# GERIATRIC IMPAIRMENTS MEDICATION AND INTERVENTIONS IN OLDER PERSONS

## with focus on patients with cardiovascular disease

Lauren Dautzenberg

# Geriatric impairments, medication and interventions in older persons

with focus on patients with cardiovascular disease

**Geriatrische aandoeningen, medicatie en interventies bij oudere patiënten – met een focus op patiënten met hart- en vaatziekten**

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Lauren Dautzenberg

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## Promotor:
Prof. dr. M.H. Emmelot-Vonk

## Copromotoren:
Dr. H.L. Koek
Dr. W. Knol

## Beoordelingscommissie:
Prof. dr. M.L. Bots
Prof. dr. A.C.G. Egberts
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Prof. dr. N. van der Velde

# Table of contents

# CHAPTER 1

1

# General introduction and outline of the thesis

Several new cardiac interventions have led to improvements in survival and quality of life in adults with cardiovascular disease (CVD), including left ventricular assist device (LVAD), heart transplantation (HTx) and transcatheter aortic valve implantation (TAVI). However, complications related to these procedures can lead to significant morbidity and mortality. The challenge in daily practice is to consider both the risks and benefits of these interventions in the decision-making process. Current cardiology guidelines focus mainly on cardiac risk factors when considering whether or not to perform an intervention. To further optimise this decision making process, particularly in older adults, more insight is needed in the prevalence and impact of geriatric impairments and medication use. Also, there is a lack of knowledge on whether interventions aimed at improvement of geriatric impairments and medication use are associated with better outcomes in patients.
This thesis focuses on the prevalence of geriatric impairments and medication use in (older) adults with different cardiovascular diseases and the association with adverse outcomes. This thesis also investigates the effect of medication review and (multicomponent) fall prevention interventions to improve adverse outcomes in community-dwelling older adults.

## Geriatric impairments in (older) adults with cardiovascular disease

Globally, the prevalence of CVD is increasing.[1] Common cardiovascular diseases that increase with age are coronary heart disease, heart failure, cerebrovascular disease, heart valve disease, cardiac arrhythmias and peripheral vascular disease.[2] The introduction of (novel) cardiac interventions such as LVAD, HTx and TAVI has led to improvements in survival and quality of life.[3,4]
Implantation of an LVAD is a relatively new cardiac intervention (2004). Worldwide, the prevalence of heart failure is increasing due to aging of the population, improved treatment of acute cardiac pathology and improvements in heart failure therapies.[5] When chronic end-stage heart failure remains refractory in spite of individualised optimal medical and conventional device therapy, advanced therapies can be considered in selected patients, including HTx and LVAD.[6] In case of donor scarcity or if the patient is considered not eligible for cardiac transplantation, an LVAD can be implanted as bridge to HTx or destination therapy, respectively. An LVAD is a mechanical pump surgically placed through a median sternotomy or thoracotomy that supports the left ventricular function.[7] Over the past two decades, the proportion of people aged 70 and over who received an LVAD or HTx has increased significantly.[8,9]
Aortic valve stenosis is the most prevalent form of valvular heart disease in western countries. It is associated with ageing and affects one in eight individuals aged 75 years and above.[10,11] When severe aortic valve stenosis is symptomatic the annual risk of sudden death is 8 to 34 percent, making early intervention in all patients strongly recommended.[12]

Treatment of severe aortic stenosis involves surgical aortic valve replacement (SAVR) or (since 2002) TAVI, provided the patient is expected to benefit from the procedure and has no concomitant condition associated with a survival of less than 1 year.[13] Trials have shown that TAVI is superior or non-inferior to SAVR in patients at high and intermediate surgical risk.[13] Possibly, TAVI is even non-inferior in patients with low surgical risk.[13]

However, with procedures such as LVAD, HTx and TAVI, the risk of complications, including mortality, is high.[14–17] The risk of adverse outcomes further increases in the presence of comorbidities and frailty in patients with CVD.[18] Patients with CVD have a high comorbidity burden.[19] In older adults with CVD the number of geriatric impairments increases with the degree of comorbidity.[20] Geriatric impairments such as delirium, falls, cognitive impairment, dizziness, syncope and urinary incontinence are clinical conditions that are most prevalent in the older population, have a multifactorial basis and thus do not fit into separate disease categories.[21] Recently, Aidoud and colleagues published a review of common geriatric impairments affecting older adults with CVD.[22] Although geriatric impairments in this population are often not well recognised in clinical practice, 10%-60% have at least one geriatric impairment, which adversely affects functional status, quality of life, frailty, survival and risk of hospitalisation.[22] Multimorbidity and polypharmacy are both common in older adults with CVD. Multimorbidity is associated with reduced functional status and quality of life and increased polypharmacy, falls and mortality. Polypharmacy is associated with adverse drug reactions, institutionalisation, hospital admissions and mortality. Frailty is present in 10%-60% of the patients with CVD and an important prognostic determinant for the above mentioned outcomes. Different definitions of frailty have been proposed over the past decades.[23] In general, frailty is a syndrome of reduced physiological reserve and resistance to stressors.[24] It is a significant predictor of adverse outcomes of surgery in general and of cardiac interventions such as LVAD, HTx and TAVI in particular.[25–28] Frailty and CVD share common pathways of chronic low-grade inflammation and insulin resistance.[29] On top of sharing causal pathways, CVD has also been shown to contribute to the development of frailty.[29] Numerous instruments are available that identify different phenotypes of patients with frailty. However, there is no standardised measurement tool for frailty in patients with CVD.[30]

Comprehensive geriatric assessment (CGA) is an appropriate generalist way to detect and, where possible, treat geriatric impairments. CGA is defined as 'a multidisciplinary diagnostic and treatment process that identifies medical, psychosocial, and functional capabilities and limitations of a (frail) older person in order to develop a coordinated plan to maximize overall health with aging.[31,32] Core components of CGA are the evaluation of the current medical situation and medical history, medication use, functional capacity, fall risk, cognition, mood, social support, living situation, healthcare consumption, goals of care, spirituality and advance care preferences.[33] The effectiveness of CGA varies by setting or specific clinical circumstances. A recent umbrella review on health outcomes of CGA in older adults showed with high certainty of evidence that CGA reduces nursing home

admission, risk of falls, risk of delirium in hip fracture and pressure sores in the hospital medical setting. CGA also decreases the risk of physical frailty in community-dwelling older adults.[34] Furthermore, CGA has been proven effective in reducing the number of prescriptions and daily doses of medication for patients by facilitating the discontinuation of unnecessary or inappropriate medication.[35]

Current cardiovascular guidelines contain critical knowledge gaps regarding care for patients with complex comorbidities and its related polypharmacy, significant physical or cognitive disabilities or frailty, as these older adults are often excluded from study participation.[36] Also, there is heterogeneity in the literature regarding definitions or tools used to diagnose geriatric impairments or frailty.[21] Providing care for this growing population is thus complex, which highlights the importance of individualized, holistic, patient-centred care to older individuals with CVD.[37] While a fair amount of evidence is available about the prevalence of geriatric impairments in coronary artery disease, less is known about it in the TAVI population and very little in LVAD or HTx candidates.[38] The same applies to knowledge about the impact of geriatric impairments on outcomes in these populations. However, awareness of the presence of geriatric impairments and knowledge of how these may influence outcomes in LVAD, HTx and TAVI candidates is essential in the decision-making process for these cardiac interventions.

In summary, there are gaps in knowledge about the prevalence of geriatric impairments in patients with CVD, specifically LVAD, HTx and TAVI candidates, and its impact on postoperative outcomes. From this comes the first aim, which is to assess the prevalence of geriatric impairments resulting from the comprehensive geriatric assessment in different populations with CVD, and the association of these impairments with postoperative adverse events.

## Medication use in patients with CVD and the impact of medication review interventions in older adults

Despite the emergence of multiple intervention options in recent decades, medication-based treatment is still the cornerstone of CVD treatment.[22] To comply with cardiology guidelines, polypharmacy is often unavoidable. Polypharmacy is mostly defined as the concomitant use of ≥5 regularly prescribed medications.[39] A recent study in adults aged ≥ 65 years with a history of CVD admitted to the cardiology ward, found an average use of 11.6 ± 4.5 medications per day. Polypharmacy was present in 95% of patients and hyperpolypharmacy (the use of at least 10 different medications) in 69%.[40] Polypharmacy may result in drug-related problems, defined as 'an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes',[41] including adverse drug reactions and poor compliance with drug prescriptions.[42,43] Plenty of research has been conducted on polypharmacy in patients with heart failure.[44] However, little is known about (hyper)polypharmacy in potential candidates for LVAD and HTx, and its association with complications postoperatively.

To optimise medical treatment, it is important to assess the appropriateness of the medication regime. Especially in older adults, it is important to consider comorbidity, drug-drug and drug-disease interactions, which diseases have the highest priority to be treated, over-treatment, under-treatment, and patient-related factors such as life expectancy, economic status, mental decline, visual impairment, and swallowing.[35] A medication review is a potential method to improve medication appropriateness. A medication review is defined as 'a structured evaluation of a patient's medicines with the aim of optimising medicines use and improving health outcomes. This entails detecting drug related problems and recommending interventions.'[45] Medication related readmissions occur frequently, particularly in older adults, and cardiovascular medication is the most important group of medication involved.[46] Hospitalisation in older adults can lead to complications such as delirium, falls, functional decline and subsequent institutionalisation or readmission.[47,48] Improvement of medication appropriateness may reduce drug-related problems such as medication related readmissions. Previous research has shown that medication review leads to better quality of prescribing.[49–51] A medication review can be carried out separately or in combination with one or more co-interventions, such as medication reconciliation, education of patients or healthcare professionals or the use of a Computerized Decision Support tool. Randomised controlled trials on the effect of medication review use different combinations of medication review with co-interventions. This leads to heterogeneity and conflicting published results regarding the effect on hospital readmissions.[52,53] Thus, it is not well established in which composition of components a medication review is most effective.

Given the aforementioned knowledge gaps, our aim is to determine the effect of medication use on postoperative outcomes in patients with CVD. Our aim is also to analyse the current literature to determine the effectiveness of different medication review interventions on clinical outcomes, particularly hospital readmissions.

## Fall prevention interventions in older adults

Falls are common in (older) adults with CVD.[54] Adults with heart failure or cardiac arrhythmias are at particularly high risk of falling. The main risk factors for falls in patients with CVD include polypharmacy, cardiovascular medication, orthostatic hypotension, cardiac syncope, frailty, sarcopenia, sensory impairment, musculoskeletal problems and cognitive impairment.[54] Falling is also a serious health problem in the general population. It occurs in one third of community-dwelling persons aged ≥65 years at least once a year.[55] In 2021, in the Netherlands, 76,800 persons aged 65 and over experienced serious injuries following a fall.[56] The most common injuries were brain injury (18%), hip fracture (15%) and wrist fracture (9%). Fall-related injuries lead to loss of functionality and quality of life, high costs and mortality.[57] Multiple risk factors for falls are known, such as gait or balance problems, a previous fall, multimorbidity, vision disorder, cognitive impairment, certain

medications and decreased functionality.[58] After a comprehensive fall risk assessment as part of CGA, fall prevention interventions can be formulated. The multifactorial nature of falls requires multicomponent interventions consistent with the finding in the four domains of CGA.[21] Fall prevention interventions address modifiable risk factors and can be divided into three main groups: 1) single interventions (participants receive one type of intervention), 2) multiple interventions (participants receive the same, fixed combination of two or more types of interventions), and 3) multifactorial interventions (participants receive a personalized selection out of two or more types of interventions, according to the results of a pre-executed, personal falls risk assessment).[59] Research has been conducted on fall prevention for decades. A Cochrane review published in 2012 on the effect of fall prevention interventions in community-dwelling older adults found that group (e.g. a supervised group training programme) and home-based (e.g. instructions to do simple exercises at home to improve strength and balance) exercise programmes, and home safety interventions (e.g. advice on removing mats or carpets for visually impaired adults) reduce rate of falls and risk of falling.[60] The review also indicated that multifactorial assessment and intervention programmes (e.g. an intervention with patient-specific recommendations for inappropriate medication, orthostatic hypotension and patient education) reduce rate of falls, but not risk of falling. Given the rapid pace at which new fall prevention studies are published after 2012, there is a need for an update. Furthermore, previous reviews did not focus on multimorbid older (age ≥75) adults. As this population has a high risk of falling, it is essential to gain more insight into which particular fall prevention interventions are most beneficial in this high risk group. Therefore, our aim is to analyse the existing literature on the effectiveness of single and multicomponent fall prevention interventions, with a special focus on multimorbid older adults.

## Aims and outline of the thesis

The general aim of this thesis is to investigate whether geriatric impairments and medication use are related to outcomes in patients with CVD. The ageing population with CVD deals with geriatric impairments such as multimorbidity, psychosocial and functional problems, polypharmacy, frailty and falls. Awareness of the presence of geriatric impairments and knowledge of how these may influence outcomes in patients with CVD is essential in the decision-making process regarding (therapeutic) treatment. This thesis also investigates the effect of (multicomponent) fall prevention and medication review interventions to improve geriatric impairments in community-dwelling older adults.

This aim is divided into the following objectives:
- To assess the prevalence of geriatric impairments resulting from the comprehensive geriatric assessment in different populations with CVD, and the association of these impairments with post-operative adverse events.

- To investigate the effect of medication use and medication review interventions in older adults and in patients undergoing various cardiac interventions.
- To investigate whether fall prevention interventions are associated with improved outcomes in older adults.

Outline of the thesis:
The studies in this thesis are presented in three parts: geriatric impairments in patients with CVD (**Part 1**), medication use and medication review interventions in older adults and patients with CVD (**Part 2**) and fall prevention interventions in older adults (**Part 3**).

In **Part 1,** we investigate the prevalence and impact of geriatric impairments in patients with CVD. In Chapter 2, we describe the prevalence of frailty and other impairments identified by CGA in potential candidates for LVAD and HTx. In Chapter 3 and 4, we assess the prevalence of frailty and geriatric impairments in TAVI candidates and examine the association with adverse outcomes of TAVI.
In **Part 2,** we focus on the impact of medication use and medication review interventions on outcomes in patients treated with various cardiac interventions. In Chapter 5, we assess the association between (hyper)polypharmacy and adverse outcomes of LVAD. In Chapter 6, we examine the association between statin therapy and short-term risk of mortality and complications in older adults undergoing TAVI. In Chapter 7, we present a systematic review and network meta-analysis on medication review interventions to reduce hospital readmissions in older community-dwelling people.
In **Part 3**, we study the impact of fall prevention interventions in older adults. Chapter 8 includes a systematic review and network meta-analysis of interventions to prevent falls and fall-related fractures in community-dwelling older people.
In Chapter 9 of this thesis, we discuss the main findings and implications of the studies presented and give suggestions for future research.

## References


1. Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J Am Coll Cardiol*. 2020;76(25):2982-3021.
2. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2022 Update: A Report from the American Heart Association. *Circulation*. 2022;145(8):E153-E639.
3. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med*. 2001;345(20):1435-1443.
4. Khush KK, Cherikh WS, Chambers DC, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult heart transplantation report — 2019; focus theme: Donor and recipient size match. *J Hear Lung Transplant*. 2019;38(10):1056-1066.
5. Roger VL. Epidemiology of heart failure. *Circ Res*. 2013;113(6):646-659.
6. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-3726.
7. DeFilippis EM, Nakagawa S, Maurer MS, Topkara VK. Left Ventricular Assist Device Therapy in Older Adults: Addressing Common Clinical Questions. *J Am Geriatr Soc*. 2019;67(11):2410-2419.
8. Jaiswal A, Gadela NV, Baran D, et al. Clinical outcomes of older adults listed for heart transplantation in the United States. *J Am Geriatr Soc*. 2021;69(9):2507-2517.
9. Rali AS, Vuddanda V, Masoomi R, et al. Trends in LVADs in the Geriatric Population: Demographics for 2003–2014. *J Card Fail*. 2017;23(8):S17.
10. Eveborn GW, Schirmer H, Heggelund G, Lunde P, Rasmussen K. The evolving epidemiology of valvular aortic stenosis. The Tromsø Study. *Heart*. 2013;99(6):396-400.
11. Osnabrugge RLJ, Mylotte D, Head SJ, et al. Aortic stenosis in the elderly: Disease prevalence and number of candidates for transcatheter aortic valve replacement: A meta-analysis and modeling study. *J Am Coll Cardiol*. 2013;62(11):1002-1012.
12. Sorgato A, Faggiano P, Aurigemma GP, Rusconi C, Gaasch WH. Ventricular Arrhythmias in Adult Aortic Stenosis: Prevalence, Mechanisms, and Clinical Relevance. *Chest*. 1998;113(2):482-491.
13. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43(7):561-632.
14. Molina EJ, Shah P, Kiernan MS, et al. The Society of Thoracic Surgeons Intermacs 2020 Annual Report. *Ann Thorac Surg*. 2021;111(3):778-792.
15. McCartney SL, Patel C, Del Rio JM. Long-term outcomes and management of the heart transplant recipient. *Best Pract Res Clin Anaesthesiol*. 2017;31(2):237-248.
16. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med*. 2017;376(14):1321-1331.
17. Abdelgawad A, Moustafa Ewiss, Hussein MA, Naeim H, Abuelatta R, Alghamdy S. A Comparative Study of TAVR versus SAVR in Moderate and High-Risk Surgical Patients: Hospital Outcome and Midterm Results. *Hear Surg Forum*. 2019;22(5):E331-E339.
18. O'Neill DE, Forman DE. Cardiovascular care of older adults. *BMJ*. 2021;374:n1593.

19. Chartbook and Charts Chronic Conditions Charts. Baltimore: Centers for Medicare & Medicaid Service; 2018.
20. Vetrano DL, Foebel AD, Marengoni A, et al. Chronic diseases and geriatric syndromes: The different weight of comorbidity. *Eur J Intern Med*. 2016;27:62-67.
21. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric Syndromes: Clinical, Research and Policy Implications of a Core Geriatric Concept. *J Am Geriatr Soc*. 2007;55(5):780-791.
22. Aïdoud A, Gana W, Poitau F, et al. High Prevalence of Geriatric Conditions Among Older Adults With Cardiovascular Disease. *J Am Heart Assoc*. 2023;12(2):e026850.
23. Gobbens RJ, Luijkx KG, Wijnen-Sponselee MT, Schols JM. Toward a conceptual definition of frail community dwelling older people. *Nurs Outlook*. 2010;58(2):76-86.
24. Clegg A. Frailty in Older People. *Lancet*. 2013;381(9868):752-762.
25. Partridge JSL, Harari D, Dhesi JK. Frailty in the older surgical patient: A review. *Age Ageing*. 2012;41(2):142-147.
26. Macdonald P. Frailty of the heart recipient. *Transplantation*. 2021;105(11):2352-2361.
27. Piankova P, Afilalo J. Prevalence and Prognostic Implications of Frailty in Transcatheter Aortic Valve Replacement. *Cardiol Clin*. 2020;38(1):75-87.
28. Joseph SM, Manghelli JL, Vader JM, et al. Prospective Assessment of Frailty Using the Fried Criteria in Patients Undergoing Left Ventricular Assist Device Therapy. *Am J Cardiol*. 2017;120(8):1349-1354.
29. Afilalo J. Frailty in Patients with Cardiovascular Disease: Why, When, and How to Measure. *Curr Cardiovasc Risk Rep*. 2011;5(5):467-472.
30. Damluji AA, Cohen MG. The Influence of Frailty on Cardiovascular Disease: The Time for a "Frailty Academic Research Consortium" Is Now! *Circ Cardiovasc Interv*. 2022;15(1):e011669.
31. Stuck A, Siu A, Wieland G, Adams J, Rubenstein L. Comprehensive geriatric assessment: a meta-analysis of controlled trials. *Lancet*. 1993;342(8878):1032-1036.
32. Devons CAJ. Comprehensive geriatric assessment: making the most of the aging years. *Curr Opin Clin Nutr Metab Care*. 2002;5(1):19-24.
33. Guideline Comprehensive geriatric assessment. Utrecht: Federatie Medisch Specialisten; 2021.
34. Veronese N, Custodero C, Demurtas J, et al. Comprehensive geriatric assessment in older people: An umbrella review of health outcomes. *Age Ageing*. 2022;51(5):1-9.
35. Sergi G, De Rui M, Sarti S, Manzato E. Polypharmacy in the Elderly Can Comprehensive Geriatric Assessment Reduce Inappropriate Medication Use? *Drugs Aging*. 2011;28(7):509-518.
36. Rich MW, Chyun DA, Skolnick AH, et al. Knowledge Gaps in Cardiovascular Care of Older Adults: A Scientific Statement from the American Heart Association, American College of Cardiology, and American Geriatrics Society: Executive Summary. *J Am Geriatr Soc*. 2016;64(11):2185-2192.
37. Goyal P, Kwak MJ, Al Malouf C, et al. Geriatric Cardiology: Coming of Age. *JACC Adv*. 2022;1(3):100070.
38. Damluji AA, Forman DE, Wang TY, et al. Management of Acute Coronary Syndrome in the Older Adult Population: A Scientific Statement from the American Heart Association. *Circulation*. 2023;147(3):E32-E62.

39. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC Geriatr*. 2017;17(1):230.
40. Sheikh-Taha M, Asmar M. Polypharmacy and severe potential drug-drug interactions among older adults with cardiovascular disease in the United States. *BMC Geriatr*. 2021;21(1):233.
41. Van Mil JWF, Westerlund LOT, Hersberger KE, Schaefer MA. Drug-Related Problem Classification Systems. *Ann Pharmacother*. 2004;38(5):859-867.
42. Barat I, Andreasen F, Damsgaard EMS. Drug therapy in the elderly: what doctors believe and patients actually do. *Br J Clin Pharmacol*. 2001;51(6):615-622.
43. Franceschi M, Scarcelli C, Niro V, et al. Prevalence, Clinical Features and Avoidability of Adverse Drug Reactions as Cause of Admission to a Geriatric Unit. A Prospective Study of 1756 Patients. *Drug Saf*. 2008;31(6):545-556.
44. Sukumar S, Orkaby AR, Schwartz JB, et al. Polypharmacy in Older Heart Failure Patients: a Multidisciplinary Approach. *Curr Heart Fail Rep*. 2022;19(5):290-302.
45. Griese-Mammen N, Hersberger KE, Messerli M, et al. PCNE definition of medication review: reaching agreement. *Int J Clin Pharm*. 2018;40(5):1199-1208.
46. 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.
47. Boyd CM, Ricks M, Fried LP, et al. Functional decline and recovery of activities of daily living in hospitalized, disabled older women: The women's health and aging study I. *J Am Geriatr Soc*. 2009;57(10):1757-1766.
48. Szlejf C, Farfel JM, Curiati JA, Couto Juniorde E de B, Jacob-Filho W, Azevedo RS. Medical adverse events in elderly hospitalized patients: A prospective study. *Clinics*. 2012;67(11):1247-1252.
49. Blenkinsopp A, Bond C, Raynor DK. Medication reviews. *Br J Clin Pharmacol*. 2012;74(4):573-580.
50. Thiruchelvam K, Hasan SS, Wong PS, Kairuz T. Residential Aged Care Medication Review to Improve the Quality of Medication Use: A Systematic Review. *J Am Med Dir Assoc*. 2017;18(1):87.e1-87.e14.
51. Khera S, Abbasi M, Dabravolskaj J, Sadowski CA, Yua H, Chevalier B. Appropriateness of Medications in Older Adults Living With Frailty: Impact of a Pharmacist-Led Structured Medication Review Process in Primary Care. *J Prim Care Community Heal*. 2019;10: 2150132719890227.
52. Hatah E, Braund R, Tordoff J, Duffull SB. A systematic review and meta-analysis of pharmacist-led fee-for-services medication review. *Br J Clin Pharmacol*. 2014;77(1):102-115.
53. Huiskes VJB, Burger DM, Van Den Ende CHM, Van Den Bemt BJF. Effectiveness of medication review: A systematic review and meta-analysis of randomized controlled trials. *BMC Fam Pract*. 2017;18(1):5.
54. Denfeld QE, Turrise S, MacLaughlin EJ, et al. Preventing and Managing Falls in Adults With Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circ Cardiovasc Qual Outcomes*. 2022;15(6):E000108.
55. National Institute for Health and Care Excell. Falls in older people : assessing risk and prevention. *NICE Clin Guidel*. 2013:1-33.

56. Cijferrapportage Letsels 2020; Kerncijfers Letsel Informatie Systeem. Amsterdam: VeiligheidNL; 2021.
57. Hartholt KA, Van Beeck EF, Polinder S, et al. Societal consequences of falls in the older population: Injuries, healthcare costs, and long-term reduced quality of life. *J Trauma - Inj Infect Crit Care*. 2011;71(3):748-753.
58. Lord SR, Sherrington C, Naganathan V. Falls in Older People: Risk Factors, Strategies for Prevention and Implications for Practice (3rd Ed.). Cambridge: Cambridge University Press; 2021.
59. Hopewell S, Adedire O, Copsey BJ, et al. Multifactorial and multiple component interventions for preventing falls in older people living in the community (Review). *Cochrane Database Syst Rev*. Published online 2018.
60. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev*. 2012;2012(9).

CHAPTER 2

# 2

# Outcomes of comprehensive geriatric assessment in potential candidates for left ventricular assist device or heart transplantation

Lauren Dautzenberg, Linda W. van Laake, Renee C.M.A. Raijman, Geert J. Lefeber, Wilma Knol, Marish I.F. Oerlemans, Faiz Z. Ramjankhan, Susan A. Braithwaite, Mieke D.J. Nagtegaal, Marielle H. Emmelot-Vonk, Huiberdina L. Koek

*Submitted*

## Abstract

**Background:** Understanding the presence of medical, mental, functional, and social capabilities and limitations in the individual patient with heart failure may lead to improved selection for advanced therapies such as left ventricular assist device (LVAD) and heart transplantation (HTx). The aim of this study was to assess the prevalence of frailty and other impairments in potential LVAD and HTx candidates by performing a preoperative comprehensive geriatric assessment (CGA) and reviewing the treatment recommendations resulting from the CGA.

**Methods:** This cross-sectional study included 73 patients aged ≥40 years who received a CGA as part of the patient selection procedure for LVAD and HTx. In every patient, a conclusion comprising frailty and other impairments was formulated based on the medical, mental, functional, and social domains and recommendations were made.

**Results:** The mean age was 58 years (range 40-71) and 70% were male. In 97% of patients, at least one impairment was identified by the CGA. The most common impairments were polypharmacy, high morbidity burden, reduced renal function, osteopenia, depression, poor quality of life, reduced functionality, (risk of) malnutrition, reduced grip strength and high caregiver burden. A small proportion of the potential LVAD and HTx candidates were frail (7% according to Fried's frailty criteria, 6% according to the Edmonton Frail Scale) and 39% were pre-frail. The domains for which most impairments were found and the domains for which most treatment recommendations were given matched well, with the functional domain as the frontrunner.

**Conclusions:** This study showed that most of the potential candidates for LVAD or HTx have impairments on at least one domain of the CGA. Impairments and associated risks can contribute to the decision making process for candidacy for LVAD and HTx.

## Introduction

The lifetime risk of heart failure is high.[1] When chronic end-stage heart failure remains refractory in spite of individualized optimal medical and conventional device therapy, advanced therapies can be considered in selected patients, including heart transplantation (HTx) and left ventricular assist device (LVAD).[2]

Although LVAD implantation and HTx improve survival and quality of life,[3,4] there is also a high risk of complications, leading to an intensive postoperative therapeutic regime and a thorough follow-up.[5,6] As recommended in the European Society of Cardiology heart failure guidelines, compliance with therapy and adequate social support are important elements of this therapeutic regime.[2,7] Furthermore, it is important that patients on LVAD support understand the technology, are able to undertake the burdensome self-care and to react appropriately to pump malfunction.[2,8] This requires substantial cognitive and functional skills.[9] Current literature refers to frailty[10] as an important predictor of outcomes after LVAD implantation.[11–15] Given the high risk of negative outcomes after LVAD or HTx, an adequate preoperative selection of potential candidates is necessary. Even when performed by a specialized, multidisciplinary team, patient selection is complex and unique to each patient.[2] The comprehensive geriatric assessment (CGA) is a multidisciplinary assessment that systematically examines a patient according to the medical, mental, functional and social domains and can determine the degree of frailty.[16,17] Recent studies showed that a CGA is potentially of added value in the evaluation and treatment of patients with heart failure.[18,19] A recent study showed that having limitations in multiple domains of the CGA was significantly associated with adverse outcomes in patients with heart failure.[20] Awareness of the presence of capabilities and limitations in the individual patient may lead to improved patient selection for advanced therapies such as LVAD or HTx, and gives the potential to optimize and individualize treatment to improve the preoperative level of fitness. A few studies showed beneficial effects of a prehabilitation program on functionality and frailty in patients awaiting HTx, however, no studies have reported the impact on outcomes of LVAD or HTx yet.[21] In addition, care goals can be explored, social or mental support offered, the risk of complications such as delirium reduced and advice given on post-operative rehabilitation.[22] However, little is known about the yield of a CGA in patients who are considered for advanced invasive therapy with LVAD or HTx in terms of found impairments and potential recommendations. Therefore, the aim of this study was to assess the prevalence of frailty and other impairments identified by a CGA in potential LVAD and HTx candidates. A secondary aim was to study which treatment recommendations resulted from the CGA.

# Methods

## Study design, setting and population

This is a single center, cross-sectional study in a collaboration between the Department of Geriatrics, Cardiology and Cardiothoracic Surgery at the University Medical Centre Utrecht, a tertiary referral hospital for advanced HF in the Netherlands. All patients over 40 years of age who were screened as potential candidate for LVAD implantation or HTx were included in this study. As biological age is expected to exceed chronological age in chronic HF,[23,24] the inclusion limit was set at 40 years. Patients intubated and/or sedated in the intensive care unit at the moment of screening were excluded from study participation, since it was not possible to perform a CGA under those conditions. Five patients who did not provide informed consent to participate in the study were also excluded. Before a patient enters the screening program for LVAD or HTx, an experienced team of cardiologists makes an informal pre-selection of patients who appear inappropriate for LVAD or HTx based on the clinical appearance, for example due to severe frailty. These patients were not included in this study.

The study has been conducted in accordance with the Declaration of Helsinki and is approved by the local medical ethics committee (reference number MvdL/mb/20/500551).

## Comprehensive geriatric assessment

A CGA was performed in every patient as part of the patient selection procedure for LVAD and HTx, including patients screened for HTx with LVAD in situ. Depending on the clinical situation of the patient, the CGA was performed at the geriatric outpatient clinic or during admission on the cardiology ward. A CGA-trained physician or nurse practitioner performed the CGA, which included evaluation of the patient's medical, mental, functional, and social capabilities and problems. The CGA was based on the Dutch national guideline for CGA and adapted where appropriate for the specific population with advanced heart failure, using the Minnesota Living with Heart Failure Questionnaire to assess quality of life and Fried's frailty criteria to determine frailty. An overview of the components of the CGA, test instruments, corresponding references, ranges, and cut-off points is shown in online supplementary Table S1.[9,18,25] In every patient, a conclusion comprising frailty and other impairments was formulated on the four mentioned domains and a plan of care was created around patient-centered goals. The treatment recommendations were grouped into the prespecified categories as mentioned in Table 2 of the manuscript and Supplementary Table S2.

## Frailty assessment

In this study, Fried's frailty criteria (Supplementary Table S3) were used to determine frailty as recommended by the Frailty Heart Workgroup of the American Society of Transplantation.[26,27]

In addition, we used the Edmonton Frail Scale (EFS) as a second and multi-domain instrument to assess frailty (Supplementary Table S4).[28] Rolfson et al. demonstrated that the EFS is a valid tool for determining frailty when compared to the CGA and the EFS is used in several cardiac populations, including heart failure patients, in literature.[29–32]

## Demographic data

Demographic data included age, sex, etiology of the cardiomyopathy, previously implanted LVAD in potential HTx candidates and the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile.[33] INTERMACS (IM) uses a classification system of profiles (IM profile 1 to 7) to represent the severity of heart failure, which ranges from advanced New York Heart Association class 3 heart failure (IM 7) to critical cardiac shock (IM 1).



## Statistical analysis

Continuous demographics are presented as mean ± standard deviation. Categorical demographics are expressed as number and corresponding percentage. Outcomes of the CGA, i.e. the impairments and treatment recommendations are also presented as means for continuous variables and numbers for categorical variables. The outcomes of the CGA were stratified by the presence of an LVAD (LVAD in situ vs. no LVAD in situ), age (40-59 years vs. ≥60 years), and IM profile (IM 1-3 vs. IM 4-6). The 60-year limit was chosen because of a median age of 59, creating roughly two equally sized groups. Differences in impairments and treatment recommendations were determined with the Student's t-test or Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Analyses were performed using the Statistical Package for the Social Sciences version 26 (SPSS Inc., Chicago III, United States).

## Results

Data is presented for 73 potential LVAD and HTx candidates who consented to participate in this study between November 2020 and November 2021. Details on patient inclusion are presented in Figure S1 of the Supplementary Material.

**Table 1.** Demographics of patients screened for left ventricular assist device or heart transplantation

| Demographics | | N=73 | % |
|---|---|---|---|
| **Screening during hospitalization** | | 28 | 38.4 |
| **Screening for** | HTx | 38 | 52.1 |
| | LVAD | 33 | 45.2 |
| | Both HTx/LVAD | 2 | 2.7 |
| **Previously implanted LVAD in potential candidates for HTx** | | 25 | 65.8 |
| **Age** | Years [Mean ± SD] | 57.9 ± 7.4 | |
| **Sex** | Male | 51 | 69.9 |
| **Etiology cardiomyopathy** | Dilated | 34 | 46.6 |
| | Ischemic | 30 | 41.1 |
| | Congenital | 2 | 2.7 |
| | Hypertrophic | 4 | 5.5 |
| | Other | 3 | 4.1 |
| **INTERMACS profile** | 2 | 4 | 5.5 |
| | 3 | 10 | 13.7 |
| | 4 | 23 | 31.5 |
| | 5 | 9 | 12.3 |
| | 6 | 1 | 1.4 |
| | Not applicable due to LVAD | 26 | 35.6 |

HTx, heart transplantation; LVAD, left ventricular assist device

## Demographics

Demographics of patients screened for LVAD or HTx are shown in Table 1. The mean age of the study population was 57.9 ± 7.4 years (range 40-71) and 51 patients (70%) were male. Half of the patients (52%) were screened for HTx, 45% for LVAD, and in two patients both options were still open at the moment of the CGA.

## Impairments resulting from the CGA

***Frailty***

According to Fried's frailty criteria, most patients were non-frail (54%), 39% of patients were pre-frail and 7% were frail. According to the EFS, the majority of patients (86%) were indicated non-frail. Six patients (9%) were pre-frail and four (6%) mildly frail. (Table 2)

***Medical status***

The mean Charlson Comorbidity index score was 2.1 ± 0.9. In one third of the patients the Charlson Comorbidity index was ≥3, indicating a high morbidity burden. Half of the patients had a BMI>25. Patients used an average of 7.3 chronic medications per day. Polypharmacy (≥5 medications) was present in 77% of the patients and hyperpolypharmacy (≥10 medications) in 14%. Bone mineral density was reduced in 63% of the patients. Renal and liver function were impaired in respectively 29% and 24% of the patients,.



***Cognitive and psychological status***

In 29% of the patients depressive symptoms were present and in 14% cognitive impairment. The majority of patients reported a reduced quality of life with almost half of the patients describing their quality of life as poor (44%).

***Functional status***

Almost half of the patients (47%) required assistance in the (instrumental) activities of daily living, mostly because of physical limitations due to heart failure. About one third (34%) of patients were at risk of malnutrition and in 8% of patients malnutrition was actually present. The Timed Up & Go test was abnormal in 6% of the study population indicating impaired mobility. Muscle strength (handgrip strength corrected for age and sex) was impaired in more than half of the patients (58%).

***Social status***

A large proportion of patients needed care while living at home: 20% of patients received caregiver assistance, 18% household help and 4% professional care. A quarter (27%) of the caregivers experienced a high caregiving burden.

Figure 1 shows the distribution of impairments resulting from the CGA across the different domains (medical, mental, functional and social). A total of 417 impairments were identified during this study. Most impairments were related to the functional domain (37%) and the medical domain (37%).

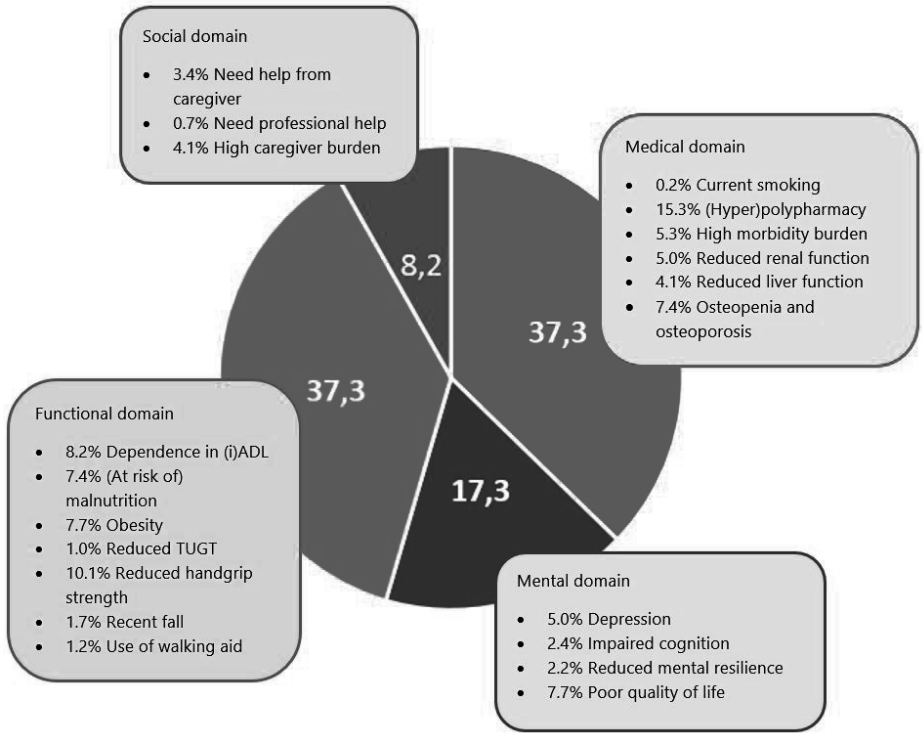



**Figure 1.** The distribution of impairments resulting from the comprehensive geriatric assessment across the different domains (medical, mental, functional and social).

(i)ADL, (instrumental) activities of daily living; TUGT, timed up and go test
All impairments were classified according to the domain to which they relate (medical, mental, functional and social). Of the impairments, frailty was not subdivided into any of the domains because all domains together lead to frailty.

## Treatment recommendations resulting from the CGA

The treatment recommendations, that are part of the integrated care plan that resulted from the CGA, are divided into 13 categories, see Table 3. The mean number of treatment recommendations per patient was 3.6 ± 1.6.

In one in eight patients (12%), the suitability for HTx or LVAD implantation was determined negative or ambiguous. Of the five patients with an ambiguous advice, one patient was non-frail and the other four were pre-frail according to the Fried's frailty criteria. According to the EFS, four patients were non-frail and one pre-frail. Clinical factors of frailty status that led to an ambiguous advice were social or financial vulnerability, (a risk of) malnutrition, obesity (BMI 31.2), problems with cognition, decreased functional reserves, and the need of mental support to improve coping strategies. Of the three patients with a negative advice, one was indicated as non-frail by Fried's frailty criteria, one person as pre-frail and one person as frail. On the EFS, one person scored non-frail, the other two mildly frail. Findings that indicated this frailty status that led to a negative advice included a high

morbidity burden, limited physical reserves, malnutrition, social vulnerability, cognitive impairment, mental problems, and decreased functionality and mobility.
Most recommendations were given for the following categories: recommendations regarding education (regarding the intervention and clinical course postoperatively), patient counselling, shared decision making and advance care planning (40%), recommendations regarding delirium risk and prevention (36%), recommendations regarding mobility and fall prevention (34%), and recommendations regarding malnutrition or weight reduction (33%).



Figure 2 presents to which domains (medical, mental, functional and social) the treatment recommendations belong. A total of 163 treatment recommendations were provided. Most recommendations were related to the functional domain (36%), followed by the mental domain (30%) and medical domain (27%).

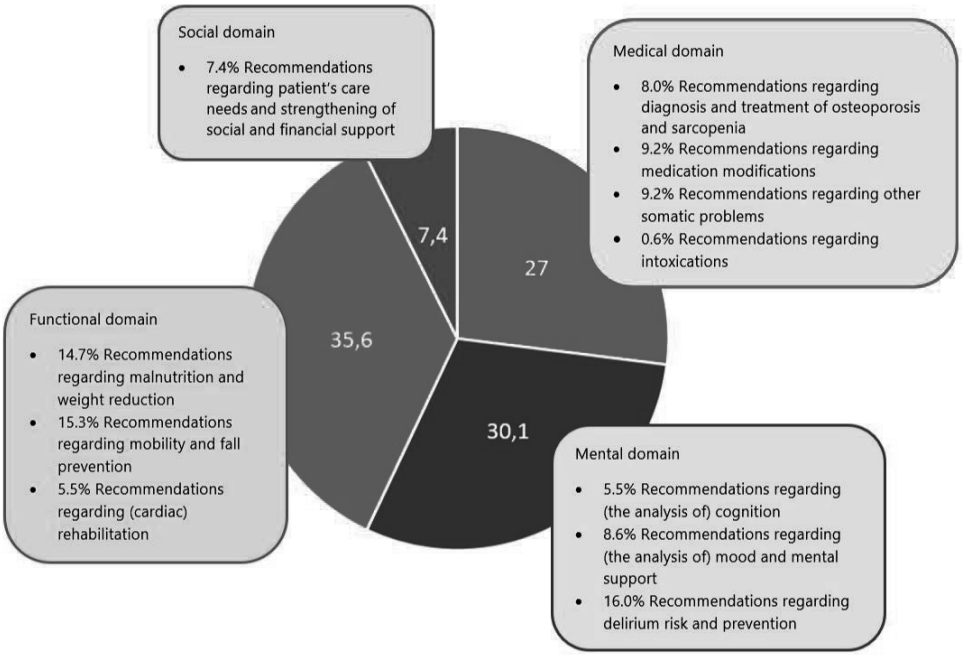



**Figure 2.** The distribution of the treatment recommendations resulting from the comprehensive geriatric assessment across the different domains (medical, mental, functional and social).

All treatment recommendations were classified according to the domain to which they relate (medical, mental, functional and social). The treatment recommendations related to the eligibility for LVAD/HTx and recommendations regarding education, patient counselling, shared decision making and advance care planning, were not assigned to one specific domain as all domains taken together result in whether a person is appropriate for the intervention and are input for an advance care planning (ACP) conversation. In ACP conversations, the healthcare professional discusses with the patient what goals of care fit with the patient's values, beliefs and health status. This way, appropriate care and treatment is determined for the short term and direction is given for appropriate care and treatment in future scenarios.

## Stratifications

Liver function was more often impaired in patients without LVAD in situ than in patients with LVAD (36 vs. 4%). Quality of life was more often poor in the group without LVAD in situ (57 vs. 19%). The group with LVAD in situ required more often assistance in activities of daily living (mainly requiring assistance with showering) than the group without LVAD in situ (27 vs 9%). There was a trend of increased dependence in instrumental activities of daily living in patients without an LVAD in situ compared with patients with an LVAD in situ, with those without LVAD needing more help with household tasks, shopping and travelling, but this difference was not statistically significant (p=0.07). There was also a trend of increased frailty in patients without an LVAD in situ when compared to patients with an LVAD in situ, however, again this difference was not statistically significant (p=0.07). (Supplementary Table S5)

Patients older than 60 years used a significantly greater amount of chronic medications (8.1 vs. 6.5), and hyperpolypharmacy was more common (25 vs. 5%), compared to patients younger than 60 years old. Renal function was more often impaired in patients over 60 years old (41 vs. 18%). (Supplementary Table S6).

There was a trend of increased frailty, and decreased functionality and mobility in patients with IM profile 1-3 compared to patients with IM profile 4-6, however, the difference was not statistically significant. (Supplementary Table S7)

In Supplementary Table S8, S9, S10 the differences in treatment recommendations for all the stratifications are presented.

**Table 2.** Results of the comprehensive geriatric assessment in patients screened for left ventricular assist device or heart transplantation

| **Frailty** | **All patients** | **N=73** | **%** |
|---|---|---|---|
| **Edmonton Frail scale** | No frailty | 59 | 85.5 |
| | Pre-frail | 6 | 8.7 |
| | Mild frail | 4 | 5.8 |
| | Moderate frail | 0 | |
| | Severe frail | 0 | |
| | Missing | 4 | 5.5 |
| **Fried frailty criteria** | No frailty | 39 | 54.2 |
| | Pre-frail | 28 | 38.9 |
| | Frail | 5 | 6.9 |
| | Missing | 1 | 1.4 |
| **Medical domain** | | | |
| **BMI** | kg/m$^2$ [Mean ± SD] | 25.7 ± 3.8 | |
| | >25 | 32 | 50.8 |
| | Missing | 10 | 13.7 |

| | | | |
|---|---|---|---|
| **BSA** | $m^2$ [Mean ± SD] | 1.98 ± 0.21 | |
| | Missing | 10 | 13.7 |
| **Smoking status** | Former | 43 | 58.9 |
| | Current | 1 | 1.4 |
| **Alcohol use status** | Current | 33 | 46.5 |
| | Missing | 2 | 2.7 |
| **Comorbidity** | CCI [Mean ± SD] | 2.1 ± 0.9 | |
| **High morbidity burden** | CCI ≥3 | 22 | 30.1 |
| **Medication use** | Number [Mean ± SD] | 7.3 ± 2.4 | |
| | Polypharmacy | 54 | 77.1 |
| | Hyperpolypharmacy | 10 | 14.3 |
| | Missing | 3 | 4.1 |
| **Reduced renal function** | eGFR<60 | 21 | 28.8 |
| **Reduced liver function** | MELD-score ≥14 | 17 | 23.9 |
| | Missing | 2 | 2.7 |
| **Bone mineral density** | Normal bone mineral density | 18 | 36.7 |
| | Osteopenia | 26 | 53.1 |
| | Osteoporosis | 5 | 10.2 |
| | Missing | 24 | 32.9 |
| **Mental domain** | | | |
| **Mood** | Depression | 21 | 29.2 |
| | Missing | 1 | 1.4 |
| **MMSE** | [Mean ± SD] | 28.9 ± 0.8 | |
| **MoCA** | [Mean ± SD] | 27.2 ± 2.0 | |
| **Impaired cognition** | MMSE ≤24 or MOCA ≤25 | 10 | 13.8 |
| **Resilience Evaluation Scale** | [Mean ± SD] | 26.8 ± 5.2 | |
| | ≤ 21 | 9 | 12.5 |
| | Missing | 1 | 1.4 |
| **Quality of life** | Good | 20 | 27.4 |
| | Moderate | 21 | 28.8 |
| | Poor | 32 | 43.8 |
| **Functional domain** | | | |
| **Dependence in ADL** | | 11 | 15.1 |
| **Dependence in iADL** | | 30 | 41.1 |
| **Dependence in (i)ADL** | | 34 | 46.6 |
| **Nutritional status** | At risk of malnutrition | 25 | 34.2 |
| | Malnutrition | 6 | 8.2 |

| | | | |
|---|---|---|---|
| **Reduced 4-meter gait speed** | | 0 | |
| | Missing | 8 | 11.0 |
| **Reduced TUGT** | | 4 | 6.1 |
| | Missing | 7 | 9.6 |
| **Reduced handgrip strength corrected for age and sex** | | 42 | 57.5 |
| **Mobility** | ≥1 fall in previous 6 months | 7 | 9.7 |
| | Missing | 1 | 1.4 |
| | Use of walking aid | 5 | 6.8 |
| **Social domain** | | | |
| **Living situation** | At home without care | 41 | 57.7 |
| | At home with household help | 13 | 18.3 |
| | At home with help from caregiver | 14 | 19.7 |
| | At home with professional care | 3 | 4.2 |
| | Missing | 2 | 2.7 |
| **Educational level** | Primary and secondary school | 27 | 37.5 |
| | Secondary vocational education | 18 | 25.0 |
| | Bachelor's/master's degree | 27 | 37.5 |
| | Missing | 1 | 1.4 |
| **Employed** | Yes | 26 | 35.6 |
| | No | 38 | 52.1 |
| | Retired | 9 | 12.3 |
| **In a relationship** | Yes | 59 | 80.8 |
| **Having children** | Yes | 58 | 79.5 |
| **Caregiver burden** | Low caregiver burden | 34 | 54.0 |
| | High caregiver burden | 17 | 27.0 |
| | No caregiver | 12 | 19.0 |
| | Missing | 10 | 13.7 |

Missing values are indicated for each variable in the table
Ranges for instruments are available in Table S1 of the supplement
ADL, activities of daily living; BMI, body mass index; BSA, body surface area; CCI, charlson comorbidity index; eGFR, estimated glomerular filtration rate; iADL, instrumental activities of daily living; MELD, model for end-stage liver disease; MMSE, mini mental state examination; MoCA, montreal cognitive assessment; TUGT, timed up and go test.

**Table 3.** Treatment recommendations resulting from the comprehensive geriatric assessment

| Treatment recommendations categories: | N=73 | % |
|---|---|---|
| **Eligibility for LVAD/HTx intervention** | 67 | 91.8 |
| **Positive** | 59 | 88.1 |
| **Negative** | 3 | 4.5 |
| **Ambiguous** | 5 | 7.5 |
| **Missing** | 6 | 8.2 |
| **Recommendations regarding diagnosis and treatment of osteoporosis and sarcopenia** | 13 | 17.8 |
| **Recommendations regarding other somatic problems** | 15 | 20.5 |
| **Recommendations regarding medication modifications** | 15 | 20.5 |
| **Recommendations regarding (the analysis of) cognition** | 9 | 12.3 |
| **Recommendations regarding (the analysis of) mood and mental support for both patients and relatives** | 14 | 19.2 |
| **Recommendations regarding delirium risk and prevention** | 26 | 35.6 |
| **Recommendations regarding malnutrition and weight reduction** | 24 | 32.9 |
| **Recommendations regarding mobility and fall prevention** | 25 | 34.2 |
| **Recommendations regarding intoxications** | 1 | 1.4 |
| **Recommendations regarding (cardiac) rehabilitation** | 9 | 12.3 |
| **Recommendations regarding patient's care needs and strengthening of social and financial support** | 12 | 16.4 |
| **Recommendations regarding education, patient counselling, shared decision making and advance care planning** | 29 | 39.7 |
| **Other recommendations** | 1 | 1.4 |

HTx, heart transplantation; LVAD, left ventricular assist device

## Discussion

This study demonstrated that a small proportion of the potential LVAD and HTx candidates were frail, while over a third of patients were pre-frail (39%). In 97% of patients, at least 1 impairment was identified by the CGA. The most common impairments were polypharmacy, high morbidity burden, reduced renal function, osteopenia, depression, poor quality of life, reduced functionality, (risk of) malnutrition, reduced grip strength and high caregiver burden. Quality of life was worse in the group without LVAD in situ and the group with LVAD in situ required more often assistance in activities of daily living. Older patients more often had hyperpolypharmacy. The most common treatment recommendation that resulted from the CGA concerned recommendations regarding education, patient counselling, shared decision making and advance care planning. The domains for which most impairments were found and the domains for which most treatment recommendations were given matched well, with the functional domain as frontrunner.

In recent years, it has been recognized that heart failure is a multidomain condition.[18] Gorodeski et al. previously emphasized that the role of frailty, depression, cognitive impairment, nutrition, social environment, and care goals are each relevant to the implementation and success of medical therapy in this population.[18] The symptoms of heart failure and the physical domain of frailty (decreased exercise tolerance, symptoms of fatigue, and cachexia) correspond partly because frailty and heart failure share common pathological pathways of low-grade inflammation and metabolic stress.[9] This may explain the difference in the number of pre-frail potential candidates according to the Fried's frailty criteria and the EFS: the Fried's frailty criteria partially overlap with symptoms of end-stage heart failure and this is less the case with the EFS. It is difficult to distinguish frailty and other impairments as symptoms of end-stage heart failure that may be reversible after LVAD or HTx from frailty and impairments that are (partially) independent of the heart failure. In case of reversibility, HTx or LVAD intervention will be considered to be more suitable than in case of irreversible impairments. Previous studies have already shown that frailty assessed by Fried's frailty criteria and handgrip strength improve significantly after LVAD and HTx.[21] There is also evidence that cognition, anxiety, and depression improve after LVAD implantation.[26,34,35]

To the best of our knowledge, no other studies have been published in which a CGA was performed in potential candidates for LVAD or HTx. There are also no studies with treatment recommendations resulting from (individual components of the) CGA in this population. One study found a modest beneficial effect of a shared decision-support intervention on the quality of decision-making among patients and caregivers considering LVAD therapy.[36] In recipients of HTx, a positive effect of cardiac rehabilitation and nutritional supplementation was found on major adverse cardiac events and in-hospital

mortality and sepsis, respectively.[37,38] Studies have been conducted in which a CGA was performed in the heart failure population[39,40] however, extrapolation of these findings to our study is hampered due to differences in heart failure severity and mean age of the study population. Studies in which some individual components of the CGA have been assessed showed that depression, anxiety, non-compliance, malnutrition, multimorbidity, psychiatric problems, reduced functionality, social support, cognition and quality of life are frequent in patients (screened for) LVAD or HTx.[41-45] Again, comparison with the results of the current study is complicated by the differences in percentage of patients with an LVAD in situ and timing of the trajectory of LVAD implantation or heart transplantation, ranging from screening for LVAD and HTx (current study) to actual implantation or transplantation and many years of follow-up.



