned at index admission (blood pressure was much too low)	DOSAGE	Recurrence of CVA	No	n.a.	Worsening of disease, despite treatment according to guideline
2	Stomach pain, shortness of breath	Too few pills to get INR at good value	DOSAGE	Shortness of breath	No	n.a.	Shortness of breath due to hyperventilation
3	Too few white blood cells	Prednisolone phased out too quickly	DOSAGE	Recurrence of Thrombotic thrombocytopenic purpura (TTP)	No	n.a.	Worsening of disease, despite treatment according to guideline
4	Clostridium infection	Vancomycin was stopped too early	DOSAGE	Aspiration pneumonia	No	n.a.	Worsening of disease, despite treatment according to guideline
5	Appendicitis surgery complication	Antibiotics should have been given some more days	DOSAGE	Stomach pain and nausea	No	n.a.	Calculated risk, treatment during index admission was in accordance with guidelines
6	Outages of the left brain	Dosage of dexamethason should have been higher	DOSAGE	Outages of the left brain	No	n.a.	Worsening of disease, despite treatment according to guideline
7	Shortness of breath	The anti-inflammatory medicines should have been given longer, then the cough/shortness of breath might not have come back	DOSAGE	STEMI	No	n.a.	Unlikely that STEMI is caused by medication

	Patient			Provider			
	Patient's reason for readmission	**Patient's explanation that medication caused a potentially preventable readmission**	**Classification**	**Providers' reason for readmission**	**Providers' medication-related**	**Providers' potentially preventable**	**Providers' explanation**
8	Shortness of breath	My inhalation medication should not have been stopped during index admission and prednisolone dosage was too low	MEDICATION CHANGE and DOSAGE	COPD exacerbation	No	n.a.	Worsening of disease, despite treatment according to guideline
9	CVA	Blood thinners were discontinued during index admission.	MEDICATION CHANGE	CVA	No	n.a.	Worsening of disease, despite treatment according to guideline
10	Shortness of breath	Confusion about diuretics, one was started and one was stopped	MEDICATION CHANGE	Heart Failure	Yes	No	Furosemide was stopped, this was a calculated risk.
11	Low blood pressure and pain in the calves	I have mixed up Oxynorm® and Oxycontin®	MEDICATION CHANGE	Worsening of infection and overall malaise	No	n.a.	Worsening of disease, despite treatment according to guideline
12	Lots of coughing and tired	Medication was out of stock in the pharmacy and the dosage was unclear. I needed more information and answers to my questions	MEDICATION CHANGE	Upper respiratory tract infection	No	n.a.	Worsening of disease, despite treatment according to guideline
13	Anxiety, could not stand up anymore	I could not pay my benzodiazepines at discharge and a lot of medication changes in my medication for depression could have caused my readmission. The hospital should not give me medication that I cannot pay.	MEDICATION CHANGE and COSTS	COPD exacerbation	No	n.a.	Worsening of disease, despite treatment according to guideline

14	High blood pressure	I discontinued indapamide, because of adverse drug reactions; I should have had more information about side effects.	ADHERENCE	hypertensive urgency	Yes	Yes	Indapamide, non-adherence
15	Urinary Infection	Interaction with medication for thyroid gland; discharge was too early.	DRUG-DRUG INTERACTION	Vomiting	No	n.a.	Worsening of disease, despite treatment according to guideline
16	Could not walk, due to Achilles tendon	I read in the package leaflet that ciprofloxacine could cause pain in the Achilles tendon	ADVERSE DRUG REACTION	Tendonitis by ciprofloxacin	Yes	No	Ciprofloxacin, adverse drug reaction
17	Vomiting	Medication that works on the stomach, my stomach had to be checked before discharge	NON-SPECIFIC	Stomach upset	No	n.a.	Complication of surgery
18	Shortness of breath	All the medication together, I got too much stress at home after discharge, and I had do to activities that I couldn't.	NON-SPECIFIC	COPD exacerbation	Yes	Yes	Seretide, non- adherence
19	Fallen at home	Side effects of metformin and paracetamol	NON-SPECIFIC	NSTEMI	Yes	No	Trastuzumab, adverse drug reaction
20	Unwell during a outpatient check	Due to side effects of oxydon or too much supplements: I should have stayed longer at index admission, to recuperate	NON-SPECIFIC	Overall malaise	No	n.a.	Worsening of disease, despite treatment according to guideline
21	Black toe	Medication could have caused my black toe: more diagnostics were needed.	NON-SPECIFIC	Worsening of diabetic foot	No	n.a.	Worsening of disease, despite treatment according to guideline

Part 2

Transfer of medication-related information after discharge

5

Quality of medication-related information in discharge letters: A prospective cohort study

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LETTER TO THE EDITOR

Transitions from one care setting to another is a well known risk factor for medication errors (1). Inaccurate or delayed information transfer between settings could lead to serious harm to patients. Coleman et al. reported more readmissions in patients with incomplete medication lists versus patients with an accurate and complete list (14.3% versus 6.1%) (2). In order to improve the transfer of medication-related information, a guideline was drafted by the Dutch healthcare inspectorate, similar to guidelines that have been published internationally (3-5). The aim of this study was to evaluate the adherence to the guideline for medication-related information in discharge letters. Secondary outcomes were determinants associated with completeness of discharge letters and timeliness of sending discharge letters to primary care.

A prospective study was performed in a 550-bed general teaching hospital in the Netherlands (OLVG), from February–April 2013. Adult patients discharged from the departments of neurology, cardiology, pulmonology, internal medicine, surgery, orthopedics, psychiatry and pediatrics, were included if they used at least one medication intended for chronic use and were admitted at least twenty-four hours.

In the OLVG hospital two different processes were carried out to assess a patient's medication use:

- On the departments of internal medicine, orthopedics, pediatrics, psychiatry and surgery, residents and nurses were responsible for assessing a patient's actual medication use by interviewing patients/carers. If regarded necessary, they could request the hospital pharmacy to obtain a dispensing history of the community pharmacist (CP). At hospital discharge, the resident uploaded information from the hospital's prescribing system or typed information into the discharge letter.
- On the departments of cardiology, pulmonology and neurology our hospital implemented a Transitional Pharmaceutical Care (TPC)-program (6). In short, hospital pharmacy teams collected medica- tion histories from the CP. The hospital pharmacy performed medication reconciliation at hospital admission and discharge using the CP's medication history and information from the patient/carer himself. Any discrepancies between a patient's actual medication use and the medication prescribed in hospital were discussed with the resident. The pharmacy team made a TPC-medication overview that the resident could upload into the discharge letter.

The Dutch guideline for transfer of medication-related information stated that the next healthcare provider needs to receive an up-to-date medication overview within 24 h after discharge from a hospital (3). The guideline included six key criteria (Table 2).

Discharge letters were collected from the hospital's electronic patient record. The primary outcome was the proportion of patients for whom the discharge letters complied with the six key criteria of the guideline. Secondary outcomes were determinants influencing the adherence and timeliness of sending of discharge

letters to primary care.
A multilevel linear regression analysis was used to adjust for differences between departments and residents of the same department. The first level was set on the patient level, the second level on resident level, and the third level on department level. A forward selection procedure was used to define the greatest predictors. The level of significance was set on $p<0.05$ with a 95% CI.

A total of 288 patients were included (mean age: 62 years, mean number of pre-admission medication: 7.3, Table 1). For 8 patients (3%) the discharge letter adhered to the six key criteria of the guideline (Table 2). Discharge letters complied the least with the actual pharmacotherapy criterion (n = 17, 6%). On average, discharge letters scored 4.6 of 6 points.

Table 1 Characteristics of included patients (n=288)

Characteristic	
Mean age, years (SD)	62 (25)
Sex male, n (%)	133 (46)
Pre-admission medication, mean (SD)	7.3 (4.8)
Use of a weekly compliance aid, n (%)	61 (21)
Planned admission, n (%)	77 (27)
Length of stay, mean days (SD)	12.4 (13.5)
Inclusion in TPC-program, n (%)	90 (31)
Discharged in weekend, n (%)	24 (8)
Patients per department	
Internal medicine, n (%)	55 (19)
Orthopedics, n (%)	45 (16)
Neurology, n (%)	40 (14)
Cardiology, n (%)	38 (13)
General surgery, n (%)	36 (13)
Pulmonology, n (%)	36 (13)
Pediatrics, n (%)	34 (12)
Psychiatry, n (%)	4 (1)
Residential situation after discharge	
Home, n (%)	235 (82)
Other (e.g. nursing home), n (%)	53 (18)

In total, 1264 (47%) of 2696 medications were documented correctly in the discharge letter. Of the incorrectly reported medications (n = 1432, 53%), 453 medications were incomplete as the drug name or the dosage were absent. Another 979 medications were incomplete as there was a discrepancy between actual use by patients and the prescription, without a reason mentioned for this discrepancy in the discharge letter (e.g. only a statement *use medication as in the home setting* was documented). In total, 979 (68%) medications revealed a discrepancy between actual use by patients and the prescription. In 50% of these cases (n = 494), the medication was absent in the discharge letter and no indication for discontinuation could be found. Also, 279 (28%) new medications were started without the reason mentioned in the discharge letter. Unexplained differences in dosages/frequencies and switches within the same drug class occurred less often.

Discharge letter adherence appeared to be significantly diminished for patients who were discharged to an institutional setting (− 0.19 points; p = 0.012), for patients with a higher number of medications (per medication − 0.03 points; p < 0.001) and for patients with prolonged stay (every day − 0.016 points; p = 0.001). However, discharge letter adherence was significantly increased if structural medication reconciliation was performed in the TPC-program (0.26 points; p= 0.003). Time between the discharge date and the actual sending date of discharge letters varied between − 1 day to + 54 days, with a median timeline of 6 days. Seventy (24%) discharge letters were sent within the required 24 h.

The results of this study show that for only 3% of patients the discharge letter adhered to the national guideline. Especially incomplete information regarding actual pharmacotherapy and a motivation for pharmacotherapeutic changes was missing. Completeness and timeliness delivery are lacking as shown in several international studies (2, 7, 8). Hammad et al. found a mean discharge summary adherence to the UK National Prescribing Centra requirements of 67% and for information about therapy changes during hospitalization of 49% (7). Since this study did not perform medication reconciliation, it may overestimate adherence. Tan et al. reported that documentation of indications for changes and follow-up was only complete in 50% (n = 82) of the 163 discharge summaries with at least one medication change (8), which is in agreement with our study.
Several determinants influence the adherence to the guideline. We found a significant effect of structured medication reconciliation in the TPC-program, as found in previous studies (9, 10). Discharge letters were less complete for patients who were discharged to an institutional setting and for patients with a prolonged hospital stay, probably due to the high complexity of care for these patients.

The incomplete medication-related information in discharge letters found in our as well as previous studies highlight the need for improvement. More awareness of the risks of incomplete information transfer is needed and structured medication reconciliation must be performed on each department, supported by information systems. Besides, transitional pharmaceutical care needs to be extended after discharge. More collaboration with the primary healthcare is needed to ensure medication-related information is incorporated by other healthcare providers and to ensure adequate follow-up of patients.

Table 2 Adherence of the actual medication overview in discharge letters to the six key criteria of the Dutch guideline for medication-related information in discharge letters (n=288)

Guidance criteria	Complete, n (%)
1. Actual pharmacotherapy and motivation for changes in pharmacotherapy	17 (6)
2. Usage of alcohol and drugs	257 (89)
3. Actual prescriber	288 (100)
4. Elementary patient characteristics	288 (100)
5. Contraindication due to a drug allergy or adverse drug event (ADE)	247 (86)
6. Abnormal laboratory results	221 (77)
Total: all six criteria	8 (3)
Completeness per ward	**Completeness max. 6 points, mean (SD)**
Pediatrics (n=34)	4.88 (0.48)
Neurology (n=40)	4.80 (0.61)
Cardiology (n=38)	4.78 (0.62)
Pulmonology (n=36)	4.69 (0.67)
Psychiatry (n=4)	4.50 (0.58)
Internal medicine (n=55)	4.42 (0.79)
Orthopedics (n=45)	4.33 (0.64)
General surgery (n=36)	4.25 (0.97)
All wards (n=288)	4.58 (0.72)

The main strength of this study is the evaluation of discharge letters on multiple departments. However, some limitations need to be discussed. First, no gold standard for identification of pre-admission medication was available. In the Netherlands, a medication history of the CP with a patient interview is considered the best option, but there remains a possibility that patients used additional medication at their own initiative. Thus, the real number of discrepancies could be higher than we found. Secondly, this study was conducted in a single centre, limiting the external generalizability. Finally, we did not classify the seriousness of the medication discrepancies, which would be an interesting addition.

In conclusion, discharge letters rarely adhere to guideline requirements and subsequently lead to incomplete information transfer to the next healthcare provider. Adherence might be improved by further education of physicians and adequate support from information systems.

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REFERENCES

1. Tam VC, Knowles SR, Cornish PL, Fine N, Marchesano R, Etchells EE. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. CMAJ. 2005;173(5):510-5.
2. Coleman EA, Smith JD, Raha D, Min S-j. Posthospital medication discrepancies: prevalence and contributing factors. Arch Intern Med. 2005;165(16):1842-7.
3. Ministry of Health and the Health Care Inspectorate. Policy document: transfer of information on medication in the continuum of care [in Dutch]. 2008. Accessed 6 February 2014 at www.medicatieoverdracht.nl/artikelen/raadplegen.asp?display=2&atoom=9008&atoomsrt=2&actie=2&menuitem=189.
4. Australian Pharmaceutical Advisory Council. Guiding principles to achieve continuity in medication management. 2005. Accessed 2 June 2014 at http://www.health.gov.au/internet/main/publishing.nsf/Content/5B47B202BBFAFE02CA257BF0001C6AAC/$File/guiding.pdf.
5. How-to Guide: Prevent Adverse Drug Events by Implementing Medication Reconciliation. Cambridge, MA: Institute for Healthcare Improvement. 2011. Accessed 2 June 2014 at www.ihi.org.
6. Karapinar-Çarkit F, Borgsteede SD, Zoer J, Egberts TC, van den Bemt PM, Tulder Mv. Effect of medication reconciliation on medication costs after hospital discharge in relation to hospital pharmacy labor costs. Ann Pharmacother. 2012;46(3):329-38.
7. Hammad EA, Wright DJ, Walton C, Nunney I, Bhattacharya D. Adherence to UK national guidance for discharge information: an audit in primary care. Br J Clin Pharmacol. 2014;78(6):1453-64.
8. Tan B, Mulo B, Skinner M. Transition from hospital to primary care: an audit of discharge summary–medication changes and follow-up expectations. Intern Med J. 2014;44(11):1124-7.
9. Karapinar-Çarkıt F, Borgsteede SD, Zoer J, Siegert C, van Tulder M, Egberts AC, et al. The effect of the COACH program (Continuity Of Appropriate pharmacotherapy, patient Counselling and information transfer in Healthcare) on readmission rates in a multicultural population of internal medicine patients. BMC Health Serv Res. 2010;10(1):39.
10. Vira T, Colquhoun M, Etchells E. Reconcilable differences: correcting medication errors at hospital admission and discharge. Qual Saf Health Care. 2006;15(2):122-6.

6

Completeness of medication-related information in discharge letters and post-discharge general practitioner overviews

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ABSTRACT

Background
Communication and documentation of medication-related information are needed to improve continuity of care.

Objective
To assess the completeness of medication-related information in discharge letters and post-discharge general practitioner (GP)-overviews.

Setting
A general teaching hospital in Amsterdam, the Netherlands.

Method
An observational study was performed. Patients from several departments were included after medication reconciliation at hospital discharge. In liaison with the resident and patient, a pharmacy team prepared a Transitional Pharmaceutical Care (TPC)-overview of current medications, including changes and allergies. The resident was instructed to download the TPC-overview into the discharge letter instead of typing a self-made medication list. Medication overviews were gathered from the GP 2 weeks after the handover of the discharge letter. The TPC-overview (gold standard) was compared with the information in the discharge letter and post-discharge GP-overviews regarding correct medications and allergies. Descriptive data analysis was used.

Main outcome measure
The number and percentage of complete medication-related information in the discharge letter and the GP-overview were compared to the TPC-overview.

Results
Ninety-nine patients were included. Medication-related information was complete in 62 (63%) of 99 discharge letters. Sixteen of 99 GP-overviews (16%) were complete. Communication of medication-related information increased documentation by the GP, but the medication history could still be incomplete, mainly regarding medication changes and allergies.

Conclusions
Medication-related information is lost in discharge letters and GP-overviews post-discharge despite in-hospital medication reconciliation. This could result in discontinuity of care.

INTRODUCTION

When patients are transferred from one healthcare setting to another, e.g. at hospital admission and hospital discharge, medication-related information is often incomplete (1, 2). This lack of information transfer between settings is seen worldwide, with a broad range in the number of discrepancies as a result of different study populations and different classification systems (1). These discrepancies in medication history may result into discontinuity of care and patient harm (3, 4). For example, Van der Linden et al. showed that 27% of the medicines, stopped during hospitalization due to an adverse drug reaction, were re-prescribed within 6 months after discharge (3). Unfortunately, the healthcare system is not equipped with one single healthcare professional who is responsible for an up-to-date medication overview (5). Therefore, clear documentation and accurate communication between healthcare providers are necessary to maintain up-to-date patient records.

At hospital discharge, discharge letters are used to inform the general practitioner (GP). The discharge letter should contain important medication-related information, including information about reasons for medication changes and allergies. However, studies have shown that discharge letters frequently arrive relatively late and are incomplete (2, 6).

In order to address the problems described above, a guideline was drafted by the Dutch healthcare inspectorate, similar to international guidelines (7-10). This guideline states that in every contact with the prescriber, there must be an up-to-date medication overview. And in case of an emergency admission or after transfer to another healthcare provider, there must be an up-to-date medication overview as soon as possible or at least within 24 h. The guideline stresses the importance of medication reconciliation and communication between healthcare settings to improve continuity of care.

Previous studies showed the positive effect of medication reconciliation on reduction of medication errors (11). Nevertheless, these studies are generally conducted in one setting, while medication reconciliation aims to reduce medication errors in the healthcare continuum (2, 12). Recently, Lefeber et al. (13) showed that communication of discharge medication, after medication reconciliation, did not improve the incorporation of these medication changes in GP files. This study focused solely on medication changes and not on the completeness and accuracy of all medication-related information, which is necessary for optimal continuity of care.

Aim of the study

The aim of this study was to assess the completeness of medication-related information in discharge letters and post-discharge general practitioner (GP)-overviews, 2 weeks after the handover of the discharge letter.

Ethical approval

This study was exempt from review by the institutional review board as the Dutch legislation does not require this for studies that do not affect the patient's integrity. Patients provided informed consent.

METHOD

Setting and population

An observational study was performed at the Sint Lucas Andreas Hospital, a 550-bed general teaching hospital in the Netherlands, from February to September 2012. Patients discharged from the departments of neurology, cardiology, pulmonology and internal medicine were included if there was at least one change in prescribed medication compared to pre-admission used medication. These departments were included because a Transitional Pharmaceutical Care program was implemented here. Exclusion criteria were: no informed consent, death, GP unknown and GPs who did not receive a discharge letter (as no comparison was possible) or did not respond after three requests for sending an overview of medications. Patients who were readmitted during the study period and patients not discharged to their were also excluded.

Usual care

A Transitional Pharmaceutical Care (TPC)-program has been implemented in the Sint Lucas Andreas Hospital since 2007 (Fig. 1), as previously described in detail elsewhere (14). This program is carried out by a pharmacy team consisting of pharmaceutical consultants and pharmacists as supervisors. Pharmaceutical consultants are pharmacy technicians who have followed an additional 3-year bachelor degree program. They are specifically trained in pharmacotherapy and communication with patients. Pharmaceutical consultants performed the TPC-program, and this process is summarized in Fig. 1. First, the *verification* step included comparing in-hospital prescribed medication with the medication used before admission using community pharmacy records and patient information. GP records were not consulted as Dutch studies have shown that community pharmacies records are more complete as patients generally attend one community pharmacy (14). Second, in the *clarification* step pharmacotherapy was checked for appropriateness (e.g. add laxative to opioid prescription or adjust medication due to a decreased kidney function). In the third *reconciliation* step, all medication changes were documented in a medication overview and discussed with the patient. In the last *transmission* step, the medication overview was communicated to the next healthcare provider. This medication overview contained information regarding allergies, all medications including any medication changes and over-the-counter medication and if relevant laboratory parameters. An example of this medication overview has been published elsewhere (15).

The resident was instructed to download the TPC-overview into the discharge letter using an electronic link. However, the resident could include a self-made overview into the discharge letter instead. The discharge letter was sent to the GP by secured e-mail.

