Enhancing care and follow-up for older individuals

Shifting towards medication optimization?

Aimée E.M.J.H. Linkens

Enhancing care and follow-up for older individuals

Shifting towards medication optimization?

Aimée Elisabeth Maria Johannes Henricus Linkens

Enhancing care and follow-up for older individuals
Shifting towards medication optimization?

ISBN: 978-90-834134-1-9

Cover design: Jean Scheijen
Lay-out:Tiny Wouters
Printing: www.Proefschriftenprinten.nl

Enhancing Care and Follow-up for Older Individuals

Shifting towards medication optimization?

Verbeteren van de zorg en follow-up voor ouderen

Op weg naar medicatieoptimalisatie?

Proefschrift

Ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

prof. dr. A.L. Bredenoord

en volgens besluit van het college voor promoties.
De openbare verdediging zal plaatsvinden op

donderdag 16 mei 2024 om 13:00 uur

Aimée Elisabeth Maria Johannes Henricus Linkens

Geboren te Maastricht.

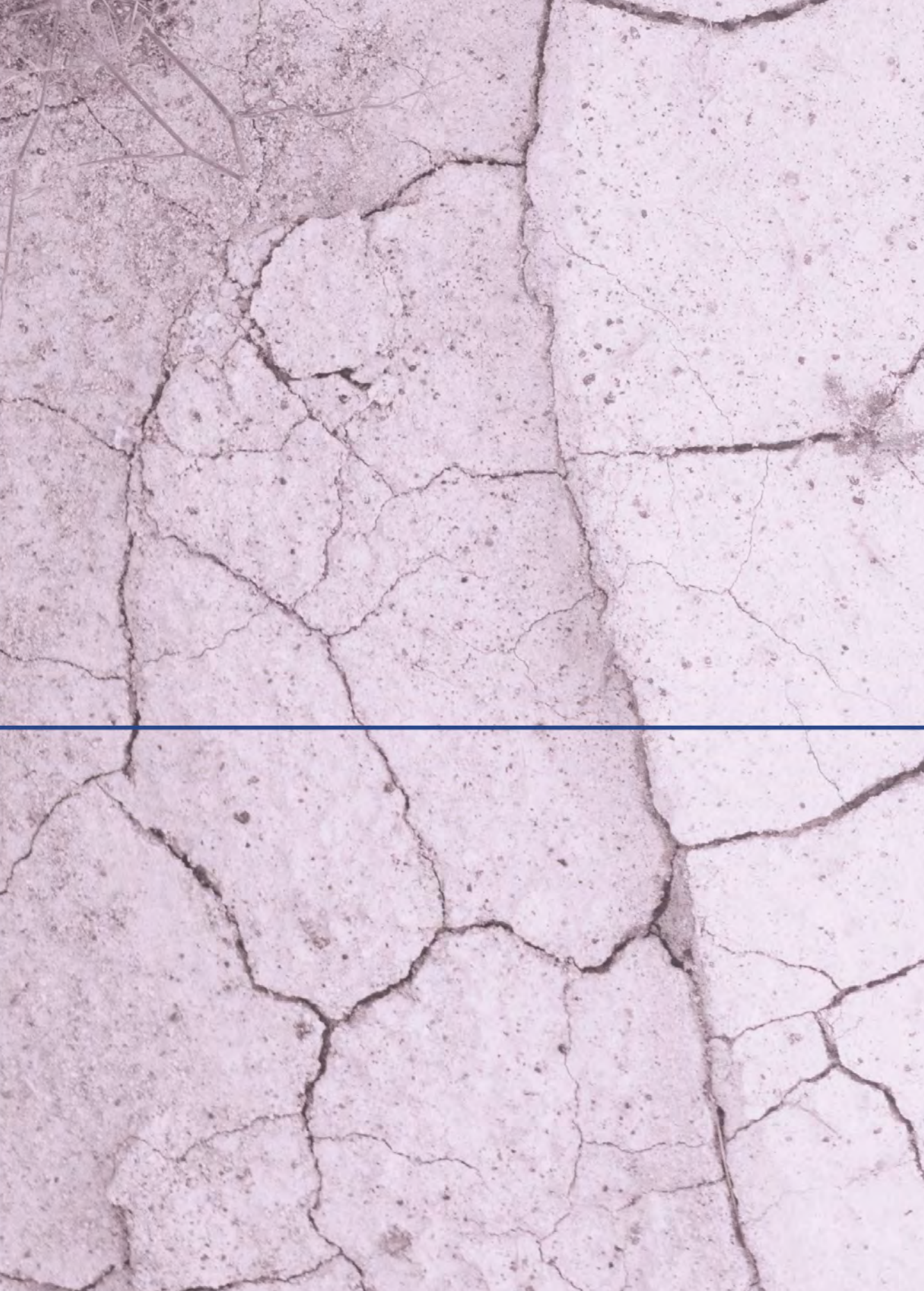
Erasmus University Rotterdam

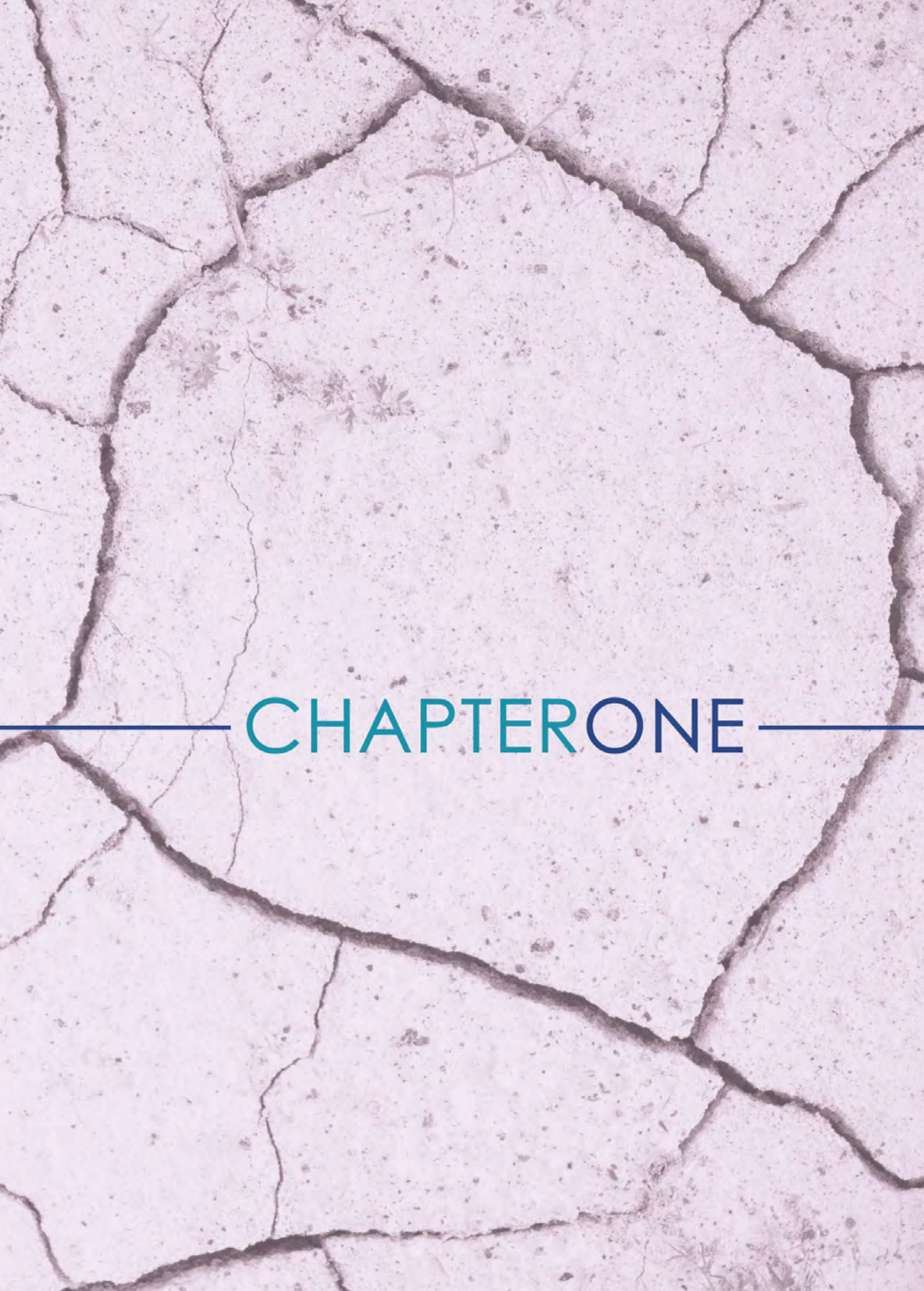
Erasmus

Promotiecommissie

Promotor:	prof. dr. P.H.M. van der Kuy
Overige leden:	prof. dr. F.U.S. Mattace-Raso prof. dr. D.J.A. Janssen prof. dr. R.P. Koopmans
Copromotoren:	dr. B.P.A. Spaetgens dr. N.C. van Nie - Visser dr. K.P.G.M. Hurkens

Table of contents





CHAPTERONE

Chapter 1

General introduction and outline of the thesis

General introduction and outline of the thesis

The ageing global population is experiencing an increase in medically complex patients due to frailty, multimorbidity, associated polypharmacy and cognitive impairment[1-3]. This increasingly frail and older population is at risk of significant morbidity and mortality, with an even higher risk when hospitalized[2,3]. Furthermore, ageing of the population is associated with increased healthcare costs, although healthcare budgets are becoming increasingly restricted to control costs[4]. Consequently, determining priorities and allocating resources while maintaining high-quality care is crucial. Potential interesting initiatives that have been implemented to improve care include (I) task delegation from physicians to other healthcare professionals; (II) physician support by other healthcare professionals; and (III) electronic tools, such as computers and computerised decision support systems (CDSS)[5-7]. Many clinical trials have investigated these initiatives with varying results in reducing adverse healthcare outcomes[8]. However, to date data on the real-life clinical setting of such initiatives are lacking. Therefore, this thesis aims to address knowledge gaps in real-life clinical settings and put initiatives to improve in-hospital management and optimize medication of frail and older individuals in a broader perspective than just clinical trials.

In-hospital management

In the context of in-hospital management, the ageing population, and thus increasing proportion of frail older individuals leads to an undisputed increase in hospital admissions[9]. Therefore, a comprehensive and multidisciplinary approach of care is necessary to address the complexity of this population and improve patient outcomes. Various models of collaborative care have been implemented for in-hospital care, such as orthogeriatric care, which has been embraced by both surgical and medical professionals[10]. However, the optimal approach to orthogeriatrics is subject to change, and there is a lack of studies comparing different types of care.

One of the key elements of successful co-management is medication optimization, including appropriate (de)prescribing[11]. However, restarting deprescribed medication automatically in the outpatient setting is common, indicating a need to optimize medication management and ensure effective communication between in-hospital and outpatient care.

Polypharmacy

Polypharmacy is commonly defined as the use of five or more medications and is a common phenomenon in older adults, particularly in those over the age of 65[12]. The prevalence of polypharmacy in this age group is estimated to be around 25%, and it increases to over 40% in adults aged 70 and above[13]. While polypharmacy may be necessary to treat multiple coexisting conditions, it may also lead to a wide range of medication-related problems (MRPs) and adverse health outcomes[14,15]. One of the most significant consequences is an increased risk of falls, which can result in fractures, hospitalizations, and even death[15,16]. Medications that affect the central nervous system, such as sedatives, hypnotics, and opioids, are particularly implicated in falls[17]. Polypharmacy is also a known risk factor for hospitalization, with older adults taking multiple medications more likely to be admitted to the hospital for medication-related issues[16]. Therefore, healthcare professionals should be vigilant when prescribing medications to older adults, carefully considering the potential benefits and risks of each drug. Comprehensive medication reviews can help identify and resolve medication-related problems, potentially improving health outcomes and reducing healthcare costs[18].

Medication-related problems

Both medication use and polypharmacy can give rise to numerous issues for patients, with varying definitions used in the literature to denote their consequences. Figure 1.1 illustrates these consequences. An "Adverse Drug Reaction" (ADR) occurs when an unintended and harmful reaction to medication occurs during the normal use[19]. An example of an ADR is diarrhoea occurring as a side effect of antibiotic use or colchicine. An "Adverse Drug Event" (ADE) refers to any undesirable medical event that occurs during drug treatment due to normal use or as a result of suboptimal treatment[20]. An example of an ADE is an allergic reaction to antibiotic treatment. "Drug-related problems" (DRPs) encompass both ADRs and ADEs, as well as problems arising from drug-drug interactions, prescription errors, and non-adherence to therapy[21,22]. An example of a DRP is the incorrect daily use (taking the weekly dosage daily) of methotrexate instead of once a week.

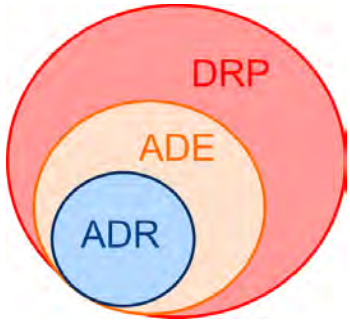


Figure 1.1 Schematic overview of medication-related problems defined as ADR, ADE and DRP; ADR: Adverse Drug Reaction; ADE: Adverse Drug Event; DRP: Drug-Related Problem.

Medication-related hospital admissions and - readmissions

Polypharmacy is a known risk factor for medication-related admissions and readmissions, which are defined inconsistently in the literature[23,24]. Such admissions are commonly attributed to ADRs, ADEs or DRPs. Variations in definitions have led to significant variability in reported prevalence rates. In the Netherlands, medication-related admissions accounted for approximately 10% of all admissions in 2006, with medication-related readmissions representing around 20% of all readmissions[25-27]. Whether an admission or readmission was medication-related was based on an expert team's assessment[25]. However, underreporting is likely, and it is recommended by the polypharmacy guideline that the triggerlist is used to evaluate the possibility of medication-related admissions in hospitalized patients aged 70 years and above and with polypharmacy[28]. The triggerlist comprises the ten most common medication-related issues that may lead to admission and medication review is advised if a medication-related admission is detected, preferably in consultation with an expert[28].

Interventions to reduce medication-related (re)admissions

Medication review is currently the most widely studied intervention for reducing medication-related (re)admissions[29]. However, interventions vary widely in terms of scope and follow-up, and measured outcomes vary considerably across different studies[29,30]. Generally, a reduction in hospital (re)admissions is the primary outcome[31]. While a medication review has been shown to reduce (re)admissions, it is difficult to determine the optimal intervention, given the diversity of interventions and outcomes, particularly since many studies have produced negative results[30,32-34].

Clinical Decision Support Systems (CDSS)

Recent studies have examined the potential benefits of implementing a Clinical Decision Support System (CDSS) in reducing hospital admissions and readmissions, and emergency department visits[35-38]. A CDSS utilizes clinical rules that integrate patient-specific characteristics, laboratory results and medication information[39]. The aim is to provide guidance on medication interactions and indications based on standardized guidelines, using START/STOPP criteria to aid pharmacists and clinicians[36]. Patient data such as medical history, age and lab results can be incorporated into the clinical rules[39]. A report of all the rules and advice is generated for the clinician or pharmacist.

Two large-scale clinical trials have explored the effectiveness of CDSS in combination with a pharmacist-led medication review on hospital admissions and ADRs[36,37]. However, both trials reported negative results, with only a small percentage of the clinical recommendations being followed (39% and 15%, respectively)[36,37,40].

Improving interventions and medication reviews to reduce medication-related problems

As indicated above, it is important to prevent medication-related problems and associated (re)admissions. Performing a medication review, with or without the use of a CDSS, is a potentially effective intervention to achieve this goal. However, it is currently unknown how these interventions can be best executed and in what way.

To improve the results of these interventions, it may be useful to improve follow-up, as the durability of medication reviews is often limited[41]. Involving primary care physicians in the follow-up process may help to improve this aspect and should therefore be further investigated.

Additionally, it has been observed that the recommendations generated by a CDSS are only followed in a small percentage of cases[36,37,40]. This may be due to various factors, such as the clinical relevance of the rules and alert fatigue[36,40,42,43]. To improve this in the future, it is important to first determine the natural course of the CDSS-generated recommendations and to evaluate whether certain rules have a greater impact on outcomes than others. This will enable the assessment of whether a rule needs to be further evaluated.

Lastly, studies have shown that the populations in which these interventions are conducted are diverse, which can influence the results and effectiveness of the intervention[44,45]. It is important to identify the most effective population group for medication reviews. While older people with polypharmacy have been predominantly

studied, it may be beneficial to include additional risk factors to make the intervention more effective and practical[34,46]. By doing so, the intervention can be targeted to a smaller, high-risk patient group and may become more feasible in clinical practice.

Outline of the thesis

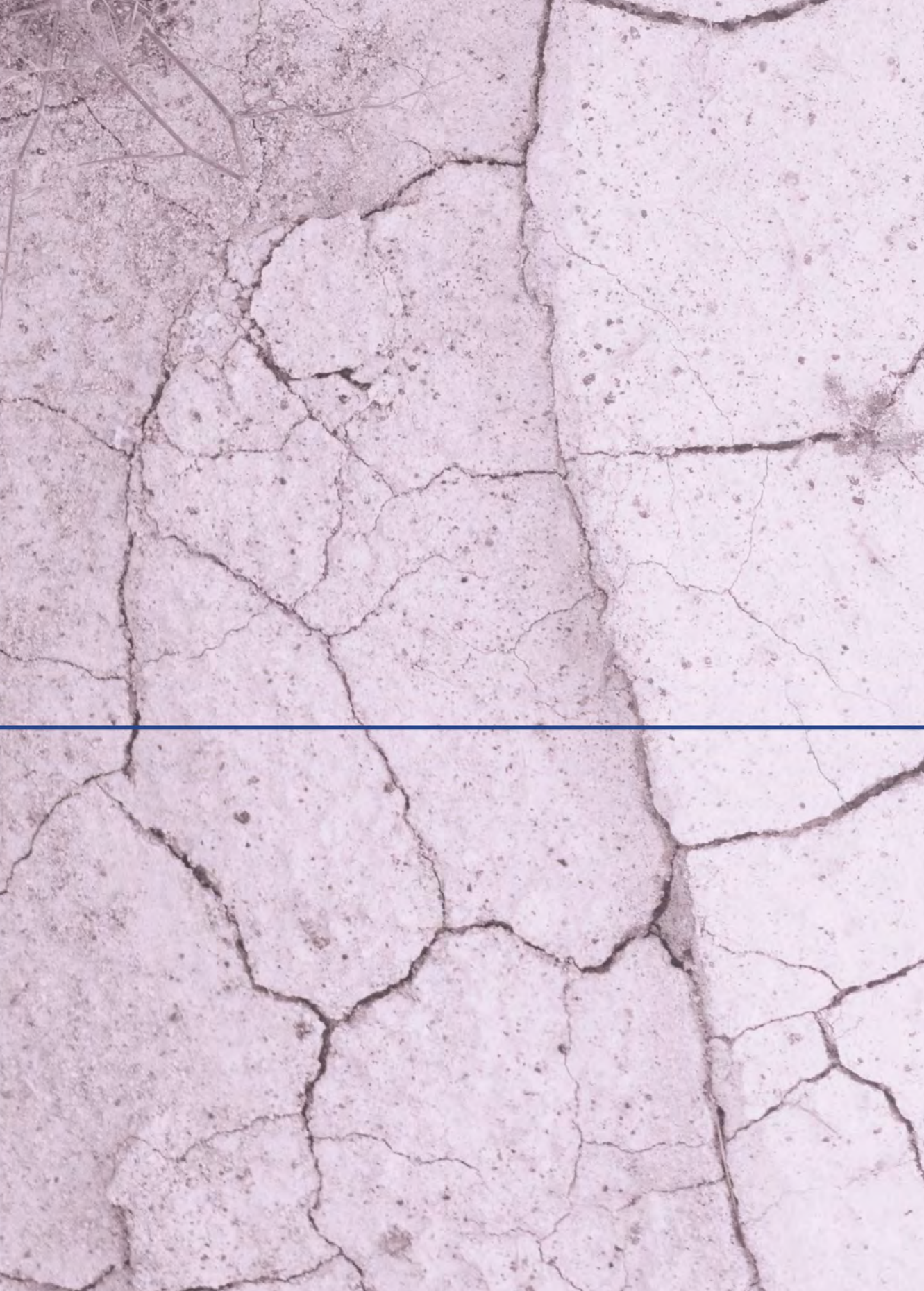
In this thesis, we aim to bridge knowledge gaps in real-life clinical settings and explore initiatives, such as co-management and the use of CDSS, to improve the in-hospital management and optimize medication of frail and older individuals beyond the scope of clinical trials. **Chapter 2** details the implementation and evaluation of a Nurse-Practitioner led Orthogeriatric Care Program, which includes as an essential part of the program medication review and follow-up, by measuring 3-month and 1-year mortality, in comparison to standard care. **Chapter 3** provides an overview on what is currently known about medication-related hospital admissions and readmissions, associated risk factors and possible interventions to reduce these (re)admissions. In **Chapter 4**, we apply the lessons learned from the literature review in chapter 3 and design the CHECkUP study protocol. This study aims to investigate whether the continuous use of a CDSS after discharge decreases the number of hospital readmissions in older patients with a history of unplanned, probably medication-related hospitalization according to the triggerlist from The Dutch multidisciplinary guideline for polypharmacy in older patients[13]. **Chapter 5** evaluates the use of the triggerlist to select high-risk patients and assesses its additional value in identifying these patients. **Chapter 6** describes a real-world study of an in-hospital implemented CDSS, in which we investigate whether generated alerts are being resolved (with or without pharmacist intervention). As such, this study contributes to the knowledge gap that describes the natural course of generated alerts and the impact of the pharmacist's action on the alert's outcome. **Chapter 7** summarizes and discusses the thesis's main findings, including its clinical relevance, some methodological considerations and future perspectives.

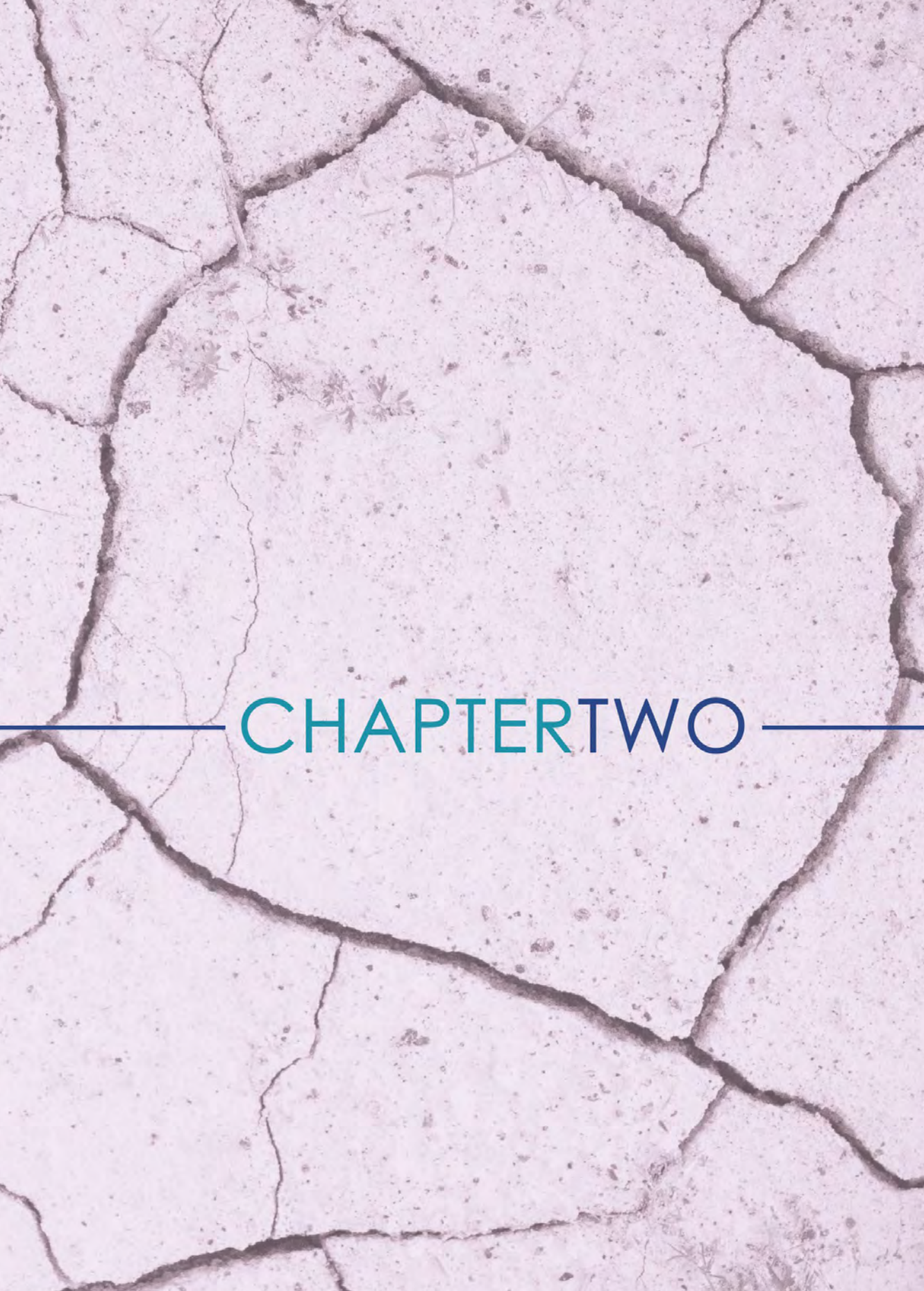
References

1. Aggarwal P, Woolford SJ, Patel HP. Multi-Morbidity and Polypharmacy in Older People: Challenges and Opportunities for Clinical Practice. Geriatrics (Basel). 2020;5(4):85.
2. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet. 2012;380(9836):37-43.
3. Vermeiren S, Vella-Azzopardi R, Beckwée D, Habbig AK, Scafoglieri A, Jansen B et al. Frailty and the Prediction of Negative Health Outcomes: A Meta-Analysis. J Am Med Dir Assoc. 2016;17(12): 1163.e1-.e17.
4. Spillman BC, Lubitz J. The effect of longevity on spending for acute and long-term care. N Engl J Med. 2000;342(19):1409-1415.
5. Vrijmoeth T, Wassenaar A, Koopmans R, Nieuwboer MS, Perry M. Generalist-Specialist Collaboration in Primary Care for Frail Older Persons: A Promising Model for the Future. J Am Med Dir Assoc. 2022;23(2):288-296.e3.
6. Lovink MH, van Vught A, Persoon A, Schoonhoven L, Koopmans R, Laurant MGH. Skill mix change between general practitioners, nurse practitioners, physician assistants and nurses in primary healthcare for older people: a qualitative study. BMC Fam Pract. 2018;19(1):51.
7. Keine D, Zelek M, Walker JQ, Sabbagh MN. Polypharmacy in an Elderly Population: Enhancing Medication Management Through the Use of Clinical Decision Support Software Platforms. Neurol Ther. 2019;8(1):79-94.
8. Monteiro L, Maricoto T, Solha I, Ribeiro-Vaz I, Martins C, Monteiro-Soares M. Reducing Potentially Inappropriate Prescriptions for Older Patients Using Computerized Decision Support Tools: Systematic Review. J Med Internet Res. 2019;21(11):e15385.
9. Chang SF, Lin HC, Cheng CL. The Relationship of Frailty and Hospitalization Among Older People: Evidence From a Meta-Analysis. J Nurs Scholarsh. 2018;50(4):383-391.
10. Van Heghe A, Mordant G, Dupont J, Dejaeger M, Laurent MR, Gielen E. Effects of Orthogeriatric Care Models on Outcomes of Hip Fracture Patients: A Systematic Review and Meta-Analysis. Calcif Tissue Int. 2022;110(2):162-184.
11. Henriksen BT, Krogseth M, Nguyen CT, Mathiesen L, Davies MN, Andersen RD et al. Medication management for patients with hip fracture at a regional hospital and associated primary care units in Norway: a descriptive study based on a survey of clinicians' experience and a review of patient records. BMJ Open. 2022;12(11):e064868.
12. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17(1):230.
13. Hosseini SR, Zabihi A, Jafarian Amiri SR, Bijani A. Polypharmacy among the Elderly. J Midlife Health. 2018;9(2):97-103.
14. Wastesson JW, Morin L, Tan ECK, Johnell K. An update on the clinical consequences of polypharmacy in older adults: a narrative review. Expert Opin Drug Saf. 2018;17(12):1185-1196.
15. Kim J, Parish AL. Polypharmacy and Medication Management in Older Adults. Nurs Clin North Am. 2017;52(3):457-468.
16. Pazan F, Wehling M. Polypharmacy in older adults: a narrative review of definitions, epidemiology and consequences. Eur Geriatr Med. 2021;12(3):443-452.
17. Izza MAD, Lunt E, Gordon AL, Gladman JRF, Armstrong S, Logan P. Polypharmacy, benzodiazepines, and antidepressants, but not antipsychotics, are associated with increased falls risk in UK care home residents: a prospective multi-centre study. Eur Geriatr Med. 2020;11(6):1043-1050.
18. Huiskes VJ, Burger DM, van den Ende CH, van den Bemt BJ. Effectiveness of medication review: a systematic review and meta-analysis of randomized controlled trials. BMC Fam Pract. 2017;18(1):5.
19. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356(9237):1255-1259.
20. 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.
21. Nivya K, Sri Sai Kiran V, Ragoo N, Jayaprakash B, Sonal Sekhar M. Systemic review on drug related hospital admissions - A pubmed based search. Saudi Pharm J. 2015;23(1):1-8.

22. Strand LM, Morley PC, Cipolle RJ, Ramsey R, Lamsam GD. Drug-related problems: their structure and function. Dicp. 1990;24(11):1093-1097.
23. Cabré M, Elias L, Garcia M, Palomera E, Serra-Prat M. Avoidable hospitalizations due to adverse drug reactions in an acute geriatric unit. Analysis of 3,292 patients. Med Clin (Barc). 2018;150(6):209-214.
24. Schönenberger N, Meyer-Massetti C. Risk factors for medication-related short-term readmissions in adults - a scoping review. BMC Health Serv Res. 2023;23(1):1037.
25. 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):1890-1896.
26. El Morabet N, Uitvlugt EB, van den Bemt BJF, van den Bemt P, Janssen MJA, Karapinar-Çarkit F. Prevalence and Preventability of Drug-Related Hospital Readmissions: A Systematic Review. J Am Geriatr Soc. 2018;66(3):602-608.
27. Vervolgonderzoek medicatieveiligheid: eindrapport. Rotterdam/Utrecht/Nijmegen: Erasmus MC, NIVEL, Radboud UMC, PHARMO, 2017. 129 p.
28. Polyfarmacie bij ouderen. Polyfarmacie bij ouderen in de 2e lijn: Federatie Medisch Specialisten - Richtlijnendatabase; 2020.
29. Mekonnen AB, McLachlan AJ, Brien JA. Effectiveness of pharmacist-led medication reconciliation programmes on clinical outcomes at hospital transitions: a systematic review and meta-analysis. BMJ Open. 2016;6(2):e010003.
30. Foot H, Scott I, Sturman N, Whitty JA, Rixon K, Connelly L et al. Impact of pharmacist and physician collaborations in primary care on reducing readmission to hospital: A systematic review and meta-analysis. Res Social Adm Pharm. 2022;18(6):2922-2943.
31. Dautzenberg L, Bretagne L, Koek HL, Tsokani S, Zevgiti S, Rodondi N et al. Medication review interventions to reduce hospital readmissions in older people. J Am Geriatr Soc. 2021;69(6):1646-1658.
32. Ravn-Nielsen LV, Duckert ML, 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):375-382.
33. Bülow C, Clausen SS, Lundh A, Christensen M. Medication review in hospitalised patients to reduce morbidity and mortality. Cochrane Database Syst Rev. 2023;1(1):Cd008986.
34. Thomas R, Huntley AL, Mann M, Huws D, Elwyn G, Paranjothy S et al. Pharmacist-led interventions to reduce unplanned admissions for older people: a systematic review and meta-analysis of randomised controlled trials. Age Ageing. 2014;43(2):174-187.
35. O'Sullivan D, O'Mahony D, O'Connor MN, Gallagher P, Gallagher J, Cullinan S et al. Prevention of Adverse Drug Reactions in Hospitalised Older Patients Using a Software-Supported Structured Pharmacist Intervention: A Cluster Randomised Controlled Trial. Drugs Aging. 2016;33(1):63-73.
36. Blum MR, Sallevelt B, Spinewine A, O'Mahony D, Moutzouri E, Feller M et al. Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults (OPERAM): cluster randomised controlled trial. Bmj. 2021;374:n1585.
37. O'Mahony D, Gudmundsson A, Soiza RL, Petrovic M, Cruz-Jentoft AJ, Cherubini A et al. Prevention of adverse drug reactions in hospitalized older patients with multi-morbidity and polypharmacy: the SENATOR* randomized controlled clinical trial. Age Ageing. 2020;49(4):605-614.
38. Iankowitz N, Dowden M, Palomino S, Uzokwe H, Worral P. The effectiveness of computer system tools on potentially inappropriate medications ordered at discharge for adults older than 65 years of age: a systematic review. JBI Libr Syst Rev. 2012;10(13):798-831.
39. Curtain C, Peterson GM. Review of computerized clinical decision support in community pharmacy. J Clin Pharm Ther. 2014;39(4):343-348.
40. Sallevelt B, Huibers CJA, Heij J, Egberts TCG, van Puijenbroek EP, Shen Z et al. Frequency and Acceptance of Clinical Decision Support System-Generated STOPP/START Signals for Hospitalised Older Patients with Polypharmacy and Multimorbidity. Drugs Aging. 2022;39(1):59-73.
41. Ocampo CC, Garcia-Cardenas V, Martinez-Martinez F, Benrimoj SI, Amariles P, Gastelurrutia MA. Implementation of medication review with follow-up in a Spanish community pharmacy and its achieved outcomes. Int J Clin Pharm. 2015;37(5):931-940.
42. Dalton K, O'Mahony D, Cullinan S, Byrne S. Factors Affecting Prescriber Implementation of Computer-Generated Medication Recommendations in the SENATOR Trial: A Qualitative Study. Drugs Aging. 2020;37(9):703-713.

43. Ranji SR, Rennke S, Wachter RM. Computerised provider order entry combined with clinical decision support systems to improve medication safety: a narrative review. BMJ Qual Saf. 2014;23(9):773-780.
44. Damoiseaux-Volman BA, Medlock S, van der Meulen DM, de Boer J, Romijn JA, van der Velde N et al. Clinical validation of clinical decision support systems for medication review: A scoping review. Br J Clin Pharmacol. 2022;88(5):2035-2051.
45. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. Arch Intern Med. 2003;163(12):1409-1416.
46. Lee JQ, Ying K, Lun P, Tan KT, Ang W, Munro Y et al. Intervention elements to reduce inappropriate prescribing for older adults with multimorbidity receiving outpatient care: a scoping review. BMJ Open. 2020;10(8):e039543.