The past 10 years, an increasing amount of research has been conducted on the prevalence of frailty in patients undergoing LVAD or HTx. In the most recent systematic review frailty was found in 21% of LVAD patients.[46] A recent study (2022) in patients who underwent LVAD implantation found that one week prior to surgery, 54% of the patients were frail according to Fried's frailty criteria.[47] This rate is higher than the 9% frailty according to Fried's criteria in patients without LVAD in situ in the current study. In the current study, informal pre-screening has already taken place, with the cardiologist already deciding not to screen for LVAD and HTx for obviously very vulnerable patients. In two recent studies of 60 and 99 patients on the HTx waiting list, 11 and 31% of the patients appeared to be frail according to the Fried's frailty criteria.[43,48] A direct comparison between the current study and other studies is limited by the fact that frailty is dynamic and heterogeneity exists with respect to heart failure severity, presence of an LVAD, INTERMACS profile, age etc.

## Strengths and limitations

This study was the first to perform a CGA in this specific group of patients with end-stage heart failure. A large amount of information was collected on this inception cohort of patients at the time of screening for LVAD and HTx, in different domains, through interviews, the use of multiple testing instruments and additional (laboratory/radiological) examination. The CGA was performed by well-trained healthcare professionals in geriatrics, ensuring the quality of the data of this study.

This study also has a few limitations. For eight patients it was not possible to perform the 4-meter walk test because they were immobile. These values were considered missing in the analyses, leading to a potential overestimation of walking speed and mobility in the study population. Second, delirium risk was often estimated during the CGA based on clinical features, but not in a systematic, quantifying way using a diagnostic instrument. For this reason, we were unable to assess an increased delirium risk as an impairment. The distribution of impairments and treatment recommendations resulting from the CGA across the four domains would be more congruent if delirium risk was included as an impairment. Third, the study population was relatively heterogeneous including patients

screened for both LVAD and HTx, both with and without LVAD in situ, screened at the geriatric outpatient clinic or during admission on the cardiology ward. Stratifications were performed to gain more insight into the effect of different patient characteristics on identified impairments and treatment recommendations. However, the stratification by IM profile included only 47 patients, which may have created a power problem.

## Clinical implications and future research

This study has demonstrated that, despite the relatively young population already informal pre-selected by cardiologists, impairments are common in all four domains of the CGA. Decision making regarding patient selection for LVAD and HTx is complex and unique for each patient. The comprehensive information obtained through a CGA can be incorporated into this (complex) decision making. Discussion of goals of care with patients and near-ones ensures that the intervention matches the patient's values. Social and mental support can be provided. Impairments are also potential targets for improving physical fitness before surgery, with exercise, physical rehabilitation and nutritional supplementation potentially effective in improving preoperative frailty in patients with heart failure; however, no studies have reported the impact of prehabilitation on the outcomes after LVAD or HTx yet.[21] Also, based on these impairments, recommendations can be made for postoperative rehabilitation or prevention of complications like delirium. A geriatrician is trained to translate findings from the CGA into the above mentioned multidisciplinary interventions. It is recommended that future research investigate the effect of these multidisciplinary interventions on the patient-selection process and outcomes of LVAD and HTx.

Previous studies have shown that components of the CGA (frailty, cognition and depression) are of prognostic value for mortality after LVAD and HTx.[49,50] Future research should examine the prognostic value of impairments identified by the CGA in order to further optimize the decision making process. Also, the reversibility of impairments after LVAD implantation or HTx should be investigated.

## Conclusion

This study showed that in 97% of the potential candidates for LVAD and HTx at least 1 impairment was identified by the CGA. A small proportion of potential candidates were indicated as frail, yet over a third of patients appeared pre-frail. The domains for which most impairments were found and the domains for which most treatment recommendations were made matched well, with the functional domain as frontrunner. Impairments and associated risks can contribute to the decision making process concerning candidacy for LVAD and HTx, and are potential targets for improving pre-operative fitness. The prognostic value of these impairments needs further investigation.

## References


1. Roger VL. Epidemiology of heart failure. Circ Res 2013;113:646-659. doi:10.1161/CIRCRESAHA.113.300268
2. McDonagh TA, Metra M, Adamo M et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599-3726. doi:10.1093/eurheartj/ehab368
3. Rose EA, Gelijns AC, Moskowitz AJ et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 2001;345:1435-1443.
4. Khush KK, Cherikh WS, Chambers DC et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult heart transplantation report — 2019; focus theme: Donor and recipient size match. J Hear Lung Transplant 2019;38:1056-1066. doi:10.1016/j.healun.2019.08.004
5. Molina EJ, Shah P, Kiernan MS et al. The Society of Thoracic Surgeons Intermacs 2020 Annual Report. Ann Thorac Surg 2021;111:778-792. doi:10.1016/j.athoracsur.2020.12.038
6. McCartney SL, Patel C, Del Rio JM. Long-term outcomes and management of the heart transplant recipient. Best Pract Res Clin Anaesthesiol 2017;31:237-248. doi:10.1016/j.bpa.2017.06.003
7. Defilippis EM, Breathett K, Donald EM et al. Psychosocial Risk and Its Association With Outcomes in Continuous-Flow Left Ventricular Assist Device Patients. Circ Hear Fail 2020;13:E006910. doi:10.1161/CIRCHEARTFAILURE.120.006910
8. Jaarsma T, Hill L, Bayes-Genis A et al. Self-care of heart failure patients: practical management recommendations from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2021;23:157-174. doi:10.1002/ejhf.2008
9. DeFilippis EM, Nakagawa S, Maurer MS, Topkara VK. Left Ventricular Assist Device Therapy in Older Adults: Addressing Common Clinical Questions. J Am Geriatr Soc 2019;67:2410-2419. doi:10.1111/jgs.16105
10. Clegg A. Frailty in Older People. Lancet 2013;381:752-762. doi:10.1016/S0140-6736(12)62167-9.
11. Aili SR, De Silva R, Wilhelm K et al. Validation of Cognitive Impairment in Combination with Physical Frailty as a Predictor of Mortality in Patients with Advanced Heart Failure Referred for Heart Transplantation. Transplantation 2022;106:200-209. doi:10.1097/TP.0000000000003669
12. Joseph SM, Manghelli JL, Vader JM et al. Prospective Assessment of Frailty Using the Fried Criteria in Patients Undergoing Left Ventricular Assist Device Therapy. Am J Cardiol 2017;120:1349-1354. doi:10.1016/j.amjcard.2017.07.074
13. Yost G, Bhat G. Relationship between Handgrip Strength and Length of Stay for Left Ventricular Assist Device Implantation. Nutr Clin Pract 2017;32:98-102. doi:10.1177/0884533616665926
14. Moayedi Y, Duero Posada JG, Foroutan F et al. The prognostic significance of frailty compared to peak oxygen consumption and B-type natriuretic peptide in patients with advanced heart failure. Clin Transplant 2018;32:e13158. doi:10.1111/ctr.13158
15. Macdonald P. Frailty of the heart recipient. Transplantation 2021;105:2352-2361. doi:10.1097/TP.0000000000003692
16. Wieland D, Hirth V. Comprehensive Geriatric Assessment. Cancer Control 2003;10:454-462. doi:10.1177/107327480301000603

17. Jones DM, Song X, Rockwood K. Operationalizing a frailty index from a standardized comprehensive geriatric assessment. J Am Geriatr Soc 2004;52:1929-1933. doi:10.1111/j.1532-5415.2004.52521.x
18. Gorodeski EZ, Goyal P, Hummel SL et al. Domain Management Approach to Heart Failure in the Geriatric Patient: Present and Future. J Am Coll Cardiol 2018;71:1921-1936. doi:10.1016/j.jacc.2018.02.059.
19. Vitale C, Spoletini I, Rosano GM. Frailty in Heart Failure: Implications for Management. Card Fail Rev 2018;4:104-106. doi:10.15420/cfr.2018.22.2
20. Wiersinga JHI, Rhodius-Meester HFM, Kleipool EEF et al. Managing older patients with heart failure calls for a holistic approach. ESC Hear Fail 2021;8:2111-2119. doi:10.1002/ehf2.13292
21. Aili SR, Villanueva JE, Joshi Y, Emmanuel S, Macdonald P. Prevention and Reversal of Frailty in Heart Failure. Circ J 2022;86:14-22. doi:10.1253/circj.CJ-21-0819
22. Squires RW, Bonikowske AR. Cardiac rehabilitation for heart transplant patients: Considerations for exercise training. Prog Cardiovasc Dis 2022;70:40-48. doi:10.1016/j.pcad.2021.12.003
23. Hamczyk MR, Nevado RM, Barettino A, Fuster V, Andrés V. Biological Versus Chronological Aging: JACC Focus Seminar. J Am Coll Cardiol 2020;75:919-930. doi:10.1016/j.jacc.2019.11.062
24. Moons P, Marelli A. Born to Age: When Adult Congenital Heart Disease Converges With Geroscience. JACC Adv 2022;1:100012. doi:10.1016/j.jacadv.2022.100012
25. Guideline Comprehensive geriatric assessment. Utrecht: Federatie Medisch Specialisten; 2021 (online). Available at: https://richtlijnendatabase.nl/richtlijn/comprehensive_geriatric_assessment_cga/startpagina_-_comprehensive_geriatric_assessment_cga.html Accessed December 12, 2022.
26. Kobashigawa J, Shah P, Joseph S et al. Frailty in heart transplantation: Report from the heart workgroup of a consensus conference on frailty. Am J Transplant 2021;21:636-644. doi:10.1111/ajt.16207
27. Fried LP, Tangen CM, Walston J et al. Frailty in older adults: Evidence for a phenotype. Journals Gerontol - Ser A Biol Sci Med Sci 2001;56A:146-157. doi:10.1093/gerona/56.3.m146
28. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age Ageing 2006;35:526-529. doi:10.1093/ageing/afl041
29. Studzińska K, Wąż P, Frankiewicz A, Stopczyńska I, Studnicki R, Hansdorfer-Korzon R. Employing the Multivariate Edmonton Scale in the Assessment of Frailty Syndrome in Heart Failure. J Clin Med 2022;11:4022. doi:10.3390/jcm11144022
30. Sze S, Pellicori P, Zhang J, Weston J, Clark AL. Identification of Frailty in Chronic Heart Failure. JACC Hear Fail 2019;7:291-302. doi:10.1016/j.jchf.2018.11.017
31. Blanco S, Ferrières J, Bongard V et al. Prognosis Impact of Frailty Assessed by the Edmonton Frail Scale in the Setting of Acute Coronary Syndrome in the Elderly. Can J Cardiol 2017;33:933-939. doi:10.1016/j.cjca.2017.03.026
32. Koizia L, Khan S, Frame A et al. Use of the Reported Edmonton Frail Scale in the assessment of patients for transcatheter aortic valve replacement. A possible selection tool in very high-risk patients? J Geriatr Cardiol 2018;15:463-466. doi:10.11909/j.issn.1671-5411.2018.06.010

33. Stevenson LW, Pagani FD, Young JB et al. INTERMACS Profiles of Advanced Heart Failure: The Current Picture. J Hear Lung Transplant 2009;28:535-541. doi:10.1016/j.healun.2009.02.015
34. Yost G, Bhat G, Mahoney E, Tatooles A. Reduced Anxiety and Depression in Patients With Advanced Heart Failure After Left Ventricular Assist Device Implantation. Psychosomatics 2017;58:406-414. doi:10.1016/j.psym.2017.02.001
35. Choi JJ, Oldham MA, Pancharovski T et al Cognitive Change After Left Ventricular Assist Device Implantation: A Case Series and Systematic Review. J Acad Consult Psychiatry 2022;63:599-606.
36. Allen LA, McIlvennan CK, Thompson JS et al. Effectiveness of an intervention supporting shared decision making for destination therapy left ventricular assist device: the DECIDE-LVAD randomized clinical trial. JAMA Intern Med 2018;178:520-529. doi:10.1001/jamainternmed.2017.8713
37. Uithoven KE, Smith JR, Medina-Inojosa JR, Squires RW, Olson TP. The Role of Cardiac Rehabilitation in Reducing Major Adverse Cardiac Events in Heart Transplant Patients. J Card Fail 2020;26:645-651. doi:10.1016/j.cardfail.2020.01.011
38. Karim AM, Aljammal M, Panhwar MS, Kalra A. Impact of Malnutrition and Interventions on Patients Receiving Heart Transplant J Hear Lung Transplant 2020;39:S256-S257. doi:10.1016/j.healun.2020.01.556
39. Kleipool EEF, Wiersinga JHI, Trappenburg MC et al. The relevance of a multidomain geriatric assessment in older patients with heart failure. ESC Hear Fail 2020;7:1264-1272. doi:10.1002/ehf2.12651
40. Rodriguez-Pascual C, Paredes-Galan E, Vilches-Moraga A, Ferrero-Martinez AI, Torrente-Carballido M, Rodriguez-Artalejo F. Comprehensive geriatric assessment and 2-year mortality in elderly patients hospitalized for heart failure. Circ Cardiovasc Qual Outcomes 2014;7:251-258. doi:10.1161/CIRCOUTCOMES.113.000551
41. Lundgren S, Poon CYM, Selim A et al. Depression and anxiety in patients undergoing left ventricular assist device implantation. Int J Artif Organs 2018;41:76-83. doi:10.5301/ijao.5000650
42. Sladen RN, Shulman MA, Javaid A et al. Postdischarge Functional Capacity, Health-Related Quality of Life, Depression, Anxiety, and Post-traumatic Stress Disorder in Patients Receiving a Long-term Left Ventricular Assist Device. J Card Fail.2022;28:83-92. doi:10.1016/j.cardfail.2021.07.019
43. Ayesta A, Valero Masa MJ, Vidán MT et al. Prevalence and characterization of frailty, depression, and cognitive impairment in patients listed for heart transplantation: Results of the FELICITAR prospective registry. Clin Transplant 2021;35:e14391. doi:10.1111/ctr.14391
44. Jain V, Karim A, Bansal A et al. Relation of Malnutrition to Outcome Following Orthotopic Heart Transplantation. Am J Cardiol 2021;142:156-157. doi:10.1016/j.amjcard.2020.12.056
45. Gomis-Pastor M, Roig Mingell E, Mirabet Perez S et al. Multimorbidity and medication complexity: New challenges in heart transplantation. Clin Transplant 2019;33:e13682. doi:10.1111/ctr.13682
46. Tse G, Gong M, Wong SH et al. Frailty and Clinical Outcomes in Advanced Heart Failure Patients Undergoing Left Ventricular Assist Device Implantation: A Systematic Review and Meta-analysis. J Am Med Dir Assoc 2018;19:255-261. doi:10.1016/j.jamda.2017.09.022

47. Uzun HG, Simsek E, Engin C et al. Relation Between Frailty and 1-Year Outcomes After Implantation of a Left Ventricular Assist Device. Am J Cardiol 2022;173:88-93. doi:10.1016/j.amjcard.2022.02.041
48. Ali U, Giudicatti L, Lee F et al. Outcomes of Cardiac Transplantation in Western Australia – A Contemporary Single Centre Experience. Hear Lung Circ 2022;31:1685-1691. doi:10.1016/j.hlc.2022.08.020
49. Pavol MA, Boehme AK, Willey JZ et al. Predicting post-LVAD outcome: Is there a role for cognition? Int J Artif Organs 2021;44:237-242. doi:10.1177/0391398820956661
50. Bürker BS, Gullestad L, Gude E et al. The predictive value of depression in the years after heart transplantation for mortality during long-term follow-up. Psychosom Med 2019;81:513-520. doi:10.1097/PSY.0000000000000702

## Supplementary Data

Supplementary Table S1. Overview of the comprehensive geriatric assessment, stratified by the medical, mental, functional and social domains

Supplementary Table S2. The prespecified categories into which the treatment recommendations were grouped

Supplementary Table S3. Criteria to determine frailty based on Fried's Frailty criteria

Supplementary Table S4. Criteria to determine frailty based on the Edmonton Frail scale

Supplementary Table S5. Demographics and results of the comprehensive geriatric assessment in patients screened for left ventricular assist device or heart transplantation, stratified by the presence of a left ventricular assist device

Supplementary Table S6. Demographics and results of the comprehensive geriatric assessment in patients screened for left ventricular assist device or heart transplantation, stratified by age

Supplementary Table S7. Demographics and results of the comprehensive geriatric assessment in patients screened for left ventricular assist device or heart transplantation, stratified by INTERMACS profile

Supplementary Table S8. Treatment recommendations resulting from the comprehensive geriatric assessment, stratified by the presence of a left ventricular assist device

Supplementary Table S9. Treatment recommendations resulting from the comprehensive geriatric assessment, stratified by age

Supplementary Table S10. Treatment recommendations resulting from the comprehensive geriatric assessment, stratified by INTERMACS profile

Supplementary Figure S1. Flow chart of patient inclusion

**Supplementary Table S1.** Overview of the comprehensive geriatric assessment, stratified by the medical, mental, functional and social domains

| Variable | Testing method | Range | Cut-off score and interpretation |
|---|---|---|---|
| Frailty | Edmonton Frail scale[1] | 0-17 | 0-5 no frailty; 6-7 pre-frail; 8-9 mild frail; 10-11 moderate frail; 12-17 severe frail |
| | Fried frailty criteria[2] | 0-5 | 0 no frailty; 1-2 pre-frail; ≥3 frail |
| Medical domain | | | |
| Comorbidity | Charlson Comorbidity Index[3] | 0-33* | ≥3 high morbidity burden |
| Medication use | | | ≥5 medications polypharmacy; ≥ 10 medications hyperpolypharmacy |
| Renal function | estimated glomerular filtration rate (eGFR) | | eGFR <60 reduced renal function |
| Liver function | MELD-score[4] | | ≥14 reduced liver function |
| Bone mineral density | DEXA-scan, T-score | | T-score -1 to -2.5 osteopenia; T-score <2.5 osteoporosis |

| | | | |
|---|---|---|---|
| Mental domain | | | |
| Cognition | Mini mental state examination[5]<br>Montreal Cognitive Assessment[6] | 0-30<br>0-30 | ≤24 cognitive impairment<br>≤25 cognitive impairment |
| Mood | Geriatric depression scale (GDS-15)[7] | 0-15 | ≥5 depression |
| Psychological resilience | Resilience Evaluation Scale[8] | 0-36 | No formal cut-off scores available. To dichotomize, we determined the cut-off score the following way: 1 standard deviation under the mean --> 21 |
| Quality of life | Minnesota Living with Heart Failure Questionnaire[9] | 0-105 | <24 good; 24-45 moderate; >45 poor quality of life |
| Functional domain | | | |
| Functional status | KATZ-6<br>KATZ-9<br>KATZ-15[10] | 0-6<br>0-9<br>0-15 | ≥1 dependence in activities of daily living (ADL)<br>≥1 dependence in instrumental ADL<br>≥1 dependence in (instrumental) ADL |
| Nutritional status | Mini Nutritional Assessment[11] | 0-14 | 12-14 normal; 8-11 at risk of malnutrition; 0-7 malnutrition |
| Body mass index | Weight in kg/ height in $m^2$ | | >25 obesity |
| Mobility | 4-meter gait speed[12]<br>Timed up and go test[13]<br>Falls in previous 6 months<br>Use of walking aid | | ≤0.8 m/s impaired gait speed<br>≥ 10 seconds impaired mobility<br>Increased fall risk |
| Handgrip strength | Hand dynamometer | | Age- and sex-specific cut-off scores for decreased handgrip strength[14] |
| Social domain | | | |
| Living situation | | | Receiving help from caregiver or professional care: living dependent |
| Caregiver burden | Caregiver Strain Index (CSI)[15] | 0-13 | CSI<7 low caregiver burden, CSI ≥7 high caregiver burden |
| Educational level, career | | | |
| Relation status, children | | | |

*The Charlson Comorbidity Index was calculated without assigning points for age

± Medications with an equal Anatomical Therapeutic Chemical (ATC)-3 code (equal therapeutic subgroup) count as 1 medicine. Dermatological preparations, eye drops, food supplements without prescription and medication only taken when necessary were not included in determining the number of medications used. Combination preparations of 2 medications with different ATC-3 codes count as 2 different medications.

DEXA, Dual-energy x-ray absorptiometry; MELD, model for end-stage liver disease

**Supplementary Table S2.** The prespecified categories into which the treatment recommendations were grouped

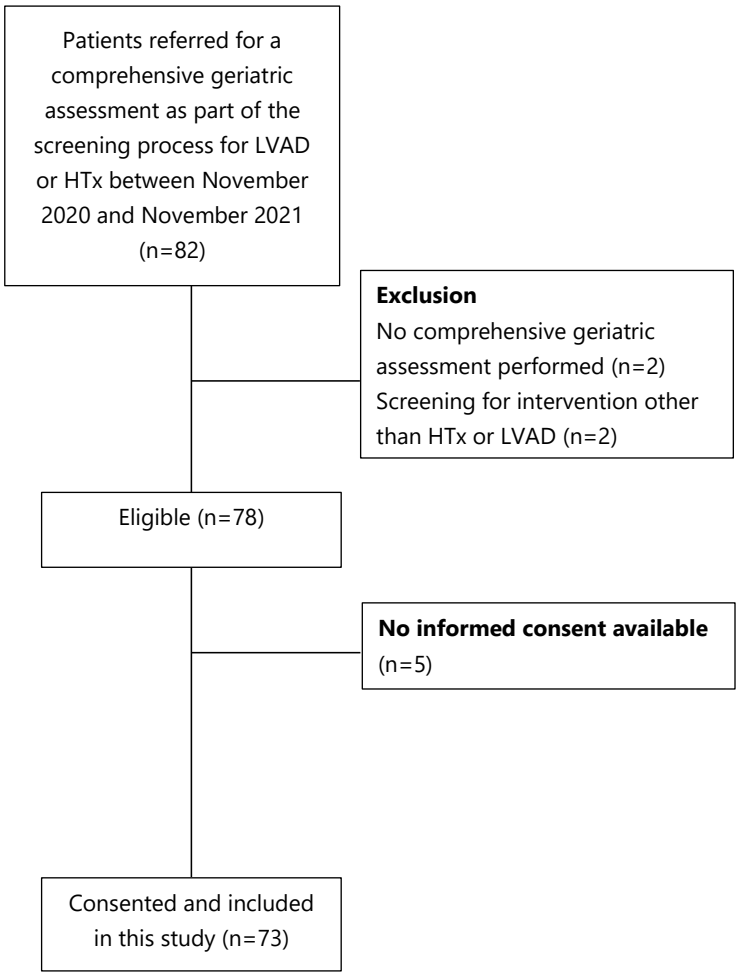
| Treatment recommendations categories |
|---|
| Recommendations on whether the patient is an appropriate candidate for LVAD or HTx |
| Recommendations regarding the diagnosis and treatment of osteoporosis and sarcopenia |
| Recommendations regarding other somatic problems |
| Recommendations regarding medication modifications |
| Recommendations regarding (the analysis of) cognition |
| Recommendations regarding (the analysis of) mood and mental support for both patients and relatives |
| Recommendations regarding delirium risk and prevention |
| Recommendations regarding malnutrition and weight reduction |
| Recommendations regarding mobility and fall prevention |
| Recommendations regarding intoxications (alcohol, tobacco, drugs) |
| Recommendations regarding (cardiac) rehabilitation |
| Recommendations regarding a patient's care needs and strengthening of social and financial support |
| Recommendations regarding education, patient counselling, shared decision making and advance care planning |
| Other recommendations |

**Supplementary Table S3.** Criteria to determine frailty based on Fried's Frailty criteria[2]

| Criteria (one point for each positive criterion) | Measurement |
|---|---|
| 1. Weight loss | Unintentional weight loss of more than 5 kilograms in the last year |
| 2. Exhaustion | Positive response to either of the statements:<br>- For the past week, most of the time (more than 3-4 days) I felt that everything I did was an effort<br>- For the past week, most of the time (more than 3-4 days) I could not get going |
| 3. Weakness | Decreased grip strength (women ≤16 kilograms, men ≤27 kilograms) |
| 4. Slow walking speed | Time to walk 4 meters >5 seconds |
| 5. Decreased physical activity | Assessed by the need for assistance with any of the activities of daily living |

**Supplementary Table S4.** Criteria to determine frailty based on the Edmonton Frail scale[1]

| Frailty domain | Item | 0 points | 1 point | 2 points |
|---|---|---|---|---|
| Cognition | Clock Drawing Test: place numbers the correct positions on a pre-drawn circle, and place hands to indicate the time of 'ten past eleven' | No errors | Minor spacing errors | Other errors |
| General health status | In the past year, how many times have you been admitted to a hospital? | 0 | 1-2 | ≥3 |
| | In general, how would you describe your health? | - Excellent<br>- Very good<br>- Good | Fair | Poor |
| Functional independence | With how many of the following activities do you require help? (meal preparation, shopping, transportation, telephone, housekeeping, laundry, managing money, taking medications) | 0-1 | 2-4 | 5-8 |
| Social support | When you need help, can you count on someone who is willing and able to meet your needs? | Always | Sometimes | Never |
| Medication use | Do you use five or more different medications on a regular basis? | No | Yes | |
| | At times, do you forget to take your medications? | No | Yes | |
| Nutrition | Have you recently lost weight such that your clothing has become looser? | No | Yes | |
| Mood | Do you often feel sad or depressed? | No | Yes | |
| Continence | Do you have a problem with losing control of urine when you don't want to? | No | Yes | |
| Functional performance | Timed Up and Go test: "sit in this chair with your back and arms resting. Then, when I say 'GO', please stand up and walk at a safe and comfortable pace to the mark on the floor (approximately 3m away), return to the chair and sit down" | 0-10 seconds | 11-20 seconds | Either: >20 seconds or patient unwilling or requires assistance |




**Supplementary Figure S1.** Flow chart of patient inclusion
HTx, heart transplantation; LVAD, left ventricular assist device

**Supplementary Table S5.** Demographics and results of the comprehensive geriatric assessment in patients screened for left ventricular assist device or heart transplantation, stratified by the presence of a left ventricular assist device

| Demographics | | No LVAD N=47 | % | LVAD N=26 | % | P-value |
|---|---|---|---|---|---|---|
| **Screening during hospitalization** | | 27 | 57.4 | 2 | 7.7 | <0.01 |
| **Screening for** | HTx | 13 | 27.7 | 25 | 96.2 | <0.01 |
| | LVAD | 32 | 68.1 | 1 | 3.8 | |
| | Both HTx/LVAD | 2 | 4.3 | 0 | | |
| **Age** | Years [Mean ± SD] | 57.1 ± 7.6 | | 59.4 ± 6.9 | | 0.22 |
| **Sex** | Male | 34 | 72.3 | 17 | 65.4 | 0.54 |
| **Aetiology cardiomyopathy** | Dilated | 20 | 42.6 | 14 | 53.8 | 0.07 |
| | Ischaemic | 18 | 38.3 | 12 | 46.2 | |
| | Congenital | 2 | 4.3 | 0 | | |
| | Hypertrophic | 4 | 8.5 | 0 | | |
| | Other | 3 | 6.4 | 0 | | |
| **INTERMACS profile** | 2 | 4 | 8.5 | 0 | | <0.01 |
| | 3 | 10 | 21.3 | 0 | | |
| | 4 | 23 | 48.9 | 0 | | |
| | 5 | 9 | 19.1 | 0 | | |
| | 6 | 1 | 2.1 | 0 | | |
| | Not applicable due to LVAD | 0 | | 26 | 100 | |
| **Frailty** | | | | | | |
| **Edmonton Frail scale** | No frailty | 35 | 79.5 | 24 | 96.0 | 0.07 |
| | Pre-frail | 5 | 11.4 | 1 | 4.0 | |
| | Mild frail | 4 | 9.1 | 0 | | |
| | Moderate frail | 0 | | 0 | | |
| | Severe frail | 0 | | 0 | | |
| | Missing | 3 | 6.4 | 1 | 3.8 | |
| **Fried frailty criteria** | No frailty | 23 | 50.0 | 16 | 61.5 | 0.55 |
| | Pre-frail | 19 | 41.3 | 9 | 34.6 | |
| | Frail | 4 | 8.7 | 1 | 3.8 | |
| | Missing | 1 | 2.1 | 0 | | |
| **Medical domain** | | | | | | |
| **BMI** | kg/m$^2$ [Mean ± SD] | 26.1 ± 3.8 | | 24.6 ± 3.5 | | 0.09 |
| | >25 | 24 | 53.3 | 8 | 44.4 | 0.52 |
| | Missing | 2 | 4.3 | 8 | 30.8 | |
| **BSA** | m$^2$ [Mean ± SD] | 2.01 ± 0.22 | | 1.92 ± 0.18 | | 0.32 |
| | Missing | 2 | 4.3 | 8 | 30.8 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Smoking status** | Former | 27 | 57.4 | 16 | 61.5 | 0.73 |
| | Current | 0 | | 1 | 3.8 | 0.36 |
| **Alcohol use status** | Current | 19 | 42.2 | 14 | 53.8 | 0.34 |
| | Missing | 2 | 4.3 | 0 | | |
| **Comorbidity** | CCI [Mean ± SD] | 2.0 ± 0.9 | | 2.4 ± 0.9 | | 0.07 |
| **High morbidity burden** | CCI ≥3 | 12 | 25.5 | 10 | 38.5 | 0.25 |
| **Medication use** | Number [Mean ± SD] | 7.2 ± 2.7 | | 7.4 ± 2.0 | | 0.89 |
| | Polypharmacy | 31 | 70.5 | 23 | 88.5 | 0.09 |
| | Hyperpolypharmacy | 7 | 15.9 | 3 | 11.5 | |
| | Missing | 3 | 6.4 | 0 | | |
| **Reduced renal function** | eGFR<60 | 17 | 36.2 | 4 | 15.4 | 0.06 |
| **Reduced liver function** | MELD-score ≥14 | 16 | 35.6 | 1 | 3.8 | <0.01 |
| | Missing | 2 | 4.3 | 0 | | |
| **Bone mineral density** | Normal | 11 | 39.3 | 7 | 33.3 | 0.08 |
| | Osteopenia | 16 | 57.1 | 10 | 47.6 | |
| | Osteoporosis | 1 | 3.6 | 4 | 19.0 | |
| | Missing | 19 | 40.4 | 5 | 19.2 | |
| | | | | | | |
| **Mood** | Depression | 15 | 32.6 | 6 | 23.1 | 0.39 |
| | Missing | 1 | 2.1 | 0 | | |
| **MMSE** | [Mean ± SD] | 28.8 ± 0.8 | | 29.3 ± 0.6 | | 0.26 |
| **MOCA** | [Mean ± SD] | 27.3 ± 1.6 | | 27.2 ± 2.6 | | 0.47 |
| **Impaired cognition** | MMSE ≤24 or MOCA ≤25 | 5 | 10.6 | 5 | 19.2 | 0.31 |
| **Resilience Evaluation Scale** | [Mean ± SD] | 27.0 ± 5.0 | | 26.4 ± 5.6 | | 0.76 |
| | ≤ 21 | 6 | 12.8 | 3 | 12.0 | 1.00 |
| | Missing | 0 | | 1 | 3.8 | |
| **Quality of life** | Good | 8 | 17.0 | 12 | 46.2 | <0.01 |
| | Moderate | 12 | 25.5 | 9 | 34.6 | |
| | Poor | 27 | 57.4 | 5 | 19.2 | |
| **Functional domain** | | | | | | |
| **Dependence in ADL** | | 4 | 8.5 | 7 | 26.9 | 0.05 |
| **Dependence in iADL** | | 23 | 48.9 | 7 | 26.9 | 0.07 |
| **Dependence in (i)ADL** | | 23 | 48.9 | 11 | 42.3 | 0.59 |
| **Nutritional status** | Normal | 23 | 48.9 | 19 | 73.1 | 0.12 |
| | At risk of malnutrition (8-11) | 19 | 40.4 | 6 | 23.1 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Malnutrition (0-7) | 5 | 10.6 | 1 | 3.8 | |
| **Reduced 4-meter gait speed** | | 0 | | 0 | | |
| | Missing | 8 | 17.0 | 0 | | |
| **Reduced TUGT** | | 3 | 7.5 | 1 | 3.8 | 0.59 |
| | Missing | 7 | 14.9 | 0 | | |
| **Reduced handgrip strength*** | | 27 | 57.4 | 15 | 57.7 | 0.98 |
| **Mobility** | ≥1 fall in previous 6 months | 4 | 8.7 | 3 | 11.5 | 0.70 |
| | Missing | 1 | 2.1 | 0 | | |
| | Use of walking aid | 4 | 8.5 | 1 | 3.8 | 0.65 |
| **Social domain** | | | | | | |
| **Living situation** | At home without care | 28 | 62.2 | 13 | 50.0 | 0.56 |
| | At home with household help | 7 | 15.6 | 6 | 23.1 | |
| | At home with help from caregiver | 9 | 20.0 | 5 | 19.2 | |
| | At home with professional care | 1 | 2.2 | 2 | 7.7 | |
| | Missing | 2 | 4.3 | 0 | | |
| **Educational level** | Primary and secondary school | 18 | 38.3 | 9 | 36.0 | 0.95 |
| | Secondary vocational education | 12 | 25.5 | 6 | 24.0 | |
| | Bachelor's/master's degree | 17 | 36.2 | 10 | 40.0 | |
| | Missing | 0 | | 1 | 3.8 | |
| **Employed** | Yes | 19 | 40.4 | 7 | 26.9 | 0.16 |
| | No | 23 | 48.9 | 15 | 57.7 | |
| | Retired | 5 | 10.6 | 4 | 15.4 | |
| **In a relationship** | Yes | 38 | 80.9 | 21 | 80.8 | 1.00 |
| **Having children** | Yes | 37 | 78.7 | 21 | 80.8 | 0.84 |
| **Caregiver burden** | Low caregiver burden | 21 | 53.8 | 13 | 54.2 | 0.94 |
| | High caregiver burden | 11 | 28.2 | 6 | 25.0 | |
| | No caregiver | 7 | 17.9 | 5 | 20.8 | |
| | Missing | 8 | 17.0 | 2 | 7.7 | |

*corrected for age and sex
Missing values are indicated for each variable in the table
ADL, activities of daily living; BMI, body mass index; BSA, body surface area; CCI, Charlson Comorbidity Index; eGFR, estimated glomerular filtration rate; iADL, instrumental activities of daily living; MELD, model for end-stage liver disease; MMSE, mini mental state examination; MoCA, montreal cognitive assessment; TUGT, timed up and go test.

**Supplementary Table S6.** Demographics and results of the comprehensive geriatric assessment in patients screened for left ventricular assist device or heart transplantation, stratified by age

| Demographics | | Age <60 N=39 | % | Age ≥60 N=34 | % | P-value |
|---|---|---|---|---|---|---|
| **Screening during hospitalization** | | 17 | 43.6 | 11 | 32.4 | 0.33 |
| **Screening for** | HTx | 21 | 53.8 | 17 | 50.0 | 0.24 |
| | LVAD | 16 | 41.0 | 17 | 50.0 | |
| | Both HTx/LVAD | 2 | 5.1 | 0 | | |
| **Age** | Years [Mean ± SD] | 52.5 ± 5.6 | | 64.1 ± 2.9 | | <0.01 |
| **Sex** | Male | 27 | 69.2 | 24 | 70.6 | 0.90 |
| **Aetiology cardiomyopathy** | Dilated | 18 | 46.2 | 16 | 47.1 | 0.22 |
| | Ischaemic | 14 | 35.9 | 16 | 47.1 | |
| | Congenital | 1 | 2.6 | 1 | 2.9 | |
| | Hypertrophic | 4 | 10.3 | 0 | | |
| | Other | 2 | 5.1 | 1 | 2.9 | |
| **INTERMACS profile** | 2 | 2 | 5.1 | 2 | 5.9 | 0.36 |
| | 3 | 7 | 17.9 | 3 | 8.8 | |
| | 4 | 13 | 33.3 | 10 | 29.4 | |
| | 5 | 6 | 15.4 | 3 | 8.8 | |
| | 6 | 1 | 2.6 | 0 | | |
| | Not applicable due to LVAD | 10 | 25.6 | 16 | 47.1 | |
| **Frailty** | | | | | | |
| **Edmonton Frail scale** | No frailty | 31 | 83.8 | 28 | 87.5 | 0.66 |
| | Pre-frail | 3 | 8.1 | 3 | 9.4 | |
| | Mild frail | 3 | 8.1 | 1 | 3.1 | |
| | Moderate frail | 0 | | 0 | | |
| | Severe frail | 0 | | 0 | | |
| | Missing | 2 | 5.1 | 1 | 2.9 | |
| **Fried frailty criteria** | No frailty | 18 | 47.4 | 21 | 61.8 | 0.28 |
| | Pre-frail | 18 | 47.4 | 10 | 29.4 | |
| | Frail | 2 | 5.3 | 3 | 8.8 | |
| | Missing | 1 | 2.6 | 0 | | |
| **Medical domain** | | | | | | |
| **BMI** | kg/m$^2$ [Mean ± SD] | 25.9 ± 4.0 | | 25.4 ± 3.5 | | 0.15 |
| | >25 | 17 | 48.6 | 15 | 53.6 | 0.69 |
| | Missing | 4 | 10.3 | 6 | 17.6 | |
| **BSA** | m$^2$ [Mean ± SD] | 1.98 ± 0.20 | | 1.99 ± 0.22 | | 0.12 |
| | Missing | 4 | 10.3 | 6 | 17.6 | |
| **Smoking status** | Former | 23 | 59.0 | 20 | 58.8 | 0.99 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Current | 0 | | 1 | 2.9 | 0.47 |
| **Alcohol use status** | Current | 15 | 38.5 | 18 | 56.3 | 0.14 |
| | Missing | 0 | | 2 | 5.9 | |
| **Comorbidity** | CCI [Mean ± SD] | 2.0 ± 1.1 | | 2.3 ± 0.8 | | 0.07 |
| **High morbidity burden** | CCI ≥3 | 9 | 23.1 | 13 | 38.2 | 0.16 |
| **Medication use** | Number [Mean ± SD] | 6.5 ± 2.4 | | 8.1 ± 2.2 | | 0.01 |
| | Polypharmacy | 30 | 78.9 | 24 | 75.0 | 0.01 |
| | Hyperpolypharmacy | 2 | 5.3 | 8 | 25.0 | |
| | Missing | 1 | 2.6 | 2 | 5.9 | |
| **Reduced renal function** | eGFR<60 | 7 | 17.9 | 14 | 41.2 | 0.03 |
| **Reduced liver function** | MELD-score ≥14 | 9 | 23.7 | 8 | 24.2 | 0.96 |
| | Missing | 1 | 2.6 | 1 | 2.9 | |
| **Bone mineral density** | Normal bone mineral density | 10 | 38.5 | 8 | 34.8 | 0.55 |
| | Osteopenia | 12 | 46.2 | 14 | 60.9 | |
| | Osteoporosis | 4 | 15.4 | 1 | 4.3 | |
| | Missing | 13 | 33.3 | 11 | 32.4 | |
| **Mental domain** | | | | | | |
| **Mood** | Depression | 13 | 34.2 | 8 | 23.5 | 0.32 |
| | Missing | 1 | 2.6 | 0 | | |
| **MMSE** | [Mean ± SD] | 28.8 ± 0.6 | | 29.0 ± 1.1 | | 0.49 |
| **MOCA** | [Mean ± SD] | 27.2 ± 2.0 | | 27.3 ± 2.1 | | 0.85 |
| **Impaired cognition** | MMSE ≤24 or MOCA ≤25 | 4 | 10.3 | 6 | 17.6 | 0.50 |
| **Resilience Evaluation Scale** | [Mean ± SD] | 26.8 ± 5.0 | | 26.7 ± 5.6 | | 0.61 |
| | ≤ 21 | 4 | 10.3 | 5 | 14.7 | 0.73 |
| **Quality of life** | Good | 11 | 28.2 | 9 | 26.5 | 0.87 |
| | Moderate | 12 | 30.8 | 9 | 26.5 | |
| | Poor | 16 | 41.0 | 16 | 47.1 | |
| **Functional domain** | | | | | | |
| **Dependence in ADL** | | 3 | 7.7 | 8 | 23.5 | 0.06 |
| **Dependence in iADL** | | 17 | 43.6 | 13 | 38.2 | 0.64 |
| **Dependence in (i)ADL** | | 18 | 46.2 | 16 | 47.1 | 0.94 |
| **Nutritional status** | At risk of malnutrition | 14 | 35.9 | 11 | 32.4 | 0.22 |
| | Malnutrition | 5 | 12.8 | 1 | 2.9 | |
| **Reduced 4-meter gait speed** | | 0 | | 0 | | |
| | Missing | 5 | 12.8 | 3 | 8.8 | |
| **Reduced TUGT** | | 2 | 5.9 | 2 | 6.3 | 0.42 |
| | Missing | 5 | 12.8 | 2 | 5.9 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Reduced handgrip strength*** | | 25 | 64.1 | 17 | 50.0 | 0.22 |
| **Mobility** | ≥1 fall in previous 6 months | 2 | 5.3 | 5 | 14.7 | 0.24 |
| | Missing | 1 | 2.6 | 0 | | |
| | Use of walking aid | 2 | 5.1 | 3 | 8.8 | 0.66 |
| **Social domain** | | | | | | |
| **Living situation** | At home without care | 23 | 60.5 | 18 | 54.5 | 0.81 |
| | At home with household help | 6 | 15.8 | 7 | 21.2 | |
| | At home with help from caregiver | 8 | 21.1 | 6 | 18.2 | |
| | At home with professional care | 1 | 2.6 | 2 | 6.1 | |
| | Missing | 1 | 2.6 | 1 | 2.9 | |
| **Educational level** | Primary and secondary school | 13 | 33.3 | 14 | 42.4 | 0.71 |
| | Secondary vocational education | 10 | 25.6 | 8 | 24.2 | |
| | Bachelor's/master's degree | 16 | 41.0 | 11 | 33.3 | |
| | Missing | 0 | | 1 | 2.9 | |
| **Employed** | Yes | 16 | 41.0 | 10 | 29.4 | <0.01 |
| | No | 23 | 59.0 | 15 | 44.1 | |
| | Retired | 0 | | 9 | 26.5 | |
| **In a relationship** | Yes | 30 | 76.9 | 29 | 85.3 | 0.37 |
| **Having children** | Yes | 30 | 76.9 | 28 | 82.4 | 0.57 |
| **Caregiver burden** | Low caregiver burden (CSI<7) | 16 | 45.7 | 18 | 64.3 | 0.34 |
| | High caregiver burden (CSI ≥7) | 11 | 31.4 | 6 | 21.4 | |
| | No caregiver | 8 | 22.9 | 4 | 14.3 | |
| | Missing | 4 | 10.3 | 6 | 17.6 | |

*corrected for age and sex

Missing values are indicated for each variable in the table

ADL, activities of daily living; BMI, body mass index; BSA, body surface area; CCI, Charlson Comorbidity Index; eGFR, estimated glomerular filtration rate; iADL, instrumental activities of daily living; MELD, model for end-stage liver disease; MMSE, mini mental state examination; MoCA, montreal cognitive assessment; TUGT, timed up and go test.

**Supplementary Table S7.** Demographics and results of the comprehensive geriatric assessment in patients screened for left ventricular assist device or heart transplantation, stratified by INTERMACS (IM) profile

| Demographics | | IM 1-3 N=14 | % | IM 4-6 N=33 | % | P-value |
|---|---|---|---|---|---|---|
| **Screening during hospitalization** | | 13 | 92.9 | 14 | 42.4 | <0.01 |
| **Screening for** | HTx | 3 | 21.4 | 10 | 30.3 | 0.36 |
| | LVAD | 11 | 78.6 | 21 | 63.6 | |
| | Both HTx/LVAD | 0 | | 2 | 6.1 | |
| **Age** | Years [Mean ± SD] | 56.4 ± 8.4 | | 57.4 ± 7.3 | | 0.68 |
| **Sex** | Male | 11 | 78.6 | 23 | 69.7 | 0.73 |
| **Aetiology cardiomyopathy** | Dilated | 8 | 57.1 | 12 | 36.4 | 0.11 |
| | Ischaemic | 4 | 28.6 | 14 | 42.4 | |
| | Congenital | 0 | | 2 | 6.1 | |
| | Hypertrophic | 0 | | 4 | 12.1 | |
| | Other | 2 | 14.3 | 1 | 3.0 | |
| **INTERMACS profile** | 2 | 4 | 28.6 | 0 | | <0.01 |
| | 3 | 10 | 71.4 | 0 | | |
| | 4 | 0 | | 23 | 69.7 | |
| | 5 | 0 | | 9 | 27.3 | |
| | 6 | 0 | | 1 | 3.0 | |
| | Not applicable due to LVAD | 0 | | 0 | | |
| **Frailty** | | | | | | |
| **Edmonton Frail scale** | No frailty | 6 | 54.5 | 29 | 87.9 | 0.08 |
| | Pre-frail | 3 | 27.3 | 2 | 6.1 | |
| | Mild frail | 2 | 18.2 | 2 | 6.1 | |
| | Moderate frail | | | | | |
| | Severe frail | | | | | |
| | Missing | 3 | 21.4 | 0 | | |
| **Fried frailty criteria** | No frailty | 5 | 38.5 | 18 | 54.5 | 0.12 |
| | Pre-frail | 5 | 38.5 | 14 | 42.4 | |
| | Frail | 3 | 23.1 | 1 | 3.0 | |
| | Missing | 1 | 7.1 | 0 | | |
| **Medical domain** | | | | | | |
| **BMI** | kg/m$^2$ [Mean ± SD] | 25.2 ± 3.6 | | 26.5 ± 3.9 | | 0.22 |
| | >25 | 4 | 28.6 | 20 | 64.5 | 0.03 |
| | Missing | 0 | | 2 | 6.1 | |
| **BSA** | m$^2$ [Mean ± SD] | 1.96 ± 0.21 | | 2.03 ± 0.22 | | 0.31 |
| | Missing | 0 | | 2 | 6.1 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Smoking status** | Former | 7 | 50.0 | 20 | 60.6 | 0.50 |
| | Current | 0 | | 0 | | |
| **Alcohol use status** | Current | 5 | 38.5 | 14 | 43.8 | 0.75 |
| | Missing | 1 | 7.1 | 1 | 3.0 | |
| **Comorbidity** | CCI [Mean ± SD] | 2.0 ± 1.0 | | 2.0 ± 0.9 | | 0.92 |
| **High morbidity burden** | CCI ≥3 | 4 | 28.6 | 8 | 24.2 | 0.73 |
| **Medication use** | Number [Mean ± SD] | 7.3 ± 3.4 | | 7.2 ± 2.5 | | 0.92 |
| | Polypharmacy | 8 | 66.7 | 23 | 71.9 | 0.92 |
| | Hyperpolypharmacy | 2 | 16.7 | 5 | 15.6 | |
| | Missing | 2 | 14.3 | 1 | 3.0 | |
| **Reduced renal function** | eGFR<60 | 4 | 28.6 | 13 | 39.4 | 0.48 |
| **Reduced liver function** | MELD-score ≥14 | 7 | 50.0 | 9 | 29.0 | 0.20 |
| | Missing | 0 | | 2 | 6.1 | |
| **Bone mineral density** | Normal | 2 | 33.3 | 9 | 40.9 | 0.40 |
| | Osteopenia | 4 | 66.7 | 12 | 54.5 | |
| | Osteoporosis | 0 | | 1 | 4.5 | |
| | Missing | 8 | 57.1 | 11 | 33.3 | |
| **Mental domain** | | | | | | |
| **Mood** | Depression | 2 | 14.3 | 13 | 40.6 | 0.10 |
| | Missing | 0 | | 1 | 3.0 | |
| **MMSE** | [Mean ± SD] | 28.5 ± 1.3 | | 28.9 ± 0.6 | | 0.55 |
| **MOCA** | [Mean ± SD] | 27.5 ± 1.6 | | 27.2 ± 1.6 | | 0.58 |
| **Impaired cognition** | MMSE ≤24 or MOCA ≤25 | 2 | 14.3 | 3 | 9.1 | 0.63 |
| **Resilience Evaluation Scale** | [Mean ± SD] | 27.3 ± 4.8 | | 26.9 ± 5.2 | | 0.80 |
| | ≤ 21 | 1 | 7.1 | 5 | 15.2 | 0.65 |
| **Quality of life** | Good | 2 | 14.3 | 6 | 18.2 | 0.83 |
| | Moderate | 3 | 21.4 | 9 | 27.3 | |
| | Poor | 9 | 64.3 | 18 | 54.5 | |
| **Functional domain** | | | | | | |
| **Dependence in ADL** | | 3 | 21.4 | 1 | 3.0 | 0.07 |
| **Dependence in iADL** | | 7 | 50.0 | 16 | 48.5 | 0.92 |
| **Dependence in (i) ADL** | | 7 | 50.0 | 16 | 48.5 | 0.92 |
| **Nutritional status** | Normal | 4 | 28.6 | 19 | 57.6 | 0.12 |
| | At risk of malnutrition (8-11) | 7 | 50.0 | 12 | 36.4 | |
| | Malnutrition (0-7) | 3 | 21.4 | 2 | 6.1 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Reduced 4-meter gait speed** | | 0 | | 0 | | |
| | Missing | 8 | 57.1 | 0 | | |
| **Reduced TUGT** | | 2 | 28.6 | 1 | 3.0 | 0.08 |
| | Missing | 7 | 50.0 | 0 | | |
| **Reduced handgrip strength*** | | 10 | 71.4 | 17 | 51.5 | 0.21 |
| **Mobility** | ≥1 fall in previous 6 months | 3 | 21.4 | 1 | 3.1 | 0.08 |
| | Missing | 0 | | 1 | 3.0 | |
| | Use of walking aid | 1 | 7.1 | 3 | 9.1 | 1.00 |
| **Social domain** | | | | | | |
| **Living situation** | At home without care | 8 | 57.1 | 20 | 64.5 | 0.48 |
| | At home with household help | 2 | 14.3 | 5 | 16.1 | |
| | At home with help from caregiver | 3 | 21.4 | 6 | 19.4 | |
| | At home with professional care | 1 | 7.1 | 0 | | |
| | Missing | 0 | | 2 | 6.1 | |
| **Educational level** | Primary and secondary school | 4 | 28.6 | 14 | 42.4 | 0.67 |
| | Secondary vocational education | 4 | 28.6 | 8 | 24.2 | |
| | Bachelor's/master's degree | 6 | 42.9 | 11 | 33.3 | |
| **Employed** | Yes | 7 | 50.0 | 12 | 36.4 | 0.07 |
| | No | 4 | 28.6 | 19 | 57.6 | |
| | Retired | 3 | 21.4 | 2 | 6.1 | |
| **In a relationship** | Yes | 13 | 92.9 | 25 | 75.8 | 0.24 |
| **Having children** | Yes | 13 | 92.9 | 24 | 72.7 | 0.24 |
| **Caregiver burden** | Low caregiver burden | 5 | 45.5 | 16 | 57.1 | 0.76 |
| | High caregiver burden | 4 | 36.4 | 7 | 25.0 | |
| | No caregiver | 2 | 18.2 | 5 | 17.9 | |
| | Missing | 3 | 21.4 | 5 | 15.2 | |

*corrected for age and sex

Missing values are indicated for each variable in the table

ADL, activities of daily living; BMI, body mass index; BSA, body surface area; CCI, Charlson Comorbidity Index; eGFR, estimated glomerular filtration rate; iADL, instrumental activities of daily living; IM, INTERMACS score; MELD, model for end-stage liver disease; MMSE, mini mental state examination; MoCA, montreal cognitive assessment; TUGT, timed up and go test.