Data collection

Medication-related information specified in the TPC-overview was considered the gold standard as this information was verified with the community pharmacy records and the patient, and approved by the resident after medication reconciliation, as

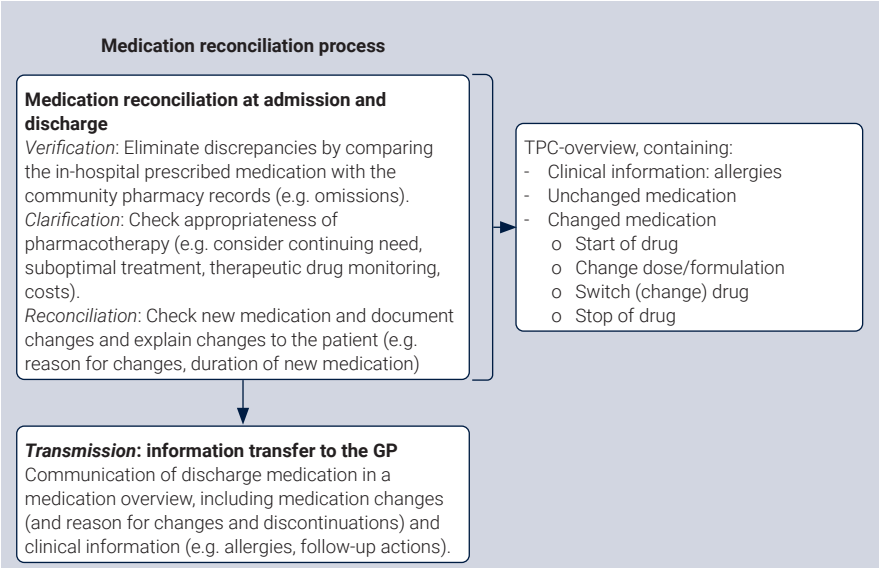

Figure 1 Transitional Pharmaceutical Care (TPC)-program (14)

described above. Medication-related information in the TPC-overview was classified as: unchanged medication, changed medication (i.e. newly started in hospital, dose change, switch to another drug or stop of medication that was used at home) and allergies.

Discharge letters of included patients were collected and compared with TPC-overviews by pharmacists (EU and checked by FK). Medication-related information in the discharge letter was considered complete if the information corresponded with the TPC-overview regarding right drug (including name, dose, frequency) and the right allergy. For stopped medication, we checked whether the medication was specified as stopped. Furthermore, the number of discharge letters that included a downloaded TPC-overview or a self-made medication list by the resident was determined.

Two weeks after sending the discharge letter to the GP, we requested the GP to send an actual medication overview as they normally would do in usual practice, including any allergies (i.e. GP-overview). The medication-related information in the GP-overview was also compared with the TPC-overview, as described above. For stopped medication, we checked whether a specification was present that the drug was stopped or whether the drug was absent in the GP-overview.

Outcomes

The outcomes were the number and percentage of complete medication-related information in the discharge letter and the GP-overview compared to the TPC-overview (gold standard). Also, the number of discrepancies between the discharge

letter and GP-overview compared to the TPC-overview was determined.

Data analysis

All data were collected in Microsoft Excel 2003 and were analysed using SPSS version 18.0.0. Frequencies of the proportion of complete medication-related information were calculated. The independent t test was used for continuous variables and the Chi-square test for frequencies.

RESULTS

A total of 160 patients were approached for this study and 99 (62%) patients were included (Fig. 2). The Main reasons for not including a patient was non-response of the GP after three attempts. No significant differences between included and excluded patients were found, based on gender, age and type of medication.

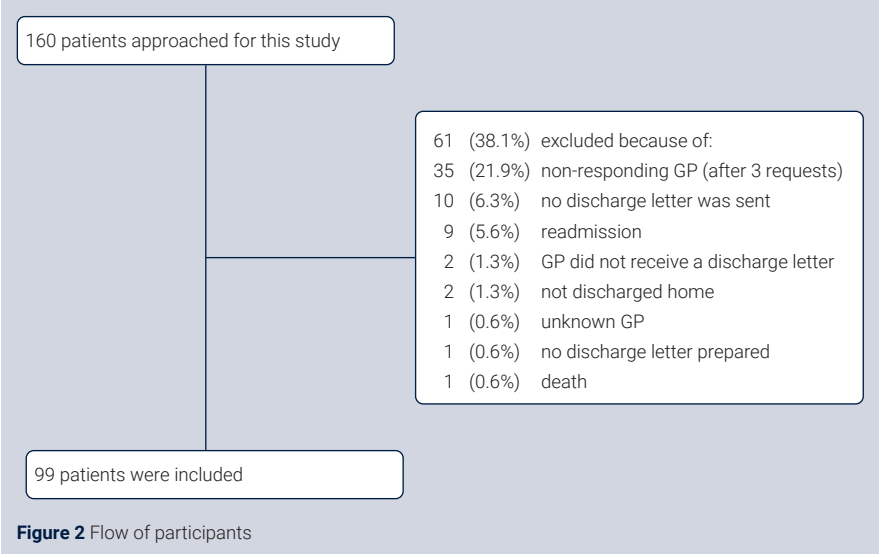

Figure 2 Flow of participants

Table 1 describes the characteristics of the included patients and the information present in the TPC-overview. Mean age of patients was 68 year, and the average number of drugs prescribed at discharge was 9 per patient. There were 1054 medication-related information items present in the TPC-overviews.

Information in the discharge letter

Sixty-two (63%) of 99 discharge letters were complete and there were 1.5 (SD 2.7) discrepancies per patient (Fig. 3). The TPC-overview was downloaded in 71 (72%) of 99 discharge letters and in 28 (28%) the resident included a self-made medication list. Of the 71 downloaded TPC-overviews, 13 (18%) were subsequently adjusted by the resident (e.g. information about stopped medication or an allergy was deleted).

Discharge letters with a downloaded TPC-overview were more frequently complete compared to discharge letters that included the resident's self-made medication list (58 vs. 4 letters). Of the 1054 medication-related information items, 908 (86%) were documented in the discharge letter (Table 2). Unchanged medication was correctly documented in 94% of the prescriptions, changed medication in 80% and allergies in 33%. Next to allergies, in particular stopped pre-admission used medication was missing.

Table 1 Patient characteristics and discharge medication of the Transitional Pharmaceutical Care (TPC)-program

Patient characteristics	**n=99**
Female, n (%)	50 (51)
Age, years, mean (SD)	68 (15)
Length of stay, days, mean(SD)	9 (7)
N. of drugs on discharge, mean (SD)	9 (4)
Department	
Cardiology, n (%)	58 (59)
Pulmonary, n (%)	12 (12)
Neurology, n (%)	5 (5)
Internal medicine, n (%)	24 (24)
TPC-overview characteristics, medication-related information	**n=1054**
Unchanged medication, n (%)	548 (52)
Changed medication, n (%)	485 (46)
New, n (%)	268 (55)
Dose/formulation, n (%)	94 (19)
Switch, n (%)	27 (6)
Stop, n (%)	96 (20)
Clinical information	
Allergies, n (%)	21(2)
Type of medication (Top 3)	
Cardiovascular, n (%)	372 (36)
Gastrointestinal and metabolism, n (%)	198 (19)
Blood and blood-forming organs, n (%)	144 (14)

Information in the GP-overview

GPs sent different types of overviews: an overview derived from the GP information system (n = 64), a copy of the discharge letter (n = 16), a handwritten overview (n = 12), prescriptions (n = 2) and community pharmacy overviews (n = 2). Overall, medication-related information was complete in 16 (16%) of the 99 GP-overviews compared to the TPC-overview, and mean discrepancies were 4.0 (SD 3.4) per patient (Fig. 3).

Of the 1054 medication-related information items, 658 (62%) were present in the GP-overview (Table 2). Unchanged medication was correctly documented in 75% of the items, changed medication in 50% and allergies in 24%.

Of the 908 medication-related information items communicated in the discharge letter, 589 (65%) were also found in the GP-overview. Of the 146 medication-related information items absent in the discharge letter, 69 (47%) were present in the GP-overview involving mainly medication that the patient already used before hospital admission. Therefore, no additional documentation activities were required by GPs.

Interestingly, of the seven allergies documented in the discharge letter, five allergies were also found in the GP-overview. Allergies not documented in the discharge letters were all lacking in GP-overviews. Medication that was absent in the GP-overview was not related to a particular type of medication and reflected the top 3 medicines used by the included patients, namely cardiovascular medicines (n = 110, 29%), gastrointestinal and metabolism medicines (n = 75, 20%), and blood and blood-forming organs medicines (n = 44, 12%).

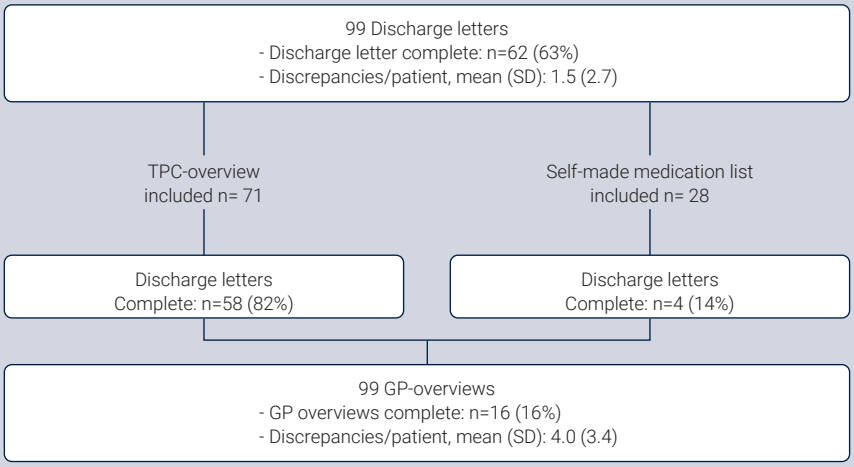

Figure 3 Completeness of discharge letters and GP-overviews with respect to the Transitional Pharmaceutical Care (TPC)-program

Table 2 Medication-related items (n = 1054) documented in the discharge letter and in the GP-overview

	Discharge letter	GP overview
	Documented, n (%)	Documented, n (%)
Medication-related items (n=1054):	908 (86)	658 (62)
Unchanged medication (n=548):	515 (94)	410 (75)
Changed medication (n=485):	386 (80)	243 (50)
Allergies (n=21):	7 (33)	5 (24)

DISCUSSION

Summary

This study shows that there is a breakdown in information even if medication reconciliation is performed. Sixty-two (63%) of the 99 discharge letters and 16 (16%) of the 99 GP-overviews contained complete medication-related information compared to the TPC-overview that was produced after medication reconciliation. The number of discrepancies increased from 1.5 per patient in the discharge letter to 4.0 per patient in the GP-overview. In particular, changed medication and allergies lacked in discharge letters and GP-overviews. In discharge letters, residents failed to download the information from the TPC-overview, adjusted the information or included self-made medication lists. This resulted into incomplete communication to GPs. Implementing a medication reconciliation program needs to be accompanied with in-hospital training and follow-up of this training to ensure that the information transfer to primary healthcare is complete. However, medication reconciliation does not end in the hospital. More collaboration is needed to make sure that medication-related information is also incorporated by other healthcare providers, such as the GP, to continue the pharmaceutical care with up-to-date information regarding a patient's pharmacotherapy.

Comparison with existing literature

Several international studies showed inaccurate communication between hospital physicians and GPs at hospital discharge (2, 12, 16). Cornu et al. found one or more discrepancies in medication-related information in almost half of the discharge letters (48%, n = 90) (12), while McMillan et al. reported discrepancies in 86% (n = 103) of discharge letters (16). We found in 63% (n = 62) of discharges at least one discrepancy. Hohmann et al. show the importance of a structured medication report as part of the discharge letter (17). Continuing discharge medication regimes by the GP significantly increases from 83 to 91% by providing detailed information to a structured medication report in the discharge letter.

McMillan et al. (16) evaluated medication discrepancies in GP-overviews on hospital admission and found in 89% (n = 107) of the overviews minimally one discrepancy. This is in line with our study where 84% (n = 83) of the GP-overviews contained

minimally one discrepancy.
Lefeber et al. investigated the effect of a TPC-intervention at hospital discharge on the incorporation of changes to medication regimens in community pharmacy and GP files (13). They found no effect on the incorporation of medication changes by the GP in his files. In contrast, we found that information communicated through the discharge letter was more often documented in the GP file, compared to information missing in the discharge letter. This difference might be explained because we requested the GP file within 2 weeks after discharge, while Lefeber et al. requested the GP files within one to 2 months. In the meantime, medication could have been changed by several healthcare providers.

Strength and limitations
The main strength of this study is the measurement of completeness of medication-related information transfer between healthcare settings, since we assessed completeness both in the discharge letter and in the post-discharge GP-overview. However, some limitations need to be discussed. First, this is an observational study and we did not perform an effect measurement. Therefore, we cannot determine the effect of the TPC-overview in the completeness of medication-related information in the discharge letter and the GP-overview. However, because not all discharge letters contained the downloaded TPC-overview, we could compare discharge letters with and without the TPC-overview. Secondly, this study was performed in a single hospital, limiting generalizability. Also, some GPs did not reply to our request for a medication overview, some discharge letters were not sent, and some patients were re-hospitalized within 3 weeks, whereby 38% of the patients were excluded. We expect that the amount of discrepancies found in this study is an underestimation. Thirdly, we did not have insight into the information system of the GP, where additional information could be documented. Furthermore, we did not know which medication changes the GP made on purpose. But given the amount of discrepancies we do not expect this to be substantial. The GP-overviews did not specify any medication changes. Finally, some GPs replied on our request by sending a copy of the discharge letter as a medication overview. Through this, the actual number of discrepancies could be underestimated.

Conclusion
Medication-related information is lost in the discharge letter and GP-overview. We found that uploading the TPC-information generated more complete medication information in the discharge letter. Communication of this information through discharge letters led to a more complete GP-overview. Nevertheless, GP-overviews lacked 35% of medication-related information that had been communicated. This study shows that the current information transfer between healthcare settings is not enough for complete documentation of relevant medication-related information. This is partly caused by the inefficient infrastructure of the healthcare system and the administrative burden experienced by healthcare providers. Future studies should determine the effect of electronic infrastructures on improving information transfer and continuity of pharmaceutical care.

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REFERENCES

1. Tam VC, Knowles SR, Cornish PL, Fine N, Marchesano R, Etchells EE. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. CMAJ. 2005;173(5):510-5.
2. Kripalani S, LeFevre F, Phillips CO, Williams MV, Basaviah P, Baker DW. Deficits in communication and information transfer between hospital-based and primary care physicians: implications for patient safety and continuity of care. JAMA. 2007;297(8):831-41.
3. van der Linden CM, Kerskes MC, Bijl AM, Maas HA, Egberts AC, Jansen PA. Represcription after adverse drug reaction in the elderly: a descriptive study. Arch Intern Med. 2006;166(15):1666-7.
4. Zhang M, Holman CDAJ, Preen DB, Brameld K. Repeat adverse drug reactions causing hospitalization in older Australians: a population-based longitudinal study 1980–2003. Br J Clin Pharmacol. 2007;63(2):163-70.
5. Greenwald JL, Halasyamani L, Greene J, LaCivita C, Stucky E, Benjamin B, et al. Making inpatient medication reconciliation patient centered, clinically relevant and implementable: a consensus statement on key principles and necessary first steps. J Hosp Med. 2010;5(8):477-85.
6. Karapinar F, van den Bemt PM, Zoer J, Nijpels G, Borgsteede SD. Informational needs of general practitioners regarding discharge medication: content, timing and pharmacotherapeutic advices. Pharm World Sci. 2010;32:172–8. 2010;32(2):172-8.
7. Ministry of Health and the Health Care Inspectorate. Policy document: transfer of information on medication in the continuum of care [in Dutch]. 2008. Accessed 6 February 2014 at www. medicatieoverdracht. nl/artikelen/raadplegen.asp?display=2&atoom=9008&atoomsrt=2&actie=2&menuitem=189.
8. Australian Pharmaceutical Advisory Council. Guiding principles to achieve continuity in medication management. 2005. Accessed 2 June 2014 at http://www.health.gov.au/internet/main/publishing.nsf/Content/5B47B202BBFAFE02CA257BF0001C6AAC/$File/guiding.pdf.
9. How-to Guide: Prevent Adverse Drug Events by Implementing Medication Reconciliation. Cambridge, MA: Institute for Healthcare Improvement. 2011. Accessed 2 June 2014 at www.ihi.org.
10. The Royal Pharmaceutical Society of Great Britain. Moving patients, moving medicines, moving safely. Guidance on discharge and transfer planning. 2005. Accessed 5 May 2014 at http://psnc.org.uk/wp-content/uploads/2013/07/Moving20Medicines20new1.pdf.
11. Karapinar-Çarkıt F, Borgsteede SD, Zoer J, Siegert C, van Tulder M, Egberts AC, et al. The effect of the COACH program (Continuity Of Appropriate pharmacotherapy, patient Counselling and information transfer in Healthcare) on readmission rates in a multicultural population of internal medicine patients. BMC Health Serv Res. 2010;10(1):39.
12. Cornu P, Steurbaut S, Leysen T, De Baere E, Ligneel C, Mets T, et al. Discrepancies in medication information for the primary care physician and the geriatric patient at discharge. Ann Pharmacother. 2012;46(7-8):983-91.
13. Lefeber GJ, Drenth-van Maanen AC, Wilting I, Jansen PA, van Marum RJ, Egberts TC. Effect of a transitional pharmaceutical care intervention at hospital discharge on registration of changes in medication regimens in primary care. J Am Geriatr Soc. 2014;62(3):565-7.
14. Karapinar-Çarkit F, Borgsteede SD, Zoer J, Egberts TC, van den Bemt PM, Tulder Mv. Effect of medication reconciliation on medication costs after hospital discharge in relation to hospital pharmacy labor costs. Ann Pharmacother. 2012;46(3):329-38.
15. Karapinar-Çarkıt F, van Breukelen BR, Borgsteede SD, Janssen MJ, Egberts AC, van den Bemt PM. Completeness of patient records in community pharmacies post-discharge after in-patient medication reconciliation: a before-after study. Int J Clin Pharm. 2014;36(4):807-14.
16. McMillan A, Trompeter J, Havrda D, Fox J. Continuity of care between family practice physicians and hospitalist services. J Healthc Qual. 2013;35(1):41-9.
17. Hohmann C, Neumann-Haefelin T, Klotz J, Freidank A, Radziwill R. Providing systematic detailed information on medication upon

hospital discharge as an important step towards improved transitional care. J Clin Pharm Ther. 2014;39(3):286-91.

7

Validity of a nationwide medication record system in the Netherlands

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ABSTRACT

Background
In the Netherlands, a nationwide Medication Record System based on pharmacy dispensing data is used to obtain information about patients' actual medication use. However, it is not clear to what extent the information of the Nationwide Medication Record System corresponds to the medication information obtained with the Best Possible Medication History.

Objective
To examine the validity of medication dispensing records collected from the Nationwide Medication Record System by comparing them to the Best Possible Medication History.

Method
An observational study was performed. Patients from several hospital departments were included at admission. To obtain the Best Possible Medication History, pharmacy technicians performed medication reconciliation at admission, using dispensing records from the Nationwide Medication Record System and information from the patient himself. Primary outcome is percentage of patients with no discrepancies between the Nationwide Medication Record System and the Best Possible Medication History. Descriptive analysis was used.

Results
Eighty-two patients were approached and 66 (80%) were included, with in total 478 medicines in the Best Possible Medication History. Seventeen percent of the patients had no discrepancies and 33% (n = 156) of the medication records contained a discrepancy between the Nationwide Medication Record System and the Best Possible Medication History. Most common type of discrepancy was omission (44%).

Conclusion
Even with a Nationwide Medication Record System medication reconciliation with the patient remains essential to obtain complete information about patient's actual medication use.

INTRODUCTION

In recent years, several studies have shown that transitions in healthcare are a risk factor for unintended discrepancies between medication what a patient is actually using and what is listed (1-4). This can affect the patient safety as discrepancies can result in medication-related harm. It is estimated that 11–59% of these discrepancies at time of hospital admission are clinically important (1). In order to reduce unintended medication discrepancies, medication reconciliation is recommended (5). Multiple sources of medication information can be used for medication reconciliation to gain insight in the medication history (e.g. general practitioner or community pharmacy dispensing records). In the Netherlands, an electronic Nationwide Medication Record System (NMRS) is available since 2011. The NMRS exchanges medication dispensing data from all pharmacies in the Netherlands, provided that the patient consents to exchanging information. The system is accessible 24-h a day for physicians and pharmacists. At the end of 2016, 73% of the general practitioners, 98% of the community pharmacists and 93% of the hospital pharmacists were connected to the NMRS. Nine million patients (out of 17 million citizens) have given their explicit consent to exchange their medication dispensing data and two million messages with medication dispensing data were exchanged per month in 2017.
To obtain the Best Possible Medication History (BPMH) of a patient the NMRS together with information provided by the patient are used. However, it is not known whether the NMRS alone would be sufficient to obtain a complete overview of patients' actual medication use. Therefore, a study was designed to compare the information in the NMRS with the information from the BPMH (patient information added to the information of the NMRS).

Aim

The aim of this study is to examine validity of medication dispensing records collected from the NMRS by comparing the NMRS information to the BPMH in patients admitted to hospital.

Ethics approval

The study was approved by the local review board of the OLVG hospital (number 15u.065).

METHODS

An observational study was conducted at the 550-bed OLVG teaching hospital in the Netherlands from July to August 2017. Adult patients admitted for at least 24 h at the pulmonology, cardiology, internal medicine, gastro-enterology, neurology or acute care department were included at admission if they used at least one medication intended for chronic use. Patients were excluded if no NMRS information was available or if patients were not able to be counseled for medication reconciliation.
To obtain the BPMH, pharmacy technicians performed a protocolled medication reconciliation interview at hospital admission using medications dispensing records from the NMRS and information from the patient. To examine the accuracy and

completeness of the NMRS, the NMRS was compared to the BPMH (gold standard: NMRS + patient information). Only active prescription lines from the NMRS were included. Medication intended for chronic use was considered active if the theoretical stop date exceeded or was within 1 month of the admission date. In case medication was only used "if needed" it was considered active if the theoretical stop date was within 3 months of the admission date. In case of insulins and coumarins (variable use), it was considered active if it was dispensed within 6 months before the admission date. Short treatments of medications, e.g. antibiotics, which did not exceed the admission date, were not considered as active.
Discrepancies between the NMRS and the BPMH were classified as following:

- Omission (if medication was not active or present in the NMRS but should be based on patient information).
- Dosage scheme (if the frequency and/or dose in the NMRS was different compared to the patient information).
- Commission (if medication was active in NMRS but should not be regarding to patient information).