CHAPTER TWO

Chapter 2

Mortality in hip fracture patients after implementation of a nurse practitioner-led orthogeriatric care program: results of a 1-year follow-up

Jannic A.A. van Leendert*, Aimée E.M.J.H. Linkens*, Martijn Poeze, Evelien Pijpers, Fabiënne Magdelijns, René H.M. ten Broeke, Bart Spaetgens
* Both authors contributed equally

Age Ageing 2021;50(5):1744-1750

Abstract

Background

Hip fractures are a major cause of mortality and disability in frail older adults. Therefore, orthogeriatrics has been embraced to improve patient outcomes. With the optimal template of orthogeriatric care still unknown, and to curtail rising healthcare expenditure we implemented a nurse-practitioner led orthogeriatric care program (NPOCP). The objective was to evaluate NPOCP by measuring 3-month and 1-year mortality, compared to usual care. In addition, length of stay (LOS) and location of hospital discharge were reported.

Methods

An anonymised data set, of hip fracture patients (n=300) who presented to Maastricht University Medical Centre, the Netherlands, a level-1 trauma centre, was used. NPOCP was implemented on one of two surgical wards, while the other ward received usual care (UC). Patient allocation to these wards was random.

Results

144 patients received NPOCP and 156 received UC. In the NPOCP, 3-month and 1-year mortality rates were 9.0% and 13.9%, compared to 24.4% and 34.0% in the UC group (P<0.001). The adjusted hazard ratio (aHR) for 3-month (aHR 0.50 [95%CI:0.26-0.97]) and 1-year mortality (aHR 0.50 [95%CI:0.29-0.85]) remained lower in NPOCP compared to UC. Median LOS was 9 days [IQR 5-13] in patients receiving UC and 7 days [IQR 5-13] in patients receiving NPOCP (P=0.08). Thirty-eight (27.5%) patients receiving UC and fifty-seven (40.4%) patients receiving NPOCP were discharged home (P=0.023).

Conclusion

Implementation of NPOCP was associated with significantly reduced mortality in hip fracture patients and may contribute positively to high quality care and improve outcomes in the frail orthogeriatric population.

Introduction

Hip fractures are a major cause of mortality and disability in frail older adults, with a rising prevalence due to ageing of the population[1]. Therefore, orthogeriatrics, entailing a holistic, multidisciplinary approach to care for this frail population, has been embraced by both surgical and medical professionals to improve patient outcomes[2]. However, the optimal template of how to perform orthogeriatric care is still unknown, which may contribute to the considerable variation in reported mortality and morbidity reduction by implementation of these programs[3].

Parallel with the rising burden of the orthogeriatric population on healthcare expenditure, healthcare providers and policy makers are deciding on priorities and resource allocation in times when healthcare budgets are becoming increasingly restricted[4]. From this health economic perspective, delegation of tasks from physicians to nurse practitioners (NP) is potentially cost-saving and might lead to more efficient care. In the non-surgical ageing population this approach has proven to be effective in several settings, such as the primary care and long-term care setting, with nurse or NP-led programs having at least comparable outcomes to physician-directed programs[5].

Furthermore, the recognition of these health-care professionals is further underscored by the fact that curricula are being developed for NPs working with frail older individuals in the hospital setting[6]. Nevertheless, to our knowledge, NP-led programs have not been explored in the orthogeriatric population, where mainly non-holistic interventions, solely focusing on osteoporosis (fracture liaison service) or delirium, by nurses or NPs have been deployed[7,8].

To improve outcomes in our orthogeriatric population, we implemented a NP-led orthogeriatric care program. The program was evaluated by measuring 3-month and 1-year mortality, compared to standard care. In addition, length of stay, location of hospital discharge and postoperative medical complications were reported as secondary outcomes.

Methods

Patients

The present study used an anonymised data set of hip fracture patients (n=300) who were registered for a yearly audit on quality of care based on the Hospital Standardized Mortality Ratio (HSMR)[9]. Diagnosis-specific HSMRs may serve as a marker for quality of care over time and also provide insight in trends of care improvement after quality improvement initiatives have been implemented[10].

In the Maastricht University Medical Centre, the Netherlands, a level-1 trauma centre, all hip fracture patients between January 1 and December 31, 2018 were included. If a patient was admitted more than once, the first fracture episode was included for analyses. The institutional review board of the MUMC approved the study with waiver of consent.

Data collection

The HSMR data set contained demographic, clinical and follow-up data including age, sex, fracture type, Charlson Comorbidity Index (CCI)[11], length of stay, discharge destination and in-hospital mortality. Additional data on American Society of Anesthesiologists Physical Status Classification System (ASA), surgical intervention rate, weight bearing restrictions, consultation by NP or geriatrician, follow-up after discharge, medication review, 3-month and 1-year mortality, and identified postoperative medical complications (delirium, infections (urinary tract infection, pneumonia), myocardial ischaemia, heart failure and acute kidney injury) were obtained using hospital medical records.

Nurse Practitioner-led Orthogeriatric Care Program (NPOCP)

The NP-led Orthogeriatric Care Program (NPOCP) was implemented on one out of two surgical wards of the MUMC. Patient allocation to these wards was random. In 2017, (a-prior to implementation) 1-year mortality between both wards was similar (Supplementary figure 2.1).

Table 2.1 shows the difference between NPOCP and usual care (UC). NPOCP was conducted by two NPs with both six years of experience in in-patient geriatric care. As such, they already had extensive experience in performing a comprehensive geriatric assessment (CGA). During the run-in period (4 weeks), the NPs were trained by the supervising geriatrician and a senior orthopaedic surgeon. The NPs were specifically trained to diagnose and manage comorbidities, postoperative (medical) complications, and polypharmacy. In addition, multiple hip fracture surgeries were attended.

During weekdays, the two NPs were alternately one week available for a total of one fulltime-equivalent for the NPOCP-ward. Figure 2.1 shows a schematic overview of NPOCP. (1) On admission, the NP performs a CGA, addressing medical, cognitive and functional capabilities or disabilities in order to develop an integrated care plan for treatment and follow-up. (2) In the acute (pre-operative) setting of NPOCP, the CGA initially focused on the diagnosis and treatment of acute medical/cognitive problems that prevent patients from safely undergoing surgery. Also, a medication review to prevent inappropriate medication use was performed. (3) Next, daily interdisciplinary ward rounds by the NP and orthopaedic resident were implemented, to ensure repeated interdisciplinary multidimensional assessment that focused on acute diagnoses, such as

acute fracture complications and timely diagnosis and/or prevention of other life-threatening postoperative complications. Also, a personalised therapeutic plan to enhance recovery (physiotherapy) and to promote independence (occupational therapy) was discussed with patients and their relatives. Furthermore, weekly grand rounds with the attending orthopaedic surgeon and geriatrician, and if necessary, (4) geriatric follow-up after discharge were implemented. For all patients, a final discharge report in which was written to be shared with the general practitioner, home care agency and/or nursing home physician.

Table 2.1 Outline of organisation usual care versus NP-led Orthogeriatric Care Program.

	Usual Care	NPOCP
Ward rounds	Daily visits solely performed by orthopaedic resident/surgeon No standard consultation NP or geriatrician	Every weekday, interdisciplinary ward rounds with NP and orthopaedic resident/surgeon takes place. Weekend days: visit by orthopaedic resident/surgeon
Consultation by NP	Consultation of NP by orthopaedic resident/surgeon to prevent delirium based on clinical suspicion or if patients are identified as frail based on hospital frailty screening tool.	Daily multidimensional assessment and follow-up by the NP Reduces consultations with other specialists.
Comprehensive Geriatric Assessment (CGA)	CGA only performed in consultation was requested Medication review as part of CGA	CGA on the first weekday after admission for all patients Medication review as part of CGA
Follow-up round (afternoon)	None	Each afternoon follow-up of lab results, X-rays, acute matters
Grand rounds	No participation from NP or geriatrician	Weekly grand rounds with orthopaedic resident/surgeon, NP and geriatrician
Physiotherapy	Daily individual training post-surgery	Daily individual training post-surgery.
Nutritional therapy	Protein enriched diet Screening nutritional status by the ward nurse and follow-up once a week	Protein enriched diet In addition to screening by the ward nurse, assessment of nutritional status on admission (within CGA) is performed. Nutritional assistance is started <24h of hospitalisation. Daily (weekdays) follow-up.
Occupational therapy	Evaluation of the need for daily living aids when deemed necessary by the ward nurse	Personalised treatment plan to enhance recovery and to promote independence is made
Discharge letter and planning	Early discharge planning. Final discharge report written by orthopaedic resident/surgeon sent to the general practitioner	Early discharge planning with a shared final discharge report sent to all relevant healthcare workers (general practitioner, rehabilitation centre, home care agency, nursing home doctor)
Training staff	Nursing staff on the ward is trained 2 times a year by NP or geriatrician on subjects in geriatric care	Nursing staff on the ward is trained bimonthly by the NPs or geriatrician (on different subjects) or geriatrician. NPs are being trained by the geriatrician (monthly) Before implementation and in the first weeks of implementation the NPs were trained by both the geriatrician and orthopaedic surgeon to diagnose and manage comorbidities, postoperative (medical) complications, and polypharmacy. They also attended several hip fracture surgeries.
Responsibility	The orthopaedic surgeon is solely responsible for patient treatment	Shared responsibility for patient treatment

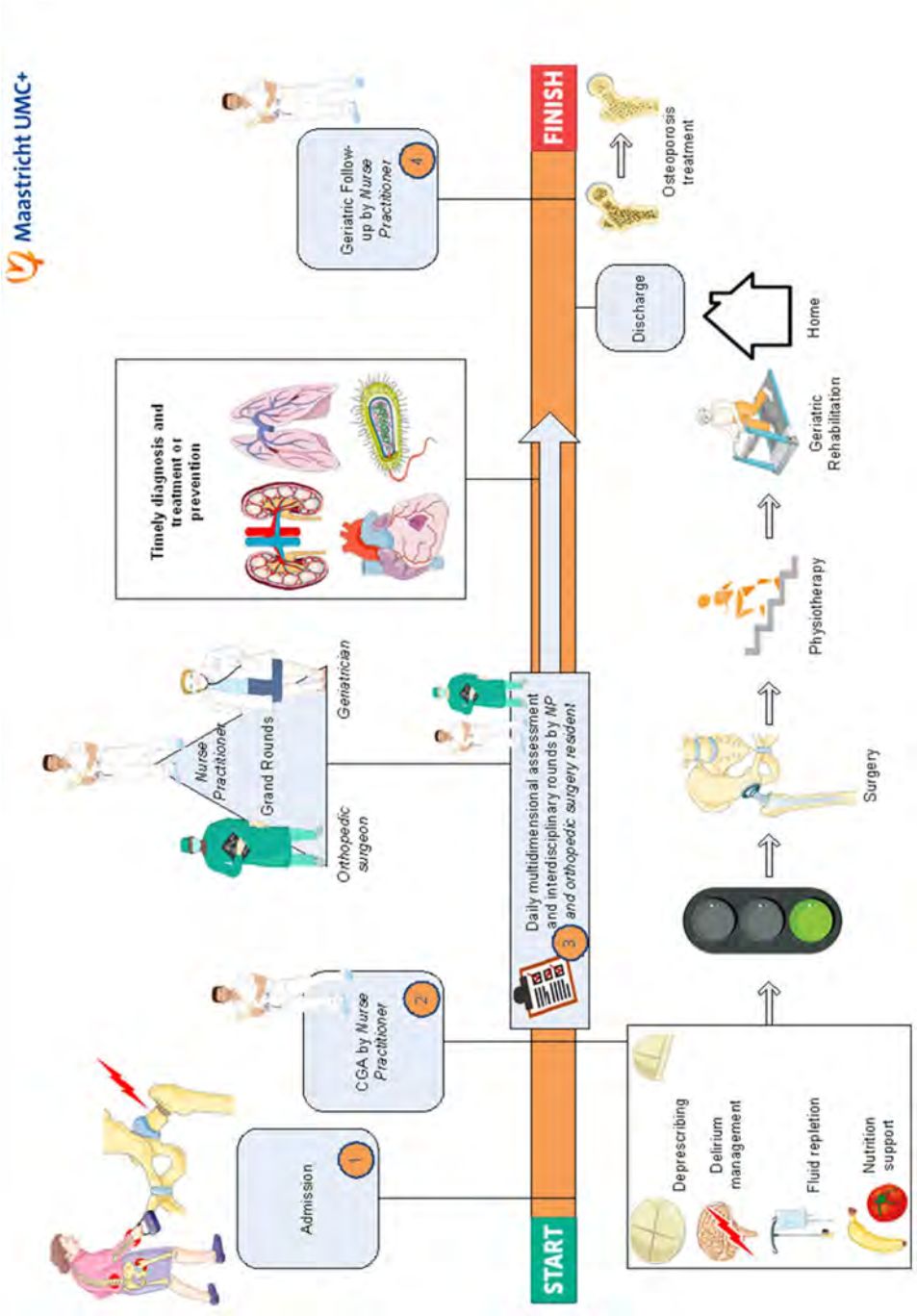

Maastricht UMC+
START
FINISH
Admission
1
CGA by Nurse Practitioner
2
Daily multidimensional assessment and interdisciplinary rounds by NP and orthopedic surgery resident
3
Geriatric Follow-up by Nurse Practitioner
4
Timely diagnosis and treatment or prevention
Nurse Practitioner
Grand Rounds
Geriatrician
Orthopedic surgeon
Deprescribing
Delirium management
Fluid repletion
Nutrition support
Surgery
Physiotherapy
Geriatric Rehabilitation
Home
Discharge
Osteoporosis treatment

Figure 2.1 Schematic overview of the Nurse Practitioner-led Orthogeriatric Care Program (NPOCP).

1 Every hip fracture patient admitted to the surgical ward is included in the NPOCP.
2 On admission a Comprehensive Geriatric Assessment (CGA) is performed by the Nurse Practitioner (NP). CGA is a multidimensional assessment process that focuses on medical, cognitive and functional capabilities or disabilities in order to develop an integrated care plan for treatment and follow-up. In the acute (pre-operative) setting of NPOCP, the CGA initially focuses on the diagnosis and treatment of acute medical/cognitive problems that prevent patients from safely undergoing surgery. Also, a medication review to prevent inappropriate medication use is performed.
3 Daily multidimensional assessment and interdisciplinary rounds by the NP and orthopedic surgery resident: In the second, postoperative, stage of the NPOCP, the daily interdisciplinary multidimensional assessment focuses on acute problems, such as acute fracture complications and timely diagnosis and/or prevention of other life-threatening postoperative complications, such as myocardial infarction, pulmonary embolism, acute kidney injury, sepsis, delirium etc. on the one hand and a therapeutic plan to enhance recovery and to promote independence on the other.
4 After discharge, most orthogeriatric care programs will end. In our NPOCP however, adequate (geriatric) follow-up is guaranteed. During the first follow-up appointment the NP will initiate the diagnostic (and if necessary therapeutic process) concerning osteoporosis. Furthermore, a follow-up CGA with special attention to (de)prescribing medication, cardiovascular risk management and kidney function, cognitive function, functional status and fall prevention will be performed.

This figure was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com.

Statistical analysis

Descriptive statistics were used to describe the population and were presented as mean (SD), median (IQR) or percentage, and T-test, Chi-square test, Mann-Whitney U test, and analysis of variance (ANOVA)-test were used as appropriate.

Our primary outcome was mortality at 3 and 12 months after hip fracture diagnosis. Secondary outcomes included length of stay, location to which patients were discharged and identified postoperative medical complications (delirium, infections, myocardial ischaemia, heart failure and acute kidney injury).

Cox proportional hazard analyses were performed to compare 3-month and 1-year mortality between the NPOCP and usual care (UC), adjusting for sex, age, fracture type, and CCI. P-values <.05 were considered statistically significant. Statistics were performed using SPSS statistics v.25 (IBM, Armonk, New York, USA). Inspection of log(-log(survival)) curves showed parallel lines, satisfying the proportional hazards assumption.

Results

A total of 300 hip fracture patients, of which 121 (40.3%) were male, with a mean age of 77.8 (SD 14.4) years and median CCI of 1 (IQR 0-2), were analysed in 2018. 155 (51.5%) patients had a ASA classification III or higher. Hip fractures were classified as femoral neck fracture in 187 (62.3%), intertrochanteric fracture in 101 (33.7%) and subtrochanteric fracture in 12 (4.0%) of the patients, respectively.

144 patients received NPOCP and 156 received UC. Patients receiving UC had a higher median CCI (1 (0-2) vs. 0 (0-2), P=0.007) and were more likely to have sustained an intertrochanteric or subtrochanteric fracture compared to patients receiving NPOCP (48.1% vs. 25.4%, P<0.001). Patients receiving NPOCP were more likely to be followed on the outpatient clinic after discharge (15.3% vs. 8.3%, P=0.072) The demographic and clinical characteristics are summarized in Table 2.2.

Table 2.2 Demographic and clinical characteristics.

	Total cohort (n=300)	NPOCP-ward (n=144)	Usual Care (n=156)	P-value
Mean age – yr (SD)	77.8 (14.4)	76.8 (12.2)	78.7 (16.1)	0.240
Male – n (%)	121 (40.3)	51 (35.4)	70 (44.9)	0.101
Type of fracture, n (%)				
Femoral neck fracture	187 (62.3)	106 (73.6)	81 (51.9)	
Intertrochanteric fracture	101 (33.7)	35 (24.3)	66 (42.3)	*<0.001*
Subtrochanteric fracture	12 (4.0)	3 (2.1)	9 (5.8)	
ASA classification, n (%)				
ASA I	26 (8.7)	11 (7.6)	15 (9.6)	
ASA II	119 (39.7)	65 (45.2)	54 (34.6)	0.321
ASA III	127 (42.3)	56 (39.0)	71 (45.5)	
ASA IV	28 (9.3)	12 (8.3)	16 (10.3)	
Surgical intervention, n (%)		136 (94.4)	147 (94.2)	1.00
Weight bearing restrictions*, n (%)				
Full weight bearing	270 (95.4)	126 (92.6)	144 (97.9)	
Partial weight bearing	8 (2.8)	6 (4.4)	2 (1.4)	NT
Non weight bearing	5 (1.8)	4 (3.0)	1 (0.7)	
Consultation by NP or geriatrician, n %)	N/A	**	96 (60.9)	
Follow-up after discharge, n (%)	35 (11.7)	22 (15.3)	13 (8.3)	0.072
Medication review	N/A	**	44 (27.8)	NT
Charlson Comorbidity Index, n (%)				
0	129 (43.0)	73 (50.7)	56 (35.9)	
1	73 (24.3)	34 (23.6)	39 (25.0)	*0.043*
2	40 (13.3)	16 (11.1)	24 (15.4)	
≥3	58 (19.3)	21 (14.6)	37 (23.7)	
Charlson Comorbidity Index median (IQR)	1 (0-2)	0 (0-2)	1 (0-2)	*0.007*

Data were presented as mean (SD), median (IQR) or percentage and T-test, Chi-square test, Mann-Whitney U test, and analysis of variance (ANOVA)-test were used as appropriate.
* = denominator is 283 for total cohort, 136 for NPOCP and 147 for UC
** = incorporated in NPOCP
N/A = Not Available
NT = Not Tested

In the NPOCP, the 3-month and 1-year mortality rates were 9.0% [95%CI: 4.9-14.9%] and 13.9% [95%CI: 8.7-20.6%], compared to 24.4% [95%CI: 17.9-31.9%] and 34.0% [95%CI: 26.6-42.0%] in the UC group, respectively (P<0.001) (Figure 2.2). The adjusted hazard ratio (aHR) for 3-month (aHR 0.50 [95%CI: 0.26-0.97]) and 1-year mortality (aHR 0.50 [95%CI: 0.29-0.85]) remained substantially lower in the NPOCP compared to UC after adjustment for sex, age, fracture type and CCI.

Age (per year, aHR: 1.06, 95%CI: 1.03-1.09), male sex (aHR: 1.64, 95%CI: 1.02-2.65) and increased CCI (score of 1, aHR: 3.85, 95%CI: 1.69-8.76, score of 2, aHR: 6.69, 95%CI: 2.88-15.49, score of 3 or greater, aHR: 7.49, 95%CI: 3.36-16.59) also remained predictive of mortality.

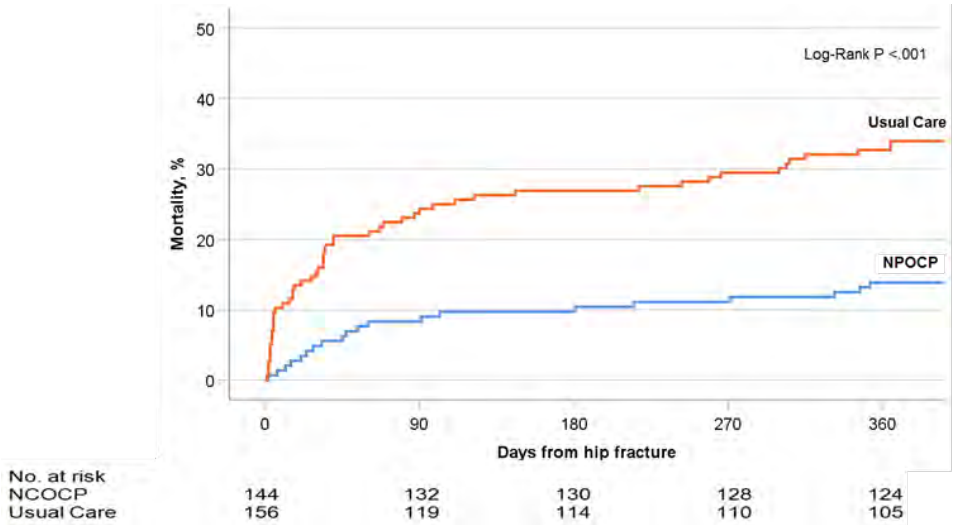


Figure 2.2 Mortality after implementation of a Nurse Practitioner-led Orthogeriatric Care Program (NPOCP).

Secondary outcomes

Median length of stay was 9 days [IQR 5-13] in patients receiving UC and 7 days [IQR 5-13] in patients receiving NPOCP, respectively (P=0.08). Thirty-eight (38/156; 27.5%) patients receiving UC and fifty-seven (57/144; 40.4%) patients receiving NPOCP were discharged to their own living environment (P=0.023) (Table 2.3).

Identified postoperative medical complications

Table 2.3 shows the percentages of patients with identified complications. The most common identified complications were delirium (32%), infection (19%) and acute kidney injury (20%). In patients receiving NPOCP, we overall observed a higher detection rate of complications, and for myocardial infarction this difference was significant (6.9% vs. 1.9%, P=0.045).

Table 2.3 Secondary outcomes, length of stay, discharge destination and identified complications.

	Total cohort (n=300)	NPOCP-ward (n=144)	Usual Care (n=156)	P-value
Length of stay, days, median (IQR)	8.0 (5.0-13.0)	7.0 (5.0-13.0)	9.0 (5.0-13.0)	0.08
Discharge destination, n (%)				
Own living environment	95 (34.0)	57 (40.4)	38 (27.5)	*0.023*
Geriatric Rehabilitation Centre	179 (64.2)	81 (57.5)	98 (71.0)	
Other Hospital	5 (1.8)	3 (2.1)	2 (1.5)	NT
Complications				
Delirium	96 (32.0)	51 (35.4)	45 (28.8)	0.265
Infections (UTI, pneumonia)	57 (19.0)	34 (23.6)	23 (14.7)	0.056
Myocardial ischaemia	13 (43.3)	10 (6.9)	3 (1.9)	*0.045*
Heart failure	24 (8.0)	16 (11.1)	8 (5.1)	0.087
Acute kidney injury	60 (20.0)	35 (24.3)	25 (16.0)	0.084
Other	9 (3.0)	5 (3.5)	4 (2.6)	NT

Chi-square test or Mann-Whitney U test were used as appropriate.

NT=Not Tested.

Discussion

This study demonstrates lower 3-month and 1-year mortality in hip fracture patients receiving NPOCP compared to UC. The program tended to shorten length of stay, with the median stay being 2 days shorter, and more patients were discharged home. An interesting additional finding was the observation that patients in NPOCP more complications were registered.

The beneficial impact of NPOCP on mortality is not surprising and consistent with other studies in which comprehensive orthogeriatric care is compared to UC[12,13] or compared to the geriatric consultation model[14]. However, to the best of our knowledge, our study is the first to show a large beneficial impact on both mortality and location of discharge as a marker of ability, in a model in which, from a geriatric point of view NPs are primarily in the lead. Key differences with existing orthogeriatric care models that may contribute to our findings are that delivery of geriatric care was started directly on admission and was predominantly delivered by a NP with a background in geriatric care, as opposed to physician-led or non-holistic nursing interventions that solely focus on one aspect of the orthogeriatric population (such as osteoporosis or delirium)[7,8]. Second, daily multidimensional assessment was performed by the same person, increasing awareness of life-threatening conditions with delirium as only symptom. Our observation that patients in NPOCP experienced more complications indirectly supports this statement. As such, we postulate that NPOCP promotes early recognition of life-threatening conditions/complications and may therefore be consistent with the observed reduction of mortality. Third, appropriate follow-up after hospital discharge, as key component of CGA was secured. Fourth, repeated medication-reviews to initiate

appropriate indicated (osteoporosis treatment) drugs and to avoid inappropriate and potentially harmful drugs, are effectuated[15].

This study has a number of strengths and limitations. Strengths include the use of HSMR-data so that the hospital acted as a natural control group in a before-and-after implementation of NPOCP and the study is reproducible to anyone with access to HSMR-data. Also, the a-prior analysis showed 2017 mortality rates were similar between both wards (Supplementary Figure 2.1). Therefore, this study could be considered as a pseudo-randomised trial. We acknowledge that mortality in the UC group was lower in the year prior to implementation of NPOCP. We were unable to find any clearly identifiable factors, such as changes in clinical practice or staffing reallocations after implementation of NPOCP, that might explain this difference. Therefore, we were not able to completely rule out an unidentified source of selection bias that might explain this discrepancy. However, mortality data are known for their year-to-year fluctuations and within group comparisons do not address the efficacy of any intervention, whereas between group assessments do prove treatment effects[16].

This study is also limited by its single-centre, retrospective and observational design. Although patient allocation to the surgical ward (and thus whether patients received NPOCP or UC) was random, patients receiving UC had more comorbidities and were more likely to have intertrochanteric or subtrochanteric fractures, which are in general associated with longer length of stay. Nevertheless, since in the UC group only three patients had partial or non-weight bearing restrictions, we believe this has not strongly influenced the results.

Despite the fact we have adjusted for baseline inequalities in our statistical analyses, residual confounding by unmeasured factors possibly related to frailty and even mortality, still may have occurred. However, given the large protective effect associated with NPOCP it is highly unlikely the positive effect of NPOCP is completely explained by residual confounding.

Furthermore, we were unable to assess cause-specific mortality limiting the conclusions drawn with regard to the influence of our NPOCP on specific death causes, such as for example, sepsis and myocardial infarction. Moreover, the current study was not suitable to address whether NPOCP influenced the incidence of complications as NPOCP, by its aim and design, led to a more proactive diagnosis (and thus identification) of complications than the usual care arm of our study. Finally, the implementation and success of NPOCP depends, as any significant system change, on the effort and attitudes of all stakeholders. Local preferences in practice may differ. In our experience, the surgical team displayed a great willingness to cooperate and foster a highly constructive collaboration with the NPs, but it is known that nurse-led programs are met with some

resistance or reservation in certain areas. Our results (or at least the magnitude) may therefore not be generalizable to other wards or other centres.

In conclusion, implementation of NPOCP significantly improved mortality in hip fracture patients, and may contribute positively to high quality, long-term care for the frail orthogeriatric population. Additional studies evaluating NP-led programs in other settings and its cost-effectiveness are urgently needed, as an approach to eventually achieve long-term and cost-effective care for the entire frail older surgical population.

References

1. Baker PN, Salar O, Ollivere BJ, Forward DP, Weerasuriya N, Moppett IK et al. Evolution of the hip fracture population: time to consider the future? A retrospective observational analysis. BMJ Open. 2014;4(4):e004405.
2. Aw D, Sahota O. Orthogeriatrics moving forward. Age Ageing. 2014;43(3):301-305.
3. Kammerlander C, Roth T, Friedman SM, Suhm N, Luger TJ, Kammerlander-Knauer U et al. Ortho-geriatric service-a literature review comparing different models. Osteoporos Int. 2010;21(Suppl 4):S637-S646.
4. Stadhouders N, Koolman X, Tanke M, Maarse H, Jeurissen P. Policy options to contain healthcare costs: a review and classification. Health Policy. 2016;120(5):486-494.
5. Lovink MH, Persoon A, Koopmans RTCM, Van Vught AJAH, Schoonhoven L, Laurant MGH. Effects of substituting nurse practitioners, physician assistants or nurses for physicians concerning healthcare for the ageing population: a systematic literature review. J Adv Nurs. 2017;73(9):2084-2102.
6. Goldberg SE, Cooper J, Blundell A, Gordon AL, Masud T, Moorchilot R. Development of a curriculum for advanced nurse practitioners working with older people with frailty in the acute hospital through a modified Delphi process. Age Ageing. 2016;45(1):48-53.
7. Hawley S, Javaid MK, Prieto-Alhambra D, Lippett J, Sheard S, Arden NK et al. Clinical effectiveness of orthogeriatric and fracture liaison service models of care for hip fracture patients: population-based longitudinal study. Age Ageing. 2016;45(2):236-242.
8. Milisen K, Foreman MD, Abraham IL, De Geest S, Godderis J, Vandermeulen E et al. A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients. J Am Geriatr Soc. 2001;49(5):523-532.
9. Jarman B, Pieter D, van der Veen AA, Kool RB, Aylin P, Bottle A et al. The hospital standardised mortality ratio: a powerful tool for Dutch hospitals to assess their quality of care? Qual Saf Health Care. 2010;19(1):9-13.
10. Scott IA, Brand CA, Phelps GE, Barker AL, Cameron PA. Using hospital standardised mortality ratios to assess quality of care--proceed with extreme caution. Med J Aust. 2011;194(12):645-648
11. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-383.
12. Neuburger J, Currie C, Wakeman R, Johansen A, Tsang C, Plant F et al. Increased orthogeriatrician involvement in hip fracture care and its impact on mortality in England. Age Ageing. 2017;46(2):187-192.
13. Friedman SM, Mendelson DA, Bingham KW, Kates SL. Impact of a comanaged Geriatric Fracture Center on short-term hip fracture outcomes. Arch Intern Med. 2009;169(18):1712-1717.
14. Middleton M, Wan B, da Assunçao R. Improving hip fracture outcomes with integrated orthogeriatric care: a comparison between two accepted orthogeriatric models. Age Ageing. 2017;46(3):465-470.
15. Berry SD, Kiel DP. Medication Review After a Fracture-Absolutely Essential. JAMA Intern Med. 2016;176(10):1539-1540.
16. Bland JM, Altman DG. Comparisons within randomised groups can be very misleading. BMJ. 2011;342:d561.

Supplementary figure 2.1

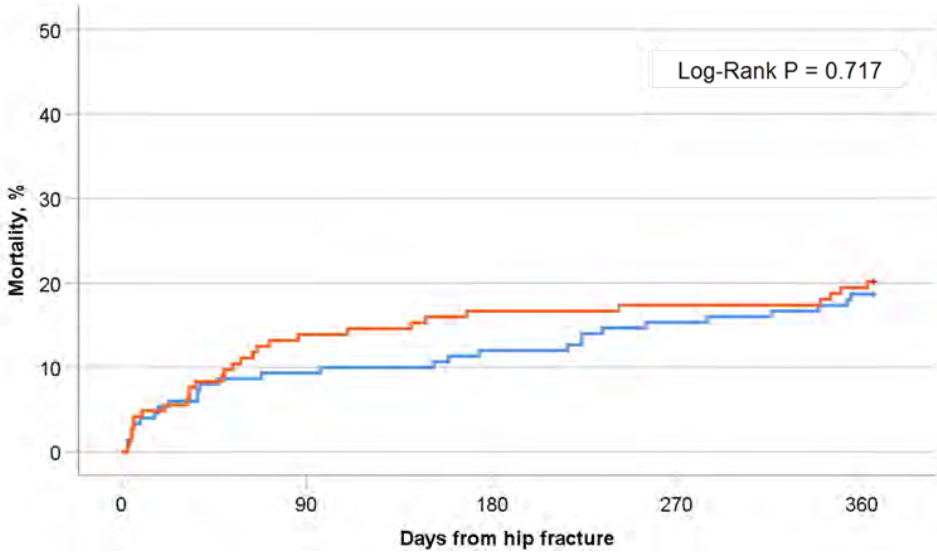
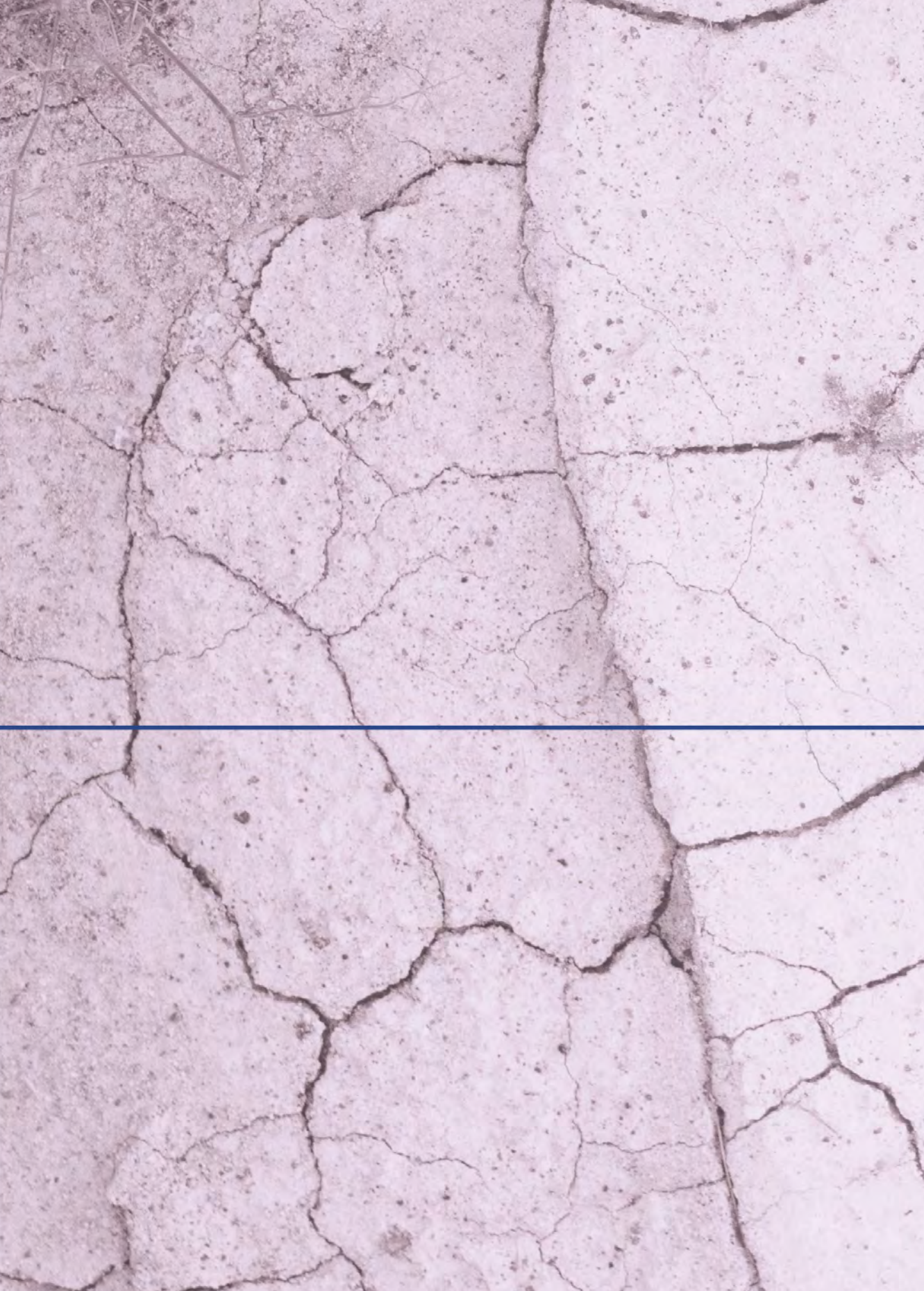


Figure S2.1 Mortality (2017) on the two surgical wards before implementation of a Nurse Practitioner-led Orthogeriatric Care Program (NPOCP).
Usual Care ward (orange)
Ward where in 2018 NPOCP was implemented (blue).