**Supplementary Table S8.** Treatment recommendations resulting from the comprehensive geriatric assessment, stratified by the presence of a left ventricular assist device

| | N=47 | % | N=26 | % | P-value |
|---|---|---|---|---|---|
| | **No LVAD** | | **LVAD** | | |
| **Recommendations per patient Mean ± SD** | 3.5 ± 1.5 | | 3.8 ± 1.7 | | 0.47 |
| **Treatment recommendations categories:*** | | | | | |
| **Eligibility LVAD/HTx intervention** | 44 | 93.6 | 23 | 88.5 | 0.66 |
| **Positive** | 38 | 80.9 | 21 | 80.8 | 0.78 |
| **Negative** | 2 | 4.3 | 1 | 3.8 | |
| **Ambiguous** | 4 | 8.5 | 1 | 3.8 | |
| **Missing** | 3 | 6.4 | 3 | 11.5 | |
| **Osteoporosis and sarcopenia** | 3 | 6.4 | 10 | 38.5 | <0.01 |
| **Other somatic problems** | 10 | 21.3 | 5 | 19.2 | 0.84 |
| **Medication modifications** | 5 | 10.6 | 10 | 38.5 | <0.01 |
| **Cognition** | 6 | 12.8 | 3 | 11.5 | 1.00 |
| **Mood, mental support** | 13 | 27.7 | 1 | 3.8 | 0.01 |
| **Delirium** | 13 | 27.7 | 13 | 50.0 | 0.06 |
| **Malnutrition, weight reduction** | 15 | 31.9 | 9 | 34.6 | 0.81 |
| **Mobility, fall prevention** | 14 | 29.8 | 11 | 42.3 | 0.28 |
| **Intoxications** | 1 | 2.1 | 0 | | 1.00 |
| **(Cardiac) rehabilitation** | 7 | 14.9 | 2 | 7.7 | 0.48 |
| **Care needs, social and financial support** | 7 | 14.9 | 5 | 19.2 | 0.74 |
| **Education, patient counseling, SDM, ACP** | 23 | 48.9 | 6 | 23.1 | 0.03 |
| **Other recommendations** | 1 | 2.1 | 0 | | 1.00 |

* Due to lack of space in the Table, the categories are indicated here in keywords only. See Table 3 of the manuscript for a full description of the treatment recommendations categories.
HTx, heart transplantation; LVAD, left ventricular assist device; SDM, shared decision making; ACP, advance care planning

**Supplementary Table S9.** Treatment recommendations resulting from the comprehensive geriatric assessment, stratified by age

| | N=39 | % | N=34 | % | P-value |
|---|---|---|---|---|---|
| | <60 years | | ≥60 years | | |
| **Recommendations per patient Mean ± SD** | 3.4 ± 1.4 | | 3.8 ± 1.8 | | 0.40 |
| **Treatment recommendations categories:*** | | | | | |
| **Eligibility LVAD/HTx intervention** | 36 | 92.3 | 31 | 91.2 | 1.00 |
| **Positive** | 32 | 82.1 | 27 | 79.4 | 0.62 |
| **Negative** | 2 | 5.1 | 1 | 2.9 | |
| **Ambiguous** | 2 | 5.1 | 3 | 8.8 | |
| **Missing** | 3 | 7.7 | 3 | 8.8 | |
| **Osteoporosis and sarcopenia** | 7 | 17.9 | 6 | 17.6 | 0.97 |
| **Other somatic problems** | 6 | 15.4 | 9 | 26.5 | 0.24 |
| **Medication modifications** | 4 | 10.3 | 11 | 32.4 | 0.02 |
| **Cognition** | 7 | 17.9 | 2 | 5.9 | 0.16 |
| **Mood, mental support** | 9 | 23.1 | 5 | 14.7 | 0.37 |
| **Delirium** | 9 | 23.1 | 17 | 50.0 | 0.02 |
| **Malnutrition, weight reduction** | 11 | 28.2 | 13 | 38.2 | 0.36 |
| **Mobility, fall prevention** | 11 | 28.2 | 14 | 41.2 | 0.24 |
| **Intoxications** | 1 | 2.6 | 0 | | 1.00 |
| **(Cardiac) rehabilitation** | 4 | 10.3 | 5 | 14.7 | 0.73 |
| **Care needs, social and financial support** | 7 | 17.9 | 5 | 14.7 | 0.71 |
| **Education, patient counseling, SDM, ACP** | 20 | 51.3 | 9 | 26.5 | 0.03 |
| **Other recommendations** | 0 | | 1 | 2.9 | 0.47 |

* Due to lack of space in the Table, the categories are indicated here in keywords only. See Table 3 of the manuscript for a full description of the treatment recommendations categories.
HTx, heart transplantation; LVAD, left ventricular assist device; SDM, shared decision making; ACP, advance care planning

**Supplementary Table S10.** Treatment recommendations resulting from the comprehensive geriatric assessment, stratified by INTERMACS (IM) profile

| | N=14 | % | N=33 | % | P-value |
|---|---|---|---|---|---|
| | **IM 1-3** | | **IM 4-6** | | |
| **Recommendations per patient Mean ± SD** | 3.9 ± 1.3 | | 3.3 ± 1.6 | | 0.08 |
| **Treatment recommendations categories:*** | | | | | |
| **Eligibility LVAD/HTx intervention** | 13 | 92.9 | 31 | 93.9 | 1.00 |
| **Positive** | 12 | 85.7 | 26 | 78.8 | 0.35 |
| **Negative** | 1 | 7.1 | 1 | 3.0 | |
| **Ambiguous** | 0 | | 4 | 12.1 | |
| **Missing** | 1 | 7.1 | 2 | 6.1 | |
| **Osteoporosis and sarcopenia** | 1 | 7.1 | 2 | 6.1 | 1.00 |
| **Other somatic problems** | 2 | 14.3 | 8 | 24.2 | 0.70 |
| **Medication modifications** | 2 | 14.3 | 3 | 9.1 | 0.63 |
| **Cognition** | 1 | 7.1 | 5 | 15.2 | 0.65 |
| **Mood, mental support** | 4 | 28.6 | 9 | 27.3 | 1.00 |
| **Delirium** | 4 | 28.6 | 9 | 27.3 | 1.00 |
| **Malnutrition, weight reduction** | 7 | 50.0 | 8 | 24.2 | 0.10 |
| **Mobility, fall prevention** | 6 | 42.9 | 8 | 24.2 | 0.30 |
| **Intoxications** | 0 | | 1 | 3.0 | 1.00 |
| **(Cardiac) rehabilitation** | 3 | 21.4 | 4 | 12.1 | 0.41 |
| **Care needs, social and financial support** | 2 | 14.3 | 5 | 15.2 | 1.00 |
| **Education, patient counseling, SDM, ACP** | 8 | 57.1 | 15 | 45.5 | 0.46 |
| **Other recommendations** | 0 | | 1 | 3.0 | 1.00 |

* Due to lack of space in the Table, the categories are indicated here in keywords only. See Table 3 of the manuscript for a full description of the treatment recommendations categories.
HTx, heart transplantation; LVAD, left ventricular assist device; SDM, shared decision making; ACP, advance care planning

## References


1. Rolfson DB, Majumdar SR, Tsuyuki RT, et al (2006) Validity and reliability of the Edmonton Frail Scale. Age Ageing 35:526–529.
2. Fried LP, Tangen CM, Walston J, et al (2001) Frailty in older adults: Evidence for a phenotype. Journals Gerontol - Ser A Biol Sci Med Sci 56A:146–157.
3. Charlson ME, Pompei P, Ales KL, MacKenzie RC (1987) A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies : Development and Validation. J Chronic Dis 40:373–383.
4. Kamath PS, Wiesner RH, Malinchoc M, et al (2001) A model to predict survival in patients with end-stage liver disease. Hepatology 33:464–470.
5. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198.
6. Nasreddine ZS, Phillips NA, Bédirian V, et al (2005) The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53:695–699.
7. Yesavage JA, Brink TL, Rose TL, et al (1982) Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 17:37–49.
8. van der Meer CAI, te Brake H, van der Aa N, et al (2018) Assessing psychological resilience: Development and psychometric properties of the English and Dutch version of the Resilience Evaluation Scale (RES). Front Psychiatry 9:169.
9. Rector T, Kubo S, Cohn J (1987) Patients' self-assessment of their congestive heart failure: part II: content, reliability and validity of a new measure: the Minnesota Living with Heart Failure Questionnaire. Heart Fail 3:198–209
10. Laan W, Zuithoff NPA, Drubbel I, et al (2014) Validity and reliability of the Katz-15 scale to measure unfavorable health outcomes in community-dwelling older people. J Nutr Health Aging 18:848–854.
11. Rubenstein LZ, Harker JO, Salvà A, et al (2001) Screening for undernutrition in geriatric practice: Developing the Short-Form Mini-Nutritional Assessment (MNA-SF). Journals Gerontol - Ser A Biol Sci Med Sci 56A:M366–M372.
12. Maggio M, Ceda GP, Ticinesi A, et al (2016) Instrumental and non-instrumental evaluation of 4-meter walking speed in older individuals. PLoS One 11:e0153583.
13. Podsiadlo D, Richardson S (1991) The Timed "Up & Go": A Test of Basic Functional Mobility for Frail Elderly Persons. J Am Geriatr Soc 39:142–148.
14. Webb AR, Newman LA, Taylor M, Keogh JB (1989) Hand grip dynamometry as a predictor of postoperative complications. Reappraisal using age standardized grip strengths. J Parenter Enter Nutr 13:30–33.
15. Robinson BC (1983) Validation of a Caregiver Strain Index. Journals Gerontol Ser A Biol Sci Med Sci 38:344–348.

CHAPTER 3

# 3

# The impact of frailty on adverse outcomes after Transcatheter Aortic Valve Replacement in older adults: a retrospective cohort study

Lauren Dautzenberg, Tessa T.M. van Aarle, Pieter R. Stella, Marielle H. Emmelot-Vonk, Marcel A. Weterman, Huiberdina L. Koek

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## Abstract

**Background:** Transcatheter aortic valve replacement (TAVR) is an effective alternative to surgical aortic valve replacement for patients who are at increased surgical risk. Consequently, frailty is common in patients undergoing TAVR.

**Objectives:** This study aims to investigate the impact of frailty on outcomes following TAVR.

**Methods**: A retrospective cohort study was conducted, including all TAVR candidates who visited the geriatric outpatient clinic for a preoperative screening. Frailty status was assessed according to the Groningen Frailty Indicator. The primary outcome of the study was defined as the occurrence of postoperative complications, and this was evaluated according to the Clavien-Dindo classification. An additional analysis was performed to assess the impact of frailty on 1-year all-cause mortality and complications within 30 days of TAVR according to the Valve Academic Research Consortium (VARC-2) criteria. The VARC-2 criteria provide harmonized endpoint definitions for TAVR studies.

**Results***:* In total, 431 patients with a mean age of 80.8 ± 6.2 years were included, of whom 56% were female. Frailty was present in 36% of the participants. Frailty was associated with a higher risk of the composite outcome of complications [adjusted OR 1.55 (95% CI 1.03-2.34)], 30-day mortality [adjusted OR 4.84 (95% CI 1.62-14.49)], three-month mortality [adjusted OR 2.52 (95% CI 1.00-6.28)] and 1-year mortality [adjusted OR 2.96 (95% CI 1.46-6.00)].

**Conclusions:** Frailty is common in TAVR patients and is associated with an increased overall risk of postoperative complications, particularly mortality. Increased optimization of screening and treatment of frailty in the guidelines for valvular heart diseases is recommended.

## Introduction

Aortic valve stenosis is the most prevalent form of valvular heart disease in western countries. The prevalence of aortic stenosis increases with age, and its incidence is expected to increase further due to aging of the population[1, 2]. Symptomatic aortic valve stenosis is associated with high mortality and morbidity rates, including heart failure and pulmonary hypertension[2, 3]. In the past, the standard treatment for aortic valve stenosis was surgical aortic valve replacement (SAVR). Transcatheter aortic valve replacement (TAVR) has been established as an alternative to SAVR for patients who are at a high risk of complications[4]. In comparison to SAVR, TAVR is a less invasive treatment strategy. In current European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) guidelines for the management of valvular heart disease, the use of TAVR is recommended over surgical procedures in older patients with an increased surgical risk[4]. Nevertheless, adverse events such as peripheral vascular complications, stroke, residual aortic regurgitation, and the need for pacemaker implantation are associated with TAVR[5, 6]. Therefore, it is important to identify risk factors that predict adverse outcomes of TAVR. Prior research has indicated that preoperative frailty is a strong predictor of 30-day mortality and late mortality among patients undergoing TAVR[7, 8]. Frailty is commonly defined as a "biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes[9]." Postoperative delirium is frequently observed following TAVR and often leads to prolonged hospital stay and increased mortality[10, 11]. A recent Dutch single-center study has confirmed the association between frailty and postoperative delirium among 213 TAVR patients[12], although a self-developed and not formally validated frailty score was used to assess frailty and the study population was relatively small. Previous studies have examined the impact of frailty on both separate TAVR outcomes and composite outcomes formulated by the Valve Academic Research Consortium (VARC)[7, 8, 13–15]. However, no study has examined the overall risk of a variety of relevant geriatric complications (including re-interventions, intensive care unit admission, falls, infections, delirium, admission to a rehabilitation center, hospital readmission and mortality). The aim of our study is to investigate, using a validated frailty instrument, the association between frailty and the total risk of different complications in a large sample of patients undergoing TAVR.

# Materials and methods

## 2.1 Study design and patient selection

This retrospective single-center cohort study was performed at the University Medical Center Utrecht, a tertiary hospital in the Netherlands. Between January 2014 and December 2019, all TAVR candidates referred to the geriatric outpatient clinic for a geriatric preoperative screening (POS) were included in this study, regardless of age. Patients referred for a POS prior to operations other than TAVR, patients in whom frailty was not determined, patients with cancelled operations, and patients with follow-up appointments after 31 December 2019 were excluded. Ethical approval was waived by The Medical Ethics Committee of the University Medical Center Utrecht due to the retrospective nature of the study and the fact that all the procedures were part of routine care. The study has been conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. According to Dutch national regulations, in the case of file research, there is no obligation to obtain informed consent where the subject himself/herself is not physically involved in the research.

## 2.2 TAVR procedure

The decision for TAVR intervention was determined by a multidisciplinary heart valve team consisting of at least one interventional cardiologist and one cardiac surgeon. The femoral artery was the preferred access site. Procedures were performed under general or local anesthesia according to the decision of the anesthesiologist.

## 2.3 Geriatric preoperative screening

The POS assessment was performed by geriatric nurse practitioners under the supervision of a geriatrician. A comprehensive anamnesis was performed, including patient medical history and current physical complaints. Patients were screened for cognitive impairment using the Mini Mental State Examination (MMSE)[16] or Montreal Cognitive Assessment (MOCA)[17] (<5% of cases), for depression using the Geriatric Depression Scale (GDS)[18], for risk of malnutrition using the Malnutrition Universal Screening Tool (MUST)[19] and for dependence in (instrumental) activities of daily living ((i)ADL) using the KATZ-15 index[20]. Patients underwent a physical examination that included measurement of handgrip strength and gait speed. The Charlson Comorbidity Index (CCI) was assessed to quantify somatic co-morbidity[21]. There is general consensus that a comprehensive geriatric assessment (CGA) is the best approach for identification of frailty[22]. During the CGA, the health of the elderly population is assessed in a systematic manner, focusing on the medical, mental, functional and social domains. Due to the time-consuming nature of the CGA, several screening tools have been developed to detect frailty. In this study, frailty was assessed with the Groningen Frailty Indicator (GFI, Supporting Information Table I)[23, 24]. The GFI is a validated 15-item instrument that determines loss of function and resources

in the four domains of the CGA[25]. After discussing the questions of the GFI with the patient, the geriatric nurse practitioner completed the GFI during the POS assessment. The GFI is widely used in clinical practice and research[24, 26]. During the study period, local guidelines for assessing frailty changed and frailty was also determined in some patients (n=155) using the Edmonton Frail Scale[27]. The EFS determines 9 domains of frailty (cognition, general health status, functional independence, social support, medication use, nutritional status, mood, continence, functional performance) using 10 questions and one physical "timed up and go" assessment. The EFS has been shown to correlate well with various geriatric conditions such as independence, drug use, mood, mental, functional and nutritional status[28]. Additional analyses were performed using frailty data determined with the EFS. It is not known which screening tool is most suitable for determining frailty in patients with cardiovascular disease. Previously, the Clinical Frailty Scale (CFS) has been used for patients with TAVR surgery.[29] Although this screening instrument is easy to use, because it does not require stopwatches, dynamometers or other specialized equipment or personnel, it is also semi-quantitative and subjective in nature, and therefore prone to interobserver variability.[30] Moreover, this instrument is primarily focused on the functional domain, with little or no attention paid to the cognitive, social and medical domains. The GFI and EFS were used in the current study, because of its multidimensional character. Furthermore, data were collected on living situation, alcohol use and smoking status. The American Society of Anesthesiologists (ASA) score was determined for each patient by the anesthesiologist involved[31]. After the geriatric assessment was completed, advice was given on the prevention of delirium, such as perioperative haloperidol prescription or involving family during the period of bedrest. In addition, advice was given on fall prevention, reduction of smoking and alcohol use, and improvement of medication use, mobility and nutritional status. When necessary, (e.g., in case of serious comorbidity or severe cognitive or functional impairment) advice was given to postpone or cancel the operation.



## 2.4 Geriatric postoperative involvement

After the TAVR procedure, patients were visited by a geriatric nurse practitioner to assist in the prevention or treatment of geriatric complications, such as postoperative delirium, falls or stroke. Patients were observed by nurses from the cardiologic department during admission and an additional assessment using the Delirium Observation Screening Scale (DOSS) was performed three times a day. The DOSS screens for typical behavioral patterns related to delirium[32]. The geriatric consulting team confirmed the diagnosis of postoperative delirium and gave treatment advice. A delirium was diagnosed using the criteria of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders[33]: an acute and fluctuating attention and awareness deficit complemented by a disturbance in cognition, which is the direct consequence of another medical condition, substance intoxication or withdrawal or exposure to a toxin. The disturbances in attention,

awareness and cognition are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.

## 2.5 Follow-up

A follow-up appointment with a geriatric nurse practitioner under the supervision of a geriatrician was scheduled for three months after TAVR. Data were collected on the occurrence of postoperative complications.

## 2.6 Data collection and processing

All data were collected from electronic medical records and imported into a database using the Statistical Package for the Social Sciences, version 25 (SPSS Inc., Chicago III, United States).

Demographic variables obtained were age, sex, alcohol status (current use, regardless of amount), smoking status (current use), body mass index (BMI) and living situation. Living situation was considered independent when patients lived in their own house, with or without homecare. Living situation was considered dependent when patients lived in an assisted nursing facility or skilled nursing facility.

Somatic variables obtained were the CCI, ASA class, and medication use. An adjusted CCI score without considering points for age-category was used, because it was assumed that there would be little variation in the age of the patients. This way, only the number of comorbidities was assessed. All types of medication were included, except for eye drops, dermal creams, food supplements without prescription and medication only taken when necessary. Polypharmacy was identified when the patient was using ≥5 medications during the POS visit[34].

Cognitive variables obtained were MMSE (or MOCA in <5% of the cases) and GDS. Functional variables obtained were KATZ-15, MUST, gait speed and handgrip strength. For the purpose of the analyses, all values except BMI were dichotomized at standard cutoff points, as explained in Table I. A cutoff value of ≥6 for the EFS and ≥4 for the GFI indicated frailty[25, 26].

## 2.7 Primary and secondary outcomes

The primary outcome of the study was the occurrence of major postoperative complications categorized by the Clavien-Dindo classification[35]. A recent study demonstrated that the Clavien-Dindo classification offers an accurate reflection of the complexity of postoperative evolution in cardiac adult surgery[36]. Under the Clavien-Dindo classification, complications are graded in five categories according to the required treatment, ranging from any deviation from the normal postoperative course to intensive care admission and death *(*Supporting Information Table II). Grade >II was considered a major postoperative complication. All postoperative complications that

occurred during admission were categorized into the five Clavien-Dindo categories. When multiple complications in different categories occurred, the highest grade was taken into the analysis.

Secondary outcomes are as follows: firstly, during admission, the presence of postoperative delirium confirmed by the geriatric consulting team, postoperative infections treated with antibiotics, occurrence of re-intervention, unplanned intensive care unit admission or admission to a rehabilitation center; and secondly, within three months of TAVR, the occurrence of falls, all-cause mortality, or one or more hospital readmissions. A composite outcome of postoperative complications was created to determine the risk of patients developing one or more of the secondary outcomes. Additionally, complication data were also reported according to the VARC-2 criteria, to determine the relationship between frailty and adverse outcomes after TAVR in a complementary manner[15]. Finally, the association between frailty and all-cause mortality 30 days and 1 year after TAVR surgery was assessed.



## 2.8 Statistical methodology

Dichotomized baseline variables were expressed as numbers and corresponding percentages. Differences in baseline characteristics between frail and non-frail patients were determined by the chi-square test or Fisher's exact test as appropriate. Continuous baseline variables were expressed as means ± standard deviation (SD) and differences between frail and non-frail patients were determined by Student's t-test. All outcome variables were entered into a univariate logistic regression analysis and subsequently into a multivariate logistic regression analysis to determine the relationship between frailty and the outcomes. Odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated. The ORs were adjusted for age and sex. In addition, the presence of effect modification by age was examined.

The number of missing values did not exceed 10%. Therefore, imputation methods were not used. A p-value $\leq 0.05$ was considered statistically significant. The data were analyzed using the Statistical Package for the Social Sciences version 25 (SPSS Inc., Chicago Ill, United States).

# Results

## 3.1 Patient inclusion and baseline characteristics

From January 2014 to December 2019, 484 patients were referred for a geriatric POS, and 431 of these patients were included in this study. Exclusions were due to operations other than TAVR (n=24), incomplete follow-up (n=17), incomplete POS assessments (n=7) and cancelled operations (n=5). A flowchart of the patient inclusion process is presented in Figure I. In most cases, the reason for operation cancelation was severe comorbidities.

Baseline characteristics are summarized in Table I. The mean age of the study population was 80.8 (SD ±6.2) years and 56% (n=240) were female. Frailty (GFI ≥ 4) was present in 36% (n=155) of the study population. Female patients were significantly more often frail. Patients with a dependence in (i)ADL, at risk of malnutrition, or with reduced mobility were significantly more often frail, as were patients with an increased CCI score and patients with polypharmacy. Furthermore, a lower MMSE score and a higher GDS score were significantly more often present in frail patients.

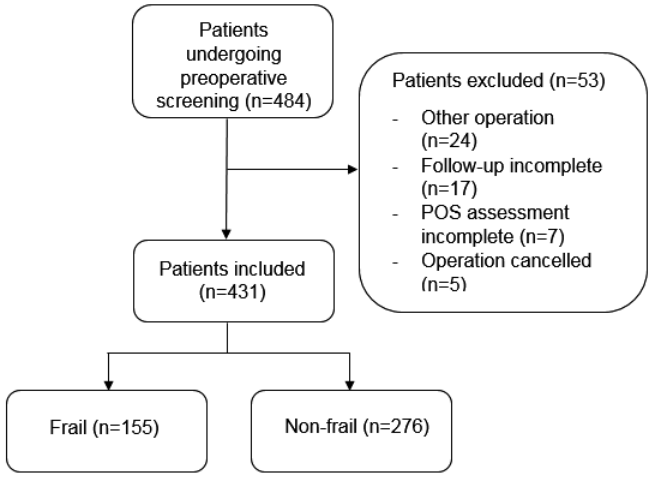


**Figure I** flowchart of patient inclusion

**Table I.** Baseline characteristics of study participants

| | | All (n=431) | Frail (n=155) | Non-frail (n=276) | P-value |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| Age | Years [Mean ± SD] | 80.8 ± 6.2 | 81.7 ± 6.3 | 80.3 ± 6.1 | 0.03 |
| | ≥ 80 years | 284 (66%) | 108 (70%) | 176 (64%) | 0.21 |
| Female sex | | 240 (56%) | 99 (64%) | 141 (51%) | 0.01 |
| Smoking | | 28 (7%) | 11 (7%) | 17 (6%) | 0.71 |
| Alcohol | | 206 (48%) | 53 (34%) | 153 (56%) | <.001 |
| BMI [kg/m$^2$] [Mean ± SD] | | 26.4 ± 4.7 | 26.3 ± 5.6 | 26.5 ± 4.2 | 0.71 |
| Living dependent | | 20 (5%) | 15 (10%) | 5 (2%) | <.001 |
| **Functional status** | | | | | |
| (i)ADL[a] [≥1] | | 268 (64%) | 134 (89%) | 134 (50%) | <.001 |
| MUST[b] [≥1] | | 67 (16%) | 46 (30%) | 21 (8%) | <.001 |
| Gait speed [<0.8 m/s] | | 91 (24%) | 55 (40%) | 36 (14%) | <.001 |
| Handgrip strength [≤20 kg (women) / ≤30 kg (men)] | | 169 (42%) | 76 (53%) | 93 (36%) | <.001 |
| **Somatic status** | | | | | |
| Charlson comorbidity index[c] [≥3] | | 224 (52%) | 97 (63%) | 127 (46%) | <.001 |
| ASA-score[d] [≥3] | | 378 (92%) | 145 (95%) | 233 (90%) | 0.04 |
| Polypharmacy [≥5 medications] | | 340 (79%) | 139 (90%) | 201 (73%) | <.001 |
| **Cognitive and psychological status** | | | | | |
| MMSE[e] [≤24] | | 44 (11%) | 30 (20%) | 14 (5%) | <.001 |
| GDS[a] [≥6] | | 10 (3%) | 8 (6%) | 2 (1%) | <.001 |

SD = Standard Deviation; BMI = Body Mass Index; (i)ADL = (instrumental) Activities of Daily Living; MUST = Malnutrition Universal Screening Tool; ASA = American Society of Anesthesiologists; MMSE = Mini Mental State Examination; GDS = Geriatric Depression Scale
Possible range: [a] 0-15, [b] 0-6, [c] 0-33 (points for age not included), [d] 1-5, [e] 0-30

## 3.2 Postoperative complications

In 28% of the patients, the maximum observed Clavien-Dindo classification grade was I. Prevalence of ascending grades was 16%, 17%, 3% and 3% (Supporting Information Table III). A Clavien-Dindo classification grade ≥II occurred in 43% (n=67) of the frail patients and in 37% (n=103) of the non-frail patients (Figure II). Occurrence of the composite outcome of postoperative complications was 45% in frail patients and 34% in non-frail patients (Figure III). Mortality within three months of TAVR occurred in 5% (n=20) of all patients. Eleven patients were frail (7%) and 9 patients were non-frail (3%). Postoperative delirium was diagnosed in 20 patients (5%); it occurred in 10 frail patients (7%) and 10 non-frail patients (4%). Re-intervention occurred in 13% of frail patients and

17% of non-frail patients. Readmission rates within three months of TAVR were similar for the frail group (10%) and the non-frail group (11%).

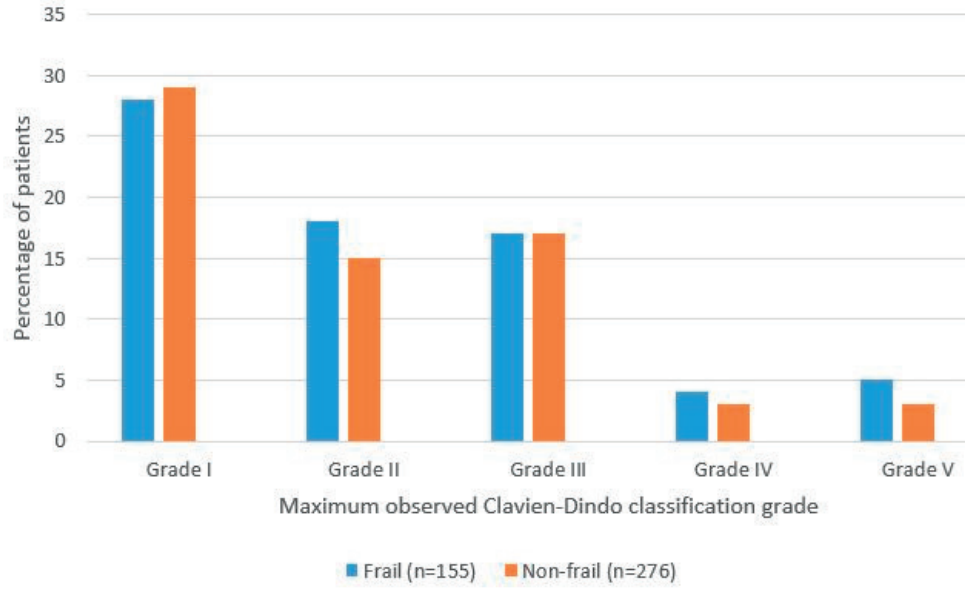


**Figure II** The percentage of patients in whom the maximum observed Clavien-Dindo classification degree was I, II, III, IV or V, respectively

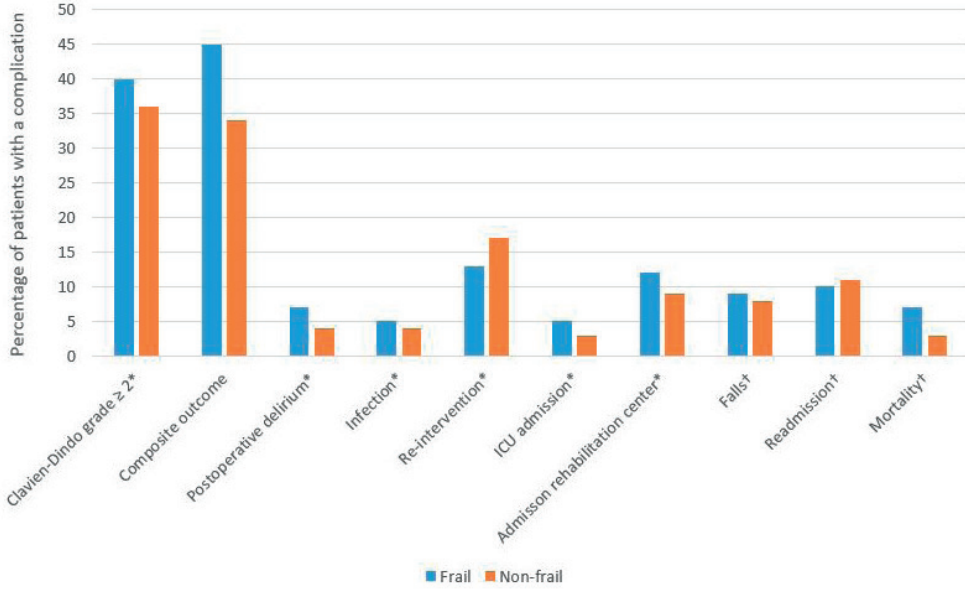


**Figure III** The occurrence of (geriatric) postoperative complications, during admission (indicated by *) and within 3 months of surgery (indicated by †), stratified by frailty status

### 3.3 Association between frailty and postoperative complications

All postoperative complications are presented in Figure III. Frailty was not significantly associated with a higher risk of major postoperative complications, defined as Clavien-Dindo grade ≥2 [OR 1.20; (95% CI 0.80-1.80) $p = 0.39$] (Table II). Frailty was associated with a significantly higher risk of the composite outcome of postoperative complications [OR 1.55; (95% CI 1.03-2.34) $p = 0.04$]. The risk of three-month mortality was significantly higher in frail patients compared to the non-frail group [OR 2.52 (95% CI 1.00-6.28) $p = 0.05$]. The risk of other postoperative complications was not significantly higher for the frail group compared to the non-frail group (all $P \geq 0.18$).

An additional analysis was performed to assess whether the effect of frailty was modified by age. In patients younger than 80 years, frailty was associated with a higher risk of the composite outcome of postoperative complications [OR 2.38 (95% CI 1.14-4.97)], while in patients of 80 years and older, frailty was not significantly associated with a higher risk of this outcome [OR 1.25 (95% CI 0.77-2.05)]. The interaction term for age-frailty was not statistically significant when entered into the multivariate model ($p = 0.28$).



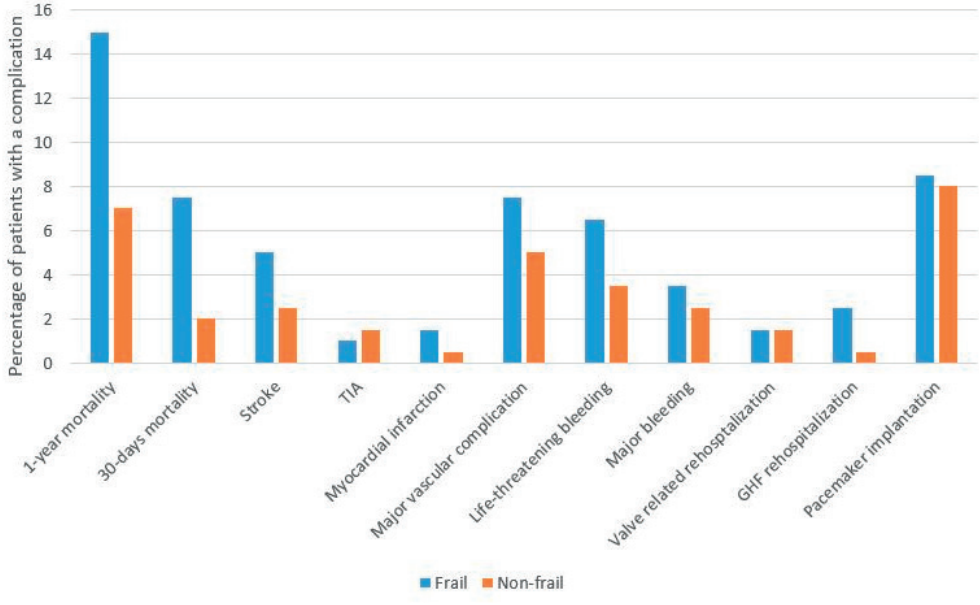


**Figure IV** The occurrence of 1-year mortality and postoperative complications according to the Valve Academic Research Consortium criteria 30-days after TAVR, stratified by frailty status

## Association between frailty, 1-year mortality and complications according to VARC-2 criteria

An additional analysis was performed to determine the association between frailty, 1-year mortality and complications according to the VARC-2 criteria 30 days after TAVR surgery (Figure IV). Frailty was determined by the EFS or, if absent, the GFI. Frailty was significantly associated with an increased mortality risk 30 days after TAVR surgery [OR 4.84 (95% CI 1.62-14.49)] and 1 year after TAVR surgery [OR 2.96 (95% CI 1.46-6.00)] when corrected for age and sex (Table II). Frailty was not significantly associated with an increased complication risk. A subgroup analysis that included only patients in whom frailty was identified by the GFI (n=431) showed that in both the unadjusted analysis [OR 3.45 (95% CI 1.20-9.91)] and the age- and sex-adjusted analysis [OR 3.89 (95% 1.32-11.47)], frailty was significantly associated with an increased risk of mortality. A subgroup analysis including only patients in whom frailty was assessed by the EFS (n=155) showed similar but not statistically significant results, probably due to a power issue [unadjusted OR 2.06 (95% CI 0.21-20.78)] and [adjusted OR 1.81 (95% CI 0.17-19.75)].

**Table II.** The association between frailty and adverse outcomes following TAVR

| | Odds Ratio (95% CI) | | |
|---|---|---|---|
| | **Unadjusted** | **Adjusted[a]** | |
| Clavien-Dindo classification grade ≥ 2[b] | 1.21 (0.81-1.81) | 1.20 (0.80-1.80) | During admission |
| Composite outcome of postoperative complications[c] | 1.55 (1.04-2.32) | 1.55 (1.03-2.34) | |
| Postoperative delirium | 1.86 (0.76-4.57) | 1.80 (0.72-4.86) | During admission |
| Infection | 1.05 (0.41-2.74) | 1.11 (0.42-2.91) | During admission |
| Re-intervention | 0.75 (0.43-1.32) | 0.73 (0.41-1.30) | During admission |
| Intensive care unit admission | 1.82 (0.67-4.96) | 1.99 (0.72-5.46) | During admission |
| Admission to rehabilitation center | 1.45 (0.76-2.77) | 1.45 (0.75-2.80) | During admission |
| Falls | 1.21 (0.57-2.55) | 1.16 (0.54-2.51) | < 3 months |
| Hospital readmission | 0.94 (0.48-1.85) | 1.00 (0.50-1.99) | < 3 months |
| All-cause mortality | 2.27 (0.92-5.60) | 2.52 (1.00-6.28) | < 3 months |
| All-cause mortality[d] | 2.41 (1.23-4.69) | 2.96 (1.46-6.00) | < 1 year |
| All-cause mortality[d] | 4.07 (1.42 – 11.7) | 4.84 (1.62-14.49) | < 30 days |
| Stroke[d] | 2.28 (0.75-6.92) | 2.2 (0.7-6.91) | < 30 days |
| TIA[d] | 0.64 (0.07-5.81) | 0.76 (0.08-7.2) | < 30 days |
| Myocardial infarction[d] | 5.24 (0.47-58.3) | 7.57 (0.61-94.12) | < 30 days |
| Major vascular complication[d] | 1.60 (0.68-3.75) | 1.48 (0.62-3.57) | < 30 days |
| Life-threatening bleeding[d] | 1.94 (0.76-4.95) | 1.92 (0.73-5.06) | < 30 days |
| Major bleeding[d] | 1.49 (0.43-5.19) | 1.77 (0.48-6.51) | < 30 days |
| Valve related rehospitalization[d] | 1.03 (0.20-5.40) | 1.08 (0.20-5.91) | < 30 days |
| Congestive heart failure related rehospitalization[d] | 7.92 (0.82-76.93) | 5.25 (0.53-51.98) | < 30 days |
| Pacemaker implantation[d] | 1.04 (0.48-2.23) | 1.00 (0.46-2.19) | < 30 days |

[a] Adjusted for sex and age

[b] Possible range I - V

[c] Composite outcome consisting of the following variables: postoperative delirium, infection, re-intervention, intensive care unit admission, admission to rehabilitation center, falls, hospital readmission and all-cause mortality within 3 months.

[d] Complications according to the VARC-2 criteria

# Discussion

## 4.1 Main findings

The aim of this study was to determine whether frailty is associated with a higher risk of adverse outcomes after TAVR. In 36% of the participants frailty was present. Frailty was significantly associated with an increased risk of the composite outcome of postoperative complications. In particular, frailty was associated with a higher risk of mortality within 30 days, three months and 1 year of TAVR.

## 4.2 Comparison with other studies

The prevalence of frailty in this study was in accordance with other studies investigating frailty in the TAVR population, ranging from 29 to 63%[8]. To the best of our knowledge, no previous study has investigated the association between frailty and adverse outcomes using the Clavien-Dindo classification. A recent systematic review found some evidence for the association between frailty and the following complications according to VARC criteria: major bleeding complications, blood transfusions, delirium, acute kidney injury, and infections. Frailty was not associated with vascular complications, stroke, or other major complications[8]. The finding of an increased three-month (7% in frail patients, 3% in non-frail patients, OR 2.52) and 1-year (15% in frail patients, 7% in non-frail patients, OR 2.96) mortality risk in frail patients was in accordance with previous studies[7, 8, 37]. A systematic review described a relative risk for six-month mortality ranging from 1.11 to 13.77 and a 30-day mortality risk of 4% to 17% in frail patients and 1% to 6% in non-frail patients, which is consistent with the risk found in this study (7.4% in frail patients and 1.9% in non-frail patients)[8]. In this study, the incidence of delirium after TAVR was 5%, while a recent systematic review found a pooled incidence of postoperative delirium of 8% (95% CI 7-9%)[10]. This small difference may be a result of the geriatric consultation team's involvement.

## 4.3 Strengths and limitations

The strengths of this study are the comprehensiveness of the geriatric assessment and the involvement of the geriatric team in TAVR care, the relatively large study population, the use of a validated multi-domain frailty instrument, and the assessment of the composite outcome. In this study, a wide variety of complications were analyzed using the Clavien-Dindo classification, and there was a focus on secondary outcomes of importance to the geriatric population: delirium, infection, re-intervention, unplanned intensive care unit admission, admission to a rehabilitation center, falls, and hospital readmissions. In order to carefully compare our results with other studies, we performed an additional analysis in which association was determined for frailty and 30-day complications according to the VARC-2 criteria. A recent article on frailty in heart failure patients indicates that decline of physical function (decreased walking speed and grip strength) is not the only phenotype

of frailty[38]. The concept of frailty is a multi-domain problem, featuring problems in physical, psychological, and social domains. This is also evident in Table I of our study, which shows a significant association between frailty and reduced walking speed, reduced grip strength and increased risk of malnutrition (the physical domain) as well as cognitive impairment and depression (the psychological domain) and living dependent (the social domain). Although the GFI aligns with this perspective on frailty, we performed a subgroup analysis including patients in whom frailty had been determined using the EFS, since the more objective "timed up and go" variable is part of the EFS.

This study has some limitations. Firstly, selection bias may exist, since the most frail patients have already been rejected for a TAVR by the cardiologist. However, the prevalence of frailty was similar to other studies. Secondly, due to a change in local guidelines regarding frailty instruments, different frailty instruments were used between January 2014 and December 2019. For this reason, the GFI for some patients was not registered by the geriatric nurse practitioner. For those patients, the GFI was calculated by using information from the preoperative screening in order to determine the frailty status by GFI in each patient. Most information was obtained reliably from medical records, for example by means of other validated scales like the GDS or KATZ-15, which were performed during preoperative screening. Thirdly, during the index admission and follow-up period, we may have missed complications. A delirium is not always well recognized, especially a hypoactive delirium. Regarding the occurrence of falls at home, a recall bias may exist. Data on complications during hospital admission was not available for patients transferred to another hospital after the intervention. Fourthly, the limited number of cases led to a potential power problem when classifying adverse events into specific complications or mortality. Finally, in this study, several screening tools were applied, all of which have been validated in older adults of whom some had cardiovascular disease. However, most of these tools have not been validated specifically in the TAVR population.



## 4.4 Clinical implications and recommendations

This study demonstrates that frailty is not associated with a higher risk of postoperative complications according to the Clavien-Dindo classification or the VARC-2 criteria. The Clavien-Dindo classification grades complications based on the actual treatment of those complications. A cardiologist or cardiac surgeon may have a cautious attitude, particularly in frail patients, regarding the performance of a re-intervention or admission to the intensive care unit. Therefore, the Clavien-Dindo classification is most likely not an appropriate tool for measuring differences in outcomes between frail and non-frail patients. However, it is recommended that the total risk of complications after TAVR is investigated by means of a composite outcome, as this study showed that frail patients had a significantly higher risk of this outcome. Mortality appears to be the most important

factor for this higher risk in frail patients, but there is likely also a cumulative contribution of multiple complications to this risk.

The current ESC guidelines for the management of valvular heart disease recommend TAVR instead of SAVR in frail patients[4]. However, the TAVR guidelines contain very few recommendations regarding screening and treatment of frailty[4, 39]. We recommend that frailty is included in conventional risk models for predicting mortality in cardiac surgery, such as The European System for Cardiac Operative Risk Evaluation (EuroSCORE) and the Society of Thoracic Surgeons (STS) risk score[40]. We advise preoperative screening by the geriatrician to assess frailty status. This screening provides balanced information on the risks and benefits of TAVR and enables shared-decision making[41]. Interventions such as family involvement, co-treatment with geriatrics, or a postoperative cardiac rehabilitation program can be useful in the prevention and postoperative treatment of geriatric complications like delirium or functional decline[40, 42, 43]. Through assessment of frailty, patients can be selected for pre-rehabilitation, as pre-operative interventions to reduce frailty can be useful. A recent systematic review and network meta-analysis on interventions to prevent or reduce the level of frailty found physical activity and nutritional supplementation to be most effective[44]. Effective interventions to improve frailty, quality of life, cognition and mood were physical activity, nutritional supplementation, medication management, psychosocial and cognitive training, and pharmacotherapy. These interventions can be performed or prescribed by geriatricians. Currently, a randomized controlled trial is being conducted in which half of the frail older TAVR candidates receive an intervention consisting of a home-based exercise program and a protein-rich oral nutritional supplement. The effect on several outcomes will be evaluated (The PERFORM-TAVR Trial). We suggest further research on the efficacy and feasibility of the afore mentioned interventions to improve frailty in TAVR candidates in order to improve clinical outcomes.

## 4.5 Conclusion

This study shows that frailty is associated with an increased overall risk of postoperative complications and particularly 30-day, three-month and 1-year mortality in older patients undergoing TAVR. Therefore, recommendations should be made in the TAVR guidelines with respect to the geriatric preoperative screening and treatment of frail patients.

## References


1. Eveborn GW, Schirmer H, Heggelund G, et al (2013) The evolving epidemiology of valvular aortic stenosis. the Tromsø Study. Heart 99:396–400. https://doi.org/10.1136/heartjnl-2012-302265
2. Osnabrugge RLJ, Mylotte D, Head SJ, et al (2013) Aortic stenosis in the elderly: Disease prevalence and number of candidates for transcatheter aortic valve replacement: A meta-analysis and modeling study. J Am Coll Cardiol 62:1002–1012. https://doi.org/10.1016/j.jacc.2013.05.015
3. Faggiano P, Antonini-Canterin F, Ribichini F (2000) Pulmonary artery hypertension in adult patients with symptomatic valvular aortic stenosis. Am J Cardiol 85:204–208
4. Vahanian A, Beyersdorf F, Praz F, et al (2021) 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 1–72. https://doi.org/10.1093/eurheartj/ehab395
5. Reardon MJ, Van Mieghem NM, Popma JJ, et al (2017) Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med 376:1321–1331. https://doi.org/10.1056/NEJMoa1700456
6. Abdelgawad A, Hussein M, Naeim H, et al (2019) A Comparative Study of TAVR Versus SAVR in Moderate and High-Risk Surgical Patients: Hospital Outcome and Midterm Results. Heart Surg Forum 22:E331-E339. https://doi.org/10.1532/hsf.2243
7. Huang LL, Zhou X, Yang XY, Yu H (2018) The impact of preoperative frailty status on outcomes after transcatheter aortic valve replacement: An update of systematic review and meta-analysis. Med 97:e13475. https://doi.org/10.1097/MD.0000000000013475
8. Piankova P, Afilalo J (2020) Prevalence and Prognostic Implications of Frailty in Transcatheter Aortic Valve Replacement. Cardiol Clin 38:75–87. https://doi.org/10.1016/j.ccl.2019.09.011
9. Fried LP, Tangen CM, Walston J, et al (2001) Frailty in older adults: Evidence for a phenotype. Journals Gerontol - Ser A Biol Sci Med Sci 56A:146–157. https://doi.org/10.1093/gerona/56.3.m146
10. Abawi M, Pagnesi M, Agostoni P, et al (2018) Postoperative Delirium in Individuals Undergoing Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis. J Am Geriatr Soc 66:2417–2424. https://doi.org/10.1111/jgs.15600
11. Eide LSP, Ranhoff AH, Fridlund B, et al (2016) Readmissions and mortality in delirious versus non-delirious octogenarian patients after aortic valve therapy: A prospective cohort study. BMJ Open 6:e012683. https://doi.org/10.1136/bmjopen-2016-012683
12. Goudzwaard JA, de Ronde-Tillmans MJAG, El Faquir N, et al (2019) The Erasmus Frailty Score is associated with delirium and 1-year mortality after Transcatheter Aortic Valve Implantation in older patients. The TAVI Care & Cure program. Int J Cardiol 276:48–52. https://doi.org/10.1016/j.ijcard.2018.10.093
13. Thongprayoon C, Cheungpasitporn W, Thamcharoen N, et al (2017) Association of frailty status with acute kidney injury and mortality after transcatheter aortic valve replacement: A systematic review and meta-analysis. PLoS One 12:e0177157. https://doi.org/10.1371/journal.pone.0177157
14. Soud M, Alahdab F, Ho G, et al (2019) Usefulness of skeletal muscle area detected by computed tomography to predict mortality in patients undergoing transcatheter aortic valve replacement:

a meta-analysis study. Int J Cardiovasc Imaging 35:1141–1147. https://doi.org/10.1007/s10554-019-01582-0

15. Kappetein AP, Head SJ, Généreux P, et al (2012) Updated standardized endpoint definitions for transcatheter aortic valve implantation: The valve academic research consortium-2 consensus document. J Am Coll Cardiol 60:1438–1454. https://doi.org/10.1016/j.jacc.2012.09.001
16. Folstein M, Folstein S, McHugh P (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198. https://doi.org/10.1016/0022-3956(75)90026-6
17. Nasreddine ZS, Phillips NA, Bédirian V, et al (2005) The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53:695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x
18. Yesavage JA, Brink TL, Rose TL, et al (1982) Development and Validation of a Geriatric Depression Screening Scale: A Preliminary Report. J Psychiatr Res 17:37-49. https://doi.org/10.1016/0022-3956(82)90033-4
19. Elia M (2003) Nutritional screening of adults: a multidisciplinary responsibility. Development and use of the 'Malnutrition Universal Screening Tool' ('MUST') for adults
20. Laan W, Zuithoff NPA, Drubbel I, et al (2014) Validity and reliability of the Katz-15 scale to measure unfavorable health outcomes in community-dwelling older people. J Nutr Health Aging 18:848–854. https://doi.org/10.1007/s12603-014-0479-3
21. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation. J Chronic Dis 40:373-383. https://doi.org/10.1016/0021-9681(87)90171-8
22. Rajabali N, Rolfson D, Bagshaw SM (2016) Assessment and Utility of Frailty Measures in Critical Illness, Cardiology, and Cardiac Surgery. Can J Cardiol 32:1157–1165. https://doi.org/10.1016/j.cjca.2016.05.011
23. Stevernik N, Slaets JPL, Schuurmans H, van Lis M (2001) Measuring frailty: development and testing the GFI (Groningen Frailty Indicator). Gerontologist 41:236–237
24. Visser L, Banning LBD, El Moumni M, et al (2019) The Effect of Frailty on Outcome After Vascular Surgery. Eur J Vasc Endovasc Surg 58:762–769. https://doi.org/10.1016/j.ejvs.2019.04.031
25. Peters LL, Boter H, Buskens E, Slaets JPJ (2012) Measurement Properties of the Groningen Frailty Indicator in Home-Dwelling and Institutionalized Elderly People. J Am Med Dir Assoc 13:546–551. https://doi.org/10.1016/j.jamda.2012.04.007
26. Dent E, Kowal P, Hoogendijk EO (2016) Frailty measurement in research and clinical practice: A review. Eur J Intern Med 31:3–10. https://doi.org/10.1016/j.ejim.2016.03.007
27. Rolfson DB, Majumdar SR, Tsuyuki RT, et al (2006) Validity and reliability of the Edmonton Frail Scale. Age Ageing 35:526–529. https://doi.org/10.1093/ageing/afl041
28. Perna S, Francis MD, Bologna C, et al (2017) Performance of Edmonton Frail Scale on frailty assessment: its association with multi-dimensional geriatric conditions assessed with specific screening tools. BMC Geriatr 17:1–8. https://doi.org/10.1186/s12877-016-0382-3

29. Shimura T, Yamamoto M, Kano S, et al (2017) Impact of the clinical frailty scale on outcomes after transcatheter aortic valve replacement. Circulation 135:2013–2024. https://doi.org/10.1161/CIRCULATIONAHA.116.025630
30. Afilalo J (2017) The clinical frailty scale: Upgrade your eyeball test. Circulation 135:2025–2027. https://doi.org/10.1161/CIRCULATIONAHA.116.025958
31. Doyle D, Goyal A, Bansal P, Garmon E (2020) American Society of Anesthesiologists Classification (ASA Class). StatPearls Treasure Isl StatPearls Publ
32. Scheffer A, van Munster B, Schuurmans M, de Rooij S (2011) Assessing severity of delirium by the Delirium Observation Screening Scale. Int J Geriatr Psychiatry 26:284–291
33. American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders (5th ed)
34. Veehof LJG, Stewart RE, Haaijer-Ruskamp FM, Meyboom-de Jong B (2000) The development of polypharmacy. A longitudinal study. Fam Pract 17:261–267. https://doi.org/10.1093/fampra/17.3.261
35. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205–213. https://doi.org/10.1097/01.sla.0000133083.54934.ae
36. Hébert M, Cartier R, Dagenais F, et al (2021) Standardizing Postoperative Complications—Validating the Clavien-Dindo Complications Classification in Cardiac Surgery. Semin Thorac Cardiovasc Surg 33:443–451. https://doi.org/10.1053/j.semtcvs.2020.09.029
37. Anand A, Harley C, Visvanathan A, et al (2017) The relationship between preoperative frailty and outcomes following transcatheter aortic valve implantation: A systematic review and meta-analysis. Eur Hear J - Qual Care Clin Outcomes 3:123–132. https://doi.org/10.1093/ehjqcco/qcw030
38. Tanaka S, Yamashita M, Saito H, et al (2021) Multidomain Frailty in Heart Failure: Current Status and Future Perspectives. Curr Heart Fail Rep 18:107–120. https://doi.org/10.1007/s11897-021-00513-2
39. Otto CM, Nishimura RA, Bonow RO, et al (2021) 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines
40. Bando K (2021) Commentary: Appropriate frailty measures should be incorporated into the development of accurate risk calculation models for evaluation of transcatheter aortic valve replacement candidates. J Thorac Cardiovasc Surg 161:2103–2104. https://doi.org/10.1016/j.jtcvs.2020.04.107
41. Skaar E, Øksnes A, Eide LSP, et al (2020) Baseline frailty status and outcomes important for shared decision-making in older adults receiving transcatheter aortic valve implantation, a prospective observational study. Aging Clin Exp Res. https://doi.org/10.1007/s40520-020-01525-z
42. Baumbusch J, Lauck SB, Achtem L, et al (2018) Understanding experiences of undergoing transcatheter aortic valve implantation: one-year follow-up. Eur J Cardiovasc Nurs 17:280–288. https://doi.org/10.1177/1474515117738991

43. Ribeiro GS, Melo RD, Deresz LF, et al (2017) Cardiac rehabilitation programme after transcatheter aortic valve implantation versus surgical aortic valve replacement: Systematic review and meta-analysis. Eur J Prev Cardiol 24:688–697. https://doi.org/10.1177/2047487316686442
44. Negm AM, Kennedy CC, Thabane L, et al (2019) Management of Frailty: A Systematic Review and Network Meta-analysis of Randomized Controlled Trials. J Am Med Dir Assoc 20:1190–1198. https://doi.org/10.1016/j.jamda.2019.08.009

## Supporting Information

*Supporting Information* **Table I.** Groningen Frailty Indicator (GFI) questionnaire[1]

| Domains and items | Yes | No |
|---|---|---|
| **Mobility (can the patient perform any of the following independently? Use of tools like walking stick, wheelchair or walker being allowed)** | | |
| 1. Go shopping | 0 | 1 |
| 2. Walk around outside (around the house or to the neighbors) | 0 | 1 |
| 3. Dressing and undressing | 0 | 1 |
| 4. Toilet visit | 0 | 1 |
| **Vision** | | |
| 5. Does the patient experience problems in daily life because of poor vision? | 1 | 0 |
| **Hearing** | | |
| 6. Does the patient experience problems in daily life because of poor hearing? | 1 | 0 |
| **Nutrition** | | |
| 7. Has the patient involuntarily lost weight (> 6 kg) in the past 6 months (or > 3 kg in one month)? | 1 | 0 |
| **Comorbidity** | | |
| 8. Does the patient currently use four or more different types of medication? | 1 | 0 |
| **Cognition** | | |
| 9. Does the patient currently have complaints about his or her memory (or have a history of dementia)? | 1 | 0 |
| **Psychosocial** | | |
| 10. Does the patient sometimes experience emptiness around him or her? | 1 | 0 |
| 11. Does the patient sometimes miss people around him or her? | 1 | 0 |
| 12. Does the patient sometimes feel abandoned? | 1 | 0 |
| 13. Has the patient recently felt sad or depressed? | 1 | 0 |
| 14. Has the patient recently felt nervous or anxious? | 1 | 0 |
| Physical fitness | | |
| 15. How would the patient grade his or her physical fitness (0–10; ranging from very bad to good)? | 0–6 =1 | 7–10 =0 |
| *A score of four or more is indicated as frail* | | |

*Supporting Information* **Table II.** Clavien-Dindo Classification of surgical complications[2,3]

| Grade | | Definition |
|---|---|---|
| I | | Any deviation from the normal postoperative course without the need for pharmacological treatment, or surgical, endoscopic, and radiological interventions.<br>Allowed therapeutic regimens are: drugs as antiemetic's, antipyretics, analgesics, diuretics and electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside. |
| II | | Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included. |
| III | | Complication requiring surgical, endoscopic, or radiological intervention |
| IIIa | Intervention not under general anesthesia | |
| IIIb | Intervention under general anesthesia | |
| IV | | Life-threatening complication (including central nervous system complications) requiring intensive care unit management |
| IVa | Single organ dysfunction (including dialysis) | |
| IVb | Multi-organ dysfunction | |
| V | | Death of a patient |

*Supporting Information* **Table III.** Highest Clavien-Dindo Classification[a] grade

| | All (n=431) | Frail (n=155) | Non-frail (n=276) |
|---|---|---|---|
| Grade I | 122 (28%) | 43 (28%) | 79 (29%) |
| Grade II | 69 (16%) | 28 (18%) | 41 (15%) |
| Grade III | 73 (17%) | 26 (17%) | 47 (17%) |
| Grade IV | 14 (3%) | 6 (4%) | 8 (3%) |
| Grade V | 14 (3%) | 7 (5%) | 7 (3%) |

[a] Possible range I - V

1. Stevernik N, Slaets JPL, Schuurmans H, et al (2001) Measuring frailty: development and testing the GFI (Groningen Frailty Indicator). Gerontologist 41:236–237.
2. Clavien PA, Barkun J, De Oliveira ML, et al. (2009) The clavien-dindo classification of surgical complications: Five-year experience. Ann Surg 250:187–196.
3. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205–213.