The primary outcome of this study was the percentage of patients with no discrepancies between the NMRS and BPMH. Secondary outcomes were mean number of discrepancies per patient, percentage of medicines with a discrepancy between the NMRS and the BPMH, type of discrepancies and the type of medication involved in the discrepancies. Medication was classified according to the ATC-system.

All data were collected in Microsoft Excel 2010 (Microsoft, Redmond, WA). Descriptive statistics were used to examine the percentage of patients with no discrepancies, the percentage and type of discrepancies between NMRS and BPMH.

RESULTS

A total of 82 patients were approached for this study and 66 (80%) were included. Exclusion reasons were: NMRS not available (n = 13), medication reconciliation not performed (n = 2) and no use of chronic medication (n = 1). Table 1 describes the characteristics of the included patients. Mean age was 66 year, and the mean number of medication per patient was 7.2 (SD 4.0). Total number of medicines in the BPMH was 478, including 77 (16%) OTC-medicines.

In 17% (n = 11) of the patients the NMRS completely corresponded with the BPMH. Mean number of discrepancies in the NMRS per patient was 2.4 (SD 2.1). Thirty-three percent (n = 156) of the medicines contained a discrepancy between the NMRS and BPMH. Of these 156 medicines, 38 (24%) included OTC-medicines.
Forty-four percent (n = 69) of these discrepancies was due to an omission, 28% (n = 44) due to a commission and 28% (n = 43) due to an incorrect dosage scheme. The three groups of medication with the highest absolute number of discrepancies were medication acting on the nervous system (n = 45, 29%), the alimentary tract and metabolism (n = 36, 23%), and the respiratory system (n = 16, 10%) (Fig. 1).

Table 1 Characteristics of the included patients (n=66)

Patient characteristics	N=66
Male, n (%)	35 (53)
Age (years), mean SD	66.4 (17.0)
Number of medications, mean SD	7.2 (4.0)
Admission ward	
pulmonology, n (%)	7 (10.6)
cardiology, n (%)	3 (4.5)
internal medicine, n (%)	16 (24.2)
gastro-enterology, n (%)	15 (22.7)
neurology, n (%)	22 (33.3)
acute care, n (%)	3 (4.5)

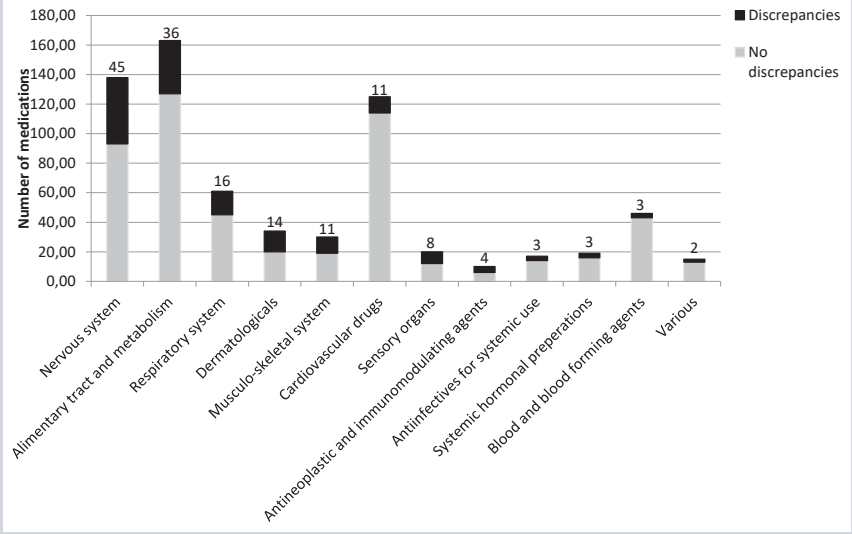

Figure 1 Number of discrepancies between the Nationwide Medication Record System (NMRS) (n=156) and the Best Possible Medication History (BPMH), per medication type. The black part of the bar represents the number of discrepancies.

DISCUSSION

This study shows that in only 17% of the patients the NMRS completely corresponded to the BPMH. The mean number of discrepancies in the NMRS per patient was 2.4. This is in line with a previous study in the UK which compared records from a national electronic summary care record system with pharmacist's medication reconciliation and found 2.2 discrepancies per patient (6). Another comparable British study revealed that 84% of the medication profiles from an electronic provincial medication database contained at least one discrepancies compared to the BPMH, similar to the results in the current study (7). They found that insulin, warfarin, salbutamol and pain relief medications were often inaccurate in the medication database which corresponds with the medication found in this current study, except for warfarin.

There are several explanations for the discrepancies identified in this study. Discrepancies due to dose and frequency issues can be explained by the fact that the NMRS is linked to pharmacy dispensing systems and pharmacists are not always informed regarding medication being prescribed intermittently or dose changes between dispensing moments (8). So the NMRS provides dispensing information instead of prescription information. In 44% of the discrepancies medication was missing in the NMRS. An explanation for this can be that patients must provide consent before a pharmacy is allowed to exchange dispensing records of the NMRS. In the Netherlands, 20% of the patients go to more than one pharmacy and consent must be given separately for each pharmacy (9). In addition, omissions can be explained by over-the-counter medication which are not registered in the NMRS. Finally commissions can be explained as discontinuation of medication is not always communicated by prescribers, and even if it is communicated, it is not always processed in the pharmacy. The infrastructure to communicate discontinuation of medication orders is inefficient (10).

To our knowledge, this is the first study investigating the validity of the Dutch NMRS. However, some limitations need to be discussed. First, this study included a small number of patients in one hospital limiting the generalizability, but as a preliminary study, the results could be helpful for optimizing the NMRS and including more hospitals is encouraged for the future. Second, the NMRS was compared to the BPMH, which included at least the NMRS and a patient interview. In practice, additional sources could be used for medication reconciliation besides the NMRS and patient interview, for example medication boxes. It was not registered in which part of the patients additional sources were used. Therefore, it is not possible to exactly establish to what extend the NMRS contributes to the BPMH. But our goal was to see whether the NMRS is sufficient as a single source, and this study clearly showed that is not the case compared to the addition of at least the patient interview as a source.

Despite the fact that the NMRS is used for more than 6 years, it is still a challenge to obtain a complete medication overview. This could be explained by the many different parties that are involved in the pharmacotherapy of a patient with various visions and interests, resulting in a fragmentation of power and responsibilities for

the NMRS. So, more cooperation between the different parties and using prescription information instead of dispensing information is needed to obtain a more complete overview and to improve the patient safety.

Conclusion
This study shows that the NMRS alone is not reliable to reflect patients' actual medication use, as in only 17% of the patients the NMRS completely corresponded to the BPMH, making clear that even with the use of a nationwide medication record system in the Netherlands, medication reconciliation with the patient is still essential.

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REFERENCES

1. Tam VC, Knowles SR, Cornish PL, Fine N, Marchesano R, Etchells EE. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. CMAJ. 2005;173(5):510-5.
2. Cornish PL, Knowles SR, Marchesano R, Tam V, Shadowitz S, Juurlink DN, et al. Unintended medication discrepancies at the time of hospital admission. Arch Intern Med. 2005;165(4):424-9.
3. Buckley MS, Harinstein LM, Clark KB, Smithburger PL, Eckhardt DJ, Alexander E, et al. Impact of a clinical pharmacy admission medication reconciliation program on medication errors in "high-risk" patients. Ann Pharmacother. 2013;47(12):1599-610.
4. Kripalani S, LeFevre F, Phillips CO, Williams MV, Basaviah P, Baker DW. Deficits in communication and information transfer between hospital-based and primary care physicians: implications for patient safety and continuity of care. JAMA. 2007;297(8):831-41.
5. The institute for healthcare improvement. How-to guide: prevent adverse drug events by implementing medication reconciliation. 2011. http://www.ihi.org/resou rces/Pages /Tools / Howto GuidePreve ntAdverseDrugEvents.aspx. Accessed 14 Nov 2018.
6. Smallwood KE JS, Basey JA. A comparison of electronic primary care medication records as sources for medicines reconciliation. Int J Pharm Pract. 2018;26:4–36.
7. Price M, Bowen M, Lau F, Kitson N, Bardal S. Assessing accuracy of an electronic provincial medication repository. BMC Med Inform Decis Mak. 2012;12:42.
8. Glintborg B, Poulsen HE, Dalhoff KP. The use of nationwide on-line prescription records improves the drug history in hospitalized patients. Br J Clin Pharmacol. 2008;65(2):265-9.
9. The Dutch Foundation for Pharmaceutical Statistics (SFK) (inDutch). https ://www.sfk.nl/publi catie s/PW/2018/ruim-80-medicijnge bruik ers-bezoe kt-slech ts-een-apoth eek. Accessed 15 June 2018.
10. Fischer S, Rose A. Responsible e-prescribing needs e-discontinuation. JAMA. 2017;317(5):469-70.

Part 3

A bridging transitional pharmaceutical care program

8

The effect of a transitional pharmaceutical care program on the occurrence of ADEs after discharge from hospital in patients with polypharmacy

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ABSTRACT

Introduction

Transitional care programs (i.e. interventions delivered both in hospital and in primary care), could increase continuity and consequently quality of care. However, limited studies on the effect of these programs on Adverse Drug Events (ADEs) post-discharge are available. Therefore, the aim of this study was to investigate the effect of a transitional pharmaceutical care program on the occurrence of ADEs four weeks post-discharge.

Methods

A multicentre prospective before-after study was performed in a general teaching hospital, a university hospital and 49 community pharmacies. The transitional pharmaceutical care program consisted of: teach-back to the patient at discharge, a pharmaceutical discharge letter, a home visit by a community pharmacist and a clinical medication review by both the community and the clinical pharmacist, on top of usual care. Usual care consisted of medication reconciliation at admission and discharge by pharmacy teams. The primary outcome was the proportion of patients who reported at least one ADE four weeks post-discharge. Multivariable logistic regression was used to adjust for potential confounders.

Results

In total, 369 patients were included (control: n=195, intervention: n= 174). The proportion of patients with at least one ADE did not statistically significant differ between the intervention and control group (general teaching hospital: 59% vs. 67%, OR_{adj} 0.70 [95% CI 0.38-1.31], university hospital: 63% vs 50%, OR_{adj} 1.76 [95% CI 0.75-4.13]).

Conclusion

The transitional pharmaceutical care program did not decrease the proportion of patients with ADEs after discharge. ADEs after discharge were common and more than 50% of patients reported at least one ADE. A process evaluation is needed to gain insight into how a transitional pharmaceutical care program could diminish those ADEs.

INTRODUCTION

Between 17-51% of patients experience Adverse Drug Events (ADEs) within 30 days after hospital discharge (1). ADEs are any injuries resulting from medication use, including physical harm, mental harm or loss of function (2). ADEs are responsible for 21% of hospital readmissions and 69% of these are deemed preventable (3). Several circumstances may contribute to the occurrence of ADEs after discharge. Firstly, changes in medication regimens made during hospital stay are not always clear to the patient (4, 5). Whereas during hospital stay patients have little control over their medication management, after discharge patients regain full responsibility. Secondly, primary healthcare providers are not always informed on patient's hospitalization and the medication changes that have been made (6). This could result in discontinuity of care and difficulties with monitoring the patient's actual medication regimen. Finally, because the length of stay in hospitals is decreasing, ADEs often reveal after discharge hampering recognition and adequate ADE management (7). The period immediately after discharge could be a stressful period for patients as they have to recover mentally and physically from the hospital admission, which may increase the risk of ADEs (8, 9).

In order to improve medication safety at transitions of care, several interventions to support continuity of care have been developed and implemented (10). Those interventions, including medication reconciliation, clinical medication review (CMR), patient education and counseling at discharge, are often implemented in just one setting, either in primary care or in-hospital. Studies on their effects report moderate and conflicting results (11-14). However, transitional pharmaceutical care programs delivered both in the hospital and primary care setting, show promising effects (15). The recent systematic review of Daliri et al. shows that transitional care interventions reduce overall hospital readmission rates within 30 days of hospital discharge (16). This reduction is probably due to a reduction in ADEs, as medication-related interventions will especially affect ADEs. However, studies exploring the effect of multicomponent pharmaceutical transitional care programs on ADEs post-discharge are rare (17-19). Therefore, the primary aim of this study was to investigate the effect of a transitional pharmaceutical care program on the occurrence of ADEs four weeks post-discharge in patients with polypharmacy compared to usual care. Secondary aims were to investigate the effect of the intervention on the Health related Quality of Life, medication satisfaction and the proportion of patients with one or more unplanned readmission(s) or emergency room visit(s), four weeks after discharge.

METHOD

Study design and setting

A multicentre prospective before-after study was performed in the Amsterdam area of the Netherlands and was called the MARCH-study. The departments of internal medicine and cardiology of a general teaching hospital (OLVG) and the departments of internal medicine, cardiology and surgery of a university hospital (Amsterdam UMC, location VUmc) collaborated with 49 community pharmacies. These departments were selected to focus on the most common causes of medication-related hospital

(re)admissions, including falls, syncope and hypoglycaemia (20). The control period was from September 2018 – April 2019, the implementation of the program took place in May 2019, whereas the intervention patients were included from June – December 2019.

Study population

Consecutive patients counselled for medication reconciliation at discharge were eligible for inclusion. Inclusion criteria were: use of at least five chronic medicines at discharge, at least one change in chronic medication during hospitalization and informed consent. These criteria were chosen because studies showed that a higher number of medication and medication changes were risk factors for ADEs after discharge (21). Exclusion criteria were: length of stay shorter than 24 hours, discharge to a nursing a home, life expectancy shorter than six months, not willing or unable to participate due to physical/mental constraints or language barrier and having a community pharmacy that was not participating in the study.

Usual Care

See appendix 1 for the description of the usual care in the hospital and community pharmacy. In brief, medication reconciliation was performed at admission and discharge by pharmacy teams. Medication surveillance during hospital admission took place based on computerized surveillance alerts (e.g. interactions, duplication, dose) and were assessed daily by clinical pharmacists. Community pharmacies received a medication overview and did not perform home visits on a regular basis. Discharge letters, composed by the hospital doctors, were used to inform the general practitioner about the admission and generally contain a medication list. Previous studies of our research group have shown that discharge letters frequently arrive relatively late and are often incomplete regarding medication-related information (6, 22).

Intervention

In addition to usual care, a transitional pharmaceutical care program was implemented, consisting of four components. See appendix 1 for a comprehensive description of the program components performed by the hospitals and community. The intervention included:

1. **Teach-back at discharge (19)**

Teach-back communication was added to the patient reconciliation at discharge. Patients were asked to restate the medication-related information on medication changes that had been presented to them, to check their understanding. If teach-back was unsuccessful, this was communicated to the community pharmacist (see 2).

2. **Pharmaceutical discharge letter composed by clinical pharmacist**

Within one working day after discharge, a pharmaceutical discharge letter was sent by mail to the community pharmacist. This letter contained: date, department and reason of hospitalization, medication list, reason for medication changes, indications of medication, relevant laboratory results, management of drug-drug interactions, side effects, practical and teach-back problems.

3. Post-discharge home visit by community pharmacist

Within five working days after discharge a home-visit was performed by the patient's community pharmacist, to discuss medication use. A home-visit was performed as previous studies have shown several benefits (19, 23). During a home-visit, medication-related problems can be identified in the patient's own surrounding, so all medicines are available and user problems (e.g. expired medication, problems with opening medication) or inappropriate storage conditions can be identified. Unnecessary medication can be taken back. In addition, a home visit may be beneficial due to the personal touch of face-to-face contact. The home visit was based on a protocol from a previous study (19) consisting of three parts: 1. Inventory of discussion items of the patient, 2. current medication use (indication, identity, dosage, time of administration, knowledge of medication changes), 3. patients' experience, concerns and beliefs regarding medication. Findings from the home visit were used as input for the transitional CMR (see 4).

4. CMR performed by both the community pharmacist and clinical pharmacist

A transitional CMR was performed within 10 working days after discharge, using teleconference. These teleconferences were coordinated by the study pharmacists (EU, SE). During this meeting, medication-related problems (MRPs) identified during the home visit were discussed. MRPs were defined as "an event or circumstance involving medication treatment that actually or potentially interferes with the patient experiencing an optimum outcome of medical care" (24).

In case of MRPs that could be solved by physicians in the hospital, the clinical pharmacist contacted the responsible physician to discuss the recommendation. In case of MRPs that could be solved by the general practitioner, the community pharmacist contacted the general practitioner to discuss the recommendation. The outcomes of the discussions with the physician in the hospital or the general practitioner were shared with the study pharmacists by means of email or telephone. Recommendations were then categorized (e.g. recommendation accepted, not accepted or unknown).

Training

To prepare participating pharmacists for the program, a training was developed. Ten medication-related readmission cases from a previous study (25) were selected for their educational value using the Delphi method. These cases were used as material to train pharmacists to timely recognize and identify ADEs that occur after hospital discharge. In total 97 community pharmacists were trained by the pharmacist-researchers (EU, SE, FK, JH), and 49 community pharmacists participated in the study. Additionally, information and instructions on the performance of the study were presented, including how to properly and consistently register the home visit outcomes. In total three clinical pharmacists (EU, PB, FS) participated in the study and got the same training.

Data collection and main outcomes

Patient and hospital admission characteristics were extracted from the medical records in the hospital information system (Epic, Verona, Wisconsin, United States) and stored in a cloud-based data platform (Castor Electronic Data Capture, Amsterdam, the Netherlands). The characteristic 'one or more hospitalizations ≤ 6 months before

index admission' was collected to compare the control and intervention group. Comorbidities were used to calculate the updated Charlson comorbidity score (26). Level of education (primary, secondary or higher) and country of birth were collected by a telephone or online questionnaire within one week after discharge.

Primary outcome was the proportion of patients who reported at least one ADE four weeks post-discharge. A period of four weeks was chosen to have enough time to resolve MRPs and is based on previous studies (19). A questionnaire, see appendix 2, based on the face- and content validated questionnaire developed by Willeboordse et al. (27) was used to determine the type and occurrence of ADEs (part a) and practical problems (part b). The patient was asked whether he or she suffers from one or more complaints of a predetermined list of adverse events (AEs), using a 4-point scale ranging from 0 (no complaints) to 3 (severe complaints). A score higher than 0 was considered as having a complaint and in that case, the patient was asked whether he or she thought it was caused by medication (ADEs). Patients could choose to receive a telephone or online questionnaire. The telephone questionnaire was conducted by 2 blinded medical students, supervised by EU and SE.

Secondary outcomes were: the number of ADEs, AEs and practical problems with medication use per patient within four weeks. In addition, Health related Quality of Life (EQ-5D-5L) (28), medication satisfaction and the proportion of patients with one or more unplanned readmission(s) or emergency room visit(s), four weeks after discharge, were determined. Index values (range -0.329 to 1) were calculated for EQ-5D-5L, with a higher score reflecting a better health state (29). Patient's medication satisfaction was measured by the Medication Satisfaction Questionnaire (MSQ) (7-point scale rated as follows: 1 = extremely dissatisfied, 2 = very dissatisfied, 3 = somewhat dissatisfied, 4 = neither satisfied nor dissatisfied, 5 = somewhat satisfied, 6 = very satisfied, 7 = extremely satisfied) (30).
Finally, the number of MRPs identified by the community and clinical pharmacist as well as the percentage of accepted interventions was measured. MRPs were classified according to the DOCUMENT system (e.g. medication errors and compliance issues) (24). Two main categories were added: overtreatment and presence of superfluous medication. MRPs were categorised into pharmacotherapy-related and patient-related MRPs (see appendix 3).

Protocol fidelity was assessed for the four components of the transitional pharmaceutical care program. For teach-back the date was registered on the inclusion form after the interview for medication reconciliation. For the pharmaceutical discharge letter the date of sending was registered. For the home visit and transitional CMR the date of performing was registered. The number of components performed per patient were scored. If all four components were performed, the full transitional pharmaceutical care program was performed.

Statistical Analysis

Based on results from a comparable study (19), a sample size of at least 195 patients per group was calculated to show a decrease from 30% to 18% of the patients reporting at least one ADE (2-sided chi-square test with alpha of 0.05 and power of 80%). Given the differences between the two hospitals as described in appendix 1, no

overall analysis was possible and stratification per hospital was applied.
Statistical analysis was performed in IBM SPSS version 22.0 (IBM Corporation, Armonk, New York, U.S.). Categorical variables were reported as percentages. Normally and non-normally distributed continuous variables are reported as mean with the standard deviation (SD) and median with the interquartile range (IQR) respectively. Univariable and multivariable logistic regression analysis were performed to compare the proportion of patients with one or more ADEs between the control and intervention group, and to compare the proportion of patients with one or more unplanned readmission or emergency room visit. Parameters showing a significant association ($p<0.10$) in the univariable analysis were added to the multivariable analysis. Data were analysed according to intention-to-treat (ITT) analysis. The primary outcome was also analysed in all patients, who received all the four components from the transitional pharmaceutical care program, in the per protocol analysis. Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) were reported. A Mann-Whitney test was used to compare number of ADEs, AEs, practical problems, quality of life and medication satisfaction between the control and intervention group.