CHAPTERTHREE

Chapter 3

Medication-related hospital admissions and readmissions in older patients: an overview of literature

Aimée E.M.J.H. Linkens, Vanja Milosevic, P. Hugo M. van der Kuy,
Sylvia VH Damen-Hendriks, Carlota Mestres Gonzalvo, Kim PGM Hurkens

Int J Clin Pharm. 2020;42(5):1243-1251

Abstract

Background

The number of medication-related hospital admissions and readmissions are increasing over the years due to the aging population. Medication-related hospital admissions and readmissions lead to decreased quality of life and high healthcare costs.

Aim of the review

To assess what is currently known about medication-related hospital admissions, medication-related hospital readmissions, their risk factors, and possible interventions which reduce medication-related hospital readmissions.

Method

We searched PubMed for articles about the topic medication-related hospital admissions and readmissions. Overall 54 studies were selected for the overview of literature.

Results

Between the different selected studies there was much heterogeneity in definitions for medication-related admission and readmissions, in study population and the way studies were performed. Multiple risk factors are found in the studies for example: polypharmacy, comorbidities, therapy non adherence, cognitive impairment, depending living situation, high risk medications and higher age. Different interventions are studied to reduce the number of medication-related readmission, some of these interventions may reduce the readmissions like the participation of a pharmacist, education programmes and transition-of-care interventions and the use of digital assistance in the form of Clinical Decision Support Systems (CDSS). However the methods and the results of these interventions show heterogeneity in the different researches.

Conclusion

There is much heterogeneity in incidence and definitions for both medication-related hospital admissions and readmissions. admissions and readmissions. Some risk factors are known for medication-related admissions and readmissions such as polypharmacy, older age and additional diseases. Known interventions that could possibly lead to a decrease in medication-related hospital readmissions are spare being the involvement of a pharmacist, education programs and transition-care interventions the most mentioned ones although controversial results have been reported. More research is needed to gather more information on this topic.

Impact on practice statements

- Medication-related admissions and medication-related readmissions are common, however we still do not know enough about them to reduce them.
- Defining a common definition for medication-related admissions and medication-related readmission may ensure less heterogeneity in the future researches.

Introduction

Thousands of medical interventions are performed each day in healthcare to improve the health status of our patients. The prescription of medication is an important intervention within the medical care for older patients[1,2]. The rising incidence of multimorbidity and consequently polypharmacy adds to the complexity of managing older patient in particular[3]. Inadequate medication management and polypharmacy are important risk factors for adverse drug events and drug-drug interactions and frequently lead to hospital admissions and hospital readmissions and other undesirable consequences such as increased morbidity, decreased self-reliance and even death[4-7]. The number of acute and medication-related hospital admissions is increasing over the years due to the aging population[8]. In medication-related hospital admissions two categories can be distinguished, namely primary admissions and readmissions. Less research is performed in the latter category. Both admissions and readmissions account for decreased quality of life and high healthcare costs[9,10].

Aim of the review

With this literature overview we aim at giving an overview on what is currently known about medication-related hospital admissions, medication-related hospital readmissions, their risk factors, and possible interventions which reduce medication-related hospital readmissions.

Methods

Search strategy

We performed an overview of literature. We did not perform a systematic review. Data source used was PubMed. We searched for articles with a set of MeSH terms and text words selected to cover articles on medication-related admissions and medication-related readmissions. The search was limited for articles published in English language. The search was performed in February 2017, with no limitations with regard to the publication date. We included articles that investigated the incidence of medication-related admissions and medication-related readmissions and their risk factors. We also included articles that investigated possible interventions which may reduce the rate of medication-related readmissions. We selected studies that were performed in hospitals. We did not differentiate between hospital types for the performed studies. All study designs were allowed. The outcomes of the selected articles were dependant of the study. It was important that the outcome was related to the incidence of the

medication-related admissions and readmissions or their risk factors. Studies which investigated possible intervention to reduce the readmissions were also included.

We first selected articles based on the title. After the first selection two authors (AL and KH) independently assessed the articles for usability based on the abstract of the articles. Excluded were articles investigating an intervention or a treatment for a disease in which they had as a primary or secondary outcome the readmission rate. The quality of the different studies was not an exclusion criteria. When there was disagreement on in/exclusion of an article, a third reviewer was consulted and consensus was reached.

Results

In total 476 records were retrieved with the PubMed search and we selected 12 records through references. Figure 3.1 shows the selection of the studies used for this literature overview. Overall 54 studies were assessed as relevant for the overview of this topic. In most of the excluded articles, the objective did not match our topic.

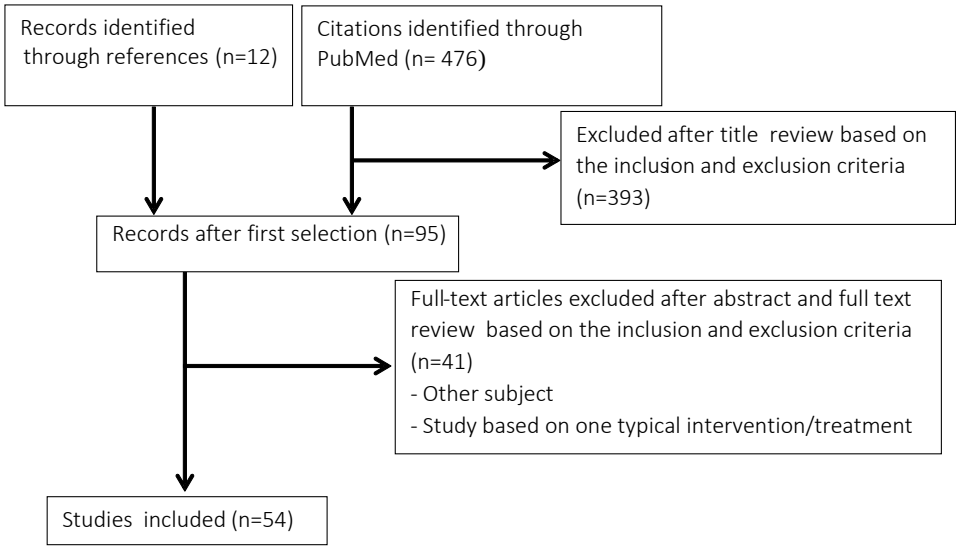


Figure 3.1 Flow diagram of the selection of studies for this literature overview.

Medication-related hospital admissions

Medication-related problems are a daily occurrence at the emergency department. However, incidence rates on hospital admissions due to medication-related problems differ because of the lack of a clear definition and the lack of identification which may underestimate the problem[11].

The most commonly used definition is an admission due to an adverse drug reaction (ADR). ADR is defined as: "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function"[12]. Another accepted definition of a medication-related hospital admission is an admission due to an adverse drug event (ADE): "any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment"[13]. Finally, medication-related hospital admissions are also defined as admissions due to drug related problems (DRP)[14,15]. A DRP is defined as an event or circumstance that involves a patient's drug treatment that actually, or potentially, interferes with the achievement of an optimal outcome[14-16].

Studies on the incidence of the association between hospital admissions and the presence of an ADR or ADE show great variety (0.5-18.9% and 5.6-19.3% respectively)[7,10,17-22]. A possible reason for the wide range of incidences is, as mentioned above, the variability in the used definition for medication-related hospital admissions. Since ADE and DRP comprises a broader set of possible problems compared to ADR, incidence numbers could be higher. Also, patient inclusion criteria differ between studies. Some studies include all adults while other studies only include patients above 60 years old[10,17,19-22]. This influences the interpretation and comparability of results. Furthermore, the type of patients differs between studies; where some studies include all unplanned admissions, other studies only include patients admitted for a specific ward[10,17,19,21,22]. Apart from the different inclusion and exclusion criteria, the study methods are also different. Different kind of designs and the selection procedure are used which may lead to a lack of identification of a medication-related admission[17,19,21,23].

In conclusion, there was much heterogeneity between studies in study population and the way studies were performed[22]. Although there was great variety in incidence, overall studies showed that medication-related hospital admissions are a significant and possible preventable cause of unfavourable outcome and high healthcare costs.

Medication-related hospital readmissions

A hospital readmission is a second admission to the hospital within a certain period of time. In literature, different time periods are being used between the hospital discharge and readmission, ranging from 30 days to three years. However, a period of 30 days is most common[24-29]. Worldwide, readmissions are an important indicator for quality of healthcare and is therefore also part of the basic set of quality indicators of the Dutch Healthcare inspectorate (IGJ)[30].

As with medication-related hospital admissions, different definitions of medication-related readmissions are being used with regard to ADRs, ADEs and DRPs. A common definition assumes that medication-related hospital readmissions are readmission due to problems around pharmacotherapy[31]. Different DRPs can occur in patients using medication, especially patients with polypharmacy. Examples for DRPs are problems with medication adherence, ADRs, inappropriate drug selection, drug use without indication, drug-drug interactions, additional therapy needed, lack of therapy monitoring, sub-therapeutic dosage and supra-therapeutic dosage. All problems in these categories can lead to a medication-related hospital readmission[31]. Another definition assumes medication-related readmissions based on ADRs and ADEs[24,32]. Because of the differences in definition, incidences of medication-related readmissions vary greatly and range from 0.09% to 64.0%[27-29]. According to the definition you would expect that the rate for medication-related readmissions based on ADRs is lower compared to ADE. The prevalence for the ADRs related hospital admission varies from 0.5%-18.9%[17-22] and for de ADEs related hospital admission varies from 5.6% till 19.3%[7,23].

Besides the variety in definitions used in the studies for medication-related hospital readmissions, the time between discharge and readmission also differs between studies, ranging from 30 days to three years[24-29]. This makes interpretation of the results difficult. To conclude, studies with regard to hospital readmissions are also difficult to interpret due to differences in study design and definitions used.

Risk factors for medication-related admission and medication-related readmissions

Several risk factors have been identified in medication-related hospital admissions due to ADE's. According to Leendertse et al, patients with impaired cognition, four or more comorbidities, dependent living situation, polypharmacy, impaired renal function and/or nonadherence to the medication regimen were found to be at greater risk of a hospital admission[7,10]. These risk factors are consistent with other studies performed on this topic[23,33]. The most common drugs associated with (potentially preventable) admissions were anticoagulants, antiplatelet drugs, vasodilators, psychotropic medications and diuretics[7,23,33]. Little is known about the risk factors of a medication-related readmission for older patients but it is likely that there is great overlap with the risk factors for

medication-related admissions. Possible additional risk factors are a higher Charles comorbidity score and inadequate follow-up due to a missed appointment with the successive physician[24,27,28]. Increased age is also found as a risk factor of ADRs or ADPs related readmissions[25,26].

Some specific medications are also associated with a higher incidence of medication-related hospital readmissions. The most frequent medications which are associated with medication-related hospital readmission are antiplatelet medications, diuretics, anti-coagulants and anti-hypertensive drugs[25,29]. Zhang et. al. found a greater risk for repeated ADRs for the drug categories hormones, primarily systemic agents (including antineoplastic, immunosuppresses and neoplastic antibiotics) and bacterial vaccines, resulting in a hospital readmission or an ADR during hospitalisation[24]. Alassaad et al, found in patients above 80 years old that drugs prescribed for peptic ulcer or gastroesophageal reflux disease and opioids are associated with an increased risk for readmission, the reason for the readmission was not mentioned[34]. Beside a higher risk for medication-related readmission due to specific medications, some studies also investigate the association between the complexity of the medication list and medication-related hospital readmission[35,36]. The Medication Regimen Complexity Index (MRCI) is a frequently used score to predict the complexity of the medication regimen. It is based on 65 items and considers dosing frequency, dosage forms and other characteristics which may influence the complexity[37,38]. A higher MRCI score reflects a more complex medication regime. Although a clear association was not established, most studies show a higher readmission rate when patients have higher MRCI[36,38-40].

Olson et al investigated if specific older patient populations are at risk for medication-related hospital readmission[41]. They found that older men with adult children as caregiver seemed to have an increased risk for hospital readmissions[41]. Possible explanations are e.g. difficulties with regard to medication adherence due to parents who want to maintain their autonomy, or in case of siblings sharing the care for parents there could be confusion about the responsibilities. Another explanation is that medication problems could be related to informal caregiving itself. More research is needed to investigate the reason why males with adult children as caregivers show an increased risk for hospital readmissions.

Other risk factors which are associated with a higher readmission rate are low adherence, experiencing a fall in the last 12 months, weight loss and medical error due to discontinuity of care from inpatient to outpatient setting[42-45]. Table 3.1 shows the different published risk factors.

Table 3.1 Risk factors for medication-related admissions and medication-related readmissions.

Risk factor	Studied in the following population	Found in the studies
High risk medication	Adult patients hospitalization at general medicine	Allaudeen et al.[44]
	50 years old and older and had one of a selection comorbidity	Schoonover et al.[39]
	Adult patients	Willson et al.[38]
	Adult patients with heart failure	Colavecchia et al.[36]
Polypharmacy	Patients 70 years old or older	Wimmer et al.[40]
	Patients hospitalized in an geriatric unit	Cabre et al.[33]
	Adult patients	McLachlan et al.[23]
Low or intermediate therapy adherence (combined) / non adherence	Patients above 65 years old or ten or more medications, heart failure, pharmacist consultation of duplications in medication list	Rosen et al.[42]
	Adult patients	Leendertse et al.[7]
Inappropriate medication	Patients hospitalized in an geriatric unit	Cabre et al.[33]
No pharmacy consult	Adult patients	Thomas et al.[27]
Work up error / missing follow up appointments	Adult patients	Moore et al.[45]
	Adult patients	Thomas et al.[27]
Older age	Adult patients	Hallgren et al.[43]
	Adult patients	Leendertse et al.[7]
	Adult patients	Thomas et al.[27]
	Adult patients	Davies et al.[25]
Male sex	Adult patients	Hallgren et al.[43]
	60 years and older	Zhang et al.[7]
Female	Patients hospitalized in an geriatric unit	Cabre et al.[33]
Black race	Adult patients hospitalization at general medicine	Allaudeen et al.[44]
Comorbidities (including high comorbidity score)	Adult patients	Hallgren et al.[43]
	Adult patients	Leendertse et al.[7]
	60 years and older	Zhang et al.[24]
Renal disease / - insufficiency	Adult patients hospitalization at general medicine	Allaudeen et al.[44]
	Patients hospitalized in an geriatric unit	Cabre et al.[33]
	Adult patients	Leendertse et al.[7]
Congestive heart failure	Adult patients hospitalization at general medicine	Allaudeen et al.[44]
Cancer	Adult patients hospitalization at general medicine	Allaudeen et al.[44]
	Patients 65 years old or older	Hauviller et al.[28]
	80 years old and older	Alassaad et al.[34]
Iron deficiency anemia	Adult patients hospitalization at general medicine	Allaudeen et al.[44]
Presence of pulmonary disease	80 years old and older	Alassaad et al.[34]
Cognitive impairment or dementia	Patients 70 years old or older	Wimmer et al.[40]
	Adult patients	Leendertse et al.[7]
Weight loss	Adult patients hospitalization at general medicine	Allaudeen et al.[44]
Falling in the last 12 months	Adult patients	Hallgren et al.[43]
Length of stay in the hospital	Adult patients	Leendertse et al.[7]
	60 years and older	Zhang et al.[24]
Discharged to nonhome setting /	Patients 70 years old or older	Wimmer et al.[40]
Depending living situation	Adult patients	Leendertse et al.[7]
Elderly men with adult children as caregivers	Adult patients	Olson et al.[41]
Responsibility	Adult patients	Hallgren et al.[43]
Feelings of loneliness	Adult patients	Hallgren et al.[43]
Self- rated health	Adult patients	Hallgren et al.[43]
Life- Satisfaction	Adult patients	Hallgren et al.[43]

Interventions which may reduce the medication-related readmissions

Different interventions to reduce the risk of medication-related admissions or readmissions are mentioned in literature. One of them is the involvement of a pharmacist as part of the medical team[46]. The effect of such an intervention is hard to evaluate due to the different ways the participation of the pharmacists is executed. Furthermore there was great difference in the way a patient is involved in his/her medication management[46-52]. Overall, studies show a possible benefit with regard to participation of a pharmacist, especially in patients with a high risk of medication-related admissions, but studies show great heterogeneity[51,53,54].

Different studies investigated whether education could improve the medication adherence, because low and intermediate medication adherence is associated with more readmissions compared to high medication adherence[42]. Some publications show that some interventions increase the medication adherence however there is a great heterogeneity and not all methods are effective[55]. Besides education to increase the medication adherences different studies investigated whether packaging of the medication would increase the medication adherence. A meta-analysis found that packaging intervention increases medication adherence[56]. As earlier mentioned, high adherence is associated with less readmissions, this means that packaging intervention might indirectly lead to less medication readmission. Different education programmes and transition-of-care interventions are used in several studies; most of them show lower readmission. However, these interventions are time consuming and the studies show great heterogeneity[55,57,58].

Digital assistance in the form of Clinical Decision Support Systems (CDSS), is also being investigated as intervention to improve outcome in medication-related problems[59,60]. CDSS supports the healthcare professional, pharmacist and/or physician, in optimizing medication. This system is based on a database that generate drug safety alerts for the use of medication based on different guidelines/criteria, laboratory values and patient characteristics[59,60]. Studies show that a CDSS can support the professional in performing a medication review[59,61]. The system is especially of additional value in recognizing absent medication when there is a clear indication and when there are contra indications or interactions for medication[59]. Another benefit of a CDSS is that the medication is monitored continuously whereas a manual medication review is performed only once or twice a year due to time pressure[59,60]. For example, the renal function changes over time, requiring adjustment of medication which will be immediately detected by the CDSS in contrary to manual medication review. Previous studies have shown that the use of CDDS has an additional value for the manual medication review[59, 61].

Discussion

The aim of this literature overview was to give an overview on what currently is known about medication-related hospital admissions, medication-related hospital readmissions, their risk factors, and possible interventions which reduce medication-related hospital readmissions. The incidence of medication-related hospital admissions shows a great variety and ranges between 0.5 and 19.3 % and is dependant of the definition used in the different studies[7,10,17-20,22]. The incidence of medication-related hospital readmissions has even a broader range, namely 0.09% up to 64.0%[27-29]. The most important identified risk factors for medication-related admissions or medication-related readmission are high risk medication, polypharmacy, therapy nonadherence, older age, comorbidities, renal disease, congestive heart failure, cognitive impairment and length of stay in the hospital[7,23-25,27,33,36,38-40,42-44]. The most common medications associated with (potentially preventable) admissions are anticoagulants, antiplatelet drugs, vasodilators, psychotropic medications and diuretics[7,23,33].

However all of the results show much heterogeneity between studies. The study designs and definitions used for medication-related admissions and medication-related readmissions are different between the studies. In the included studies, different interventions are investigated such as the involvement of pharmacists in medication reviews during the admissions of patients, different education programs and transition-care interventions. Some studies show less medication-related readmissions, however the results are controversial. Probably due to the different methods, study populations and interventions which are investigated. For example the involvement of pharmacist in medication reviews during an admission is different in the selected articles, however overall there is a possible benefit with regard to participation of a pharmacist, especially in patients with a high risk of medication-related admissions. Beside the involvement of a pharmacist in the medication reviews during the admission, other studies investigated the value of the use of CDDS. As mentioned earlier previous studies have shown that the use of CDDS has an additional value for the manual medication review[59,61]. But the effect on the readmission rate is not known yet.

The limitation of this study is that the review was not systematic and the search was limited to the PubMED database. The aim of the study and the search were both broad, however we only performed one search. Afterwards it was possibly better to specify the aim and to convert the search for the more specific aim. With this search used for this review we found a lot of articles not related on this subject. Possibly we also missed articles on this subject because we only performed one search. The strength of this review is that this review gives an overview about a topic which is important in the daily care. Although there is a great variety in results, overall the studies show the importance to get more knowledge about this topic to prevent potential preventable unfavourable outcomes and high healthcare costs.

In the future we want to investigate the additional value of the CDSS in medication-related hospital readmissions in people older than 60 years. Because there is a lack of a definition in the literature for a medication-related admission and readmission, we have chosen to select unplanned admissions which are possible medication-related. The Dutch guideline "Polypharmacy in the older patient" includes a trigger list that can be used to establish whether an admission is possibly medication-related[62]. The trigger list is mainly based on three studies namely the HARM-, IPCI- and Quadret, and presents the most frequent medication-related problems which can lead to an admission[7,11,63,64].

Patients aged 60 years and older with an unplanned hospital admission will be included in the study if the unplanned hospital admission is assessed to be medication-related according to the trigger list. Participants will be randomized in intervention or control group. In the control group care as usual will be continued. In the intervention group a medication check will be performed weekly using the CDSS. The generated alerts/recommendations will be sent to the general practitioner and/or home pharmacist. Follow-up will be one year. With the assistance of the CDSS we aim at reducing the medication related readmissions from 20% to 15%.

Conclusion

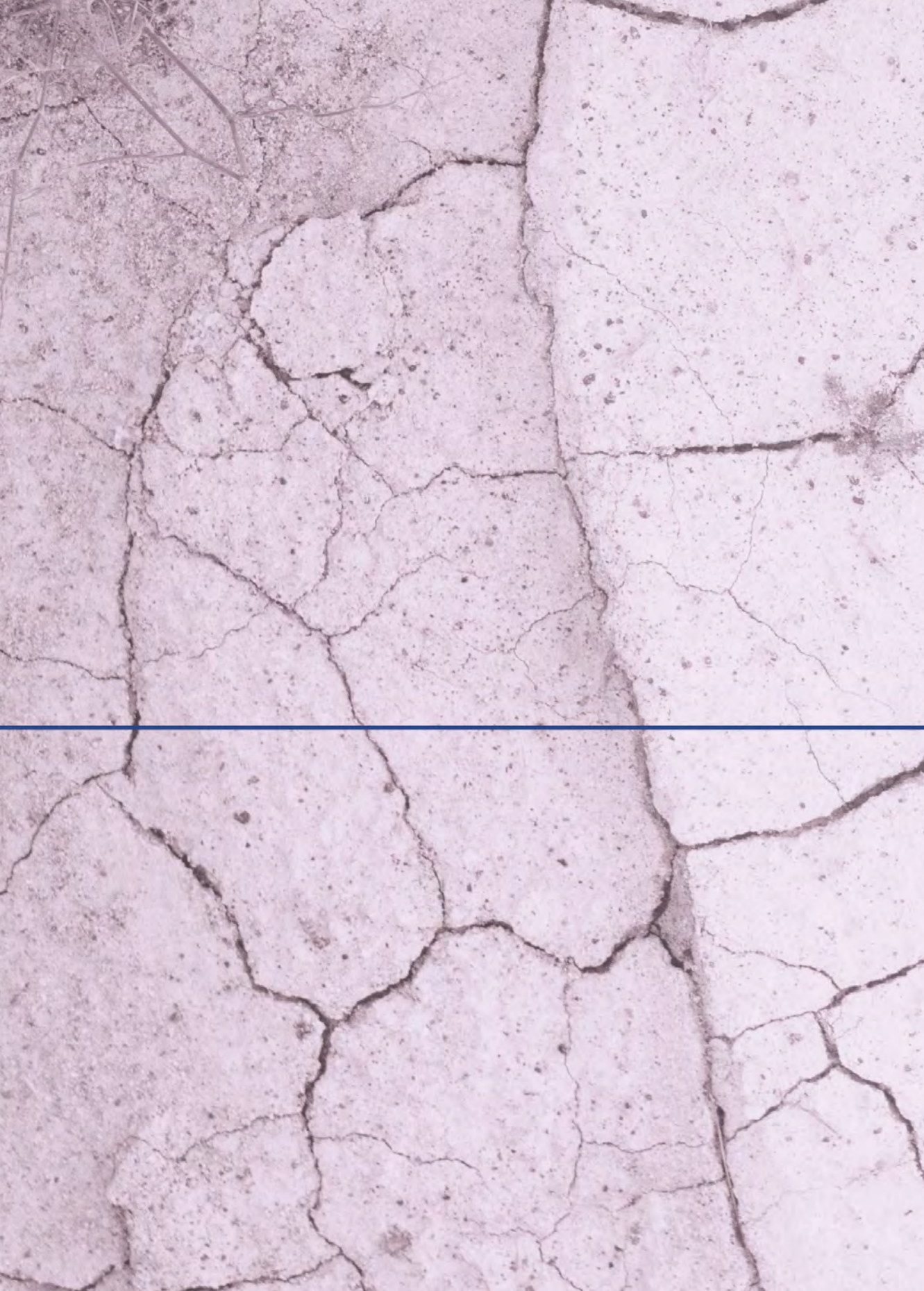
The definition for both medication-related hospital admissions and readmissions varies in different studies leading to a great incidence range. Several risk factors related to medication-related hospital admissions and/or readmissions have been identified: high risk medication, polypharmacy, therapy nonadherence, older age, comorbidities, renal disease, congestive heart failure, cognitive impairment and length of stay in the hospital. Known interventions that could possibly lead to a decrease in medication-related hospital readmissions are spare being the involvement of a pharmacist, education programs and transition-care interventions the most mentioned ones although controversial results have been reported. More research is needed to gather more information on this topic.

References

1. Hellstrom LM, Hoglund P, Bondesson A, Petersson G, Eriksson T. Clinical implementation of systematic medication reconciliation and review as part of the Lund Integrated Medicines Management model--impact on all-cause emergency department revisits. J Clin Pharm Ther. 2012;37(6):686-692.
2. Hellstrom LM, Bondesson A, Hoglund P, Midlov P, Holmdahl L, Rickhag E et al. Impact of the Lund Integrated Medicines Management (LIMM) model on medication appropriateness and drug-related hospital revisits. Eur J Clin Pharmacol. 2011;67(7):741-752.
3. Blanda MP. Pharmacologic issues in geriatric emergency medicine. Emerg Med Clin North Am. 2006;24(2):449-465, viii.
4. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014;13(1):57-65.
5. Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. Lancet. 2007;370(9582):185-191.
6. Bourgeois FT, Shannon MW, Valim C, Mandl KD. Adverse drug events in the outpatient setting: an 11-year national analysis. Pharmacoepidemiol Drug Saf. 2010;19(9):901-910.
7. 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):1890-1896.
8. Sturkenboom MCJM, Vanrolleghem AN, van den Bemt PMLA, de Smet PAGM, Hek K, Said FL-O et al. Eindrapport: Vervolgonderzoek Medicatieveiligheid. Ministerie van VWS, Utrecht. 2017.
9. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. N Engl J Med. 2009;360(14):1418-1428.
10. Leendertse AJ, Van Den Bemt PM, Poolman JB, Stoker LJ, Egberts AC, Postma MJ. Preventable hospital admissions related to medication (HARM): cost analysis of the HARM study. Value Health. 2011;14(1): 34-40.
11. van der Hooft CS, Dieleman JP, Siemes C, Aarnoudse AJ, Verhamme KM, Stricker BH et al. Adverse drug reaction-related hospitalisations: a population-based cohort study. Pharmacoepidemiol Drug Saf. 2008;17(4):365-371.
12. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356(9237):1255-1259.
13. 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.
14. Nivya K, Sri Sai Kiran V, Ragoo N, Jayaprakash B, Sonal Sekhar M. Systemic review on drug related hospital admissions - A pubmed based search. Saudi Pharm J. 2015;23(1):1-8.
15. Singh H, Kumar BN, Sinha T, Dulhani N. The incidence and nature of drug-related hospital admission: A 6-month observational study in a tertiary health care hospital. J Pharmacol Pharmacother. 2011;2(1): 17-20.
16. Roxburgh A, Degenhardt L. Characteristics of drug-related hospital separations in Australia. Drug Alcohol Depend. 2008;92(1-3):149-155.
17. Bordet R, Gautier S, Le Louet H, Dupuis B, Caron J. Analysis of the direct cost of adverse drug reactions in hospitalised patients. Eur J Clin Pharmacol. 2001;56(12):935-941.
18. Bouvy JC, De Bruin ML, Koopmanschap MA. Epidemiology of adverse drug reactions in Europe: a review of recent observational studies. Drug Saf. 2015;38(5):437-453.
19. Alexopoulou A, Dourakis SP, Mantzoukis D, Pitsariotis T, Kandyli A, Deutsch M et al. Adverse drug reactions as a cause of hospital admissions: a 6-month experience in a single center in Greece. Eur J Intern Med. 2008;19(7):505-510.
20. Oscanoa TJ, Lizaraso F, Carvajal A. Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. Eur J Clin Pharmacol. 2017;73(6):759-770.
21. Parameswaran Nair N, Chalmers L, Bereznicki BJ, Curtain C, Peterson GM, Connolly M et al. Adverse Drug Reaction-Related Hospitalizations in Elderly Australians: A Prospective Cross-Sectional Study in Two Tasmanian Hospitals. Drug Saf. 2017;40(7):597-606.
22. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. Bmj. 2004;329(7456):15-19.

23. McLachlan CY, Yi M, Ling A, Jardine DL. Adverse drug events are a major cause of acute medical admission. Intern Med J. 2014;44(7):633-638.
24. Zhang M, Holman CD, 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.
25. 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):749-755.
26. 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 AGEd multicenter randomized controlled trial. J Am Geriatr Soc. 2013;61(1):113-121.
27. 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.
28. 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):631-639.
29. 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):948-949.
30. Inspectie Gezondheidszorg en Jeugd; Ministerie van Volksgezondheid Welzijn en sport. Kwaliteitsindicatoren 2016 Basisset ziekenhuizen. Utrecht; 2015.
31. 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):602-608.
32. Dalleur O, Beeler PE, Schnipper JL, Donze J. 30-Day Potentially Avoidable Readmissions Due to Adverse Drug Events. J Patient Saf. 2021;17(5):e379-e386.
33. Cabre M, Elias L, Garcia M, Palomera E, Serra-Prat M. Avoidable hospitalizations due to adverse drug reactions in an acute geriatric unit. Analysis of 3,292 patients. Med Clin (Barc). 2018;150(6):209-214.
34. Alassaad A, Melhus H, Hammarlund-Udenaes M, Bertilsson M, Gillespie U, Sundstrom J. A tool for prediction of risk of rehospitalisation and mortality in the hospitalised elderly: secondary analysis of clinical trial data. BMJ Open. 2015;5(2):e007259.
35. Tesfaye WH, Peterson GM, Castelino RL, McKercher C, Jose MD, Wimmer BC et al. Medication Regimen Complexity and Hospital Readmission in Older Adults With Chronic Kidney Disease. Ann Pharmacother. 2019;53(1):28-34.
36. Colavecchia AC, Putney DR, Johnson ML, Aparasu RR. Discharge medication complexity and 30-day heart failure readmissions. Res Social Adm Pharm. 2017;13(4):857-863.
37. George J, Phun YT, Bailey MJ, Kong DC, Stewart K. Development and validation of the medication regimen complexity index. Ann Pharmacother. 2004;38(9):1369-1376.
38. Willson MN, Greer CL, Weeks DL. Medication regimen complexity and hospital readmission for an adverse drug event. Ann Pharmacother. 2014;48(1):26-32.
39. Schoonover H, Corbett CF, Weeks DL, Willson MN, Setter SM. Predicting potential postdischarge adverse drug events and 30-day unplanned hospital readmissions from medication regimen complexity. J Patient Saf. 2014;10(4):186-191.
40. Wimmer BC, Dent E, Bell JS, Wiese MD, Chapman I, Johnell K et al. Medication Regimen Complexity and Unplanned Hospital Readmissions in Older People. Ann Pharmacother. 2014;48(9):1120-1128.
41. Olson CH, Dey S, Kumar V, Monsen KA, Westra BL. Clustering of elderly patient subgroups to identify medication-related readmission risks. Int J Med Inform. 2016;85(1):43-52.
42. Rosen OZ, Fridman R, Rosen BT, Shane R, Pevnick JM. Medication adherence as a predictor of 30-day hospital readmissions. Patient Prefer Adherence. 2017;11:801-810.
43. Hallgren J, Aslan AKD. Risk factors for hospital readmission among Swedish older adults. Eur Geriatr Med. 2018;9(5):603-611.
44. Allaudeen N, Vidyarthi A, Maselli J, Auerbach A. Redefining readmission risk factors for general medicine patients. J Hosp Med. 2011;6(2):54-60.
45. Moore C, Wisnivesky J, Williams S, McGinn T. Medical errors related to discontinuity of care from an inpatient to an outpatient setting. J Gen Intern Med. 2003;18(8):646-651.