CHAPTER 4

# 4

# Predictors of clinical outcome following transcatheter aortic valve implantation: a prospective cohort study

Lauren Dautzenberg, Judith E.M. Pals, Geert J. Lefeber, Pieter R. Stella, Masieh Abawi, Marielle H. Emmelot-Vonk, Huiberdina L. Koek

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## Abstract

**Objective:** In recent years, transcatheter aortic valve implantation (TAVI) has become the treatment of choice for patients with symptomatic aortic valve stenosis considered to be at increased or high surgical risk. The aim of this study was to identify predictors of postoperative adverse events in older adults undergoing TAVI.

**Methods:** A prospective observational cohort study of patients who were referred to a geriatric outpatient clinic for a geriatric assessment prior to TAVI was conducted. The outcomes were mortality and hospital readmission within three months of TAVI and the occurrence of major postoperative complications during hospitalisation according to the Clavien-Dindo classification. These three outcomes were also combined to a composite outcome. Univariate and multivariate logistic regression analyses were performed to identify predictors of the outcomes and composite outcome of adverse events.

**Results:** This cohort included 490 patients who underwent TAVI (mean age 80.7 ± 6.2 years, 47.3% male). Within 3 months of TAVI, 19 (3.9%) patients died and 46 (9.4%) patients experienced a hospital readmission. A total of 177 (36.1%) patients experienced one or more major complications according to the Clavien-Dindo classification during hospitalisation and 193 patients (39.4%) experienced the composite outcome of adverse events. In multivariate analyses, cognitive impairment was identified as an independent predictor of major postoperative complications (OR 2.16; 95% CI 1.14-4.19) and the composite outcome of adverse events (OR 2.40; 95% CI: 1.21-4.79). No association was found between the other variables and the separate outcomes and composite outcome.

**Conclusion:** cognitive impairment is associated with postoperative adverse events in older patients undergoing TAVI. Therefore, it is important to screen for cognitive impairment prior to TAVI and it is recommended to include this in current TAVI guidelines.

## Introduction

Stenosis of the aortic valve is one of the most common cardiovascular diseases in the Western population.(1,2) It is associated with ageing and affects one in eight individuals aged 75 years and above.(1–3) In recent years, transcatheter aortic valve implantation (TAVI) has become the treatment of choice for patients with symptomatic aortic valve stenosis, considered to be at increased or high surgical risk.(1–3) Common surgical risk scores, such as the European System for Cardiac Operative Risk Evaluation (EuroSCORE) and Society of Thoracic Surgeons (STS) score, are widely used to guide treatment options based on the predicted risk of poor outcomes.(3) These models were created and validated in a standard surgical risk population.(3,4) Therefore, these models do not include relevant risk factors that are specifically prevalent in the geriatric population. (1–3) In recent years, the evidence has grown that frailty can help identify patients who are at increased risk of mortality after a TAVI procedure.(3,4) Therefore, the European Society of Cardiology (ESC) guidelines for the management of valvular heart disease and the guidelines of the American College of Cardiology (ACC) recommend to use frailty scores to determine a patients' suitability for TAVI.(1,2) Previous studies aimed to identify preoperative factors predictive of postoperative adverse outcomes in older patients undergoing TAVI.(3,4) Several predictors of 1-year mortality in older patients has been found, including the presence of frailty, a reduced gait speed and dependence in Activities of Daily Living (ADL). With regard to predictors of short-term outcomes (e.g. 30-day mortality), there have been conflicting results, in particular with respect to frailty.(5–7) The majority of recently created prediction models in older patients focused on the occurrence of long term mortality.(8–10) Since the occurrence of postoperative complications results in substantial burden for patients and health care systems, it is necessary to focus both on postoperative mortality and morbidity and the overall occurrence of these negative outcomes. (11,12)

In this study, we aimed to identify predictors of postoperative adverse events, including mortality, hospital readmissions, major postoperative complications and the composite of these outcomes in older patients undergoing TAVI.



## Methods

### Study design and population

This prospective, single-centre cohort study was conducted at the University Medical Centre Utrecht, a tertiary hospital in the Netherlands. All consecutive patients who visited the geriatric outpatient clinic for a geriatric assessment prior to TAVI between January 2014 and June 2020 were included. Patients were excluded if a) they were referred for a preoperative geriatric assessment prior to another operation than TAVI, b) the TAVI operation was cancelled, or c) the 3-month follow-up appointment was planned after

30 June 2020. Data was collected from patients' electronical medical records during the outpatient clinic visit prior to TAVI, during the TAVI admission and three months post-TAVI. The study involved data obtained from usual care and ethical approval was waived by the local Ethics Committee of the University Medical Centre Utrecht. According to Dutch national regulations, in case of file research, there is no obligation to obtain informed consent. An anonymized data set was used in this study.

## TAVI-procedure

A multidisciplinary heart team consisting of at least one interventional cardiologist and one cardiac surgeon evaluated the patients' suitability for a TAVI-procedure according to current guidelines. A preoperative complete cardiac assessment was performed. The preferred access site was the transfemoral artery. Procedures were performed under local or general anaesthesia. After the TAVI procedure, patients had to take six hours bedrest.

## Preoperative geriatric assessment

The preoperative geriatric assessment was performed by a geriatric nurse practitioner under supervision of a geriatrician and involved a comprehensive geriatric assessment (CGA) in which the following domains were assessed: somatic, psychological, social and functional. An anamnesis was performed and data were collected on medical history, medication use (in particular the presence of (hyper)polypharmacy), smoking status, alcohol use, living situation, dependence in (instrumental) activities of daily living ((i) ADL), nutritional status, the presence of a fall in the previous six months and the presence of a delirium in the past. With regard to the medical history, the Charlson Comorbidity Index (CCI) score was calculated.(13) An adjusted CCI score without scoring points for age-category was used. A cut-off value of ≥3 was defined as multimorbidity. Polypharmacy was defined as the use of five or more medications, excluding food supplements without prescription, medication only taken when necessary, dermal creams and eye drops. Hyperpolypharmacy was defined as the use of ten or more medications. With regard to alcohol use and smoking status patients scored positive if they were current users, regardless of the amount. Patients lived dependent when they lived in a skilled nursing or assisted nursing facility. Patients lived independent when they lived in their own house, with or without homecare. To assess the dependence in (i)ADL the KATZ-15 questionnaire was conducted.(14) Dependence in (i)ADL was defined as a KATZ-15 score ≥2. The nutritional status was assessed using the Malnutrition Universal Screening Tool (MUST).(15) Malnutrition was suspected when the MUST score was ≥1. In addition, the American Society of Anaesthesiologists (ASA) score, determined by an anaesthesiologist, was obtained from the patients' electronical medical records.(16)

Furthermore, a psychical examination was performed, which consisted of measurement of vital signs, gait speed and handgrip strength and a neurological- and functional examination. A decreased gait speed was defined as a gait speed of ≤0.80 meters per

second and a decreased handgrip strength was defined as ≤20 kilograms for women and ≤30 kilograms for men.(17) In addition, a minimal mental state examination (MMSE) or Montreal Cognitive Assessment (<5% of the cases, MoCA) was conducted to assess cognitive function.(18,19) A MMSE score ≤24 or MoCA score <26 was indicative for cognitive impairment. To assess the possible presence of a depression, the Geriatric Depression Scale (GDS) questionnaire was conducted. A GDS-15 score ≥6 was suggestive of a depression.(20)

Frailty was assessed according to the Groningen Frailty Indicator (GFI).(21) This is an internationally applied, validated frailty instrument which offers a multidomain view on the degree of frailty. The GFI questionnaire consists of 15 questions, covering all domains of the CGA. Frailty was present in case of a GFI score of ≥4. Due to varying standard instruments to determine frailty in recent years, the GFI score was not reported in all patients by the geriatric nurse practitioner. In these cases, the GFI score was determined by the authors based on information collected during the preoperative geriatric assessment. A few questions of the GFI could not be filled in retrospectively. Therefore, the answers to these questions were rated as missing and the total GFI score was calculated, excluding these questions. Based on the results of the CGA, advice was provided on perioperative delirium prevention including both non-pharmacologic interventions and pharmacological interventions if indicated. Furthermore, advice was provided concerning fall-prevention, medication management, mobility, optimising nutritional status and reducing alcohol use and smoking. In some cases, it was recommended to cancel or postpone the TAVI procedure, for example in case of multimorbidity or severe functional or cognitive impairment. Nonetheless, the cardiologist made the ultimate decision.



## Postoperative geriatric involvement

One day after the TAVI procedure, a geriatric nurse practitioner visited the patient on the cardiac ward to assist in the prevention or treatment of complications prevalent in the geriatric population (e.g. falls, delirium, stroke). Nurses from the cardiac ward observed the patients during the hospital stay and in case a postoperative delirium was suspected, the Delirium Observation Screening Scale (DOSS) was assessed three times a day. The DOSS is an early recognition tool for delirium, based on observations by nurses. A score of three and higher indicates a delirium.(22) A postoperative delirium was confirmed by the geriatric consulting team, based on criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).(23) A postoperative delirium was treated by non-pharmacological interventions and if indicated, by pharmacological treatment like haloperidol.

## Follow-up

Three months after the TAVI procedure there was a follow-up appointment with a geriatric nurse practitioner, mostly by phone. Patients were asked about their general well-being

and physical complaints compared to the situation before the procedure. Data was collected on the occurrence of postoperative complications. Patients were also followed by their cardiologist six and twelve months after TAVI.

## Outcomes

The outcomes were mortality and hospital readmissions within three months of TAVI and major postoperative complications during hospitalisation according to the Clavien-Dindo classification (Supplement Table 1).(24,25) The Clavien-Dindo classification was already successfully implemented as outcome classification method in other surgical specialties (e.g. noncardiac thoracic surgery, colorectal surgery and urologic surgery) (26–30) and a recent study proved that this classification adequately measures the quantity and severity of postoperative complications in adult cardiac surgery.(31) The Clavien-Dindo classification consists of five categories, each category represents the type of therapy which was required to correct the complication. The need for pharmacological treatment is reflected in category I and II. Category III to IV range from a complication requiring a surgical, endoscopic or radiological intervention to a life-threatening complication requiring intensive care (unit) management. For example, an arrhythmia requiring the placement of a pacemaker is a Clavien-Dindo grade III complication. Category V reflects the death of a patient.(24,25) A composite outcome was created in which the three outcomes were combined. A Clavien-Dindo grade of II and higher was considered a major postoperative complication. When a patient suffered from two or more complications in different grade categories, the highest grade was used in the analysis.

## Statistical analysis

The prevalence of dichotomized baseline variables is presented as numbers and corresponding percentages. Continuous baseline variables are expressed as mean and standard deviation. In case there were more than 10% missing values for a variable (which holds for the GDS), the Little's MCAR test was performed to determine whether missing values were completely at random or not. Since the results of the Little's MCAR test showed no significance ($p>0.05$), multiple imputation methods were not indicated. Univariate logistic regression analyses were performed to identify potential predictors of the outcomes and the composite outcome. Before entering continuous variables into the univariate logistic regression analysis, we first performed the Box-Tidwell procedure to assess whether the continuous variables were linearly related to the logit of the dependent variable. All variables with p-value $\leq 0.10$ in univariate analyses were entered into a stepwise multivariate analysis. Odds Ratios (OR) with a 95% Confidence Interval (CI) were calculated. Analyses were performed using IBM Statistical Package for the Social Sciences, version 25 (SPSS Inc., Chicago III, United States).

# Results

## Patient inclusion and baseline characteristics

A total of 555 patients visited the geriatric outpatient clinic for a geriatric assessment prior to TAVI between January 2014 and June 2020. 65 patients were excluded from this study. Reasons for exclusion were referral to the geriatric outpatient clinic because of a preoperative assessment for an intervention other than TAVI (n=31), no three-month follow-up data available because the follow-up appointment was scheduled after 30 June 2020 (n=20), insufficient information collected during preoperative assessment (n=10) and cancellation of the TAVI procedure (n=4). Operations were mostly cancelled due to severe comorbidities. Finally, 490 patients were included in the study. The baseline characteristics of the study population are outlined in Table 1. Mean age was 80.7 ± 6.2 years. 5 percent were between the age of 50 and 70 and 28% 85 years or older. 232 patients (47.3%) were male. A total of 170 patients (34.7%) were frail. The mean logistic EuroSCORE was 14.8%.

**Table 1.** Baseline characteristics

| | | N | % |
|---|---|---|---|
| **All patients** | | 490 | |
| **Demographics** | | | |
| Age | Years [Mean ±SD] | 80.7 ±6.2 | |
| | Age ≥80 years | 319 | 65.1 |
| Sex | Male | 232 | 47.3 |
| Smoking | Current smoker | 31 | 6.3 |
| | Ex-smoker | 198 | 40.4 |
| Alcohol use | Current alcohol user | 241 | 49.2 |
| **Frailty** | | | |
| GFI[a] | ≥4 | 170 | 34.7 |
| **Somatic status** | | | |
| ASA class[b] | ≥3 | 456 | 93.1 |
| CCI[c] | ≥3* | 258 | 52.7 |
| Medication use | Number [Mean ±SD] | 8.4 ±4.5 | |
| | Polypharmacy (≥5 medications) | 408 | 83.3 |
| | Hyperpolypharmacy (≥10 medications) | 163 | 33.3 |
| **Cognitive and psychological status** | | | |
| MMSE[d] | [Mean ±SD] | 27.5 ±2.5 | |
| | MMSE ≤24 | 47 | 9.6 |
| MOCA[d] | [Mean ±SD] | 26 ±3.4 | |
| | MOCA <26 | 8 | 1.6 |
| Impaired cognition | MMSE ≤24 or MOCA <26 | 55 | 11.2 |
| GDS[a] | ≥6 | 17 | 3.5 |

| | | | |
|---|---|---|---|
| Delirium | In past | 48 | 9.8 |
| **Social status** | | | |
| Living situation | Dependent | 22 | 4.5 |
| **Functional status** | | | |
| Dependence in ADL[e] | KATZ6 ≥1 | 114 | 23.3 |
| Dependence in iADL[f] | KATZ9 ≥1 | 287 | 60.5 |
| Dependence in (i)ADL[a] | KATZ15 ≥2 | 225 | 45.9 |
| (At risk of) malnutrition[e] | MUST ≥1 | 75 | 15.3 |
| Gait speed | <0.8 m/s | 98 | 20 |
| Handgrip strength | ≤20 kg female / ≤30 kg male | 246 | 50.2 |
| Falls | ≥1 in previous 6 months | 93 | 19.1 |

* Points for age category not included

SD: standard deviation GFI: Groningen Frailty Indicator, ASA: American Society of Anaesthesiologists, CCI: Charlson Comorbidity Index, MMSE: Mini-Mental State Examination, MOCA: Montreal Cognitive Assessment, GDS: Geriatric Depression Scale, (i)ADL: (Instrumental) Activities of Daily Living, MUST: Malnutrition Universal Screening Tool, m/s: meters per second, kg: kilograms

[a]Score range from 0 to 15, [b]score range from 1 to 5, [c]score range from 0 to 24, [d]score range from 0 to 30, [e]score range from 0 to 6, [f]score range from 0 to 9.

**Table 2.** Occurrence of outcome measures

| | N | % |
|---|---|---|
| Mortality within three months of TAVI | 19 | 3.9 |
| Hospital readmission within three months of TAVI | 46 | 9.4 |
| Complications according to Clavien-Dindo during admission | 177 | 36.1 |
| Clavien-Dindo Grade I | 144 | 29.4 |
| Clavien-Dindo Grade II | 69 | 14.1 |
| Clavien-Dindo Grade IIIa | 66 | 13.5 |
| Clavien-Dindo Grade IIIb | 15 | 3.1 |
| Clavien-Dindo Grade IVa | 14 | 2.9 |
| Clavien-Dindo Grade IVb | 2 | 0.4 |
| Clavien-Dindo Grade V | 12 | 2.4 |
| Composite outcome* | 193 | 39.4 |

*Including mortality and hospital readmission within three months of TAVI and the occurrence of major postoperative complications (Clavien-Dindo Grade ≥II) during hospitalisation

### Mortality and hospital readmissions within three months of TAVI

Occurrence of outcome measures are displayed in Table 2. Twelve patients (2.4%) died during hospital admission and 19 patients (3.9%) died within three months of TAVI. In total, there were 46 readmissions (9.4%), of which 22 (48%) were cardiac, 23 (50%) non-cardiac and for one readmission (2%) the reason could not be traced in the patient file. Cardiac reasons for readmission were often arrhythmias requiring pacemaker implantation or acute decompensated heart failure. Non-cardiac reasons were among others infections (requiring intravenous antibiotics) or cerebrovascular events. Due to the limited number of outcome events within three months of TAVI, logistic regression analyses to identify independent predictors were not feasible.

### Occurrence of major postoperative complications during hospitalisation

A total of 177 (36.1%) patients experienced one or more major postoperative complications (Clavien-Dindo Grade ≥II) during hospital admission. Results of the univariate and multivariate analysis are displayed in Table 3. Univariate analysis showed that cognitive impairment (OR 2.30; 95% CI 1.30-4.07), dependence in (i)ADL (OR 1.57; 95% CI 1.08-2.30), and a decreased gait speed (OR 1.64; 95% CI 1.04-2.60) were significantly associated with a higher risk of a major postoperative complication during hospitalisation. Multivariate analysis showed that cognitive impairment was independently associated with a higher risk of a major postoperative complication during hospital admission (OR 2.16; 95% CI 1.14-4.19).

**Table 3.** Variables associated with major postoperative complications* during hospitalisation

| Demographics | Univariate OR [95% CI] | p value | Multivariate OR [95% CI] | p value |
|---|---|---|---|---|
| Age | 1.00 [0.97-1.03] | 0.91 | | |
| Sex (male) | 1.37 [0.94-1.98] | 0.10 | 0.91 [0.59-1.40] | 0.66 |
| Current smoker | 1.12 [0.53-2.37] | 0.76 | | |
| Alcohol user | 0.62 [0.42-0.89] | **0.01** | 0.78 [0.50-1.21] | 0.26 |
| **Frailty** | | | | |
| GFI ≥4[a] | 1.43 [0.96-2.13] | 0.08 | 0.73 [0.42-1.24] | 0.24 |
| **Somatic status** | | | | |
| ASA class ≥3[b] | 0.91 [0.44-1.86] | 0.79 | | |
| CCI ≥3**[c] | 1.37 [0.94-1.98] | 0.10 | 1.22 [0.80-1.87] | 0.35 |
| Polypharmacy | 1.11 [0.67-1.83] | 0.68 | | |
| Hyperpolypharmacy | 1.27 [0.86-1.88] | 0.22 | | |
| **Cognitive and psychological status** | | | | |
| MMSE ≤24 or MOCA <26[d] | 2.30 [1.30-4.07] | <0.01 | 2.16 [1.14-4.19] | 0.02 |
| GDS ≥6[a] | 0.57 [0.18-1.77] | 0.33 | | |
| Delirium in past | 1.06 [0.57-1.96] | 0.85 | | |
| **Social status** | | | | |
| Living dependent | 2.20 [0.93-5.21] | 0.07 | 1.59 [0.60-4.23] | 0.35 |
| **Functional status** | | | | |
| Katz15 ≥2[a] | 1.57 [1.08-2.30] | **0.02** | 1.20 [0.73-1.97] | 0.47 |
| MUST ≥1[e] | 1.06 [0.64-1.77] | 0.81 | | |
| Gait speed < 0.8m/s | 1.64 [1.04-2.60] | **0.03** | 1.47 [0.85-2.55] | 0.17 |
| Handgrip strength ≤20 kg/≤30 kg*** | 1.00 [0.68-1.47] | >0.99 | | |
| Falls in previous 6 months | 1.37 [0.86-2.17] | 0.18 | | |

*Clavien-Dindo Grade ≥II

** Points for age category not included

***≤20 kg female / ≤30 kg male

GFI: Groningen Frailty Indicator, ASA: American Society of Anaesthesiologists, CCI: Charlson Comorbidity Index, MMSE: Mini-Mental State Examination, MOCA: Montreal Cognitive Assessment, GDS: Geriatric Depression Scale, MUST: Malnutrition Universal Screening Tool, m/s: meters per second, kg: kilograms

[a]Score range from 0 to 15, [b]score range from 1 to 5, [c]score range from 0 to 24, [d]score range from 0 to 30, [e]score range from 0 to 6.

## Composite outcome of adverse events

A total of 193 (39.4%) patients experienced the composite outcome consisting of mortality or hospital readmission within three months of TAVI and occurrence of major postoperative complications (Clavien-Dindo Grade ≥ II) during hospitalisation. Results from the univariate and multivariate analyses of the composite outcome are presented in Table 4. Cognitive impairment was statistically significant associated with an increased risk of the composite outcome in both univariate (OR 2.56; 95% CI 1.41-4.65) and multivariate analysis (OR 2.40; 95% CI 1.21-4.79). Univariate analysis showed that current alcohol use was associated with a lower risk (OR 0.62; 95% CI 0.43-0.90) and living dependently (OR 2.49; 95% CI 1.01-6.13), dependence in (i)ADL (OR 1.74; 95% CI 1.20-2.54) and a decreased gait speed (OR 1.62; 95% CI 1.02-2.56) with a higher risk of the composite outcome. In the multivariate analysis, these factors were not identified as independent predictors of the composite outcome.

**Table 4.** Variables associated with the composite outcome consisting of mortality or hospital readmission within three months of TAVI and occurrence of major postoperative complications (Clavien-Dindo Grade ≥ II) during hospitalisation

| Composite outcome: postoperative adverse events | Univariate OR [95% CI] | p value | Multivariate OR [95% CI] | p value |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age | 1.01 [0.98-1.04] | 0.51 | | |
| Sex (male) | 0.87 [0.60-1.25] | 0.45 | | |
| Current smoker | 1.13 [0.54-2.38] | 0.75 | | |
| Alcohol user | 0.62 [0.43-0.90] | **0.01** | 0.77 [0.50-1.19] | 0.23 |
| **Frailty** | | | | |
| GFI ≥4[a] | 1.47 [0.99-2.19] | 0.06 | 0.67 [0.39-1.15] | 0.14 |
| **Somatic status** | | | | |
| ASA class ≥3[b] | 1.11 [0.54-2.27] | 0.78 | | |
| CCI ≥3*[c] | 1.38 [0.96-2.00] | 0.09 | 1.23 [0.81-1.86] | 0.34 |
| Polypharmacy | 1.18 [0.72-1.95] | 0.52 | | |
| Hyperpolypharmacy | 1.27 [0.86-1.87] | 0.23 | | |
| **Cognitive and psychological status** | | | | |
| MMSE ≤24 or MOCA <26[d] | 2.56 [1.41-4.65] | <0.01 | 2.40 [1.21-4.79] | 0.01 |
| GDS ≥6[a] | 0.46 [0.15-1.45] | 0.19 | | |
| Delirium in past | 1.20 [0.66-2.21] | 0.55 | | |
| **Social status** | | | | |
| Living dependent | 2.49 [1.01-6.13] | **0.05** | 1.85 [0.66-5.19] | 0.24 |
| **Functional status** | | | | |
| Katz15 ≥2[a] | 1.74 [1.20-2.54] | **<0.01** | 1.42 [0.87-2.31] | 0.16 |

| | | | | |
|---|---|---|---|---|
| MUST ≥1[e] | 1.03 [0.62-1.71] | 0.90 | | |
| Gait speed < 0.8m/s | 1.62 [1.02-2.56] | **0.04** | 1.32 [0.76-2.28] | 0.32 |
| Handgrip strength ≤20 kg/≤30 kg*** | 1.11 [0.76-1.63] | 0.58 | | |
| Falls in previous 6 months | 1.39 [0.88-2.19] | 0.16 | | |

* Points for age category not included **≤20 kg female / ≤30 kg male

GFI: Groningen Frailty Indicator, ASA: American Society of Anaesthesiologists, CCI: Charlson Comorbidity Index, MMSE: Mini-Mental State Examination, MOCA: Montreal Cognitive Assessment, GDS: Geriatric Depression Scale, MUST: Malnutrition Universal Screening Tool, m/s: meters per second, kg: kilograms

[a]Score range from 0 to 15, [b]score range from 1 to 5, [c]score from range 0 to 24, [d]score range from 0 to 30, [e]score range from 0 to 6.

## Discussion

The aim of this study was to identify predictors of postoperative adverse outcomes in older patients undergoing TAVI. Cognitive impairment was identified as an independent predictor of major postoperative complications during hospitalisation and the composite outcome of major complications, hospital readmissions and mortality. No association was found between the other variables and the composite and separate outcomes.

The finding of cognitive impairment as an independent predictor of worse outcomes in older patients is in line with previous studies conducted in patients undergoing TAVI. Yanagisawa et al. evaluated if the presence of preoperative cognitive impairment was associated with postoperative adverse outcomes, in particular 1-year cumulative mortality. (32) They included TAVI patients aged 70 or higher, whose cognitive performance was assessed using the MMSE. They found that patients with cognitive impairment had more in-hospital adverse outcomes (major bleeding, vascular complications, acute kidney injury, prolonged hospital stay) and that cognitive impairment was an independent predictor of 1-year all-cause mortality.(32)

Khan et al. included TAVI patients who were screened on the presence of geriatric risk factors. (33) They found that the presence of cognitive deficits (according to the Mini-Cog test) was associated with the occurrence of a postoperative delirium and 30-day mortality.(33)

A possible explanation for this finding could be that patients with cognitive impairment are more prone to develop a postoperative delirium and that this is reflected in our outcome 'major postoperative complications during hospitalisation according to the Clavien-Dindo classification' and the composite outcome. However, only a minority (11.3%) of all patients with a Clavien-Dindo grade II complication experienced a delirium for which pharmacological treatment was necessary. Another explanation, as stated by Yanagisawa et al., could be that a part of the patients with cognitive deficits are known to suffer from vascular cognitive impairment caused by systemic vascular risk factors.(32) The presence of these vascular risk factors might explain the increased risk of postoperative morbidity in patients with cognitive impairment. In contrast to previous studies conducted in TAVI patients(3,4), we did not find an association between other variables, like frailty, and

postoperative adverse outcomes. A possible explanation for this finding could be that all TAVI patients included in our study had a preoperative CGA. Based on the results of the CGA, an extensive advice was given with regard to identified risk factors. Therefore, our study population differs from the study population in previous studies, since all patients in our study had a preoperative intervention consisting of a CGA and the subsequent advice for appropriate treatment to prevent/reduce postoperative adverse outcomes.

This study has several strengths. The study design was prospective and a relatively large number of patients was included. Whereas previous studies mostly focused on separate outcomes, in particular mortality, this study also assessed a composite outcome, including mortality and hospital readmission within three months of TAVI and the occurrence of major postoperative complications during hospitalisation, assessing both postoperative mortality and morbidity. Therefore, an advantage of this composite outcome is that it reflects the overall course following TAVI. Furthermore, we included a wide variety of potential preoperative predictive factors, covering all the different domains of the CGA. In this study, frailty was assessed by a validated frailty instrument that includes all domains of the CGA and therefore it offers a broad assessment of frailty in comparison to other frailty instruments that cover less domains of the CGA.(21)

This study has some limitations. Due to the limited number of events for mortality and hospital readmission within 3 months of TAVI, planned logistic regression analyses were not feasible. Furthermore, during the study period, the local guidelines regarding frailty instruments were changing. Therefore, for a number of patients, the GFI score was not reported by the geriatric nurse practitioner and had to be calculated by the authors. However, some questions of the GFI are subjective and could not be filled in retrospectively. The answers for these questions were rated as missing, and the total GFI score was calculated, excluding these questions. This might have resulted in an underestimation of the number of frail patients. However, the frailty prevalence in this study corresponded to the prevalence range (29 to 63%) of frailty in patients undergoing TAVI that was found in a recent meta-analysis.(34) Lastly, during the 3-month follow-up appointment with the geriatric nurse practitioner, patients were often not explicitly asked if they had been readmitted to a hospital within three months of TAVI. This may lead to an underestimation of the number of participants with a readmission if a patient was admitted to a hospital other than the University Medical Centre Utrecht.



## Clinical implications

The results of this study have some important clinical implications. We found cognitive impairment to be independently associated with a higher risk of postoperative adverse events. Screening for cognitive impairment with a screening tool like the MMSE or MoCA could help identify patients who are at increased risk of unfavourable outcomes and will provide additional information on the potential risks of TAVI, which improves shared-decision making. Therefore, we advise to include screening for cognitive impairment in

the current local and international guidelines.(1) The 2017 ACC expert consensus on a decision pathway for TAVI in the management of adults with aortic stenosis, is innovative by advising to assess cognition by means of the MMSE, however, cognitive function is not yet included in their four proposed risk categories.(2) In addition, if a patient is suspected of cognitive decline or impairment after screening for cognitive impairment, he or she could be monitored more closely during admission and afterwards, especially by a geriatric team in order to detect and anticipate on problems in an early stage.

## Conclusion

This study identified cognitive impairment as an independent predictor of postoperative adverse events in older patients undergoing TAVI. Therefore, it is important to screen for cognitive impairment prior to TAVI, as this can identify patients who are at increased risk to develop a postoperative adverse event. It is recommended to include screening for cognitive impairment in current TAVI guidelines.

## References


1. Falk V, Baumgartner H, Bax JJ, et al. Guidelines for the management of valvular heart disease. Eur J cardio-thoracic Surg . 2017;52(4):616–64.
2. Otto CM, Kumbhani DJ, Alexander KP, et al. 2017 ACC Expert Consensus Decision Pathway for Transcatheter Aortic Valve Replacement in the Management of Adults With Aortic Stenosis: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol . 2017;69(10):1313–46.
3. Anand A, Harley C, Visvanathan A, et al. The relationship between preoperative frailty and outcomes following transcatheter aortic valve implantation: A systematic review and meta-analysis. Eur Hear J - Qual Care Clin Outcomes. 2017;3(2):123–32.
4. van Mourik MS, Velu JF, Lanting VR, et al. Preoperative frailty parameters as predictors for outcomes after transcatheter aortic valve implantation: a systematic review and meta-analysis. Netherlands Hear J. 2020;28(5):280–92.
5. Green P, Arnold S V., Cohen DJ et al. Relation of Frailty to Outcomes After Transcatheter Aortic Valve Replacement (from the PARTNER Trial). Am J Cardiol. 2015;116(2):264–9.
6. Green P, Woglom AE, Genereux P, et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: A single-center experience. JACC Cardiovasc Interv . 2012;5(9):974–81.
7. Assmann P, Kievit P, Van Der Wulp K, et al. Frailty is associated with delirium and mortality after transcatheter aortic valve implantation. Open Hear. 2016;3(e000478).
8. Skaar E, Eide LSP, Norekvål TM, et al. A novel geriatric assessment frailty score predicts 2-year mortality after transcatheter aortic valve implantation. Eur Hear J - Qual Care Clin Outcomes. 2019;5(2):153–60.
9. Goudzwaard JA, de Ronde-Tillmans MJAG, El Faquir N et al. The Erasmus Frailty Score is associated with delirium and 1-year mortality after Transcatheter Aortic Valve Implantation in older patients. The TAVI Care & Cure program. Int J Cardiol. 2019;276:48–52.
10. Rogers T, Alraies MC, Moussa Pacha H, et al. Clinical Frailty as an Outcome Predictor After Transcatheter Aortic Valve Implantation. Am J Cardiol. 2018;121(7):850–5.
11. Sieber FE, Barnett SR. Preventing Postoperative Complications in the Elderly. Anesth Clin. 2011;29(1):83–97.
12. Karakoc D. Surgery of the elderly patient. Int Surg. 2016;101:161–6.
13. 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):373–83.
14. Laan W, Zuithoff NPA, Drubbel I, et al. Validity and reliability of the Katz-15 scale to measure unfavorable health outcomes in community-dwelling older people. J Nutr Heal Aging. 2014;18(9):848–54.
15. Elia M. Nutritional Screening of Adults: A Multidisciplinary Responsibility. Development and Use of the 'Malnutrition Universal Screening Tool' ('MUST') for Adults. Bapen. 2003;127.
16. Doyle D, Goyal A, Bansal P, et al. American Society of Anesthesiologists Classification (ASA Class). StatPearls Treasure 2020.

17. Reiss J, Iglseder B, Alzner R, et al. Sarcopenia and osteoporosis are interrelated in geriatric inpatients. Z Gerontol Geriatr. 2019;52(7):688–93.
18. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189–98.
19. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairmen. J Am Geriatr Soc. 2005;53(4):695–9.
20. Yesavage JA, Brink TL, Rose TL, et al. Development and Validation of a Geriatric Depression Screening Scale: A Preliminary Report. J Psychiatr Res. 1982;17(1):37–49.
21. Stevernik N, Slaets JPL, Schuurmans H, van Lis M. Measuring frailty: development and testing the GFI (Groningen Frailty Indicator). Gerontologist. 2001;41(1):236–7.
22. Schuurmans MJ, Shortridge-Baggett LM, Duursma SA. The Delirium Observation Screening Scale: a screening instrument for delirium. Res Theory Nurs Pr. 2003;17(1):31–50.
23. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (5th Edition). 2013;
24. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205–13.
25. Clavien PA, Barkun J, De Oliveira ML, et al. The clavien-dindo classification of surgical complications: Five-year experience. Ann Surg. 2009;250(2):187–96.
26. Seely AJE, Ivanovic J, Threader J, et al. Systematic classification of morbidity and mortality after thoracic surgery. Ann Thorac Surg. 2010;90:936–42.
27. Bosma E, Pullens MJJ, de Vries J, Roukema JA. The impact of complications on quality of life following colorectal surgery: a prospective cohort study to evaluate the Clavien-Dindo classification system. Color Dis. 2016;18:594–602.
28. Geskin AA, Westney OL, Graber WJ, Smith TG, et al. Complications of peri-operative ureteral catheter placement: experience at a major cancer center. Urology. 2021;S0090-4295.
29. Wakita N, Hinata N, Suzuki K et al. Comparison of robot-assisted partial nephrectomy for complex ( RENAL scores ≥ 10 ) and non-complex renal tumors : A single-center experience.
30. Winter R, Haug I, Lebo P et al. Standardizing the complication rate after breast reduction using the Clavien-Dindo classification. Surg (United States). 2017;161:1430–5.
31. Hébert M, Cartier R, Dagenais F et al. Standardizing Postoperative Complications—Validating the Clavien-Dindo Complications Classification in Cardiac Surgery. Semin Thorac Cardiovasc Surg. 2021;33:443–51.
32. Yanagisawa R, Tanaka M, Yashima F, et al. Frequency and Consequences of Cognitive Impairment in Patients Underwent Transcatheter Aortic Valve Implantation. Am J Cardiol. 2018;122(5):844–50.
33. Khan MM, Lanctôt KL, Fremes SE, et al. The value of screening for cognition, depression, and frailty in patients referred for TAVI. Clin Interv Aging. 2019;14:841–8.
34. Piankova P, Afilalo J. Prevalence and Prognostic Implications of Frailty in Transcatheter Aortic Valve Replacement. Cardiol Clin. 2020;38(1):75–87.

## Supplementary data

**Supplementary Table S1.** Clavien-Dindo Classification of surgical complications[1,2]

| Grade | Definition |
|---|---|
| I | Any deviation from the normal postoperative course without the need for pharmacological treatment, or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetic's, antipyretics, analgesics, diuretics and electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside. |
| II | Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included. |
| III | Complication requiring surgical, endoscopic, or radiological intervention |
| IIIa | Intervention not under general anesthesia |
| IIIb | Intervention under general anesthesia |
| IV | Life-threatening complication (including central nervous system complications) requiring intensive care unit management |
| IVa | Single organ dysfunction (including dialysis) |
| IVb | Multi-organ dysfunction |
| V | Death of a patient |



[1] Clavien PA, Barkun J, De Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The clavien-dindo classification of surgical complications: Five-year experience. Ann Surg. 2009;250:187–96. https://doi.org/10.1097/SLA.0b013e3181b13ca2.

[2] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205–13. https://doi.org/10.1097/01.sla.0000133083.54934.ae.

CHAPTER 5

5

# Hyperpolypharmacy is a predictor of mortality after Left Ventricular Assist Device (LVAD) implantation

Lauren Dautzenberg*, Lieke Numan*, Wilma Knol, Monica Gianoli, Manon G. van der Meer, Anne-Marie Troost-Oppelaar, Aline F. Westendorp, Marielle H. Emmelot-Vonk, Linda W. van Laake, Huiberdina L. Koek

* These authors contributed equally to this work

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## Abstract

**Background:** The prevalence of (hyper)polypharmacy in patients on left ventricular assist device (LVAD) support and its effect on clinical outcome is unknown. Therefore, we aimed to determine the prevalence of (hyper)polypharmacy in LVAD patients and evaluate its association with mortality and complications.

**Materials and methods:** 210 patients aged ≥40 years who received a primary LVAD implantation between 2011 and 2019 were included for analysis. Polypharmacy and hyperpolypharmacy were defined as the concomitant use of 5–9 and ≥10 medications at discharge after LVAD implantation, respectively. Cause specific cox regression was used to assess the association of ≥10 medications with mortality, cardiac arrhythmia, driveline infection and major bleeding.

**Results:** The median age of the patients was 57.5 years, and 35.7% were female. The average number of discharge medications was 8.8 ± 2.3 per patient. The prevalence of patients with 5-9 medications and ≥10 medications was 62.9% and 34.8%, respectively. The median follow-up duration was 948 days (interquartile range 874 days). The prescription of ≥10 medications was significantly associated with a higher risk of mortality (HR 2.03; 95% CI 1.15-3.6, p-value 0.02) adjusted for sex, age, comorbidity and stratified for device type. The prescription of ≥10 medications was not associated with a higher risk of major bleeding, cardiac arrhythmia or driveline infection.

**Conclusions:** (Hyper)polypharmacy is highly prevalent in LVAD patients and is independently associated with a higher risk of mortality. Future research is needed to assess the efficacy of individual risk-benefit profiling of (cardiovascular) medication to ensure appropriate polypharmacy and decreasing negative health outcomes.

## Introduction

Heart failure (HF) is a chronic and progressive clinical syndrome affecting at least 26 million people worldwide and its prevalence continues to increase.[1] Treatment options include lifestyle changes, pharmacological treatment, device therapy, coronary revascularisation and cardiac rehabilitation according to HF severity. In case of therapy-resistant symptomatic end-stage HF, there may be an indication for heart transplantation or mechanical support with a Left Ventricular Assist Device (LVAD).[2] Due to the progressive nature of HF and current donor heart scarcity, patients on the heart transplant waiting list often need LVAD implantation to maintain adequate cardiac output (bridge to transplantation). LVAD implantation is also a permanent therapy for those who do not qualify or opt for heart transplantation (destination therapy). The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial has shown that LVAD destination therapy leads to a higher survival rate and quality of life in patients ineligible for transplantation.[3] Current survival at one, two and three years after LVAD implantation in the Netherlands is 83%, 76% and 70%, respectively.[4] Despite these promising results, major adverse events are common after LVAD implantation: one year after LVAD implantation 41% of the patients have suffered from a major infection (a clinical infection treated by anti-microbial agents), 21% from gastro-intestinal bleeding and 13% from stroke.[5]

HF patients have a higher prevalence of co-morbidities when compared to patients of similar age without HF.[6] This is especially the case of patients for LVAD destination therapy, not eligible for heart transplantation due to advanced age, non-cardiac comorbidities or frailty.[7] The pharmacological treatment of these cardiac and non-cardiac comorbidities in patients with end stage HF generates a high prevalence of polypharmacy (17 to 99%),[8] usually defined as the concomitant use of ≥5 regularly prescribed medications, and even of hyperpolypharmacy (26% to 74%),[9,10] which is defined as the use of at least 10 different medications. Although sometimes unavoidable in order to comply with guidelines, (hyper)polypharmacy should not be considered harmless. In patients with HF, polypharmacy is associated with a higher risk of overtreatment, undertreatment, medication errors, poor adherence, adverse drug-reactions and drug-drug interactions.[11–13] Kennel et al. showed that hyperpolypharmacy in patients with HF is independently associated with an increased rate of ambulatory contacts and hospital admissions.[9] No studies are available on the prevalence of polypharmacy and hyperpolypharmacy in patients on LVAD support and the association with adverse outcomes after LVAD implantation. The aim of our study was to determine the prevalence of polypharmacy (5-9 medications) and hyperpolypharmacy (≥10 medications) in patients after primary LVAD implantation and to evaluate the association of hyperpolypharmacy with overall mortality and complications while on LVAD support.

# Methods

## 2.1 Study design, setting and population

We conducted a retrospective cohort study at the University Medical Centre Utrecht, a tertiary hospital in the Netherlands. All consecutive patients who underwent primary LVAD implantation between 01-01-2011 and 31-12-2019 were included if they were 40 years or older at implantation and survived the index admission. Data on mortality and complications were collected until 1-1-21, so each patient was followed for at least one year. We included patients 40 years of age or older, because a medication review is part of a comprehensive geriatric assessment (CGA) and we assume that a CGA in patients younger than 40 years will provide relatively few clinically relevant findings, since a CGA focuses on problems that occur particularly in older age (including impaired cognition, decreased functionality, limited social network). Patients who died during the index admission, i.e. the admission in which the LVAD was implanted, were not included in this study as no discharge medication was available for these patients. For these patients, it was not possible to use the medication list that was in use at the time of death to determine whether they were taking ≥10 medications because it often involved intercurrent medications (antibiotics, strong analgesics, inotropics), and this biased the presence of the prescription of ≥10 medications. The local medical ethics committee gave approval for a waiver to obtain informed consent (reference number WAG/mb/20/013298) given the anonymity of data collection and the non-interventional nature of the study.

## 2. 2 Data collection

Data were collected on patient characteristics (age at implantation, sex, body mass index), aetiology of cardiomyopathy, device type and Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile before primary implantation. The INTERMACS classification comprises 7 severity profiles corresponding to New York Heart Association class III and IV, with INTERMACS 7 corresponding to advanced New York Heart Association class III heart failure and INTERMACS 1 representing the situation of critical cardiogenic shock.[14] Data were also collected on mortality and the occurrence of complications.[15]

The medical history, both cardiac and non-cardiac, was obtained from the discharge letter of the index admission. Chronic conditions and acute somatic problems from which a patient had not yet recovered during admission were documented using the 2016 version of the tenth edition of the International Classification of Diseases.[16] This data was then used to determine the Charlson Comorbidity Index (CCI) score.[17] The CCI scores the presence of certain comorbidities, with a maximum score of 33, and predicts the 10-year survival in patients with multiple comorbidities. Originally, age is included in the calculation of 10-year survival using the CCI. However, because we already included age as a variable in the cox proportional hazards models, we calculated the CCI for each patient without assigning points to age.

Discharge medication was also collected from the discharge letter of the index admission. Medications were grouped to present medication use in a convenient way and to perform analyses of associations between specific medication groups and outcomes. The internationally widely and long-used Anatomical Therapeutic Chemical (ATC) classification system was used for this purpose.[18] In the ATC classification system, the active substances are classified at five levels. We chose to use discharge medication to determine medication use because it better reflects the overall medical situation after LVAD implantation than admission medication, where some of the patients are not yet on cardiac medication or medication for other co-morbidities. The following medication was excluded from data collection: medication prescribed as needed, medication administered by cutaneous (skin cream) or ophthalmic routes (eye drops), medication without an existing ATC code and over-the-counter vitamins. Medication use was divided into 0-4 medications (no polypharmacy), 5-9 medications (polypharmacy) and ≥10 medications (hyperpolypharmacy).

## 2.3 Primary and secondary endpoints

The primary endpoint of the study was death or urgent heart transplantation (HTx). We chose to combine these two outcomes under the assumption that without receiving the heart transplantation (urgent recipient) the patient would die in the very short term. Urgent heart transplantation was defined as heart transplantation for which the patient received a priority status on the waiting list (national 1A, national 1B, or international HU). The secondary outcomes were defined using the adverse event definitions formulated by INTERMACS that occurred in at least 50 patients after discharge: cardiac arrhythmia, driveline infection and major bleeding.[15]



## 2.4 Statistical analysis

Baseline variables are expressed as numbers and percentages for categorical variables, and mean and standard deviations (SD) or median and inter quartile ranges (IQR) for continuous variables. Differences in baseline variables and prevalence of mortality and complications between patients with 0-9 medications and ≥10 medications were determined by the Fisher's exact test for categorical variables, and independent T-tests or Mann-Whitney U test for continuous variables.

Kaplan-Meier analysis was performed, categorized in patients with 0-9 medications and ≥10 medications. Cox proportional hazards models were applied, to assess the association of the prescription ≥10 medications with our primary outcome. Patients on ongoing support at the end of follow-up and patients that received a non-urgent heart transplantation were censored. Hazard Ratios (HR) and 95% Confidence Intervals (95% CI) were calculated. In addition, the HRs were stratified for device type and adjusted for age at implantation, sex, comorbidities (by means of the CCI score), to examine whether the prescription ≥10 medications merely reflects the presence of comorbidities or an independent factor. As

a sensitivity analysis, an additional cox model was used with the number of medications as a continuous variable. In addition, in another cox model tertiles of the number of medications were used as a variable to study the association with the primary outcome. Because most of the deceases had a neurologic (stroke) or cardiac cause, an additional cox analysis was performed to examine the association of medications to prevent stroke and cardiac medication, with the primary outcome. Medications to prevent stroke concerned the medication groups antihypertensives (ATC groups C07-C09), antithrombotics (B01) and lipid-lowering agents (C10). Cardiac medications involved the ATC groups B01, C01, C03, C07, C08, C09, C10. Another sensitivity analysis was performed, similar to the primary multivariate cox regression analysis. However, now patients were also censored for urgent heart transplantation, as this was usually done in literature. The proportional hazard assumption was met in all cox models. The predictor variables age, sex, CCI, device type and the prescription ≥10 medications were tested for multicollinearity by inspection of correlation coefficients and variance inflation factor (VIF) values, and there was no indication of multicollinearity. To determine whether the effect of ≥10 medications on mortality was modified by age, a cox model with the interaction between age and the prescription ≥10 medications was performed.

To evaluate the association between the prescription ≥10 medications and the secondary outcomes, cause-specific cox models were used, censoring for competing outcomes (death, heart transplantation, explanation). In case of recurrent adverse events, the first event was used for analysis. HR's were stratified for device type and adjusted for age, sex and CCI. For all tests, a p-value ≤0.05 was considered statistically significant. All analyses were performed using R version 3.6.3.

# Results

## 3.1 Patient inclusion and baseline characteristics

A total of 232 consecutive patients aged 40 years and older underwent primary LVAD implantation between January 2011 and January 2020. For 22 patients (9%) discharge medication was not available due to postoperative in-hospital mortality. These patients were excluded from the study. In total, 210 patients were included in the study. Baseline characteristics are presented in Table 1.

The median age was 57.5 years at the time of LVAD implantation and 35.7% were female. The number of comorbidities and the CCI score was significantly higher in the group of patients with ≥ 10 medications than in the group of patients with 0-9 medications (number of comorbidities 6.3 ± 2.4 versus 5.0 ± 1.8, CCI score 2.0 ± 0.9 versus 1.7 ± 0.8).

**Table 1.** Baseline characteristics of patients with 0-9 medications and ≥10 medications

| **Demographics** | | **All patients** (n = 210) | **0-9 medications** (n = 137) | **>10 medications** (n = 73) | **P-value** |
|---|---|---|---|---|---|
| **Sex** number (%) -Female | | 75 (35.7) | 51 (37.2) | 24 (32.9) | 0.64 |
| **Age at implantation** (years) median [IQR] | | 57.5 [11] | 57.0 [13] | 58 [10] | 0.44 |
| **Body mass index** (kg/m$^2$) median [IQR] | | 24.2 [6] | 23.7 [6] | 25.2 [5] | 0.04 |
| **Comorbidities** mean ± SD<br>- Total number<br>- Charlson Comorbidity Index* | | <br>5.5 ± 2.1<br>1.8 ± 0.8 | <br>5.0 ± 1.8<br>1.7 ± 0.8 | <br>6.3 ± 2.4<br>2.0 ± 0.9 | <br><0.001<br>0.002 |
| **Number of discharge medications** mean ± SD | | 8.8 ± 2.3 | 7.4 ± 1.4 | 11.3 ± 1.6 | <0.001 |
| **Ischemic cardiomyopathy** number (%) | | 66 (31.4) | 43 (31.4) | 23 (31.5) | 1.00 |
| **Dilated cardiomyopathy** number (%) | | 129 (61.4) | 87 (63.5) | 42 (57.5) | 0.49 |
| **Device type** number (%) | **HeartMate II** | 70 (33.3) | 48 (35.0) | 22 (30.1) | 0.57 |
| | **HeartWare** | 75 (35,7) | 49 (35.8) | 26 (35.6) | 1.00 |
| | **HeartMate 3** | 65 (31.0) | 40 (29.2) | 25 (34.2) | 0.55 |
| **INTERMACS profile** number (%) | Temporary support | 37 (17.6) | 28 (20.4) | 9 (12.3) | 0.20 |
| | 1 | 7 (3.3) | 2 (1.5) | 5 (6.8) | 0.10 |
| | 2 | 61 (29.0) | 38 (27.7) | 23 (31.5) | 0.68 |
| | 3 | 71 (33.8) | 46 (33.6) | 25 (34.2) | 1.00 |
| | 4 | 32 (15.2) | 22 (16.1) | 10 (13.7) | 0.80 |
| | 5 | 2 (1.0) | 1 (0.7) | 1 (1.4) | 1.00 |
| | 6 | 0 (0) | 0 (0) | 0 (0) | 1.00 |
| | 7 | 0 (0) | 0 (0) | 0 (0) | 1.00 |

IQR: interquartile range, SD: standard deviation.