RESULTS

Patient characteristics

Of 835 patients screened for inclusion 369 patients were included in the study (195 in the control group, 174 in the intervention group) (figure 1). Of the 466 excluded patients, 229 (49%) did not give informed consent whereas 237 (51%) reported other reasons (e.g. patient was already discharged, participation in conflicting study).
Due to loss to follow up, complete data for the primary outcome ADEs were available for 277 patients (75%). No statistically significant differences were found between the baseline characteristics of patients with complete data (n=277) and patients with missing primary outcome (n=92), based on gender (male 56% vs. 57%, p=0.925), age (70.5 vs. 70.5 years, p=0.976), number of medications (11.5 vs. 11.5, p=0.92) and CCI score (1.64 vs. 1.59, p=0. 795).
The baseline characteristics of both groups were similar, see table 1. However, for teaching hospital patients, the control patients were more often admitted at the internal medicine ward (55% vs. 42%. P=0.042).

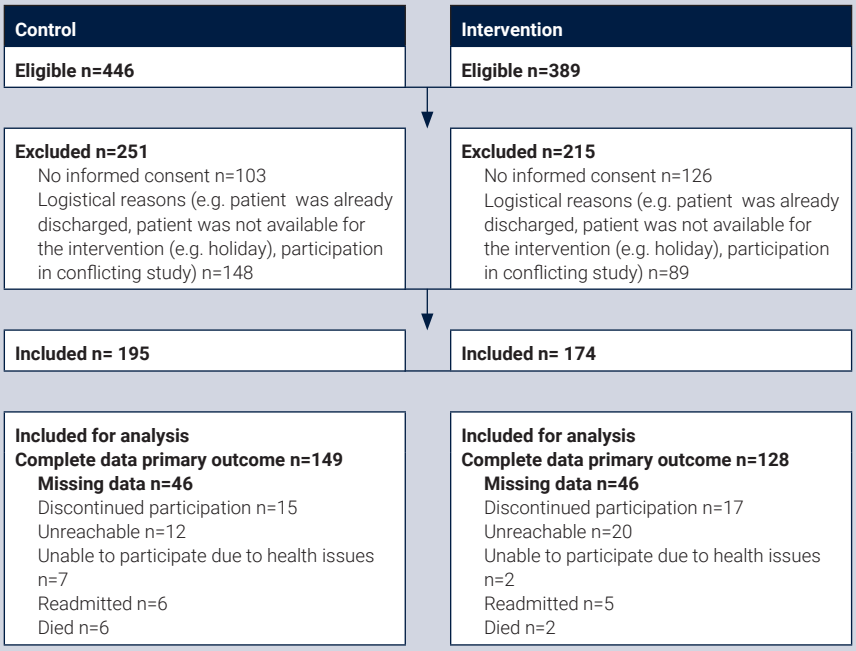

Figure 1 Study flow

Table 1 Baseline characteristics

	General Teaching Hospital			University Hospital		
	Control N=146	Intervention N=106	p-value	Control N=49	Intervention N= 68	p-value
Age, mean ± SD	71.3 (13.6)	72.0 (12.2)	0.67	65.4 (14.6)	69.9 (12.3)	0.08
Gender, male, n (%)	70 (48)	63 (59)	0.07	32 (65)	42 (62)	0.70
CCI score, median (IQR)	2 (1-3)	1 (0-2.25)	0.25	1 (0-2.5)	1 (0-2)	0.83
Country of birth, n (%)[a]			0.62			0.77
Netherlands	77 (53)	58 (55)		32 (65)	48 (71)	
Other	49 (34)	32 (30)		10 (20)	13 (19)	
Living Situation, n (%)[b]			0.83			0.18
Alone	62 (42)	46 (43)		20 (41)	21 (31)	
Together	63 (43)	44 (42)		22 (45)	40 (59)	
Education, n (%)[c,d]			0.93			0.78
Primary	56 (38)	45 (42)		11 (22)	19 (28)	
Secondary	56 (38)	29 (27)		16 (33)	20 (29)	
Higher	13 (9)	14 (13)		15 (31)	22 (32)	
Department, n (%)			0.04			0.56
Cardiology	65 (45)	61 (58)		27 (55)	35 (51)	
Internal Medicine	81 (55)	45 (42)		17 (35)	23 (34	
Surgery	-	-		5 (10)	10 (15)	
Unplanned admission, n (%)	142 (97)	106 (100)	0.99	34 (69)	49 (72)	0.75
Length of hospitalization, mean ± SD	7.2 (6.8)	7.3 (8.2)	0.91	9.0 (6.0)	10.0 (7.9)	0.46
Hospitalization ≤ 6 months before index admission, n (%)[e]	39 (27)	32 (30)	0.44	11 (22)	21 (31)	0.35
Multi-dose drug dispensing system, n (%)	55 (38)	40 (38)	0.99	7 (14)	11 (16)	0.78
Help with medication use, n (%)[e]	88 (60)	57 (54)	0.37	12 (24)	15 (22)	0.69
EQ5D-5L, Index value, <1 week after discharge, median (IQR) [f]	0.7 (0.4-0.8)	0.6 (0.3-0.8)	0.52	0.7 (0.6-0.8)	0.7 (0.5-0.8)	0.77

Table 1 *Continued*

	General Teaching Hospital			University Hospital		
	Control N=146	**Intervention N=106**	**p-value**	**Control N=49**	**Intervention N= 68**	**p-value**
MSQ <1 week after discharge, mean ± SD [f]	3 (3-4)	3 (3-4)	0.76	3 (3-3)	3 (2-4)	0.54
Number of medicines at discharge, median (IQR) ± SD	12.4 (4.4)	11.6 (4.4)	0.39	10.5 (4.7)	9.6 (3.1)	0.23
Number of medication changes, mean ± SD	4.4 (2.4)	4.1 (2.4)	0.39	5.4 (4.7)	5.0 (3.5)	0.60
Medication changes:						
New, n (%)	113 (77)	78 (74)	0.47	41 (84)	58 (85)	0.81
Stop, n (%)	92 (63)	60 (57)	0.43	24 (49)	39 (57)	0.59
Dosage change, n (%)	79 (54)	55 (52)	0.73	24 (49)	34 (50)	0.91
Switch, n (%)	35 (24)	30 (28)	0.44	14 (29)	26 (38)	0.28

IQR: Interquartile range
[a] 27 missing values in control group and 23 missing values in intervention group.
[b] 28 missing values in control group and 23 missing values in intervention group.
[c] Primary education: elementary or primary school. Secondary education: pre-vocational, senior general or pre-university. Higher education: higher professional or university.
[d] 28 missing values in control group and 25 missing values in intervention group.
[e] 27 missing values in control group and 25 missing values in intervention group.
[f] 35 missing values in control group and 29 missing values in intervention group.

Protocol fidelity

In the general teaching hospital 71 patients (66%) received the full transitional pharmaceutical care program and in the university hospital 49 patients (72%) (table 2). In total 49 community pharmacies participated in the intervention. Table 2 shows how often the components of the program were performed. Main reasons for an incomplete transitional pharmaceutical care program were due to unavailability of the patient, e.g. study discontinuation or readmission of the patient.
Teach-back took place at the day of discharge and the discharge letter was sent in the general teaching hospital within a median of 1 (IQR 0-3) day and in the university hospital within a median of 2 (IQR 1-4) days after discharge. The transitional CMR took place in the general teaching hospital within a median of 14 (IQR 10-21) days and in university hospital within in a median of 16.5 (IQR 14-23.8) days.

Table 2 Protocol fidelity

Component	General Teaching Hospital		University Hospital	
	Patients, n (%) N=106	**Days after discharge, median (IQR)**	**Patients, n (%) N=68**	**Days after discharge, median (IQR)**
Teach-back	106 (100)	0	68 (100)	0
Pharmaceutical discharge letter	105 (99)	1 (0-3)	68 (100)	2 (1-4)
Home visit	73 (69)	8 (5-15)	54 (79)	10.5 (8-16.3)
Transitional CMR	75 (71)	14 (10-21)	52(75)	16.5 (14-23.8)
Complete transitional pharmaceutical care program	71 (66)	-	49 (72)	-
Reasons for incomplete program fidelity	**Patients, n (%) n=35**		**Patients, n (%) n=19**	
Study discontinuation of the patient	19 (54)		6 (32)	
Patient readmitted	6 (17)		3 (16)	
Patient unreachable	2 (6)		3 (16)	
No community pharmacist available (e.g. holiday)	5 (14)		2 (11)	
Patient died	1(3)		0	
Transitional CMR performed after study period	2 (6)		5 (26)	

CMR= clinical medication review

Patient reported Adverse Drug Events four weeks after discharge

In both hospitals, the proportion of patients with at least one ADE four weeks post-discharge was not statistically significant different between the intervention and usual care group (general teaching hospital 59% vs. 67%, OR_{adj} 0.70 [95% CI 0.38-1.31]), (university hospital: 63% vs 50%, OR adj 1.76 [95% CI 0.75-4.13]) (see table 3). According to the per protocol analysis in the general teaching hospital (n=60), the proportion of patients with at least 1 ADE four weeks post-discharge was lower in the intervention group (52% vs. 67%, OR_{adj} 0.51 [95% CI 0.26-0.99]). The per protocol analysis in the university hospital (n=41) showed no statistically significant difference between the intervention and usual care group (68% vs. 50%, OR 2.15 [95% CI 0.86-5.38]).

Table 3 Patient reported Adverse Drug Events (ADEs) four weeks post-discharge in patients from general teaching and university hospital.

	General Teaching Hospital					University Hospital				
	Control	Intervention				Control	Intervention			
		Intention-to-treat		Per-protocol			Intention-to-treat		Per-protocol	
	n=111	n=76	OR (95% CI)	n=60	OR (95% CI)	n=38	n=52	OR (95% CI)	n=41	OR (95% CI)
Patients with any ADE, n (%)	74 (67)	45 (59)	0.73 (0.39-1.33)	31 (52)	0.53 (0.28-1.02)	19 (50)	33 (63)	1.74 (0.74-4.06)	28 (68)	2.15 (0.86-5.37)
			Adj[a]: 0.70 (0.38-1.31)		Adj[a]: 0.51 (0.26-0.99)			Adj[b]: 1.76 (0.75-4.13)		Adj[b]: 2.15 (0.86-5.38)

[a] adjusted for department and gender.
[b] adjusted for age.

Secondary outcomes four weeks post-discharge

No effect of the transitional pharmaceutical care program on the number of ADEs, AEs and practical problems per patient, or on the quality of life and medication satisfaction was found, see table 4. The other secondary outcomes (the proportion of patients with one or more unplanned readmission(s), and with one or more ER-visits) were not affected by the transitional pharmaceutical care program as well.

Table 4 Number of ADEs, patient reported Adverse Events (AEs) and practical problems per patient, Quality of Live, Medication Satisfaction, Unplanned readmissions and emergency room visits 4 weeks after discharge.

	General teaching hospital			University hospital		
	Control	Intervention	p-value	Control	Intervention	p-value
	n=111	n=76		n=38	n=52	
Number of ADEs per patient, median (IQR)	1 (0-3)	1 (0-2)	0.30	0.5 (0-2)	1 (0-1)	0.26
Number of AEs per patient, median (IQR)	4 (2-8)	4 (2.25-6)	0.45	4 (2-6)	4.5 (3-9)	0.44
Number of practical problems per patient, median (IQR)	0 (0-0)	0 (0-0)	0.59	0 (0-0)	0 (0-0)	0.78
EQ5D-5L, Index value median (IQR)*	0.71 (0.39-0.83)	0.67 (0.44-0.85)	0.64	0.78 (0.66-0.86)	0.75 (0.67-0.83)	0.56
Medication Satisfaction, median (IQR)**	3 (3-4)	3 (3-4)	0.79	3 (3-4)	3 (3-4)	0.23
	n=140	n=104	p-value	n=49	n=68	p-value
≥ 1 Unplanned readmission <4 weeks after discharge, n (%)	18 (13)	14 (13)	0.89	8 (16)	5 (7)	0.14
≥ 1 ER-visit SEH <4 weeks after discharge, n (%)	12 (9)	12 (12)	0.44	3 (6)	3 (4)	0.68

* 2 missing values in control group of the general teaching hospital.

Type of Medication-Related Problems

In the general teaching hospital 237 MRPs were detected in 71 patients during the transitional pharmaceutical care program: of these patients, 77% (n=55) of patients had at least one pharmacotherapy-related MRP and 78% (n=56) had at least one patient-related MRP (appendix 3). In the university hospital 217 MRPs were detected in 49 patients during the transitional pharmaceutical care program: of these patients, 92% (n=45) of patients had at least one pharmacotherapy-related MRP and 86% (n=42) had at least one patient-related MRP. Of the pharmacotherapy-related MRPs, overtreatment, dosing and drug selection problems were the most common problems in both hospitals. Of the recommendations to resolve MRPs, 64% was accepted by the physician involved, 7% was not accepted and of 29% the acceptance was unknown in the general teaching hospital. In the university hospital 49% was accepted, 8% was not accepted and of 44% the acceptance by physicians was unknown.

DISCUSSION

In this study, no effect of a transitional pharmaceutical care program on the proportion of patients with at least one ADE four weeks post-discharge was found. Only in the per protocol analysis of the general teaching hospital data a reduction of ADEs was found. No effect of the program was found on secondary outcomes.

Three previous studies have investigated the effect of a transitional pharmaceutical care program on the occurrence of ADEs post-discharge. Only the study of Daliri et al. found a reduction in the proportion of patients with ADEs from 25% to 16% (p =0.04) (19). The proportion of patients with ADEs in the current study is higher. This may be due to the way ADEs were questioned: in both studies ADEs were self-reported by patients. In our study a check-list based questionnaire was used, while in the study of Daliri et al. an open-ended questionnaire was used. Previous studies show that more adverse events are reported in a check-list based questionnaire compared to an open-ended questionnaire (31). However, as no validated questionnaire to examine post-discharge ADEs exists, further research is needed to find out the best way to gather post-discharge ADEs. The composition of the intervention in study of Daliri et al. was comparable with our transitional pharmaceutical care program. Both programs contained a pharmacist education and both pharmacotherapeutic and clinical information transfer. In contrast, the studies from Kripalani et al. and Phatak et al. investigated the effect of a combined in- and out-hospital intervention with only educational and pharmacotherapeutic components (17, 18), and they found no effect of their intervention on ADEs 30 days after discharge. This suggests that including all three components is essential to be effective (15). This is also confirmed in two studies from the UK, that showed that a combination of electronic transmission of medication-related information between the hospital and community pharmacy in combination with medication reconciliation and medication review after discharge may result in lower rates of readmissions (32, 33).

Some explanations for the lack of an effect of our transitional pharmaceutical care program can be given. First, the intended sample size was not reached. One third of the eligible patients did not give informed consent and also 25% of the included patients did not complete the ADE questionnaire. Patients indicated that they already had to arrange a lot around the period after discharge and were reluctant to fill out the questionnaire. Second, only 66% (n=71) of the patients in the general teaching hospital and 72% (n=49) of the patients in the university hospital received the complete transitional pharmaceutical care program. In contrast, in the study of Daliri et al. nearly 90% (n=197) of the patients received a complete intervention (19). Fourteen percent of the patients discontinued the intervention and in 8% of the patients there was no pharmacist available or the pharmacists were unable to complete the program within four weeks. Pharmacists mentioned that additional pharmacy team members were required to perform the intervention and not always available. Third, in 29% (general teaching hospital) and 44% (university hospital) of the suggested recommendations to resolve pharmacotherapy related MRPs, it was unknown whether they were accepted or not. Previous studies have shown that a lack of effect of pharmacist-led home visits could be caused by insufficient collaboration between physicians and pharmacists (34-36). Pharmacists are not authorized to adjust prescriptions independently, so there is a dependence on general practitioners or hospital physicians to read and act on recommendations. Even if recommendations were accepted, we did not know whether they were implemented as the period of 4 weeks may have been too short to implement changes. The transitional CMR took place in the general teaching hospital within a median of 14 days and in the university hospital within a median of 16.5 days, which was later than the intended time frame of 10 working days. Therefore, maybe more than 4 weeks were needed to solve ADEs. In addition, the study of Parekh et al. showed that the highest risk period for medication-related harm after leaving the hospital is up to 8 weeks (21). So the follow-up period of 4 weeks after discharge may have been too short to detect and resolve medication-related harm. Fourth, in both hospitals a high standard of usual care was already implemented during hospitalization (including medication reconciliation both at hospital admission and discharge (37)). This made it more challenging to show a further improvement with the transitional pharmaceutical care program. On the other hand, in 77% of the patients in the general teaching hospital and 92% patients in the university hospital at least one MRP was identified during the intervention. This indicates there is ample room for improvement.

To address the explanations as described above, more attention should be paid to the implementation of the transitional pharmaceutical care program e.g. by conducting a process evaluation and contextual analysis (34). During this study differences in the implementation of the intervention between the general teaching and the university hospital were experienced. In the general teaching hospital the usual care was more extensive than in the university hospital, as described in appendix 1, making it easier to implement the intervention compared to the university hospital. Also, the type of patients differed between the hospitals. In general, in the university hospital more complex patients are hospitalized compared to the general teaching hospital. However, no more ADEs were found in the patients from the university hospital. Meanwhile, the higher age and number of medications at discharge, together with the more unplanned admissions, use of multi-drug dispensing systems and help

with medication use in patients from the general teaching hospital compared to patients from the university hospital, suggest that patients from the general teaching were at higher risk for ADEs. This could explain the higher proportion of patients with an ADE in the general teaching hospital in the control group. The differences in the implementation of the intervention and patient characteristics may explain why there was an effect of the intervention in the per-protocol-analysis in the general teaching hospital but not in the university hospital. Barriers and facilitators that impact the implementation of the program should be investigated to identify how the program should be adapted for the setting.

The strengths of this study were the participation of both a general teaching and university hospital and the design of the intervention consisting of components performed in- and outside the hospital by both clinical and community pharmacists. However, some limitations need to be discussed. First, this study was performed in one urban region of the Netherlands, limiting generalizability. Especially for the university hospital, many patients could not be included as the their community pharmacy was outside the urban region and was not participating in this study. Second, patients were not randomized because of the risk of contamination bias at the hospital and community pharmacy level. Instead a before-after design was used. This design has some sources of potentially bias, including the comparability of patients before and after the intervention and the influence of developments in the services over the time. Multivariable statistics may partly correct for these biases but unmeasured confounders and bias remains a concern. Third, detection bias could have occurred as patients in the intervention group were triggered by the home visit to report ADEs. No causality assessment was performed as we did not know the actual medication use at 4 weeks after discharge, which is necessary to make a valid statement about the causality. To find out the medication use 4 weeks after discharge, medication reconciliation should have been performed again and this was not included in our study protocol. However, previous studies have identified patients' valuable in reporting ADEs (38, 39). Fourth, we measured protocol fidelity by scoring whether the different components of the intervention were performed, but we did not measure the quality of the performance of the interventions. In total 49 community pharmacists participated in the study and 120 patients received the complete intervention, so most of the participating pharmacists performed the intervention only a few times. This limited the opportunity to gain experience in performing the intervention and could lead to differences in the implementation between hospitals. Also, as the general teaching hospital had already performed several studies on medication-related admissions and transitional interventions, some of the components of the intervention, e.g. teach-back, had already been adopted in the usual care. This could have diluted the effect of the transitional pharmaceutical care program as healthcare providers could perform the components for both patients in the control and intervention group.

In conclusion, this study shows that a transitional pharmaceutical care program did not decrease the proportion of patients with ADEs after discharge. This indicates that another approach is needed to reduce ADEs, especially since ADEs four weeks post-discharge were common, affecting more than 50% of the patients in both control group and intervention group. A process evaluation is needed to gain insight into how a transitional pharmaceutical care program could diminish those ADEs.