46. 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.
47. Farris KB, Carter BL, Xu Y, Dawson JD, Shelsky C, Weetman DB et al. Effect of a care transition intervention by pharmacists: an RCT. BMC Health Serv Res. 2014;14:406.
48. Hawes EM, Maxwell WD, White SF, Mangun J, Lin FC. Impact of an outpatient pharmacist intervention on medication discrepancies and health care resource utilization in posthospitalization care transitions. J Prim Care Community Health. 2014;5(1):14-18.
49. Mekonnen AB, McLachlan AJ, Brien JA. Effectiveness of pharmacist-led medication reconciliation programmes on clinical outcomes at hospital transitions: a systematic review and meta-analysis. BMJ Open. 2016;6(2):e010003.
50. 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.
51. Haag JD, Davis AZ, Hoel RW, Armon JJ, Odell LJ, Dierkhising RA et al. Impact of Pharmacist-Provided Medication Therapy Management on Healthcare Quality and Utilization in Recently Discharged Elderly Patients. Am Health Drug Benefits. 2016;9(5):259-268.
52. Luder HR, Frede SM, Kirby JA, Epplen K, Cavanaugh T, Martin-Boone JE et al. TransitionRx: Impact of community pharmacy postdischarge medication therapy management on hospital readmission rate. J Am Pharm Assoc. 2015;55(3):246-254.
53. Cheen MHH, Goon CP, Ong WC, Lim PS, Wan CN, Leong MY et al. Evaluation of a care transition program with pharmacist-provided home-based medication review for elderly Singaporeans at high risk of readmissions. Int J Qual Health Care. 2017;29(2):200-205.
54. Kalista T, Lemay V, Cohen L. Postdischarge community pharmacist-provided home services for patients after hospitalization for heart failure. J Am Pharm Assoc. 2015;55(4):438-442.
55. Conn VS, Hafdahl AR, Cooper PS, Ruppar TM, Mehr DR, Russell CL. Interventions to improve medication adherence among older adults: meta-analysis of adherence outcomes among randomized controlled trials. Gerontologist. 2009;49(4):447-462.
56. Conn VS, Ruppar TM, Chan KC, Dunbar-Jacob J, Pepper GA, De Geest S. Packaging interventions to increase medication adherence: systematic review and meta-analysis. Curr Med Res Opin. 2015;31(1):145-160.
57. Kamermayer AK, Leasure AR, Anderson L. The Effectiveness of Transitions-of-Care Interventions in Reducing Hospital Readmissions and Mortality: A Systematic Review. Dimens Crit Care Nurs. 2017;36(6):311-316.
58. Dizon ML, Reinking C. Reducing Readmissions: Nurse-Driven Interventions in the Transition of Care From the Hospital. Worldviews Evid Based Nurs. 2017;14(6):432-439.
59. de Wit HA, Hurkens KP, Mestres Gonzalvo C, Smid M, Sipers W, Winkens B et al. The support of medication reviews in hospitalised patients using a clinical decision support system. Springerplus. 2016;5(1):871.
60. de Wit HA, Mestres Gonzalvo C, Hurkens KP, Mulder WJ, Janknegt R, Verhey FR et al. Development of a computer system to support medication reviews in nursing homes. Int J Clin Pharm. 2013;35(5):668-672.
61. Mestres Gonzalvo C, Hurkens KP, de Wit HA, van Oijen BP, Janknegt R, Schols JM et al. To what extent is clinical and laboratory information used to perform medication reviews in the nursing home setting? the CLEAR study. Ther Clin Risk Manag. 2015;11:767-777.
62. Multidisciplinaire richtlijn Polyfarmacie bij ouderen, 2012. Utrecht: Nederlands Huisartsen Genootschap; 2012.
63. Warle-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.
64. Leendertse AJ, Visser D, Egberts AC, van den Bemt PM. The relationship between study characteristics and the prevalence of medication-related hospitalizations: a literature review and novel analysis. Drug Saf. 2010;33(3):233-244.




CHAPTERFOUR

Chapter 4

Control in the Hospital by Extensive Clinical rules for Unplanned hospitalizations in older Patients (CHECkUP); study design of a multicentre randomized study

Aimée E.M.J.H. Linkens, Vanja Milosevic, Noémi van Nie, Anne Zwietering, Peter W. de Leeuw, Marjan van den Akker, Jos M.G.A. Schols, Silvia M.A.A. Evers, Carlota Mestres-Gonzalvo, Bjorn Winkens, Bob P.A. van de Loo, Louis de Wolf, Lucretia Peeters, Monique de Ree, Bart Spaetgens, Kim P.G.M. Hurkens, P. Hugo M. van der Kuy

BMC Geriatr. 2022;22(1):36.

Abstract

Background

Due to ageing of the population the incidence of multimorbidity and polypharmacy is rising. Polypharmacy is a risk factor for medication-related (re)admission and therefore places a significant burden on the healthcare system. The reported incidence of medication-related (re)admissions varies widely due to the lack of a clear definition. Some medications are known to increase the risk for medication-related admission and are therefore published in the triggerlist of the Dutch guideline for Polypharmacy in older patients. Different interventions to support medication optimization have been studied to reduce medication-related (re)admissions. However, the optimal template of medication optimization is still unknown, which contributes to the large heterogeneity of their effect on hospital readmissions. Therefore, we implemented a clinical decision support system (CDSS) to optimize medication lists and investigate whether continuous use of a CDSS reduces the number of hospital readmissions in older patients, who previously have had an unplanned probably medication-related hospitalization.

Methods

The CHECkUP study is a multicentre randomized study in older (≥60 years) patients with an unplanned hospitalization, polypharmacy (≥5 medications) and using at least two medications from the triggerlist, from Zuyderland Medical Centre and Maastricht University Medical Centre+ in the Netherlands. Patients will be randomized. The intervention consists of continuous (weekly) use of a CDSS, which generates a Medication Optimization Profile, which will be sent to the patient's general practitioner and pharmacist. The control group will receive standard care. The primary outcome is hospital readmission within one year after study inclusion. Secondary outcomes are one-year mortality, number of emergency department visits, nursing home admissions, time to hospital readmissions and we will evaluate the quality of life and socio-economic status.

Discussion

This study is expected to add evidence on the knowledge of medication optimization and whether use of a continuous CDSS ameliorates the risk of adverse outcomes in older patients, already at an increased risk of medication-related (re)admission. To our knowledge, this is the first large study, providing one-year follow-up data and reporting not only on quality of care indicators, but also on quality-of-life.

Introduction

The population is ageing, leading to an increased incidence of multimorbidity and related polypharmacy[1]. Polypharmacy is a well-known risk factor for hospital (re)admissions, which can have detrimental effects on older patients and therefore are considered an important measure of quality of care[2]. As such, it is not surprising that a significant number of these hospital readmissions is directly medication-related and that medication-related hospital (re)admissions occur more frequently in older individuals[3,4].

The incidence of both medication-related hospital admissions and readmissions varies widely, ranging from 0.5 to 19.3% and 0.09% to 64.0%, respectively[5]. Several explanations might be given for this wide range. First, there is lack of a clear definition of "medication-related hospital admission" and "medication-related hospital readmission". Most definitions are based on the assumption that (re)admissions are directly related to problems around pharmacotherapy and are defined as (I) drug-related problems, such as drug-drug interactions, inappropriate drug use, sub- and supra-therapeutic dosage, and adverse drug reactions[3,6]. Second, another explanation for the wide range in incidence of medication-related hospital (re)admissions might be the difference in time-at-risk of adverse outcome, i.e. the time between discharge after the first hospital admission and subsequent readmission in different studies. The follow-up time of these studies ranges from 30 days to three years and it is self-evident that the percentages of readmissions rise substantially when the follow-up time increases[6-12]. Third, medication-related (re)admissions are probably under recognized, especially in older patients who often tend to have an atypical presentation of illness.

While there is ongoing discussion and a clear definition about medication-related hospital (re)admissions is lacking, the Dutch multidisciplinary guideline for polypharmacy in older patients published the (so-called) triggerlist with clinical events (triggers) and often involved medications that are known to be associated with an increased risk of medication-related admissions[13]. As such, this list could serve as a guide whether to call a hospital (re)admission medication-related. Table 4.1 shows the triggerlist, which is compiled based on data from the HARM-, IPCI- and QUADRAT studies[14-17].

In order to reduce medication-related hospital (re)admissions, several interventions that involve medication review have been investigated. Although a recent systematic review showed that an isolated medication review had no effect on readmission rates, multiple studies claim the opposite by showing involvement of a pharmacist does lead to a reduction in readmission rates[18-21]. This discrepancy might be explained by the fact that medication reviews often are a part of more comprehensive interventions[22] and also that pharmacists do not just perform isolated medication reviews, but often (implicitly) combine it to a multifaceted program that includes medication reconciliation, patient counseling and adequate follow-up[23]. Nevertheless, these programs performed during admission are very time consuming, relatively expensive and the quality may vary

considerably between pharmacists[21]. To overcome these problems a clinical decision support system (CDSS) that monitors medication and patient characteristics continuously and sends recommendations to general practitioners (GPs) and pharmacists after detecting a medication-related problem, could be used[24]. Consequently, possible medication-related problems will be detected immediately in contrast to manual medication reviews that are usually performed only once or twice a year. Currently available research on the continuous use of a CDSS mainly focuses on the inpatient (hospital and nursing home) setting[24-26]. As such, there exists a critical knowledge gap in the outpatient setting that needs to be addressed.

In view of the considerations above, the aim of this study is to investigate whether the continuous use of a CDSS decreases the number of hospital readmissions in older patients who previously have had an unplanned probably medication-related hospitalization according to the triggerlist from The Dutch multidisciplinary guideline for polypharmacy in older patients[13].

Table 4.1 Triggerlist from the Dutch guideline "Polypharmacy in the older patient"[13].

Trigger (adverse clinical event)	Often involved medication
Fracture / fall	Psychotropic medication (falls)/ corticosteroids / antihypertensive drugs
Collapse / hypotension / dizziness	Cardiac medication (antihypertensive drugs and antiarrhythmics)/ psychotropic medication
Bleeding (GI tract)/ supratherapeutic INR	Anticoagulants Antiplatelet drugs NSAID
Electrolyte imbalance / dehydration	Diuretics, ACEi, AII-blocker, NSAID, antidepressants
Renal insufficiency	ACEi, AII-blocker, NSAID
Hypo- or hyperglycaemia	Insulin/oral antidiabetics, Corticosteroids
Heart failure	NSAID
Obstipation / ileus	Opioids / calcium blockers
Vomiting / diarrhea	Antibiotics
Delirium / confusion / drowsiness	Psychotropic medication / cardiac medication / medication for micturition complaints / benzodiazepines

Methods/Design

Study design and setting

The "Control in the Hospital by Extensive Clinical rules for Unplanned hospitalizations in older Patients" (CHECkUP) is a multicentre, prospective and randomized study. This study will be embedded in two hospitals namely Zuyderland Medical Centre (MC) (location Sittard-Geleen and location Heerlen) and Maastricht University Medical Centre + (MUMC+), The Netherlands. Zuyderland MC is a large teaching hospital and MUMC+ is an academic hospital. The patients will be randomized by block randomizations with a size of two. This study is blinded for patients as well as for the participating GPs and pharmacists.

Study population

All patients aged 60 years and older with an unplanned hospital admission are eligible for inclusion if they meet the inclusion criteria. The inclusion criteria are polypharmacy (defined as using ≥5 medications chronically), using at least two medications from the triggerlist and the ability to give informed consent.

Patients with a life expectancy of less than three months (assessed by the involved practitioners); patients with an intentional auto-intoxication; and patients treated with cytostatic will be excluded.

Outcomes

Primary outcome

The primary outcome of this study is hospital readmission within one year after study inclusion.

Secondary outcomes

The secondary outcomes of this study are (I) mortality within one year after study inclusion; (II) the number of emergency department visits; (III) the number of nursing home admissions; (IV) time to hospital readmission; and (V) the number of hospital readmissions after 30 and 180 days. Next, we will analyze whether the readmission is (probably) medication-related. Whether a hospital readmission is medication-related will be defined afterwards, using the triggerlist. The information for secondary outcomes will be obtained from the electronic prescription system and electronic patient record. Furthermore, quality of life (QoL) and costs measured from a societal perspective will be assessed at baseline (hospital discharge) and after three, six and/or twelve months (see questionnaires).

Study procedures

Three times a week the electronic prescription system is used to select the patients of 60 years and older admitted to the hospital with polypharmacy and at least two medications from the triggerlist. A research nurse will visit the patient at the ward and assess whether the patient is eligible for inclusion. The patients will receive written information about the study and after two days the research nurse will visit them again. Then they have to indicate whether they are willing to participate by signing informed consent. Inclusion already started in April 2019 and will finish in August 2022.

After inclusion, patients will be randomized into the intervention or the control group by using a digital randomization system with block randomization. The randomization is blinded for the patients, the GP and the pharmacist. Figure 4.1 illustrates the study design and randomization procedure.

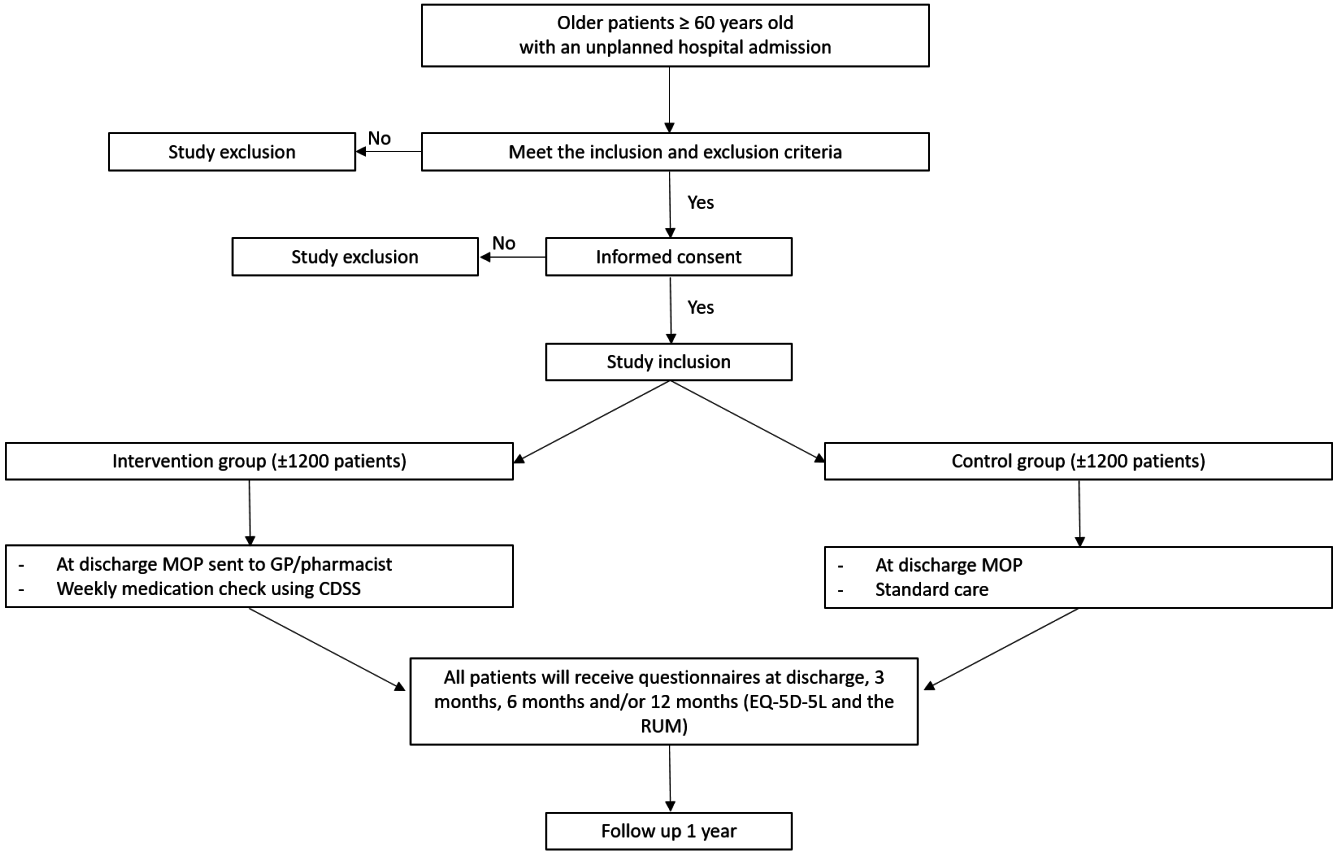


Figure 4.1 Study design and randomization procedure of CHECkUP.
MOP: Medication Optimisation Profile; GP: General practitioner; CDSS: clinical decision support system; EQ-5D-5L: EuroQol-5D-5L; RUM: Resource Use Measurement.

CDSS

In the present study we use a CDSS (we use the Clinical Rule Reporter, developed by Digitalis) to optimise medication on a continuous basis, ensuring that new medication interactions or problems, e.g. related to comorbidity, laboratory data (renal function) are quickly identified. This software has been validated and is currently used in multiple settings i.e. hospital and nursing homes[24-26]. The CDSS analyses the pharmacotherapy of patients using data regarding the patient's medication, patient characteristics such as age, sex and laboratory values, and different guidelines/criteria specific for medication assessment, such as the START/STOPP criteria[24,25,27]. Combined with the patient's medication list and characteristics, these different guidelines and criteria are summarized in 151 different clinical rules (see supplementary file 4.1, Table S4.1). These clinical rules aim to optimize the medication list and gives clinically relevant recommendations, such as lab orders, dose adjustment, stop medication. Then, the different recommendations per patients are summarized into a Medication Optimization Profile (MOP). Figure 4.2 shows a schematic overview of the CDSS and an example of how different characteristics can trigger different recommendations.

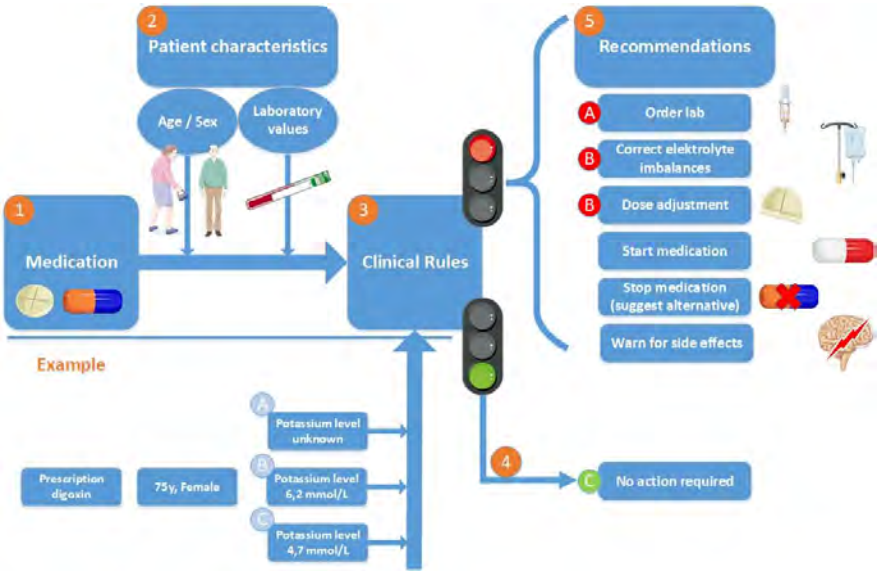


Figure 4.2 Schematic overview of the CDSS and example. When running the CDSS, the patient's medication list (1) is combined with his/her characteristics (2), such as age, sex and laboratory values (renal function, potassium level etc.). Next, these data are run through the 225 different clinical rules (3). When no clinical rules apply, a green signal is given (4) and no further actions are required(C). When clinical rules do apply a red signal is given and clinical recommendations (5) will be sent to the GP and/or pharmacist. The figure also shows an example of a 75 year-old female that is prescribed digoxin. The clinical rule about 'potassium and digoxin' is applied and different scenario's in which the potassium level is unknown (A), 6.2 mmol/L (B) or 4.7 mmol/L (C) lead to different clinical recommendations with the recommendation to order lab (A), correct electrolyte imbalances or dose adjustment (B) or no action is required (C), respectively. This figure was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com.

Participation GPs and pharmacist

During the one year study period, the patient's own GP and pharmacist receive the MOPs, to optimize pharmacotherapy. All GPs and pharmacists in the region were approached to voluntarily participate in the study. Only patients of GPs and pharmacists who had indicated to take part in the study will be able to participate.

Intervention group

Patients included in the intervention group will undergo continuous medication checks using the CDSS once the patient is discharged. At discharge, the GP and pharmacist will receive their patient's MOP. From then on the MOPs will be sent on a weekly basis for the period of one year. The GPs and the pharmacists can access this MOP and make necessary changes to the medication when appropriate. When they decide not to follow the recommendation made by the CDSS they are asked to indicate a reason.

Control group

The control group will receive standard care. The GPs and the pharmacists are not informed of which patients are participating as control. Therefore the GPs and pharmacists are blinded for this part of the study. The CDSS will also generate a MOP at discharge for patients in the control group. However this will not be sent to the patient's GP and pharmacist and is only generated for analysis at the end of the study.

Questionnaires

All patients (both intervention and control group) will be sent standardized questionnaires about the quality of life (EuroQol 5D-5L (EQ-5D-5L)) and costs from a societal perspective (Resource Use Measurement (RUM)) at hospital discharge, and after three, six and/or twelve months after inclusion[28,29]. The research nurse will determine whether the included patient will receive the second RUM questionnaire at three, six or twelve months after inclusion, in order to make sure that the groups are equal. The patients will receive the questionnaires via email and receive an automatically generated reminder after one week. The questionnaire must be completed within one month.

Sample size calculation

Based on a pilot-study the readmission rate for this selected group is estimated to be 20%[30]. The aim of this study is to reduce the readmission rate from 20% to 15%. To demonstrate this reduction (power 80%; significance level 5%; dropout 20%) at least 1130 evaluable patients are necessary per group. The target population is 2400 patients. The study will include 1200 patients in the intervention group and 1200 patients in the control group divided over the two hospitals with a minimum of 600 patients per location (300 per group).

Data analysis / Statistical analysis

The effect evaluation will be analyzed according to the intention to treat principle. The difference in primary and secondary outcome variables between the intervention and the control group will be assessed using mixed effect models to account for the clustering of patients within physician and/or repeated measurements. A logit link function will be used for the binary outcomes and an identify link for numerical outcomes. A likelihood-based approach will be applied to account for missing outcomes variables, assuming missingness at random (MAR). The stratification variable (hospital location), variables related to missing data/drop outs (to ensure MAR) and variables related to the outcome such as age and sex, will be included in the fixed part of the models.

Economic evaluation/ Cost analysis

The economic evaluation will be performed according to the Dutch guidelines of the national health care institute[31]. As mentioned earlier, the study will include 1200 patients in the intervention group and 1200 patients in the control group. As it is impossible to follow each patient, during one year follow-up we will use intermittent data collection instead of continuous data collection, because results showed that the best estimations of annual impact can be obtained by random cohort data collection, using 3 random cohorts, enduring that at least a third of the participants will be measured at each measured point[31]. Intermittent measurement combined with individual mean (IM_ imputation) will be used to calculate the annual costs per Quality Adjusted Life Years (QALYs). This means that at each measurement point 400 patients per group will complete the RUM instrument for the costs and EQ-5D-5L for the QALYs during every three – six months after inclusion.

Discussion

This study is expected to add evidence on the knowledge of medication optimization and whether continuous use of a CDSS ameliorates the risk of hospital readmission and other adverse outcomes in older patients who have already had an unplanned hospitalization.

Hospital (re)admissions place a significant burden on the healthcare system, with impact on quality of life from the patient perspective and being an important cost driver from the societal perspective. In earlier studies, different interventions have been investigated to reduce readmissions, but the results were inconclusive due to large heterogeneity in study designs and therefore their effect on hospital readmissions. As such, the optimal template of medication optimization is still unknown. This is the first study that includes patients with a high risk of having a medication-related admission based on the triggerlist. We deliberately chose to include all readmissions as primary

outcome and not specifically medication-related readmissions because a clear definition is lacking. By using a suboptimal definition it is likely we would miss readmissions that later turn out to be medication-related.

To our knowledge, this is the first large randomized blinded study providing one-year follow-up data and reporting not only on quality of care indicators (readmissions), but also on quality-of-life and costs. This contrasts to other studies in the field, which usually have a follow up of 30 or 60 days at most. This is an important strength of our study, while we believe that in this population healthcare status and medication prescriptions alter frequently and a follow up of only 30 or 60 days is too short to identify all possible consequences and the time to the occurrence of adverse outcome might vary considerably. Another strength of this study is that it will be conducted in the outpatient setting and directly in daily clinical practice and therefore improves the possibility to implement the CDSS in the shortest possible notice. The inclusion of patients has already started in April 2019, but the patient inclusion was slower than expected due to different causes. The participation of GPs and pharmacists was lower than expected, we experienced several IT problems (not related to CDSS itself) that affected inclusion and from March 2020 we had to deal with the COVID-19 pandemic. As such, during many months the inclusion was discontinued.

In conclusion, we strongly believe that the continuous use of a CDSS reduces the number of hospital readmissions in older patients already at an increased risk of medication-related hospital admission. It is of vital importance to determine the optimal template of medication optimization and further improve this essential process to eventually achieve high-quality and cost-effective care, especially in older patients with polypharmacy.

References

1. Blanda MP. Pharmacologic issues in geriatric emergency medicine. Emerg Med Clin North Am. 2006;24(2):449-viii.
2. Fabbietti P, Di Stefano G, Moresi R, Cassetta L, Di Rosa M, Fimognari F et al. Impact of potentially inappropriate medications and polypharmacy on 3-month readmission among older patients discharged from acute care hospital: a prospective study. Aging Clin Exp Res. 2018;30(8):977-984.
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):602-608.
4. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med. 2011;365(21):2002-2012.
5. Linkens A, Milosevic V, van der Kuy PHM, Damen-Hendriks VH, Mestres Gonzalvo C, Hurkens K. Medication-related hospital admissions and readmissions in older patients: an overview of literature. Int J Clin Pharm. 2020;42(5):1243-1251.
6. Zhang M, Holman CD, 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.
7. 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.
8. 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):631-639.
9. 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):948-949.
10. 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):749-755.
11. 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 AGEd multicenter randomized controlled trial. J Am Geriatr Soc. 2013;61(1):113-121.
12. Glans M, Kragh Ekstam A, Jakobsson U, Bondesson Å, Midlöv P. Risk factors for hospital readmission in older adults within 30days of discharge - a comparative retrospective study. BMC Geriatr. 2020;20(1):467.
13. Multidisciplinaire richtlijn Polyfarmacie bij ouderen, 2012. Utrecht: Nederlands Huisartsen Genootschap; 2012.
14. Leendertse AJ, Visser D, Egberts AC, van den Bemt PM. The relationship between study characteristics and the prevalence of medication-related hospitalizations: a literature review and novel analysis. Drug Saf. 2010;33(3):233-244.
15. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM; HARM Study Group. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med. 2008 Sep 22;168(17):1890-1896.
16. van der Hooft CS, Dieleman JP, Siemes C, Aarnoudse AJ, Verhamme KM, Stricker BH et al. Adverse drug reaction-related hospitalisations: a population-based cohort study. Pharmacoepidemiol Drug Saf. 2008;17(4):365-371.
17. Warle-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.
18. Dautzenberg L, Bretagne L, Koek HL, Tsokani S, Zevgiti S, Rodondi N et al. Medication review interventions to reduce hospital readmissions in older people. J Am Geriatr Soc. 2021;69(6):1646-1658.
19. Haag JD, Davis AZ, Hoel RW, Armon JJ, Odell LJ, Dierkhising RA et al. Impact of Pharmacist-Provided Medication Therapy Management on Healthcare Quality and Utilization in Recently Discharged Elderly Patients. Am Health Drug Benefits. 2016;9(5):259-268.

20. Luder HR, Frede SM, Kirby JA, Epplen K, Cavanaugh T, Martin-Boone JE et al. TransitionRx: Impact of community pharmacy postdischarge medication therapy management on hospital readmission rate. J Am Pharm Assoc (2003). 2015;55(3):246-254.
21. Cheen MHH, Goon CP, Ong WC, Lim PS, Wan CN, Leong MY et al. Evaluation of a care transition program with pharmacist-provided home-based medication review for elderly Singaporeans at high risk of readmissions. Int J Qual Health Care. 2017;29(2):200-205.
22. Van der Linden L, Hias J, Dreessen L, Milisen K, Flamaing J, Spriet I et al. Medication review versus usual care to improve drug therapies in older inpatients not admitted to geriatric wards: a quasi-experimental study (RASP-IGCT). BMC Geriatr. 2018;18(1):155.
23. Ravn-Nielsen LV, Duckert ML, 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):375-382.
24. de Wit HA, Hurkens KP, Mestres Gonzalvo C, Smid M, Sipers W, Winkens B et al. The support of medication reviews in hospitalised patients using a clinical decision support system. Springerplus. 2016;5(1):871.
25. de Wit HA, Mestres Gonzalvo C, Hurkens KP, Mulder WJ, Janknegt R, Verhey FR et al. Development of a computer system to support medication reviews in nursing homes. Int J Clin Pharm. 2013;35(5):668-672.
26. Mestres Gonzalvo C, Hurkens KP, de Wit HA, van Oijen BP, Janknegt R, Schols JM et al. To what extent is clinical and laboratory information used to perform medication reviews in the nursing home setting? the CLEAR study. Ther Clin Risk Manag. 2015;11:767-777.
27. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2015;44(2):213-218.
28. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-1736.
29. Bouwmans C, Hakkaart-van Roijen L, Koopmanschap M, Krol M, Severens H, Brouwer W. Medical Consumption Questionnaire productivity and Health Research Group [Internet]. Institute for Medical Technology Assessment; [cited 2021Dec10].
30. Milosevic V WB, Hurkens K, Zwietering A, Mestres Gonzalvo C, van der Kuy H. The association between medication indicators and hospital readmission in individuals aged 60 and over. 2016. [poster].
31. Ijzerman MJ. Guideline for Economic Evaluations in Healthcare [Internet]. Guideline | National Health Care Institute. Ministerie van Volksgezondheid, Welzijn en Sport; 2016 [cited 2021Dec10].

Supplementary table 4.1

Table S4.1 Overview of the clinical rules.