* Points for age not included

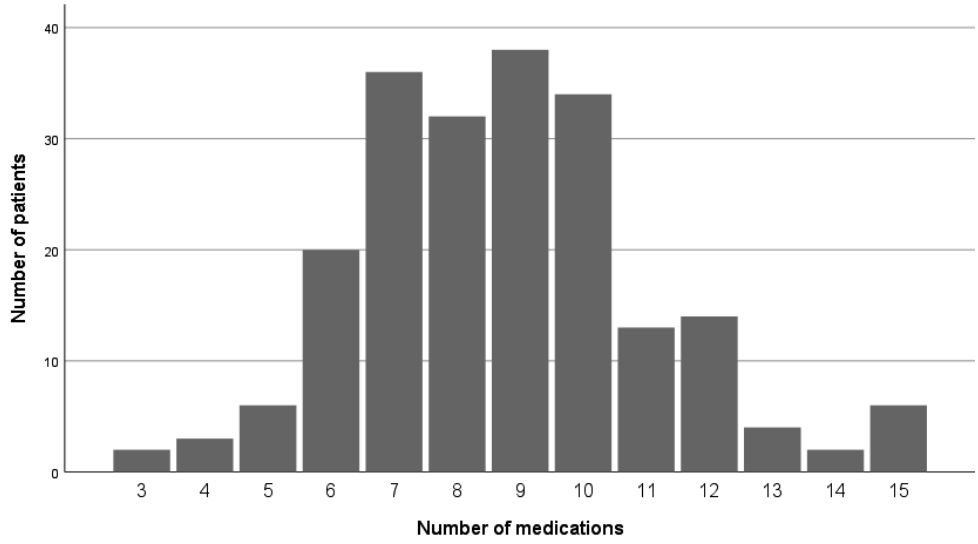



**Figure 1.** Distribution of the numbers of discharge medication of the LVAD patients**.**

## 3.2 Prevalence of polypharmacy and hyperpolypharmacy

The average number of discharge medications was 8.8 ± 2.3. Five patients (2.4%) used 0-4 medications (no polypharmacy), with a mean number of 3.6 medications per patient. The majority (132 patients, 62.9%) used 5-9 medications (polypharmacy), with a mean of 7.6 prescriptions per patient. A total of 73 patients (34.8%) used ≥10 medications (hyperpolypharmacy), with on average 11.3 medications per patient. Figure 1 shows the distribution of the number of medications per patient, ranging from 3 to 15. Since only 5 patients met the criterion for no polypharmacy (0-4 medications), this group was combined with patients with 5-9 medications and compared to patients with ≥10 medications.

Of the total of 1839 prescribed medications, 1001 (54.4%) were cardiovascular medications. Most frequently prescribed were antithrombotics (vitamin K antagonists and acetylsalicylic acid are routine medications for patients with an LVAD), diuretics, agents acting on the renin-angiotensin system and antiarrhythmic medications (predominantly amiodarone). (Supplementary Table S1) Most commonly used non-cardiovascular medications were medications for acid related disorders (in particular proton pump inhibitors), analgesics (predominantly paracetamol), and mineral supplements (mainly potassium chloride). Finally, sildenafil was commonly used. Sildenafil falls under urological agents according to the ATC classification system, but the patients in this study used it to lower pulmonary pressure (right ventricle afterload reduction).

Supplementary Figure S1 presents the difference in medication use between patients who survived during the follow-up period and those who died or underwent urgent

HTx. Antithrombotics, medication for acid related disorders and diuretics were the most commonly used medication groups. There were no differences between both patient groups.

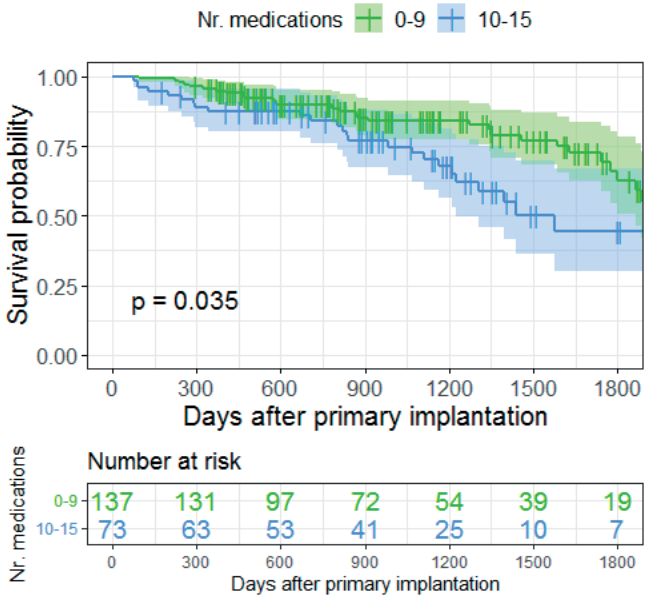



**Figure 2.** Survival (time to death or urgent heart transplantation) of patients with 0-9 medications and ≥10 medications.

5

## 3.3 Mortality and complications

The median follow-up duration was 948 days (interquartile range 874 days). Figure 2 shows the survival (time to death or urgent HTx, as a proxy of mortality) of patients with 0-9 medications and ≥10 medications. Patients with ≥10 medications had a significantly lower survival compared to patients 0-9 medications (crude HR 1.76; 95% CI 1.03-2.98, p-value 0.04) (Table 2). This association remained significant after adjusting for age, sex, CCI and stratified for device type (adjusted HR 2.03; 95% CI 1.15-3.6, p-value 0.02). A total of 56 patients (27%) died after a median of 828 days following LVAD implantation. Table 3 lists the causes of death. A total of 56 patients received a heart transplant after a median of 1029 days, of which 32% (n=18) were urgent transplants. The adjusted hazard ratio was 1.23 (95% CI 1.09-1.38, p-value 0.001) for the number of medications as a continuous variable in the multivariate cox proportional hazards model of the primary outcome (mortality or urgent HTx).

The tertiles for the number of medications were determined. The first tertile concerned 3-8 medications, the second tertile 8-10 medications and the third tertile 10-15 medications. Compared with the first tertile, the use of 8-10 medications did not significantly increase

the risk of the combined outcome of mortality and urgent HTx (HR adjusted for age, sex, CCI and stratified for device type 1.79; 95% CI 0.84-3.81, p-value 0.13), but the use of 10-15 medications did (adjusted HR 2.96; 95% CI 1.40-6.26, p-value <0.01). Figure 3 displays the survival for the three different tertiles. Supplementary Tables S2 and S3 show the association of the use of medications to prevent stroke and cardiac medications, respectively, with survival.

The sensitivity analysis with additional censoring for urgent heart transplantation also showed a significantly higher mortality (urgent HTx not included) for patients with ≥10 medications (adjusted HR 1.77; 95% CI 1.07-2.95, p-value 0.03). An additional analysis was performed to assess whether the effect of ≥10 medications was modified by age at the time of implantation. The interaction term for age - ≥10 medications was not statistically significant when entered into the multivariate model (p-value 0.43), i.e. the association between ≥10 medications and mortality was not different for persons younger and older than 60 years.

The prescription of ≥10 medications was not associated with any of the adverse events as listed in Table 4.

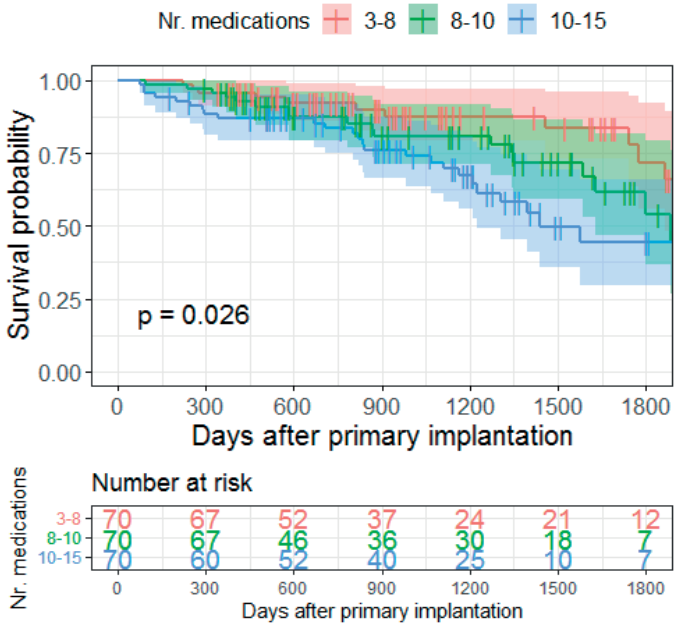



**Figure 3.** Survival (time to death or urgent heart transplantation) of patients with 3-8 medications, 8-10 medications and 10-15 medications (tertiles)

**Table 2.** The association between the prescription of ≥10 medications and survival (mortality and urgent heart transplantation)

| Variables added to the cox proportional hazards models | Univariate model | | | Multivariate model* | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P-value | HR | 95% CI | P-value |
| ≥ 10 medications | 1.76 | 1.03-2.98 | 0.04 | 2.03 | 1.15-3.62 | 0.02 |
| Age | | | | 1.04 | 0.99-1.08 | 0.04 |
| Sex | | | | 0.92 | 0.53-1.62 | 0.78 |
| Charlson Comorbidity Index | | | | 0.96 | 0.69-1.35 | 0.83 |

CI: confidence interval, HR: hazard ratio.
* Stratified for device type

**Table 3.** Numbers and causes of death

| Cause of death | All = 56<br>n (%) |
|---|---|
| **Device malfunction** | 3 (5.4) |
| **Infection** | 7 (12.5) |
| **Multi-organ failure** | 7 (12.5) |
| **Neurological** | 18 (32.1) |
| **Right ventricle failure** | 7 (12.5) |
| **Other** | 14 (25) |

**Table 4.** Cause specific cox regression: association of the prescription of ≥10 medications with complications.

| Complication type | Number of patients (after index discharge) n (%) | Crude | | | Adjusted for age, sex, CCI, stratified for device type | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | P-value | HR | 95% CI | P-value |
| Cardiac arrhythmia | 98 (47) | 0.80 | 0.53-1.25 | 0.35 | 0.76 | 0.48-1.20 | 0.24 |
| Driveline infection | 65 (31) | 0.82 | 0.49-1.40 | 0.47 | 0.99 | 0.57-1.71 | 0.96 |
| Major bleeding | 74 (35) | 1.26 | 0.78-2.02 | 0.34 | 1.29 | 0.78-2.15 | 0.31 |

CI: confidence interval, CCI: Charlson Comorbidity Index (without points for age), HR: hazard ratio.

## Discussion

This study showed that the prescription of 5-9 medications (polypharmacy) is highly prevalent (62.9%) in patients after LVAD implantation. The prescription of ≥10 medications (hyperpolypharmacy) was also common (34.8%) with on average 11.3 medications per patient. Hyperpolypharmacy was independently associated with the risk of mortality, but not with the risk of complications (major bleeding, cardiac arrhythmia or driveline infection). Supplementary Figure S1 and Supplementary Table S3 and S4 indicate that not the type but the number of medications are associated with survival.

The prevalence and the association of (hyper)polypharmacy with outcomes in patients with an LVAD has not been investigated before. However, several previous studies addressed polypharmacy in patients with HF. A recent systematic review on the identification of a standard definition and the prevalence of polypharmacy in patients with HF, concluded that there is no standard definition of polypharmacy in HF literature and the prevalence ranged from 17.2% to 99%.[8] In four studies where a definition of ≥10 medications was used, the prevalence of hyperpolypharmacy varied from 26-74%.[9,10,19,20] Extrapolating these findings to our study, however, is of limited value due to heterogeneity of the study populations, particularly concerning the severity of HF. Where LVAD patients have severe, end-stage HF during admission for an LVAD implantation, the overall HF population has a broad case-mix ranging from mild HF to end-stage HF. A number of medications are used routinely in every patient who receives an LVAD. In our tertiary centre, patients are prescribed at least a vitamin K antagonist, an antiplatelet drug and a proton pump inhibitor after LVAD. Blood pressure is also strictly regulated (mean arterial pressure< 80 mmHg) to reduce the risk of stroke and other complications.

The evidence on the association of polypharmacy with mortality in the general HF population is conflicting. Again, comparison with the results of the current study is hampered by the heterogeneity of the study populations. Sunaga et al. evaluated the relationship between various clinical factors and mortality in patients with HF.[20] They found that patients who were taking <6 medications on admission experienced a significantly lower all-cause 2 year-mortality than patients taking ≥6 medications (10.0% vs. 25.0%, P = 0.045). However, the study by Sunaga et al concerned the number of medications before admission and this study determined the number of medications on discharge from hospital, with the study of Sunaga et al not taking into account medication changes during admission. Wu et al. examined the association between the use of 10-14 medications and several adverse outcomes in patients with HF with preserved ejection fraction (HFpEF). Contrary to the finding in this study and the study of Senaga et al, Wu et al. found that the prescription of 10-14 medications was associated with a reduced risk of all-cause mortality (HR 0.61; 95% CI 0.39-0.96, P=0.031), and an increased risk of HF hospitalisation (HR 2.83; 95% CI 1.37-5.86, P=0.01) and all-cause hospitalisation (HR 1.81; 95% CI 1.29-2.53, P=0.001).[19] However, Wu et al. included relatively stable patients with HF,

whereas the study of Sunaga and our study included patients with unstable or advanced/ end stage HF.

## 4.1 Strengths and limitations

This study was the first to examine the prevalence of the prescription of 5-9 medications (polypharmacy) and ≥10 medications (hyperpolypharmacy) and its association with adverse outcomes in a large sample of patients after primary LVAD implantation. The risk of selection bias is very small, because an existing prospective database was used for patient selection, in which data of all consecutive LVAD patients was registered. Data on the occurrence of a selection of complications were collected, using the definition of the international INTERMACS registry, making the results internationally interpretable.

This study has some limitations. The medical history and discharge medication were extracted from the discharge letter. There is a chance that these letters contained incomplete or incorrect information due to human error. Second, due to the retrospective collection of medication data, we could not take into account medication adherence, correct use or changes in medication after hospital discharge. Third, the incidence of many adverse events was very low, and therefore were not included for analysis in the current study, as there was not enough power here to demonstrate a significant association. Finally, although this study showed that there is a significant association between the prescription of ≥10 medications and mortality, it cannot be determined whether there is a causal relationship. Despite adjustment for age, sex, device type and comorbidities, it is still possible that hyperpolypharmacy reflects the presence of frailty. Several observational studies demonstrated a significant association between an increased number of medications and frailty (possibly bidirectional) and frailty is a known risk factor for mortality in patients with HF.[21,22] Because there is no agreement on the definition of frailty and the way it should be assessed in (end stage) heart failure, hyperpolypharmacy as a proxy of frailty would in that case simplify prognostication of patients post LVAD.



## 4.2 Clinical implications and future research

Over the last few years, awareness of polypharmacy in patients with HF has been growing. The fact that this study showed that the prescription of ≥10 medications was associated with mortality, independent of the presence of comorbidities, demonstrates the importance of adequately addressing hyperpolypharmacy. However there is a lack of clarity on how best to manage polypharmacy.[23–25] Thereby, it is important to realise that polypharmacy in a number of patients with heart failure cannot be prevented and is indicated if current guidelines are followed. The common ground for addressing (hyper)polypharmacy seems to be a multidisciplinary individual approach, where a risk-benefit profile of (cardiovascular) medication should be determined and inappropriate polypharmacy should be identified and prevented. In our study, more non-cardiovascular medications were used in the hyperpolypharmacy group (reflecting the presence of more

comorbidities) than in the group with 0-9 medications, which are possible targets for a medication review. A medication review leads to improved medication appropriateness, reduced polypharmacy and reduced adverse drug reactions[26], however, there is little evidence for an effect on clinical outcomes.[27,28] Future research should confirm the association between hyperpolypharmacy and mortality, adjust for the presence of frailty, assess the appropriateness of the hyperpolypharmacy and study the effect of optimising polypharmacy in a randomised controlled trial. It is recommended to collect the medication data prospectively. The completeness of the medication list, medication adherence and the correct use of medication should be verified. For longer follow-up periods, information on changes in medication use should also be collected.

## Conclusion

This study showed that polypharmacy is highly prevalent in patients with primary LVAD implantation. Hyperpolypharmacy also occurred frequently, and was independently associated with mortality. Future research is warranted to confirm this association and to assess the efficacy of individual risk-benefit profiling of (cardiovascular) medication to ensure appropriate polypharmacy and to decrease negative health outcomes.

## References


1. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. *Card Fail Rev*. 2017;3:7-11.
2. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2016;37:2129-2200.
3. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-Term Use of a Left Ventricular Assist Device for End-Stage Heart Failure. *N Engl J Med*. 2001;345:1435-1443.
4. Felix SEA, de Jonge N, Caliskan K, et al. The role of long-term mechanical circulatory support in patients with advanced heart failure. *Netherlands Hear J*. 2020;28:S115-S121.
5. Molina EJ, Shah P, Kiernan MS, et al. The Society of Thoracic Surgeons Intermacs 2020 Annual Report. *Ann Thorac Surg*. 2021;111:778-792.
6. Van Deursen VM, Damman K, Van Der Meer P, et al. Co-morbidities in Heart failure. *Heart Fail Rev*. 2014;19:163-172.
7. Arnold S V., Jones PG, Allen LA, et al. Frequency of Poor Outcome (Death or Poor Quality of Life) After Left Ventricular Assist Device for Destination Therapy: Results from the INTERMACS Registry. *Circ Hear Fail*. 2016;9:e002800.
8. Beezer J, Al Hatrushi M, Husband A, Kurdi A, Forsyth P. Polypharmacy definition and prevalence in heart failure: a systematic review. *Heart Fail Rev*. 2022;27:465-492.
9. Kennel PJ, Kneifati-hayek J, Bryan J, et al. Prevalence and determinants of Hyperpolypharmacy in adults with heart failure : an observational study from the National Health and Nutrition Examination Survey ( NHANES ). *BMC Cardiovasc Disord*. 2019;19:76.
10. Brinker LM, Konerman MC, Navid P, et al. Complex and Potentially Harmful Medication Patterns in Heart Failure with Preserved Ejection Fraction. *Am J Med*. 2021;134:374-382.
11. Spreafico M, Gasperoni F, Barbati G, et al. Adherence to Disease-Modifying Therapy in Patients Hospitalized for HF: Findings from a Community-Based Study. *Am J Cardiovasc Drugs*. 2020;20:179-190.
12. Niriayo YL, Kumela K, Kassa TD, Angamo MT. Drug therapy problems and contributing factors in the management of heart failure patients in Jimma University Specialized Hospital, Southwest Ethiopia. *PLoS One*. 2018;13:e0206120.
13. Georgiev KD, Hvarchanova N, Georgieva M, Kanazirev B. The role of the clinical pharmacist in the prevention of potential drug interactions in geriatric heart failure patients. *Int J Clin Pharm*. 2019;41:1555-1561.
14. Stevenson LW, Pagani FD, Young JB, et al. INTERMACS Profiles of Advanced Heart Failure: The Current Picture. *J Hear Lung Transplant*. 2009;28:535-541.
15. Kirklin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: Special focus on framing the impact of adverse events. *J Hear Lung Transplant*. 2017;36:1080-1086.
16. World Health Organisation. International statistical classification of diseases and related health problems : tenth revision, ICD-10. Version: 2016. Published 2004. Accessed August 12, 2021. https://icd.who.int/browse10/2016/en

17. Charlson ME, Pompei P, Ales KL, MacKenzie RC. A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies : Development and Validation. *J Chronic Dis*. 1987;40:373-383.
18. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC Classification and DDD Assignment, 2017. Oslo. Published 2016. Accessed August 10, 2021. https://www.whocc.no/atc_%0Addd_index_and_guidelines/atc_ddd_index/%0A
19. Wu Y, Zhu W, He X, et al. Influence of polypharmacy on patients with heart failure with preserved ejection fraction: A retrospective analysis on adverse outcomes in the TOPCAT trial. *Br J Gen Pract*. 2020;71:E62-E70.
20. Sunaga T, Yokoyama A, Nakamura S, et al. Association of Potentially Inappropriate Medications With All-Cause Mortality in the Elderly Acute Decompensated Heart Failure Patients: Importance of Nonsteroidal Anti-Inflammatory Drug Prescription. *Cardiol Res*. 2020;11:239-246.
21. Tse G, Gong M, Wong SH, et al. Frailty and Clinical Outcomes in Advanced Heart Failure Patients Undergoing Left Ventricular Assist Device Implantation: A Systematic Review and Meta-analysis. *J Am Med Dir Assoc*. 2018;19:255-261.
22. Gutiérrez-Valencia M, Izquierdo M, Cesari M, Casas-Herrero A, Inzitari M, Martínez-Velilla N. The relationship between frailty and polypharmacy in older people: A systematic review. *Br J Clin Pharmacol*. 2018;84:1432-1444.
23. Rao VN, Fudim M, Savarese G, Butler J. Polypharmacy in Heart Failure with Reduced Ejection Fraction: Progress, Not Problem. *Am J Med*. 2021;134:1068-1070.
24. Cogswell R, Alam A, Joseph SM. Letter by Cogswell et al Regarding Article, "Polypharmacy in Older Adults Hospitalized for Heart Failure." *Circ Hear Fail*. 2021;14:e008160.
25. Goyal P, Mangal S, Krishnaswami A, Rich MW. Polypharmacy in Heart Failure: Progress But Also Problem. *Am J Med*. 2021;34:1071-1073.
26. O'Mahony D. STOPP/START criteria for potentially inappropriate medications/potential prescribing omissions in older people: origin and progress. *Expert Rev Clin Pharmacol*. 2020;13:15-22.
27. Christensen M, Lundh A. Medication review in hospitalised patients to reduce morbidity and mortality. *Cochrane Database Syst Rev*. 2016;2016:1-52.
28. Johansson T, Abuzahra ME, Keller S, et al. Impact of strategies to reduce polypharmacy on clinically relevant endpoints: a systematic review and meta-analysis. *Br J Clin Pharmacol*. 2016;82:532-548.

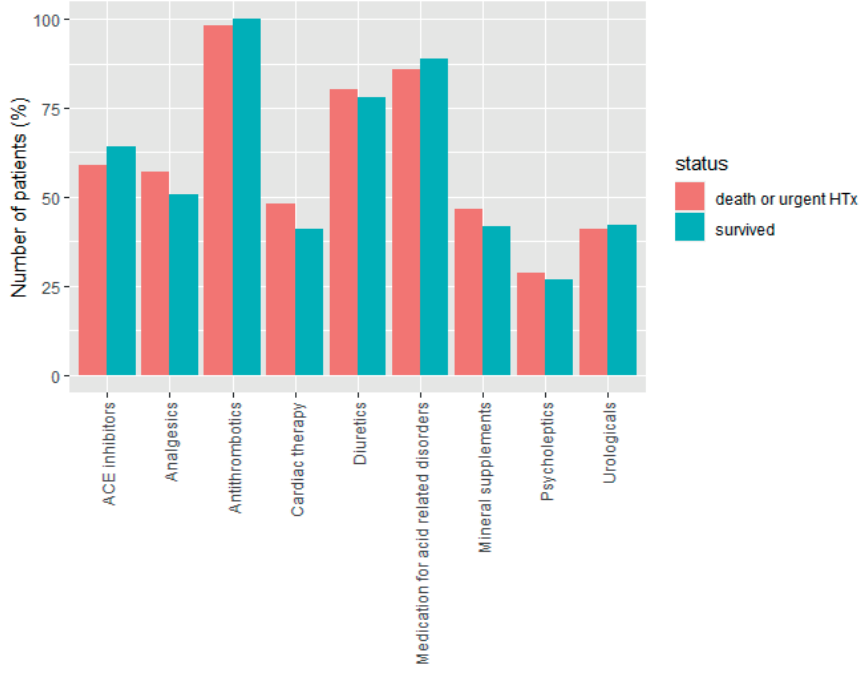
# Supplementary data

**Supplementary Table S1.** Use of cardiovascular medication and non-cardiovascular medication in patients with LVAD categorised according to the Anatomical Therapeutic Chemical (ATC) classification (second level) and stratified by the level of polypharmacy

| ATC code (second level) | all patients (n=210) | 0-9 medications (n=137) | >10 medications (n=73) |
|---|---|---|---|
| **Cardiovascular medications**[1] | | | |
| B01 Antithrombotic agents | 209 (99.5%) | 137 (100%) | 72 (98.6%) |
| C01 Cardiac therapy (cardiac glycosides (i.a. digitalis), antiarrhythmics, cardiac vasodilators (i.a. nitrates)) | 90 (42.9%) | 49 (35.8%) | 41 (56.2%) |
| C03 Diuretics | 165 (78.6%) | 99 (72.3%) | 66 (90.4%) |
| C07 B-blockers | 15 (7.1%) | 8 (5.8%) | 7 (9.6%) |
| C08 Calcium channel blockers | 20 (9.5%) | 13 (9.5%) | 7 (9.6%) |
| C09 ACE inhibitors, angiotensin II receptor blockers | 132 (62.9%) | 79 (57.7%) | 53 (72.6%) |
| C10 Lipid modifying agents | 79 (37.6%) | 39 (28.5%) | 40 (54.8%) |
| **Non-cardiovascular medications**[1] | | | |
| A02 Medications for acid related disorders | 185 (88.01%) | 117 (85.4%) | 68 (93.2%) |
| A03 Medications for functional gastrointestinal disorder | 1 (0.5%) | 1 (0.7%) | 0 |
| A06 Medications for constipation | 26 (12.4%) | 13 (9.5%) | 13 (17.8%) |
| A07 Antidiarrheals, intestinal antiinflammatory/antiinfective agents | 3 (1.4%) | 0 | 3 (4.1%) |
| A10 Medications used in diabetes | 25 (11.9%) | 7 (5.1%) | 18 (24.7%) |
| A11 Vitamins | 10 (4.8%) | 6 (4.4%) | 4 (5.5%) |
| A12 Mineral supplements | 90 (42.9%) | 55 (40.1%) | 35 (47.9%) |
| B03 Antianemic preparations | 33 (15.7%) | 12 (8.8%) | 21 (28.8%) |
| B05 Blood substitutes and perfusion solutions | 4 (1.9%) | 1 (0.7%) | 3 (4.1%) |
| G03 Sex hormones and modulators of the genital system | 5 (2.4%) | 1 (0.7%) | 4 (5.5%) |
| G04 Urologicals (I.a. medications used in prostatic hypertrophy) | 88 (41.9%) | 50 (36.5%) | 38 (52.1%) |
| H01 Pituary and hypothalamic hormones and analogues | 2 (1.0%) | 0 | 2 (2.7%) |
| H02 Corticosteroids for systemic use | 9 (4.3%) | 2 (1.5%) | 7 (9.6%) |
| H03 Thyroid therapy | 20 (9.5%) | 9 (6.6%) | 11 (15.1%) |
| H05 Calcium homeostasis | 1 (0.5%) | 1 (0.7%) | 0 |
| J01 Antibacterials for systemic use | 23 (11.0%) | 10 (7.3%) | 13 (17.8%) |
| J02 Antimycotics for systemic use | 2 (1.0%) | 1 (0.7%) | 1 (1.4%) |
| J05 Antivirals for systemic use | 1 (0.5%) | 0 | 1 (1.4%) |
| J06 Immune sera and immunoglobulins | 1 (0.5%) | 0 | 1 (1.4%) |
| L01 Antineoplastic agents | 1 (0.5%) | 0 | 1 (1.4%) |
| L02 Endocrine therapy | 3 (1.4%) | 2 (1.5%) | 1 (1.4%) |
| L04 Immunosuppressants | 4 (1.9%) | 0 | 4 (5.5%) |

| | | | |
|---|---|---|---|
| M04 Antigout preparations | 23 (11.0%) | 5 (3.6%) | 18 (24.7%) |
| M05 Medications for treatment of bone disease | 2 (1.0%) | 0 | 2 (2.7%) |
| N02 Analgesics | 110 (52.4%) | 64 (46.7%) | 46 (63.0%) |
| N03 Antiepileptics | 8 (3.8%) | 3 (2.2%) | 5 (6.8%) |
| N04 Anti-parkinson medications | 1 (0.5%) | 1 (0.7%) | 0 |
| N05 Psycholeptics | 57 (27.1%) | 24 (17.5%) | 33 (45.2%) |
| N06 Psychoanaleptics | 15 (7.1%) | 7 (5.1%) | 8 (11.0%) |
| N07 Other nervous system medications (parasympathicomimetics, medications used in addictive disorders, antivertigo preparations) | 1 (0.5%) | 0 | 1 (1.4%) |
| P01 Antiprotozoals | 2 (1.0%) | 1 (0.7%) | 1 (1.4%) |
| R01 Nasal preparations | 3 (1.4%) | 3 (2.2%) | 0 |
| R03 Medications for obstructive airway diseases | 11 (5.2%) | 4 (2.9%) | 7 (9.6%) |
| R05 Cough and cold preparations | 4 (1.9%) | 2 (1.5%) | 2 (2.7%) |
| R06 Antihistamines for systemic use | 2 (1.0%) | 0 | 2 (2.7%) |
| S01 Ophtalmologicals | 1 (0.5%) | 0 | 1 (1.4%) |

[1] ATC categories of medications used by at least one patient are presented.
ACE, angiotensin-converting enzyme; ATC, Anatomical Therapeutic Chemical; LVAD, left ventricular assist device; NOAC, non-vitamin K antagonists;




**Supplementary Figure S1.** The percentage of patients using a particular medication (i.e. the 10 most commonly used medications in the entire study population), stratified by survival

**Supplementary Table S2.** The association between the prescription of medications preventing stroke (antihypertensives, antithrombotics and lipid-lowering agents) and survival (mortality and urgent heart transplantation)

| Variables added to the Cox proportional hazards model | Univariate model | | | Multivariate model* | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P-value | HR | 95% CI | P-value |
| Medications to prevent stroke± | 0.88 | 0.67-1.74 | 0.40 | 0.83 | 0.61-1.12 | 0.22 |
| Age | | | | 1.04 | 1.00-1.07 | 0.06 |
| Sex | | | | 1.05 | 0.60-1.82 | 0.88 |
| Charlson Comorbidity Index | | | | 1.14 | 0.81-1.60 | 0.45 |

* Stratified for device type
± ATC groups C07-C09, B01, C10

**Supplementary Table S3.** The association between the prescription of cardiac medications and survival (mortality and urgent heart transplantation)

| Variables added to the Cox proportional hazards model | Univariate model | | | Multivariate model* | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P-value | HR | 95% CI | P-value |
| Cardiac medications± | 1.16 | 0.93-1.44 | 0.20 | 1.17 | 0.93-1.49 | 0.19 |
| Age | | | | 1.03 | 1.00-1.07 | 0.06 |
| Sex | | | | 0.99 | 0.57-1.73 | 0.97 |
| Charlson Comorbidity Index | | | | 1.03 | 0.74-1.44 | 0.86 |

* Stratified for device type
± ATC groups B01, C01, C03, C07, C08, C09, C10.

CHAPTER 6

# 6

# The association between perioperative statin treatment and short-term clinical outcomes following transcatheter aortic valve implantation: a retrospective cohort study

Geert J. Lefeber, Lauren Dautzenberg, Wilma Knol, Carla Huijbers, Michiel Voskuil, Adriaan Kraaijeveld, Marcel L Bouvy, Anthonius de Boer, Marielle H. Emmelot-Vonk, Huiberdina L Koek

*Submitted*

## Abstract

**Background:** Studies have found statin treatment to be associated with improved one-year survival after transcatheter aortic valve implantation (TAVI), suggesting pleiotropic effects of statins on preventing perioperative complications. Statin treatment is not associated with postoperative cardiovascular complications or mortality, however, other postoperative complications have not been investigated.

**Aim:** To explore whether preoperative statin treatment is associated with a lower short-term risk of mortality, readmission, and major postoperative complications in older patients undergoing TAVI.

**Methods:** A retrospective cohort study including patients aged 65 years and older who had undergone a comprehensive geriatric assessment prior to TAVI between January 2014 and January 2021. The primary outcomes were 90-day mortality, 90-day readmissions, and major postoperative complications according to the Clavien-Dindo classification. Multivariable logistic regression was performed with adjustment for potential confounders, namely age, gender, comorbidity, body-mass index, smoking, diminished renal function, alcohol use and falls.

**Results:** This study included 584 patients, of whom 324 (55.5%) were treated with a statin. In the statin treated group, 15 (4.6%) patients died within 90 days of TAVI compared with 10 (3.8%) patients in the non-statin group (adjusted OR 1.17; 95% CI 0.51 to 2.70). The number of 90-day readmissions was 39 (12.0%) and 34 (13.1%) (adjusted OR 0.91; 95% CI 0.54 to 1.52), respectively. In the statin treated group, 115 (35.5%) patients experienced a major complication compared to 98 (37.7%) in the non-statin group (adjusted OR 0.95; 95% CI 0.67 to 1.37).

**Conclusion:** Preoperative statin treatment is not associated with improved short-term outcomes after TAVI. A randomized controlled trial with different statin doses may be warranted to investigate whether initiating statin treatment before TAVI improves both post-operative outcomes and long term survival.

## Introduction

Aortic valve stenosis is the most common valvular heart disease in developed countries and becomes more prevalent with age. In people aged 75 years and older, the prevalence is 12.4% (1). Due to the poor prognosis of untreated symptomatic aortic valve stenosis, even in the absence of severe comorbidities, early treatment is recommended. Transcatheter aortic valve implantation (TAVI) is recommended in patients who are unsuitable for surgical aortic valve replacement. The criteria for TAVI include increased surgical risk, age ≥75 years and frailty (2). Although TAVI is a well-established therapy in older patients, especially in more frail patients, the five year survival rate after TAVI is only 48% (3).

Periprocedural statin treatment, among other treatments, has been the subject of investigations to improve patient survival after TAVI. In a meta-analysis of observational studies on statin treatment at the time of TAVI, statin treatment was found to be associated with reduced all-cause mortality two years after TAVI (4). Since this meta-analysis, three more observational studies have been published, the results of which were in line with the original meta-analysis (5–7). In two of these studies, the observed association was strongest in patients without coronary artery disease and within the first months after TAVI (5,7). One could discuss whether this association was caused by residual confounding or by direct, pleiotropic effects of statin treatment on post-TAVI complications. Suggested pleiotropic effects include anti-inflammatory effects, the inhibition of cytokine-mediated induction of proadhesive and procoagulant substances, the reduction of neointimal thickening and the induction of endothelial nitric oxide synthase leading to improved vascular remodelling (8–10). However in studies on short-term cardiovascular outcomes after TAVI, no association has been found between statin treatment and periprocedural cardiovascular outcomes or 30 day mortality (11,12). This finding is in line with two randomised controlled trials (RCTs) that have indicated no effect of statin treatment in preventing perioperative myocardial injury in cardiothoracic surgery (13,14). Furthermore, the available studies on short-term outcomes have focused on cardiovascular outcomes and mortality, not on other post-operative complications. Therefore, in the present study, we aimed to determine whether statin treatment is associated with a short-term risk of mortality and readmissions, as well as with major postoperative complications in older patients undergoing TAVI.

# Methods

## Study design

This retrospective cohort study was conducted at the University Medical Center Utrecht, a tertiary teaching hospital in the Netherlands. All patients aged 65 years and older who had undergone a comprehensive geriatric assessment (CGA) within 90 days prior to TAVI between January 2014 and January 2021 were included. Patients were excluded if no CGA was performed or if they declined permission for their healthcare data to be re-use for research. Due to the retrospective nature of this study, it did not fall within the scope of the Medical Research Involving Human Subjects Act, which was confirmed by the local Ethics Committee (reference number WAG/mb/18/019289).

## Data collection

### *Baseline*

Patients visited the geriatric outpatient clinic for a CGA prior to TAVI. During this visit, the patients' somatic, psychological, functional and social domains were assessed as described in an earlier study (15). After the CGA had been performed, the patients were advised regarding the feasibility of TAVI, how to optimise their health prior to the intervention, and how to reduce the risk of complications. Data from the CGA (Supplementary table I) were collected from electronic medical charts. The Charlson comorbidity index at baseline was calculated for each patient., A score of 3 or higher was defined as multimorbid. Moreover, statin treatment was determined based on structured medication reconciliation at hospital admission and actual statin treatment at hospital admission before and after TAVI. Furthermore, the intensity of statin treatment was divided into low-to-moderate intensity statin (LMIS) and high intensity statin (HIS) therapy (16). HIS therapy was defined as daily dosage of atorvastatin ≥40 mg or rosuvastatin ≥20 mg. Lower daily doses of these medications and the use of other types of statins were defined as LMIS therapy.

### *Follow-up*

During hospitalisation for TAVI (index hospitalisation), a geriatric nurse practitioner performed patient follow-up to diagnose and treat geriatric complications such as falls, delirium, functional decline, and stroke. During a follow-up appointment three months after TAVI, a geriatric nurse practitioner checked whether rehospitalisation had occurred. This practitioner was supervised by a geriatrician.

### *Outcomes*

The primary outcomes were 90-day mortality, 90-day readmissions and major postoperative complications during hospitalisation. The Clavien-Dindo classification system was used to classify of postoperative complications through reviewing patient

charts of all patients (17,18). All complications that occurred during index hospitalization were collected and classified according to the treatment needed for the complication. Grades I complications require no intervention or mainly basic pharmacological treatment; Grade II complications require more advanced pharmacological treatment; Grade III complications require surgical, endoscopic, or radiological intervention; Grade IV complications require intensive care; and Grade V indicates death. This study considered a Clavien-Dindo grade II complications or higher to be major postoperative complications (Supplement Table II). For secondary outcomes, we divided these major postoperative complications, into cardiovascular complications, respiratory complications, neurologic complications, renal complications, and complications with other organ systems. Cardiovascular complications encompassed various conditions such as arrythmia requiring medication or pacemaker insertion, tamponade, myocardial infarction, and resuscitation; pulmonary complications were mainly pneumonia; neurologic complications included delirium, transient ischaemic attacks and stroke; renal complications primarily consisted of urinary tract infections; and other complications included post-procedural bleeding or anaemia requiring transfusion. Furthermore, acute kidney injury (AKI) was evaluated as a postoperative complication, as it is often only a Clavien-Dindo Grade I complication according to the Clavien-Dindo classification. AKI was defined as an increase in serum creatinine of ≥26.5 μmol/l from baseline or to ≥1.5 times the baseline value(19).

## Statistical analysis

Categorical baseline variables were expressed as numbers and corresponding percentages. Continuous baseline variables were presented as means and standard deviations. Between-group differences for categorical variables were determined using Pearson's chi square and Fisher's exact test where appropriate. For continuous variables, an independent two-sample *t*-test was used to test for group differences. In the case of more than 10% missing values for a variable, we performed Little's Missing Completely At Random test to determine whether the missing values were missing completely at random. Since no variables were missing in more than 10% of patients, multiple imputation methods were not indicated. Furthermore, we performed a logistic regression analysis to assess the association between statin treatment and the various outcomes. For the multivariate analysis, the number of independent variables included was limited to 1 per 10 outcomes. The selected variables were age, gender, a Charlson Comorbidity Index three or higher, BMI≥30, smoking, eGFR<60, alcohol use and falls in the previous 6 months. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Additional analyses were performed to assess for effect modification by LMIS or HIS therapy, and age (<80 years and ≥ 80 years). All analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) software version 26.0 (SPSS Inc., Chicago III, United States).

# Results

## Patient inclusion and baseline characteristics

During the study period, 620 patients underwent TAVI. Seven patients did not permit their data to be reused for clinical research, while 29 patients did not receive a CGA prior to TAVI. A total of 584 patients were included in this study, of whom 324 were treated with a statin before TAVI (55.5%). Moreover, 65 patients were treated with HIS (20% of the statin users). Table 1 presents the patients' baseline characteristics. Compared with non-users, statin users were younger (79.8 vs 81.7 years); were more often male (53.7% vs 38.5%); had a higher BMI (27.1 vs 26.3); were more often multimorbid (51.2% vs 35.8%) including prior stroke (21.9% vs 13.1%), prior myocardial infarction (18.8% vs 6.9%), and diabetes (29.6% vs 12.3%); used more medications (10.6 vs 7.5), and were less often at risk of malnutrition (14.8% vs 21.9%). The statin treatment status did not change for any patient during their hospital stay.

**Table 1.** Baseline characteristics

| | | Statin | No statin | P-value |
|---|---|---|---|---|
| | | (n=324) | (n=260) | |
| **Demographics** | | | | |
| Age | Years [Mean ±SD] | 79.8 ±6.2 | 81.7 ±5.9 | <0.001 |
| | Age ≥80 years | 187 (57.7%) | 190 (73.1%) | <0.001 |
| Gender | Male | 174 (53.7%) | 100 (38.5%) | <0.001 |
| BMI | Kg/m2 [Mean ±SD] | 27.1 ±4.8 | 26.3 ±4.8 | 0.05 |
| Smoking | Current smoker | 28 (8.6%) | 17 (6.5%) | 0.38 |
| | Missing | 4 (1.2%) | 8 (3.1%) | |
| Alcohol use | Current alcohol user | 163 (50.3%) | 128 (49.2%) | 0.99 |
| | Missing | 4 (1.2%) | 9 (3.5%) | |
| **Frailty** | | | | |
| EFS [a] or GFI [b] | ≥6 or ≥4, respectively | 81 (25.0%) | 64 (24.6%) | 0.936 |
| | Missing | 20 (6.2%) | 17 (6.5%) | |
| **Somatic status** | | | | |
| CCI [c]* | ≥3 | 166 (51.2%) | 93 (35.8%) | <0.001 |
| - Diabetes | n (%) | 96 (29.6%) | 32 (12.3%) | <0.001 |
| - Stroke | n (%) | 70 (21.9%) | 34 (13.3%) | 0.008 |
| - Myocardial infarction | n (%) | 61 (18.8%) | 18 (6.9%) | <0.001 |
| - Any malignancy | n (%) | 41 (12.7%) | 29 (11.2%) | 0.58 |
| Medication use | Number [Mean ±SD] | 10.6 ±4.2 | 7.5 ±4.0 | <0.001 |
| | Polypharmacy (≥5 medications) | 312 (96.3%) | 196 (75.4%) | <0.001 |

| | | | | |
|---|---|---|---|---|
| | Hyperpolypharmacy (≥10 medications) | 175 (54.0%) | 73 (28.1%) | <0.001 |
| eGFR | < 60 ml/min/1.73m2 | 109 (33.6%) | 78 (30.0%) | 0.35 |
| **Cognitive and psychological status** | | | | |
| Impaired cognition | MMSE [d] ≤24, MOCA [d] <26, 6-CIT≥8 [e] | 5 (1.5%) | 3 (1.2%) | 0.68 |
| | Missing | 33 (10%) | 24 (9.2%) | |
| GDS-15[b] | ≥6 | 14 (4.3%) | 10 (3.8%) | 0.77 |
| Delirium in past | | 41 (12.7%) | 23 (8.8%) | 0.14 |
| | Missing | 3 (0.9%) | 2 (0.8%) | |
| **Functional status** | | | | |
| Dependence in (i)ADL | KATZ-15 [b] ≥2 | 154 (47.5%) | 122 (46.9%) | 0.81 |
| | Missing | 21 (6.5%) | 15 (5.8%) | |
| At risk of malnutrition | MNA [f] ≤11, MUST [g] ≥1 | 48 (14.8%) | 57 (21.9%) | 0.03 |
| | Missing | 7 (2.2%) | 5 (1.9%) | |
| Falls | ≥1 in previous 6 months | 63 (19.4%) | 45 (17.3%) | 0.55 |
| | Missing | 10 (3.1%) | 11 (4.2%) | |
| **Social status** | | | | |
| Living situation | Living dependent | 15 (4.6%) | 8 (3.1%) | 0.37 |
| | Missing | 27 (8.3%) | 28 (10.8%) | |

* not adjusted for age

BMI: Body Mass Index; EFS: Edmonton Frail Scale; GFI: Groningen Frailty Indicator; ASA: American Society of Anaesthesiology; CCI: Charlson Comorbidity Index; eGFR: estimated glomerular filtration rate; MMSE: Mini-Mental State Examination; MOCA: Montreal Cognitive Assessment; 6-CIT: six item cognitive impairment test; GDS: Geriatric Depression Scale; (i)ADL: (Instrumental) Activities of Daily Living; MNA: Mini Nutritional Assessment; MUST: Malnutrition Universal Screening Tool.
[a] Score range from 0 to 17, [b] Score range from 0 to 15, [c] Score range from 0 to 33, [d] Score range from 0 to 30, [e] Score range from 0-28, [f] Score range from 0 to 14, [g] Score range from 0 to 6



## Primary outcomes

Statin treatment was found not to be associated with a decreased short-term risk of mortality, readmissions, or major complications (Table 2). The 90-day mortality rate was 4.6% among statin users compared with 3.8% among non-users (adjusted OR 1.17; 95% CI 0.51–2.70). Furthermore, readmission risks at 90 days was 12.0% (39) in statin users and 13.1% (34) in non-users (adj. OR 0.91; 95% CI 0.54–1.52). Of the statin users, 35.5% experienced a major complication compared with 37.7% of non-users (adjusted OR 0.95; 95% CI 0.67–1.37). The effect of statin use on the short-term risks of mortality, readmissions, or postoperative complications was not significantly modified by the intensity of statin treatment (i.e. LIMS or HIS) or age (Table 3).

## Secondary outcomes

No significant associations were observed between statin treatment and the risk of postoperative complications in any specific organ system, including major cardiac or neurologic complications or AKI (Table 2). The rate of cardiovascular complications was 18.2% among statin users compared with 19.6% among non-users (adjusted OR 0.95; 95% CI 0.62–1.45). Pulmonary complications occurred in 2.5% of statin users and 3.1% in non-users (adjusted OR 0.84; 95% CI 0.30–2.32), while neurological complications were found in 7.1% of statin users compared with 7.7% in non-users (adjusted OR 1.05; 95% CI 0.56–2.00). Renal complications were seen in 3.7% of statin users compared with 2.3% of non-users (adjusted OR 1.54; 95% CI 0.56–4.23) and other complications occurred in 15.1% of statin users compared with 18.8% of non-users (adjusted OR 1.05; 95% CI 0.65–1.68). Acute kidney injury occurred in 5.9% of statin users and 3.5% of non-users (adjusted OR 0.88; 95% CI 0.40–1.85).

**Table 2.** The association between statin treatment and short-term outcomes after TAVI.

| Outcomes | Statin | No statin | OR [95% CI] | P-value | adj OR [95% CI] | P-value |
|---|---|---|---|---|---|---|
| **Primary outcomes** | **n=324** | **n=260** | | | | |
| 90-day mortality | 15 (4.6%) | 10 (3.8%) | 1.21 [0.54-2.75] | 0.64 | 1.17 [0.51-2.70][c] | 0.71 |
| 90-day readmission | 39 (12.0%) | 34 (13.1%) | 0.91 [0.56-1.49] | 0.71 | 0.91 [0.54-1.52][d] | 0.70 |
| Major postoperative complications[a] | 115 (35.5%) | 98 (37.7%) | 0.91 [0.65-1.28] | 0.58 | 0.95 [0.67-1.37][e] | 0.79 |
| **Secondary outcomes** | | | | | | |
| Cardiovascular complications | 59 (18.2%) | 52 (20.0%) | 0.93 [0.621.41] | 0.74 | 1.05 [0.67-1.63][e] | 0.84 |
| Respiratory complications | 8 (2.5%) | 8 (3.1%) | 0.80 [0.30-2.15] | 0.66 | 0.86 [0.32-2.36][f] | 0.77 |
| Neurologic complications | 23 (7.1%) | 20 (7.7%) | 0.92 [0.49-1.71] | 0.78 | 1.05 [0.55-2.01][g] | 0.87 |
| Renal complications | 12 (3.7%) | 6 (2.3%) | 1.63 [0.60-4.40] | 0.34 | 1.60 [0.59-4.36][f] | 0.36 |
| Other complications | 49 (15.1%) | 36 (13.8%) | 1.11 [0.70-1.77] | 0.66 | 1.01 [0.61-1.66][e] | 0.97 |
| Acute kidney injury[b] | 15 (4.6%) | 14 (5.4%) | 0.88 [0.41-1.85] | 0.73 | 0.86 [0.40-1.85][c] | 0.70 |
| - Missing | 19 (5.9%) | 9 (3.5%) | - | | | |

[a] Clavien-Dindo Grade ≥II

[b] increase in serum creatinine of ≥26.5 μmol/l from baseline or an increase in serum creatinine to ≥1.5 times the baseline value

[c] Adjusted for age and gender

[d] Adjusted for age, gender, a CCI three or higher, BMI≥30, smoking, eGFR<60 and alcohol use

[e] Adjusted for age, gender, a CCI three or higher, BMI≥30, smoking, eGFR<60, alcohol use and falls in previous 6 months

[f] Adjusted for age

[g] Adjusted for age, gender, a CCI three or higher and BMI≥30

**Table 3.** The association between statin treatment and short-term outcomes after TAVI, stratified by age and intensity of statin therapy

| | Statin | No statin | OR [95% CI] | P-value | adj OR [91% CI] | P-value |
|---|---|---|---|---|---|---|
| **Age <80 years (n=207)** | **n=137** | **n=70** | | | | |
| 90-day mortality | 4 (2.9%) | 4 (5.7%) | 0.50 [0.12-2.05] | 0.33 | na.[b] | |
| 90-day readmission | 19 (13.9%) | 7 (10.0%) | 1.45 [0.58-3.63] | 0.43 | 1.45 [0.57-3.69][c] | 0.43 |
| Major postoperative complications[a] | 48 (35.0%) | 23 (32.9%) | 1.10 [0.60-2.03] | 0.76 | 0.88 [0.45-1.70][d] | 0.69 |
| **Age ≥80 years (n=377)** | **n=187** | **n=190** | | | | |
| 90-day mortality | 11 (5.9%) | 6 (3.2%) | 1.92 [0.69-5.29] | 0.21 | 1.91 [0.89-5.29][e] | 0.21 |
| 90-day readmission | 20 (10.7%) | 27 (14.2%) | 0.72 [0.39-1.34] | 0.30 | 0.72 [0.38-1.36][f] | 0.31 |
| Major postoperative complications[a] | 67 (35.8%) | 75 (39.5%) | 0.86 [0.56-1.30] | 0.47 | 0.91 [0.59-1.42][g] | 0.69 |
| **LMIS (n=519)** | **n=259** | **n=260** | | | | |
| 90-day mortality | 14 (5.4%) | 10 (3.8%) | 1.43 [0.62-3.28] | 0.40 | 1.37 [0.59-3.19][c] | 0.46 |
| 90-day readmission | 32 (12.4%) | 34 (13.1%) | 0.94 [0.56-1.57] | 0.81 | 0.93 [0.54-1.58][h] | 0.78 |
| Major postoperative complications[a] | 95 (36.7%) | 98 (37.7%) | 0.96 [0.67-1.37] | 0.81 | 1.02 [0.70-1.48][g] | 0.94 |
| **HIS (n=325)** | **n=65** | **n=260** | | | | |
| 90-day mortality | 1 (1.5%) | 10 (3.8%) | 0.39 [0.05-3.11] | 0.37 | 0.35 [0.04-2.86][e] | 0.33 |
| 90-day readmission | 7 (10.8%) | 34 (13.1%) | 0.80 [0.34-1.90] | 0.62 | 0.70 [0.28-1.74][f] | 0.45 |
| Major postoperative complications[a] | 20 (30.8%) | 98 (37.7%) | 0.74 [0.41-1.32] | 0.30 | 0.69 [0.37-1.29][g] | 0.24 |

LMIS: Low-moderate intensity statin; HIS: High intensity statin (atorvastatin ≥40mg or rosuvastatin ≥20 mg).

[a] Clavien-Dindo Grade ≥II

[b] not applicable, less than 10 outcomes

[c] Adjusted for age and gender

[d] Adjusted for age, gender, a CCI three or higher, BMI≥30, smoking, eGFR<60 and alcohol use

[e] Adjusted for age

[f] Adjusted for age, gender, a CCI three or higher, BMI≥30

[g] Adjusted for age, gender, a CCI three or higher, BMI≥30, smoking, eGFR<60, alcohol use and falls in previous 6 months

[h] Adjusted for age, gender, a CCI three or higher, BMI≥30, smoking and eGFR<60

## Discussion

This study found no association between statin treatment before TAVI and a decreased risk of negative short-term outcomes, including 90-day mortality, 90-day readmissions, and major postoperative complications. Although several studies have suggested a direct pleiotropic effect of statins during the postoperative period after TAVI, we found no association between statin treatment and any postoperative complications.

The difference between our study and the two previous studies that have suggested a direct pleiotropic effect directly after TAVI is that they were propensity score matched (5,7). In the first study, which included 3,956 patients, a total of 626 matched pairs were formed, accounting for 31% of the initial cohort (5). In the second study which included 2,588 patients, 936 matched pairs were created, accounting for 72% of the initial study population(7). In both studies, 40% of patients who were not using statins could not be successfully matched. It is important to consider that propensity score matching might have led to the exclusion of patients without an indication for statin treatment while including patients with a high cardiovascular risk who were not using statin treatment. This could have led to higher mortality risks in the included non-users compared to the included users. This could have potentially accounted for the observed positive effect of statin use on mortality in these two studies, as matching was performed based on variables such as prior cardiovascular events, cholesterol levels, and other coexisting medical conditions.

In addition, the finding that statin treatment was not significantly associated with short-term outcomes after TAVI is consistent with previous observational studies on short-term cardiovascular complications and short-term mortality. Merdler et al. found no significant effect of statin treatment on one-month mortality and postoperative cardiologic complications (11). Moreover, Huded et al. found no significant effect of statin treatment on post-TAVI myocardial infarction, AKI, in-hospital mortality and 30-day mortality (12). Furthermore, Klinkhammer et al. demonstrated no effect of statin treatment on postoperative cardiological complications or mortality one and six months after TAVI (20). In all studies, including our study, statin non-use in patients with an indication for statins treatment was highly prevalent. Therefore, matching on covariates indicative of high cardiovascular risk, including prior cardiovascular events, diabetes, hypercholesterolemia and hypertension, poses a risk of overestimating statin treatment after TAVI by selecting high-risk patients already known to benefit from statin treatment. Our outcomes are in line with RCTs on statin treatment during coronary artery bypass grafting surgery, which revealed no association with short-term mortality and postoperative complications (21).