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REFERENCES

1. Parekh N, Ali K, Page A, Roper T, Rajkumar C. Incidence of medication-related harm in older adults after hospital discharge: a systematic review. J Am Geriatr Soc. 2018;66(9):1812-22.
2. Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, et al. Incidence of adverse drug events and potential adverse drug events: implications for prevention. JAMA. 1995;274(1):29-34.
3. El Morabet N, Uitvlugt EB, van den Bemt BJF, van den Bemt P, Janssen MJA, Karapinar-Carkit F. Prevalence and Preventability of Drug-Related Hospital Readmissions: A Systematic Review. J Am Geriatr Soc. 2018;66(3):602-8.
4. Knight DA, Thompson D, Mathie E, Dickinson A. 'Seamless care? Just a list would have helped!' Older people and their carer's experiences of support with medication on discharge home from hospital. Health Expect. 2013;16(3):277-91.
5. Eibergen L, Janssen MJA, Blom L, Karapinar-Carkit F. Informational needs and recall of in-hospital medication changes of recently discharged patients. Res Social Adm Pharm. 2018;14(2):146-52.
6. Uitvlugt EB, Siegert CE, Janssen MJ, Nijpels G, Karapinar-Çarkit F. Completeness of medication-related information in discharge letters and post-discharge general practitioner overviews. Int J Clin Pharm. 2015;37(6):1206-12.
7. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. The incidence and severity of adverse events affecting patients after discharge from the hospital. Ann Intern Med. 2003;138(3):161-7.
8. Fylan B, Armitage G, Naylor D, Blenkinsopp A. A qualitative study of patient involvement in medicines management after hospital discharge: an under-recognised source of systems resilience. BMJ Qual Saf. 2018;27(7):539-46.
9. Fylan B, Marques I, Ismail H, Breen L, Gardner P, Armitage G, et al. Gaps, traps, bridges and props: a mixed-methods study of resilience in the medicines management system for patients with heart failure at hospital discharge. BMJ open. 2019;9(2):bmjopen-2018-023440.
10. World Health Organization. Medication Without Harm WHO Global Patient Safety Challenge; 2017. https://www.who.int/patientsafety/medication-safety/en/. Accessed 20 May 2020.
11. Huiskes VJB, Burger DM, van den Ende CHM, van den Bemt BJF. Effectiveness of medication review: a systematic review and meta-analysis of randomized controlled trials. BMC Fam Pract. 2017;18(1):5.
12. Redmond P, Grimes TC, McDonnell R, Boland F, Hughes C, Fahey T. Impact of medication reconciliation for improving transitions of care. Cochrane Database of Systematic Reviews. 2018(8).
13. Hohl CM, Wickham ME, Sobolev B, Perry JJ, Sivilotti ML, Garrison S, et al. The effect of early in-hospital medication review on health outcomes: a systematic review. Hohl CM, Wickham ME, Sobolev B, Perry JJ, Sivilotti ML, Garrison S, et al. The effect of early in-hospital medication review on health outcomes: a systematic review. 2015;80(1):51-61.
14. Spinewine A, Claeys C, Foulon V, Chevalier P. Approaches for improving continuity of care in medication management: a systematic review. Int J Qual Health Care. 2013;25(4):403-17.
15. Tomlinson J, Cheong V-L, Fylan B, Silcock J, Smith H, Karban K, et al. Successful care transitions for older people: a systematic review and meta-analysis of the effects of interventions that support medication continuity. Age Ageing. 2020;49(4):558-69.
16. Daliri S, Boujarfi S, el Mokaddam A, op Reimer WJS, ter Riet G, den Haan C, et al. Medication-related interventions delivered both in hospital and following discharge: a systematic review and meta-analysis. BMJ Qual Saf. 2020;30(2):146-56.
17. Phatak A, Prusi R, Ward B, Hansen LO, Williams MV, Vetter E, et al. Impact of pharmacist involvement in the transitional care of high-risk patients through medication reconciliation, medication education, and postdischarge call-backs (IPITCH Study). J Hosp Med. 2016;11(1):39-44.
18. Kripalani S, Roumie CL, Dalal AK, Cawthon C, Businger A, Eden SK, et al. Effect of a pharmacist intervention on clinically important medication errors after hospital discharge: a randomized trial. Ann Intern Med. 2012;157(1):1-10.
19. Daliri S, Hugtenburg JG, ter Riet G, van den Bemt BJ, Buurman BM, op Reimer WJS, et al.

The effect of a pharmacy-led transitional care program on medication-related problems post-discharge: A before—After prospective study. PloS one. 2019;14(3).

20. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med. 2008;168(17):1890-6.
21. Parekh N, Ali K, Davies JG, Stevenson JM, Banya W, Nyangoma S, et al. Medication-related harm in older adults following hospital discharge: development and validation of a prediction tool. BMJ Qual Saf. 2020 Feb;29(2):142-153.
22. Uitvlugt EB, Suijker R, Janssen MJ, Siegert CE, Karapinar-Çarkit F. Quality of medication related information in discharge letters: a prospective cohort study. Eur J Intern Med. 2017;46:e23-e5.
23. Ensing HT, Koster ES, Stuijt CC, van Dooren AA, Bouvy ML. Bridging the gap between hospital and primary care: the pharmacist home visit. Int J Clin Pharm. 2015;37(3):430-4.
24. Williams M, Peterson GM, Tenni PC, Bindoff IK, Stafford AC. DOCUMENT: a system for classifying drug-related problems in community pharmacy. Int J Clin Pharm. 2012;34(1):43-52.
25. Uitvlugt EB, Janssen MJA, Siegert CEH, Kneepkens EL, van den Bemt BJF, van den Bemt PMLA et al. Medication-Related Hospital Readmissions Within 30 Days of Discharge: Prevalence, Preventability, Type of Medication Errors and Risk Factors. Front Pharmacol. 2021; 12:567424.
26. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173(6):676-82.
27. Willeboordse F, Grundeken LH, van den Eijkel LP, Schellevis FG, Elders PJ, Hugtenburg JG. Information on actual medication use and drug-related problems in older patients: questionnaire or interview? Int J Clin Pharm. 2016;38(2):380-7.
28. EQ-5D instruments. https://euroqol.org/eq-5d-instruments/. Accessed 20 May 2020.
29. Versteegh MM, Vermeulen KM, Evers SM, de Wit GA, Prenger R, Stolk EA. Dutch tariff for the five-level version of EQ-5D. Value Health. 2016;19(4):343-52.
30. Vernon MK, Revicki DA, Awad AG, Dirani R, Panish J, Canuso CM, et al. Psychometric evaluation of the Medication Satisfaction Questionnaire (MSQ) to assess satisfaction with antipsychotic medication among schizophrenia patients. Schizophr Res. 2010;118(1-3):271-8.
31. Bent S, Padula A, Avins AL. Brief communication: better ways to question patients about adverse medical events: a randomized, controlled trial. Ann Intern Med. 2006;144(4):257-61.
32. Mantzourani E, Nazar H, Phibben C, Pang J, John G, Evans A, et al. Exploring the association of the discharge medicines review with patient hospital readmissions through national routine data linkage in Wales: a retrospective cohort study. BMJ open. 2020;10(2).
33. Nazar H, Brice S, Akhter N, Kasim A, Gunning A, Slight SP, et al. New transfer of care initiative of electronic referral from hospital to community pharmacy in England: a formative service evaluation. BMJ open. 2016;6(10).
34. Kwint H-F, Bermingham L, Faber A, Gussekloo J, Bouvy ML. The relationship between the extent of collaboration of general practitioners and pharmacists and the implementation of recommendations arising from medication review. Drugs Aging. 2013;30(2):91-102.
35. Holland R, Lenaghan E, Smith R, Lipp A, Christou M, Evans D, et al. Delivering a home-based medication review, process measures from the HOMER randomised controlled trial. Int. J. Pharm. Pract. 2006;14(1):71-9.
36. Abbott RA, Moore DA, Rogers M, Bethel A, Stein K, Coon JT. Effectiveness of pharmacist home visits for individuals at risk of medication-related problems: a systematic review and meta-analysis of randomised controlled trials. BMC Health Serv Res. 2020;20(1):39.
37. Karapinar-Çarkit F, Borgsteede SD, Zoer J, Egberts TC, van den Bemt PM, Tulder Mv. Effect of medication reconciliation on medication costs after hospital discharge in relation to hospital pharmacy labor costs. Ann Pharmacother. 2012;46(3):329-38.
38. Zhu J, Stuver SO, Epstein AM, Schneider EC, Weissman JS, Weingart SN. Can we rely on patients' reports of adverse events? Med. care. 2011:948-55.
39. Weingart SN, Gandhi TK, Seger AC, Seger DL, Borus J, Burdick E, et al. Patient-reported medication symptoms in primary care. Arch Intern Med. 2005;165(2):234-40.

Appendix 1 Differences in usual care and interventions in the teaching and university hospital

Usual Care

		Teaching hospital	University hospital
Hospital	Medication surveillance during hospital admission with computerized surveillance signals (e.g. interactions, duplication, dose) and assessed by hospital pharmacists (based on a national database)	Performed	Performed
	Medication reconciliation at admission and discharge:	Performed by pharmaceutical consultants 1 day before discharge*.	Performed by pharmacy technicians specially trained for medication reconciliation, at day of discharge.
	Verification: Obtaining a recent medication list based on community pharmacy records and patient information	Performed	Performed
	Clarification: Pharmacotherapy is checked for appropriateness (e.g. add laxative to opioid prescription or adjust medication due to a decreased kidney function)	Performed	Performed for a selection of drugs
	Reconciliation: All medication changes are documented in a medication overview and discussed with the patient	Including reasons for medication changes and duration of therapy.	Without reasons for changes and sometimes duration of therapy.
	Transmission: The medication overview is sent to the next healthcare provider	Community pharmacy: by fax/ electronically ≤24 hours after discharge. General practitioner: added to the discharge summary by residents.	Community pharmacy and general practitioner: by fax/electronically/mail ≤24 hours after discharge.

Community Pharmacy	- Document discharge medication in the pharmacy information system - Clinical decision support with medication alerts, including drug-drug interactions and medication–disease interactions, dosage checks - Contact prescriber if needed - A medication review is performed in a proportion of older patients once a year - Home visits occur exceptionally, e.g. in preparation for a medication review	Several studies on medication-related admissions and bridging interventions were performed. Therefore, collaborations between hospital and community pharmacies in the urban region of the hospital already existed (19) (6).	No existing bridging interventions at transitions in care were performed previously between hospital and community pharmacies in the urban region of the hospital.

* Pharmaceutical consultants are pharmacy technicians who have followed an additional 3-year bachelor degree program. They are specifically trained in pharmacotherapy and communication with patients.

Intervention, added to Usual Care

	Bridging Care intervention	Teaching hospital	University hospital
	Teach-back communication at discharge: - Patients are asked to restate the medication-related information that had been presented to them - In case of teach-back problems, the information is clarified or modified and checked again - If teach-back is unsuccessful, this is communicated to the community pharmacist in the pharmaceutical discharge letter	Teach-back was already implemented in different wards during a previous study (6).	Teach-back was implemented as part of the training.
Hospital	*Pharmaceutical discharge letter,* - ≤1 working day after discharge sent by mail to the community pharmacist	Contains: all discharge medication.	Contains: changed medication with attached the full medication list.
	Letter could contain:		
	- date, department and reason of hospitalization	Performed	Performed
	- actual medication list	Performed	Performed
	- reason for medication changes	Performed (checked with prescriber)	Performed (only if documented in hospital information system)
	- indications of medication	Performed (checked with prescriber)	Performed (only if documented)
	- relevant lab values	Performed	Performed
	- handling of drug-drug interactions or side effects	Performed	Performed
	- practical and teach-back problems	Performed	Performed

Community Pharmacy	*Post-discharge home visit by community pharmacist:* - ≤5 working days after discharge Discussing with patient: - Medication use - Medication changes - Side effects - Doubts on effectiveness of medication - Practical problems/ medication management - Medication adherence	Most of the participating community pharmacists in the urban region of the hospital had performed home visits in a previous study.	Most of the participating community pharmacists in the urban region of the hospital had not performed home visits previously.
Hospital and Community Pharmacy	*Transitional medication review performed by the community pharmacist and hospital pharmacist* - ≤10 working days after discharge (by teleconference) - Discussing medication-related problems (MRPs) identified during the home visit - the hospital pharmacist contacts the responsible physician for MRPs due to hospital care - the community pharmacist contacts the general practitioner for MRPs due to GP care - Interventions to solve MRPs are shared between the hospital and community pharmacist and communicated to the patient	Performed	Performed

Appendix 2 Questionnaire four weeks post-discharge

a. Physical Complaints

The first questions are about complaints that can occur with the use of medication. Not everyone suffers from these complaints, we are curious whether you suffer from these.

		Non	Mild	Mode-rately	Severe	Do you think a complaint is caused by your medication?	If yes, which drug?
	In the past week, did you have pain (such as headache, sore throat, stomach pain, back pain, muscle pain)?						
1	Headache	0	1	2	3	Yes / No	
2	Sore throat	0	1	2	3	Yes / No	
3	Stomach pain	0	1	2	3	Yes / No	
4	Back pain	0	1	2	3	Yes / No	
5	Pain hands/feet	0	1	2	3	Yes / No	
6	Muscle pain/joint pain	0	1	2	3	Yes / No	
7	Other, namely: ……	0	1	2	3	Yes / No	
	No complaints						
	In the past week, did you have any problems with eating / drinking, dry mouth, heartburn or nausea?						
8	Can not eat anymore	0	1	2	3	Yes / No	
9	Decreased appetite	0	1	2	3	Yes / No	
10	Nausea and vomiting	0	1	2	3	Yes / No	
11	Gastric acid	0	1	2	3	Yes / No	
12	Dry mouth / often thirsty	0	1	2	3	Yes / No	
	No complaints						

	In the past week, did you have any problems with your stools (such as diarrhea, constipation, black stools, bloated stomach)?						
13	Diarrhea	0	1	2	3	Yes / No	
14	Blockage	0	1	2	3	Yes / No	
15	Black stools	0	1	2	3	Yes / No	
16	Bloating in the abdomen	0	1	2	3	Yes / No	
	No complaints						
	In the past week, did you have trouble passing urine or not being able to control your urine?						
17	Urinating less	0	1	2	3	Yes / No	
18	Urinating more often	0	1	2	3	Yes / No	
19	Inability to hold urine properly (incontinence)	0	1	2	3	Yes / No	
	No complaints						
	During the past week, did you have any problems with your balance (e.g., falling, dizziness, or feeling faint)?						
20	Fall for no apparent cause	0	1	2	3	Yes / No	
21	Dizziness / vertigo	0	1	2	3	Yes / No	
22	Fatigue / weak feeling	0	1	2	3	Yes / No	
	No complaints						
	During the past week, did you have trouble falling asleep or feeling sleepy?						
23	Drowsiness	0	1	2	3	Yes / No	
24	Insomnia	0	1	2	3	Yes / No	
	No complaints						

	In the past week, did you have heart or lung problems?						
25	Cough	0	1	2	3	Yes / No	
26	Distress	0	1	2	3	Yes / No	
27	Pain / Pressure in the chest	0	1	2	3	Yes / No	
28	Palpitations	0	1	2	3	Yes / No	
29	Thick ankles / legs	0	1	2	3	Yes / No	
	No complaints						
	In the past week, have you had itching, rash or bruising?						
30	Skin reaction (itching / rash)	0	1	2	3	Yes / No	
31	Bruising	0	1	2	3	Yes / No	
	No complaints						
	Have you had nosebleeds or eye irritation / poor vision in the past week?						
32	Skin reaction (itching / rash)	0	1	2	3	Yes / No	
33	Bruising	0	1	2	3	Yes / No	
	No complaints						
	In the past week, did you have a fever or sweating?						
33	Fever	0	1	2	3	Yes / No	
34	Sweating	0	1	2	3	Yes / No	
	No complaints						
	In the past week, did you have any other complaints that were not included in this questionnaire?						
	Other:						
36	Namely	0	1	2	3	Yes / No	

b. Practical Problems

Some people may have trouble taking medications as prescribed by the doctor.

Are you struggling to use your medications as prescribed by your doctor? **You can give several reasons:**		
Yes, because it is a lot of drugs (at the same time)	agree	disagree
Yes, because one or more resources are not working	agree	disagree
Yes, because I don't know what I'm taking it for	agree	disagree
Yes, because there are side effects	agree	disagree
Yes, because I fear side effects	agree	disagree
Yes, because I don't feel like it	agree	disagree
Yes, because I forget to take the medication	agree	disagree
Yes, because I can't tell the drugs apart	agree	disagree
Yes, for other reasons, namely.....		

Do you have practical difficulties using your medicines? **You can give several reasons:**		
Yes, because I have problems with the times of the day	agree	disagree
Yes, because it is difficult for me to swallow the pill / capsule	agree	disagree
Yes, because the medicine strip or packaging is difficult to open	agree	disagree
Yes, because I cannot read and / or understand the label on the packaging	agree	disagree
Yes, because the medicine tastes bad	agree	disagree
Yes, because I find it difficult to administer the medicine (e.g. inhalation, eye drops)	agree	disagree
Yes, for other reasons, namely.....		

Appendix 3 Medication-Related Problems (MRPs) detected during the intervention and classified according to DOCUMENT (24)

		General teaching hospital					University hospital				
		patients (n=71)	MRPs				patients (n=49)	MRPs			
Code	Type of MRP		MRPs n=237	action accepted	action not accepted	unknown		MRPs (n=217)	action accepted	action not accepted	unknown
	Pharmacotherapy-related, n (%)	55 (77)	121 (51)	78 (64)	8 (7)	35 (29)	45 (92)	116 (53)	55 (49)	9 (8)	52 (44)
D	**D**rug selection, n(%)	17 (24)	19 (8)	12 (63)	2 (11)	5 (26)	19 (39)	22 (10)	18 (82)	1(5)	3 (14)
	Example: inhalation medication was prescribed due to shortness of breath, however this was due to heart failure										
D7	**O**vertreatment, n(%)	24 (34)	39 (16)	22 (56)	5 (13)	12 (31)	24 (49)	29 (13)	10 (34)	1 (3)	18 (62)
	Example: proton-pump-inhibitor without indication										
O	**O**ver or underdose, n(%)	18 (25)	21 (9)	20 (95)	0 (0)	1 (5)	17 (35)	23 (11)	12 (52)	1 (4)	10 (43)
	Example: unclear how long clopidogrel has to be taken										
U	**U**ndertreatment, n(%)	16 (23)	21 (9)	8 (38)	1 (5)	12 (57)	13 (27)	14 (6)	3 (21)	2 (14)	9 (64)
	Example: low dairy intake and no calcium supplementation										
M	**M**onitoring, n(%)	8 (11)	8 (3)	8 (100)	0	0	15 (31)	15 (7)	8 (53)	1 (7)	6 (40)
	Example: Vitamin B12 monitoring indicated with metformin and pantoprazole use because of tingling hands										

T	**T**oxicity or ADR, n(%)	11 (15)	13 (5)	8 (62)	0	5 (38)	12 (24)	13 (6)	4 (31)	3 (23)	6 (46)
	Example: side effects of dipyridamole headache and dizziness										
	Patient-related, n (%)	**56 (78)**	**116 (49)**				**42 (86)**	**101 (47)**			
E	**E**ducation needed, n(%)	39 (55)	50 (21)				26 (53)	29 (15)			
	Example: patient does not know when to use the nitroglycerin spray										
-	Presence of expired medication, n(%)	18 (25)	19 (8)				22 (45)	23 (11)			
	Example: expired metoprolol at home										
C	**C**ompliance issues, n(%)	32 (45)	47 (20)				27 (55)	49 (23)			
	Example: overview in medication is missing, need of multi-dose drug dispensing system										

9

General Discussion

GENERAL DISCUSSION

For several years, transitions in care have been known to be a risk factor for adverse drug events (ADEs), especially when patients are transferred from one healthcare setting to another, e.g., at hospital discharge. Seventeen to fifty-one percent of older adults experience ADEs within 30 days after discharge (1-4). Three main reasons for why ADEs occur after discharge were introduced in *Chapter 1*: confusion among patients about medication regimens that have been changed during hospitalization; suboptimal communication of medication-related information at discharge; and inadequate follow-up of patients after discharge (5). These ADEs after discharge may result in unplanned readmissions. As the epidemiology of these ADEs and readmissions due to ADEs are still not completely understood, the aims of this thesis were to study the prevalence and preventability of medication-related readmissions, to evaluate the transfer of medication-related information between secondary and primary care and to develop and explore a transitional care program to reduce medication-related harm after discharge.
To address ADEs after discharge, the following elements are important(6):

1. **patient engagement** to improve patient's understanding of their medication,
2. the implementation of **a personal health record** to improve availability of medication-related information,
3. better **collaboration within the healthcare network** of the patient to realize seamless care,
4. better incorporation of **implementation aspects** of successful interventions to facilitate large-scale dissemination and implementation to other settings.

In this final chapter our main results are reviewed in relation to these four key elements. Finally, methodological issues and clinical implications of this thesis are described.

1. Patient engagement

Traditionally, the patient's role was regarded as a passenger in an airplane that was controlled by healthcare providers. Nowadays, this role is changing and patient engagement, including the patient's caregiver, has become a cornerstone of quality of care (7). This patient engagement is facilitated by the fact that patients are better informed, become more assertive and get access to their own medical record (8). Healthcare providers have to take patients' opinions into account in order to optimize their treatment based on individual wishes and needs (9-11).
The results of the study described in *Chapter 4* suggest that patient engagement is insufficiently embedded during hospital stay, as patients and healthcare providers differ substantially regarding their perspectives on the medication-related care that has been delivered during the hospital stay. Patients were more likely to view medication-related readmissions as preventable compared to healthcare providers. They reported most often that actions in the hospital were needed to potentially prevent readmissions. In addition, these patients more often reported that they missed information regarding medicines and side effects and written instructions. Previous studies have also shown the relevance of patient perspectives on the preventability

of readmissions (11-13). Van der Does et al. found that the patient interview was mentioned by healthcare providers as a crucial source to assess preventability of all-cause readmissions in 7% of readmission cases (15 of 227 interviews with patients) (11). Van Galen et al. found that not feeling ready for discharge by the patient was a strong predictor for preventability and predictability of readmissions (12). These results indicate that patients' individual needs have not been met during hospital admission and after discharge.
The degree of patient engagement will vary between patients and depends on contextual factors such as physical and cognitive abilities, emotions, and social support mechanisms, such as the role of a family caregiver, or home care (14). Figure 1 shows the continuum of decision-making, varying from "consumerism" implying that the patient decides entirely by him/herself, to "paternalism", implying that the full responsibility is in the hands of healthcare providers (10). In the middle is shared decision-making, with a balance involving both the input of the patient and the healthcare provider. Patients who stated that their readmission was preventable were less satisfied about the information regarding medicines (*Chapter 4*). This indicates that they expected more accompaniment from healthcare providers. Therefore, healthcare providers should pay attention to where the patient is located within the continuum of decision-making (9), in order to provide tailored care and to address patient perspectives regarding the reasons for their hospital stay.