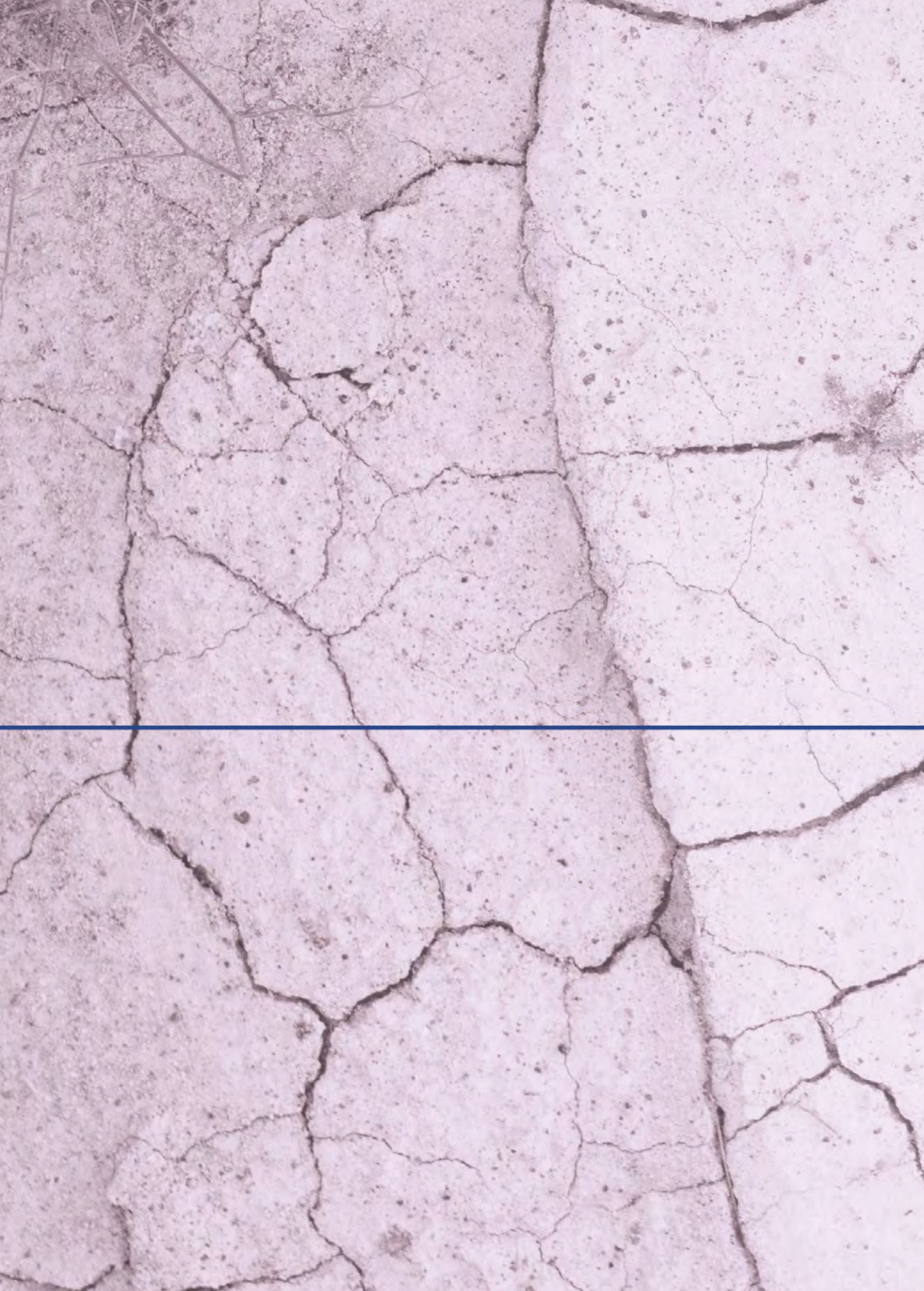
	Title of the rule
1	Check whether Benzodiazepine deprescribing is possible
2	Check whether Brotizolam deprescribing is possible
3	Check whether Flunitrazepam deprescribing is possible
4	Check whether Flurazepam deprescribing is possible
5	Check whether Loprazolam deprescribing is possible
6	Check whether Lorazepam deprescribing is possible
7	Check whether Lormetazepam deprescribing is possible
8	Check whether Midazolam deprescribing is possible
9	Check whether Nitrazepam deprescribing is possible
10	Check whether Oxazepam deprescribing is possible
11	Check whether Temazepam deprescribing is possible
12	Check whether Zolpidem deprescribing is possible
13	Check whether Zopiclon deprescribing is possible
14	Gastric protection (version 2)
15	Treatment with antihypertensive medications: Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)
16	Low-density lipoprotein (LDL) optimalisation
17	MDRD & ACE for older patient
18	MDRD or CKD-EPI and ACR are required
19	Carbamazepine/Oxcarbamazepine + hyponatraemia
20	Potassium levels
21	Potassium levels + digoxin
22	selective serotonin reuptake inhibitor (SSRI's) with significant hyponatremia
23	Thiazides and hyponatraemia
24	Unknown potassium serum level
25	MDRD required
26	Renal dysfunction + Aciclovir - Oral
27	Renal dysfunction + Acipimox
28	Renal dysfunction + Alendronic acid
29	Renal dysfunction + Amantadine
30	Renal dysfunction + Amoxicillin
31	Renal dysfunction + Apixaban
32	Renal dysfunction + Barnidipine
33	Renal dysfunction + Benzylpenicillin
34	Renal dysfunction + Carbasalate calcium (analgesic)
35	Renal dysfunction + Cefalexin
36	Renal dysfunction + Cefazolin
37	Renal dysfunction + Cefotaxime
38	Renal dysfunction + Ceftazidime
39	Renal dysfunction + Cefuroxime
40	Renal dysfunction + Cetirizine
41	Renal dysfunction + Chloroquine
42	Renal dysfunction + Chlortalidone
43	Renal dysfunction + Cimetidine
44	Renal dysfunction + Ciprofloxacin - IV
45	Renal dysfunction + Ciprofloxacin - Oral
46	Renal dysfunction + Co-amoxiclav
47	Renal dysfunction + Colchicine
48	Renal dysfunction + Dabigatran
49	Renal dysfunction + Dalteparine

Table S4.1 (continued)

	Title of the rule
50	Renal dysfunction + Danaparoide
51	Renal dysfunction + Daptomycine
52	Renal dysfunction + Deferasirox
53	Renal dysfunction + Edoxaban
54	Renal dysfunction + Entecavir
55	Renal dysfunction + Ertapenem
56	Renal dysfunction + Fluconazole
57	Renal dysfunction + Ganciclovir
58	Renal dysfunction + Hydroxychloroquine
59	Renal dysfunction + Imipenem/cilastatin
60	Renal dysfunction + Lacosamide
61	Renal dysfunction + Levetiracetam
62	Renal dysfunction + Levocetirizine
63	Renal dysfunction + Levofloxacin
64	Renal dysfunction + Lithium
65	Renal dysfunction + Memantine
66	Renal dysfunction + Meropenem
67	Renal dysfunction + Metformine
68	Renal dysfunction + Midazolam
69	Renal dysfunction + Nitrofurantoin
70	Renal dysfunction + Norfloxacin
71	Renal dysfunction + Ofloxacin
72	Renal dysfunction + Oseltamivir
73	Renal dysfunction + Paliperidone
74	Renal dysfunction + Parathyroid hormone
75	Renal dysfunction + Pergolide
76	Renal dysfunction + Piracetam
77	Renal dysfunction + Pramipexole
78	Renal dysfunction + Probenecid
79	Renal dysfunction + Proguanil
80	Renal dysfunction + Quinine
81	Renal dysfunction + Risperidone
82	Renal dysfunction + Rivaroxaban
83	Renal dysfunction + Rosuvastatin
84	Renal dysfunction + Solifenacin
85	Renal dysfunction + Sotalol (1)
86	Renal dysfunction + Sotalol (2)
87	Renal dysfunction + Sucralfate
88	Renal dysfunction + Sulfadiazine
89	Renal dysfunction + Tazocin/Piperacillin
90	Renal dysfunction + Teicoplanin
91	Renal dysfunction + Terbinafine
92	Renal dysfunction + Tetracycline
93	Renal dysfunction + Tranexamic acid
94	Renal dysfunction + Valaciclovir
95	Renal dysfunction + Varenicline
96	Renal dysfunction + Venlafaxine
97	Acetosal and acenocoumarol or fenprocoumon
98	Bisphosphonates and calcium, and vitamin D supplementation
99	Bisphosphonates, Calcium and Vitamin D supplementation
100	Chronic use of laxatives
101	Concomitant use of an ACE-inhibitor with codeine

Table S4.1 (continued)

	Title of the rule
102	Diclofenac, celecoxib and etoricoxib should not be used in patients with angina pectoris or ischemic heart disease
103	Diclofenac, celecoxib and etoricoxib should not be used in patients with stroke in the anamnesis
104	Dipyridamol usage and no antihypertensive medication
105	Gastric protection
106	Nitrate and no beta blocker
107	Use of dipyridamol without acetosal
108	Use of LMWH and acenocoumarol for more than 5 days
109	Anticholinergic antispasmodic drugs + chronic constipation
110	Anticholinergic antispasmodic drugs + chronic constipation
111	Anticholinergics to treat extrapyramidal side effects of neuroleptic medications
112	Aspirin, clopidogrel or dipyridamole + concurrent bleeding disorder
113	Beta blockers with diabetes mellitus(DM) and hypoglycaemic episode a month
114	Bladder antimuscarinic drugs with constipation
115	Bladder antimuscarinic drugs with constipation
116	Bladder antimuscarinic drugs with dementia
117	Bladder antimuscarinic drugs with dementia
118	Bladder antimuscarinic drugs with glaucoma
119	Bladder antimuscarinic drugs with glaucoma
120	Bladder antimuscarinic drugs with prostatism
121	Bladder antimuscarinic drugs with prostatism
122	Calcium channel blockers with chronic constipation (1)
123	Calcium channel blockers with chronic constipation (2)
124	Estrogens with history of breast cancer or venous thromboembolism
125	Glibenclamide or Chlorpropamide with DM type 2
126	Glibenclamide or Chlorpropamide with DM type 2
127	Long term neuroleptics with parkinsonism
128	Long term neuroleptics with parkinsonism
129	Long-acting Benzodiazepines or long-acting metabolites
130	Nebulized ipratropium and/or beta2 adrenergics with glaucoma
131	Nebulized ipratropium and/or beta2 adrenergics with glaucoma
132	Non-cardioselective beta-blocker with Chronic obstructive pulmonary disease (COPD)
133	Non-cardioselective beta-blocker with COPD
134	Phenothiazines in patients with epilepsy
135	Phenothiazines in patients with epilepsy
136	Prochlorperazine or metoclopramide with Parkinsonism
137	Prochlorperazine or metoclopramide with Parkinsonism
138	Prolonged use of 1st generation antihistamines
139	Theophylline as monotherapy for COPD
140	Thiazide diuretic with a history of gout (1)
141	Thiazide diuretic with a history of gout (2)
142	Tricyclic antidepressants with cardiac conductive abnormalities (1)
143	Tricyclic antidepressants with cardiac conductive abnormalities (2)
144	Tricyclic antidepressants with constipation (1)
145	Tricyclic antidepressants with constipation (2)
146	Tricyclic antidepressants with dementia (1)
147	Tricyclic antidepressants with dementia (2)
148	Tricyclic antidepressants with glaucoma (1)
149	Tricyclic antidepressants with glaucoma (2)
150	Tricyclic antidepressants with prostatism or prior history of urinary retention (1)
151	Tricyclic antidepressants with prostatism or prior history of urinary retention (2)




CHAPTERFIVE

Chapter 5

Additional value of a triggerlist as selection criterion in identifying patients at high risk of medication-related hospital admission: a retrospective cohort study

Aimée E.M.J.H. Linkens, Myrthe J.M. Janssen, Noémi van Nie, Lucretia Peeters, Bjorn Winkens, Vanja Milosevic, Bart Spaetgens, Kim P.G.M. Hurkens, P. Hugo M. van der Kuy

Int J Clin Pharm 2022;44(5):1205-1210.

Abstract

Background

Of all hospital admissions in older patients, 10-30% seem to be medication-related. However, medication-related admissions are often unidentified in clinical practice. To increase the identification of medication-related hospital admissions in older patients a triggerlist is published in the Dutch guideline for polypharmacy.

Aim

To assess whether the triggerlist has value as selection criterion to identify patients at high risk of medication-related hospital admissions.

Method

This retrospective cohort study was carried out in 100 older (≥60 years) patients with polypharmacy and having two triggers from the triggerlist. The admissions were assessed as either possibly or unlikely medication-related according to the Assessment Tool for identifying Hospital Admissions Related to Medications.

Results

Of all the admissions 48% were classified as possibly medication-related. Patients with a possible medication-related hospital admission were more likely to have an impaired renal function (p=0.015), but no differences with regard to age, sex, comorbidity or number of medicines were found.

Conclusion

The high prevalence of medication-related hospital admissions, suggests the triggerlist may have added value as selection criterion in a cohort of older patients with polypharmacy and can be used to improve the identification of a population at high risk of medication-related hospital admissions.

Impact of findings on practice statements

- The triggerlist may be used in clinical practice to improve the identification of patients with a medication-related hospital admission.
- The triggerlist can be easily automated and may therefore contribute to a feasible and easy-to-implement approach in future research studies to select a population at high risk of medication-related hospital admissions.
- Further prospective studies will be conducted to assess the prevalence of medication-related hospital admission in a cohort of older patients with polypharmacy and two triggers of the triggerlist.

Introduction

Polypharmacy increases the risk of medication-related hospital admissions (MRAs)[1,2]. Overall, 10-30% of the hospital admissions in older patients seem to be medication-related[3-6]. However, MRAs are often unidentified in clinical practice or under recognized by definition, since many studies define MRAs based on adverse drug reactions (ADRs)[3]. However, MRAs may also be defined as a hospital admission where medication-related problems (MRPs) are the main cause or at least a significant contributing factor[7]. Since MRPs, besides ADRs, also encompass drug-drug interactions, medication errors, problems with medication adherence, inappropriate drug selection and for example sub- and supra-therapeutic dosage, it is expected that the prevalence of MRAs will significantly increase due to this broader definition[8]. To increase the identification of MRAs in older patients the Dutch multidisciplinary guideline for polypharmacy in older patients published a triggerlist that can be used to establish whether an admission is medication-related. This list contains adverse clinical events, also called triggers (such as falls, electrolyte disturbances or bleeding) and medication (such as psychotropic medication and/or cardiac medication) that are often related to MRAs. Table 5.1 shows the triggerlist[1,9]. Nevertheless, although included in the aforementioned guideline, it has not been investigated whether the triggerlist can be used to identify a population at high risk of MRAs.

Table 5.1 Triggerlist from the Dutch guideline "Polypharmacy in the older patient".

Trigger (adverse clinical event)	Often involved medication
Fracture / fall	Psychotropic medication (falls) / corticosteroids/ antihypertensive drugs
Collapse / hypotension / dizziness	Cardiac medication (antihypertensive drugs and antiarrhytmics) / psychotropic medication
Bleeding (GI tract) / supratherapeutic INR	Anticoagulants Antiplatelet drugs NSAID
Electrolyte imbalance / dehydration	Diuretics, ACEi, AII-blocker, NSAID, antidepressants
Renal insufficiency	ACEi, AII-blocker, NSAID
Hypo- or hyperglycaemia	Insulin / oral antidiabetics, Corticosteroids
Heart failure	NSAID
Obstipation / ileus	Opioids / calcium blockers
Vomiting/ diarrhea	Antibiotics
Delirium/ confusion / drowsiness	Psychotropic medication / cardiac medication / medication for micturition complaints/ benzodiazepines

Based on this hypothesis, the triggerlist is currently being used in the CHECkUP study as an additional selection criterion, next to age (≥60 years) and polypharmacy[10]. Especially for the purpose of selection, the use of a triggerlist is interesting in terms of feasibility, as it is convenient to complete and can be easily automated, without the need for an expert panel or other time-consuming tools or questionnaires.

Aim

The aim of the present study was to assess whether the triggerlist has value (added to age and polypharmacy) as selection criterion to identify patients at high risk of a possible MRA.

Ethics approval

This retrospective cohort study is a sub-study of the CHECkUP study, which has received approval from the Medical Research Ethics Committee of Zuyderland Medical Centre (METC number: METCZ20180091) on October 29, 2018 prior to study initiation. All participants gave written informed consent before any data was collected.

Methods

Setting and population

This sub-study was carried out within the first 100 inclusions in the CHECkUP study. CHECkUP is a randomised controlled trial that assesses whether an extensive weekly medication screening using a clinical decision support system reduces hospital readmissions within one year in older (≥60 years) patients with polypharmacy and having at least two triggers from the triggerlist. Further details are described elsewhere[10].

Data collection

On admission, demographic data (age, sex) and clinical patient characteristics (Charlson Comorbidity Index (CCI)[11], number of medications prior to admission, eGFR, number of trigger diagnoses and number of medications which causes trigger diagnoses) were collected. We evaluated the number of trigger diagnoses and -medication based on the medication list before admission. The inclusion criteria of CHECkUP (polypharmacy and having at least two triggers from the triggerlist) were assessed on the first day after admission.

Two independent reviewers, a student researcher and general pharmacist with 40 years of working experience, assessed whether an admission was either *possibly* or *unlikely* medication-related according to the Assessment Tool for identifying Hospital Admissions Related to Medications (AT-HARM10) (See Supplementary Table S5.1)[7]. Data from the admission letter, medication list upon admission, laboratory data and discharge letter were used to complete AT-HARM10. A geriatrician and hospital pharmacist

independently assessed discrepancies and finally all discrepancies were discussed with the entire team to reach consensus. All reviewers read the instructions for use and the examples supplemented to AT-HARM10. Six training cases were performed by the reviewers and discussed with the researchers of Uppsala University who developed AT-HARM10.

Statistical analysis

Descriptive statistics were used to present the demographics and results as means with standard deviation (SD) or medians with interquartile ranges [IQR], whichever appropriate. Statistical analyses to compare the demographic and clinical characteristics of both groups (the *possibly* and *unlikely* MRAs) were performed using IBM SPSS version 27.0. P-values <0.05 were considered statistically significant.

Results

The mean age of the 100 patients included in this study was 75.2 years (SD 8.6). Forty-five were female, the median CCI was 2 (IQR 1-3) and the mean number of medicines prior to admission was 10.7 (SD 4.5). Demographic and clinical characteristics are shown in Table 5.2.

Table 5.2 also shows the most frequent triggerlist diagnoses and medications of the total cohort.

Ultimately, 48 [48%] admissions were assessed as being *possibly* medication-related, 51 [51%] as *unlikely* medication-related, and on one [1%] admission no consensus could be reached. The independent reviewers agreed on 64 of the admissions, identifying 35 [35%] as *possibly* medication-related and 29 [29%] as *unlikely* medication-related, respectively. After discussing the discrepancies, another 13 [13%] admissions were assessed as *possibly* medication-related and 22 [22%] admissions as *unlikely* medication-related. These results are summarized in Figure 5.1.

We found no significant differences with regard to age, sex, CCI, number of medicines or triggerlist diagnoses/medications when comparing *possibly* and *unlikely* MRAs. Patients with a possible MRA were more likely to have an impaired renal function (p=0.015, Table 5.2).

Table 5.2 Baseline characteristics of older patients with polypharmacy during index admission.

Variable	All admissions (n=100)*	MRA *possibly* (n=48)	MRA *unlikely* *(n=51)*	P value
Sex: n (%)				0.787
Female	45	22 (45.8)	22 (43.1)	
Male	55	26 (54.2)	29 (56.9)	
Age at admission, (years) n (%) :				0.443
60-74	44	22 (45.8)	21 (41.2)	
75-89	52	23 (47.9)	29 (56.9)	
≥ 90	4	3 (6.3)	1 (2.0)	
Mean ± SD	75.2 ± 8.6	74.7 ± 9.0	75.8 ± 8.2	0.504
Charlson Comorbidity Index Score (%) :				0.110
0	11	3 (6.3)	8 (15.7)	
1-2	52	24 (50.0)	28 (54.9)	
3-4	32	16 (33.3)	15 (29.4)	
5-6	4	4 (8.3)	0 (0.0)	
≥7	1	1 (2.1)	0 (0.0)	
Median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	0.136
Renal function, eGFR (ml/min/1.73m^2), n (%)				0.015
0-29	21	16 (33.3)	5 (9.8)	
30-50	24	9 (18.8)	15 (29.4)	
≥ 51	55	23 (47.9)	31 (60.8)	
Number of medicines at index admission, n (%)				0.407
0-4	4	1 (2.1)	3 (5.9)	
5-9	43	19 (39.6)	24 (47.1)	
≥10	53	28 (58.3)	24 (47.1)	
Mean ± SD	10.7 ± 4.5	10.9 ± 4.3	10.5 ± 4.7	0.641
Trigger diagnoses				0.962
0-2	13	6 (12.5)	7 (13.7)	
3-5	44	21(43.8)	23 (45.1)	
≥6	42	21 (43.8)	21 (41.2)	
Mean ± SD	5.0 ± 1.9	5.0 ± 1.8	5.0 ± 2.0	0.997
Trigger medications				0.911
0-2	21	10 (20.8)	11 (21.6)	
3-5	45	21 (43.8)	24 (47.1)	
≥6	33	17 (35.4)	16 (31.4)	
Mean ± SD	4.4 ± 2.2	4.5 ±2.2	4.3 ± 2.3	0.747
Trigger diagnoses – Most common of the cohort				
1. Delirium / confusion / drowsiness				
2. Collapse / hypotension / dizziness				
3. Elektrolyte imblance / dehydration				
4. Bleeding / supratherapeutic INR				
5. Renal insufficiency				
Trigger medications – Most common of the cohort				
1. Diuretics				
2. Beta blockers				
3. Platelet aggregation inhibitors				
4. Angiotensin receptor blockers (ARBs)				
5. Metformin				

SD: Standard Deviation, IQR= Interquartile Range. * one patient was excluded from the comparative analyses between *possibly* and unlikely MRA.

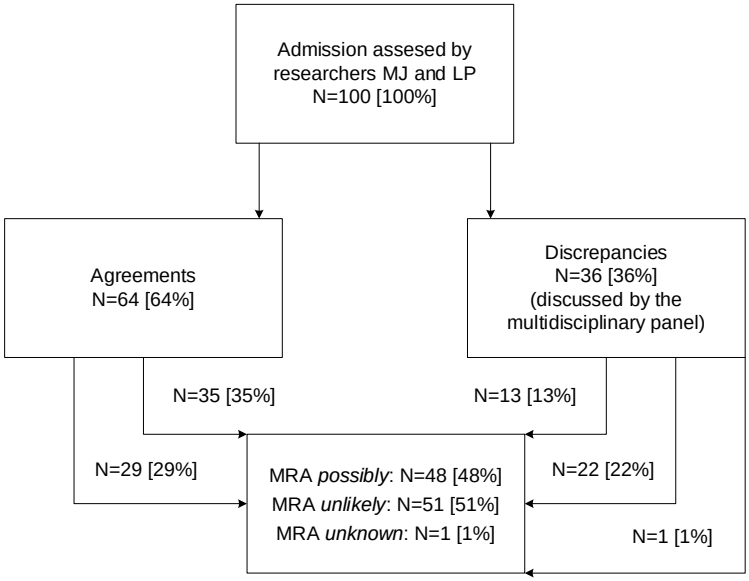


Figure 5.1 Number of *possibly* and *unlikely* medication-related hospital admissions according AT-HARM10.

Discussion

This sub-study of the CHECkUP is the first to show that adding the triggerlist as selection criterion in a cohort of older patients (≥60 years) with polypharmacy, might improve the identification of a population at high risk of MRA, as 48% of the admissions were classified as *possibly* medication-related by using the AT-HARM10.

The triggerlist was first introduced in the Dutch multidisciplinary guideline for polypharmacy in older patients and was proposed as a list to recognize possible MRAs. Although it has high face validity (i.e. the individual components (adverse clinical events) in itself are associated with MRPs[1,2,9,12,13]), when it was introduced its use had not been investigated yet. To date, only one study has used the triggerlist and in this study it was not even used to assess whether a hospital admission was medication-related but to investigate whether emergency department visits of patients that were not hospitalized, were possibly medication-related[14].

While due to different definitions and the lack of a gold standard the prevalence of MRAs varies considerably, it is important to adequately identify the population of interest, i.e. those at high risk of MRA. This is especially important in intervention studies like CHECkUP and other studies that aim to optimize medication in (frail) older

patients[10,15]. Although by including older patients with polypharmacy the a-priori risk of a MRA is already high, we hypothesized that by additionally using the triggerlist as selection criterion, the posteriori probability might increase even further. Although we were, by design, unable to directly test this hypothesis, the current literature supports our assumption that selecting patients with risk factors leads to a higher prevalence of MRAs. The prevalence of MRAs varies between 5.6% and 30% in adult patients without any risk factors[2,4,5,6,12], while studies that select patients with a higher risk for MRAs found a prevalence of hospitalizations being medication-related between 38% and 42%[16,17].

We did not find any significant differences with regard to age, sex, CCI, number of medicines or triggerlist diagnoses/medications when comparing *possibly* and *unlikely* MRAs. This is not surprising as in this study, by including only older patients (≥60 years) with polypharmacy and two trigger diagnoses, the number of patients using <5 medicines is minimal and not sufficient to demonstrate a significant association, which is in agreement with Lea et al[16]. Another explanation might be that this study is underpowered to detect differences for these subcategories.

This study is not without limitations. First, the study is limited by its retrospective design. All hospital admissions were evaluated based on the data in the hospital electronic information systems, which were registered by other physicians. We also had no information about compliance or over-the-counter drugs. The trigger diagnoses and medications were assessed on the medication list used before admission which explains that some included patients used less than five medications. Second, patients were recruited from a single centre limiting the generalizability of our results. Third and finally, when assessing whether a hospital admission was medication-related, the two independent reviewers reached agreement in 64% of the admissions by using AT-HARM10. This is lower compared to the 80% agreement found in the study of Coppes et al[18]. We believe this might be due to the difference in clinical experience between both reviewers (a pharmacy student and a general pharmacist with 40 years of working experience). For future research it is important to assess the possible MRAs, identified with AT-HARM10, in terms of degrees of certainty, preventability and level of causality. Nevertheless, since all discrepancies were discussed by a multidisciplinary panel, which is considered the gold standard, we believe our final point estimate of MRAs is realistic. Despite this, the application of AT-HARM10 in another patient population in another country and also its feasibility still contribute to the further validation of this assessment tool to identify MRAs.

Conclusion

The high prevalence of MRAs, suggests the triggerlist has added value as selection criterion in a cohort of older patients (≥60 years) with polypharmacy and can be used to improve the identification of a population at high risk of MRA, as 48% of the admissions were classified as *possibly* medication-related by using AT-HARM10.

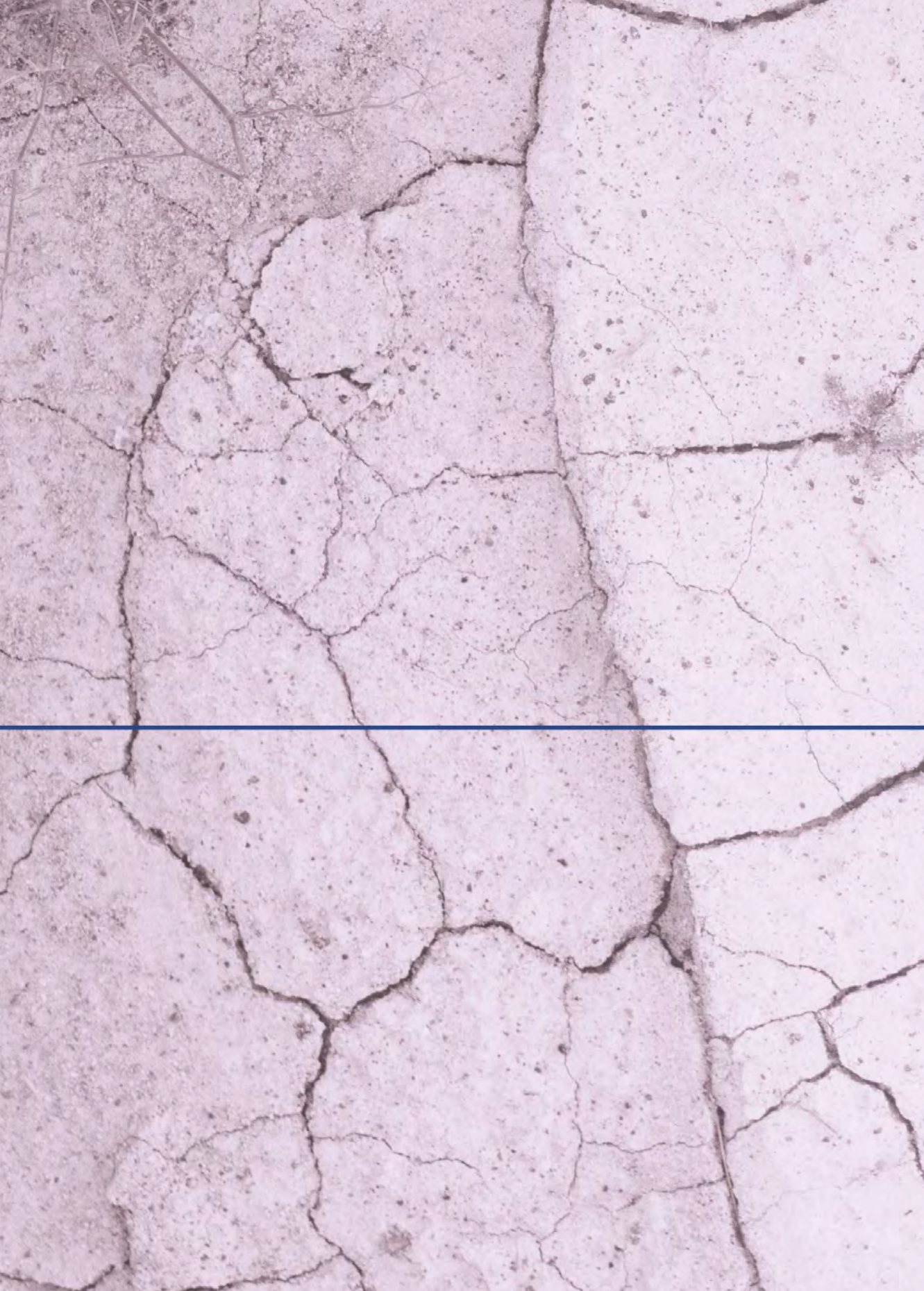
References

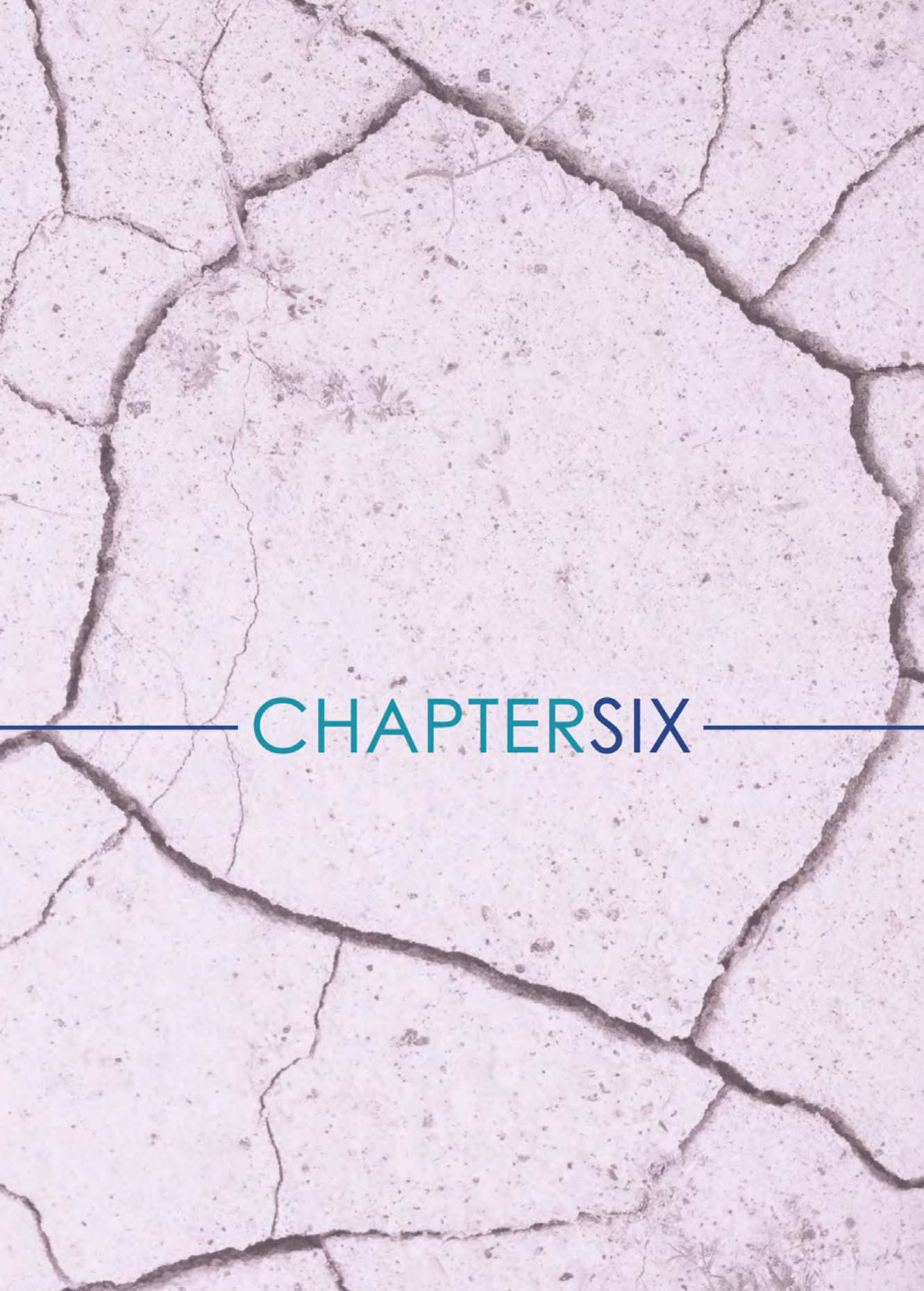
1. Multidisciplinaire richtlijn Polyfarmacie bij ouderen, 2012. Utrecht: Nederlands Huisartsen Genootschap; 2012.
2. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM; HARM Study Group. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med. 2008;168(17):1890-1896.
3. 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;66(3):602-608.
4. Chan M, Nicklason F, Vial JH. Adverse drug events as a cause of hospital admission in the elderly. Intern Med J. 2001;31(4):199-205.
5. McLachlan CY, Yi M, Ling A, Jardine DL. Adverse drug events are a major cause of acute medical admission. Intern Med J. 2014;44(7):633-638.
6. Oscanoa TJ, Lizaraso F, Carvajal A. Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. Eur J Clin Pharmacol. 2017;73(6):759-770.
7. Kempen TGH, Hedström M, Olsson H, Johansson A, Ottosson S, Al-Sammak Y et al. Assessment tool for hospital admissions related to medications: development and validation in older patients. Int J Clin Pharm. 2019;41(1):198-206.
8. Linkens AEMJH, Milosevic V, van der Kuy PHM, et al. Medication-related hospital admissions and readmissions in older patients: an overview of literature. Int J Clin Pharm. 2020;42:1243-1251.
9. Leendertse AJ, Visser D, Egberts AC, et al. The relationship between study characteristics and the prevalence of medication-related hospitalizations: a literature review and novel analysis. Drug Saf. 2010;33:233-244.
10. Linkens AEMJH, Milosevic V, van Nie N, Zwietering A, de Leeuw PW, van den Akker M et al. Control in the Hospital by Extensive Clinical rules for Unplanned hospitalizations in older Patients (CHECkUP); study design of a multicentre randomized study. BMC Geriatr. 2022;22(1):36.
11. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-383.
12. van der Hooft CS, Dieleman JP, Siemes C, Aarnoudse AJ, Verhamme KM, Stricker BH et al. Adverse drug reaction-related hospitalisations: a population-based cohort study. Pharmacoepidemiol Drug Saf. 2008;17(4):365-371.
13. 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.
14. Reijers EMC, van Strien AM, Derijks HJ, van Marum RJ. Geneesmiddelgerelateerde SEH-bezoeken zonder opname bij ouderen. Nederlands Platform voor Farmaceutisch Onderzoek. 2021;6:a1734
15. Saeed D, Carter G, Parsons C. Interventions to improve medicines optimisation in frail older patients in secondary and acute care settings: a systematic review of randomised controlled trials and non-randomised studies. Int J Clin Pharm. 2022;44(1):15-26.
16. Lea M, Mowe M, Mathiesen L, Kvernrød K, Skovlund E, Molden E. Prevalence and risk factors of drug-related hospitalizations in multimorbid patients admitted to an internal medicine ward. PLoS One. 2019;14(7):e0220071.
17. Zerah L, Henrard S, Thevelin S, Feller M, Meyer-Massetti C, Knol W et al. Performance of a trigger tool for detecting drug-related hospital admissions in older people: analysis from the OPERAM trial. Age Ageing. 2022;51(1):afab196.
18. Coppes T, van der Kloes J, Dalleur O, Karapinar-Çarkit F. Identifying medication-related readmissions: Two students using tools vs a multidisciplinary panel. Int J Clin Pract. 2021;75(11):e14768.

Supplementary table

Table S5.1 The AT-HARM10 tool
The first three questions are used to identify admissions that are unlikely to be medication-related while questions 4-10 are used to identify admissions that are possibly medication-related. When one of the ten questions is answered with 'yes', the assessment is finished. When all questions are answered with 'no' , an expert panel is needed to assess whether an admission is medication-related.

U1.	Was the admission caused by an infection or a previously undiagnosed disease (e.g. diabetes or heart failure) that is not medication-related?
U2.	Was the admission caused by progression of a previously diagnosed disease that is not medication-related?
U3.	Was the admission caused by physical trauma, substance intoxication, social circumstances or allergies that are not medication-related?
P4.	Is it hinted or stated in the medical record that the admission was medication-related (including non-compliance)?
P5.	Might (side) effects of the medications the patient was taking (prescribed or not prescribed) prior to hospitalization have caused the admission (including over-treatment)?
P6.	Are there abnormal laboratory results or vital signs that could be medication-related and have might caused the admission?
P7.	Was there any drug-drug interaction or drug-disease interaction (i.e. a contraindication) that might have caused the admission?
P8.	Did the patient have any previously diagnosed untreated or sub-optimally treated (e.g. dose too low) indications that might have caused the admission?
P9.	Was the patient admitted because of a problem with the dosage form or pharmaceutical formulation (i.e. failure to receive the medication)?
P10.	Is the cause of the admission a response to cessation or withdrawal of medication therapy?





CHAPTER SIX

Chapter 6

Clinical Decision Support Systems in hospitalized older patients: an exploratory analysis in a real-life clinical setting

Aimée E.M.J.H. Linkens, Dennis Kurstjens, N. Anne Zwietering, Vanja Milosevic, Kim P.G.M. Hurkens, Noémi van Nie, Bob P.A. van de Loo, P. Hugo M. van der Kuy, Bart Spaetgens

Drugs Real World Outcomes 2023;10(3):363-370

Abstract

Background

Inappropriate prescribing is associated with negative patient outcomes. In hospitalised patients, the use of Clinical Decision Support Systems (CDSS) may reduce inappropriate prescribing and thereby improve patient-related outcomes. However, recently published large clinical trials (OPERAM and SENATOR) have showed negative results on the use of CDSS and patient outcome and strikingly low acceptance of recommendations.