### Strengths and limitations

This study has several strengths. First, the data were collected from a relatively large cohort that included patients over a long period of time. Together with the broad inclusion criteria, this has probably resulted in a high representation of the study population

for the total older population of TAVI patients and thus good external validity of the outcomes. Second, this study examined the effect of statin treatment on the overall risk of short-term negative outcomes using both short-term mortality and morbidity. Third, all postoperative complications occurring after TAVI were classified according to the Clavien-Dindo classification, therefore, in addition to the standard reported complications, such as myocardial infarction, stroke, and AKI, all other postoperative complications were included as relevant clinical outcomes. However, due to the retrospective nature of the study, we were not able to report on all endpoints specified by the Valve Academic Research Consortium (22).

This study also has several limitations. First, the number of events was relatively low, which could have led to residual confounding in the analyses, as only a limited number of possible confounding variables could be included. Second, due to the retrospective nature of the study, a possibility of residual confounding also exists, since reasons for non-use were not available. Third, we only had information on statin treatment before hospitalisation from a structured medication review and on statin exposure during the hospital stay for the TAVI procedure. Fourth, we did not have access to public pharmacy outpatient dispensing records; therefore, we did not have information on the duration of statin treatment before the procedure or its continuation after TAVI. Lastly, the HIS subgroup was small, which could have resulted in insufficient power to demonstrate significant associations between HIS and the outcomes.

### Clinical implications and recommendations for future research

Based on the lack of an association between statin treatment and short-term outcomes post-TAVI in this study as well as in previous studies, the initiation of statin treatment is not specifically advised for improving short-term outcomes after TAVI. Yet, statins are often indicated to improve long-term negative outcomes, as atherosclerotic comorbidity is common in these patients. A clinical trial could answer critical questions about the short-term effects of statin treatment after TAVI as well as whether initiating statin treatment before TAVI improves long-term outcomes. Furthermore, because our study included a relatively small number of patients treated with HIS, different statin dosages could be incorporated into a trial as well to determine whether HIS treatment has an effect on short-term outcomes in patients who can tolerate high statin dosages.



## Conclusion

This study demonstrated that preoperative statin treatment is common in TAVI patients, but is not associated with decreased risks of negative short-term outcomes after a TAVI, including 90-day mortality, 90-day readmissions, and major postoperative complications. Given the magnitude of statin non-use in all observational TAVI statin studies, an RCT with different statin doses could be warranted for investigating whether initiating statin treatment before TAVI improves both post-operative outcomes and long-term survival.

## References


1. Osnabrugge RLJ, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, Lereun CM, et al. Aortic stenosis in the elderly: Disease prevalence and number of candidates for transcatheter aortic valve replacement: A meta-analysis and modeling study. J Am Coll Cardiol. 2013;62(11):1002–12.
2. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2022 Feb 12;43(7):561–632.
3. Chakos A, Wilson-Smith A, Arora S, Nguyen TC, Dhoble A, Tarantini G, et al. Long term outcomes of transcatheter aortic valve implantation (TAVI): a systematic review of 5-year survival and beyond. Ann Cardiothorac Surg [Internet]. 2017 Sep;6(5):432–43. Available from: http://www.annalscts.com/article/view/16396/16527
4. Takagi H, Hari Y, Nakashima K, Kuno T, Ando T. Meta-Analysis for Impact of Statin on Mortality After Transcatheter Aortic Valve Implantation. American Journal of Cardiology [Internet]. 2019;124(6):920–5. Available from: https://doi.org/10.1016/j.amjcard.2019.05.069
5. Peri-Okonny PA, Liu Y, Malaisrie SC, Huded CP, Kapadia S, Thourani VH, et al. Association of Statin Use and Mortality After Transcatheter Aortic Valve Replacement. J Am Heart Assoc. 2019;8(8):1–12.
6. Fischer-Rasokat U, Renker M, Bänsch C, Weferling M, Liebetrau C, Herrmann E, et al. Effects of Statins After Transcatheter Aortic Valve Implantation in Key Patient Populations. J Cardiovasc Pharmacol [Internet]. 2021 Nov;78(5):e669–74. Available from: https://journals.lww.com/10.1097/FJC.0000000000001114
7. Yashima F, Hara M, Inohara T, Jinzaki M, Shimizu H, Fukuda K, et al. Statin therapy for patients with aortic stenosis who underwent transcatheter aortic valve implantation: a report from a Japanese multicentre registry. BMJ Open [Internet]. 2021 Jun 11;11(6):e044319. Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2020-044319
8. Schönbeck U, Libby P. Inflammation, Immunity, and HMG-CoA Reductase Inhibitors. Circulation [Internet]. 2004 Jun;109(21_suppl_1). Available from: https://www.ahajournals.org/doi/10.1161/01.CIR.0000129505.34151.23
9. Chen Z, Fukutomi T, Zago AC, Ehlers R, Detmers PA, Wright SD, et al. Simvastatin Reduces Neointimal Thickening in Low-Density Lipoprotein Receptor–Deficient Mice After Experimental Angioplasty Without Changing Plasma Lipids. Circulation [Internet]. 2002 Jul 2;106(1):20–3. Available from: https://www.ahajournals.org/doi/10.1161/01.CIR.0000022843.76104.01
10. Sen-Banerjee S, Mir S, Lin Z, Hamik A, Atkins GB, Das H, et al. Kruppel-Like Factor 2 as a Novel Mediator of Statin Effects in Endothelial Cells. Circulation [Internet]. 2005 Aug 2;112(5):720–6. Available from: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.104.525774
11. Merdler I, Rozenbaum Z, Finkelstein A, Arbel Y, Banai S, Bazan S, et al. Effect of Statin Therapy and Long-Term Mortality Following Transcatheter Aortic Valve Implantation. American Journal of Cardiology [Internet]. 2019;123(12):1978–82. Available from: https://doi.org/10.1016/j.amjcard.2019.03.016

12. Huded CP, Benck LR, Stone NJ, Sweis RN, Ricciardi MJ, Malaisrie SC, et al. Relation of Intensity of Statin Therapy and Outcomes After Transcatheter Aortic Valve Replacement. Am J Cardiol. 2017 Jun 1;119(11):1832–8.
13. Zheng Z, Jayaram R, Jiang L, Emberson J, Zhao Y, Li Q, et al. Perioperative Rosuvastatin in Cardiac Surgery. New England Journal of Medicine [Internet]. 2016 May 5;374(18):1744–53. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1507750
14. Billings FT, Hendricks PA, Schildcrout JS, Shi Y, Petracek MR, Byrne JG, et al. High-Dose Perioperative Atorvastatin and Acute Kidney Injury Following Cardiac Surgery. JAMA [Internet]. 2016 Mar 1;315(9):877. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2016.0548
15. Dautzenberg L, Pals JEM, Lefeber GJ, Stella PR, Abawi M, Emmelot-Vonk M, et al. Predictors of clinical outcome following transcatheter aortic valve implantation: a prospective cohort study. Open Heart [Internet]. 2021 Sep 23;8(2):e001766. Available from: https://openheart.bmj.com/lookup/doi/10.1136/openhrt-2021-001766
16. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation [Internet]. 2019 Jun 18;139(25). Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000000625
17. Seely AJE, Ivanovic J, Threader J, Al-Hussaini A, Al-Shehab D, Ramsay T, et al. Systematic Classification of Morbidity and Mortality After Thoracic Surgery. Ann Thorac Surg [Internet]. 2010 Sep;90(3):936–42. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0003497510010611
18. Hébert M, Cartier R, Dagenais F, Langlois Y, Coutu M, Noiseux N, et al. Standardizing Postoperative Complications—Validating the Clavien-Dindo Complications Classification in Cardiac Surgery. Semin Thorac Cardiovasc Surg [Internet]. 2021;33(2):443–51. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1043067920303026
19. Ostermann M, Joannidis M. Acute kidney injury 2016: diagnosis and diagnostic workup. Crit Care [Internet]. 2016 Dec 27;20(1):299. Available from: http://ccforum.biomedcentral.com/articles/10.1186/s13054-016-1478-z
20. Klinkhammer B. Statin Therapy is not Associated with Improved Overall Survival after Transcatheter Aortic Valve Replacement (TAVR). J Cardiovasc Dis Res [Internet]. 2018 Aug 25;9(2):54–8. Available from: http://www.jcdronline.org/article/2018/9/2/105530jcdr2018214
21. Putzu A, de Carvalho e Silva CMPD, de Almeida JP, Belletti A, Cassina T, Landoni G, et al. Perioperative statin therapy in cardiac and non-cardiac surgery: a systematic review and meta-analysis of randomized controlled trials. Ann Intensive Care [Internet]. 2018 Dec 27;8(1):95. Available from: https://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-018-0441-3
22. Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, Pibarot P, et al. Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research. J Am Coll Cardiol. 2021 Jun;77(21):2717–46.

## Supplementary data

**Supplementary table S1.** Individual elements of the applied comprehensive geriatric assessment stratified by the somatic, psychological, functional and social domains

| Elements of the CGA | Instrument/test | Cut-off score | Interpretation |
|---|---|---|---|
| **Somatic domain** | | | |
| Medical history | | | |
| Comorbidity | Charlson Comorbidity Index[1] | ≥3 | Multimorbidity |
| Medication use | | 1. ≥5 drugs<br>2. ≥ 10 drugs | 1. Polypharmacy<br>2. Hyperpolypharmacy |
| Smoking status | | | Current smoker |
| Alcohol use | | | Current alcohol user |
| BMI | $Kg/m^2$ | | |
| Renal function | Estimated glomerular filtration rate | < 60 ml/min/1.73$m^2$ | Impaired kidney function |
| **Psychological domain** | | | |
| Cognition | Mini-Mental State Examination[2] | ≤24 | Cognitive impairment |
| Cognition | Montreal Cognitive Assessment[3] | <26 | Cognitive impairment |
| Cognition | Six item cognitive impairment test[4] | ≥8 | Cognitive impairment |
| Mood | Geriatric Depression Scale[5] | ≥6 | Depression |
| Previous delirium | | Yes | Increased risk of delirium |
| **Functional domain** | | | |
| (Instrumental) activities of daily living | KATZ-15[6] | ≥2 | Dependence |
| Nutritional status | Malnutrition Universal Screening Tool[7] | ≥1 | Increased risk of malnutrition |
| Nutritional status | Mini Nutritional Assessment[8] | ≤11 | Increased risk of malnutrition |
| History of falling | | ≥1 in previous 6 months | Increased risk of falling |
| Gait speed | 4 meter walk gait speed test[9] | ≤0.80 meters per second | Decreased gait speed |
| Handgrip strength | Hand dynamometer[9] | ≤20 kilograms for women and ≤30 kilograms for men | Decreased handgrip strength |
| **Social domain** | | | |
| Living situation | | 1. At home<br>2. At a skilled nursing or assisted nursing facility | 1. Independent<br>2. Dependent |
| **Frailty** | | | |
| Frailty status | Edmonton Frail Scale[10] | ≥6 | Frail |
| Frailty status | Groningen Frailty Indicator[11] | ≥4 | Frail |

## References


1. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis [Internet] 1987;40(5):373–83. Available from: https://linkinghub.elsevier.com/retrieve/pii/0021968187901718
2. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." J Psychiatr Res [Internet] 1975;12(3):189–98. Available from: https://linkinghub.elsevier.com/retrieve/pii/0022395675900266
3. Nasreddine ZS, Phillips NA, BÃ©dirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. J Am Geriatr Soc [Internet] 2005;53(4):695–9. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1532-5415.2005.53221.x
4. Brooke P, Bullock R. Validation of a 6 item cognitive impairment test with a view to primary care usage. Int J Geriatr Psychiatry [Internet] 1999;14(11):936–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10556864
5. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: A preliminary report. J Psychiatr Res [Internet] 1982;17(1):37–49. Available from: https://linkinghub.elsevier.com/retrieve/pii/0022395682900334
6. Laan W, Zuithoff NPA, Drubbel I, Bleijenberg N, Numans ME, De Wit NJ, et al. Validity and reliability of the Katz-15 scale to measure unfavorable health outcomes in community-dwelling older people. J Nutr Health Aging [Internet] 2014;18(9):848–54. Available from: http://link.springer.com/10.1007/s12603-014-0558-5
7. Stratton RJ, Hackston A, Longmore D, Dixon R, Price S, Stroud M, et al. Malnutrition in hospital outpatients and inpatients: prevalence, concurrent validity and ease of use of the 'malnutrition universal screening tool' ('MUST') for adults. Br J Nutr [Internet] 2004;92(5):799–808. Available from: https://www.cambridge.org/core/product/identifier/S0007114504002429/type/journal_article
8. Vellas B, Guigoz Y, Garry PJ, Nourhashemi F, Bennahum D, Lauque S, et al. The mini nutritional assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition [Internet] 1999;15(2):116–22. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0899900798001713
9. Reiss J, Iglseder B, Alzner R, Mayr-Pirker B, Pirich C, Kässmann H, et al. Sarcopenia and osteoporosis are interrelated in geriatric inpatients. Z Gerontol Geriatr [Internet] 2019;52(7):688–93. Available from: http://link.springer.com/10.1007/s00391-019-01553-z
10. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age Ageing [Internet] 2006;35(5):526–9. Available from: https://academic.oup.com/ageing/article/35/5/526/9782
11. Peters LL, Boter H, Buskens E, Slaets JPJ. Measurement Properties of the Groningen Frailty Indicator in Home-Dwelling and Institutionalized Elderly People. J Am Med Dir Assoc [Internet] 2012;13(6):546–51. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1525861012001144

**Supplementary Table S2.** Clavien-Dindo Classification of surgical complications.

| Grades | Definition |
|---|---|
| Grade I | Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.<br>Allowed therapeutic regimens are: drug as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside. |
| Grade II | Requiring pharmacological treatment with drugs other than such allowed for grade I complications.<br>Blood transfusions and total parenteral nutrition are also included. |
| Grade III | Requiring surgical, endoscopic or radiological intervention |
| - IIIa | Intervention not under general anesthesia |
| - IIIb | Intervention under general anesthesia |
| Grade IV | Life-threatening complications (including central nervous system complications)* requiring IC/ICU-management |
| - IVa | Single organ dysfunction (including dialysis) |
| - IVb | Multiorgandysfunction |
| Grade V | Death of a patient |

* Brain hemorrhage, ischemic stroke, subarachnoid haemorrhage, but excluding transient ischemic attacks;
IC: intermediate care; ICU: intensive care unit

CHAPTER 7

7

# Medication review interventions to reduce hospital readmissions in older people

Lauren Dautzenberg, Lisa Bretagne, Huiberdina L. Koek, Sofia Tsokani, Stella Zevgiti, Nicolas Rodondi, Rob J.P.M. Scholten, Anne W. Rutjes, Marcello Di Nisio, Renee C.M.A. Raijmann, Marielle H. Emmelot-Vonk, Emma L.M. Jennings, Olivia Dalleur, Dimitris Mavridis, Wilma Knol

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## Abstract

**Objective:** To assess the efficacy of medication review as an isolated intervention and with several co-interventions for preventing hospital readmissions in older adults.

**Methods:** Ovid MEDLINE, Embase, The Cochrane Central Register of Controlled Trials and CINAHL were searched for randomized controlled trials evaluating the effectiveness of medication review interventions with or without co-interventions to prevent hospital readmissions in hospitalized or recently discharged adults aged ≥ 65, until September 13 2019. Included outcomes were 'at least one all-cause hospital readmission within 30 days and at any time after discharge from the index admission.'

**Results**: Twenty-five studies met the inclusion criteria. Of these, 11 studies (7,318 participants) contributed to the network meta-analysis (NMA) on all-cause hospital readmission within 30 days. Medication review in combination with a) medication reconciliation and patient education (risk ratio (RR) 0.45; 95% confidence interval (CI) 0.26–0.80) and b) medication reconciliation, patient education, professional education and transitional care (RR 0.64; 95% CI 0.49–0.84) were associated with a lower risk of all-cause hospital readmission compared to usual care. Medication review in isolation did not significantly influence hospital readmissions (RR 1.06; 95% CI 0.45-2.51). The NMA on all-cause hospital readmission at any time included 24 studies (11,677 participants). Medication review combined with medication reconciliation, patient education, professional education and transitional care resulted in a reduction of hospital readmissions (RR 0.82; 95% CI 0.74-0.91) compared to usual care.
The quality of the studies included in this systematic review raised some concerns, mainly regarding allocation concealment, blinding and contamination.

**Conclusion:** Medication review in combination with medication reconciliation, patient education, professional education and transitional care, was associated with a lower risk of hospital readmissions compared to usual care. An effect of medication review without co-interventions was not demonstrated. Trials of higher quality are needed in this field.

## Introduction

Hospitalizations can have detrimental effects on older patient outcomes.[1,2] Following hospitalization, older adults are at risk for complications like delirium, falls, functional decline and subsequent institutionalization or readmission.[1,2] Medication related readmissions occur frequently, particularly in older adults.[3]

Improving medication appropriateness may reduce medication related problems and the number of hospital readmissions. Medication appropriateness is present when therapeutic objectives are being achieved or there is a reasonable chance they will be achieved and the benefits of the medication outweigh the risks for an individual patient.[4]

Relevant systematic reviews often recommend a medication review to improve the quality of prescriptions in older patients.[5–8] Christensen *et al*. conducted a Cochrane review assessing the effect of medication review in hospitalized patients.[9] A medication review is an intervention which can be carried out in isolation or in combination with one or more co-interventions. Co-interventions i.e. medication reconciliation, education of patients/healthcare professionals, use of Computerized Decision Support tool, prescribing criteria like START/STOPP criteria[10] or the Beers' criteria,[11] complement or structure the basic critical evaluation of a patient's medication, and may all have a different effects on hospital readmissions.

Frequently the terms for medication review and co-interventions as listed previously are erroneously used interchangeably. Thus, leading to substantial heterogeneity. Medication related problems frequently occur on transition from one health care setting to another.[12,13] However, Christensen *et* al. excluded studies where medication review recommendations were implemented after discharge.

An internationally accepted standardized approach for implementing medication reviews in research and clinical settings is lacking. It is unclear whether a medication review alone or in combination with co-interventions, effectively prevents hospital readmissions. Published data are conflicting, possibly due to the heterogeneity of the interventions evaluated and the timing of execution.[5,6,14–17] To address this, we categorized all medication review interventions by the presence of associated co-interventions. A network meta-analysis (NMA) permitted the synthesis of relative effects from studies comparing competing interventions, even if these interventions were not directly compared to each other in the literature.[18,19] We included studies where the intervention was carried out during admission or within 2 weeks of discharge.

The aim of this systematic review and NMA was to determine and compare the impact of medication review in isolation or with co-interventions, during hospitalization or within 2 weeks of discharge, on hospital readmissions.

# Methods

## Protocol

The study protocol was registered online. (PROSPERO, registration number CRD42020150799)

## Study identification

Replicating the search strategy of Christensen *et al.*[9] we searched online repositories Ovid MEDLINE, Embase, The Cochrane Central Register of Controlled Trials and CINAHL from January 1 2014 to September 13 2019, without language restriction (Supplementary Table S11-14). Original studies of Christensen *et al.* were identified via reference lists and rescreened. Bibliographical hand searches of relevant systematic reviews were also conducted.[7-9,15,17,21-27]

## Eligibility Criteria

Controlled trials (randomized, quasi and cluster) evaluating the effectiveness of medication review interventions with or without co-interventions to prevent hospital readmissions in adults aged 65 years and older were included. Participants were hospitalized or recently discharged (the medication review was conducted within 2 weeks of discharge) to the community, nursing home or rehabilitation center. Comparison treatments were usual care, a sham intervention or another version of a medication review intervention.

Included outcomes were; i) at least one all-cause hospital readmission, ii) at least one medication-related readmission at any time and iii) all-cause hospital readmission rate. Details of the study population, interventions, comparators and outcomes are described in Supplementary Table S10.

## Study Selection

Study selection was performed by two researchers (LD and LB). A supervised test screening (RJPMS) of application of inclusion criteria was conducted prior to the start of the title/abstract screening phase and the full text screening phase to ensure consistency i.e. 50 studies with 98% agreement between researchers. Each researcher independently screened half of the titles and abstracts identified by the systematic search. Each researcher subsequently independently screened half of the included full texts for inclusion. Uncertainties were resolved by discussion or by involvement of a third author (WK, RJPMS, HLK). Several publications from the same patient cohort were considered as one study with one or more companion reports.

## Data extraction

One researcher (LD) extracted all descriptive and outcome data. Outcome data were verified by a second researcher (LB). Conflicts were discussed and resolved by the two researchers. For every included study data was extracted by means of a bespoke report-

form capturing study design, population characteristics, intervention characteristics and reported outcomes (Supplementary Table S15).
Reported interventions were categorized into nine intervention components: medication review, medication reconciliation, shared decision making, patient education/ medication counselling, health professional education, use of validated methods, use of Computerized Decision Support, compliance aid and transitional care (Table 1 and Supplementary Table S1). The list of the nine intervention components was developed during the preparation of the study protocol. The list is based on medication review interventions in previously published RCTs and clinical experience of several pharmacologists among the co-authors. One researcher (LD) categorized the interventions of the included studies by this list. A second researcher (HK) blindly evaluated this categorization for a random sample of included studies (n=10, 40%), and there was a 90% overlap. Inconsistencies were solved during a consensus meeting. Information about the co-interventions found in the included studies is presented in Supplementary Table S2.

## Risk of bias assessment

The risk of bias assessment was performed using the Effective Practice and Organisation of Care (EPOC) version of Cochrane's Risk of Bias tool.[20] The risk of bias assessment was performed by one researcher (LD) and verified by a second researcher (LB). Discrepancies were discussed and resolved.

## Data Analysis

When the number of included studies was sufficient (i.e. less interventions than studies providing data), we performed random-effects NMA for each of the aforementioned outcomes using the netmeta command in R Statistical Software (Team RC. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2013).[18,19,21,22] After categorization of the interventions of included studies (Table 1), many studies turned out to consist of multi-component interventions (e.g. medrev + medrec + pedu). Therefore, as per protocol, we analyzed the effect of the (combination of) components, also known as component NMA (CNMA) (for details: see Supplement, additional information regarding NMA).[23] We calculated risk ratios (RR) along with their 95% confidence intervals (CI) for each intervention versus usual care. For each outcome we used P-scores to rank intervention effects.[23] P-scores measure the certainty that an intervention is better than the competing interventions of the network, and take values between 0 and 1; the higher the P-score, the more beneficial the intervention.
We did not check for inconsistency, i.e. the occurrence of conflicting direct and indirect evidence, as for none of the interventions versus usual care there was both direct and indirect evidence available. We assessed transitivity clinically.[18]
Further subgroup analyses (participants aged ≥75 years, multi-morbid participants and nursing home residents) were not feasible due to the low number of studies identified.

### Confidence in the NMA results

We evaluated the credibility of the NMA results using the CINeMA approach.[24] CINeMA is an online web application, considering six domains (within-study bias, across-study bias, indirectness, imprecision, heterogeneity, and incoherence) to judge the confidence on NMA results. For each treatment comparison we rated the corresponding treatment effect on each of the aforementioned six domains as either 'no concerns', 'minor concerns' or 'major concerns' (for details: see online Supplement, additional information regarding the CINeMA approach).

**Table 1.** Intervention components to prevent hospital readmissions

| Intervention component | Abbreviation |
|---|---|
| Medication review | Mdrev |
| Medication reconciliation | Mdrec |
| Shared decision making | Sdm |
| Patient education/ medication counselling | Pedu |
| Health professional education | Hpedu |
| Use of validated methods | Vm |
| Use of Computerized Decision Support | Cds |
| Compliance aid | Ca |
| Transitional care | Tc |

## Results

### Study selection

We identified 4,045 studies through database search. Supplementary Figure S1. illustrates study identification and selection. Five additional RCTs were identified, two[25,26] from the list of excluded studies of Christensen *et al*. and three[27–29] from screening reference lists of 12 relevant systematic reviews. After screening, 25 studies[25–49] and 1 companion report[50] were included in the final analysis.

### Study and participant characteristics

An executive summary of included study and participant characteristics is presented in Table 2. (detailed individual study description is available in Supplementary Table S2 and S3). In 12 studies (48%)[26,28,31,33,36–38,43–45,48,49], the mean/median age was 75-84 years and in four studies (16%) ≥85 years.[25,29,32,34] In the majority of the studies, at least half of the study population was female (n=19, 76%).[25–29,31–33,35–40,43–45,48,49]

In four studies (16%)[28,29,42,43], the intervention was community based within 2 weeks of discharge. The duration of follow-up of all studies varied from 4 weeks to 1 year. Study size ranged from 22 – 4049, over half (n=21, 84%) of included studies had a study population

≥100.[25–33,35,39–49] The mean/median number of regularly used medication was at least 6 and in most studies ranged between 6 and 10 (n=18, 72%).[25–30,32,33,35,37–40,43,44,46–48]
A summary of the characteristics of the medication review interventions is provided in Supplementary Table S5.

**Table 2.** Summary of participant and study characteristics of the 25 included randomized controlled trials

| Participant or study characteristic | Number of studies (%) | Citation number for each study in each row |
|---|---|---|
| **Mean/median age (years)** | | |
| 65-74 | 9 (36%) | 27,30,35,39–42,46,47 |
| 75-84 | 12 (48%) | 26,28,31,33,36–38,43–45,48,49 |
| ≥ 85 | 4 (16%) | 25,29,32,34 |
| **Female (%)** | | |
| 25-49 | 5 (20%) | 30,34,42,46,47 |
| 50-74 | 19 (76%) | 25–29,31–33,35–40,43–45,48,49 |
| Not reported | 1 (4%) | 41 |
| **Year of publication** | | |
| 2000-2004 | 1[a] (4%) | 28 |
| 2005-2009 | 5[a] (20%) | 26,27,29,32,41 |
| 2010-2014 | 3[a] (12%) | 25,38,45 |
| 2015-2019 | 16 (64%) | 30,31,33–37,39,40,42–44,46–49 |
| **Continent** | | |
| Europe | 16 (64%) | 25,26,43– 46,48,49,27,29,30,32,37,38,41,42 |
| North America | 6 (24%) | 30,31,34,35,42,49 |
| Australia/New Zealand | 1 (4%) | 28 |
| South America | 1 (4%) | 46 |
| Asia | 1(4%) | 48 |
| **Study design** | | |
| Parallel | 19 (76%) | 25,27–29,31–34,36–42,45–47,49 |
| Quasi randomized | 4 (16%) | 26,35,44,48 |
| Cluster | 2 (8%) | 30,43 |
| **Site** | | |
| Single center | 17 (68%) | 26–28,30–32,34,36–38,42,44–49 |
| Multicenter | 8 (32%) | 25,29,33,35,39–41,43 |
| **Setting** | | |
| Hospital | 21 (84%) | 25–27,30–41,44–49 |
| Community | 3 (12%) | 28,29,42 |
| Community pharmacy | 1 (4%) | 43 |

| | | |
|---|---|---|
| **Duration of follow-up (weeks)** | | |
| 0-4 | 7 (28%) | 30,34,35,44,46,47,49 |
| 5-12 | 6 (24%) | 28,31,37,38,42,48 |
| 13-26 | 7 (28%) | 25,27,29,33,40,43,45 |
| 27-52 | 5 (20%) | 26,32,36,39,41 |
| **Sample size** | | |
| <100 | 4 (16%) | 34,36–38 |
| 100-499 | 16 (64%) | 26–28,30–33,39,42–49 |
| 500-999 | 3 (12%) | 25,29,41 |
| ≥1000 | 2 (8%) | 35,40 |
| **Regular used medication, mean/ median number** | | |
| 0-5 | 0 | |
| 6-10 | 18 (72%) | 25–30,32,33,35,37–40,43,44,46–48 |
| 11-15 | 1 (4%) | 42 |
| >15 | 2 (8%) | 34,36 |
| Not reported | 4 (16%) | 31,41,45,49 |
| **Chronic conditions, mean/median number** | | |
| 0-5 | 4 (16%) | 25,28,43,46 |
| Not reported | 21 (84%) | 26,27,29–42,44,45,47–49 |

[a] These studies were identified from screening the reference list of relevant systematic reviews and the list of included and excluded studies by Christensen *et al*. The studies identified through database search were all published after 2014.

## Risk of bias of included studies

Individual risk of bias assessments of included studies are presented in Supplementary Table S4 and the aggregate risk of bias assessment per domain in Supplementary Figure S2. Most studies had a low risk of bias for the domains 'random sequence generation' (n=19, 76%)[25,27–29,31–34,36–42,45–47,49], 'similarity of baseline characteristics' (n=24, 96%)[25–32,34–49]. Allocation concealment was adequately performed in one third, inadequately in one third and unclear in the remaining third of the trials. In 76% of the studies, no information was reported at baseline on hospital (re)admissions in the preceding months (n=19).[27,29–39,42–48] Blinding of participants or personnel was not performed in the majority of studies. Blinded outcome assessment was performed in 17 studies (68%).[25,26,28–30,32–37,39–41,45–47] In 19 studies (76%) there was a high risk of bias for contamination.[25–29,31–34,36–40,42,45,47–49] For the domains 'incomplete outcome data' (n=16, 64%)[25,27–38,40,42,47] and 'selective outcome reporting' (n=13, 52%)[26,30–33,36,37,39,40,42,44,45,49], more than half of the studies scored a low risk of bias.

## Network meta-analysis

NMA was performed for the outcomes 'all-cause hospital readmissions within 30 days' and 'all-cause hospital readmissions at any time.' There was insufficient reported data to perform a NMA for other outcomes as the number of interventions evaluated was higher than the number of studies providing data.

### *All-cause hospital readmissions within 30 days*

For the outcome 'at least one all-cause hospital readmission within 30 days after discharge', the NMA included 11 studies (7,318 participants)[30,31,33–35,40,44,46–49] and 10 interventions that were all compared with usual care (Supplementary Figure S3). Each intervention was directly compared to usual care, except for the medication review intervention without any co-interventions, for which only indirect evidence was present. The RRs and 95% CIs for every intervention versus usual care resulting from the primary analysis in which each existing combination of components was analyzed as a distinct intervention, are presented in Table 3 and Figure 1.

Two interventions were associated with a statistically significant decrease in hospital readmissions: a) medication review in combination with medication reconciliation and patient education (RR 0.45; 95% CI 0.26–0.80; P-score 0.92) and b) medication review in combination with medication reconciliation, patient education, professional education and transitional care (RR 0.64; 95% CI 0.49–0.84; P-score 0.76).

Analysis of effects of single components (Supplementary Table S7) showed that patient education significantly reduced hospital readmissions (RR 0.64; 95% CI 0.41–0.99).

Analysis of effects of the compound interventions (interventions rebuilt by adding up the separate effects of the components) (Supplementary Table S6) demonstrated a statistically significant effect for a) medication review in combination with medication reconciliation and patient education (RR 0.54; 95% CI 0.35–0.85) and b) medication review in combination with medication reconciliation, patient education, professional education and transitional care (RR 0.63; 95% CI 0.48–0.82).

### *All-cause hospital readmissions at any time*

For the outcome 'at least one all-cause hospital readmission at any time', the NMA included 24 studies (11,677 participants)[25–35,37–49] and 17 interventions. (Supplementary Figure S4). All interventions consisting of multiple components were compared with usual care. There was no direct evidence for medication review without any co-interventions versus usual care. Table 3 and Figure 2 present the RRs for each intervention versus usual care from the primary analysis. The combination of medication review, medication reconciliation, patient education, professional education and transitional care, was associated with a statistically significant reduction of hospital readmission at any time (RR 0.82; 95% CI 0.74-0.91; P-score 0.77).

Two interventions were associated with a statistically significant increase of hospital readmissions: a) medication review in combination with patient education, professional education, compliance aid and transitional care (RR 1.22; 95%CI 1.01-1.46; P-score 0.17) and b) medication review in combination with medication reconciliation, patient education, professional education, use of validated methods and transitional care (RR 2.22; 95% CI 1.29–3.83; P-score 0.02).

For the separate components and for the compound interventions, there were no statistically significant effects on hospital readmissions (Supplementary Table S8 and S9).

We performed an additional pairwise meta-analysis for those studies in which medication review was performed after discharge, to compare the effect of a medication review in general with usual care. NMA was not possible due to the limited number of studies (n=4*)*. Medication review had no statistically significant effect on hospital readmissions at any time, when compared to usual care (RR 1.14; 95% CI 0.75-1.74).

## Confidence in the NMA results

For all comparisons, major concerns for 'within-study bias' and 'reporting bias' were present, mainly due to lack of blinding of personnel and participants (which is the result of the nature of the intervention) and due to the fact that there are no established statistical methods to explore reporting bias, respectively, resulting in low overall confidence in all effects. To allow for discrimination based on the other domains, we also assessed the confidence rating for every comparison by only taking into account the ratings for the remaining four domains. Table 3 presents these confidence ratings for every intervention versus usual care, along with the reason(s) for downgrading. Based on these four domains only, the confidence in the NMA results was moderate to high for the majority of the comparisons.

**Table 3.** Risk ratios with 95% confidence intervals (95% CI), P-scores and CINeMA confidence ratings for the interventions versus usual care for the outcomes all-cause hospital readmissions within 30 days and all-cause hospital readmissions at any time

| Intervention | Studies (N) | Participants (N) | Risk ratio (95% CI) | P-score | Confidence rating all domains[a] | Confidence rating 4 remaining domains[a] |
|---|---|---|---|---|---|---|
| **All-cause hospital readmissions within 30 days** | | | | | | |
| mdrev+mdrec+pedu | 1 | 207 | 0.45 (0.26 to 0.80) | 0.92 | Low[b,c] | Moderate[d,e] |
| mdrev+pedu+tc | 1 | 104 | 0.59 (0.18 to 1.91) | 0.67 | Low[b,c] | Moderate[e,f] |
| mdrev+mdrec+pedu+ hpedu+tc | 1 | 1467 | 0.64 (0.49 to 0.84) | 0.76 | Low[b,c] | Moderate[d,e] |
| mdrev +cds | 1 | 254 | 0.73 (0.43 to 1.22) | 0.61 | Low[b,c] | Moderate[d,e,f] |
| mdrev+mdrec+tc | 1 | 429 | 0.79 (0.52 to 1.22) | 0.52 | Low[b,c] | Low[d,e,f,g] |

| | | | | | | |
|---|---|---|---|---|---|---|
| mdrev+mdrec | 2 | 4201 | 0.88 (0.72 to 1.07) | 0.40 | Low[b,c] | Moderate[d,e,f] |
| mdrev+mdrec+ hpedu+vm | 1 | 166 | 0.88 (0.59 to 1.31) | 0.40 | Low[b,c] | Moderate[e,f] |
| mdrev+tc | 2 | 380 | 0.89 (0.55 to 1.42) | 0.39 | Low[b,c] | Moderate[e,f] |
| mdrev+hpedu | 1 | 1467 | 0.89 (0.70 to 1.14) | 0.37 | Low[b,c] | Moderate[d,e,f] |
| mdrev | 0 | NA | 1.06 (0.45 to 2.51) | 0.26 | Low[b,c] | Moderate[d,f,g] |
| **All-cause hospital readmissions at any time** | | | | | | |
| mdrev+pedu+tc | 1 | 104 | 0.59 (0.18 to 1.91) | 0.78 | Low[b,c] | Moderate[f] |
| mdrev+pedu+mdt+tc | 1 | 121 | 0.62 (0.38 to 1.02) | 0.90 | Low[b,c] | High |
| mdrev+mdrec+pedu | 1 | 207 | 0.76 (0.55 to 1.04) | 0.80 | Low[b,c] | High |
| mdrev+mdrec+ pedu+hpedu+tc | 2 | 2229 | 0.82 (0.74 to 0.91) | 0.77 | Low[b,c] | High |
| mdrev+mdrec+ hpedu+vm | 1 | 166 | 0.88 (0.59 to 1.31) | 0.61 | Low[b,c] | Moderate[f] |
| mdrev+tc | 2 | 380 | 0.89 (0.55 to 1.42) | 0.59 | Low[b,c] | Moderate[f] |
| mdrev+mdrec+ pedu+tc | 3 | 1205 | 0.91 (0.79 to 1.04) | 0.60 | Low[b,c] | High |
| mdrev+mdrec | 5 | 4708 | 0.92 (0.82 to 1.05) | 0.56 | Low[b,c] | High |
| mdrev+mdrec+tc | 1 | 429 | 0.94 (0.74 to 1.19) | 0.52 | Low[b,c] | Moderate[f,g] |
| mdrev+hpedu | 1 | 1467 | 0.97 (0.86 to 1.10) | 0.46 | Low[b,c] | High |
| mdrev+mdrec+ pedu+hpedu | 1 | 141 | 1.01 (0.58 to 1.76) | 0.44 | Low[b,c] | Moderate[f,g] |
| mdrev+pedu+cds+tc | 1 | 345 | 1.02 (0.82 to 1.26) | 0.39 | Low[b,c] | Moderate[d,f] |
| mdrev+cds | 2 | 554 | 1.02 (0.79 to 1.31) | 0.40 | Low[b,c] | Moderate[f] |
| mdrev+pedu+ hpedu+ca+tc | 1 | 855 | 1.22 (1.01 to 1.46) | 0.17 | Low[b,c] | High |
| mdrev | 0 | NA | 1.50 (0.84 to 2.69) | 0.13 | Low[b,c] | Moderate[d,f,g] |
| mdrev+mdrec+pedu+ hpedu+vm+tc | 1 | 123 | 2.22 (1.29 to 3.83) | 0.02 | Low[b,c] | High |

Abbreviations: **mdrev**, medication review; **mdrec**, medication reconciliation; **pedu**, patient education/medication counselling; **hpedu**, health professional education; **vm**, use of validated methods; **cds**, use of Computerized Decision Support; **ca**, compliance aid; **tc**, transitional care.
[a] The result of the assessment for the domains 'within-study bias' and 'reporting bias' was the same for every comparison, i.e. major concerns for 'within-study bias' and 'reporting bias' was suspected (first column). To maintain a distinctive character, the remaining four of the six planned domains were taken into account, i.e. 'indirectness', 'imprecision', 'heterogeneity' and 'incoherence' (second column).
[b] within-study bias; [c] reporting bias; [d] heterogeneity; [e] incoherence; [f] imprecision; [g] indirectnes

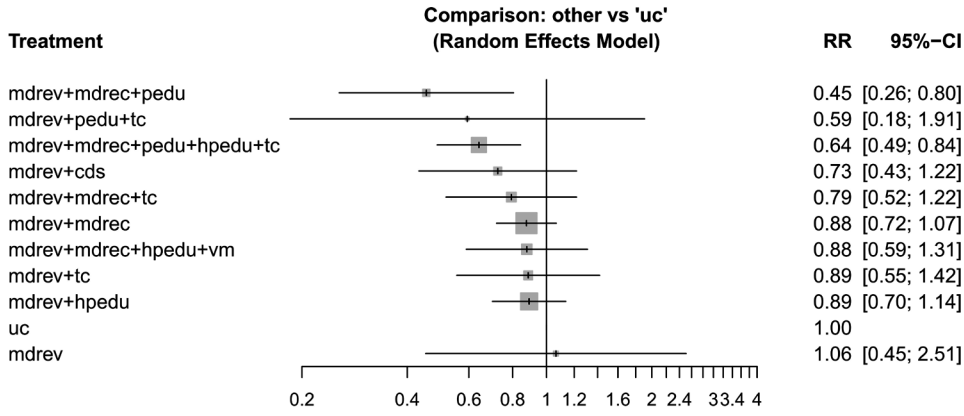



**Figure 1.** Summary risk ratios (RR) with 95% confidence intervals (95%-CI) resulting from the primary network meta-analysis for every intervention consisting of one or more components versus usual care for the outcome all-cause hospital readmissions within 30 days, including 11 studies

Abbreviations: **mdrev**, medication review; **mdrec**, medication reconciliation; **pedu**, patient education/medication counselling; **hpedu**, health professional education; **vm**, use of validated methods; **cds**, use of Computerized Decision Support; **ca**, compliance aid; **tc**, transitional care.

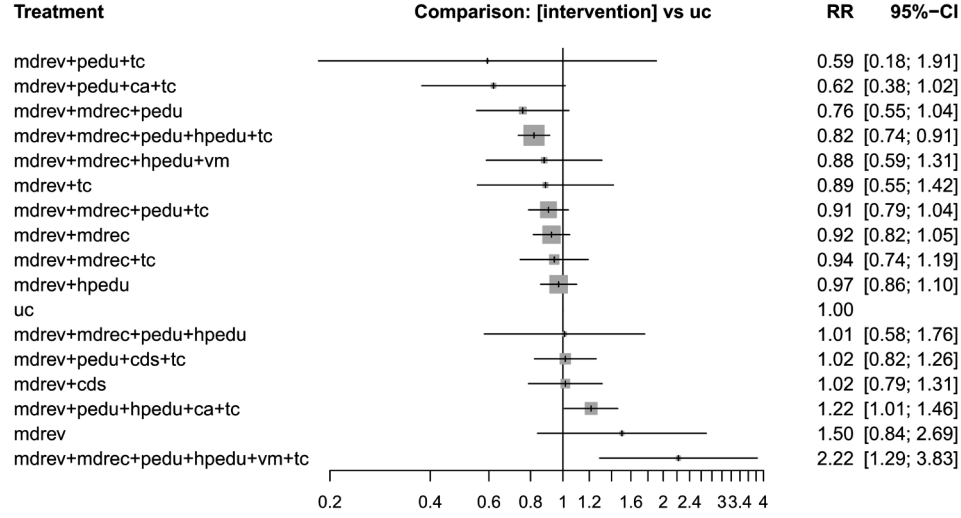



**Figure 2.** Summary risk ratios (RR) with 95% confidence intervals (95%-CI) resulting from the primary network meta-analysis for every intervention consisting of one or more components versus usual care for the outcome all-cause hospital readmissions at any time, including 24 studies

Abbreviations: **mdrev**, medication review; **mdrec**, medication reconciliation; **pedu**, patient education/medication counselling; **hpedu**, health professional education; **vm**, use of validated methods; **cds**, use of Computerized Decision Support; **ca**, compliance aid; **tc**, transitional care.

## Discussion

This systematic review and NMA updated current literature on the effect of different medication review interventions during hospital admission and transition of care, on prevention of hospital readmissions in participants aged 65 years and older.[9] Medication review in combination with medication reconciliation and patient education was associated with a significant reduction of all-cause hospital readmissions within 30 days. This also applied for medication review in combination with medication reconciliation, patient education, professional education and transitional care. Medication review as an isolated intervention had no significant effect on hospital readmissions. This comparison was based on the NMA with indirect evidence. In this review, most studies compared active interventions to usual care, resulting in most effect estimates being informed either by direct or indirect evidence. Hence, most effect estimates are imprecise. This was evidenced both by the wide 95% confidence intervals and the CINeMA analysis where non-significant effect estimates extended to clinically relevant regions (RR<0.8 or RR>1.25). In the CNMA, the risk ratio for medication review as an isolated intervention was also not statistically significant. For the outcome 'at least one all-cause hospital readmission at any time', medication review in combination with medication reconciliation, patient education, professional education and transitional care was associated with a statistically significant reduction, although the risk reduction was less pronounced than for hospital readmissions 30 days after discharge. An effect of medication review as an isolated intervention or performed after discharge was not demonstrated.

A number of previous studies have highlighted the importance of co-interventions.[7,12,15,40] Multifaceted programs including a medication review, medication reconciliation, patient counselling and follow-up by primary care physician, pharmacists, and nursing home physicians, reduced the risk of hospital readmissions.[12,40] A previous meta-analysis on the effectiveness of medication review as an isolated short-term intervention also found no effect on hospital admissions.[5]

The two combinations of intervention components that were associated with a statistically significant increase of hospital readmissions at any time, were both investigated by one study each, with a high summary risk of bias and were directly compared to usual care.[29,43] In these two studies, possible explanations for this unexpected finding were a) an increase of help seeking behavior after disease-specific education from the pharmacist leading to better recognition of warning signs b) more adverse events as a result of improved compliance c) study-related involvement in medication management may have increased the complexity of care causing anxiety, confusion or dependence on health services, or d) chance (type I error).[29,43]

A strength of this study is the application of standard NMA as well as CNMA, in which we determined the effect of both the individual intervention components and the

combinations of these components. Medication review is a very heterogeneous strategy and we investigated which particular combination of components of a medication review was most effective. An additional advantage of NMA is the ranking of interventions according to their effectiveness using P-scores.

Another strength is that we focused both on studies in which the intervention was carried out during admission and studies that applied the intervention within 2 weeks of discharge. By including the latter studies, the medication review was performed at a time period in which the risk of medication related harm or medication errors is expected to be the highest (i.e. during transition of care).[12,13]

This study has some limitations relating to the studies we included. The quality of the included studies raised some concerns. In two third of the studies, the risk of bias for allocation concealment was high or unclear. However, baseline characteristics were similar between study arms in all but one study,[33] indicating that randomization worked well. Although blinding of participants or personnel was not possible due to the nature of the interventions, blinded outcome assessment was performed in 68% of the studies. In addition, the outcome of hospital readmissions is a fairly objective outcome as often data on hospital readmissions was extracted from national registers. We also noted a high risk of bias for contamination in 76% of the studies: the pharmacist's recommendations in the intervention group probably have led to a learning effect for the prescriber, and this may have also influenced the way the prescriber managed the medication in the control group. This type of bias, however, may have resulted in an underestimation of the intervention effect in those studies. Also, we found that the majority of the studies did not report on mean number of chronic conditions, medication appropriateness and number of recommendations following the medication review, while this information may give an indication of the potential effect of the medication review. The use of different inclusion criteria regarding polypharmacy, use of a specific drug class and comorbidities, might also impact the effect of the intervention.

There were some limitations to the review process. Firstly, the outcome all-cause hospital readmissions at any time is inherently heterogeneous. We accepted any time point for hospital readmissions which ranged from one month to 1 year after intervention. This heterogeneity may explain why the effect of medication review interventions was more pronounced for the outcome hospital readmissions within 30 days than readmissions at any time.

The evaluation of many (combinations of) intervention components permitted identification of the most effective combination. However, this also may have decreased the power of the analyses, due to the large number of components relatively to the low number of studies. A second reason for a reduced power of the analyses is the previously mentioned fact that most effect estimates were informed either by direct or indirect evidence

The results of this study showed that it is not the medication review in itself, medication reconciliation, patient education, healthcare professional education and transitional care are essential elements that need to be implemented in clinical practice to reach effect on hospital readmissions.

For future studies, we advise adequate allocation concealment and we suggest to report on hospital (re)admissions in the preceding months at baseline, as multiple previous hospital (re)admissions are associated with an increased risk for readmissions.[51]

In the included studies, follow-up duration was heterogeneous and often short. To determine the effect of a medication review in both the short and long term, we recommend that future studies pursue longer follow-up duration. Outcome definition, including 'hospital readmissions', was very heterogeneous.[52] Use of a recently published core outcome set for clinical trials of medication review could overcome this challenge and enable NMA.[53] Furthermore, we recommend future studies that perform a medication review after hospital discharge to confirm the current finding of no effect of this intervention on hospital readmissions. Finally, we propose to focus on participants with multi-morbidity, polypharmacy and increasing age (>75 years), who are at higher risk of medication related problems and medication errors, but have been poorly represented in studies.

## Conclusion

This systematic review and NMA demonstrates that medication review in combination with medication reconciliation, patient education, professional education and transitional care is associated with a decreased risk of hospital readmissions within 30 days, compared to usual care. Therefore it is important to combine it with these co-interventions when implementing a medication review. An effect of medication review as an isolated intervention or performed after discharge could not be demonstrated. The effect of a medication review with co-interventions on hospital readmissions during a longer period of time after discharge was less pronounced.