Several tools can be used to engage and educate patients (15, 16). To ensure that instructions are properly communicated to the patient, it is important that healthcare providers focus on what patients and their family caregivers actually pick up from these instructions (6). To assess a patient's and/or caregiver's understanding of instructions and information, teach-back should be used. Teach-back is a strategy in which patients are asked to restate information that has been presented to them (17, 18). As shown in the study by Mahajan et al., the use of teach-back can be an efficient and non-time-consuming method to improve patient's comprehension of discharge information (18). The percentage of patients with a comprehension deficit declined from 49% to 12%, and the teach-back conversations took less than two minutes on average. In addition, another tool to stimulate patient engagement regarding their medication use is self-administration of medication during admission. This may improve recognition of medication and timely detection of problems with medication use (19-21).

2. Personal Health Record

To be able to deliver high-quality and effective care within the healthcare network of the patient, the exchange and availability of information independent of place and time, for both healthcare providers and the patient and his or her family caregivers, is essential.
As shown in *chapters 5* and *6*, the transfer of medication-related information between healthcare providers after discharge is currently incomplete. In the Netherlands, a guideline for transfer of medication-related information exists, however only 3% of the discharge letters that were sent to the next healthcare provider were compliant to all the criteria of the guideline (*Chapter 5*). In particular, information regarding current pharmacotherapy and motivation for pharmacotherapeutic changes was missing. Even if medication reconciliation is performed and information is communicated

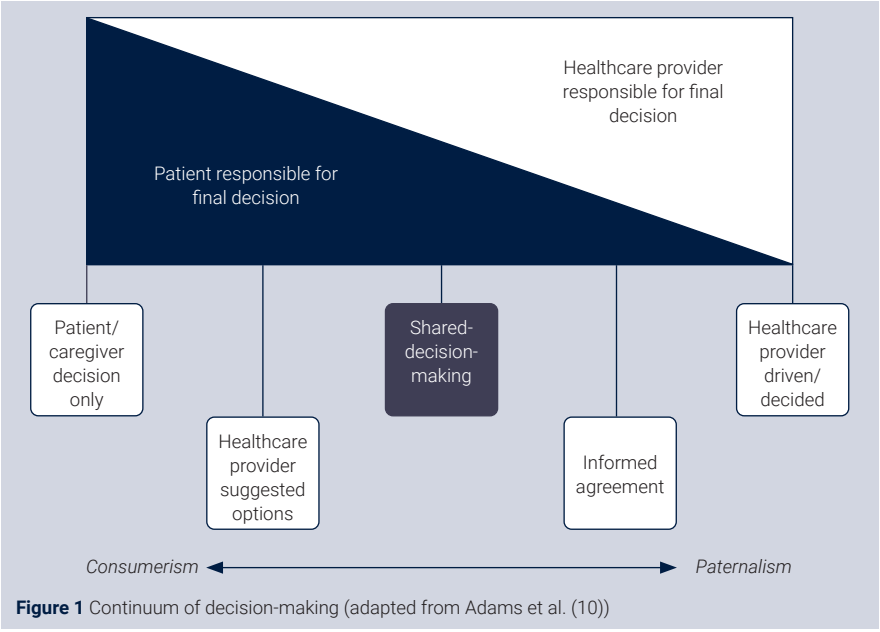

Figure 1 Continuum of decision-making (adapted from Adams et al. (10))

to the next healthcare provider, the updated medication overview is not always incorporated. Our results show that the number of discrepancies between the reconciled medication overview and the discharge letter was 1.5 per patient. After discharge, the number of discrepancies between the reconciled medication overview and post-discharge general practitioner overview increased to 4.0 per patient (*Chapter 6*). Instead of communicating information between healthcare providers, the use of an online platform where health information from different healthcare providers comes together could be useful. This can be obtained with a personal health record, a website or app which gives the patient access to his or her own health information, collected from different healthcare providers. Currently, we have a Nationwide Medication Record System (NMRS), based on pharmacy dispensing data, as a source to obtain information on the patient's current dispensed medication. *Chapter 7* showed that in only 17% of the patients admitted to the hospital, the medication dispensing records from the NMRS corresponded with the patient's medication use. This means that just linking the NMRS with a personal health record will not result in accurate medication-related information within the personal health record. Several issues need to be resolved in order to achieve such an accurate medication list.

First, currently the NMRS contains dispensing data. Therefore, information from a prescription without medication dispensing, such as discontinuation of medication or a dosage change, is lost. To solve this problem, information standards are being developed which separate dispensing and therapeutic data (22). In these standards, a clear distinction is made between what the prescriber has started, changed or discontinued, what the pharmacy has dispensed and what the patient actually uses. Changes – for example interrupted medication due to hospitalization, stopped medication due to an allergy or medication that started later because it was not

immediately available in the pharmacy – become visible this way.
Second, even if the NMRS contains medication-related data according to the information standards, medication reconciliation remains crucial to obtain a complete overview. As shown in Chapter 7, in 44% of the discrepancies between the NMRS and the patient's medication use, medication was missing in the NMRS and this was partly caused by over-the-counter medication. Also, in almost one third of the discrepancies, the dosage scheme of the NMRS did not correspond with the patient's current use. A personal health record could help to make the medication reconciliation process more efficient if patients are empowered to manage their own medication use. Previous studies show that patients were able to detect important medication discrepancies in the personal health record (23-26). Van der Nat et al. compared the level of agreement of identified medication discrepancies between traditional medication reconciliation by pharmacy technicians and online medication reconciliation by patients within a personal health record, and the correctness of identified medication discrepancies by patients (27). They found that significantly more discrepancies were identified during traditional medication reconciliation (mean 6.2) compared with online medication reconciliation by patients (mean 4.7), but more than eighty percent of medication information noted by the patient was correct and up to ninety-nine percent of the discrepancies between traditional medication reconciliation and online had no clinical relevance. Therefore, a personal health record seems to have the potential to facilitate medication reconciliation performed by patients themselves. However, the individual needs and capacities of patients must be taken into account, and will depend on the patient's health and digital literacy.
Third, in order to create a good working personal health record, patients' and healthcare providers' experiences in the use of the personal health record and the processes around it should be explored. For example, *Chapter 6* showed that despite the availability of a medication overview drafted after medication reconciliation, residents failed to download the information, adjusted the information or included self-made medication lists in one third of the discharge letters. As a result, the information that is transferred is incomplete. It is important to explore residents' barriers for using the medication-related information as intended and to adapt the work processes so that it fits the needs of the residents. Patient barriers for using the personal health record should be explored to improve the use of the personal health record as well. In a pilot to test the link between NMRS and personal health record, only 7 out of 15 patients gave permission to exchange medication-related information between the NMRS and personal health record (28). In the study by van der Nat et al. only one third of the patients responded to the request to verify their medication list in the personal health record (27).
Finally, it is important to properly coordinate responsibilities. For example, who ensures that patients understand the content of the personal health record? Providing insight into health data for the patient will also raise questions, and which healthcare provider will invest time to answer those questions? Do pharmacists have to check for drug-drug interactions if over-the-counter medication has been added by the patient? To ensure that a personal health record can be used safely, agreement on the responsibilities is required, including those of the patient.

3. Collaboration within the healthcare network of the patient

The current healthcare is disease-specific and monodisciplinary-oriented (29). As a result, different healthcare providers who are involved in a patient's care have contact with the patient, but usually not with each other (30). Because of this, different healthcare providers are not always up to date about the patient's current healthcare status and this could result in conflicting treatment advice during the patient's journey. Especially at discharge, when patients move from one healthcare setting to another, it is a challenge to successfully continue care that has been started during hospitalization. The lack of communication and collaboration among healthcare providers has been associated with negative outcomes among patients, such as unplanned readmissions (31). Our systematic review (*Chapter 2*) showed that medication-related readmissions frequently occur worldwide, as a median of 21% (range 3% to 64%) of the readmissions are medication-related and a median of 69% (range 5% to 87%) are deemed preventable. *Chapter 3* showed that the types of medication errors involved in potentially preventable medication-related readmissions included prescribing errors (35%), non-adherence (35%) and transition errors (30%).

The care that is needed to prevent potentially preventable readmissions, requires a better collaboration between healthcare providers inside and outside the hospital (6, 32). Studies show that successful interventions to reduce all-cause readmission are generally those that focus on patient follow-up after discharge, while inpatient-only interventions are less successful (33). This means that the medication-related interventions to reduce ADEs after discharge that were introduced in *Chapter 1*, including medication reconciliation, medication review and techniques to improve patient knowledge, have to be initiated during hospital admission and continued after discharge in order to be successful. This is also illustrated by the systematic review and meta-analysis of Daliri et al. showing that medication-related interventions (n=1820 patients) delivered both in hospital and following discharge from hospital to home, reduced hospital readmissions within 30 days by 3.8 percentage points (number needed to treat=27, risk ratio 0.79 (95% CI 0.65–0.96)) (34). The randomized controlled trial of Ravn-Nielsen et al. showed that a multifaceted clinical pharmacist intervention performed within a multidisciplinary healthcare network, resulted in a reduction of hospital readmissions and emergency department visits (35). The effect of the intervention was limited to patients receiving the extended intervention, including collaboration with the patient, collaboration between primary and secondary healthcare providers, as opposed to patients receiving usual care or a basic pharmacist intervention in the hospital only.

The urgency to involve different healthcare providers within the healthcare network of the patient is also described in the vision documents of the Dutch Association of Medical Specialists (FMS) and Dutch Association of Hospital Pharmacists (NVZA) (9, 36). Several initiatives have been started in healthcare to create digital collaboration platforms to support the collaboration of different healthcare providers within the healthcare network of the patient (30, 37, 38). These platforms ensure that different healthcare providers are connected intra- and inter-professionally.

Within the network, everyone can ask specific questions and provide answers, including the patient. This provides a clear and actual overview of healthcare providers who are involved in the patient's care. As a result, the care of the different care providers can be mutually coordinated and aligned to the needs of the patient.

These platforms can help to share information and goals of patients to ensure that interventions started in one setting can be continued in another. It is important that these platforms align with the patient's personal health record to prevent breakdown of information among different platforms.

4. Implementation aspects

It takes an estimated average of 17 years for research evidence to reach clinical practice and two-thirds of organizations' efforts to implement changes fail (39, 40). Therefore, during the development and testing of an intervention, attention should be paid to the implementation of interventions (41, 42). In *Chapter 8*, we evaluated the effectiveness of a transitional pharmaceutical care program (MARCH-program). However, during the study important implementation lessons were also learned. Therefore, in the paragraphs below, we evaluate the implementation of the MARCH-program. For this evaluation we used the RE-AIM (Reach, Effectiveness, Adoption, Implementation and Maintenance) planning and evaluation framework. This framework is frequently used to evaluate the implementation of interventions within public health and health behavior change research (43). As the long-term effects of the MARCH-program are yet unknown, the "maintenance" is not described.

Reach

In the RE-AIM model, reach focuses on the absolute number, proportion, and representativeness of individuals who are willing to participate in a program (43). The MARCH-program was developed for patients 18 years and older, with at least five chronic medicines at discharge and at least one change in chronic medication during hospitalization. These criteria were chosen because studies showed that a higher number of medication and medication changes were risk factors for ADEs after discharge (44) (*Chapter 3*). We did not reach our calculated sample size (n=195 per group) as fewer patients than expected gave informed consent and completed the MARCH-program. In total 389 patients were eligible for inclusion during the intervention period and of these, 126 (32%) patients did not give informed consent. It would be interesting to find out why patients did not want to participate in the MARCH-program. For ethical reasons, this was not possible within this study.

Effectiveness

The effectiveness focuses on the impact of an intervention on important individual outcomes, including potential negative effects, and broader impact including quality of life; and variability across subgroups (generalizability or heterogeneity of effects) (43). We studied the effect of the MARCH-program on the proportion of patients with one or more ADEs four weeks post-discharge and found no effect. The secondary outcomes (number of ADEs, practical problems per patient, quality of life, medication satisfaction, unplanned readmissions and Emergency-Room visits) were not affected by the MARCH-program either. However, according to the per-protocol analysis in the general teaching hospital (n=60), the proportion of patients with at least one ADE four weeks post-discharge was lower in the intervention group (52% vs. 67%, OR_{adj} 0.51 [95% CI 0.26–0.99]). Some explanations can be provided for these results.

Although performing medication-related interventions both inside and outside the hospital seems to reduce all-cause hospital readmissions within 30 days, previous

studies show that implementing interventions in that way in clinical practice is challenging (45). Due to the involvement of healthcare providers from different healthcare settings, the MARCH-program was a complex intervention that was a challenge to implement. In the general teaching hospital usual care was more extensive than in the university hospital, making it easier to implement the program compared to the university hospital. For example, in the general teaching hospital, teach-back was already implemented in different wards during a previous study, while in the university hospital it was newly implemented because of the MARCH-program (44). In addition, in the general teaching hospital several studies on medication-related admissions and bridging interventions had been performed before. Therefore, experiences with transitional interventions already existed in the general teaching hospital, in contrast to the university hospital. This may explain why a higher degree of pharmacotherapy-related recommendations were accepted in the general teaching hospital compared to the university hospital (64% vs. 49%) and may explain why there was an effect of the MARCH-program in the per-protocol analysis in the general teaching hospital but not in the university hospital. Also, usual care in community pharmacies varied. For example, one pharmacist had a more intensive collaboration with the general practitioner than the other, which may have influenced the acceptance of recommendations. These differences in the baseline situations between settings should be taken into account when complex care interventions are developed and implemented.
Another explanation for a lack of an effect of the MARCH-program may be the timing of our outcome assessment, which was set at four weeks after discharge. Because at that moment, it was unknown for 36% (n=87) of the pharmacotherapy-related recommendations arising from the program whether they were accepted by the prescriber. And even if recommendations were accepted, we did not know whether they were realized in practice as the period of four weeks may have been too short to implement those recommendations. Therefore, it is difficult to determine whether the lack of effect of the MARCH-intervention was due to the quality of the recommendations or due to the lack of time to realize the recommendations in practice.

Adoption

Adoption describes the extent to which intervention agents (people who deliver the program) are willing to initiate a program (43). Both community and clinical pharmacists were involved in the MARCH-program. In total 126 community pharmacists were invited to participate in the study and of these, 97 (77%) community pharmacists were willing to participate and were trained by the pharmacist-researchers. In total 49 community pharmacies performed the MARCH-program, as those pharmacies had one or more patients included in the study. Three clinical pharmacists were invited and all of them participated in the study and received the same training as the community pharmacists. Reasons to participate in the MARCH-program were to improve the transfer of medication-related information at discharge and the post-discharge pharmaceutical care. Reasons for not participating included lack of time and lack of a financial compensation.

We did not involve general practitioners and hospital physicians in the training,

leading to a lower sense of urgency among them regarding the MARCH-program (46). In addition, an unclear allocation of tasks and responsibilities among healthcare providers about how and by whom activities should be performed was also a barrier for implementation (47). For the MARCH-program, responsibilities for different healthcare providers may have been insufficiently established. This may explain why it was unknown in 36% of the pharmacotherapy-related recommendations whether those were accepted or not. Therefore, more effort should have been put into the engagement of all healthcare providers involved and the allocation of tasks and responsibilities.

Implementation

Implementation refers to the extent to which the intervention was delivered as intended (43). The MARCH-program consisted of four different components (teach-back at discharge, composing and sending a pharmaceutical discharge letter, a home-visit and a clinical medication review) and was performed by healthcare providers from secondary and primary care. All 174 patients received teach-back at discharge, the discharge letter was sent for 173 (99%) patients, 127 (73%) patients received a home visit and 127 (73%) patients received a clinical medication review. In total, 120 (69%) patients received all elements of the MARCH-program. The following recommendations may improve implementation for future transitional care studies.

First, it was time-consuming to coordinate the different components of the MARCH-program as the community and hospital pharmacy do not share the same electronic health records. As a consequence, information had to be transferred by secure e-mail and the pharmacists had to keep each other informed about the status of the various components and the follow-up of recommendations by e-mail and telephone. A shared digital platform may improve the coordination of the MARCH-program and could contribute to keeping pharmacists up to date (47).

Second, a financial compensation for the program may improve its adoption. It was sometimes a challenge to find the time and manpower to perform the MARCH-program and because financial compensation was not possible, it did not always have priority over other activities. Third, the differences in usual care between hospitals may have influenced the implementation of the different elements, as described previously. Therefore, more time should have been spent on piloting the program in the different settings.

Methodological issues and implications for further research

As shown in the systematic review in *Chapter 2*, substantial methodological heterogeneity exists among studies investigating the prevalence and preventability of medication-related readmissions. The heterogeneity includes: type of readmissions (unplanned or planned); the population studied (only older adults versus all ages); the methods used to assess causality and preventability (previous reported criteria versus author-defined method or not reported); the sources used to assess readmissions (using solely medical charts or also including lab values, interviews with healthcare providers or patient or adherence information); outcome definition (drug-related problems, ADEs, adverse drug reactions); and follow-up period after discharge (28 days up to 4.2 years). Our systematic review suggested that a lack of consensus on conducting and reporting research on medication-related readmissions hampers a clear understanding of the epidemiology and burden of medication-related

readmissions. Therefore, consensus in defining medication-related readmissions, collection of data, assessing causality and preventability and reporting of findings is needed. Different definitions for adverse drug reactions, ADEs and medication errors exist and are sometimes contradictory (5, 48, 49). For example, according to the WHO definition, an adverse drug reaction cannot be preventable as it is "a response to a drug which is noxious and unintended and which occurs at doses normally used in man" (50). In contrast, according to Edwards and Aronson, adverse drug reactions might be preventable as they include "any appreciably harmful or unpleasant reaction, resulting from an intervention related to the use" (48). Future studies should clearly report medication-related readmissions due to (not-preventable) adverse drug reactions, and those due to medication errors and non-adherence as this reflects the real-world situation (5).
Another important issue in studies on medication-related readmissions is the recognition of those readmissions. In the study by Ravn-Nielson a multifaceted clinical pharmacist intervention resulted in a statistically significant reduction in all-cause readmissions, but not in medication-related readmissions (35). An explanation for this counterintuitive result may be that medication-related readmissions were not recognized. For example, if a patient is readmitted because of nonadherence, this will typically manifest as a worsening of his or her underlying disease and unless the patient confesses to being non-adherent, the readmission will not be recognized as medication-related. A validated questionnaire to detect post-discharge ADEs for multiple medication groups does not exist. Therefore, further research is needed to find out the best way to gather those post-discharge outcomes.

Clinical implications

The findings of this thesis have the following clinical implications:

- To reduce overall readmission rates in hospitals, attention should be paid especially to the role of medication as 16% of readmitted patients have a medication-related readmission, with a potential preventability of 40%.
- To reduce the types of medication errors involved in potentially preventable medication-related readmissions, including prescribing errors (35%), non-adherence (35%) and transitions errors (30%), interventions are needed which start in the hospital and continue outside the hospital.
- More patient engagement during hospitalization and in the discharge process is needed to ensure that the patient's individual needs are met during hospital admission and after discharge.
- Structured medication reconciliation increases the completeness of medication overviews in discharge letters, however the implementation of a medication reconciliation program needs to be accompanied with in-hospital training of prescribers and follow-up of this training to ensure that medication reconciliation is performed as intended.
- More collaboration between healthcare settings and good information standards are needed to make sure that medication-related information is also incorporated by other healthcare providers.
- Even with the use of a nationwide medication record system, active medication reconciliation with the patient remains essential to obtain an accurate medication list in patients admitted to hospital.
- More than 50% of patients is affected by ADEs four weeks post-discharge,

however it remains unclear how these ADEs can be reduced. More attention should be paid to the engagement of healthcare providers inside and outside the hospital and the implementation of transitional pharmaceutical care programs in different healthcare settings.

In conclusion, medication-related readmissions frequently occur and, despite several interventions, we are still struggling to reduce medication-related harm after discharge. To improve the transitional pharmaceutical care, intensifying patient engagement, implementing a personal health record and more collaboration within the healthcare network of the patient seems important, with proper attention being paid to implementation.