Objective

The purpose of the present study was to investigate the use of a CDSS, in a real-life clinical setting of hospitalized older patients. As such, we report on the real-life pattern of this in-hospital implemented CDSS, including: (I) whether generated alerts were resolved; (II) whether a recorded action by the pharmacist led to an improved number of resolved alerts; and (III) describe the natural course of generated alerts, in particular of those in the non-intervention group; as these data are largely lacking in current studies.

Methods

Hospitalised patients, aged 60 years and older, admitted to Zuyderland Medical Centre, the Netherlands in 2018 were included. The evaluation of the CDSS was investigated using a database used for standard care. Next to demographic and clinical data, we also collected: the total numbers of CDSS alerts, the number of alerts 'handled' by the pharmacist, those with an action of the pharmacist, and finally the outcome of the alerts at day one and day three after the alert was generated.

Results

3,574 unique hospitalized patients, mean age 76.7 (SD 8.3) years and 53% female, were included. From these patients, in total 8,073 alerts were generated, of which 7,907 (97.9% of total) were handled by the pharmacist (day one). In 51.6% of the alerts handled by the pharmacist an action was initiated, resulting in 36.1% of the alerts resolved after day one, compared to 27.3%, if the pharmacist did not perform an action ($P<0.001$). On day three, in 52.6% of the alerts an action by the pharmacist was initiated, resulting in 62.4% resolved alerts, compared to 48.0% when no action was performed ($P<0.001$). In the category renal function, the percentages differed significantly between an action vs. no action of the pharmacist at day one and at day three (16.6% vs. 10.6%, $P<0.001$ (day one), 29.8 % vs. 19.4 %, $P<0.001$ (day three).

Conclusion

This study demonstrates the pattern and natural course of clinical alerts of an in-hospital implemented CDSS in a real-life clinical setting of hospitalized older patients. Besides the already known beneficial effect of actions by pharmacists, we have also shown that many alerts become resolved without any specific intervention. As such, our study provides important insight in the spontaneous course of resolved alerts, since these data are currently lacking in the literature.

Introduction

The population is ageing rapidly and as a result multimorbidity and associated polypharmacy is an increasing health risk leading to considerable mortality and morbidity[1-3]. As such, 30% of emergency department visits and hospital admissions in older age are attributable to side effects and inappropriate prescription of medicine, since the risk of inappropriate medication use, adverse drug events (ADE) and medication-related problems (MRPs) is increasing[4-6]. These risks increase even further when older patients are hospitalized, at least in part due to the fact that acutely ill older patients are often exposed to new prescriptions by multiple prescribers[7,8]. Thus, a variety of interventions to reduce MRPs in older hospitalized individuals has been studied with widely varying impact[3,9]. Most of these interventions studied the participation of pharmacists to ideally prevent, and otherwise reduce the impact of MRPs, although in recent years the involvement of a clinical decision support system (CDSS) has emerged, showing possibilities to reduce potentially inappropriate prescribing in hospitalised older patients[7,9,10,11].

Recently, two large clinical trials, the OPERAM (OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people) trial and the SENATOR (Software ENgine for the Assessment and optimisation of drug and non-drug Therapy in Older peRsons) trial investigated medication optimisation supported by a CDSS including the Screening Tool of Older Persons' Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) recommendations[3,12]. However, both studies found no significant differences in incidence of adverse drug reactions, drug-related hospital admissions and mortality between the intervention and control arms, and only a low proportion of the recommendations accepted by the pharmacotherapy team or attending physicians[12,13]. Potential explanations for these low acceptance rates were the fact that recommendations were deemed of low clinical relevance by clinicians as well as variable attitudes to the intervention and/or participation in clinical trials and patient-specific factors[14,15].

The ultimate goal of a CDSS is to improve patient-related outcomes, however, as long as only low proportions of recommendations are accepted and rules with low clinical relevance are used in CDSSs, it is unlikely this goal will be achieved[13,16,17]. These specific factors, presumably leading to low response rates and alert fatigue, have not been recorded in the initial trials evaluating CDSSs. Therefore, the purpose of the present study was to report on existing knowledge gaps in a real-life clinical setting of hospitalized older patients, in order to describe, evaluate and optimise the use of the CDSS in clinical practice.

To this end, we investigated the real-life pattern of an in-hospital implemented CDSS, including

(I) whether generated alerts were resolved;
(II) whether a recorded action by the pharmacist led to an improved number of resolved alerts; and
(III) describe the natural course of generated alerts, in particular of those in the non-intervention group, as these data are largely lacking in current studies.

Methods

System details - Description of CDSS system – Clinical Rule Reporter (CRR)

The CDSS used in Zuyderland Medical Centre, a large teaching hospital in the Netherlands, is the Clinical Rule Reporter (CRR). The CRR has been implemented in daily practice since 2016 and is mainly based on guidance for medication-related laboratory testing, dosing support in patients with renal impairment, guidance for optimal use for antibiotics and anticoagulation[18,19]. It is used for medication surveillance using demographic, medication and laboratory data from admitted patients and contains several clinical rules[19]. The CDSS in this study consisted of 80 rules (Supplementary Data Table S6.1).

The CDSS analyses the medication from all admitted patients on a daily basis. The clinical pharmacist receives (per patient) a report in which all alerts are given. The clinical pharmacist then assesses whether further action is indicated according to a distinct rule. For this study, we defined this action as 'an action by the pharmacist' when a rule was discussed extensively (i.e. consultation between pharmacist and physician) or when an intervention was performed by the pharmacist or by the physician (after consultation).

Patients

We included patients of 60 years and older, hospitalized in 2018 , from January 01, 2018 to December 31, 2018, in Zuyderland Medical Centre, the Netherlands. Patients admitted to rehabilitation wards and short stay departments were excluded. Demographic data (age and sex) were collected. The evaluation of the CRR was investigated in a retrospective study using a database used for standard care, which is why this study did not require ethical approval.

Data collection

The data of the generated alerts of the included patients and their management were extracted to Qlik Sense version September 2020 SR1. Qlik Sense is a tool which visualizes data in an interactive way. All rules were categorized in one of the following: renal function, potassium, antibiotics (intravenous (IV) to oral), antibiotics (long use),

opioids/laxatives, anticoagulant therapy and unknown lab value. Next to the number of unique patients, the following data was collected in order to evaluate the use of the CRR: 1. The total number of alerts, 2. The number of alerts 'handled' by the pharmacist, 3. The number of alerts resulting in an action of the pharmacist, 4. The outcome of the alert (described as 'green' (resolved), 'red' (unresolved) and 'unknown'. We also calculated the percentage of resolved and unresolved alerts, after excluding the 'unknown' alerts. The latter being excluded because it is unknown whether an 'unknown' alert was actually resolved by discontinuing the medication (and thus the rule that generated the alert did not apply anymore) or because the patient was discharged.

Statistical analyses

Descriptive statistics were used to describe the study population and presented as mean (SD) or median (IQR) whichever appropriate. To test the differences in percentages in the groups with or without an action by the pharmacist a Chi-square test was used. Statistical analyses were performed using SPSS Statistics v25 (IBM, Armonk, NY, USA).

Results

Baseline characteristics

In 2018, anonymised data from 3,574 unique hospitalized patients were included for the current analyses. The mean age was 76.7 (SD 8.3) years and 53% were female. From these patients, in total 8,073 alerts were generated, of which 7,907 (97.9% of total) were handled by the pharmacist (day one). The patient characteristics and subdivision of the clinical alerts per category and subdivision whether the pharmacist performed or did not perform an action are described in Table 6.1. The percentages of actions performed varied between the different rule categories from 33.8% (opioids/laxatives) to 94% (anticoagulant therapy), respectively (Table 6.1).

In 4,083 (51.6%) of the handled alerts an action was performed by the pharmacist, resulting in 1,297 (36.1% after excluding unknown) resolved alerts after day one, while when the pharmacist did not perform an action, which was the case in 3,824 alerts, 915 (27.3% after excluding unknown) alerts were resolved (36.1% vs. 27.3 %, P<0.001). These results are schematically summarized in Figure 6.1.

For the evaluation of day three, 5,750 handled alerts were analysed. In 3,025 (52.6%) alerts an action by the pharmacist was performed, resulting in 1,242 (62.4% after excluding unknown) resolved alerts after day three, while when no action was performed, which was the case in 2,725 alerts, 772 (48.0% after excluding unknown) alerts were resolved (62.4% vs. 48.0%, P<0.001). These results are schematically summarized in Figure 6.2.

Table 6.1 Baseline characteristics.

Characteristics		
Unique patients (n=3,754)		
Age, mean (SD), years	76.7 (8.3)	
Male sex, n (%)	1,764 (47.0)	
Clinical alerts - handled -	Day one	Day three
Total	7,907 (100)	5,750 (100)
Rule category, n (%)		
Renal Function	2,865 (36.2)	1,730 (30.1)
Potassium	2,417 (30.6)	1,748 (30.4)
Antibiotics [Intravenous to Oral]	446 (5.6)	382 (6.6)
Antibiotics [Long antibiotics use]	366 (4.6)	338 (5.9)
Opioids/Laxatives	225 (2.8)	206 (3.6)
Anticoagulant therapy	587 (7.4)	412 (7.2)
Unknown laboratory value	1,001 (12.7)	934 (16.2)
All actions by pharmacist	4,083 (51.6)	3,025 (52.6)
*Rules per category with action by pharmacist, n (%)**		
Renal Function	1,221 (42.6)	815 (47.1)
Potassium	1,519 (62.8)	1,106 (63.3)
Antibiotics [Intravenous to Oral]	197 (44.2)	164 (42.9)
Antibiotics [Long antibiotics use]	160 (43.7)	151 (44.7)
Opioids/Laxatives	76 (33.8)	70 (34.0)
Anticoagulant therapy	552 (94.0)	389 (94.4)
Unknown laboratory value	358 (35.8)	330 (35.3)

* Percentage is the number of actions by pharmacists divided by the number of clinical rule alerts per category. The denominator is the number of clinical rule alerts per category

Rule categories

When we analysed the different rule categories separately, we found that only in the category 'renal function' the percentages differed significantly between an action vs. no action of the pharmacist (16.6% vs. 10.6%, P<0.001). In other rule categories, we observed small positive effects when an action was performed by the pharmacist i.e. in the categories potassium, antibiotics (both IV to oral and long antibiotics use) and anticoagulants therapy, however these differences did not differ statistically significant (Figure 6.3).

On day three, similar results were observed, with only in the category 'renal function' a significant difference between those with and without an action of the pharmacist (29.8 % vs. 19.4%, P<0.001) (Figure 6.4).

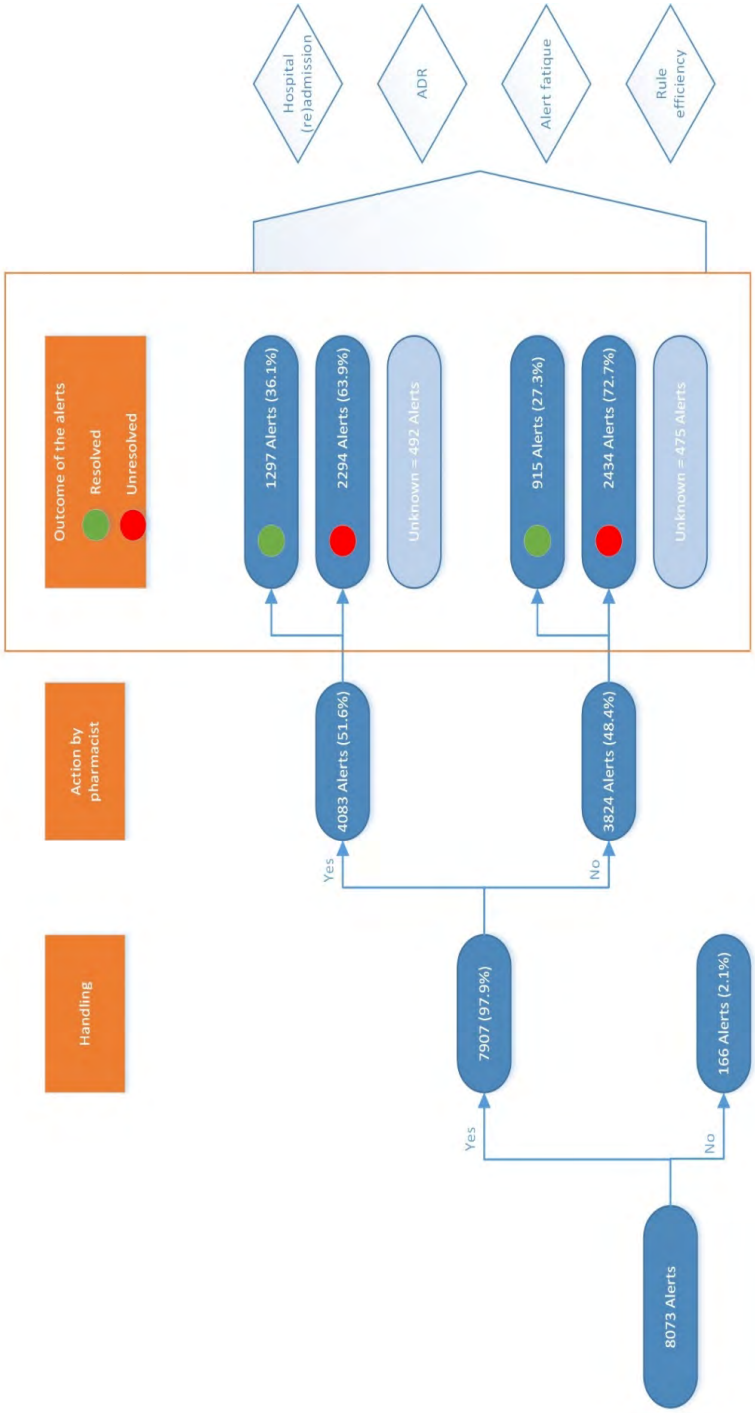


Figure 6.1 Schematic overview of alerts trajectories and outcome of the alerts (day one). The orange frame represents a knowledge gap that is not studied in other studies on this subject.

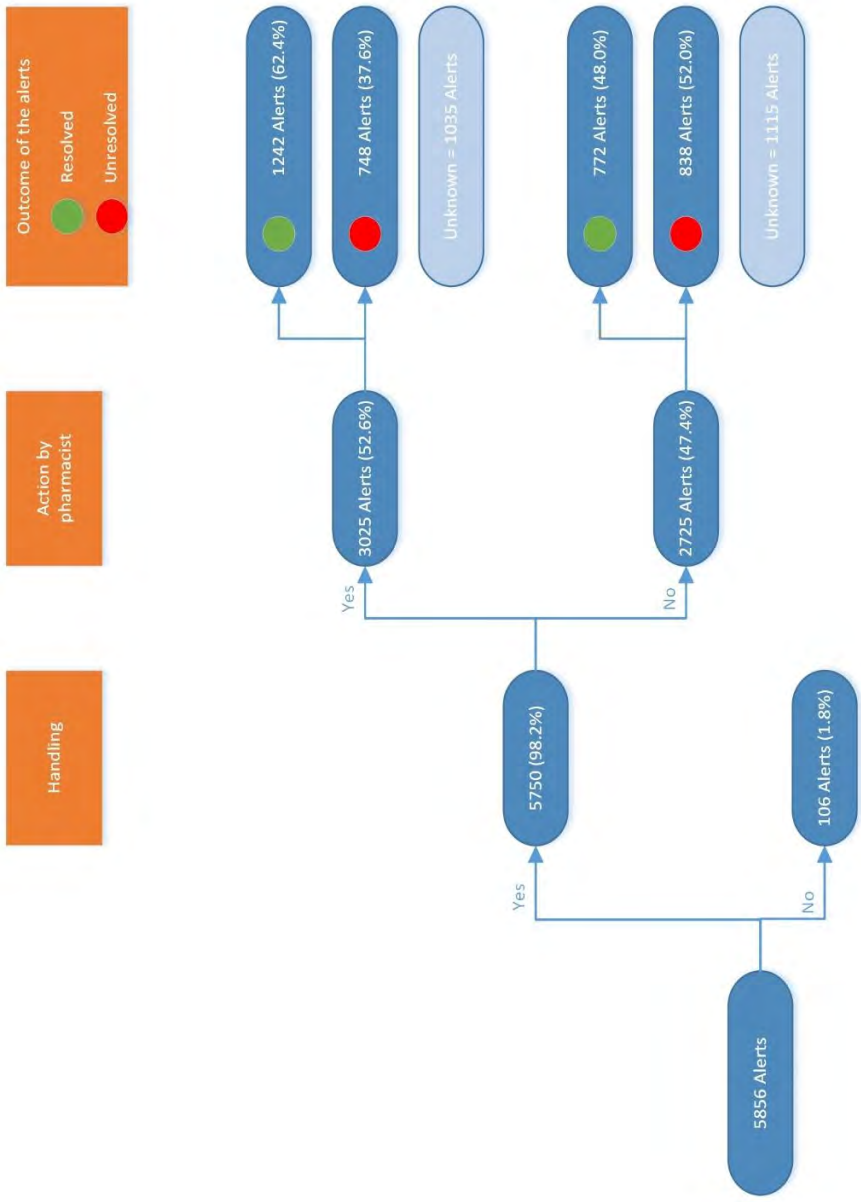


Figure 6.2 Schematic overview of alerts trajectories and outcome of the alerts (day three).

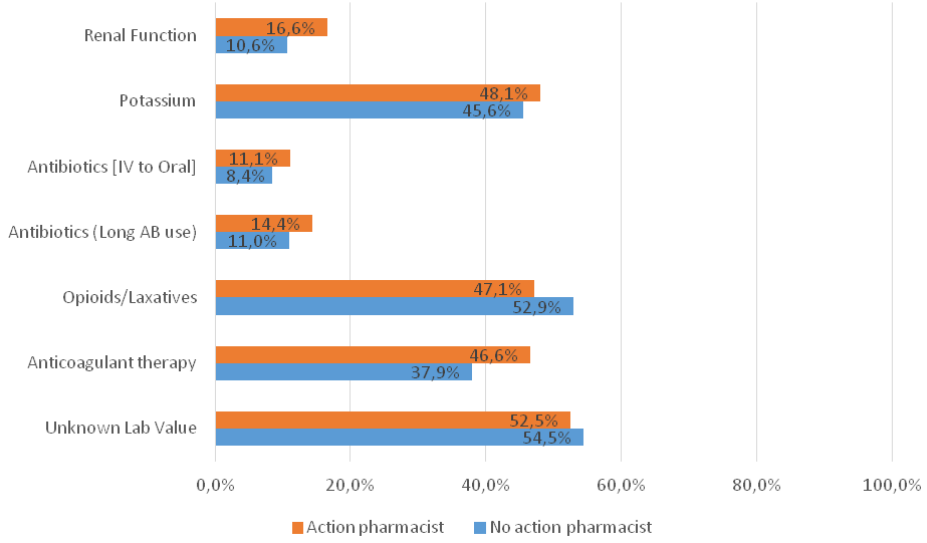


Figure 6.3 Number of 'positive' outcome alerts per clinical rule category divided per action by pharmacist day one. * P-value <0.001.

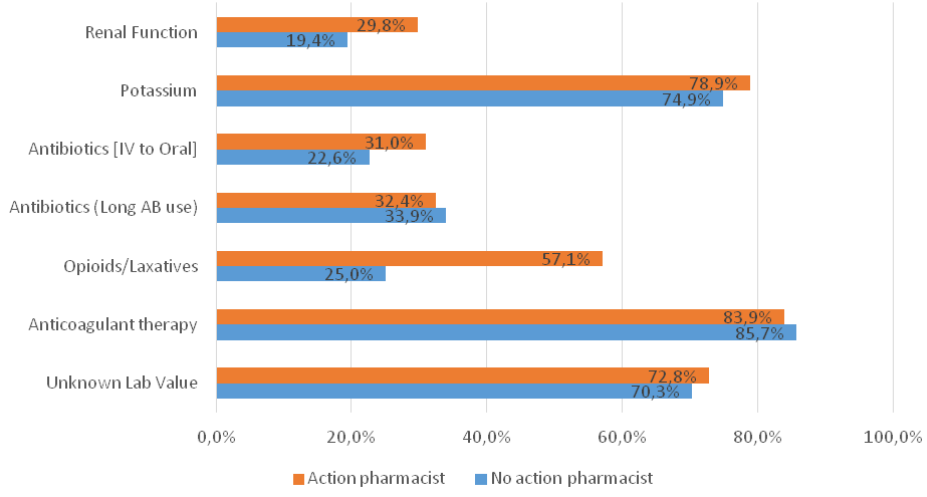


Figure 6.4 Number of 'positive' outcome alerts per clinical rule category divided per action by pharmacist day three. * P-value <0.001.

Discussion

This study demonstrates the real-life pattern and natural course of clinical alerts of an in-hospital implemented CDSS. As such, we have shown that when the pharmacist did not perform an action, 27% and 48% of the generated alerts are resolved after one and three days, respectively. These percentages improved to 36% and 62% on day one and three, when an action by the pharmacist was performed. Also, we found that the percentages of resolved alerts varied widely between different rule categories.

The finding that actions taken by pharmacists in response to the generated alerts were beneficial and led to an improved total number of resolved alerts was not surprising, since this has been studied extensively in the past[20,21]. However, this study reveals that many alerts are resolved without a specific intervention by the pharmacist. Our study therefore may provide important insight in the null effect of CDSS in the OPERAM, SENATOR trials, since alerts that are resolved without intervention are also addressed per usual care and therefore are unlikely to improve clinical outcomes[3,12]. We speculate that these "false positive" alerts may distract from potentially more clinically relevant alerts and therefore lead to a reduced effect of CDSS interventions. We believe that the CDSS may be particularly useful for rare MRPs with for instance uncommon high risk medications, and that therefore the initial clinical trials may have been underpowered to detect the impact of a CDSS on these events.

Our observational study shows some reassuring findings, given the total number of resolved alerts on one hand, but also the total number of resolved alerts in specific categories on the other hand, which are generally considered as more clinically relevant. Most notably, are the number of resolved 'anticoagulant therapy' and 'potassium' alerts, which may indicate that clinicians themselves are perfectly able to determine the clinical relevance and also prioritization of these alerts. This is moreover substantiated by the low number of resolved 'opioid + laxative' alerts, an otherwise clinically relevant recommendation, which is likely to have been deemed as of lower priority in the acute setting.

The discrepancy in acceptance of recommendations between our real-life clinical data and data from recent trials may be explained by several factors. First, in the two largest clinical trials to date, START/STOPP recommendations were used and therefore alert fatigue may have occurred due to lower prioritization of otherwise clinically relevant recommendations[3,12,14,15]. This observation contrasts to our set of clinical rules that are largely directly clinically relevant and also of more priority in the hospital setting, although our figures also show that clinicians seem to be perfectly able to prioritize this themselves. Second, variable attitudes towards the interventions itself (both OPERAM and SENATOR: software generated recommendations) or participating in trials by investigators or participants might have played a role, while when implemented in

clinical practice these factors play no significant role. Third, in the SENATOR trial, specific exclusion criteria, such as admission to a geriatric ward, were applied that not only limit the generalizability of the findings, but also excluded a large proportion of the population concerned, namely the geriatric population[12,22]. Nevertheless, since OPERAM had only minimal exclusion criteria, it is unlikely this explains this discrepancy completely[3,23].

We have shown that different rule categories show varying percentages of resolved alerts. When investigating the impact of computerized interventions, acceptance rates (or agreement with recommendations) vary widely between different studies and interventions[7]. Recommendations may be not accepted by clinicians as the recommendation might be deemed of low clinical relevance, patients insists on medication continuation or that possible interactions will be monitored, instead of direct medication discontinuation[7,24-26].

Our study has several strengths and limitations. Strengths include the large sample size of 3,754 unique patients and real-life clinical setting of an already implemented CDSS. Our study also has some limitations. First, our definition of 'action taken by the pharmacist' is broad, because we defined 'an action taken by the pharmacist' when a rule was discussed extensively (i.e. consultation between pharmacist and physician) or when an intervention was performed by the pharmacist or the physician (after consultation). This might increase the effect of the pharmacist, because a part of the interventions of the pharmacist was already performed by the physician. Second, our study is limited by its retrospective and observational design. Third, in 2018 our CDSS only consisted of 80 clinical rules. As such, clinically relevant, but also well-known rules (such as START/STOPP) have not been included in this version of the CDSS, making this study difficult to interpret in the current field of studies investigating generic CDSSs. Fourth, although this is a relatively large study, we only had access to a limited set of clinical data and were therefore unable to investigate the impact of clinical predictors on the percentage of alerts resolved. Despite this, we have included a cohort of patients in which MRPs are of particular interest, namely the geriatric population, often excluded in clinical trials.

Conclusion

This study demonstrates the pattern and natural course of clinical alerts of an in-hospital implemented CDSS in a real-life clinical setting of hospitalized older patients. Next to the beneficial effect of actions by pharmacists, we have also shown that many alerts are resolved without specific interventions. As such, our study provides insight in the spontaneous course of resolved alerts, since these data are currently lacking in the literature. Further research is needed to completely understand the effectiveness of CDSS interventions and our proposed 'natural course of clinical alerts' may be an important parameter in assessing the quality of clinical rules and thereby a potential target to optimize CDSS.

References

1. Fortin M, Hudon C, Haggerty J, Akker Mv, Almirall J. Prevalence estimates of multimorbidity: a comparative study of two sources. BMC Health Serv Res. 2010;10:111.
2. Aubert CE, Streit S, Da Costa BR, Collet TH, Cornuz J, Gaspoz JM et al. Polypharmacy and specific comorobidities in university primary care settings. Eur J Intern Med 2016; 35:35-42.
3. Blum MR, Sallevelt B, Spinewine A, O'Mahony D, Moutzouri E, Feller M et al. Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults (OPERAM): cluster randomised controlled trial. Bmj. 2021;374:n1585.
4. Thorell K, Midlöv P, Fastbom J, Halling A. Importance of potentially inappropriate medications, number of chronic conditions and medications for the risk of hospitalisation in elderly in Sweden: a case-control study. BMJ Open. 2019;9(9):e029477.
5. Luttikhuis HM, Blomaard LC, van der Kaaij MAE, Gombert-Handoko KB, de Groot B, Mooijaart SP. Geriatric characteristics and the risk of drug-related hospital admissions in older Emergency Department patients. Eur Geriatr Med. 2022;13(2):329-337.
6. Haag JD, Bellamkonda VR, Perinpam L, Peters BJ, Sunga KL, Gross CL et al. Prevalence and Categorization of Drug-Related Problems in the Emergency Department. J Emerg Med. 2022;63(2):192-199.
7. Dalton K, O'Brien G, O'Mahony D, Byrne S. Computerised interventions designed to reduce potentially inappropriate prescribing in hospitalised older adults: a systematic review and meta-analysis. Age Ageing. 2018;47(5):670-678.
8. Page RL 2nd, Linnebur SA, Bryant LL, Ruscin JM. Inappropriate prescribing in the hospitalized elderly patient: defining the problem, evaluation tools, and possible solutions. Clin Interv Aging. 2010;5:75-87.
9. Rankin A, Cadogan CA, Patterson SM, Kerse N, Cardwell CR, Bradley MC et al. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst Rev. 2018;9(9):CD008165.
10. Mulder-Wildemors LGM, Heringa M, Floor-Schreudering A, Jansen PAF, Bouvy ML. Reducing Inappropriate Drug Use in Older Patients by Use of Clinical Decision Support in Community Pharmacy: A Mixed-Methods Evaluation. Drugs Aging. 2020;37(2):115-123.
11. O'Sullivan D, O'Mahony D, O'Connor MN, Gallagher P, Cullinan S, O'Sullivan R et al. The impact of a structured pharmacist intervention on the appropriateness of prescribing in older hospitalized patients. Drugs Aging. 2014;31(6):471-481.
12. O'Mahony D, Gudmundsson A, Soiza RL, Petrovic M, Cruz-Jentoft AJ, Cherubini A et al. Prevention of adverse drug reactions in hospitalized older patients with multi-morbidity and polypharmacy: the SENATOR* randomized controlled clinical trial. Age Ageing. 2020;49(4):605-614.
13. Sallevelt BTGM, Huibers CJA, Heij JMJO, Egberts TCG, van Puijenbroek EP, Shen Z et al. Frequency and Acceptance of Clinical Decision Support System-Generated STOPP/START Signals for Hospitalised Older Patients with Polypharmacy and Multimorbidity. Drugs Aging. 2022;39(1):59-73.
14. Dalton K, O'Mahony D, Cullinan S, Byrne S. Factors Affecting Prescriber Implementation of Computer-Generated Medication Recommendations in the SENATOR Trial: A Qualitative Study. Drugs Aging. 2020;37(9):703-713.
15. Dalton K, Curtin D, O'Mahony D, Byrne S. Computer-generated STOPP/START recommendations for hospitalised older adults: evaluation of the relationship between clinical relevance and rate of implementation in the SENATOR trial. Age Ageing. 2020;49(4):615-621.
16. O'Sullivan D, O'Mahony D, O'Connor MN, Gallagher P, Gallagher J, Cullinan S et al. Prevention of Adverse Drug Reactions in Hospitalised Older Patients Using a Software-Supported Structured Pharmacist Intervention: A Cluster Randomised Controlled Trial. Drugs Aging. 2016;33(1):63-73.
17. Olakotan OO, Mohd Yusof M. The appropriateness of clinical decision support systems alerts in supporting clinical workflows: A systematic review. Health Informatics J. 2021;27(2):14604582211007536.
18. de Wit HA, Hurkens KP, Mestres Gonzalvo C, Smid M, Sipers W, Winkens B et al. The support of medication reviews in hospitalised patients using a clinical decision support system. Springerplus. 2016;5(1):871.

19. de Wit HA, Mestres Gonzalvo C, Cardenas J, Derijks HJ, Janknegt R, van der Kuy PH et al. Evaluation of clinical rules in a standalone pharmacy based clinical decision support system for hospitalized and nursing home patients. Int J Med Inform. 2015;84(6):396-405.
20. Arvisais K, Bergeron-Wolff S, Bouffard C, Michaud AS, Bergeron J, Mallet L et al. A Pharmacist-Physician Intervention Model Using a Computerized Alert System to Reduce High-Risk Medication Use in Elderly Inpatients. Drugs Aging. 2015;32(8):663-670.
21. Bankes D, Pizzolato K, Finnel S, Awadalla MS, Stein A, Johnson J et al. Medication-related problems identified by pharmacists in an enhanced medication therapy management model. Am J Manag Care. 2021 Sep;27(16 Suppl):S292-S299.
22. Lavan AH, O'Mahony D, Gallagher P, Fordham R, Flanagan E, Dahly D et al The effect of SENATOR (Software ENgine for the Assessment and optimisation of drug and non-drug Therapy in Older peRsons) on incident adverse drug reactions (ADRs) in an older hospital cohort - Trial Protocol. BMC Geriatr. 2019;19(1):40.
23. Adam L, Moutzouri E, Baumgartner C, Loewe AL, Feller M, M'Rabet-Bensalah K et al. Rationale and design of OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people (OPERAM): a cluster randomised controlled trial. BMJ Open. 2019;9(6):e026769.
24. Griffey RT, Lo HG, Burdick E, Keohane C, Bates DW. Guided medication dosing for elderly emergency patients using real-time, computerized decision support. J Am Med Inform Assoc. 2012;19(1):86-93.
25. Terrell KM, Perkins AJ, Dexter PR, Hui SL, Callahan CM, Miller DK. Computerized decision support to reduce potentially inappropriate prescribing to older emergency department patients: a randomized, controlled trial. J Am Geriatr Soc. 2009;57(8):1388-1394.
26. Mattison ML, Afonso KA, Ngo LH, Mukamal KJ. Preventing potentially inappropriate medication use in hospitalized older patients with a computerized provider order entry warning system. Arch Intern Med. 2010;170(15):1331-1336.

Supplementary table

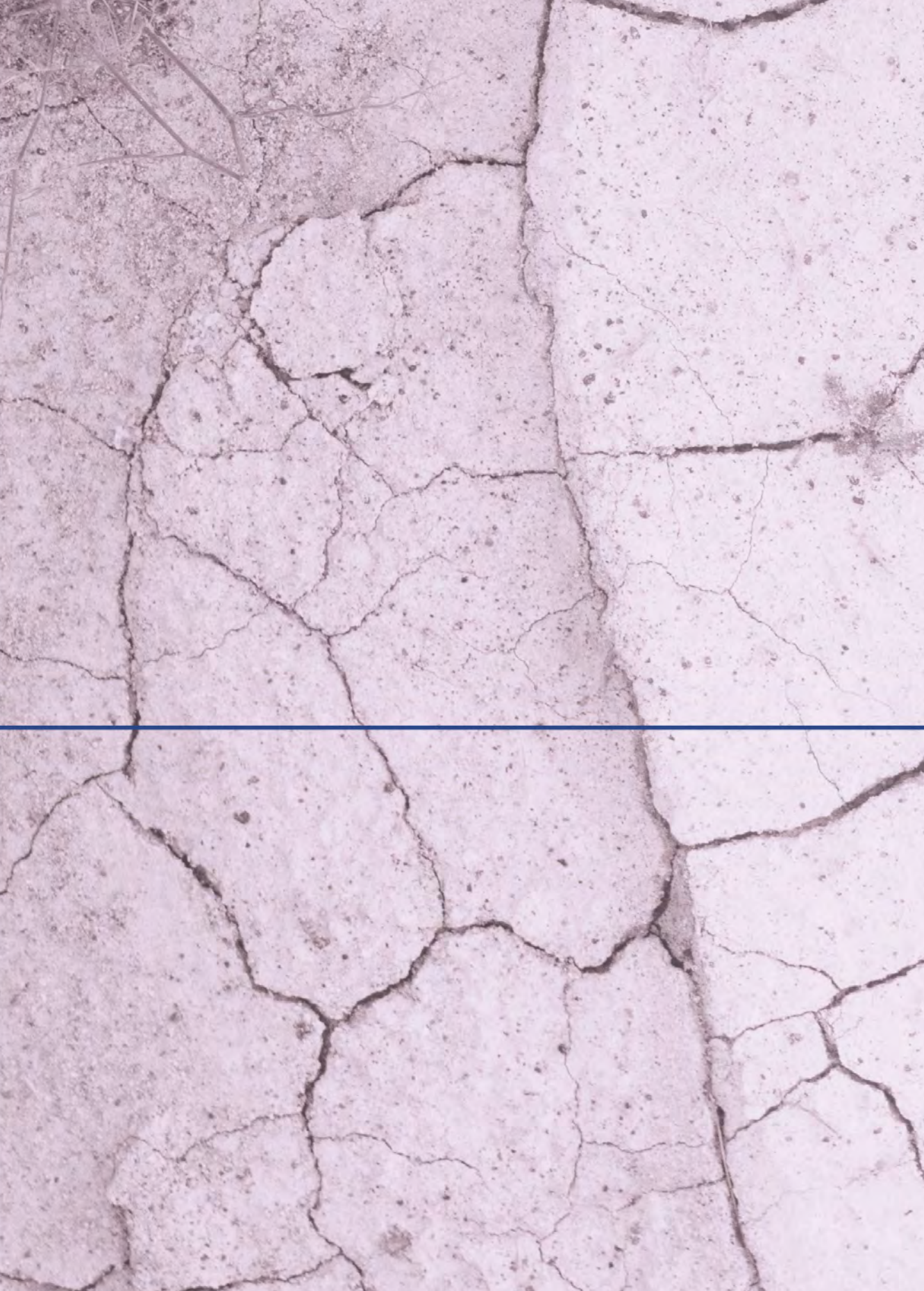
Table S6.1 Overview of the clinical rules.