## References


1. Boyd CM, Ricks M, Fried LP, et al. Functional decline and recovery of activities of daily living in hospitalized, disabled older women: The women's health and aging study I. *J Am Geriatr Soc*. 2009;57(10):1757-1766. doi:10.1111/j.1532-5415.2009.02455.x
2. Szlejf C, Farfel JM, Curiati JA, Couto Juniorde E de B, Jacob-Filho W, Azevedo RS. Medical adverse events in elderly hospitalized patients: A prospective study. *Clinics*. 2012;67(11):1247-1252. doi:10.6061/clinics/2012(11)04
3. 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. doi:10.1056/NEJMsa1103053
4. Hanlon JT, Schmader KE, Samsa GP, Weinberger M, Uttech KM, Lewis IK. A method for assessing drug therapy appropriateness. *J Clin Epidemiol*. 1992;45(10):1045-1051.
5. Huiskes VJB, Burger DM, Van Den Ende CHM, Van Den Bemt BJF. Effectiveness of medication review: A systematic review and meta-analysis of randomized controlled trials. *BMC Fam Pract*. 2017;18(1). doi:10.1186/s12875-016-0577-x
6. Holland R, Desborough J, Goodyer L, Hall S, Wright D, Loke YK. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. *Br J Clin Pharmacol*. 2008;65(3):303-316. doi:10.1111/j.1365-2125.2007.03071.x
7. GraabækT, Kjeldsen L. Medication Reviews by Clinical Pharmacists at Hospitals Lead to Improved Patient Outcomes: A Systematic Review. *Basic Clin Pharmacol Toxicol*. 2013;112(6):359-373. doi:10.1111/bcpt.12062
8. Blenkinsopp A, Bond C, Raynor DK. Medication reviews. *Br J Clin Pharmacol*. 2012;74(4):573-580. doi:10.1111/j.1365-2125.2012.04331.x
9. Christensen M, Lundh A. Medication review in hospitalised patients to reduce morbidity and mortality. *Cochrane Database Syst Rev*. 2016;2016(2). doi:10.1002/14651858.CD008986.pub3
10. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther*. 2008;46(2):72–83. doi:10.5414/cpp46072
11. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Arch Intern Med*. 1997;157(14):1531–1536.
12. Ensing HT, Stuijt CCM, Van Den Bemt BJF, et al. Identifying the optimal role for pharmacists in care transitions: A systematic review. *J Manag Care Spec Pharm*. 2015;21(8):614-638. doi:10.18553/jmcp.2015.21.8.614
13. Wheeler AJ, Scahill S, Hopcroft D, Stapleton H. Reducing medication errors at transitions of care is everyone's business. *Aust Prescr*. 2018;41(3):73-77. doi:10.18773/austprescr.2018.021
14. Viswanathan M, Kahwati LC, Golin CE, et al. Medication therapy management interventions in outpatient settings: A systematic review and meta-analysis. *JAMA Intern Med*. 2015;175(1):76-87. doi:10.1001/jamainternmed.2014.5841
15. Hatah E, Braund R, Tordoff J, Duffull S. A systematic review and meta-analysis of pharmacist-led fee-for-services medication review. *Br J Clin Pharmacol*. 2014;77(1):102-115. doi:10.1111/bcp.12140

16. Wallerstedt SM, Kindblom JM, Nylén K, Samuelsson O, Strandell A. Medication reviews for nursing home residents to reduce mortality and hospitalization: Systematic review and meta-analysis. *Br J Clin Pharmacol*. 2014;78(3):488-497. doi:10.1111/bcp.12351
17. Thomas R, Huntley AL, Mann M, 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. doi:10.1093/ageing/aft169
18. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods*. 2012;3(2):80-97. doi:10.1002/jrsm.1037
19. Mavridis D, Giannatsi M, Cipriani A, Salanti G. A primer on network meta-analysis with emphasis on mental health. *Evid Based Ment Health*. 2015;18(2):40-46. doi:10.1136/eb-2015-102088
20. *Cochrane Effective Practice and Organisation of Care (EPOC). Suggested Risk of Bias Criteria for EPOC Reviews. EPOC Resources Fo r Review Authors, 2017. Available at: Http://Epoc.Cochrane.Org/Resources/Epoc-Resources-Review-Authors*.
21. Rücker G, Schwarzer G. Reduce dimension or reduce weights? Comparing two approaches to multi-arm studies in network meta-analysis. *Stat Med*. 2014;33(25):4353-4369. doi:10.1002/sim.6236
22. Rücker G, Schwarzer G, Krahn U, König J, Schwarzer MG. Package 'netmeta'. Network Meta-Analysis using Frequentist Methods (Version 0.7-0). Published online 2015.
23. Rücker G, Petropoulou M, Schwarzer G. Network meta-analysis of multicomponent interventions. *Biometrical J*. 2020;62:808-821. doi:10.1002/bimj.201800167
24. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, et al. Cinema: An approach for assessing confidence in the results of a network meta-analysis. *PLoS Med*. 2020;17(4):e1003082. doi:10.1371/JOURNAL.PMED.1003082
25. Legrain S, Tubach F, Bonnet-Zamponi D, et al. A New Multimodal Geriatric Discharge-Planning Intervention to Prevent Emergency Visits and Rehospitalizations of Older Adults: The Optimization of Medication in AGEd Multicenter Randomized Controlled Trial. *J Am Geriatr Soc*. 2011;59(11):2017-2028. doi:10.1111/j.1532-5415.2011.03628.x
26. Spinewine A, Swine C, Dhillon S, et al. Effect of a collaborative approach on the quality of prescribing for geriatric inpatients: A randomized, controlled trial. *J Am Geriatr Soc*. 2007;55(5):658-665. doi:10.1111/j.1532-5415.2007.01132.x
27. Mannheimer B, Ulfvarson J, Eklöf S, et al. Drug-related problems and pharmacotherapeutic advisory intervention at a medicine clinic. *Eur J Clin Pharmacol*. 2006;62(12):1075-1081. doi:10.1007/s00228-006-0214-z
28. Naunton M, Peterson GM. Evaluation of Home-Based Follow-Up of High-Risk Elderly Patients Discharged from Hospital. *J Pharm Pract Res*. 2003;33(3):176-182. doi:10.1002/jppr2003333176
29. Holland R, Lenaghan E, Harvey I, et al. Does home based medication review keep older people out of hospital? The HOMER randomised controlled trial. *Br Med J*. 2005;330(7486):293. doi:10.1136/bmj.38338.674583.AE

30. Edey R, Edwards N, Von Sychowski J, Bains A, Spence J, Martinusen D. Impact of deprescribing rounds on discharge prescriptions: an interventional trial. *Int J Clin Pharm*. 2019;41(1):159-166. doi:10.1007/s11096-018-0753-2
31. Elliott LS, Henderson JC, Neradilek MB, Moyer NA, Ashcraft KC, Thirumaran RK. Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: A prospective pilot randomized controlled trial. *PLoS One*. 2017;12(2):e0170905. doi:10.1371/journal.pone.0170905
32. Gillespie U, Alassaad A, Henrohn D, 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. doi:10.1001/archinternmed.2009.71
33. Gustafsson M, Sjölander M, Pfister B, Jonsson J, Schneede J, Lövheim H. Pharmacist participation in hospital ward teams and hospital readmission rates among people with dementia: a randomized controlled trial. *Eur J Clin Pharmacol*. 2017;73(7):827-835. doi:10.1007/s00228-017-2249-8
34. Haag JD, Davis AZ, Hoel RW, et al. Impact of pharmacist-provided medication therapy management on healthcare quality and utilization in recently discharged elderly patients. *Am Heal Drug Benefits*. 2016;9(5):259-268.
35. Hohl CM, Partovi N, Ghement I, et al. Impact of early in-hospital medication review by clinical pharmacists on health services utilization. *PLoS One*. 2017;12(2):e0170495. doi:10.1371/journal.pone.0170495
36. Lenssen R, Schmitz K, Griesel C, et al. Comprehensive pharmaceutical care to prevent drug-related readmissions of dependent-living elderly patients: A randomized controlled trial. *BMC Geriatr*. 2018;18(1):135. doi:10.1186/s12877-018-0814-3
37. Lisby M, Bonnerup DK, Brock B, et al. Medication Review and Patient Outcomes in an Orthopedic Department: A Randomized Controlled Study. *J Patient Saf*. 2018;14(2):74-81. doi:10.1097/PTS.0000000000000173
38. Lisby M, Thomsen A, Nielsen LP, et al. The effect of systematic medication review in elderly patients admitted to an acute ward of internal medicine. *Basic Clin Pharmacol Toxicol*. 2010;106(5):422-427. doi:10.1111/j.1742-7843.2009.00511.x
39. Nielsen TRH, Honoré PH, Rasmussen M, Andersen SE. Clinical Effects of a Pharmacist Intervention in Acute Wards – A Randomized Controlled Trial. *Basic Clin Pharmacol Toxicol*. 2017;121(4):325-333. doi:10.1111/bcpt.12802
40. Ravn-Nielsen LV, Duckert M-L, Lund ML, 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. doi:10.1001/jamainternmed.2017.8274
41. Scullin C, Scott MG, Hogg A, McElnay JC. An innovative approach to integrated medicines management. *J Eval Clin Pract*. 2007;13(5):781-788. doi:10.1111/j.1365-2753.2006.00753.x
42. Tuttle KR, Alicic RZ, Short RA, et al. Medication therapy management after hospitalization in CKD: A randomized clinical trial. *Clin J Am Soc Nephrol*. 2018;13(2):231-241. doi:10.2215/CJN.06790617

43. van der Heijden AAWA, de Bruijne MC, Nijpels G, Hugtenburg JG. Cost-effectiveness of a clinical medication review in vulnerable older patients at hospital discharge, a randomized controlled trial. *Int J Clin Pharm*. 2019;41(4):963-971. doi:10.1007/s11096-019-00825-3
44. Van der Linden L, Decoutere L, Walgraeve K, et al. Combined Use of the Rationalization of Home Medication by an Adjusted STOPP in Older Patients (RASP) List and a Pharmacist-Led Medication Review in Very Old Inpatients: Impact on Quality of Prescribing and Clinical Outcome. *Drugs and Aging*. 2017;34(2):123-133. doi:10.1007/s40266-016-0424-8
45. Bladh L, Ottosson E, Karlsson J, Klintberg L, Wallerstedt SM. Effects of a clinical pharmacist service on health-related quality of life and prescribing of drugs: A randomised controlled trial. *BMJ Qual Saf*. 2011;20(9):738-746. doi:10.1136/bmjqs.2009.039693
46. Bonetti AF, Bagatim BQ, Mendes AM, et al. Impact of discharge medication counseling in the cardiology unit of a tertiary hospital in Brazil: A randomized controlled trial. *Clinics*. 2018;73(8):e325. doi:10.6061/clinics/2018/e325
47. Brühwiler LD, Beeler PE, Böni F, et al. A RCT evaluating a pragmatic in-hospital service to increase the quality of discharge prescriptions. *Int J Qual Heal Care*. 2019;31(8):1-7. doi:10.1093/intqhc/mzz043
48. Chiu PKC, Lee AWK, See TYW, Chan FHW. Outcomes of a pharmacist-led medication review programme for hospitalised elderly patients. *Hong Kong Med J*. 2018;24(2):98-106. doi:10.12809/hkmj176871
49. Cossette B, Éthier J-F, Joly-Mischlich T, et al. Reduction in targeted potentially inappropriate medication use in elderly inpatients: a pragmatic randomized controlled trial. *Eur J Clin Pharmacol*. 2017;73(10):1237-1245. doi:10.1007/s00228-017-2293-4
50. Wallerstedt SM, Bladh L, Ramsberg J. A cost-effectiveness analysis of an in-hospital clinical pharmacist service. *BMJ Open*. 2012;2(1):e000329. doi:10.1136/bmjopen-2011-000329
51. Hallgren J, Aslan AKD. Risk factors for hospital readmission among Swedish older adults. *Eur Geriatr Med*. 2018;9(5):603-611. doi:10.1007/s41999-018-0101-z
52. Beuscart JB, Pont LG, Thevelin S, et al. A systematic review of the outcomes reported in trials of medication review in older patients: the need for a core outcome set. *Br J Clin Pharmacol*. 2017;83(5):942-952. doi:10.1111/bcp.13197
53. Beuscart JB, Knol W, Cullinan S, et al. International core outcome set for clinical trials of medication review in multi-morbid older patients with polypharmacy. *BMC Med*. 2018;16(1). doi:10.1186/s12916-018-1007-9

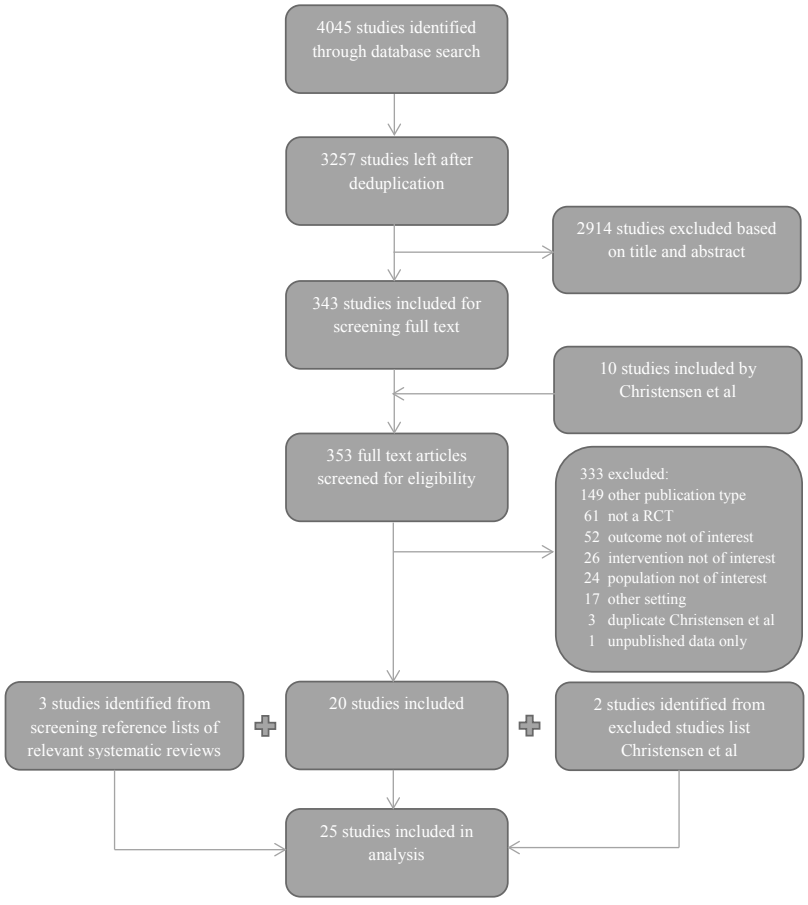
## Supplementary Content

Supplementary Table S1. Medication review interventions categorized into 9 components
Supplementary Figure S1. Flow diagram of study selection
Supplementary Table S2. Individual study characteristics of the 25 randomized controlled studies included in the analysis
Supplementary Table S3. Individual participant characteristics of the 25 randomized controlled studies included in the analysis
Supplementary Table S4. Individual Cochrane EPOC risk of bias assessment of the included studies
Supplementary Figure S2. Aggregate risk of bias assessment per domain
Characteristics of the medication review
Results from (component) NMA for all-cause hospital readmissions within 30 days
Results from (component) NMA for all-cause hospital readmissions at any time

Additional information about methods
1.1 Additional information regarding study population, interventions, comparators and outcomes
1.2 Additional information regarding NMA
1.3 Additional information regarding the CINeMA approach
1.4 Electronic search strategy
1.5 List and definition of all variable data collected

**Supplementary Table S1.** Medication review interventions categorized into 9 components

| Intervention component | Definitions | | | |
|---|---|---|---|---|
| **Medication review** (mdrev) | Medication review is a structured evaluation of a patient's medicines with the aim of optimizing medicine use and improving health outcomes. This entails detecting medication-related problems and recommending interventions. | | | |
| | **Performed by:**<br>- Pharmacist alone<br>- Pharmacist and physician team<br>- Physician alone<br>- Nurse<br>- Pharmacy technician<br>- Other | **Context:**<br>- Solely a medication review<br>- Medication review as part of a Comprehensive Geriatric Assessment | **How many times performed?**<br>- Once<br>- Daily<br>- Weekly<br>- Certain number of times | **Delivery of recommendations:**<br>- Written report<br>- Oral report/ deliberation<br>- Directly executed |
| **Medication reconciliation** (mdrec) | The process of identifying the most accurate list of a patient's current medicines including the name, dosage, frequency and route – and comparing them to the current list in use, recognizing and documenting any discrepancies, thus resulting in a complete list of medications. | | | |
| **Shared decision making** (sdm) | The process of information exchange, deliberation and making a decision between patient and physician. | | | |
| **Patient education/ medication counselling** (pedu) | Interventions designed to provide patient support, typically via tailored education to inform the patient about their condition(s), medication indications and its correct use, supporting medication adherence or using motivational interviewing. There is a focus on medications which had been commenced or discontinued too. | | | |
| **Health professional education** (hpedu) | Education of health professionals on how to perform a medication review or raising awareness about the importance of medication reviews. | | | |
| **Use of validated methods** (vm) | The use of validated criteria for determining inappropriate medication use, like Beers' criteria[1] or START/STOPP criteria[2]. | | | |
| **Use of Computerized Decision Support** (cds) | Computerized decision-making support (CDS) for medication management involves a programme on the health professional's computer to guide the prescriber to the selection of appropriate treatment(s) by means of electronic alerts. | | | |
| **Compliance aid** (ca) | The use of tools to improve compliance with the medication regimen, e.g. dosette or Webster pack. | | | |
| **Transitional care** (tc) | The development of an individualized discharge plan for a patient prior to them leaving hospital for home. Discharge planning may also extend across healthcare settings and include postdischarge support.<br>Regarding medication use: the preparation of a medicines record sheet, outlining all medications and dosage instructions. The distribution of this information to the patient's general practitioner and community pharmacist.<br>(Telephone) follow-up by the clinical pharmacist or physician. | | | |




**Supplementary Figure S1.** Flow diagram of study selection

**Supplementary Table S2.** Individual study characteristics of the 25 randomized controlled studies included in the analysis

| First author, year | Study design | Comparison(s)[a] | Outcome(s)[b] | Duration of follow-up (weeks) |
|---|---|---|---|---|
| Bladh, 2011 | Parallel | Mdrev+pedu+cds+tc; uc | 1,3 | 26 |
| Bonetti, 2018 | Parallel | Mdrev+pedu+tc; uc | 1,2 | 4 |
| Brühwiler, 2019 | Parallel | Mdrev+mdrec; uc | 1,2 | 4 |
| Chiu, 2018 | Quasi | Mdrev+mdrec+pedu; uc | 1,2 | 12 |
| Cossette, 2017 | Parallel | Mdrev+cds; uc | 1,2 | 4 |
| Edey, 2019 | Cluster | Mdrev+tc; uc | 1,2 | 4 |
| Elliott, 2017 | Parallel | Mdrev+cds; mdrev | 1,2 | 8 |
| Gillespie, 2009 | Parallel | Mdrev+mdrec+pedu+tc; uc | 1,4 | 52 |
| Gustafsson, 2017 | Parallel | Mdrev+mdrec+tc; uc | 1,2,3,5 | 26 |
| Haag, 2016 | Parallel | Mdrev+tc; uc | 1,2 | 4 |
| Hohl, 2017 | Quasi | Mdrev+mdrec; uc | 1,2 | 4 |
| Holland, 2005 | Parallel | Mdrev+pedu+hpedu+ca+tc; uc | 1,3,6 | 26 |
| Legrain, 2011 | Parallel | Mdrev+mdrec+pedu+tc; uc | 1,3 | 26 |
| Lenssen, 2018 | Parallel | Mdrev+mdrec+tc; uc | 5 | 52 |
| Lisby, 2018 | Parallel | Mdrev+mdrec; uc | 1 | 12 |
| Lisby, 2010 | Parallel | Mdrev+mdrec; uc | 1 | 12 |
| Mannheimer, 2006 | Parallel | Mdrev+cds; uc | 1,3 | 26 |
| Naunton, 2003 | Parallel | Mdrev+pedu+ca+tc; uc | 1,5 | 12 |
| Nielsen, 2017 | Parallel | Mdrev+mdrec; uc | 1,4 | 52 |
| Ravn-Nielsen, 2018 | Parallel | Mdrev+mdrec+pedu+hpedu+tc; mdrev+hpedu; uc | 1,2,3,5 | 26 |
| Scullin, 2007 | Parallel | Mdrev+mdrec+pedu+hpedu+tc; uc | 1,4 | 52 |
| Spinewine, 2007 | Quasi | Mdrev+mdrec+pedu+tc; uc | 1,4 | 52 |
| Tuttle, 2018 | Parallel | Mdrev+mdrec+pedu+hpedu; uc | 1 | 12 |
| van der Heijden, 2019 | Cluster | Mdrev+mdrec+pedu+ hpedu+vm+tc; uc | 1,3 | 26 |
| Van der Linden, 2017 | Quasi | Mdrev+mdrec+hpedu+vm; uc | 1,2 | 4 |

[a] Abbreviations: mdrev, medication review; mdrec, medication reconciliation; pedu, patient education/ medication counselling; hpedu, health professional education; vm, use of validated methods; cds, use of Computerized Decision Support; ca, compliance aid; tc, transitional care; uc, usual care.

[b] Outcomes abbreviations:

Outcome 1 = all-cause hospital readmissions at any time

Outcome 2 = all-cause hospital readmissions within 30 days after discharge from the index admission

Outcome 3 = all-cause hospital readmissions within 180 days after discharge from the index admission

Outcome 4 = all-cause hospital readmissions within 1 year after discharge from the index admission

Outcome 5 = Persons experiencing medication-related readmissions

Outcome 6 = Hospital readmission rate (number of all-cause hospital readmissions per certain number of people and time units)

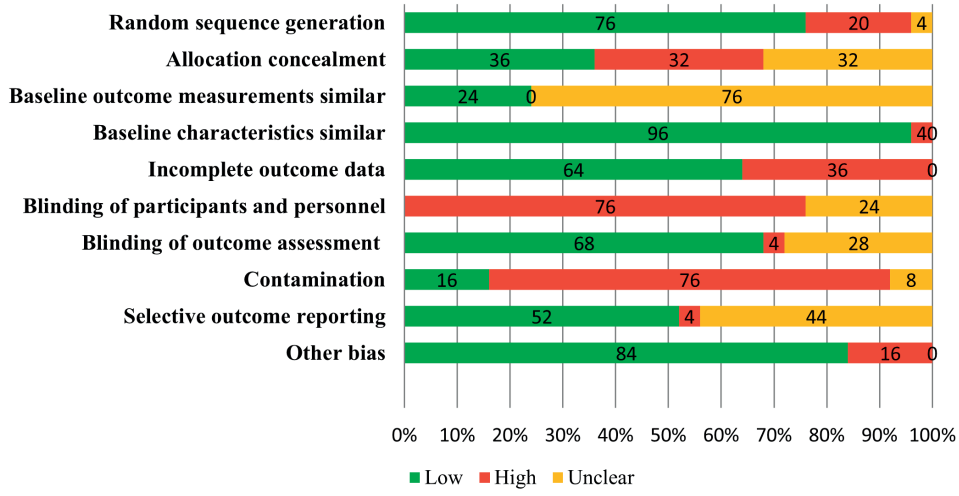
**Supplementary Table S3.** Individual participant characteristics of the 25 randomized controlled studies included in the analysis

| First author, year | Country | Setting | Sample size | Mean/ median age (years) | Female (%) | Regular used medication, mean/ median number |
|---|---|---|---|---|---|---|
| Bladh, 2011 | Sweden | Hospital | 345 | 81;82* | 60.9 | NR |
| Bonetti, 2018 | Brazil | Hospital | 104 | 65 | 31.3;35.8* | 7;8* |
| Brühwiler, 2019 | Switzerland | Hospital | 152 | 72;71* | 36.8;43.4* | 6 |
| Chiu, 2018 | China | Hospital | 207 | 83.3 | 50;53.8* | 9.4 |
| Cossette, 2017 | Canada | Hospital | 254 | 81.5;80.5* | 61.9;58.6* | NR |
| Edey, 2019 | Canada | Hospital | 358 | 69 | 48.4 | 7.5 |
| Elliott, 2017 | United States | Hospital | 110 | 75.6 | 61.8 | NR |
| Gillespie, 2009 | Sweden | Hospital | 368 | 86.6 | 58.7 | 8.7;7.3* |
| Gustafsson, 2017 | Sweden | Hospital | 429 | 83.1 | 63;64* | 8.4;8.3* |
| Haag, 2016 | United States | Hospital | 22 | 81;86* | 31;17* | 17;15.5* |
| Hohl, 2017 | Canada | Hospital | 4049 | 71;69* | 56.4;55.1* | 8.1;7.7* |
| Holland, 2005 | United Kingdom | Community | 855 | 85.4;85.5* | 61.1;63.8* | 6.0;5.8* |
| Legrain, 2011 | France | Hospital | 665 | 85.8;86.4* | 69.7;62.6* | 6.9;6.6* |
| Lenssen, 2018 | Germany | Hospital | 60 | 77.6 | 60 | 16.8 |
| Lisby, 2018 | Denmark | Hospital | 98 | 80.4;80.5* | 72;71* | 7.0;6.4* |
| Lisby, 2010 | Denmark | Hospital | 99 | 80.2;78.2* | 60;61* | 10.2;10.1* |
| Mannheimer, 2006 | Sweden | Hospital | 300 | 71;74* | 51;48* | 7.4;6.9* |
| Naunton, 2003 | Australia | Community | 121 | 74;77* | 56;69* | 7;6.5* |
| Nielsen, 2017 | Denmark | Hospital | 310 | 74.1;72.1* | 54;46* | 8 |
| Ravn-Nielsen, 2018 | Denmark | Hospital | 1467 | 72 | 53.7 | 10;10;9* |
| Scullin, 2007 | United Kingdom | Hospital | 762 | 70.3;69.9* | NR | NR |
| Spinewine, 2007 | Belgium | Hospital | 172 | 82.4;81.9* | 71.9;66.7* | 7.9;7.3* |
| Tuttle, 2018 | United States | Community | 141 | 69 | 48 | 13 |
| van der Heijden, 2019 | The Netherlands | Community pharmacy | 123 | 75.5;73.9* | 48.1;56.4* | 8.9;8.4* |
| Van der Linden, 2017 | Belgium | Hospital | 166 | 84.5 | 48;56* | 9;10* |

* Data reported per study arm. NR; not reported

**Supplementary Table S4.** Individual Cochrane EPOC risk of bias assessment of the included studies

| First author, year | Random sequence generation | Allocation concealment | Similar baseline outcome measures | Similar baseline characteristics | Incomplete outcome data | Blinding of participants and personnel | Blinding of outcome assessment | Contamination | Selective outcome reporting | Other bias |
|---|---|---|---|---|---|---|---|---|---|---|
| Bladh, 2011 | Low | Low | Unclear | Low | High | Unclear | Low | High | Low | Low |
| Bonetti, 2018 | Low | Unclear | Unclear | Low | High | High | Low | Unclear | Unclear | Low |
| Brühwiler, 2019 | Low | High | Unclear | Low | Low | High | Low | high | Unclear | Low |
| Chiu, 2018 | High | High | Unclear | Low | High | High | Unclear | High | Unclear | Low |
| Cossette, 2017 | Low | Unclear | Low | Low | High | High | Unclear | high | Low | High |
| Edey, 2019 | High | High | Unclear | Low | Low | High | Low | Low | Low | High |
| Elliott, 2017 | Low | Unclear | Unclear | Low | Low | High | Unclear | High | Low | Low |
| Gillespie, 2009 | Low | Unclear | Unclear | Low | Low | High | Low | High | Low | Low |
| Gustafsson, 2017 | Low | Low | Unclear | High | Low | High | Low | High | Low | Low |
| Haag, 2016 | Low | Low | Unclear | Low | Low | High | Low | High | Unclear | Low |
| Hohl, 2017 | High | High | Unclear | Low | Low | High | Low | Unclear | Unclear | Low |
| Holland, 2005 | Low | Low | Unclear | Low | Low | High | Low | High | Unclear | Low |
| Legrain, 2011 | Low | High | Low | Low | Low | High | Low | High | Unclear | Low |
| Lenssen, 2018 | Low | High | Unclear | Low | Low | Unclear | Low | High | Low | Low |
| Lisby, 2018 | Low | Low | Unclear | Low | Low | High | Low | High | Low | Low |
| Lisby, 2010 | Low | Unclear | Unclear | Low | Low | High | Unclear | High | Unclear | Low |
| Mannheimer, 2006 | Low | Low | Unclear | Low | Low | High | Unclear | High | Unclear | Low |
| Naunton, 2003 | Low | Unclear | Low | Low | Low | High | Low | High | Unclear | High |
| Nielsen, 2017 | Low | Low | Unclear | Low | High | High | Low | High | Low | Low |
| Ravn-Nielsen, 2018 | Low | Low | Low | Low | Low | High | Low | High | Low | Low |
| Scullin, 2007 | Low | Unclear | Low | Low | High | Unclear | Low | Low | Unclear | High |
| Spinewine, 2007 | High | High | Low | Low | High | Unclear | Low | high | Low | Low |
| Tuttle, 2018 | Low | Low | Unclear | Low | Low | High | Unclear | High | Low | Low |
| van der Heijden, 2019 | Unclear | Unclear | Unclear | Low | High | Unclear | High | Low | High | High |
| Van der Linden, 2017 | High | High | Unclear | Low | High | Unclear | Unclear | Low | Low | Low |




**Supplementary Figure S2.** Aggregate risk of bias assessment per domain

## Characteristics of the medication review

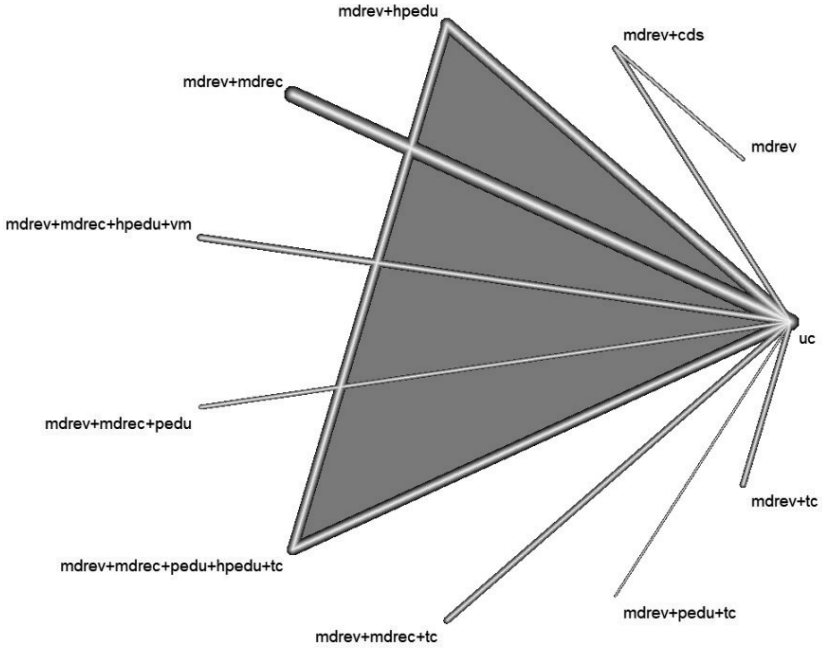
A summary of medication review methodology is presented in Supplementary Table S5. All medication review interventions were performed in combination with at least one co-intervention. In 20 studies (80%) the medication review was performed by a pharmacist or clinical pharmacologist alone. Medication review was performed by a geriatrician in one study only.[3] The number of times the medication review was performed varied from once (n=10, 40%) to several times (n=3, 12%) and daily (n=6, 24%). Recommendations following medication review were directly implemented in one study.[4] While advice for the physician was given verbally (n=5, 20%), written (n=7, 28%) or both (n=4, 16%) in the remaining studies. The number of recommendations that followed from the medication review was described in only 3 studies, but the acceptance rate was reported in 10 studies, ranging from 18 to 82%. The studies barely reported on medication appropriateness or potentially inappropriate medication.

**Supplementary Table S5.** Description of how the medication review was conducted

| Aspects of the medication review | Number of studies (%) |
|---|---|
| Type of intervention | |
| Single component | 0 |
| Multiple components | 25 (100%) |
| Who performed the medication review | |
| Pharmacist or clinical pharmacologist | 20 (80%) |
| Pharmacist and clinical pharmacologist | 2 (8%) |

| | |
|---|---|
| Pharmacist and pharmacy technician | 1 (4%) |
| Pharmacist and trial nurse | 1 (4%) |
| Geriatrician | 1 (4%) |
| Number of times the medication review was conducted | |
| Once | 10 (40%) |
| Multiple times | 3 (12%) |
| Daily | 6 (24%) |
| Not reported | 6 (24%) |
| The way the recommendations were delivered | |
| Directly executed | 1 (4%) |
| Written report | 7 (28%) |
| Oral report/deliberation | 5 (20%) |
| Both written and oral | 4 (16%) |
| Not reported | 8 (32%) |

Results from (component) NMA for all-cause hospital readmissions within 30 days



A network plot provides an overview of the intervention data resulting from all included randomized controlled trials and visualizes the studied interventions and the direct comparisons between these interventions.

Nodes represent interventions consisting of one or more components and their size is proportional to the number of participants randomized to this intervention. Edges represent direct evidence obtained from randomized controlled trials directly comparing the interventions linked by this edge. Thickness of edges is proportional to the number of participants randomized to this comparison. The blue shadow connecting multiple interventions indicates a multi-arm trial.

Abbreviations: mdrev, medication review; mdrec, medication reconciliation; pedu, patient education/medication counselling; hpedu, health professional education; vm, use of validated methods; cds, use of Computerized Decision Support; ca, compliance aid; tc, transitional care; uc, usual care.

**Supplementary Figure S3.** Network plot for the outcome all-cause hospital readmissions within 30 days

**Supplementary Table S6.** Risk ratios (RR) with 95% confidence intervals (95% CI) resulting from network meta-analysis (left) and component network meta-analysis (right) for every intervention versus usual care for the outcome all-cause hospital readmissions within 30 days

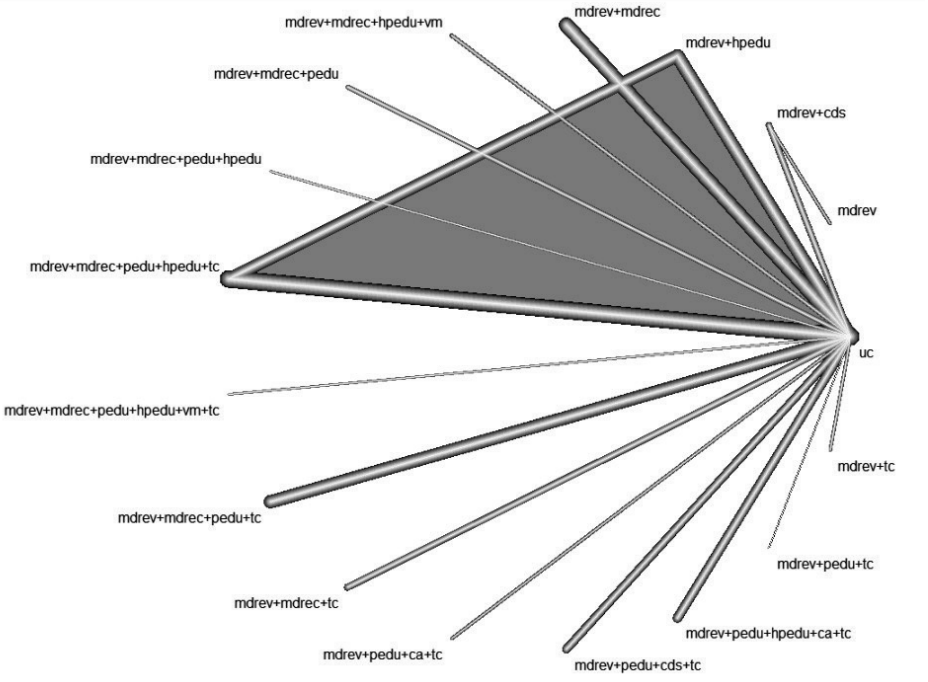
| | FULL NMA | | | CNMA | | |
|---|---|---|---|---|---|---|
| **Interventions** | **RR** | **95% CIL** | **95% CIH** | **RR** | **95% CIL** | **95% CIH** |
| mdrev | 1.06 | 0.45 | 2.51 | 0.83 | 0.60 | 1.13 |
| mdrev+cds | 0.73 | 0.43 | 1.22 | 0.66 | 0.43 | 1.02 |
| mdrev+mdrec | 0.88 | 0.72 | 1.07 | 0.85 | 0.71 | 1.03 |
| mdrev+mdrec+pedu | 0.45 | 0.26 | 0.80 | 0.54 | 0.35 | 0.85 |
| mdrev+mdrec+pedu+hpedu+tc | 0.64 | 0.49 | 0.84 | 0.63 | 0.48 | 0.82 |
| mdrev+mdrec+tc | 0.79 | 0.52 | 1.22 | 0.89 | 0.66 | 1.22 |
| mdrev+mdrec+hpedu+vm | 0.88 | 0.59 | 1.31 | 0.88 | 0.59 | 1.31 |
| mdrev+pedu+tc | 0.59 | 0.18 | 1.91 | 0.55 | 0.30 | 1.01 |
| mdrev+tc | 0.89 | 0.55 | 1.42 | 0.87 | 0.59 | 1.27 |
| mdrev+hpedu | 0.89 | 0.70 | 1.14 | 0.91 | 0.71 | 1.15 |
| uc | - | - | - | 1.00 | 1.00 | 1.00 |

Abbreviations: mdrev, medication review; mdrec, medication reconciliation; pedu, patient education/medication counselling; hpedu, health professional education; vm, use of validated methods; cds, use of Computerized Decision Support; ca, compliance aid; tc, transitional care; uc, usual care.

**Supplementary Table S7.** Risk ratios with 95% confidence intervals (95% CI) resulting from the component network meta-analysis for every intervention component versus usual care for the outcome all-cause hospital readmissions within 30 days

| Component | Risk ratio | 95% CI |
|---|---|---|
| Use of Computerized Decision Support | 0.80 | 0.51-1.27 |
| Medication reconciliation | 1.03 | 0.73-1.46 |
| Medication review | 0.83 | 0.60-1.13 |
| Patient education/medication counselling | 0.64 | 0.41-0.99 |
| Transitional care | 1.05 | 0.78-1.42 |
| Health professional education | 1.10 | 0.76-1.58 |
| Use of validated methods | 0.94 | 0.54-1.64 |

Results from (component) NMA for all-cause hospital readmissions at any time




A network plot provides an overview of the intervention data resulting from all included randomized controlled trials and visualizes the studied interventions and the direct comparisons between these interventions.

Nodes represent interventions consisting of one or more components and their size is proportional to the number of participants randomized to this intervention. Edges represent direct evidence obtained from randomized controlled trials directly comparing the interventions linked by this edge. Thickness of edges is proportional to the number

of participants randomized to this comparison. The blue shadow connecting multiple interventions indicates a multi-arm trial.
Abbreviations: mdrev, medication review; mdrec, medication reconciliation; pedu, patient education/medication counselling; hpedu, health professional education; vm, use of validated methods; cds, use of Computerized Decision Support; ca, compliance aid; tc, transitional care; uc, usual care.

**Supplementary Figure S4.** Network plot for the outcome all-cause hospital readmissions at any time

**Supplementary Table S8.** Risk ratios (RR) with 95% confidence intervals (95% CI) resulting from network meta-analysis (left) and component network meta-analysis (right) for every intervention versus usual care for the outcome all-cause hospital readmissions at any time

| | FULL NMA | | | CNMA | | |
|---|---|---|---|---|---|---|
| **Interventions** | **RR** | **95% CIL** | **95% CIU** | **RR** | **95% CIL** | **95% CIU** |
| mdrev | 1.50 | 0.84 | 2.69 | 1.00 | 0.79 | 1.26 |
| mdrev+cds | 1.02 | 0.79 | 1.31 | 0.95 | 0.76 | 1.20 |
| mdrev+mdrec | 0.92 | 0.82 | 1.05 | 0.88 | 0.75 | 1.03 |
| mdrev+mdrec+pedu | 0.76 | 0.55 | 1.04 | 0.84 | 0.64 | 1.10 |
| mdrev+mdrec+pedu+tc | 0.91 | 0.79 | 1.04 | 0.87 | 0.75 | 1.02 |
| mdrev+mdrec+pedu+hpedu | 1.01 | 0.58 | 1.76 | 0.86 | 0.66 | 1.13 |
| mdrev+mdrec+pedu+hpedu+tc | 0.82 | 0.74 | 0.91 | 0.89 | 0.74 | 1.08 |
| mdrev+mdrec+pedu+hpedu+vm+tc | 2.22 | 1.29 | 3.83 | 1.25 | 0.85 | 1.84 |
| mdrev+mdrec+tc | 0.94 | 0.74 | 1.19 | 0.91 | 0.71 | 1.16 |
| mdrev+mdrec+hpedu+vm | 0.88 | 0.59 | 1.31 | 1.25 | 0.86 | 1.82 |
| mdrev+pedu+cds+tc | 1.02 | 0.82 | 1.26 | 0.95 | 0.74 | 1.21 |
| mdrev+pedu+ca+tc | 0.62 | 0.38 | 1.02 | 1.02 | 0.74 | 1.40 |
| mdrev+pedu+tc | 0.59 | 0.18 | 1.91 | 1.00 | 0.72 | 1.38 |
| mdrev+pedu+hpedu+ca+tc | 1.22 | 1.01 | 1.46 | 1.04 | 0.79 | 1.37 |
| mdrev+tc | 0.89 | 0.55 | 1.42 | 1.03 | 0.77 | 1.40 |
| mdrev+hpedu | 0.97 | 0.86 | 1.10 | 1.02 | 0.80 | 1.29 |
| uc | - | - | - | 1.00 | 1.00 | 1.00 |

Abbreviations: mdrev, medication review; mdrec, medication reconciliation; pedu, patient education/medication counselling; hpedu, health professional education; vm, use of validated methods; cds, use of Computerized Decision Support; ca, compliance aid; tc, transitional care; uc, usual care.

**Supplementary Table S9.** Risk ratios with 95% confidence intervals (95% CI) resulting from the component network meta-analysis for every intervention component versus usual care for the outcome all-cause hospital readmissions at any time

| Component | Risk ratio | 95% CI |
|---|---|---|
| Use of Computerized Decision Support | 0.95 | 0.70-1.30 |
| Medication reconciliation | 0.88 | 0.68-1.14 |
| Medication review | 1.00 | 0.79-1.26 |
| Compliance aid | 1.02 | 0.69-1.51 |
| Patient education/medication counselling | 0.96 | 0.74-1.25 |
| Transitional care | 1.04 | 0.82-1.31 |
| Health professional education | 1.02 | 0.82-1.27 |
| Use of validated methods | 1.40 | 0.92-2.14 |

Additional information about methods

## Additional information regarding study population, interventions, comparators and outcomes

**Supplementary Table S10.** Study population, interventions, comparators and outcomes

| | |
|---|---|
| **Population** | Adults aged ≥65 years<br>Included: - Hospitalized patients or recently* discharged to the community, nursing home or rehabilitation center after hospital admission<br>Excluded: studies that included, in particular:<br>- Persons with solely end of life care<br>- Persons with psychiatric diseases, such as schizophrenia or depression<br>- Persons with specific diseases, receiving disease-specific medication (e.g. COPD or heart failure)<br>- Persons recruited from intensive care units<br>- Outpatients and persons seen at the emergency department but not admitted to a hospital |
| **Intervention** | Medication review as an isolated intervention or with co-interventions performed during hospital admission, at discharge or shortly after*.<br>Interventions of included studies were classified into the 9 intervention components presented in Supplementary Table S1.<br>Excluded: - Medication reviews targeting specific medication types instead of the whole medication list |
| **Comparator** | Usual care, a sham intervention or another medication review intervention |
| **Outcomes** | 1. Persons experiencing at least one all-cause hospital readmission<br>- within 30 days after discharge from the index admission<br>- within 180 days after discharge from the index admission<br>- within 1 year after discharge from the index admission<br>- at any time<br>2. Persons experiencing at least one medication-related readmissions at any time<br>3. Hospital readmission rate (number of all-cause hospital readmissions per certain number of people and time units) |

* the medication review was performed within 2 weeks of discharge

## 1.2 Additional information regarding NMA:

We compared the relative intervention efficacy using frequentist NMA.[5,6] When the number of included studies was sufficient, we performed random-effects NMA for each of the aforementioned outcomes, using the graph-theoretical method. Network plots were used to examine the network geometry, and forest plots and league tables (that rank the interventions from most effective to least effective) to present the results. We computed the restricted maximum likelihood estimate of the heterogeneity variance, the index that shows the proportion of variance that is due to heterogeneity rather than sampling variance and we evaluated the confidence in the treatment effect estimates using the CINeMA approach that compares 95% confidence intervals to 95% predictive intervals in terms of their agreement in statistically significant and clinically important effects.[7] This approach also compares heterogeneity variance estimates to those estimated from empirical distributions and evaluates how large the estimates are.[8]

After we had categorized the interventions of included studies into the nine components (Supplementary Table S1), many studies turned out to consist of interventions with more than one component (e.g. medrev + medrec + pedu). We analyzed the effect of the (combination of) components in three steps:

1. Each existing combination of components was considered to be a distinct intervention. The effect of these combinations was compared with usual care (e.g. medrev + medrec + pedu as a distinct intervention versus usual care).
2. The effect of a single component was determined by disentanglement of combinations of components that included this particular single component. This means that the effect of a single component results from every combination this component was part of. For example, to determine the effect of medrev versus usual care, data is used from comparisons such as 'medrev + medrec + pedu versus usual care' and 'mdrev+pedu+pl versus usual care.'
3. Next, we rebuilt interventions by adding up the separate effects of single components. For example, to determine the effect of medrev+medrec+pedu versus usual care, we add up the effect of the single components (determined in step 2) medrev, medrec, and pedu via an algorithm. The data for the effect of this compound intervention came from many more studies than just those that have investigated precisely this combination of components.

Step one was our primary analysis, for step 2 and 3 we applied the additive model of component network meta-analysis (CNMA).

## 1.3 Additional information regarding the CINeMA approach:

For each treatment comparison we summarized within study biases and indirectness by the average risk of bias and indirectness assessments in the respective studies. We considered risk ratios less than 0.8 or larger than 1.25 to be clinically relevant and we

evaluated imprecision by comparing statistical significance to clinical relevance. For more information about the CINeMA assessments we refer to Nikolakopoulou et al.[7]
For each treatment comparison we rated the corresponding treatment effect at each of the six domains (within-study bias, across-study bias, indirectness, imprecision, heterogeneity, and incoherence) as either 'no concerns', 'minor concerns' and 'major concerns'. If there was at most one domain with minor concerns and the other domains with no concerns, we rated the overall confidence as high. If there were at most two domains with minor concerns or at most one domain with major concerns and the other domains with no concerns, we rated the overall confidence as moderate. If there were three or more domains with minor concerns or two or more domains with major concerns, we rated the overall confidence as low.

## 1.4 Electronic search strategy

**Supplementary Table S11.** Electronic search strategy MEDLINE

| Search Line | Search Terms |
|---|---|
| 1 | Pharmacy service, hospital/ [ML] |
| 2 | ((PHARMACEUTICAL CARE or PHARMACY or PHARMACIES or PHARMACIST? or PRESCRIBING) and (inpatient? or hospital$ or WARD? or UNIT or UNITS)).ti. |
| 3 | ((PHARMACEUTICAL CARE or PHARMACY or PHARMACIES or PHARMACIST? or PRESCRIBING) adj2 (inpatient? or hospital$ or WARD? or UNIT or UNITS)).ab. |
| 4 | Medication Systems, Hospital/ [ML] |
| 5 | ((medication? or prescribing or prescription? or dispensing) adj2 system?).ti,ab. and (hospital$ or WARD or WARDS or (CARE adj2 UNIT?) or INPATIENT?).ti,hw. |
| 6 | (stopp or beer's criteria).ti,ab. [Term added Aug 2011] |
| 7 | or/1-6 [Hosp Pharm/Med Systems] |
| 8 | exp Hospitals/ or exp Hospital Units/ [ML] |
| 9 | (hospital$ or WARD or WARDS).ti. |
| 10 | Hospitalization/ [ML] |
| 11 | hospital$.ab. |
| 12 | "length of stay"/ or Patient admission/ or Patient discharge/ or Patient readmission/ or Patient transfer/ [ML] |
| 13 | ((patient? or hospital$).ti,hw. and (discharg$ or admission? or admitting or readmission? or readmit$ or transfer?).ti.) or "length of stay".ti. |
| 14 | (((patient? or hospital?) adj2 (discharg$ or admission? or admitting or readmission? or transfer?)) or "length of stay").ab. |
| 15 | Inpatients/ [ML] |
| 16 | (inpatient? or in-patient?).ti. |
| 17 | exp HOSPITAL DEPARTMENTS/ or HOSPITAL SHARED SERVICES/ [ML] |
| 18 | MEDICAL STAFF, HOSPITAL/ or HOSPITALISTS/ [ML] |
| 19 | or/8-18 [Hospitals/Hospitalization/Inpatients] |
| 20 | (pharmacy or pharmacies or pharmacist? or prescription? or prescribing).ti. |
| 21 | (pharmacist-led or pharma$ initiated or ((driven or lead or led) adj2 pharmacist?)).ab. |
| 22 | (PRESCRIBING adj2 PATTERN?).ab. |

| | |
|---|---|
| 23 | ("physician-pharmacist?" or "doctor-pharmacist?").ti,ab. |
| 24 | ((IMPROV$ or OPTIMI?ING or OPTIMI?E? or OPTIMAL$) and (DOSING or DOSAGE or PHARMAC$ or PRESCRIB$ or PRESCRIPT$)).ti. or ((IMPROV$ or OPTIMI?ING or OPTIMI?E? or OPTIMAL$) adj2 (PHARMACEUTICAL CARE or PHARMACY or PRESCRIB$ or PRESCRIPT$)).ab. |
| 25 | ((pharmaceutical adj (care or consult$)) or (pharmacist? adj2 (care or consult$ or intervention? or managed))).ab. |
| 26 | (((prescription? or prescribing or medication?) adj4 review$) or (pharmacist? adj2 review$)).ti,ab. |
| 27 | ((drug therapy or drug regime? or medication? or medicineS or pharmacy or pharmacist? or pharmaceutical or PRESCRIB$ or prescription?) adj2 (audit$ or monitor$ or RECONCIL$ or review?)).ti,ab. |
| 28 | ((medication? or prescrib$ or pharmac$) adj2 (manage? or management or service? or system?)).ti,ab. |
| 29 | (("drug therapy" or dosage? or dose? or medication? or PRESCRIPTION? or PRESCRIB$ or PHARMACIST? or PHARMACEUTICAL CARE) adj2 (managing or management or monitor$)).ti,ab. |
| 30 | (drug? review? or drug? assess$ or drug? audit? or drug? reconcil$).ti,ab. |
| 31 | ("drug utili?ation" adj2 (review? or reconcil$ or audit?)).ab. or ("drug utili?ation" and (review? or reconcil$ or audit?)).ti. |
| 32 | Medication adherence/ [ML] |
| 33 | Pharmacists/ or Pharmacists' Aides/ [ML] |
| 34 | Pharmaceutical Services/ or Drug Information Services/ [ML] |
| 35 | Clinical Pharmacy Information Systems/ [ML] |
| 36 | Prescriptions/ or Drug Prescriptions/ or Pharmaceutical Preparations/ or Drug Therapy/ or Drug Dosage Calculations/ or Electronic Prescribing/ or Medication Systems/ [ML] |
| 37 | Drug Monitoring/ or Medication Therapy Management/ [ML] |
| 38 | Drug Therapy/ or Drug Therapy, Computer-Assisted/ [ML] |
| 39 | POLYPHARMACY/ or POLYPHARM$.ti. [ML] |
| 40 | MEDICATION ERRORS/ [ML] |
| 41 | Drug utilization review/ [ML] |
| 42 | Drug Utilization/ [ML] |
| 43 | inappropriate prescribing/ [Term added Aug 2011] |
| 44 | ((Medication? or prescrib$ or prescription? or drug therap$) adj2 assessment?).ti,ab. [Term added Aug 2011] |
| 45 | (inappropriate$ adj2 (medicine? or medication? or prescrib$ or drug?)).ti,ab. [Term added Aug 2011] |
| 46 | or/20-45 [PHARMA/DRUG CONCEPTS --combine with hospital concepts] |
| 47 | (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti. |
| 48 | exp animals/ not humans.sh. |
| 49 | 47 not 48 [Cochrane RCT Filter 6.4.d Sens/Precision Maximizing] |
| 50 | 7 and 49 [Hosp Pharma & RCT] |
| 51 | 19 and 46 and 49 [Hospitals & Pharma/Drug sets & RCT] |
| 52 | 50 or 51 |
| 53 | limit 52 to yr="1980 -Current" |
| 54 | (2012$ or 2013$ or 2014$).ed,ep,dp. [Entry date, E-pub date, Pub Date] |
| 55 | (198$ or 199$ or 2$).ep. [Electronic publication date 1980 to present] |

| | |
|---|---|
| 56 | (201108$ or 201109$ or 20111$).ed,dp. [August 2011-Dec2011] |
| 57 | 52 and 54 |
| 58 | (52 and 55) not 57 |
| 59 | (52 and 56) not (or/57-58) |
| 60 | 52 and 2011$.dp,ep,yr,ed. [2011 all date search] |
| 61 | 60 not (or/57-59) |
| 62 | 57 or 58 or 59 or 61 [Results to export Jan 7 2013 update search] |
| 63 | remove duplicates from 62 |
| 64 | limit 63 to yr="2014 -Current" |

**Search run at 13-09-2019 using Ovid MEDLINE(R)**

**Supplementary Table S12.** Electronic search strategy Embase

| Search Line | Search Terms |
|---|---|
| 1 | 1 *hospital pharmacy/ not outpatient?.ti. [EM] |
| 2 | hospital? pharmacy.ti. |
| 3 | ((pharmaceutical care or pharmacist? or prescribing) adj4 (inpatient? or hospital$ or ward? or ICU or intensive care or (emergency adj2 (room? or department? or unit or units)))).ti. |
| 4 | ((pharmaceutical care or pharmacist? or prescribing) adj3 (inpatient? or hospital$ or ward? or ICU or intensive care or (emergency adj2 (room? or department? or unit or units)))).ab. |
| 5 | ((medication? or prescribing or prescription? or dispensing) adj2 system?).ti,ab. and (hospital$ or ward or wards or (care adj2 unit?) or inpatient?).ti,hw. |
| 6 | (medication? adj4 (review$ or audit$)).ti. and (hospital$ or ward or wards or (care adj2 unit?) or inpatient?).ti,hw. |
| 7 | (stopp or beer's criteria).ti,ab. [Term added Aug 2011] |
| 8 | or/1-7 [Hosp Medication Rev or Hosp Pharm--combine with Filters] |
| 9 | ((medication? or medicine?) adj4 (review or audit)).ti. |
| 10 | ((medication? or medicine?) adj2 (review or audit)).ab. |
| 11 | (((prescription? or prescribing) adj4 review$) or (pharmacist? adj2 review$)).ti,ab. |
| 12 | ((drug formulary or drug therapy or drug regime? or medication? or medicines or pharmacy or pharmacist? or pharmaceutical or prescrib$ or prescription?) adj3 (audit$ or monitor$ or reconcil$)).ti,ab. |
| 13 | (drug? review? or drug? assess$ or drug? audit? or drug? reconcil$).ti,ab. |
| 14 | ("drug utili?ation" adj2 (reconcil$ or audit?)).ab. or ("drug utili?ation" adj4 (reconcil$ or audit?)).ti. [line moved] |
| 15 | inappropriate prescribing/ [Term added Aug 2011] |
| 16 | ((Medication? or prescrib$ or prescription? or drug therap$) adj2 assessment?).ti,ab. [Term added Aug 2011] |
| 17 | (inappropriate$ adj2 (medicine? or medication? or prescrib$ or drug?)).ti,ab. [Term added Aug 2011] |
| 18 | or/9-17 [Medication Review/Audit] |
| 19 | exp *Hospital/ [EM] |
| 20 | exp *Ward/ [EM] |
| 21 | (hospital$ or WARD or WARDS).ti. |
| 22 | *Hospitalization/ [EM] |

| | |
|---|---|
| 23 | *Hospital care/ or *Intensive care/ [EM] |
| 24 | *"length of stay"/ or *hospital admission/ or *Hospital discharge/ or *Hospital readmission/ or *Patient transport/ [EM] |
| 25 | (((patient? or hospital$) and (discharg$ or admission? or admitting or readmission? or readmit$ or transfer?)) or "length of stay").ti. |
| 26 | (((patient? or hospital?) adj2 (discharg$ or admission? or admitting or readmission? or transfer?)) or "length of stay").ab. |
| 27 | *hospital patient/ [EM] |
| 28 | (inpatient? or in-patient?).ti. |
| 29 | *Hospital service/ [EM] |
| 30 | *Hospital personnel/ or *Hospital physician/ or *Medical staff/ or *Resident/ [EM] |
| 31 | or/19-30 [Hospitals/Hospitalization/Inpatients] |
| 32 | (pharmacy or pharmacies or pharmacist? or prescription? or prescribing).ti. |
| 33 | (pharmacist-led or pharma$ initiated or ((driven or lead or led) adj2 pharmacist?)).ab. |
| 34 | (prescribing adj2 pattern?).ab. |
| 35 | ("physician-pharmacist?" or "doctor-pharmacist?").ti,ab. |
| 36 | ((improv$ or optimi?ing or optimi?e? or optimal$) and (dosing or dosage or pharmac$ or prescrib$ or prescript$)).ti. or ((improv$ or optimi?ing or optimi?e? or optimal$) adj2 (pharmaceutical care or pharmacy or prescrib$ or prescript$)).ab. |
| 37 | ((pharmaceutical adj (care or consult$)) or (pharmacist? adj2 (care or consult$ or intervention? or managed))).ab. |
| 38 | ((medication? or prescrib$ or pharmac$) adj2 (manage? or management or service? or system?)).ti,ab. |
| 39 | (("drug therapy" or dosage? or dose? or medication? or PRESCRIPTION? or PRESCRIB$ or PHARMACIST? or PHARMACEUTICAL CARE) adj2 (managing or management or monitor$)).ti,ab. |
| 40 | *Patient compliance/ and (medication? or pharmac$ or drug? or prescrib$ or prescription?).ti. |
| 41 | *Pharmacist/ or *Pharmacy technician/ [EM] |
| 42 | *Pharmaceutical care/ [EM] |
| 43 | *medical information system/ and (medication? or pharmac$ or drug? or prescrib$ or prescription?).ti,hw. [EM] |
| 44 | *Prescription/ [EM] |
| 45 | *Medication therapy management/ or *Recommended drug dose/ or *Optimal drug dose/ [EM] |
| 46 | *Polypharmacy/ or POLYPHARM$.ti. [EM] |
| 47 | *Medication error/ [EM] |
| 48 | *"drug use"/ [EM] |
| 49 | *Drug utilization/ [EM] |
| 50 | *DRUG FORMULARY/ |
| 51 | or/32-50 [Pharmacy/Prescribing/Med Use] |
| 52 | medical audit/ |
| 53 | *medical audit/ or *monitoring/ [EM] |
| 54 | monitoring/ |
| 55 | (audit? or monitoring or reconcil$).ti. |
| 56 | or/52,54-55 [Monitoring/Audit broad] |
| 57 | randomized controlled trial/ or controlled study/ or controlled clinical trial/ [EM] |

| | |
|---|---|
| 58 | pretest posttest control group design/ |
| 59 | clinical study/ or major clinical study/ or clinical trial/ |
| 60 | multicenter study/ |
| 61 | random$.ti. or (randomi?ed or randomly).ab. or controlled.ti. |
| 62 | (clinical study/ or major clinical study/ or clinical trial/) and random$.ti. |
| 63 | crossover-procedure/ or double-blind procedure/ or single-blind procedure/ [EM] |
| 64 | or/57-63 [Trials Filter EM] |
| 65 | (animal model? or animal experiment? or animal study? or animal trial? or canine or feline or bovine or cow or cows or mice or dog? or cat or cats or rabbit? or rat or rats or veterinar$).ti. or (animal or veterinary).hw. [EM] |
| 66 | (editorial or letter or note or "review" or trade or survey).pt. [EM] |
| 67 | systematic review/ or meta-analysis/ or (systematic adj3 review).ti. or (meta-analy$ or metaanaly$).ti. or (literature adj2 review).ti. |
| 68 | 64 not (or/65-67) [EPOC RCT Filter EM] |
| 69 | 18 and 31 [Drug Review/Audit & Hosp] |
| 70 | 31 and 51 and 56 [Hosp & Pharma & Monitoring--Broad search] |
| 71 | (or/69-70) and 68 [RCT Results 2] |
| 72 | 8 and 68 [Med Rev Hosp & RCT Results 1] |
| 73 | 72 or 71 [RCT Results] |
| 74 | (20113$ or 20114$ or 20115$ or 2012$ or 2013$ or 2014$).em. [Entry week Aug 2011 to Nov 2014] |
| 75 | ("2011" or "2012" or "2013" or "2014").yr. |
| 76 | 73 and (74 or 75) [Results Nov 18, 2014] |
| 77 | remove duplicates from 76 |
| 78 | limit 77 to yr="2014 -Current" |