REFERENCES

1. Laugaland K, Aase K, Barach P. Interventions to improve patient safety in transitional care–a review of the evidence. Work. 2012;41 Suppl1:2915-24.
2. Mohammed MA, Moles RJ, Chen TF. Medication-related burden and patients' lived experience with medicine: a systematic review and metasynthesis of qualitative studies. BMJ open. 2016;6(2).
3. Mistiaen P, Duijnhouwer E, Wijkel D, Bont Md, Veeger A. The problems of elderly people at home one week after discharge from an acute care setting. J Adv Nurs. 1997;25(6):1233-40.
4. Knight DA, Thompson D, Mathie E, Dickinson A. 'Seamless care? Just a list would have helped!' Older people and their carer's experiences of support with medication on discharge home from hospital. Health Expect. 2013;16(3):277-91.
5. Parekh N, Ali K, Page A, Roper T, Rajkumar C. Incidence of medication-related harm in older adults after hospital discharge: a systematic review. J Am Geriatr Soc. 2018;66(9):1812-22.
6. Rutherford P, Nielsen G, Taylor J, Bradke P, Coleman E. How-to guide: improving transitions from the hospital to community settings to reduce avoidable rehospitalizations. Cambridge, MA: Institute for Healthcare Improvement. 2013.
7. Bombard Y, Baker GR, Orlando E, Fancott C, Bhatia P, Casalino S, et al. Engaging patients to improve quality of care: a systematic review. Implement Sci. 2018;13(1):98.
8. De unieke patiënt en de moderne medisch specialist. http://arts-patient.2025.demedischspecialist.nl/3/. Accessed 19 januari 2021.
9. Netwerkgeneeskunde 2025. De medisch specialist. http://netwerkgeneeskunde.2025.demedischspecialist.nl/. Accessed 19 januari 2021.
10. Adams RC, Levy SE. Shared decision-making and children with disabilities: pathways to consensus. Pediatrics. 2017;139(6).
11. van der Does AM, Kneepkens EL, Uitvlugt EB, Jansen SL, Schilder L, Tokmaji G, et al. Preventability of unplanned readmissions within 30 days of discharge. A cross-sectional, single-center study. PloS one. 2020;15(4):e0229940.
12. van Galen LS, Brabrand M, Cooksley T, van de Ven PM, Merten H, So RK, et al. Patients' and providers' perceptions of the preventability of hospital readmission: a prospective, observational study in four European countries. BMJ Qual Saf. 2017;26(12):958-69.
13. Carter J, Ward C, Wexler D, Donelan K. The association between patient experience factors and likelihood of 30-day readmission: a prospective cohort study. BMJ Qual Saf. 2018;27(9):683-90.
14. Murray J, Hardicre N, Birks Y, O'Hara J, Lawton R. How older people enact care involvement during transition from hospital to home: A systematic review and model. Health Expect. 2019;22(5):883-93.
15. Horwitz LI, Moriarty JP, Chen C, Fogerty RL, Brewster UC, Kanade S, et al. Quality of discharge practices and patient understanding at an academic medical center. JAMA Intern Med. 2013;173(18):1715-22.
16. Graham S, Brookey J. Do patients understand? Perm J. 2008;12(3):67.
17. Eibergen L, Janssen MJ, Blom L, Karapinar-Çarkit F. Informational needs and recall of in-hospital medication changes of recently discharged patients. Res Social Adm Pharm. 2018;14(2):146-52.
18. Mahajan M, Hogewoning JA, Zewald JJA, Kerkmeer M, Feitsma M, van Rijssel DA. The impact of teach-back on patient recall and understanding of discharge information in the emergency department: the Emergency Teach-Back (EM-TeBa) study. Int J Emerg Med. 2020;13(1):1-8.
19. van Herpen-Meeuwissen LJ, van den Bemt BJ, Derijks HJ, van den Bemt PM, de Vries F, Maat B, et al. Economic impact of Patient's Own Medication use during hospitalisation: a multicentre pre-post implementation study. Int J Clin Pharm. 2019;41(6):1658-65.
20. James CR, Leong CK, Martin RC, Plumridge RJ. Patient's Own Drugs and One-Stop Dispensing: Improving Continuity of Care and Reducing Drug Expenditure. J Pharm Pract Res. 2008;38(1):44-6.
21. Lummis H, Sketris I, Veldhuyzen van Zanten S.

Systematic review of the use of patients' own medications in acute care institutions. J Clin Pharm Ther. 2006;31(6):541-63.

22. Medicatieproces 9.0 https://www.nictiz.nl/standaardisatie/informatiestandaarden/medicatieproces. Accessed 3 February 2020.
23. Russ AL, Jahn MA, Patel H, Porter BW, Nguyen KA, Zillich AJ, et al. Usability evaluation of a medication reconciliation tool: embedding safety probes to assess users' detection of medication discrepancies. J Biomed Inform. 2018;82:178-86.
24. Buning AW, Klopotowska JE, Duyvendak M, Engelen LJ, Arts J. Patient empowerment through provision of a mobile application for medication reconciliation: a proof of concept study. BMJ Innov. 2016;2:152-7.
25. Heyworth L, Paquin AM, Clark J, Kamenker V, Stewart M, Martin T, et al. Engaging patients in medication reconciliation via a patient portal following hospital discharge. J Am Med Inform Assoc. 2014;21(e1):e157-e62.
26. Prey JE, Polubriaginof F, Grossman LV, Masterson Creber R, Tsapepas D, Perotte R, et al. Engaging hospital patients in the medication reconciliation process using tablet computers. J Am Med Inform Assoc. 2018;25(11):1460-9.
27. van der Nat DJ, Taks M, Huiskes VJ, van den Bemt BJ, van Onzenoort HA. A comparison between medication reconciliation by a pharmacy technician and the use of an online personal health record by patients for identifying medication discrepancies in patients' drug lists prior to elective admissions. Int J Med Inform. 2020:104370.
28. Dit is een grote doorbraak: patiënt kijkt mee in het ais. Pharm Weekbl. 2020;12.
29. Verhoeff M, Meijer-Smit O, de Rooij S, van Munster B. Multiple chronic conditions: the need for integrated secondary care. Neth J Med. 2019;77(6):220-3.
30. With the help of a "virtual ward" healthcare providers can improve their collaboration. https://www.inholland.nl/nieuws/virtual-ward-verbindt-patient-vanuit-huis-met-heel-zorgnetwerk/. Accessed 5 February 2021.
31. Hirschman KB, Shaid E, McCauley K, Pauly MV, Naylor MD. Continuity of care: the transitional care model. Online J Issues Nurs. 2015;20(3).
32. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. N Engl J Med. 2009;360(14):1418-28.
33. Hansen LO, Young RS, Hinami K, Leung A, Williams MV. Interventions to reduce 30-day rehospitalization: a systematic review. Ann Intern Med. 2011;155(8):520-8.
34. Daliri S, Boujarfi S, el Mokaddam A, op Reimer WJS, ter Riet G, den Haan C, et al. Medication-related interventions delivered both in hospital and following discharge: a systematic review and meta-analysis. BMJ Qual Saf. 2020;30(2):146-56.
35. Ravn-Nielsen LV, Duckert M-L, Lund ML, Henriksen JP, Nielsen ML, Eriksen CS, et al. Effect of an in-hospital multifaceted clinical pharmacist intervention on the risk of readmission: a randomized clinical trial. JAMA Intern Med. 2018;178(3):375-82.
36. Hoofdlijnen akkoord medisch specialistische zorg 2019-2022. https://www.rijksoverheid.nl/documenten/kamerstukken/2018/06/04/kamerbrief-over-hoofdlijnenakkoord-medisch-specialistische-zorg-2019-2022. Accessed 4 december 2020.
37. OZO verbind zorg. https://www.ozoverbindzorg.nl/. Accessed 5 February 2021.
38. Cboards. https://www.caresharing.com/cboards/. Accessed 5 February 2021.
39. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci. 2009;4(1):1-15.
40. Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. J R Soc Med. 2011;104(12):510-20.
41. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. BMJ. 2015;350.
42. Carroll C, Patterson M, Wood S, Booth A, Rick J, Balain S. A conceptual framework for implementation fidelity. Implement Sci. 2007;2(1):40.
43. Glasgow RE, Harden SM, Gaglio B, Rabin B, Smith ML, Porter GC, et al. RE-AIM planning and evaluation framework: adapting to new science and practice with a 20-year review. Front Public Health. 2019;7:64.

44. Parekh N, Ali K, Davies JG, Stevenson JM, Banya W, Nyangoma S, et al. Medication-related harm in older adults following hospital discharge: development and validation of a prediction tool. BMJ Qual Saf. 2020;29(2):142-153.

45. Kempen TG, Cam H, Kälvemark A, Lindner KJ, Melhus H, Nielsen EI, 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;45(5):1021-9.

46. Kotter J. The 8-step process for leading change. Kotter International. 2012.

47. Kempen TGH, Kälvemark A, Sawires M, Stewart D, Gillespie U. Facilitators and barriers for performing comprehensive medication reviews and follow-up by multiprofessional teams in older hospitalised patients. Eur J Clin Pharmacol. 2020:1-10.

48. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356(9237):1255-9.

49. Otero M-J, Schmitt E, Nebeker JR, Samore MH, Barach P. Clarifying terminology for adverse drug events. Ann Intern Med. 2005;142(1):77.

50. Definitions. World Health Organization. .https://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf. Accessed 27 November 2019.

10

Summary
Samenvatting

SUMMARY

For several years transitions in care have been known to be a risk factor of adverse drug events (ADEs), especially when patients are transferred from one healthcare setting to another. Seventeen to fifty-one percent of adults experience ADEs within 30 days after hospital discharge. As the epidemiology of these ADEs and readmissions due to ADEs are still not completely understood, the aims of this thesis were to study the prevalence and preventability of medication-related readmissions, to evaluate the transfer of medication-related information between secondary and primary care and to develop and explore a transitional care program to reduce medication-related harm after discharge.

The first part of this thesis focused on medication-related readmissions. In *Chapter 1* the scope, objective and outline of this thesis were described. In *Chapter 2* the literature on the prevalence and preventability of medication-related readmissions was summarized. After a systematic literature search in several scientific databases 19 studies were included. Rates of readmissions due to medication varied from 3% to 64% (median 21%, interquartile range (IQR) 14–23%). Readmissions were deemed preventable in 5% to 87% of cases (median 69%, IQR 19–84%). Evidence regarding the risk factors of medication-related readmissions and medication causing these readmissions was inconsistent. Studies showed high variability in prevalence and preventability of medication-related hospital readmissions and considerable heterogeneity existed among the studies. Consequently, it was difficult to state how often medication-related readmissions occur and a clear understanding of the impact and risk factors of ADEs on readmissions was lacking. Therefore, in *Chapter 3*, we performed a cross-sectional observational study in the Netherlands to assess the prevalence and preventability of medication-related readmissions within 30 days after hospital discharge. Risk factors, type of medication errors and types of medication involved in preventable readmissions were also identified. Patients with an unplanned readmission within 30 days after discharge from an earlier hospitalization to one of the participating departments (cardiology, gastroenterology, internal medicine, neurology, psychiatry, pulmonology and general surgery) were multidisciplinarily reviewed by pharmacists and physicians. Of the 1111 included readmissions, 181 (16%) were medication-related, of which 72 (40%) were potentially preventable. The number of medication changes at index admission (adjusted odds ratio [OR_{adj}]: 1.14; 95%CI: 1.05–1.24) and having ≥ three hospitalizations six months before index admission (OR_{adj}: 2.11; 95%CI: 1.12–3.98) were associated with a preventable medication-related readmission. Of the preventable readmissions, 35% were due to prescribing errors, 35% due to non-adherence and 30% due to transition errors. Medications most frequently involved in preventable readmissions were diuretics and antidiabetics. The results of this study indicate that more attention should be paid to medication-related harm in readmissions.

As the patient is the only constant factor in the care continuum, information from the patient is needed to gain insight into medication-related problems occurring between discharge from hospital and readmission. Therefore, we compared the patients' perspectives on the medication relatedness and potential preventability of their

readmissions with the healthcare providers' perspectives in *Chapter 4*. We found that, according to patients, 36 of 172 (21%) readmissions were medication-related and of these, 21 (58%) were potentially preventable. According to healthcare providers 26 (15%) readmissions were medication-related and six (23%) of these were potentially preventable. Patients and healthcare providers agreed on the medication relatedness in 11 of the 172 readmissions, and in two of these, agreement on the potential preventability existed. Thus, patients and healthcare providers differ substantially in their perspectives regarding the medication relatedness and preventability of readmissions. According to patients, preventive interventions (n=23) belonged mostly to the hospital level (78%), followed by the primary care level (9%) and patient level (9%). Patients who stated that their readmission was preventable, more often reported that they lacked information regarding medicines, side effects and written instructions. This suggests that more patient engagement during hospitalization and the discharge process is needed from a patient perspective.

To ensure continuity of care within the healthcare continuum, a complete transfer of medication-related information between healthcare settings is essential. Therefore, in the second part of this thesis the completeness of medication-related information after discharge was evaluated. In order to improve the transfer of medication-related information, a national guideline was drafted. In *Chapter 5*, the adherence to this Dutch guideline for medication-related information in discharge letters was evaluated. Six key criteria of the guideline (e.g. current pharmacotherapy, clarification of medication changes) were evaluated from patients' discharge letters. Also, the timeliness of communicating a discharge letter to the next healthcare provider was assessed. A total of 288 patients were included and in 3% of them the discharge letter complied with the six guideline criteria. Most deficiencies were found in the current medication overview. Of the 2696 medications, 1264 (46.9%) were present in discharge letters with the dose and frequency the patient used. Increasing number of medications ($p<0.001$), prolonged length of stay ($p=0.001$) and discharge to an institutional setting ($p=0.012$) were statistically significantly associated with less adherence to the guideline criteria. Adherence to discharge letters improved when structured medication reconciliation ($p=0.003$) had been performed. For 70(24%) patients the discharge letter was sent to the next healthcare provider within the required 24 hours.
Besides communication of information, incorporation of this information by the next healthcare providers is also important. Therefore, in *Chapter 6*, the completeness of medication-related information in discharge letters and post-discharge general practitioner (GP)-overviews was assessed. Patients from several departments were included after medication reconciliation was performed at hospital discharge. Medication-related information was complete in 62 (63%) of 99 discharge letters. Sixteen of 99 GP-overviews (16%) were complete. Conclusively, this study showed that there is a breakdown in information even if medication reconciliation is performed. Medication-related information was missing in discharge letters and even more in GP-overviews post-discharge. Presumably, this is partly caused by the inefficient infrastructure of the healthcare system and the administrative burden experienced by healthcare providers.

In the Netherlands, a Nationwide Medication Record System based on pharmacy

dispensing data is used to obtain information about patients' actual medication use. However, it is not clear to what extent the information of the Nationwide Medication Record System corresponds to the medication information obtained with the Best Possible Medication History. The Best Possible Medication History in medication reconciliation could be obtained by using dispensing records from the Nationwide Medication Record System, together with information from the patient themself. In *Chapter 7*, the validity was examined of medication dispensing records collected from the Nationwide Medication Record System by comparing them to the Best Possible Medication History. Sixty-six patients were included, and the mean number of medications per patient was 7.2 (SD 4.0). The total number of medicines in the Best Possible Medication History was 478. Thirty-three percent (n = 156) of the medication records contained a discrepancy between the dispensing records from the Nationwide Medication Record System and the Best Possible Medication History. The most common type of discrepancy was omission (44%). In only 17% of the patients admitted to the hospital, the medication dispensing records from the NMRS corresponded with the patient's current medication use. So, this means that even with a Nationwide Medication Record System patient interviews remain essential.

The previous chapters showed that medication-related readmissions are common and the transfer of medication-related information between settings could be improved. Transitional care programs (i.e., interventions delivered both in hospital and in primary care), are reported to reduce overall hospital readmission rates within 30 days of hospital discharge. This reduction is probably due to a reduction in ADEs, as medication-related interventions will especially affect ADEs. However, only a limited number of studies investigated the effect of these programs on ADEs post-discharge. Therefore, in the last part of this thesis the effect of a pharmaceutical transitional care program on the occurrence of ADEs post-discharge was studied. In *Chapter 8*, the results are reported of a multicenter prospective before–after study in a general teaching hospital, a university hospital and 49 community pharmacies. In addition to usual care, the transitional pharmaceutical care program consisted of: teach-back to the patient at hospital discharge; a pharmaceutical discharge letter for the community pharmacist; a home visit by the community pharmacist; and a clinical medication review by both the community and the clinical pharmacist. Usual care consisted of medication reconciliation at admission and discharge by pharmacy teams. In total, 369 patients were included (control: n=195, intervention: n= 174). The proportion of patients with at least one ADE four weeks post-discharge did not statistically significantly differ between the intervention and control group (general teaching hospital: 59% vs. 67%, OR_{adj} 0.70 [95% CI 0.38–1.31], university hospital: 63% vs 50%, OR_{adj} 1.76 [95% CI 0.75–4.13]). In the per protocol analysis in the general teaching hospital, however, the proportion of patients with at least one ADE four weeks post-discharge was lower in the intervention group (52% vs. 67%, OR_{adj} 0.51 [95% CI 0.26–0.99]). The per protocol analysis in the university hospital showed no statistically significant difference between the intervention and usual care group (68% vs. 50%, OR 2.15 [95% CI 0.86–5.38]). Differences in the implementation of the intervention and patient characteristics may explain why there was an effect of the intervention in the per-protocol analysis in the general teaching hospital but not in the university hospital. Future research should investigate which barriers and facilitators impact the implementation of the transitional care program to identify

how the program could be adapted for the setting.

Finally, in *Chapter 9* we discussed the findings of the studies, the methodological issues and clinical implications. To improve the transitional pharmaceutical care four elements are important. First, patient engagement to improve the patient's understanding of their medication. Second, the implementation of a personal health record to improve availability of medication-related information. Third, better collaboration within the healthcare network of the patient to realize seamless care. Fourth, better incorporation of implementation aspects of successful interventions to facilitate large-scale dissemination and implementation to other settings. Future studies should focus on creating consensus on the definition of medication-related readmissions, collection of data, assessment of causality and preventability and reporting of findings, as a lack of consensus hampers clear understanding of the epidemiology and burden of medication-related readmissions. Furthermore, clear understanding is crucial to identify effective interventions that reduce ADEs leading to preventable readmissions.

In conclusion, medication-related readmissions frequently occur and despite several interventions, we are still struggling to reduce medication-related harm after discharge. The findings of this thesis provide insight into the types of harm after discharge and could assist with the organization and better implementation of transitional pharmaceutical care to reduce medication-related harm after discharge.

SAMENVATTING

De overgang van patiënten van het ziekenhuis naar de thuissituatie is een risicovolle periode voor het optreden van medicijngerelateerde schade (Adverse Drug Events, ADEs). Tot vijftig procent van de patiënten heeft last van een ADE binnen 30 dagen na ontslag uit het ziekenhuis. Na een ziekenhuisopname kan ook een ongeplande heropname volgen. Op dit moment is niet duidelijk welke rol ADEs spelen bij deze ongeplande heropnames. De doelen van dit proefschrift zijn daarom: het onderzoeken hoe vaak medicijngerelateerde heropnames voorkomen en hoe vermijdbaar ze zijn (1), het evalueren hoe de overdracht van medicijngegevens tussen de tweede en eerste lijn verloopt (2) en het onderzoeken wat het effect van een intensievere samenwerking tussen de eerste en tweede lijn is op het optreden van ADEs na ziekenhuisontslag (3).

Het eerste deel van dit proefschrift is gericht op medicijngerelateerde heropnames. In *hoofdstuk 1* is het doel en de opzet van het proefschrift beschreven. In *hoofdstuk 2* is de literatuur over medicijngerelateerde heropnames samengevat. Na een systematisch literatuuronderzoek in verschillende wetenschappelijke databases zijn negentien onderzoeken geïncludeerd. Het percentage heropnames als gevolg van ADEs varieerde van 3% tot 64%. Heropnames werden in 5% tot 87% van de gevallen als vermijdbaar beschouwd. Risicofactoren voor medicijngerelateerde heropnames en het type medicijnen die deze heropnames veroorzaken werden niet consistent beschreven. De onderzoeken lieten dus een grote variatie zien in het voorkomen van medicijngerelateerde heropnames en de vermijdbaarheid ervan. Daardoor was het moeilijk om aan te geven hoe vaak medicijngerelateerde heropnames optreden. Ook inzicht in risicofactoren voor het optreden van ADEs die tot heropnames leiden ontbrak. Daarom hebben we in *hoofdstuk 3* een onderzoek in Nederland uitgevoerd om te kijken hoe vaak medicijngerelateerde heropnames binnen 30 dagen na ziekenhuisontslag optraden en hoe vermijdbaar deze waren. Ook risicofactoren, type medicijnfouten en type medicijnen betrokken bij vermijdbare heropnames werden bekeken. Patiënten met een ongeplande heropname binnen 30 dagen na ontslag na een eerdere ziekenhuisopname op één van de deelnemende afdelingen (cardiologie, gastro-enterologie, interne geneeskunde, neurologie, psychiatrie, longgeneeskunde en algemene chirurgie) werden beoordeeld door apothekers en artsen. Van de 1111 heropnames waren er 181 (16%) medicijngerelateerd en daarvan waren er 72 (40%) mogelijk vermijdbaar. Het aantal veranderingen in de medicijnen bij indexopname en meer dan drie ziekenhuisopnames zes maanden voor de indexopname waren mogelijke risicofactoren voor een vermijdbare medicijngerelateerde heropname. Van de vermijdbare heropnames was 35% te wijten aan voorschrijffouten, 35% aan therapieontrouw en 30% aan overdrachtsfouten. Medicijnen die het vaakst waren betrokken bij vermijdbare heropnames waren diuretica (zogenaamde plaspillen) en middelen tegen suikerziekte. De resultaten van dit onderzoek geven aan dat er meer aandacht moet komen voor de rol van medicijnen bij ongeplande heropnames om deze heropnames te kunnen verminderen.