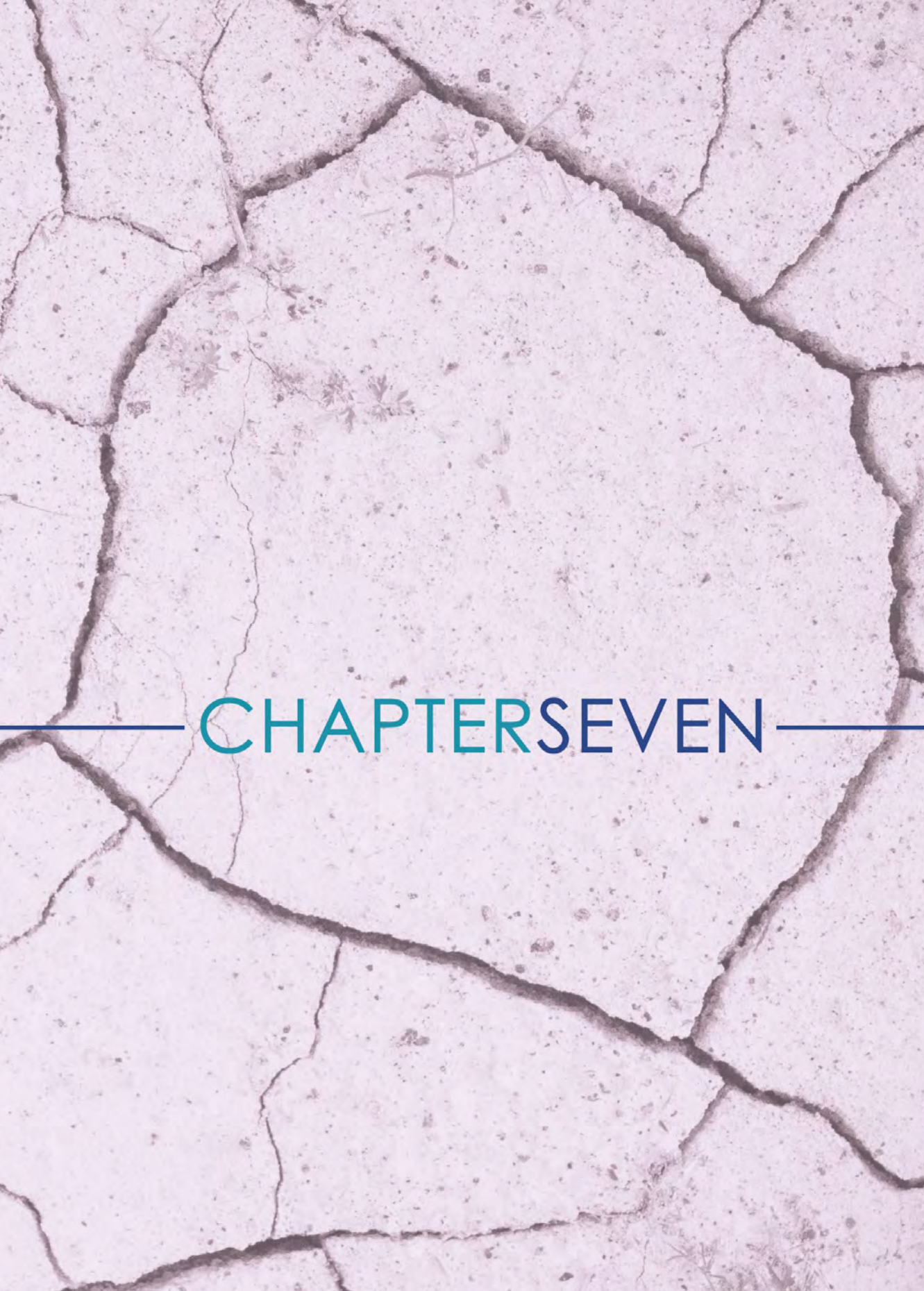
	Title of the rule
1	Anticoagulation therapy and INR
2	Intravenous to oral antibiotic switch therapy - Amoxicillin and beta-lactamase inhibitor
3	Intravenous to oral antibiotic switch therapy - Benzyl penicillin
4	Intravenous to oral antibiotic switch therapy - Cefuroxime
5	Intravenous to oral antibiotic switch therapy - Clindamycin
6	Intravenous to oral antibiotic switch therapy - Erythromycin
7	Intravenous to oral antibiotic switch therapy - Flucloxacillin
8	Intravenous to oral antibiotic switch therapy - Levofloxacin
9	Intravenous to oral antibiotic switch therapy - Rifampicin
10	Intravenous to oral antibiotic switch therapy - Amoxicillin
11	Intravenous to oral antibiotic switch therapy - Ciprofloxacin
12	Intravenous to oral antibiotic switch therapy - Doxycycline
13	Intravenous to oral antibiotic switch therapy - Fluconazole
14	Intravenous to oral antibiotic switch therapy - Metronidazole
15	Intravenous to oral antibiotic switch therapy - Moxifloxacin
16	Intravenous to oral antibiotic switch therapy - Sulfamethoxazole and trimethoprim
17	Long use antibiotic therapy
18	MDRD required
19	Melphalan with specific resting period
20	Methotrexate weekly use
21	Opioids without laxative agents
22	Potassium levels
23	Potassium levels + Digoxin
24	Renal dysfunction + Aciclovir - Oral
25	Renal dysfunction + Acipimox
26	Renal dysfunction + Alendronic acid
27	Renal dysfunction + Amantadine
28	Renal dysfunction + Amoxicillin
29	Renal dysfunction + Apixaban
30	Renal dysfunction + Barnidipine
31	Renal dysfunction + Benzyl penicillin
32	Renal dysfunction + Carbasalate calcium
33	Renal dysfunction + Cefazolin
34	Renal dysfunction + Cefotaxime
35	Renal dysfunction + Ceftazidime
36	Renal dysfunction + Cefuroxime
37	Renal dysfunction + Cetirizine
38	Renal dysfunction + Chloroquine
39	Renal dysfunction + Chlortalidone
40	Renal dysfunction + Cimetidine
41	Renal dysfunction + Ciprofloxacin - intravenous
42	Renal dysfunction + Ciprofloxacin - Oral
43	Renal dysfunction + Co-amoxiclav
44	Renal dysfunction + Colchicine
45	Renal dysfunction + Dabigatran etexilate
46	Renal dysfunction + Fluconazole
47	Renal dysfunction + Ganciclovir
48	Renal dysfunction + Hydroxychloroquine
49	Renal dysfunction + Lacosamide

Table S6.1 (continued)

	Title of the rule
50	Renal dysfunction + Levetiracetam
51	Renal dysfunction + Levocetirizine
52	Renal dysfunction + Levofloxacin
53	Renal dysfunction + Lithium
54	Renal dysfunction + Memantine
55	Renal dysfunction + Meropenem
56	Renal dysfunction + Metformine
57	Renal dysfunction + Midazolam
58	Renal dysfunction + Nitrofurantoin
59	Renal dysfunction + Norfloxacin
60	Renal dysfunction + Ofloxacin
61	Renal dysfunction + Oseltamivir
62	Renal dysfunction + Paliperidone
63	Renal dysfunction + Piperacillin and beta-lactamase inhibitor
64	Renal dysfunction + Piracetam
65	Renal dysfunction + Pramipexole
66	Renal dysfunction + Risperidone
67	Renal dysfunction + Rivaroxaban
68	Renal dysfunction + Rosuvastatin
69	Renal dysfunction + Solifenacin
70	Renal dysfunction + Sotalol (o)
71	Renal dysfunction + Sotalol (p)
72	Renal dysfunction + Sucralfate
73	Renal dysfunction + Teicoplanin
74	Renal dysfunction + Terbinafine
75	Renal dysfunction + Tetracycline
76	Renal dysfunction + Tranexamic acid
77	Renal dysfunction + Valaciclovir
78	Renal dysfunction + Varenicline
79	Renal dysfunction + Venlafaxine
80	Unknown potassium serum level

INR, International Normalized Ratio; MDRD, Modification of Diet in Renal Disease-formula to calculate the estimated Glomerular Filtration Rate (eGFR).




CHAPTERSEVEN

Chapter 7

General discussion and summary

General discussion and summary

With the ageing of the population and the resulting increase in multimorbidity, a notable consequence is the rise in hospital admissions and readmissions of (frail) older individuals[1]. It has been estimated that approximately 10-30% of these hospitalizations and readmissions are medication-related, of which about 50% could have been prevented[2-4]. Therefore, it is important to gain insight into several aspects regarding the in-hospital management and follow-up care of older individuals in general, with a specific focus on medication-related problems. These insights are crucial not only for enhancing their health outcomes but also for mitigating the occurrence of readmissions, medication-related problems and other adverse health outcomes. Moreover, these insights are also essential for overseeing healthcare expenditures and alleviating the economic burden in the future.

As described in **Chapter 1,** the main aim of this thesis was to address critical knowledge gaps within real-life clinical contexts, offering initiatives to enhance in-hospital management and optimize medication strategies for older, frail individuals. This approach extends beyond the scope of conventional clinical trials, aiming to provide a comprehensive perspective on addressing the difficulties linked with this specific demographic shift. The specific knowledge gaps that have been studied are presented in **Figure 7.1**, that visualizes an overview of the entire thesis.

In this chapter, we begin by summarizing the main results of each chapter and discuss them while integrating information from different chapters and literature. Finally, methodological aspects will be highlighted, overarching conclusions will be drawn and we will offer insights into potential future directions.

In-hospital management

In **Chapter 2**, we investigated the implementation of a Nurse Practitioner-led Orthogeriatric Care Program (NPOCP), which is a comprehensive and multidisciplinary approach of care for the orthogeriatric population. As part of this program, a Comprehensive Geriatric Assessment (CGA) along with a medication review was conducted for all admitted patients. Additionally, both nurse practitioners and the orthopaedic surgeon conducted regular daily rounds for the included patients. The effectiveness of this intervention was compared against standard usual care (UC). As such, we have shown that the intervention group (NPOCP group) exhibited a statistically significant reduction in both 3-month and 1-year mortality rates. Specifically, the 3-month mortality rate decreased to 9.0% [95%CI: 4.9–14.9%], and the 1-year mortality rate decreased to 13.9% [95%CI: 8.7–20.6%], as compared to 24.4% [95%CI: 17.9-31.9%] and 34.0% [95%CI: 26.6–42.0%] for the UC group, respectively (both $P<0.001$).

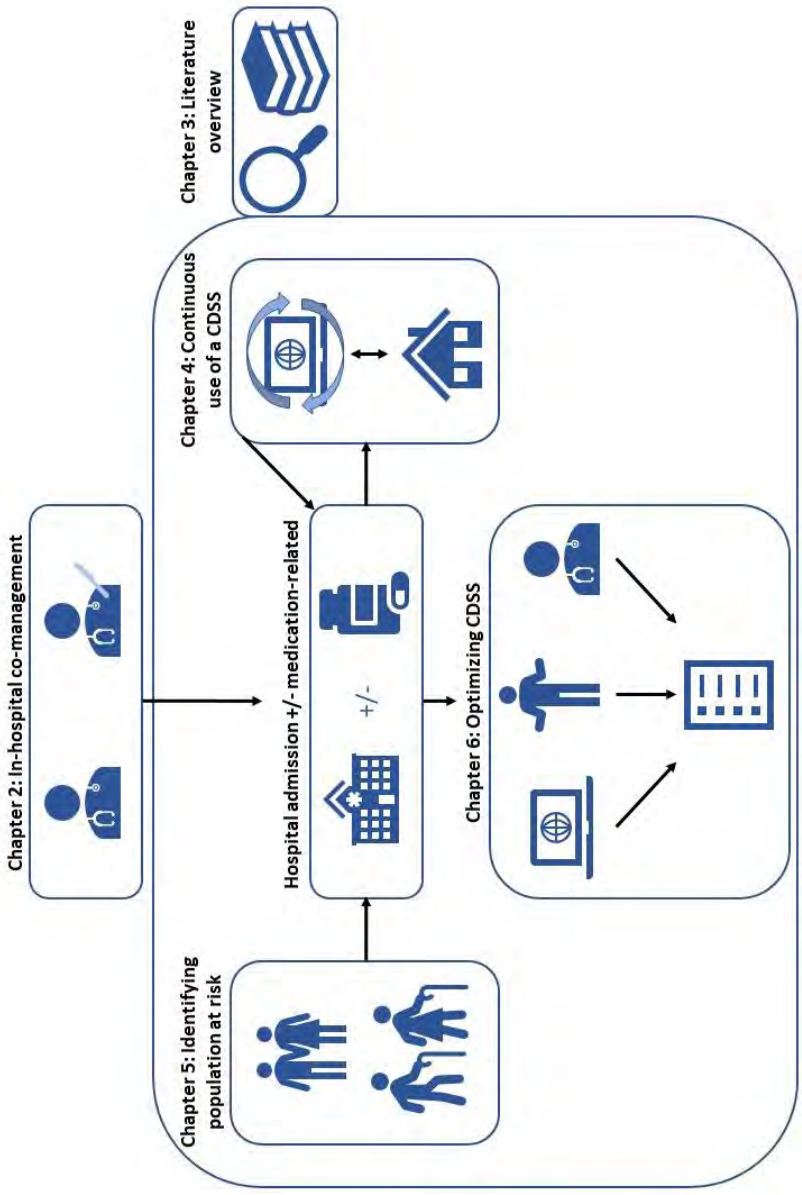


Figure 7.1 Summary of the chapters included in this thesis. CDSS: Clinical Decision Support Systems.

Furthermore, we found a higher detection rate of complications and comorbidities in the NPOCP group, suggesting a possible mechanism of action. Our findings align with similar studies that highlight reduced mortality rates upon introducing co-management protocols for hip fracture patients[5-8].

Another pivotal aspect of NPOCP was considered the optimization of medication, which included appropriate prescribing and deprescribing practices. Changes made during hospitalization were effectively communicated to the general practitioners (GPs) through a written medication list upon discharge that was included in the discharge letter. Nevertheless, we were unable to investigate this in further detail and upon follow-up in the outpatient clinic we observed more than once that previously discontinued medications were automatically resumed, underscoring the urgency of improving medication oversight and ensuring smooth communication between in-hospital and outpatient care settings. Previous studies on this topic, for instance on the initiation of osteoporosis medication, showed that in patients who received orthogeriatric co-management significantly higher rates of osteoporosis medication was prescribed[7,9]. However, within these and other studies, there was no significant difference in the risk of recurrent fractures over the course of one year[7,9,10]. These findings should stimulate to extend future research beyond mortality rates and also include other clinically relevant outcome measures, such as readmissions, functional status and quality of life.

Medication-related admissions and readmissions

In **Chapter 3**, we performed a literature review regarding what is known about medication-related admissions and readmissions, their risk factors, and possible interventions which reduce medication-related hospital (re)admissions. As such, we have observed a wide variation in the incidence of medication-related hospital admissions, ranging from 0.5% to 19.3%[11-13]. This difference is often related to the varying definitions used in the different studies. Furthermore, the incidence of medication-related hospital readmissions has an even broader range, namely 8.7% to 64.0%, illustrating the difficulty of capturing this 'entity'[4,14]. The most important identified risk factors for medication-related (re)admissions were not surprising as high-risk medication (such as anticoagulants, antiplatelet drugs, vasodilators, psychotropic medications and diuretics), polypharmacy, therapy non-adherence, older age, comorbidities, renal disease, congestive heart failure, cognitive impairment and hospital length of stay were already known to be associated with medication-related (re)admission[3,15-20]. Another aspect that contributes to the wide variety of incidence figures is the fact that there is (next to the definition) substantial heterogeneity in study populations, interventions and methodologies[21-23]. Study populations often differ with regard to age, co-morbidities and settings, while the interventions frequently investigated to prevent medication-related

readmissions often involve medication reviews, but how they were performed and/or communicated was very different. Also, the type of professional which performed the medication review differed, as some were performed by a pharmacist, others by a geriatrician or a combination[24,25]. To conclude, there is considerable diversity in the methods of conducting these medication reviews and in the follow-up procedures. All of these aforementioned differences contribute to widely varying outcomes and results.

A recent meta-analysis indeed confirms that there is no intervention proven to demonstrate a reduction in readmissions following the implementation of a standalone medication review[26]. However, when a medication review is integrated with comprehensive education, medication verification, and effective transition of care, a positive impact on readmission rates seems to emerge[26]. It is postulated that the one-time medication review is insufficient, due to factors such as the "shelf life" of a medication review, which could be enhanced through education, verification, and transition of care[27]. The consistency of medication reviews can vary, and this inconsistency, along with the growing complexity arising from increased polypharmacy and multimorbidity, is why there has been increasing research into the potential added value of Clinical Decision Support Systems (CDSS) in recent years[28,29]. This is often seen as complementary to manual medication reviews. Furthermore, research has been conducted on the repetitive use of CDSS, but this was typically limited to the hospital stay without subsequent follow-up in the primary care setting[30,31]. Given the limited literature on the frequent and repetitive use of CDSS, as it is often employed only sporadically, we have developed a study to investigate whether weekly deployment of a CDSS will reduce readmissions within 1 year. Chapter 4 describes therefore the CHECkUP (Control in the Hospital by Extensive Clinical rules for Unplanned hospitalizations in older Patients) study protocol. This study aims to decrease readmissions within one year through a weekly medication review utilizing a CDSS, with recommendations sent to GPs and/or pharmacists. For this study, patients aged 60 years or older with an unplanned hospital admission are included. In addition, the inclusion criteria are polypharmacy (defined as the use of five or more medications), and patients had to have two triggers from the triggerlist[32]. With these patient characteristics, the goal was to select a high-risk population for medication-related admissions.

The triggerlist is included in the Dutch guideline on polypharmacy and was developed in order to raise awareness for identifying patients with medication-related admissions since there is likely an underreporting of the number of medication-related admissions[32]. The triggerlist is based on a list where the triggers, or the reasons for admission, pose an increased risk of medication-related admissions[32]. These triggers are then linked to medications that are often the cause of these specific admission reasons. In the current literature, the use of this triggerlist is not commonly employed for identifying medication-related admissions or for identifying patients at a heightened risk of medication-related admissions. It has been used in the setting of the emergency

department (ED), were it was used to identify whether ED visits (without admission) were medication-related[33]. This study investigated ED visits in older adults aged 70 and older without admission, they concluded that 23% were potentially medication-related based on the triggerlist[33].

After inclusion in CHECkUP, the patients are randomized into the intervention group or the control group. In the intervention group, a weekly medication assessment via the CDSS is performed, and when there are recommendations, they are sent to GPs and/or pharmacists. The control group receives standard care. The primary outcome measure is hospital readmission within one year after study inclusion. Secondary outcome measures include mortality within one year after study inclusion, number of ED visits, number of nursing home admissions, time to hospital readmission, and whether the readmission is medication-related or not. This study differs from other studies in that the CDSS assesses medication on a weekly basis for a duration of one year, providing a more thorough assessment and longer follow-up period for patients. However, this direct transmission of recommendations to GPs and/or pharmacists could also be a limitation of the study, as it adds extra workload to the general practitioner's or pharmacist's regular duties and may result in suboptimal timing, potentially leading to some alerts not being reviewed. Another limitation could be the quality of the CDSS rules, as it was primarily developed for hospital use and may not be sufficiently adapted for primary care.

Identifying high-risk older patients

In line with the growing challenges posed by an ageing population suffering from multiple chronic illnesses and their impact on healthcare expenditure, healthcare providers and policymakers are faced with the task of determining where to focus their efforts and allocate resources, especially in times when healthcare budgets are becoming more limited[34]. From a health economic perspective, it is therefore important to identify individuals who are at a high-risk of experiencing adverse health outcomes and for whom interventions could potentially be life- and cost saving and which may lead to more efficient healthcare delivery[35]. Therefore, it is essential to identify individuals who are at increased risk of being hospitalized due to medication-related issues. It is for this reason that in the CHECkUP study (protocol in **Chapter 4**) we are selecting patients aged 60 and older, with polypharmacy and two triggers from the triggerlist, in order to create a group in which patients have a high-risk of medication-related hospital admissions. Initially, this was a pragmatic and intuitive decision, likely to select patients at a higher risk of medication-related hospital admission. After inclusion of the first 100, patients we investigated whether this approach was adequate. As such, in **Chapter 5**, we examined whether adding the triggerlist contributes to the selection of high-risk patient groups. We selected the first 100 consecutive patients from the

CHECkUP study and assessed their hospital admissions using the AT-HARM10 tool, which showed that these patients could be identified as probable medication-related admissions in 48% of cases[36]. This percentage is significantly higher than the average percentage of medication-related admissions (5-20% in patients older than 70), which might indeed suggest that selecting patients by two triggers from the triggerlist identifies a high-risk population[3,37,38]. Furthermore, using these characteristics, i.e. age and triggerlist, not only can the group be quickly recognized, but the procedure can also be automated.

The CHECkUP study is not the first study attempting to select patients at high-risk of medication-related admissions. It is known that when selecting patients with risk factors for medication-related admissions, there is a higher percentage of medication-related admissions. Studies selecting patients with multimorbidity, or older patients with multimorbidity and polypharmacy, found an incidence of medication-related admissions of 38% and 42% respectively[39,40]. Although these patients exhibit an increased risk of medication-related admissions, our preference lies in selecting patients through the triggerlist because it can be automated based exclusively on medication data.

As previously mentioned, the definition of a medication-related admission varies, but so does the assessment of what qualifies as such an admission. Typically, a panel that includes pharmacologists or geriatricians evaluates an admission and its underlying reason to determine whether the admission is medication-related or not[3,41,42]. There are also tools available used to assess whether an admission is medication-related, such as the AT-HARM10 tool (which was also used in **Chapter 5**)[36]. This tool consists of ten questions, with three specifically designed to assess that the admission is probably not medication-related and seven questions designed to identify that the admission may be medication-related (possible medication-related admission). These questions can be easily answered by treating physicians and pharmacists, allowing for a relatively quick assessment of whether an admission is medication-related or not. However, it is not a tool easily automated for selecting a high-risk group, such as an ED or primary care setting.

Recently, a tool has been developed that lists 26 triggers to improve the identification of medication-related admissions in older adults[40]. This trigger tool was developed based on the OPERAM study, namely the drug-related admissions adjudication guide[40,43]. This trigger tool starts from the admission diagnosis and additional questions are asked from there to assess whether this admission is likely medication-related or not. Recent research using this tool to assess whether an admission is medication-related found a percentage of 15.6%[44]. Therefore, more tools have been developed to increase identification of medication-related admissions and raise awareness of this issue. It is certainly important to recognize medication-related admissions in order to try to

prevent admissions or other medication-related problems in these patients. Identifying this problem can be particularly challenging, especially in the older population.

Furthermore, in older adults, an ADE often manifests as a geriatric syndrome, adding complexity to the identification[40]. Nevertheless, the debate centres around whether the priority should be identifying medication-related admissions or proactively selecting a group with the highest likelihood of experiencing such admissions and readmissions, similar to the approach used for patients with cardiovascular risk factors who are already being treated and monitored according to cardiovascular risk management protocols[45]. Since we know that medication-related problems, including medication-related admissions, are frequent, it is imperative that we shift away from narrowly defining medication-related admissions. Instead, we should strongly prioritize future studies that aim to identify the population at highest risk of medication-related problems. It is important that this group is easily identifiable so that both primary and secondary care can quickly identify this group and provide the necessary care. As previously indicated in Chapter 5 of our study, the selection of patients aged 60 and older, with polypharmacy, and having two triggers from the triggerlist leads to a percentage of 48% for medication-related issues. This percentage is even higher than the previously mentioned 42% found in a group of older patients with multimorbidity and polypharmacy[40]. However, it is important to note that these groups were not examined simultaneously. Nevertheless, the advantage of this selection is its automation, allowing for the rapid identification of a patient group. However, this identification has not been validated yet and needs further development, but it may hold promise as potential future approach to select patients at high-risk of medication-related admissions and possibly other medication-related problems. The anticipation is that the interventions implemented to mitigate medication-related issues in this group will yield greater significance and effectiveness although additional research is required. This approach is applicable to both primary and secondary healthcare settings.

In conclusion, the near future should focus on developing a tool that can quickly select patients at high-risk of medication-related admissions, and interventions aimed at reducing medication-related readmissions, such as the previously mentioned medication review combined with education and medication verification, should be tested in this group. Comparing this approach to patients with a high cardiovascular risk, discussing the triggerlist, and automating the selection of high-risk patients for medication-related admissions in both primary and secondary care are essential considerations.

Improving CDSS

Recently, two major studies have been conducted to assess the effect of implementing a CDSS, namely the OPERAM and SENATOR trials, which evaluate the impact on readmissions within one year and adverse drug reactions (ADRs), respectively[43,46]. Both studies did not find a significant reduction in readmissions and ADRs with the use of a CDSS. Both investigations evaluated the use of the CDSS in combination with an one-time medication review. Possible explanations for this negative result include a low implementation of medication recommendations, specifically 15% and 39% in the SENATOR and OPERAM trials, respectively[43,46,47]. Additionally, in both studies, the medication review was conducted only once, which might have also influenced the results.

These studies did also assess how many of the recommendations generated by the CDSS were followed by the assessor; however, there is limited understanding of how to evaluate the quality of a CDSS, and there have been no studies published so far that demonstrate the routine daily use of a CDSS in practice[46,47].

In **Chapter 6**, we therefore investigated the use of a CDSS in daily practice and the impact of the pharmacist on the CDSS's outcomes. We observed that involvement of a pharmacist had a positive effect on the alert outcomes, with 36.1% of the alerts being resolved after day one when the pharmacist took action, compared to 27.3% when no pharmacist action was taken (P<0.001). On day three, in 52.6% of the alerts, a pharmacist's action was initiated, resulting in 62.4% of resolved alerts, compared to 48.0% when no action was taken (P<0.001). When we evaluated these results per category, we noticed that this effect was particularly significant in the category renal dysfunction, with 16,6% and 29.8% of the alerts being resolved after day one and day three respectively with an action of the pharmacist compared to 10.6% and 19.4% when no action was taken (both P<0.001). Another interesting finding was that the percentage of resolved rules varies significantly among all groups. Both findings suggest that an action by a pharmacist may not add value to every rule, and it also suggests that the number of resolved rules depends on the knowledge of the treating physicians in the clinic. High percentages of resolved rules were found in the "anticoagulant therapy" and "potassium" groups. This is likely due to the basic knowledge (and sense of urgency) of the clinicians because a significant number of rules gets resolved, and we also found no difference in percentages in these categories when the pharmacist took action[48,49]. These findings are important to consider in future research on evaluating the quality of a CDSS and to assess which rules are essential, as the goal is to create a scenario where each triggered rule offers enhanced value compared to standard care. In this particular scenario, you may choose to exclude the rules related to "potassium" and "anticoagulant therapy" from the CDSS because it does not enhance care but likely contributes to alert fatigue. Another way to look at it is considering the potential severity of side effects and

the negative outcomes of specific rules and then it might be advisable to retain them in the CDSS. To assess the effect of a CDSS, it is important to evaluate the quality of the CDSS. However, there is limited research on this topic, and this is the first study to examine the use of a CDSS in daily practice and the natural course of the rules without the intervention of an assessor on the rules. How to evaluate the quality of a CDSS is also not yet known. Figure 7.2 illustrates the factors influencing a CDSS.

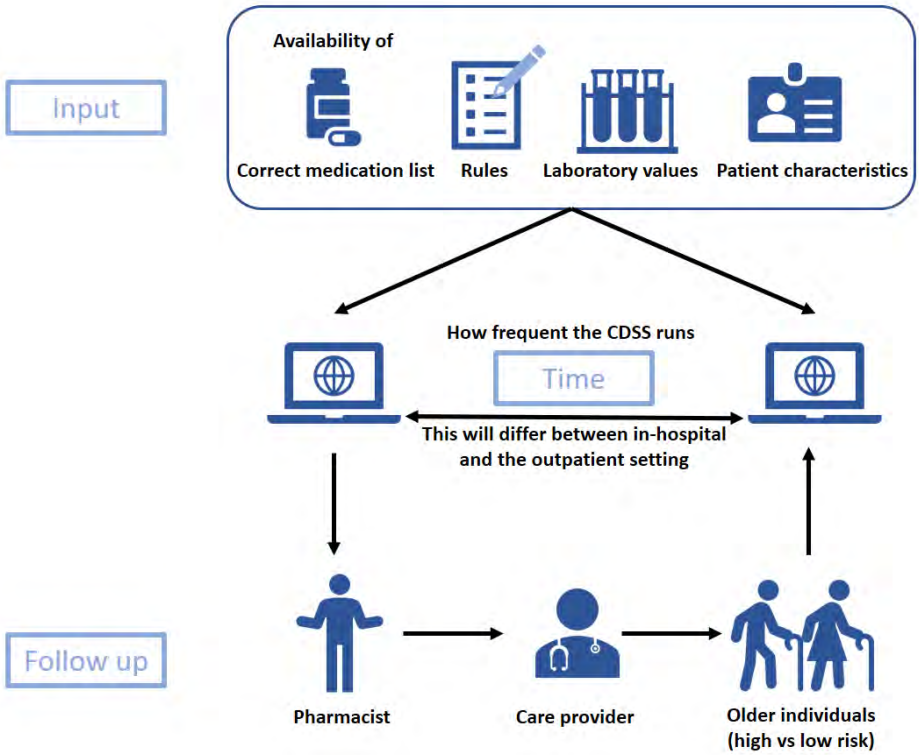


Figure 7.2 Influencing factors and improvement opportunities for CDSS; the figure represents use of CDSS in the inpatient as well as the outpatient setting. CDSS: Clinical Decision Support System.

The quality of a CDSS is determined by various factors, including the quality of the rules incorporated into the CDSS, the accuracy/precision of information such as laboratory results and other patient characteristics, the added value of a rule compared to the clinician's standard knowledge, the clinical relevance of a rule, and the potential severity of consequences if the medication adjustment is not implemented[48-51]. Finally, the frequency and follow-up of CDSS usage is important. Ideally, you want a situation in which the clinician receives alerts that directly impact the patient in most instances because not taking action would pose a risk to the patient or other compelling reasons for sending an alert due to exceptional medication adjustments that are not recognized

by all clinicians in regular care. In this regard, both categories could be prioritized differently. If every rule is clinically relevant, alert fatigue will decrease. Currently, the focus is mainly on whether the rule itself is clinically relevant (based on the opinion of the pharmacist or physician) and sometimes, clinical relevance is also assessed based on the pharmacist's handling. However, if clinicians always recognize this rule, it has no added value. Therefore, an approach must be developed to ensure that the pharmacist's assessment in combination with the CDSS always provides added value compared to the clinician alone.

The SENATOR trial has previously examined the factors contributing to non-compliance with rules. They found the following factors affecting the implementation of the recommendations: setting and timing of the recommendation, clinical relevance of the recommendations, the expertise and specialization of the prescriber, therapeutic relationship with the patient and the patient[48].

It is not yet known how to assess the quality of a CDSS. Additionally, consideration can be given to how often such a rule should be triggered. In the studies published so far, CDSSs were run only once, while in clinical practice, CDSSs are run daily, and in the CHECkUP study, it will be run on a weekly basis. Further research is needed to determine how often the CDSS should be run to achieve the most effective intervention, and this should be investigated in different settings, including primary care, secondary care, both in the clinical and outpatient settings.

Methodological considerations

The main strengths and limitations of the various studies included in this thesis have been discussed in their respective chapters. Nevertheless, before we can draw overarching conclusions about this work and consider future prospects, it is essential to engage in a broad reflection on methodology and the patient populations involved.

Each chapter of this thesis is based on different data, and from various perspectives, we have attempted to examine how we can improve care for older and frail individuals.
Although the older patient is central to this thesis, different inclusion criteria were used for the various studies. For example, in **Chapter 2**, patients aged 70 years and older were included, while in **Chapters 4-6,** patients aged 60 years and older were included. Nevertheless, although age limits vary in different studies when researching older adults, we mainly aimed at selecting the most vulnerable group to improve care, and by adding risk factors (depending on the subject), we attempted to select patients at high-risk of adverse outcomes.

Secondly, all the studies were conducted at a single centre. NPOCP was investigated at the Maastricht University Medical Centre (MUMC+) in Chapter 2, and the studies on medication-related admissions and the CDSS in Chapters 5 and 6 were conducted at the Zuyderland Medical Centre, both in the Netherlands. Since all our studies are single centre studies, the results may not be replicable to other hospitals. However, the focus is on older patients with issues that occur in all hospitals, and we are also investigating interventions that are part of standard or additional care. Therefore, we expect the results of these studies to be relevant and applicable to other hospitals.

Thirdly, it is important to note that all the studies conducted were retrospective and, to some extent, observational, grounded in an examination of routine clinical practices. An important limitation of this approach is that the effectiveness of the interventions is influenced in part by the competency and performance of healthcare providers and pharmacists during the study period, which are usually a (too) positive reflection of reality because of their engagement and interest in the subject, clinical care, and any potential study on this topic[52]. Single centre studies, observational designs and the analysis of real-world clinical scenarios introduce a degree of variability that may hinder direct reproducibility of the findings. Nevertheless, the advantage of investigating daily clinical practices is that it offers valuable insights into standard care procedures, and the knowledge gained from such research can promptly inform and facilitate improvements in healthcare delivery.

Fourthly, as also discussed in Chapter 3, there exists a substantial body of research on medication-related hospital admissions and readmissions, along with corresponding interventions and definitions. Nonetheless, this research landscape is marked by significant heterogeneity in study design and population. This makes it difficult to compare our study results with any other research. That being said, this brings us to another important topic, namely the lack of an universally accepted definition for identifying medication-related (re)admissions, and also the evaluation of CDSSs remains underexplored, with no established gold standard. However, we consider this topic so important that more research needs to be conducted. It would be better if the research became more homogeneous in terms of setting, population, and intervention. Our studies can serve as a stepping stone to help determine the most suitable setting, population, and intervention for future research in this area.

Conclusion and future perspectives

This thesis contributes to the knowledge on several aspects of the care for older individuals during hospital admission. With the ageing of the population, it is crucial to enhance the care for older individuals and assess the quality of care. Additionally, it is important to determine which patients stand to benefit the most. In this thesis, we

examined in-hospital management, medication-related admissions, and the use of a CDSS. We demonstrated (I) that implementing a NPOCP for patients with a hip fracture leads to significantly lower one-year mortality rates, (II) a clear definition for medication-related admissions is lacking, as is an effective intervention to reduce them, (III) selecting high-risk patients for future research on medication-related admissions is of utmost importance, using the triggerlist may contribute to this endeavour, (IV) furthermore, we demonstrate that pharmacist engagement in a CDSS offers added value, even though notable variations exist among different rules.

This thesis presents new insights on enhancing the care provided to older individuals and the prospective identification of high-risk patients for medication-related hospital admissions. It is imperative to establish more consistency in the care of older individuals and direct interventions toward those who stand to gain the most. This thesis centres its attention on patients with a high susceptibility to medication-related hospitalizations, and it finds that the triggerlist can be used for this purpose. Nonetheless, while this approach enables automated patient selection, it necessitates further validation.

Future studies should focus on interventions targeted at mitigating medication-related problems and admissions within this high-risk patient group. Established measures such as medication reviews may have a a more substantial impact, rendering them more feasible for practical implementation. Furthermore, this thesis also addresses another recognized intervention, the use of a CDSS. To date, there has been limited exploration into the quality of CDSS and the natural evolution of rules within such systems. In future research evaluating the effectiveness of a CDSS, it is crucial to evaluate the CDSS on multiple fronts, including (I) the quality of the rules themselves, (II) assessing whether the rules and the actions of pharmacists enhance standard care, and (III) monitoring the frequency and follow-up regarding the rules.

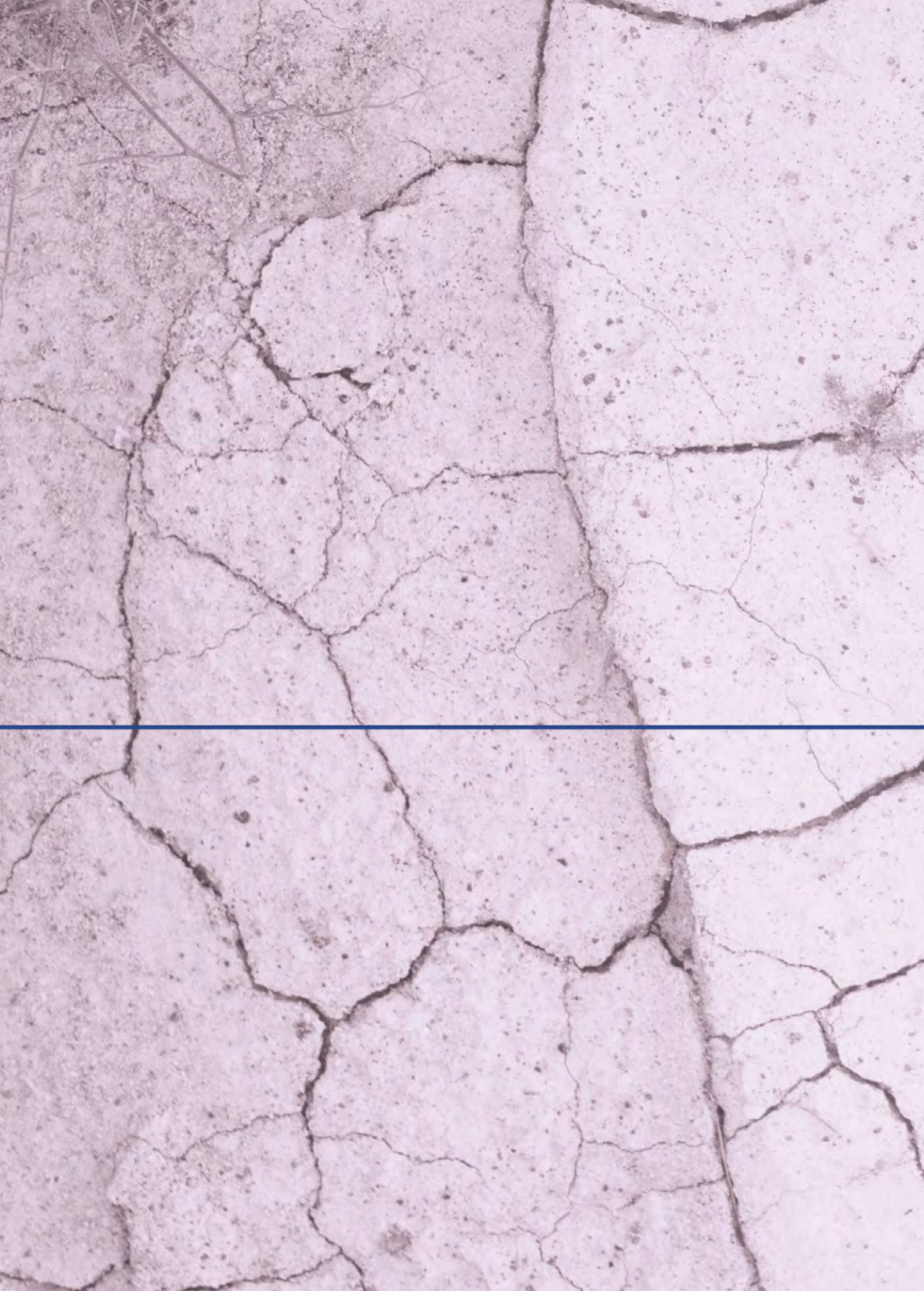
Therefore, future research must prioritize the enhancement of CDSS quality in order to potentially achieve improvements in clinical outcome measures, such as medication-related problems or readmissions. Ultimately, these interventions are crucial for ensuring the accessibility, effectiveness, and affordability of healthcare for older individuals in the years to come.

References

1. Rodrigues LP, de Oliveira Rezende AT, Delpino FM, Mendonça CR, Noll M, Nunes BP et al. Association between multimorbidity and hospitalization in older adults: systematic review and meta-analysis. Age Ageing. 2022;51(7):afac155.
2. Vervolgonderzoek medicatieveiligheid: eindrapport. Rotterdam/Utrecht/Nijmegen: Erasmus MC, NIVEL, Radboud UMC, PHARMO, 2017. 129 p.
3. 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):1890-1896.
4. El Morabet N, Uitvlugt EB, van den Bemt BJF, van den Bemt P, Janssen MJA, Karapinar-Çarkit F. Prevalence and Preventability of Drug-Related Hospital Readmissions: A Systematic Review. J Am Geriatr Soc. 2018;66(3):602-608.
5. Rapp K, Becker C, Todd C, Rothenbacher D, Schulz C, König HH et al. The Association Between Orthogeriatric Co-Management and Mortality Following Hip Fracture. Dtsch Arztebl Int. 2020;117(4): 53-59.
6. Yee DKH, Lau TW, Fang C, Ching K, Cheung J, Leung F. Orthogeriatric Multidisciplinary Co-Management Across Acute and Rehabilitation Care Improves Length of Stay, Functional Outcomes and Complications in Geriatric Hip Fracture Patients. Geriatr Orthop Surg Rehabil. 2022;13:21514593221085813.
7. Li Y, Tung KK, Cho YC, Lin SY, Lee CH, Chen CH. Improved outcomes and reduced medical costs through multidisciplinary co-management protocol for geriatric proximal femur fractures: a one-year retrospective study. BMC Geriatr. 2022;22(1):318.
8. Neuerburg C, Förch S, Gleich J, Böcker W, Gosch M, Kammerlander C et al. Improved outcome in hip fracture patients in the aging population following co-managed care compared to conventional surgical treatment: a retrospective, dual-center cohort study. BMC Geriatr. 2019;19(1):330.
9. Van Camp L, Dejaeger M, Tournoy J, Gielen E, Laurent MR. Association of orthogeriatric care models with evaluation and treatment of osteoporosis: a systematic review and meta-analysis. Osteoporos Int. 2020;31(11):2083-2092.
10. Gregersen M, Mørch MM, Hougaard K, Damsgaard EM. Geriatric intervention in elderly patients with hip fracture in an orthopedic ward. J Inj Violence Res. 2012;4(2):45-51.
11. Bouvy JC, De Bruin ML, Koopmanschap MA. Epidemiology of adverse drug reactions in Europe: a review of recent observational studies. Drug Saf. 2015;38(5):437-453.
12. Bordet R, Gautier S, Le Louet H, Dupuis B, Caron J. Analysis of the direct cost of adverse drug reactions in hospitalised patients. Eur J Clin Pharmacol. 2001;56(12):935-941.
13. McLachlan CY, Yi M, Ling A, Jardine DL. Adverse drug events are a major cause of acute medical admission. Intern Med J. 2014;44(7):633-638.
14. 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):631-639.
15. Schoonover H, Corbett CF, Weeks DL, Willson MN, Setter SM. Predicting potential postdischarge adverse drug events and 30-day unplanned hospital readmissions from medication regimen complexity. J Patient Saf. 2014;10(4):186-191.
16. Wimmer BC, Dent E, Bell JS, Wiese MD, Chapman I, Johnell K et al. Medication Regimen Complexity and Unplanned Hospital Readmissions in Older People. Ann Pharmacother. 2014;48(9):1120-1128.
17. Cabré M, Elias L, Garcia M, Palomera E, Serra-Prat M. Avoidable hospitalizations due to adverse drug reactions in an acute geriatric unit. Analysis of 3,292 patients. Med Clin (Barc). 2018;150(6):209-214.
18. Hallgren J, Aslan AKD. Risk factors for hospital readmission among Swedish older adults. Eur Geriatr Med. 2018;9(5):603-611.
19. Zhang M, Holman CD, 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.
20. Allaudeen N, Vidyarthi A, Maselli J, Auerbach A. Redefining readmission risk factors for general medicine patients. J Hosp Med. 2011;6(2):54-60.
21. 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.

22. Mekonnen AB, McLachlan AJ, Brien JA. Effectiveness of pharmacist-led medication reconciliation programmes on clinical outcomes at hospital transitions: a systematic review and meta-analysis. BMJ Open. 2016;6(2):e010003.
23. 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.
24. Khalil H, Bell B, Chambers H, Sheikh A, Avery AJ. Professional, structural and organisational interventions in primary care for reducing medication errors. Cochrane Database Syst Rev. 2017;10(10):Cd003942.
25. Zwietering NA, Linkens A, van der Kuy PHM, Cremers H, van Nie-Visser N, Hurkens K et al. Evaluation of a multifaceted medication review in older patients in the outpatient setting: a before-and-after study. Int J Clin Pharm. 2023;45(2):483-490.
26. Dautzenberg L, Bretagne L, Koek HL, Tsokani S, Zevgiti S, Rodondi N et al. Medication review interventions to reduce hospital readmissions in older people. J Am Geriatr Soc. 2021;69(6):1646-1658.
27. Ravn-Nielsen LV, Duckert ML, 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):375-382.
28. Taheri Moghadam S, Sadoughi F, Velayati F, Ehsanzadeh SJ, Poursharif S. The effects of clinical decision support system for prescribing medication on patient outcomes and physician practice performance: a systematic review and meta-analysis. BMC Med Inform Decis Mak. 2021;21(1):98.
29. Meulendijk MC, Spruit MR, Drenth-van Maanen AC, Numans ME, Brinkkemper S, Jansen PA et al. Computerized Decision Support Improves Medication Review Effectiveness: An Experiment Evaluating the STRIP Assistant's Usability. Drugs Aging. 2015;32(6):495-503.
30. de Wit HA, Hurkens KP, Mestres Gonzalvo C, Smid M, Sipers W, Winkens B et al. The support of medication reviews in hospitalised patients using a clinical decision support system. Springerplus. 2016;5(1):871.
31. Damoiseaux-Volman BA, van der Velde N, Ruige SG, Romijn JA, Abu-Hanna A, Medlock S. Effect of Interventions With a Clinical Decision Support System for Hospitalized Older Patients: Systematic Review Mapping Implementation and Design Factors. JMIR Med Inform. 2021;9(7):e28023.
32. Polyfarmacie bij ouderen. Polyfarmacie bij ouderen in de 2e lijn: Federatie Medisch Specialisten - Richtlijnendatabase; 2020.
33. Reijers EMC, van Strien AM, Derijks HJ, van Marum R. Geneesmiddelgerelateerde SEH-bezoeken zonder opname bij ouderen. Nederlands Platform voor Farmaceutisch Onderzoek. 2016.
34. Picco L, Achilla E, Abdin E, Chong SA, Vaingankar JA, McCrone P et al. Economic burden of multimorbidity among older adults: impact on healthcare and societal costs. BMC Health Serv Res. 2016;16:173.
35. Crowley C, Perloff J, Stuck A, Mechanic R. Challenges in predicting future high-cost patients for care management interventions. BMC Health Serv Res. 2023;23(1):992.
36. Kempen TGH, Hedström M, Olsson H, Johansson A, Ottosson S, Al-Sammak Y et al. Assessment tool for hospital admissions related to medications: development and validation in older patients. Int J Clin Pharm. 2019;41(1):198-206.
37. Rogers S, Wilson D, Wan S, Griffin M, Rai G, Farrell J. Medication-related admissions in older people: a cross-sectional, observational study. Drugs Aging. 2009;26(11):951-961.
38. Bayoumi I, Dolovich L, Hutchison B, Holbrook A. Medication-related emergency department visits and hospitalizations among older adults. Can Fam Physician. 2014;60(4):e217-e222.
39. Lea M, Mowe M, Mathiesen L, Kvernrød K, Skovlund E, Molden E. Prevalence and risk factors of drug-related hospitalizations in multimorbid patients admitted to an internal medicine ward. PLoS One. 2019;14(7):e0220071.
40. Zerah L, Henrard S, Thevelin S, Feller M, Meyer-Massetti C, Knol W et al. Performance of a trigger tool for detecting drug-related hospital admissions in older people: analysis from the OPERAM trial. Age Ageing. 2022;51(1).
41. Lghoul-Oulad Saïd F, Hek K, Flinterman LE, Herings RM, Warlé-van Herwaarden MF, de Bie S et al. Prevalence and incidence rate of hospital admissions related to medication between 2008 and 2013 in The Netherlands. Pharmacoepidemiol Drug Saf. 2020;29(12):1659-1668.
42. Osanlou R, Walker L, Hughes DA, Burnside G, Pirmohamed M. Adverse drug reactions, multimorbidity and polypharmacy: a prospective analysis of 1 month of medical admissions. BMJ Open. 2022;12(7):e055551.

43. Blum MR, Sallevelt B, Spinewine A, O'Mahony D, Moutzouri E, Feller M et al. Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults (OPERAM): cluster randomised controlled trial. Bmj. 2021;374:n1585.
44. Očovská Z, Maříková M, Kočí J, Vlček J. Drug-Related Hospital Admissions via the Department of Emergency Medicine: A Cross-Sectional Study From the Czech Republic. Front Pharmacol. 2022;13:899151.
45. Richtlijn Cardiovasculair risicomanagement (CVRM). Schatten van risico op hart- en vaatziekten. 2019.
46. O'Mahony D, Gudmundsson A, Soiza RL, Petrovic M, Cruz-Jentoft AJ, Cherubini A et al. Prevention of adverse drug reactions in hospitalized older patients with multi-morbidity and polypharmacy: the SENATOR* randomized controlled clinical trial. Age Ageing. 2020;49(4):605-614.
47. Sallevelt B, Huibers CJA, Heij J, Egberts TCG, van Puijenbroek EP, Shen Z et al. Frequency and Acceptance of Clinical Decision Support System-Generated STOPP/START Signals for Hospitalised Older Patients with Polypharmacy and Multimorbidity. Drugs Aging. 2022;39(1):59-73.
48. Dalton K, O'Mahony D, Cullinan S, Byrne S. Factors Affecting Prescriber Implementation of Computer-Generated Medication Recommendations in the SENATOR Trial: A Qualitative Study. Drugs Aging. 2020;37(9):703-713.
49. Dalton K, Curtin D, O'Mahony D, Byrne S. Computer-generated STOPP/START recommendations for hospitalised older adults: evaluation of the relationship between clinical relevance and rate of implementation in the SENATOR trial. Age Ageing. 2020;49(4):615-621.
50. Kim J, Chae YM, Kim S, Ho SH, Kim HH, Park CB. A Study on User Satisfaction regarding the Clinical Decision Support System (CDSS) for Medication. Healthc Inform Res. 2012;18(1):35-43.
51. Westerbeek L, Ploegmakers KJ, de Bruijn GJ, Linn AJ, van Weert JCM, Daams JG et al. Barriers and facilitators influencing medication-related CDSS acceptance according to clinicians: A systematic review. Int J Med Inform. 2021;152:104506.
52. Boyko EJ. Observational research--opportunities and limitations. J Diabetes Complications. 2013;27(6):642-648.



appendix

Appendix

Nederlandse samenvatting

Nederlandse samenvatting

Onze samenleving vergrijst met een steeds ouder wordende bevolking. Dit leidt tot een toename van mensen met chronische aandoeningen en kwetsbare ouderen, wat resulteert in polyfarmacie (het gebruik van vijf of meer medicijnen), ziekenhuisopnames en -heropnames, vaak gerelateerd aan medicatie. Hierdoor stijgen de zorgkosten.

De zorg voor (kwetsbare) oudere patiënten is complex. Er wordt al veel onderzoek gedaan om de zorg voor deze groep patiënten te verbeteren. Vaak wordt er gekeken naar "collaborative care", waarbij zorgverleners uit verschillende disciplines samenwerken om optimale zorg te bieden, ook wel co-management genoemd. Orthogeriatrisch co-management is een goed voorbeeld, waar orthopedisch chirurgen nauw samenwerken met klinisch geriaters en/of internisten-ouderengeneeskunde om de zorg voor patiënten met een heupfractuur te verbeteren. Medicatiebeoordelingen en –optimalisatie spelen een belangrijke rol in deze vorm van zorg.

Met als doel de zorg voor (kwetsbare) ouderen te verbeteren, wordt ook onderzoek gedaan naar het optimaliseren van medicijngebruik om medicatiegerelateerde problemen te voorkomen. Dit onderzoek omvat zowel handmatige medicatie-beoordelingen, alsook de beoordelingen met behulp van computerondersteuning, waarbij gebruik wordt gemaakt van een Clinical Decision Support System (CDSS); wat een computergestuurd systeem is dat artsen en apothekers ondersteunt bij het beoordelen van medicatie. Een CDSS biedt deze ondersteuning door geïntegreerde klinische informatie, richtlijnen, suggesties en waarschuwingen te verstrekken op basis van de medische geschiedenis van de patiënt, laboratoriumresultaten, symptomen en andere relevante gegevens bij deze beoordelingen.

Het doel van dit proefschrift was om de effectiviteit van verschillende initiatieven gericht op het verbeteren van de zorg en follow-up voor (kwetsbare) ouderen te onderzoeken. Dit omvatte co-management, het identificeren van hoog-risico patiënten en medicatie-optimalisatie met behulp van computerondersteuning, gebaseerd op gegevens uit de dagelijkse praktijk.

Hoofdstuk 2 beschreef een vorm van orthogeriatrisch co-management, waarbij de verpleegkundig specialist primair samen met de orthopedisch chirurg zorg verleende aan kwetsbare oudere patiënten met een heupfractuur. De verpleegkundig specialist bracht iedere patiënt volledig in kaart en beoordeelde de medische, cognitieve en functionele mogelijkheden en beperkingen van de patiënten en voerde een medicatiebeoordeling uit. Deze multidisciplinaire aanpak werd vergeleken met de normale zorg zonder co-management en resulteerde in een aanzienlijke afname (50%) van de sterfte na zowel 3 maanden als 1 jaar. Tevens werden er meer complicaties en ziektebeelden geregistreerd in de interventiegroep, wat suggereert dat de (h)erkenning van deze complicaties en

aandoeningen het werkingsmechanisme zou kunnen zijn waardoor co-management bijdraagt aan de vermindering van sterfgevallen.

In hoofdstuk 3 werd er een samenvatting gegeven over de literatuur die tot op heden bekend is over medicatiegerelateerde (her)opnames, inclusief de risicofactoren en mogelijke interventies om deze opnames te reduceren. We vonden een grote spreiding in de gerapporteerde percentages van medicatiegerelateerde opnames en -heropnames, variërend van 0.5% tot 19.3% en 8.7% tot 64%, respectievelijk. Deze variatie kan worden toegeschreven aan het gebruik van verschillende definities voor medicatiegerelateerde (her)opnames in de literatuur. Het verschil kan worden verklaard door de specifieke aard van het medicatieprobleem dat de opname heeft veroorzaakt, zoals bijwerkingen, interacties of therapieontrouw. De meest voorkomende risicofactoren voor een medicatiegerelateerde (her)opname zijn polyfarmacie, verminderde therapietrouwheid, oudere leeftijd, comorbiditeiten, nierfalen, geheugenproblematiek, hartfalen en langere duur van ziekenhuisopnames. Bovendien is bekend dat het gebruik van bepaalde medicijnen het risico verhoogt, zoals bloedverdunners, bloeddrukverlagende middelen en psychotrope (bewustzijns-veranderende) medicijnen. We beschreven ook dat er al meerdere interventies zijn onderzocht om medicatiegerelateerde (her)opnames te verminderen, waarbij de medicatiebeoordeling het meest voorkomend is. Echter, de medicatiebeoordeling wordt op veel verschillende manieren uitgevoerd en door verschillende professionals zoals de apotheker of de klinisch geriater. Daarnaast kan deze medicatiebeoordeling zowel handmatig als met ondersteuning van een computersysteem worden uitgevoerd. Tot op heden is er nog geen eenduidige interventie geïdentificeerd die consistent leidt tot een vermindering van opnames, en deze diversiteit in benaderingen kan een factor zijn die hieraan bijdraagt.

In hoofdstuk 4 beschreven wij het onderzoeksprotocol van de CHECkUP (Control in the Hospital by Extensive Clinical rules for Unplanned hospitalizations in older Patients). Deze studie heeft als doel te onderzoeken of een wekelijkse medicatiebeoordeling, ondersteund door een computersysteem, kan leiden tot een lager aantal ziekenhuisheropnames binnen 1 jaar. Voor deze studie includeerden we patiënten die 60 jaar of ouder zijn, ongepland zijn opgenomen in het ziekenhuis, vijf of meer medicijnen gebruiken en die twee triggers hebben van de triggerlijst. Met deze inclusiecriteria trachtten we een patiëntengroep te selecteren die een hoog risico hebben op een medicatiegerelateerde opname. De triggerlijst is opgenomen in de Nederlandse richtlijn over polyfarmacie en is ontwikkeld om meer bewustwording te creëren bij behandelaren voor medicatiegerelateerde opnames omdat deze vaak niet herkend worden. De lijst bevat de tien meest voorkomende medicatiegerelateerde problemen die een ziekenhuisopname kunnen veroorzaken zoals bijvoorbeeld een fractuur of een achteruitgang van de nierfunctie. Daarnaast wordt in deze lijst per trigger de medicijnen benoemd die het vaakst deze problemen veroorzaken.

De interventie die we binnen de CHECkUP onderzoeken bestaat uit een medicatiebeoordeling middels een computersysteem. Dit computersysteem beoordeelt de medicatie gebruikmakend van patiëntgegevens, laboratoriumgegevens en richtlijnen die geïntegreerd zijn in het computersysteem. Het computersysteem geeft dan een advies om eventueel medicatie aan te passen, te stoppen, te starten of geeft bijvoorbeeld het advies om laboratoriumgegevens te verkrijgen van de patiënt omdat dat belangrijk is op basis van het medicatiegebruik. Deze adviezen worden verstuurd naar de behandelaar in de 1e lijn (de huisarts en/of de apotheker). Wekelijks beoordeelt het systeem de medicatie en bij nieuwe bevindingen zal de 1e lijn het advies ontvangen.

Voor de CHECkUP studie hebben we getracht patiënten te includeren die een hoog risico hebben op een medicatiegerelateerde opname, dit was initieel een pragmatische keuze en dit is de eerste studie die deze selectiecriteria gebruikt. In hoofdstuk 5 toetsten we of deze aanname correct was. We selecteerden de eerste 100 patiënten die we geïncludeerd hadden voor de studie. Van deze 100 patiënten hebben we geëvalueerd of de opname waarschijnlijk gerelateerd was aan medicatie, gebaseerd op de AT-HARM tool. Deze tool bestaat uit tien vragen waarvan er drie specifiek bedoeld zijn om te beoordelen of de opname waarschijnlijk niet gerelateerd is aan medicatie, en zeven vragen die bedoeld zijn om te identificeren of de opname juist wel gerelateerd is aan medicatie. Wij constateerden dat 48% van de geïncludeerde patiënten waarschijnlijk waren opgenomen vanwege een potentieel medicatiegerelateerd probleem. Dit percentage ligt hoger dan het gemiddelde percentage medicatiegerelateerde opnames (5-20% bij patiënten ouder dan 70), wat suggereert dat we ouderen hebben geselecteerd met een hoog risico op een medicatiegerelateerde opname. Het voordeel van deze selectie is dat je deze groep snel en automatisch kunt identificeren op basis van leeftijd en de medicatielijst. Deze identificatie is echter nog niet gevalideerd en behoeft verdere ontwikkeling en validatie. Als blijkt dat deze selectie in staat is om ouderen met een verhoogd risico op medicatiegerelateerde opnames en problemen te identificeren, kunnen bekende en nieuwe interventies onderzocht worden in deze hoog-risico populatie met als doel deze problemen te verminderen.

Naast het selecteren van de hoog-risico ouderen is het ook belangrijk dat de kwaliteit van de computersystemen die worden gebruikt om medicatie te beoordelen verbeterd worden. Daarom hebben we in hoofdstuk 6 gekeken naar het gebruik van een computersysteem in de dagelijkse praktijk en naar de invloed van de apotheker op het resultaat van de adviezen van het computersysteem. Dagelijks beoordeelde het computersysteem de medicatie van alle opgenomen patiënten in het Zuyderland MC, de beoordelingen van 2018 hebben we onderzocht. Wanneer er actie nodig was, gaf het computersysteem een rode waarschuwing en wanneer er geen actie nodig was dan was de waarschuwing groen. Wanneer het probleem was opgelost, werd een rode waarschuwing groen. We hebben enerzijds gekeken naar hoeveel van de adviezen/waarschuwingen van het computersysteem werden opgelost en daarnaast

naar de invloed van de apotheker wanneer die een actie uitvoerde bij een rode waarschuwing. Zowel op dag 1 en als op dag 3 zagen we dat het percentage van opgeloste waarschuwingen hoger was wanneer de apotheker een actie uitvoerde.

Daarnaast zagen we dat het percentage van opgeloste waarschuwingen op dag 3 hoger lag ten opzichte van dag 1, ook wanneer de apotheker geen actie uitvoerde. Dit suggereert dat adviezen/waarschuwingen ook worden opgelost zonder de tussenkomst van een apotheker. Dit is de eerste studie die een computersysteem in de dagelijkse praktijk beoordeelde en keek naar het natuurlijk beloop van de adviezen van het computersysteem.

Samenvattend hebben wij middels dit proefschrift meer inzicht gekregen in de zorg voor ouderen in de vorm van co-management, het selecteren van hoog-risico ouderen op een medicatiegerelateerde opname en in het gebruik van een medicatiebeoordeling middels een computersysteem in de dagelijkse praktijk. Desalniettemin is het van belang om verder te onderzoeken hoe we de zorg en de follow-up kunnen verbeteren voor de (kwetsbare) ouderen en dient er aandacht te zijn voor hoe we het gebruik en de kwaliteit van computersystemen die ondersteunen bij medicatie-optimalisatie kunnen verbeteren.

Appendix

Curriculum Vitae

Curriculum Vitae

Aimée Elisabeth Maria Johannes Henricus Linkens was born on 13 August 1989 in Maastricht, The Netherlands. After graduation from pre-university education (VWO), Porta Mosana College, Maastricht in 2007, she started studying medicine in Maastricht University in the same year and received her medical degree in 2013. After her graduation she started a position as resident internal medicine at the Maxima Medical Centre in Veldhoven. In 2015 she started her residency in internal medicine at the Zuyderland Medical Centre in Heerlen and Sittard-Geleen. During this period she also started the PhD program, of which this thesis is the result. She was supervised by prof. dr. P.H.M. van der Kuy, dr. B.P.A. Spaetgens, dr. N.C. van Nie – Visser and dr. K.P.G.M. Hurkens.
In 2019 she started her fellowship in geriatric medicine at the Maastricht University Medical Centre. In August 2021 she graduated and started her current position of internist-geriatric medicine at the Maastricht University Medical Centre.

Appendix

List of publications

List of publications

Linkens AEMJH, Kurstjens D, Zwietering NA, Milosevic V, Hurkens KPGM, van Nie N, van de Loo BPA, van der Kuy PHM, Spaetgens B. Clinical Decision Support Systems in Hospitalized Older Patients: An Exploratory Analysis in a Real-Life Clinical Setting. *Drugs Real World Outcomes.* 2023;10(3):363-370.

Zwietering NA, **Linkens AEMJH**, van der Kuy PHM, Cremers H, van Nie-Visser N, Hurkens KPGM, Spaetgens B. Evaluation of a multifaceted medication review in older patients in the outpatient setting: a before-and-after study. *Int J Clin Pharm.* 2023;45(2):483-490.

Spaetgens B, Brouns SHA, **Linkens AEMJH**, Poeze M, Ten Broeke RHM, Brüggemann RAG, Sipers W, Henry RMA, Hanssen NMJ. Associations between presence of diabetes, mortality and fracture type in individuals with a hip fracture. *Diabetes Res Clin Pract.* 2022;192:110084.

Linkens AEMJH, Janssen MJM, van Nie N, Peeters L, Winkens B, Milosevic V, Spaetgens B, Hurkens KPGM, van der Kuy PHM. Additional value of a triggerlist as selection criterion in identifying patients at high risk of medication-related hospital admission: a retrospective cohort study. *Int J Clin Pharm.* 2022;44(5):1205-1210.

Linkens AEMJH, Milosevic V, van Nie N, Zwietering A, de Leeuw PW, van den Akker M, Schols JMGA, Evers SMAA, Gonzalvo CM, Winkens B, van de Loo BPA, de Wolf L, Peeters L, de Ree M, Spaetgens B, Hurkens KPGM, van der Kuy HM. Control in the Hospital by Extensive Clinical rules for Unplanned hospitalizations in older Patients (CHECkUP); study design of a multicentre randomized study. *BMC Geriatr*. 2022;22(1):36.

Melis LCB, **Linkens AEMJH**, Antonides-Göbbels S, Pijls N, Ten Broeke RHM, Sipers W, Spaetgens B. Perceptions of Medical and Surgical Health Care Providers Toward Orthogeriatric Care Delivery: An Exploratory Survey. *J Am Med Dir Assoc.* 2022;23(4):698-700.

Milosevic V, **Linkens A**, Winkens B, Hurkens KPGM, Wong D, van Oijen BPC, van der Kuy HM, Mestres-Gonzalvo C. Fall incidents in nursing home residents: development of a predictive clinical rule (FINDER). *BMJ Open*. 2021;11(5):e042941.

van Leendert JAA, **Linkens AEMJH**, Poeze M, Pijpers E, Magdelijns F, Ten Broeke RHM, Spaetgens B. Mortality in hip fracture patients after implementation of a nurse practitioner-led orthogeriatric care program: results of a 1-year follow-up. *Age Ageing.* 2021;50(5):1744-1750.

Linkens AEMJH, Milosevic V, van der Kuy PHM, Damen-Hendriks VH, Mestres Gonzalvo C, Hurkens KPGM. Medication-related hospital admissions and readmissions in older patients: an overview of literature. *Int J Clin Pharm.* 2020;42(5):1243-1251.

Appendix

PhD Portfolio

PhD Portfolio

Name PhD student:	Aimée Elisabeth Maria Johannes Henricus Linkens
Erasmus MC Department:	Pharmacy
PhD period:	01.01.2019 – 31.12.2023
Promotor/Supervisor:	prof. dr. P.H.M. van der Kuy
Co-promotors/co-supervisors	dr. B.P.A. Spaetgens
	dr. N.C. van Nie - Visser
	dr. K.P.G.M. Hurkens

PhD training

Courses	**Year**	**ECTS**
Scientific Integrity	2017	0.3
Basic Course clinical research rules and regulations training	2017	0.3
Scientific writing	2018	1.5
Good Clinical Practice	2018	1.5
JNIV Leiderschap	2019	1.0
SEH introductie + ABCD cursus	2019	1.0
Discipline overstijgend onderwijs– communicatie	2019	0.3
Bekostiging van de zorg	2021	0.5
Herregistratie GCP	2022	0.5
Klinisch opleiden: Beoordelen op de werkplek	2022	0.3
Klinisch opleiden: Basisvaarigheden	2022	0.7
Gebruik van EPA's in de medische vooropleidingen	2022	0.2
Introductional coruse in principles of PBL	2022	0.3
BROK	2022	2.0
NIV echocursus	2023	1.0
Tutor Cursus	2023	1.0
Mentor cursus	2023	0.5

Conferences	**Year**	**ECTS**
Internistendagen	2016-2017	1.5
Wetenschapsdag ouderengeneeskunde	2018	0.3
Fellowdagen ouderengeneeskunde	2018-2019	1.0
Wetenschapsdag ouderengeneeskunde	2019	0.3
Fellowdag ouderengeneeskunde	2020	0.3
CHECkUP project groep bijeenkomst – oral presentation	2020	0.3
Fellowdag ouderengeneeskunde – oral presentation	2020	0.5
Wetenschapsdag ouderengeneeskunde	2020	0.3

Fellowdag ouderengeneeskunde	2021	0.3
Internistendagen	2021	1.0
Webinar NVIAG Designer Drugs	2021	0.1
KNMG-webinar: Euthanasie bij dementie	2021	0.1
Spoedzorg voor ouderen: besluitvorming	2021	0.1
Wetenschappelijke kring Klinische Geriatrie Limburg	2022	0.1
Geriatriedagen	2022	0.4
Ouderengeneeskunde Maastricht 2.0	2022	1.00
CHECkUP project groep bijeenkomst – oral presentation	2022	0.3
Internistendagen	2022	1.0
Interne ouderengeneeskunde – oral presentation CHECkUP	2022	0.5
E-learning samen beslissen	2023	0.5
Fellowdag ouderengeneeskunde – oral presentation	2023	0.5
CHECkUP project groep bijeenkomst – oral presentation	2023	0.6

Teaching and supervisor activities	Year	ECTS
Teaching medical students	2021	1.0
Teaching nursing home doctor in training	2022	0.3
Supervising master thesis M. Janssen	2022	1.5
Tutor groep medical students	2023	1.5
Supervising research nurses CHECkUP	2023	1.5
Mentor medical students	2023	1.0