De patiënt is de enige constante factor gedurende ziekenhuisopname en na ontslag. Daarom is informatie van de patiënt cruciaal om inzicht te krijgen in mogelijke

medicijngerelateerde problemen na ontslag. In *hoofdstuk 4* hebben we gekeken wat patiënten en zorgverleners vinden van de rol van medicijnen bij het optreden van een heropname. Volgens patiënten waren 36 van de 172 (21%) heropnames medicijngerelateerd en 21 (58%) hiervan mogelijk te voorkomen. Volgens zorgverleners waren 26 (15%) heropnames medicijngerelateerd en zes (23%) hiervan mogelijk te voorkomen. De overlap tussen patiënten en zorgverleners was beperkt: bij 11 van de 172 heropnames was overeenstemming over de rol van medicijnen en bij twee daarvan was er overeenstemming over de vermijdbaarheid. Patiënten en zorgverleners verschillen dus aanzienlijk in hun mening over de rol van medicijnen en de vermijdbaarheid van heropnames. Preventieve maatregelen (n = 23) waren volgens patiënten vooral mogelijk vanuit het ziekenhuis (78%), gevolgd door acties vanuit de eerste lijn (9%) en de patiënt zelf (9%). Patiënten die aangaven dat hun heropname te voorkomen was, gaven vaker aan dat ze geen informatie hadden ontvangen over het gebruik van de medicijnen, bijwerkingen en schriftelijke instructies. Dit geeft aan dat de patiënt beter betrokken moet worden tijdens ziekenhuisopname en het ontslagproces, zodat de zorg beter is afgestemd op de behoefte van de patiënt.

Om de continuïteit van de zorg tussen zorgverleners te waarborgen, is een volledige overdracht van medicijngerelateerde informatie essentieel. Daarom werd in het tweede deel van dit proefschrift de volledigheid van informatie over medicijnen na ontslag geëvalueerd. Om de overdracht van deze informatie tussen zorgverleners te verbeteren, is een landelijke richtlijn opgesteld. In *hoofdstuk 5* is de naleving van deze Nederlandse richtlijn in ontslagbrieven voor de volgende zorgverlener zoals de huisarts geëvalueerd. Zes punten van de richtlijn (zoals actueel medicijngebruik en reden van wijzigingen, aandoeningen waarbij de medicijnen niet gebruikt mogen worden, afwijkende bloedwaardes) werden geëvalueerd op basis van ontslagbrieven van patiënten. Ook werd beoordeeld in hoeverre ontslagbrieven op tijd naar zorgverleners werden verstuurd. Bij slechts 3% van de 280 patiënten voldeed de ontslagbrief aan de zes richtlijncriteria. De meeste tekortkomingen werden gevonden in het actuele medicijngebruik en de reden van wijzigingen. Van de 2696 voorgeschreven medicijnen stonden er 1264 (47%) goed in de ontslagbrieven. Meer medicijnen, langere opnameduur en ontslag naar een instelling waren mogelijke risicofactoren voor een slechtere naleving van de richtlijn. De naleving van de richtlijn verbeterde wanneer er een medicijngesprek met overdracht naar de eerste lijn was uitgevoerd. Voor zeventig (24%) patiënten was de ontslagbrief binnen de vereiste 24 uur naar de volgende zorgverlener gestuurd.

Naast het doorgeven van medicijngerelateerde informatie is ook het verwerken van deze informatie door de volgende zorgverleners van belang. Daarom is in *hoofdstuk 6* de volledigheid van medicijnoverzichten van huisartsen na ontslag beoordeeld. Patiënten van verschillende afdelingen werden geïncludeerd na het medicijngesprek bij ontslag uit het ziekenhuis. Medicijngerelateerde informatie was volledig in 62 (63%) van de 99 ontslagbrieven. Maar slechts 16 van de 99 huisartsoverzichten (16%) waren compleet. Er gaat dus informatie verloren na overdracht naar de volgende zorgverlener. Dit wordt mogelijk veroorzaakt doordat systemen van de huisarts niet gekoppeld zijn aan ziekenhuissystemen. Hierdoor moet de informatie handmatig ingevoerd worden. Dit kost de zorgverleners veel tijd.

In Nederland wordt het Landelijk Schakelpunt (LSP) gebruikt om gegevens over het medicijngebruik van patiënten uit te wisselen. Met behulp van het LSP kan uitgewisseld worden welke medicijnen zijn verstrekt door apotheken. Het is echter niet duidelijk of deze gegevens volledig en juist zijn. In *hoofdstuk 7* is dit nader onderzocht. Dit werd gedaan door de gegevens uit het LSP te vergelijken met het Best Mogelijke Medicijnoverzicht. Het Best Mogelijke Medicijnoverzicht werd verkregen bij opname van de patiënt in het ziekenhuis. De gegevens uit het LSP en de informatie van de patiënt zelf over welke medicijnen hij/zij gebruikte werden hiervoor gebruikt. De 66 patiënten in het onderzoek gebruikten gemiddeld 7,2 medicijnen. Alle Best Mogelijke Medicijnoverzichten samen bevatten 478 medicijnen. Bij 156 (33%) van deze medicijnen kwam het Best Mogelijke Medicijnoverzicht niet overeen met het LSP. Het vaakst voorkomende verschil was het ontbreken van medicijnen (44%) in het LSP. Bij slechts 17% van de patiënten kwamen de gegevens uit het LSP overeen met het daadwerkelijke medicijngebruik van de patiënt. Dus ook met het gebruik van het LSP blijft informatie vanuit de patiënt over het daadwerkelijke medicijngebruik nodig.

De vorige hoofdstukken lieten zien dat medicijngerelateerde heropnames veel voorkomen en dat de overdracht van medicijngerelateerde informatie tussen zorgverleners kan worden verbeterd. Medicijngerelateerde transmurale zorgprogramma's zijn verbetermaatregelen die zowel in het ziekenhuis als in de eerste lijn worden uitgevoerd. Deze zijn bedoeld om ziekenhuisopnames door ADEs binnen 30 dagen na ontslag te verminderen. Er is echter beperkt onderzoek gedaan naar het effect van deze transmurale zorgprogramma's op het optreden van ADEs na ontslag. *In hoofdstuk 8* van dit proefschrift is dit nader beschreven. In een topklinisch ziekenhuis, een academisch ziekenhuis en 49 openbare apotheken is het zorgprogramma onderzocht. Eerst werd er gekeken hoeveel ADEs optraden bij de gebruikelijke zorg. Vervolgens is dezelfde meting gedaan na het invoeren van een transmuraal medicijngerelateerd zorgprogramma. Dit zorgprogramma bestond uit: 1) verbeterde voorlichting over medicijnen aan de patiënt bij ziekenhuisontslag, 2) een ontslagbrief over de medicijnen voor de openbaar apotheker, 3) een huisbezoek bij de patiënt na ontslag uit het ziekenhuis door de openbaar apotheker en 4) een medicatiebeoordeling door de apotheker van het ziekenhuis en de openbaar apotheker. In totaal deden 369 patiënten mee in het onderzoek (gebruikelijke zorg: 195, zorgprogramma: 174). Het percentage patiënten met minstens één ADE vier weken na ontslag verschilde niet tussen het zorgprogramma en de gebruikelijke zorg (topklinisch ziekenhuis: 59% vs. 67%, academisch ziekenhuis : 63% vs. 50%). Apart is gekeken naar alleen de patiënten die daadwerkelijk het volledige transmuraal medicijngerelateerd zorgprogramma hadden ontvangen. Dan werd in het topklinisch ziekenhuis wel een effect gevonden. In het academisch ziekenhuis werd ook dan geen effect gezien. Verschillen in de uitvoering van het programma en patiëntkenmerken kunnen dit mogelijk verklaren. Toekomstig onderzoek zal moeten uitwijzen welke factoren van invloed zijn op de uitvoering van het transmurale zorgprogramma, zodat het programma succesvol toegepast kan worden in verschillende ziekenhuizen en in de eerste lijn.

Ten slotte beschrijven we in *hoofdstuk 9* de bevindingen van alle onderzoeken in dit proefschrift, de onderzoekstechnische uitdagingen en de gevolgen. Om de medicijngerelateerde transmurale zorg te verbeteren zijn vier punten van belang.

Ten eerste dient de patiënt meer betrokken te worden bij zijn zorgproces. Zo kan er beter voldaan worden aan de individuele behoeftes van de patiënt. Ten tweede zal een persoonlijk gezondheidsdossier van de patiënt de beschikbaarheid van medicijngerelateerde informatie voor zorgverleners en patiënten verbeteren. Ten derde kan een intensievere samenwerking tussen de zorgverleners binnen het zorgnetwerk van de patiënt bijdragen aan een betere afstemming van de zorg. Tot slot, zal een betere implementatie van zorgprogramma's helpen om deze breder toepasbaar te krijgen in diverse zorginstellingen.

Hoe onderzoek naar medicijngerelateerde heropnames precies uitgevoerd moet worden is nog niet volledig duidelijk. Dit belemmert het begrip van de oorzaken en gevolgen van medicijngerelateerde heropnames. Daarom moet eerst overeenstemming bereikt worden over de definitie van medicijngerelateerde heropnames, het verzamelen van gegevens, het beoordelen van de oorzaak en vermijdbaarheid en de rapportage van bevindingen. Deze zaken zijn van cruciaal belang om effectieve programma's op te kunnen zetten die ADEs en vermijdbare heropnames verminderen.

De conclusie van dit proefschrift is dat medicijngerelateerde heropnames vaak voorkomen ondanks verschillende maatregelen. De bevindingen van dit proefschrift geven inzicht in de schade door medicijnen die na ontslag kan optreden en kunnen helpen bij een betere implementatie van transmurale zorgprogramma's. Met deze programma's kan medicijngerelateerde schade na ontslag verminderd worden.

Appendices

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Publication list
PhD portfolio
Curriculum Vitae

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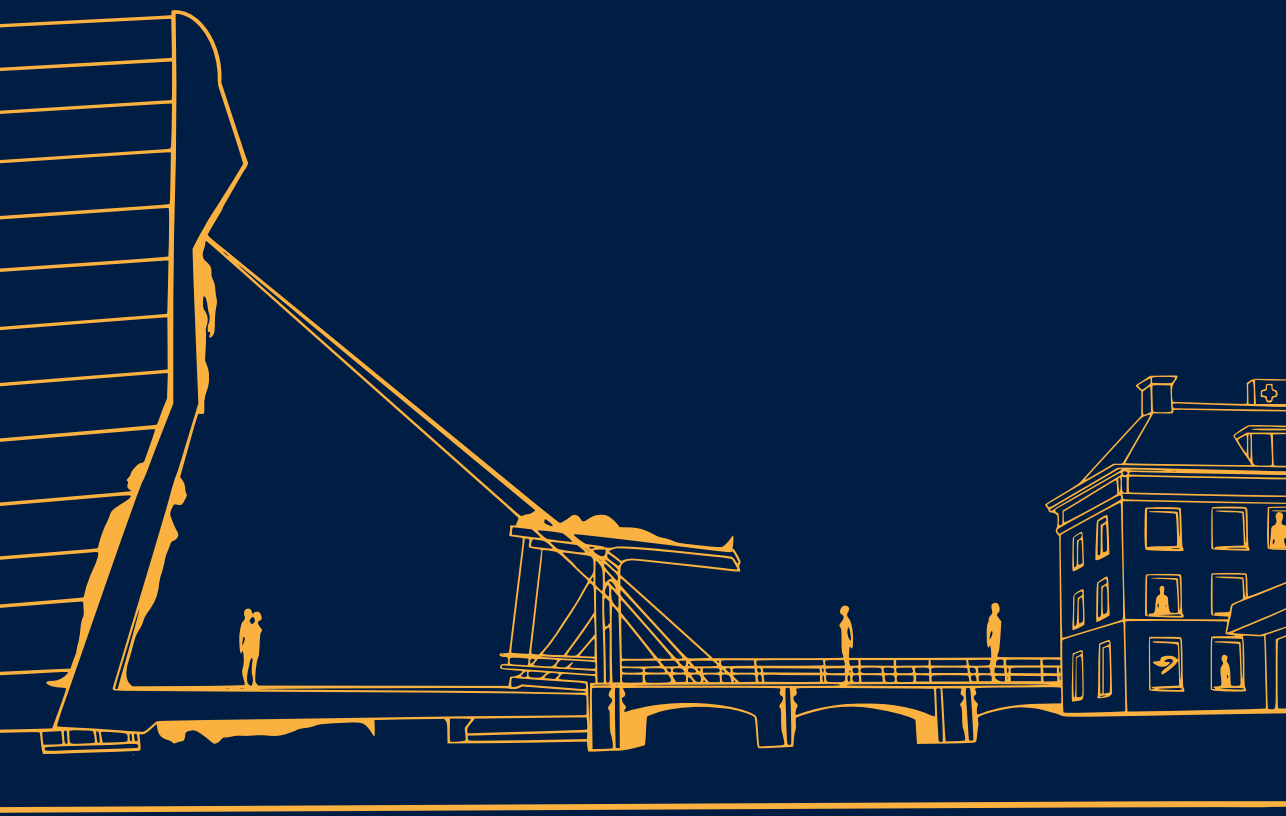
Liefdevolle ondersteuners: Familie, schoonfamilie, vrienden en Roel

DANKWOORD

"Bij elkaar komen is een begin, bij elkaar blijven is vooruitgang, met elkaar samenwerken is succes"

- Henry Ford -

Dank jullie wel voor de fijne samenwerking!



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PUBLICATION LIST

Related to this thesis

1. **Uitvlugt EB***, En-nasery-de Heer S*, van den Bemt BJF, Bet PM, Sombogaard F, Hugtenburg JG, van den Bemt PMLA, Karapinar-Çarkit F. The effect of a transitional pharmaceutical care program on the occurrence of ADEs after discharge from hospital in patients with polypharmacy. Accepted for publication in Research in Social and Administrative Pharmacy.

2. **Uitvlugt EB**, Janssen MJA, Siegert CEH, Kneepkens EL, van den Bemt BJF, van den Bemt PMLA and Karapinar-Çarkit F. Medication-Related Hospital Readmissions Within 30 Days of Discharge: Prevalence, Preventability, Type of Medication Errors and Risk Factors. Front. Pharmacol. 2021 12:567424. doi: 10.3389/fphar.2021.567424.

3. **Uitvlugt EB**, Janssen MJA, Siegert CEH, Leenders AJA, van den Bemt BJF, van den Bemt PMLA, Karapinar-Çarkit F. Patients' and providers' perspectives on medication relatedness and potential preventability of hospital readmissions within 30 days of discharge. Health Expect. 2020 Feb;23(1):212-219. doi: 10.1111/hex.12993.

4. **Uitvlugt EB**, van den Bemt BJF, Chung WL, Dik J, van den Bemt PMLA, Karapinar-Çarkit F. Validity of a nationwide medication record system in the Netherlands. Int J Clin Pharm. 2019 Jun;41(3):687-690. doi: 10.1007/s11096-019-00839-x.

5. **Uitvlugt EB**, Janssen MJA, Kneepkens EL, van den Bemt BJF, van den Bemt PMLA, Karapinar F. Medicatiegerelateerde heropnames binnen 30 dagen na ontslag. Nederlands Platform voor Farmaceutisch Onderzoek. 2018;3:a1686.

6. El Morabet N, **Uitvlugt EB**, van den Bemt BJF, van den Bemt PMLA, Janssen MJA, Karapinar-Çarkit F. Prevalence and Preventability of Drug-Related Hospital Readmissions: A Systematic Review. J Am Geriatr Soc. 2018 Mar;66(3):602-608. doi: 10.1111/jgs.15244.

7. **Uitvlugt EB**, Suijker R, Janssen MJA, Siegert CEH, Karapinar-Çarkit F. Quality of medication related information in discharge letters: A prospective cohort study. Eur J Intern Med. 2017 Dec;46:e23-e25. doi: 10.1016/j.ejim.2017.09.015.

8. **Uitvlugt EB**, Siegert CE, Janssen MJ, Nijpels G, Karapinar-Çarkit F. Completeness of medication-related information in discharge letters and post-discharge general practitioner overviews. Int J Clin Pharm. 2015 Dec;37(6):1206-12. doi: 10.1007/s11096-015-0187-z.

9. **Uitvlugt EB**, Siegert CEH, Oosterhof P, Janssen MJA, Nijpels G en Karapinar-Çarkıt F. Medicatieoverdracht: onvoldoende implementatie in de praktijk. PW Wetenschappelijk Platform 2014;8:a1444

Not related to this thesis

10. **Uitvlugt EB**, Soeng DFY, van der Linden P, van de Garde EMW. The dynamics in applied COVID-19 pharmacotherapy and the influence of national guidance in the Netherlands: a quantitative and qualitative study. Submitted for publication.

11. van der Does AMB, Kneepkens EL, **Uitvlugt EB**, Jansen SL, Schilder L, Tokmaji G, Wijers SC, Radersma M, Heijnen JNM, Teunissen PFA, Hulshof PBJE, Overvliet GM, Siegert CEH, Karapinar-Çarkit F. Preventability of unplanned readmissions within 30 days of discharge. A cross-sectional, single-center study. PLoS One. 2020 Apr 2;15(4):e0229940. doi: 10.1371/journal.pone.0229940.

12. van Weringh G, **Uitvlugt EB**, Ponjee GHM, M Jalink G. Confusion caused by dietary supplement lithium orotate. Tijdschr Psychiatr. 2017;59(4):234-237.

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PHD PORTFOLIO

	Year	Workload (ECTS)
1. General courses		
- Scientific writing in English for publication in Biomedical Journals	2013	1.0
- E-learning Practical Biostatistics (AMC)	2015	1.5
- Oral Presentation	2015	1.0
- Basic course on Regulations and Organization for Clinical Investigators (BROK)	2017	1.5
- Onderzoek dag 1 en 2 CORAZ (PUOZ)	2016	2.0
- The skill of writing an article – and getting it published in a peer reviewed journal	2016	1.0
- Klinisch Geneesmiddelenonderzoek	2016	1.0
- Geriatrie (PUOZ)	2018	1.0
- Introduction in Data Analysis (NIHES)	2018	0.7
- Principles of Research in Medicine and Epidemiology (NIHES)	2018	0.7
- Regression (NIHES)	2018	1.4
2. Conferences and presentations		
- Wetenschapsdag Sint Lucas Andreas Ziekenhuis, poster	2013	0.3
- Wetenschapsdag OLVG, poster	2017	0.3
- Geriatrie dagen, poster	2017	0.3
- Prisma symposium, Amersfoort, oral presentation	2017	0.8
- Congres Integrale Medicatiezorg, Amsterdam, oral presentation	2017	0.8
- Nederlandse Ziekenhuisfarmacie dagen, oral presentation	2017	0.8
- NVZA-CWZO wetenschappelijke vergadering, oral presentation	2018	0.8
- BMJ Quality and Safety, Amsterdam, poster	2018	0.3

-	Prisma symposium, Amersfoort, oral presentation	2018	0.8
-	Wetenschapsdag OLVG, poster	2018	0.3
-	STZ event, poster	2018	0.3
-	Nederlandse Ziekenhuisfarmacie dagen, oral presentation	2018	0.8
-	EAHP, Barcelona, seminar	2019	1.2
-	PCNE, Egmond aan Zee, poster	2019	0.3

3. Supervising of research project of Master students

-	Najla el Morabet (Utrecht University) "Assessing the causality and preventability of drug-related hospital readmissions"	2016	2.0
-	Wai Lung Chung (Utrecht University) "Differences and accuracy of medication dispensing records"	2016	2.0
-	Anna Leenders (University of Groningen) "De heropnamestudie: de vermijdbaarheid van (geneesmiddel gerelateerde) heropnames vanuit een patiëntperspectief"	2017	1.0
-	Ninora Korkis (Utrecht University)" Prevalence, potential preventability and the factors associated with unplanned medication-related readmissions ≤ 30 days after discharge"	2018	2.0
-	Atiya Mohammad (Utrecht University)" Needs of community pharmacists, hospital pharmacists and patients on the content of a pharmaceutical discharge letter: a qualitative focus group study"	2018	2.0
-	Salwa el Ghouch (University of Groningen) "Patient-reported ADEs four weeks after hospital discharge"	2018	2.0
-	Doortje de Bruijn (VU University Amsterdam) "The needs of hospital pharmacists, community pharmacists and patients regarding the pharmaceutical discharge process: a qualitative focus-group study"	2019	2.0
-	Roos-Marije Schotsman (University Utrecht) "Medication Actions to Reduce Hospital admissions through a collaboration of Community and Hospital pharmacists: A prospective before- and after study"	2019	2.0
		Total:	**35.9**

CURRICULUM VITAE

Elien Uitvlugt werd op 15 februari 1988 geboren in Den Ham. Na het behalen van haar gymnasium diploma aan RSG De Borgen in Leek, startte zij in 2006 met de studie Farmacie aan de Rijksuniversiteit Groningen. In juli 2012 behaalde ze haar apothekersdiploma waarna ze in september 2012 begon als projectapotheker in OLVG in Amsterdam. In april 2014 startte ze met de opleiding tot ziekenhuisapotheker. Als projectapotheker werkte zij reeds mee aan wetenschappelijk onderzoek wat ze verder uitbouwde tijdens haar opleiding tot promotieonderzoek. Na haar opleiding heeft Elien gewerkt in het St. Antonius Ziekenhuis in Nieuwegein als ziekenhuisapotheker met als aandachtsgebied de transmurale zorg. Tevens heeft ze in samenwerking met ZonMw, de SWAB, UMC Utrecht en Santeon onderzoek gedaan naar de implementatie van landelijke COVID-19 behandeladviezen gedurende de eerste COVID-19 golf in Nederland. Sinds april 2021 is Elien werkzaam als ziekenhuisapotheker binnen de transmurale zorg in OLVG. Elien woont samen met haar partner Roel Beek in Amsterdam.