### Search run at 13-09-2019 using Embase Classic+Embase

**Supplementary Table S13.** Electronic search strategy The Cochrane Library

| Search Line | Search Terms |
|---|---|
| 1 | ("PHARMACEUTICAL CARE" near/2 inpatient* or PHARMACY near/2 inpatient* or PHARMACIES near/2 inpatient* or PHARMACIST* near/2 inpatient* or PRESCRIBING near/2 inpatient*):ab or (stopp or (Beer N2 criteria)):ti,ab |
| 2 | ("PHARMACEUTICAL CARE" near/2 hospital*or PHARMACY near/2 hospital* or PHARMACIES near/2 hospital* or PHARMACIST* near/2 hospital* or PRESCRIBING near/2 hospital*):ab |
| 3 | ("PHARMACEUTICAL CARE" near/2 WARD* or PHARMACY near/2 WARD* or PHARMACIES near/2 WARD* or PHARMACIST* near/2 WARD* or PRESCRIBING near/2 WARD*):ab |
| 4 | ("PHARMACEUTICAL CARE" near/2 UNIT or PHARMACY near/2 UNIT or PHARMACIES near/2 UNIT or PHARMACIST* near/2 UNIT or PRESCRIBING near/2 UNIT):ab |
| 5 | ("PHARMACEUTICAL CARE" near/2 UNITS or PHARMACY near/2 UNITS or PHARMACIES near/2 UNITS or PHARMACIST* near/2 UNITS or PRESCRIBING near/2 UNITS):ab |
| 6 | (medication* near/2 system* or prescribing near/2 system* or prescription* near/2 system* or dispensing near/2 system*):ti,kw and (hospital* or WARD or WARDS or INPATIENT* or CARE near/2 UNIT*):ti,kw |
| 7 | MeSH descriptor: [Pharmacy Service, Hospital] this term only |

| | |
|---|---|
| 8 | MeSH descriptor: [Medication Systems, Hospital] this term only |
| 9 | (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8) |
| 10 | MeSH descriptor: [Hospitalization] explode all trees |
| 11 | MeSH descriptor: [Inpatients] this term only |
| 12 | MeSH descriptor: [Hospital Departments] explode all trees |
| 13 | MeSH descriptor: [Hospital Shared Services] this term only |
| 14 | MeSH descriptor: [Hospital Units] explode all trees |
| 15 | MeSH descriptor: [Medical Staff, Hospital] explode all trees |
| 16 | (hospital* or WARD or WARDS):ti |
| 17 | hospital*:ab |
| 18 | (patient* or hospital*):ti,kw and (discharge* or admission* or admitting or readmission* or readmit* or transfer*):ti or "length of stay":ti |
| 19 | (Patient* near/2 discharg* or Patient* near/2 admission* or Patient* near/2 admitting or Patient* near/2 readmission* or Patient* near/2 transfer*) or "length of stay":ab |
| 20 | (hospital* near/2 discharg* or hospital* near/2 admission* or hospital near/2 admitting or hospital near/2 readmission* or hospital near/2 transfer*) or "length of stay":ab |
| 21 | (inpatient* or in-patient*):ti |
| 22 | (#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21) |
| 23 | (pharmacy or pharmacies or pharmacist* or prescription* or prescribing):ti |
| 24 | ("pharmacist-led" or "pharma* initiated" or pharmacist* near/2 driven or pharmacist* near/2 lead or pharmacist* near/2 led):ab |
| 25 | Prescribing near/2 Pattern*:ab |
| 26 | ("physician-pharmacist*" or "doctor-pharmacist*"):ti,ab |
| 27 | (IMPROV* or OPTIMI*ING or OPTIMI*E* or OPTIMAL*):ti and (DOSING or DOSAGE or PHARMAC* or PRESCRIB* or PRESCRIPT*):ti |
| 28 | (IMPROV* near/2 "PHARMACEUTICAL CARE" or OPTIMI*ING near/2 "PHARMACEUTICAL CARE" or OPTIMI*E* near/2 "PHARMACEUTICAL CARE" or OPTIMAL* near/2 "PHARMACEUTICAL CARE"):ab |
| 29 | (IMPROV* near/2 PHARMACY or OPTIMI*ING near/2 PHARMACY or OPTIMI*E* near/2 PHARMACY or OPTIMAL* near/2 PHARMACY):ab |
| 30 | (IMPROV* near/2 PRESCRIB* or OPTIMI*ING near/2 PRESCRIB* or OPTIMI*E* near/2 PRESCRIB* or OPTIMAL* near/2 PRESCRIB*):ab |
| 31 | (IMPROV* near/2 PRESCRIPT* or OPTIMI*ING near/2 PRESCRIPT* or OPTIMI*E* near/2 PRESCRIPT*or OPTIMAL* near/2 PRESCRIPT*):ab |
| 32 | "pharmaceutical care" or "pharmaceutical consult*" or (pharmacist* near/2 care or pharmacist* near/2 consult* or pharmacist* near/2 intervention* or pharmacist* near/2 managed):ab |
| 33 | (prescription* near/4 review* or prescribing near/4 review* or medication* near/4 review*OR pharmacist* near/2 review*):ti,ab |
| 34 | ("drug therapy" near/2 audit* or "drug regime*" near/2 audit* or medication* near/2 audit* or medicine* near/2 audit* or pharmacy near/2 audit* or pharmacist* near/2 audit* or pharmaceutical near/2 audit* or PRESCRIB* near/2 audit* or prescription* near/2 audit*):ti,ab |
| 35 | ("drug therapy" near/2 monitor* or "drug regime*" near/2 monitor* or medication* near/2 monitor* or medicine* near/2 monitor* or pharmacy near/2 monitor* or pharmacist* near/2 monitor* or pharmaceutical near/2 monitor* or PRESCRIB* near/2 monitor* or prescription* near/2 monitor*):ti,ab |

| | |
|---|---|
| 36 | ("drug therapy" near/2 RECONCIL* or "drug regime*" near/2 RECONCIL* or medication* near/2 RECONCIL* or medicine* near/2 RECONCIL* or pharmacy near/2 RECONCIL* or pharmacist* near/2 RECONCIL* or pharmaceutical near/2 RECONCIL* or PRESCRIB* near/2 RECONCIL* or prescription* near/2 RECONCIL*):ti,ab |
| 37 | ("drug therapy" near/2 review* or "drug regime*" near/2 review* or medication* near/2 review* or medicine* near/2 review* or pharmacy near/2 review* or pharmacist* near/2 review* or pharmaceutical near/2 review* or PRESCRIB* near/2 review* or prescription* near/2 review*):ti,ab |
| 38 | (medication* near/2 manage* or prescrib* near/2 manage* or phamac* near/2 manage*):ti,ab |
| 39 | (medication* near/2 management or prescrib* near/2 management or pharmac* near/2 management):ti,ab |
| 40 | (medication* near/2 service* or prescrib* near/2 service* or pharmac* near/2 service*):ti,ab |
| 41 | (medication* near/2 system* or prescrib* near/2 system* or pharmac* near/2 system*):ti,ab |
| 42 | ("drug therapy" near/2 managing or dosage* near/2 managing or dose* near/2 managing or medication* near/2 managing or PRESCRIPTION* near/2 managing or PRESCRIB* near/2 managing or PHARMACIST* near/2 managing or "PHARMACEUTICAL CARE" near/2 managing):ti,ab |
| 43 | ("drug therapy" near/2 management or dosage* near/2 management or dose* near/2 management or medication* near/2 management or PRESCRIPTION* near/2 management or PRESCRIB* near/2 management or PHARMACIST* near/2 management or "PHARMACEUTICAL CARE" near/2 management):ti,ab |
| 44 | ("drug therapy" near/2 monitor* or dosage* near/2 monitor* or dose* near/2 monitor* or medication* near/2 monitor* or PRESCRIPTION* near/2 monitor* or PRESCRIB* near/2 monitor* or PHARMACIST* near/2 monitor* or "PHARMACEUTICAL CARE" near/2 monitor*):ti,ab |
| 45 | ("drug* review*" or "drug* assess*" or "drug* audit*" or "drug* reconcil*"):ti,ab |
| 46 | ("drug utili*ation" near/2 review* or "drug utili*ation" near/2 reconcil* or "drug utili*ation" near/2 audit*):ab |
| 47 | (review* or reconcil* or audit*):ti and "drug utili*ation":ti |
| 48 | MeSH descriptor: [Medication Adherence] this term only |
| 49 | MeSH descriptor: [Pharmacists] this term only |
| 50 | MeSH descriptor: [Pharmacists' Aides] explode all trees |
| 51 | MeSH descriptor: [Pharmaceutical Services] this term only |
| 52 | MeSH descriptor: [Drug Information Services] this term only |
| 53 | MeSH descriptor: [Clinical Pharmacy Information Systems] this term only |
| 54 | MeSH descriptor: [Prescriptions] this term only |
| 55 | MeSH descriptor: [Drug Prescriptions] this term only |
| 56 | MeSH descriptor: [Drug Dosage Calculations] this term only |
| 57 | MeSH descriptor: [Pharmaceutical Preparations] this term only |
| 58 | MeSH descriptor: [Electronic Prescribing] this term only |
| 59 | MeSH descriptor: [Medication Systems] this term only |
| 60 | MeSH descriptor: [Drug Monitoring] this term only |
| 61 | MeSH descriptor: [Medication Therapy Management] this term only |
| 62 | MeSH descriptor: [Drug Therapy] this term only |
| 63 | MeSH descriptor: [Drug Therapy, Computer-Assisted] this term only |

| | |
|---|---|
| 64 | MeSH descriptor: [Medication Errors] this term only |
| 65 | MeSH descriptor: [Drug Utilization Review] this term only |
| 66 | MeSH descriptor: [Drug Utilization] this term only |
| 67 | MeSH descriptor: [Polypharmacy] this term only |
| 68 | Polypharm*:ti |
| 69 | Polypharmacy or polypharm*:ti |
| 70 | MeSH descriptor: [Inappropriate Prescribing] this term only |
| 71 | ((Medication or medications or prescrib* or prescription or prescriptions or drug therap*) near/2 assessment):ti,ab |
| 72 | (inappropriate* near/2 (medicine or medicines or medication or medications or prescrib* or drug or drugs)):ti,ab |
| 73 | (#23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72) |
| 74 | (#9 or (#22 and #73)) |
| 75 | limit to (2014,2015,2016,2017,2018,2019) |

**Search run at 13-09-2019 using The Cochrane Library**

**Supplementary Table S14.** Electronic search strategy CINAHL

| Search Line | Search Terms |
|---|---|
| 1 | (MH "Pharmacy Service") |
| 2 | TI ( pharmaceutical care or pharmacy or pharmacies or pharmacist* or prescribing ) |
| 3 | (MH "Medication Systems") OR TI (medication* n2 system) or (prescribing n2 system) or (prescription* n2 system) or (dispensing n2 system) OR TI (medication* n2 systems) or (prescribing n2 systems) or (prescription* n2 systems) or (dispensing n2 systems) OR TI ((medication N2 assessment) or (prescrib* N2 assessment) or (prescription N2 assessment) or (drug therap* N2 assessment)) OR AB ((medication N2 assessment) or (prescrib* N2 assessment) or (prescription N2 assessment) or (drug therap* N2 ass ... |
| 4 | TI ( hospital* OR inpatient ward or wards or intensive care or ICU or emergency department* or unit ) OR MW ( hospital* OR inpatient ward or wards or intensive care or ICU or emergency department* ) |
| 5 | (MH "Adolescent, Hospitalized") OR (MH "Aged, Hospitalized") OR (MH "Child, Hospitalized") OR (MH "Emergency Patients") OR (MH "Infant, Hospitalized") OR (MH "Inpatients") |
| 6 | (MH "Hospitals+") OR (MH "Hospital Units+") OR TI ( inpatient* or hospital$ or WARD* or UNIT or UNITS ) |
| 7 | (MH "Hospitalization") OR (MH "Length of Stay") OR (MH "Patient Admission") OR (MH "Patient Discharge") OR (MH "Discharge Planning+") OR (MH "Patient Discharge Education") OR (MH "Early Patient Discharge") OR (MH "Transfer, Discharge") OR (MH "Patient Dumping") OR (MH "Readmission") OR (MH "Transfer, Intrahospital") |
| 8 | (MH "Medication Reconciliation") |

| | |
|---|---|
| 9 | TI ( (drug therapy N2 reconcil*) or (drug therapy N2 audit*) or (drug therapy N2 review*) ) or AB ( (drug therapy N2 reconcil*) or (drug therapy N2 audit*) or (drug therapy N2 review*) ) OR TI ( (medicine* N2 reconcil*) or (medicine* N2 audit*) or (medicine* N2 review*) ) or AB ( (medicine* N2 reconcil*) or (medicine* N2 audit*) or (medicine* N2 review*) ) |
| 10 | (MH "Nursing Audit") OR (MH "Audit") |
| 11 | TI ( medication* or medicine* or drug therap* or prescrib* or prescript* or medication* ) or MW ( medication* or medicine* or drug therap* or prescrib* or prescript* or medication* ) |
| 12 | S10 and S11 |
| 13 | S1 or S2 or S3 |
| 14 | S4 or S5 or S6 or S7 |
| 15 | S8 or S9 or S12 |
| 16 | S13 and S14 |
| 17 | S14 and S15 |
| 18 | TI ( (multicent* n2 design*) or (multicent* n2 study) or (multicent* n2 studies) or (multicent* n2 trial*) ) or AB ( (multicent* n2 design*) or (multicent* n2 study) or (multicent* n2 studies) or (multicent* n2 trial*) ) |
| 19 | (MM "Clinical Trials+") |
| 20 | TI ( "clinical study" or "clinical studies" ) or AB ( "clinical study" or "clinical studies") |
| 21 | TI random* or AB random* |
| 22 | TI controlled or AB controlled |
| 23 | TI ( "control* N1 clinical" or "control* N1 group*" or "control* N1 trial*" or "control* N1 study" or "control* N1 studies" or "control* N1 design*" or "control* N1 method*" ) or AB ( "control* N1 clinical" or "control* N1 group*" or "control* N1 trial*" or "control* N1 study" or "control* N1 studies" or "control* N1 design*" or "control* N1 method*" ) |
| 24 | S18 or S19 or S20 or S21 or S22 or S23 |
| 25 | TI ( (stopp or "beer's criteria") ) OR AB ( (stopp or "beer's criteria") ) |
| 26 | S16 or S17 or S25 |
| 27 | S24 and S26 |
| 28 | TI medication review* |
| 29 | S27 or S28 |
| 30 | (MH "Pharmacy Service") |
| 31 | TI ( pharmaceutical care or pharmacy or pharmacies or pharmacist* or prescribing ) |
| 32 | (MH "Medication Systems") OR TI (medication* n2 system) or (prescribing n2 system) or (prescription* n2 system) or (dispensing n2 system) OR TI (medication* n2 systems) or (prescribing n2 systems) or (prescription* n2 systems) or (dispensing n2 systems) OR TI ((medication N2 assessment) or (prescrib* N2 assessment) or (prescription N2 assessment) or (drug therap* N2 assessment)) OR AB ((medication N2 assessment) or (prescrib* N2 assessment) or (prescription N2 assessment) or (drug therap* N2 ass ... |
| 33 | TI ( hospital* OR inpatient ward or wards or intensive care or ICU or emergency department* or unit ) OR MW ( hospital* OR inpatient ward or wards or intensive care or ICU or emergency department* ) |
| 34 | (MH "Adolescent, Hospitalized") OR (MH "Aged, Hospitalized") OR (MH "Child, Hospitalized") OR (MH "Emergency Patients") OR (MH "Infant, Hospitalized") OR (MH "Inpatients") |
| 35 | (MH "Hospitals+") OR (MH "Hospital Units+") OR TI ( inpatient* or hospital$ or WARD* or UNIT or UNITS ) |

| | |
|---|---|
| 36 | (MH "Hospitalization") OR (MH "Length of Stay") OR (MH "Patient Admission") OR (MH "Patient Discharge") OR (MH "Discharge Planning+") OR (MH "Patient Discharge Education") OR (MH "Early Patient Discharge") OR (MH "Transfer, Discharge") OR (MH "Patient Dumping") OR (MH "Readmission") OR (MH "Transfer, Intrahospital") |
| 37 | (MH "Medication Reconciliation") |
| 38 | TI ( (drug therapy N2 reconcil*) or (drug therapy N2 audit*) or (drug therapy N2 review*) ) or AB ( (drug therapy N2 reconcil*) or (drug therapy N2 audit*) or (drug therapy N2 review*) ) OR TI ( (medicine* N2 reconcil*) or (medicine* N2 audit*) or (medicine* N2 review*) ) or AB ( (medicine* N2 reconcil*) or (medicine* N2 audit*) or (medicine* N2 review*) ) |
| 39 | (MH "Nursing Audit") OR (MH "Audit") |
| 40 | TI ( medication* or medicine* or drug therap* or prescrib* or prescript* or medication* ) or MW ( medication* or medicine* or drug therap* or prescrib* or prescript* or medication* ) |
| 41 | S39 and S40 |
| 42 | S30 or S31 or S32 |
| 43 | S33 or S34 or S35 or S36 |
| 44 | S37 or S38 or S41 |
| 45 | S42 and S43 |
| 46 | S43 and S44 |
| 47 | TI ( (multicent* n2 design*) or (multicent* n2 study) or (multicent* n2 studies) or (multicent* n2 trial*) ) or AB ( (multicent* n2 design*) or (multicent* n2 study) or (multicent* n2 studies) or (multicent* n2 trial*) ) |
| 48 | (MM "Clinical Trials+") |
| 49 | TI ( "clinical study" or "clinical studies" ) or AB ( "clinical study" or "clinical studies") |
| 50 | TI random* or AB random* |
| 51 | TI controlled or AB controlled |
| 52 | TI ( "control* N1 clinical" or "control* N1 group*" or "control* N1 trial*" or "control* N1 study" or "control* N1 studies" or "control* N1 design*" or "control* N1 method*" ) or AB ( "control* N1 clinical" or "control* N1 group*" or "control* N1 trial*" or "control* N1 study" or "control* N1 studies" or "control* N1 design*" or "control* N1 method*" ) |
| 53 | S47 or S48 or S49 or S50 or S51 or S52 |
| 54 | TI ( (stopp or "beer's criteria") ) OR AB ( (stopp or "beer's criteria") |
| 55 | S45 or S46 or S54 |
| 56 | S53 and S55 |
| 57 | TI medication review* |
| 58 | S56 or S57 |
| 59 | S56 or S57 (limit: Publicationdate: 20140101-20191231) |

**Search run at 13-09-2019 using CINAHL**

**Supplementary Table S15.** List and definition of all variable data collected

| Variable name | Definition |
|---|---|
| ***Study characteristics and patient characteristics*** | |
| **1st author** | Name |
| **Year** | Publication year |
| **Country** | Country of study |
| **Study design RCT** | Parallel, cluster, cross-over, quasi, other |
| **Sample size** | Total number of participants analyzed |
| **Mean age** | Mean age study population in years |
| **Median age** | Median age study population in years |
| **% Female** | % Female of the study population |
| **Mean follow-up** | Mean follow-up duration in weeks |
| **Regular used med** | Mean number of regularly used medication |
| **Medication appropriateness index** | Mean medication appropriateness index |
| **Chronic conditions** | Mean number of chronic conditions |
| **Study setting** | Hospital, community, community pharmacy, other |
| **Study sites** | Single center, multicenter |
| **ITT/PP** | Intention to treat analysis, per-protocol analysis, not reported |
| **Funding source of study** | Governmental organisation, research funding body, commercial organisation, mixed, charitable trust, no funding, other |
| **Inclusion criteria** | Applied inclusion criteria |
| **Exclusion criteria** | Applied exclusion criteria |
| **Intervention - arm 1** | Description of the intervention in words |
| **Intervention type - arm 1** | Single component, multiple component |
| **N - arm 1** | Number of participants that received intervention arm 1 |
| **Performed by – arm 1** | Who performed the medication review? Pharmacist or clinical pharmacologist, pharmacist and clinical pharmacologist, pharmacist and pharmacy technician, pharmacist and trial nurse, geriatrician |
| **Context – arm 1** | What was the context of the medication review? Solely a medication review or the medication review was part of a Comprehensive Geriatric Assessment |
| **Times performed – arm 1** | How many times was the medication review performed? Once, daily, multiple times. |
| **Delivery – arm 1** | The way the recommendations were delivered: directly executed, written report, oral report/deliberation, both written and oral, not reported |
| **Arm 2 and 3** | All arm 1 variables are repeated for arm 2 and 3 (if indicated) |
| **Component 1** | Medication review: is medication review part of the study intervention? |
| **Component 2** | Medication reconciliation: is medication reconciliation part of the study intervention? |
| **Component 3** | Shared decision making: is shared decision making part of the study intervention? |
| **Component 4** | Patient education/ medication counselling: is patient education/ medication counselling part of the study intervention? |
| **Component 5** | Health professional education: is health professional education part of the study intervention? |

| | |
|---|---|
| **Component 6** | Use of validated methods: is the use of validated methods part of the study intervention? |
| **Component 7** | Use of Computerized Decision Support: is the use of a Computerized Decision Support part of the study intervention? |
| **Component 8** | Compliance aid: is the application of a compliance aid part of the study intervention? |
| **Component 9** | Transitional care: is transitional care part of the study intervention? |
| **Missing data** | Have any attempts been made to impute missing data |
| **Missing data >10%** | Is more than 10% of the data missing? |
| ***Data extraction results: Dichotomous outcomes*** | |
| **Timepoint** | Timepoint at which the result was measured in weeks |
| **Outcome** | Which outcome was addressed?<br>Persons experiencing all cause hospital readmissions at any time<br>Persons experiencing all cause hospital readmissions within 30 days<br>Persons experiencing all cause hospital readmissions within 180 days<br>Persons experiencing all cause hospital readmissions within 1 year<br>Persons experiencing medication-related readmissions at any time |
| **Subgroup analysis** | For which subgroup analysis can we use this data?<br>None<br>Participants aged 65-75 year<br>Participants aged >75 years<br>Participants with 2 or less comorbidities<br>Participants with 3 or more comorbidities<br>Community residents<br>Nursing home residents |
| **Events** | Number of events in arm 1, 2 and 3 (when indicated) |
| **Comparison** | Which arms are compared |
| **Effect size** | Type of effect size, effect size value, lower bound 95% confidence interval, upper bound 95% confidence interval. Is the effect size adjusted for confounding factors? |
| ***Data extraction results: rate outcomes*** | |
| **Timepoint** | Timepoint at which the result was measured in weeks |
| **Outcome** | Which outcome was addressed?<br>Hospital readmission rate |
| **Subgroup analysis** | For which subgroup analysis can we use this data?<br>None<br>Participants aged 65-75 year<br>Participants aged >75 years<br>Participants with 2 or less comorbidities<br>Participants with 3 or more comorbidities<br>Community residents<br>Nursing home residents |
| **Events** | Number of events in arm 1, 2 and 3 + total person time at risk (when indicated) |
| **Rate** | Rate and 95% confidence interval arm 1, 2, 3 + person time |
| **Comparison** | Which arms are compared |
| **Rate ratio** | Rate ratio + 95% confidence interval. Is the rate ratio adjusted for confounding factors? |
| ***Risk of bias*** | |

| | |
|---|---|
| **1. Was the allocation sequence adequately generated?** | |
| **2. Was allocation adequately concealed?** | |
| **3. Were baseline outcome measurements similar?** | |
| **4. Were baseline characteristics similar?** | |
| **5. Were incomplete outcome data adequately addressed?** | |
| **6. Was knowledge of the allocated intervention adequately prevented during the study?** | |
| **7. Was the study adequately protected against contamination?** | |
| **8. Is there evidence that outcomes have been reported selectively?** | |
| **9. Other sources of bias** | |
| **Directness** | Are there any issues affecting directness? |
| ***Data extraction notes*** | |
| **Notes** | Additional notes by review authors |

## References


1. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. Arch Intern Med 1997;157:1531–1536.
2. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther 2008;46:72–83. doi:10.5414/cpp46072
3. Legrain S, Tubach F, Bonnet-Zamponi D et al. A New Multimodal Geriatric Discharge-Planning Intervention to Prevent Emergency Visits and Rehospitalizations of Older Adults: The Optimization of Medication in AGEd Multicenter Randomized Controlled Trial. J Am Geriatr Soc 2011;59:2017-2028. doi:10.1111/j.1532-5415.2011.03628.x
4. Scullin C, Scott MG, Hogg A, McElnay JC. An innovative approach to integrated medicines management. J Eval Clin Pract 2007;13:781-788. doi:10.1111/j.1365-2753.2006.00753.x
5. Rücker G, Schwarzer G, Krahn U, König J, Schwarzer MG. Package 'netmeta'. Network Meta-Analysis using Frequentist Methods (Version 0.7-0). 2015.
6. Rücker G, Schwarzer G. Reduce dimension or reduce weights? Comparing two approaches to multi-arm studies in network meta-analysis. Stat Med 2014;33:4353-4369. doi:10.1002/sim.6236
7. Nikolakopoulou A, Higgins JPT, Papakonstantinou T et al. Cinema: An approach for assessing confidence in the results of a network meta-analysis. PLoS Med 2020;17:e1003082. doi:10.1371/JOURNAL.PMED.1003082
8. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. Int J Epidemiol 2012;41:818-827. doi:10.1093/ije/dys041

CHAPTER 8

# Interventions for preventing falls and fall-related fractures in community-dwelling older adults: a systematic review and network meta-analysis

Lauren Dautzenberg*, Shanthi Beglinger*, Sofia Tsokani, Stella Zevgiti, Renee C.M.A. Raijmann, Nicolas Rodondi, Rob J.P.M. Scholten, Anne W.S. Rutjes, Marcello Di Nisio, Marielle H. Emmelot-Vonk, Andrea C. Tricco, Sharon E. Straus, Sonia Thomas, Lisa Bretagne, Wilma Knol, Dimitris Mavridis, Huiberdina L. Koek

* These authors contributed approximately equally to this work

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## Abstract

**Objective:** To compare the effectiveness of single, multiple and multifactorial interventions to prevent falls and fall-related fractures in community-dwelling older persons.

**Methods:** MEDLINE, Embase and Cochrane Central Register of Controlled Trials were systematically searched for randomized controlled trials evaluating the effectiveness of fall prevention interventions in community-dwelling adults aged ≥65 years, from inception until February 27, 2019. Two large RCTs (published in 2020 after the search closed) were included in post-hoc analyses. Pairwise meta-analysis and network meta-analysis (NMA) were conducted.

**Results:** NMA including 192 studies revealed that the following single interventions, compared to usual care, were associated with reductions in number of fallers: exercise (risk ratio (RR) 0.83; 95% confidence interval (CI) 0.77 to 0.89) and quality improvement strategies (e.g. patient education) (RR 0.90; 95% CI 0.83 to 0.98). Exercise as a single intervention was associated with a reduction in falls rate (RR 0.79; 95% CI 0.73 to 0.86). Common components of multiple interventions significantly associated with a reduction in number of fallers and falls rate were exercise, assistive technology, environmental assessment and modifications, quality improvement strategies and basic falls risk assessment (e.g. medication review). Multifactorial interventions were associated with a reduction in falls rate (RR 0.87; 95% CI 0.80 to 0.95), but not with a reduction in number of fallers (RR 0.95; 95% CI 0.89 to 1.01). The following single interventions, compared to usual care, were associated with reductions in number of fall-related fractures: basic falls risk assessment (RR 0.60; 95% CI 0.39 to 0.94) and exercise (RR 0.62; 95% CI 0.42 to 0.90).

**Conclusions:** In keeping with Tricco et al. 2017, several single and multiple fall prevention interventions are associated with fewer falls. In addition to Tricco, we observe a benefit at the NMA-level of some single interventions on preventing fall-related fractures.

## Introduction

Falls in older adults are a highly prevalent problem. Falls occur in one third of community-dwelling people aged ≥65 years at least once a year.[1] Twenty percent of these falls lead to a fall-related injury.[2,3]

Many intrinsic and extrinsic risk factors for falling have been identified.[4] Suffering from multiple chronic conditions, e.g. rheumatic disease, vertigo, may pose an even higher risk of falling; these medical conditions are prevalent in older people.[4]

Fall prevention interventions target risk factors that are modifiable and can be divided into three main groups: 1) single interventions **(**participants receive one type of intervention), 2) multiple interventions **(**participants receive the same, fixed combination of two or more types of interventions), and 3) multifactorial interventions (participants receive a personalized selection out of two or more types of interventions, according to the results of a pre-executed, personal falls risk assessment).[5] Until Tricco 2017[6], previous systematic reviews (SR) and meta-analyses were restricted to looking at combinations of multifactorial/multiple interventions on fall prevention as a whole, rather than being able to disentangle the effect of the individual components from the entire combination[5,7] It is, however, important to determine which particular components are most effective, as this can result in a more accurate prevention strategy. Network meta-analysis (NMA) enables the evaluation of individual components from multiple comparisons estimating the relative effectiveness between any pair of interventions, even if these interventions have never been compared directly.[8,9]

Furthermore, previous reviews did not focus on multimorbid older (age ≥75) adults.[10] As this population have a high risk of falling, it is essential to gain more insight into which particular fall prevention interventions are most beneficial in this high risk group.

Therefore, the aim of this SR and NMA was to update the Tricco et al. search on the effectiveness of single, multiple and multifactorial interventions and their individual components for preventing falls and fall-related fractures in community-dwelling older persons, with a particular focus on multimorbidity and age >75 years.

# Methods

## Protocol

The protocol for this SR and NMA was registered online with PROSPERO (PROSPERO 2019 CRD42019137466) and was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement.

## Study identification

We updated the Tricco et al.[6] SR and NMA of fall prevention interventions in older adults. We applied the same search terms as used in the original Tricco et al. review and updated the search from 1st December 2015 until 27th February 2019. The following electronic databases were searched: MEDLINE (via PubMed), Embase (OVID) and Cochrane Central Register of Controlled Trials. The search strategies with limitations are included in the Supplement: Appendix S11. The electronic search was supplemented with manual searches for additional randomized controlled trials (RCTs), by reviewing the reference lists of previous reviews,[5,7] a recommendations statement,[11] and NMA.[12] We extended Tricco et al.'s search by searching for additional interventions (management of urinary incontinence, management of orthostatic hypotension, walking aids and chiropractic care) from database inception to February 2019. As a NMA is time-consuming, new papers might be published after the search period. To check whether the findings of the current NMA are consistent with most recent literature, the outcomes from 2 large RCTs published after the search date[13,14] were incorporated into a post-hoc analysis.

## Eligibility criteria

We included (cluster) randomized and quasi-randomized controlled trials published in any language that evaluated the effectiveness of interventions for preventing falls in community-dwelling persons aged ≥65 years. For details of the eligible study population, interventions, comparators and outcomes, as well as the exclusion criteria see Supplementary Table S11. We excluded studies on specific conditions (e.g. stroke, Parkinson's Disease), where the effects of the interventions cannot be generalized to most community-dwelling older people.

## Study Selection

Two authors each reviewed half of the study titles and abstracts that resulted from the search, and then both independently reviewed the full text of all studies that were retained. Any disagreement was resolved by consensus with a third author. To ensure consistency of the eligibility criteria applied, the authors performed a pilot-test screening beforehand.

## Data extraction and outcome definition

We created a data extraction sheet for the following variables: study characteristics; participant characteristics; and primary and secondary outcome information. We categorized the interventions into the same intervention components as used by Tricco et al[6], and added additional intervention components (Table 1). Primary outcomes were number of fallers and number of fall-related fractures. Secondary outcomes were number of repeated fallers, number of hip fractures, falls rate and fracture rate.

## Risk of bias assessment

To assess risk of bias, we used the Effective Practice and Organisation of Care (EPOC) version of Cochrane's Risk of Bias tool.[15] This EPOC version fully overlaps with the original tool, yet adds the following criteria: contamination, similar baseline values of the outcome measures and similarity of baseline characteristics. Risk of bias assessment was performed by two authors independently and any disagreement resolved by consensus with a third author. The authors first performed a pilot-test to ensure consistency in applying the risk of bias criteria.

## Measures of treatment effect

For dichotomous outcomes, we calculated risk ratios (RR) accompanied by their 95%-confidence intervals (CI). For rates, whereby each participant may experience the event of interest more than once, we extracted the number of events and total participant-time (e.g. number of person-weeks of follow-up) and calculated rate ratios with 95%-CIs, assuming that the risk of the event occurring is constant across participants and over time.

## Synthesis of results

For a detailed description of the meta-analysis methods see Supplement: Appendix S11. The primary analysis followed the standard approach whereby each distinct combination of intervention components is treated as a separate intervention, e.g. assistive technology + exercise, versus usual care. We employed additional statistical models to disentangle the effect (i.e. determine effect sizes) of each separate intervention component, e.g. assistive technology versus usual care, and exercise versus usual care (component-NMA (C-NMA)). A non-technical review of C-NMA is previously given.[16] A basic assumption of the C-NMA is the additivity assumption, in which the total effect of a multiple/multifactorial intervention is derived from the sum of the relevant components (Intervention $_{a+b}$ = Intervention $_{a}$ + Intervention $_{b}$), thus the effect size of each individual intervention component can be determined.[17,18] We used statistically significant effect estimates with the highest P-scores to rank interventions[19] and estimate the average probability of a treatment being superior to other competing treatments.

## Certainty of the evidence

We used the Confidence in Network Meta-Analysis (CINeMA) approach, a quality assessment tool, to determine the degree of confidence in NMA effect estimates (see Supplement: Appendix S11).[20,21] CINeMA rates six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. Specifically important for NMAs, CINeMA helpfully considers the degree of incoherence i.e. the disagreement between direct and indirect evidence.

## Subgroup and Sensitivity Analyses

A priori subgroup NMAs were planned if sufficient available data: participants aged ≥75 years (subgroup age 75+) and participants with >3 co-existent chronic conditions (subgroup multimorbidity).[22]

A planned sensitivity NMA was to exclude studies with one or more domains considered high risk of bias, (caveat: with the exception of the domain for "blinding", since most studies were unable to conceal the intervention from participants).

Post-hoc, we performed a sensitivity analysis comparing multifactorial interventions with usual care to determine whether multifactorial interventions as a whole were associated with a lower risk of falls. Taking power into account, we performed this analysis for the two outcomes with the largest networks: number of fallers and falls rate.

**Table 1.** Interventions to prevent falls categorized into 14 components

| Intervention component (abbreviation) | Description |
|---|---|
| 1. Exercise (exerc) | Including gait- balance- and functional training, strength/ resistance training, flexibility, 3D training (e.g. Tai Chi, Qigong, dance and square stepping), general physical activity (e.g. walking groups), endurance training, and other |
| 2. Medication (med) | Vitamin D (cholecalciferol, alphacalcidol, sunlight, calcitriol, and ergocalciferol) |
| 3. Surgery (surg) | E.g. pacemaker implantation, hip prosthesis or cataract removal surgery |
| 4. Management of urinary incontinence[a] (incont) | Assisted toileting, bladder retraining, medication (e.g. tamsulosin, finasteride, botox injections), surgery (e.g. colposuspension surgery, sling procedures) |
| 5. Fluid or nutrition therapy (nutr) | Changes in diet, provision of supplements, nutritional therapy, protein drinks |
| 6. Psychological interventions (psych) | Cognitive behavioral therapy |
| 7. Environmental assessment and modifications (envir) | Assessment and correction of home environment (e.g. flooring, home check, home safety devices, home visits by occupational therapist, home furnishings and adaptations) |

| | |
|---|---|
| 8. Assistive technology (assist) | Provision of aids for personal protection (e.g. hip protector) or personal mobility (e.g. walking aids[a], comprehensive podiatry assessment and treatment, orthosis), aids for communication/information/signaling (e.g. vision assessment and correction with glasses, personal alarm systems, hearing aids) |
| 9. Social engagement (social) | Social group activities (watching films, leisure reading, singing, conversation), community activities, peer support (from peers or caregivers), seminars on non–health-related topics of general interest to older adults. |
| 10. Quality improvement strategies (qualt) | - Patient-level quality improvement strategies: promotion of self-management, patient education, patient reminders, and motivational interviewing<br>- Clinic-level or care team level quality improvement strategies: case management, team changes, electronic patient registry, facilitated relay of information to clinicians, audit and feedback, staff education, and clinician reminders<br>- Health system-level quality improvement strategies: Interventions with positive or negative financial incentives directed at clinicians (e.g. linked to adherence to some process of care or achievement of some target outcome). This strategy also includes positive or negative financial incentives directed at patients or system-wide changes in reimbursement systems |
| 11. Management of orthostatic hypotension[a] (hypot) | Wearing elastic stockings, rising slowly, sleeping in a bed with head raised, pharmacological interventions |
| 12. Basic falls risk assessment (brisk) | Cardiovascular assessment (vital signs, ECG, loop recorder, pacemaker interrogation), medication review (review, modification, withdrawal/deprescribing), fracture risk screening (bone mineral density) |
| 13. Whole-body vibration (vibr) | Transferring vibration of any frequency to the human body |
| 14. Chiropractic care[a] (chiro) | Improving sensorimotor function associated with fall risk |

[a] additional fall-prevention interventions not previously investigated by Tricco et al.

In general, we categorised interventions into similar components as used by Tricco et al. 2017 in order to assist with later merging of data extraction results. We also categorized the multifactorial interventions into the 14 interventions components. In order to be able to carry out analyses, we had to assume that all participants received these multifactorial intervention components.

**Table 2.** Summary of participant and study characteristics of the 220 randomized controlled trials (n=104,638) identified in our original search.

| Participant and study characteristics | Number of studies (%) |
|---|---|
| Mean age (years) | |
| 65-74 | 68 (30.9) |
| 75-84 | 128 (58.2) |
| ≥ 85 | 11 (5.0) |
| Not reported | 13 (5.9) |
| Female (%) | |
| 0-49 | 18 (8.2) |
| 50-100 | 198 (90.0) |
| Not reported | 4 (1.8) |
| History of falls in the last 12 months | |
| Fallers only | 33 (15.0) |
| Mixed | 103 (46.8) |
| Non-fallers only | 0 |
| Not reported | 84 (38.2) |
| Year of publication | |
| 1990-2002 | 36 (16.4) |
| 2003-2007 | 45 (20.5) |
| 2008-2012 | 54 (24.5) |
| 2013-2017 | 67 (30.5) |
| 2018-2019 | 18 (8.2) |
| Continent | |
| Europe | 87 (39.5) |
| Australia/New Zealand | 49 (22.3) |
| North America | 48 (21.8) |
| Asia | 29 (13.2) |
| South America | 5 (2.3) |
| Multicontinent | 2 (0.9) |
| Study design | |
| Parallel | 192 (87.3) |
| Cluster | 27 (12.3) |
| Both | 1 (0.5) |
| Site | |
| Multicenter | 91 (41.4) |
| Single center | 129 (58.6) |

| | |
|---|---|
| Sample size | |
| <100 | 54 (24.5) |
| 100-299 | 78 (35.5) |
| 300-999 | 71 (32.3) |
| ≥1000 | 17 (7.7) |
| Duration of intervention (weeks) | |
| 0-26 | 114 (51.8) |
| 27-52 | 53 (24.1) |
| ≥52 | 32 (14.5) |
| Not reported | 21 (9.6) |
| Duration of follow-up (weeks) | |
| 0-26 | 62 (28.2) |
| 27-52 | 111 (50.5) |
| ≥52 | 46 (20.9) |
| Not available/reported | 1 (0.5) |
| Number of components | |
| Single intervention | 99 (45.0) |
| Multiple intervention[a] | 75 (34.1) |
| Multifactorial intervention[b] | 46 (20.9) |

[a] participants received the same, fixed combination of two or more types of interventions
[b] participants received a combination of two or more types of interventions, which were personalized according to the results of a pre-executed falls risk assessment

# Results

## Study selection

Figure 1 presents an overview of the study selection. For a complete list of included references see Supplement: Appendix S12.

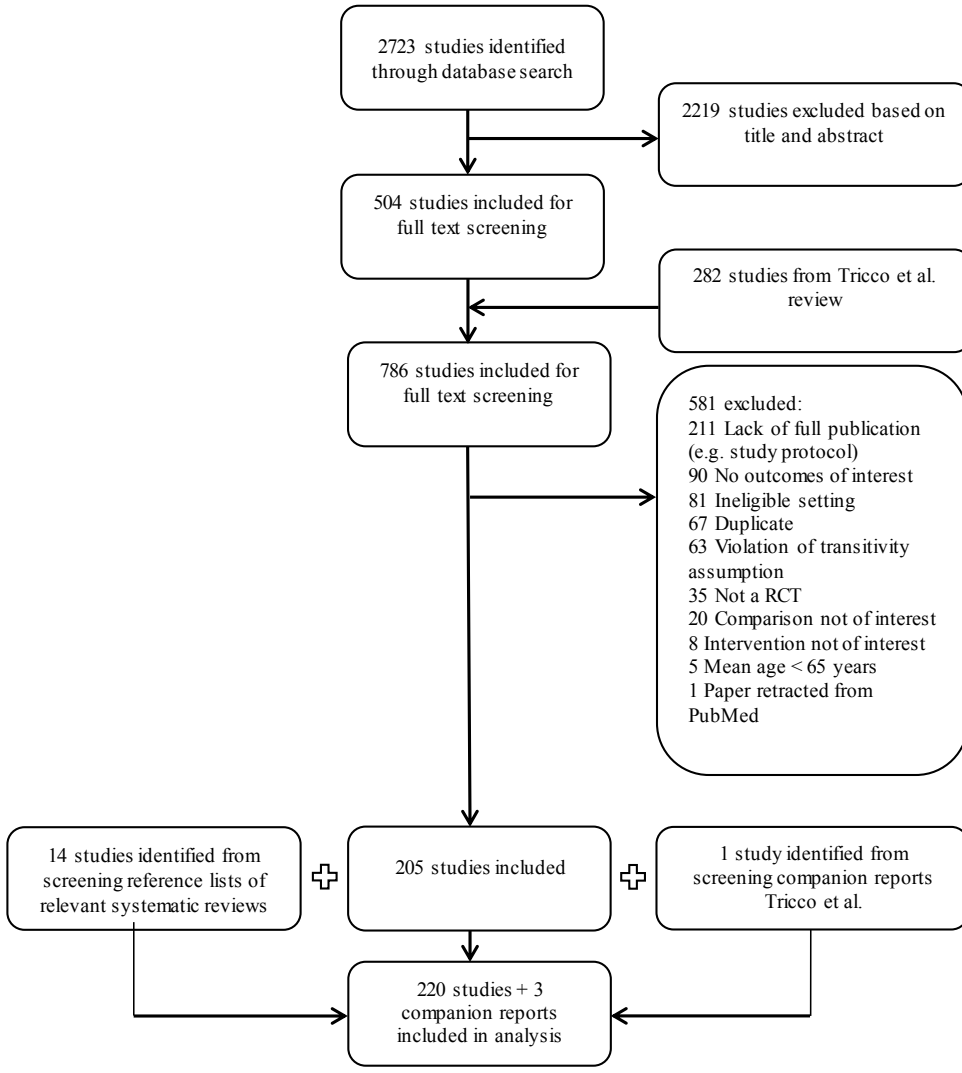


**Figure 1.** Flow diagram of study selection

## Study and participant characteristics

The study and participant characteristics of the original 220 studies identified in our search are presented in Supplement: Appendix S1 and summarized in Table 2.

In 128 studies (58.2%), the mean age of participants was between 75-84 years and in 11 studies (5.0%) >85 years.

## Risk of bias assessment

The risk of bias assessment was performed at the study level (see Supplement: Appendix S2). Most studies had a low risk of bias for random sequence generation, similar baseline characteristics, similar baseline outcome measures, incomplete outcome data and other bias. Over half of the studies had an unclear risk of bias for allocation concealment (i.e. concealment method not described or insufficient detail to allow judgement), contamination and selective outcome reporting. Most studies had a high risk of bias for blinding and one in five studies a high risk of bias for incomplete outcome data. Given the methodological shortcomings emphasized here, one must interpret the findings from these studies with caution. Post-hoc inclusion of 2 RCTs[13,14] did not alter these conclusions, namely a high risk of bias for blinding.

## Number of fallers

The NMA for this primary outcome included 192 studies (98,388 participants), and 63 different interventions all compared to usual care. These numbers also reflect the inclusion of 2 RCTs published after our search period was closed, in order to present most up-to-date results. One study was not connected to the network, because the combinations of components reported (exerc+nutr+envir+brisk vs. exerc+nutr+envir) were not investigated by any of the other included RCTs. Therefore, this study (152 participants) was excluded from the primary analysis, but was included in the C-NMA (Supplementary Figure S2). Supplementary Appendix S3 reports the risk ratios and P-scores for every intervention versus usual care, in which each existing combination of components was analyzed as a distinct intervention (primary analysis). The interventions with significant associations are presented in Table 3, together with rating confidence in the results using CINeMA.

Based on statistically significant effect estimates and high P-scores, the following single and multiple interventions were most strongly associated with reductions in number of fallers:

a) combination of assistive technology (e.g. provision of aids for mobility) and basic falls risk assessment (e.g. medication review),

b) combination of assistive technology and quality improvement strategies (e.g. patient education),

c) standing on a whole body vibration platform to improve muscle strength and balance, and

d) combination of home modification, assistive technology, quality improvement strategies, management of orthostatic hypotension and basic falls risk assessment (Table 3).
Post-hoc inclusion of data from 2 RCTs[13,14] had little effect on our conclusions, except in one small aspect where the intervention "quality improvement" rose to statistical significance.[13]
There were no concerns about inconsistency as evaluated by the node-splitting method, overall test for inconsistency and net-heat plot.
In the C-NMA, in which the relative effects of each individual intervention component can be disentangled, the following were associated with a decrease in number of fallers, compared to usual care: a) whole body vibration (RR 0.61; 95%CI 0.42-0.90) and b) exercise (RR 0.92; 95%CI 0.88-0.97). Management of urinary incontinence was associated with an increase in number of fallers (RR 1.39; 95%-CI 1.08-1.79). (Supplementary Table S3)

We performed an additional analysis in which all multifactorial interventions were considered as one intervention type. A multifactorial intervention wasn't significantly associated with a reduction in number of fallers (RR 0.95; 95%-CI 0.89-1.01, P-score 0.33; 188 studies, 91,137 participants).

We performed a sensitivity NMA excluding studies at high risk of bias, for the outcome number of fallers; the results were largely similar to the main analysis including all studies.

## Subgroup analyses number of fallers

The NMA for subgroup age 75+ included 19 studies (28,945 participants, mean age 79.8 years SD = 4.9) and 14 interventions that were all compared with usual care (Supplementary Appendix S4). Two studies were excluded from the primary analysis, as they were unconnected to the network (Supplementary Figure S4). Both studies compared vitamin D to placebo and were later included as an additional pairwise meta-analysis. Compared to placebo, vitamin D was not associated with a reduction in falls nor fractures.
The RRs and P-scores for every intervention versus usual care are reported in Supplementary Figure S5, whereas the five interventions with a statistically significant association in Table 4. The interventions with a statistically significant association in the subgroups were consistent with the findings from the main analysis, yet fewer were observed in subgroups likely due to the smaller size of the subgroup analysis. Based on statistically significant effect estimates and high P-scores, the single intervention exercise was most strongly associated with a reduction in number of fallers in subgroup analysis age 75+. In the C-NMA, none of the intervention components was associated with a significant change in the number of fallers (Supplementary Table S4).
The NMA for the subgroup multimorbidity included 14 studies (7,879 participants), and 11 interventions that were all compared with usual care (Supplementary Appendix S5). For this subgroup there were no statistically significant effects on number of fallers

resulting from the primary analysis or C-NMA. For number of fall-related fractures and for the secondary outcomes, only a few studies reported on subgroups age 75+ and multimorbidity, thus data was insufficient for further subgroup analysis.

### Number of fall-related fractures

The number of fall-related fractures NMA, included 46 studies (43,811 participants) and 27 interventions compared with usual care (Supplementary Figure S8). In 60% of studies fractures were verified radiologically or through review of hospital records. Supplementary Appendix S6 reports the RRs and P-scores for every intervention versus usual care. Based on statistically significant effect estimates with the highest P-scores, the single interventions basic falls risk assessment and exercise were most strongly associated with a reduction in number of fall-related fractures; the latter with higher CINeMA confidence rating (Table 3). However, these significant reductions were lost at the C-NMA level. Strangely, the intervention component assistive technology was significantly associated with an increase in the number of fall-related fractures (RR 1.66; 95%-CI 1.07-2.59). (Supplementary Table S6).

### Secondary outcomes

The results of the primary analysis (excluding post-hoc analyses) and C-NMA, comparing all intervention components with usual care for the outcomes number of repeated fallers, falls rate, number of hip fractures and fracture rate are presented in Supplement: Appendix S7 to S10. Table 3 reports the effect sizes and P-scores of interventions (including post-hoc analyses) with a statistically significant association and the corresponding CINeMA confidence rating.

For falls rate, we performed an additional analysis in which all multifactorial interventions were considered as one intervention type. Compared to usual care, multifactorial interventions were significantly associated with a reduced fall frequency (RR 0.88; 95%-CI 0.81-0.96, P-score 0.54; 111 studies, 53,923 participants).

### CINeMA confidence rating

Table 3 and 4 present the CINeMA confidence ratings for interventions that were statistically significant associated with a lower risk of falls and fall-related fractures. Supplement: Appendix S11 provides detailed results from the CINeMA approach.

**Table 3.** Risk ratios[a] and rate ratios[b] with 95% confidence interval (CI), P-scores and CINeMA confidence ratings for the interventions with a statistically significant association

| Intervention | Studies (N) | Participants (N) | Effect size (95% CI) | P-score | CINeMA all domains | CINeMA four domains[c] |
|---|---|---|---|---|---|---|
| **Number of fallers[a]** | | | | | | |
| assist+brisk | 1 | 96 | 0.52 (0.30 to 0.90) | 0.89 | Low | High |
| assist+qualt | 3 | 366 | 0.58 (0.41 to 0.81) | 0.89 | Low | High |
| vibr | 3 | 798 | 0.61 (0.42 to 0.89) | 0.86 | Low | High |
| envir+assist+qualt+ hypot+brisk | 1 | 397 | 0.62 (0.43 to 0.88) | 0.86 | Low | Moderate[d] |
| exerc+envir+qualt | 3 | 3,646 | 0.74 (0.57 to 0.97) | 0.75 | Low | High |
| exerc+assist | 3 | 1,338 | 0.77 (0.62 to 0.95) | 0.73 | Low | High |
| exerc | 56 | 14,825 | 0.83 (0.77 to 0.90) | 0.65 | Low | High |
| qualt+brisk | 10 | 9,230 | 0.84 (0.73 to 0.96) | 0.62 | Low | High |
| exerc+envir+assist+ qualt+brisk | 5 | 5,391 | 0.85 (0.74 to 0.98) | 0.60 | Low | High |
| exerc+qualt | 30 | 8,064 | 0.87 (0.80 to 0.96) | 0.56 | Low | High |
| qualt | 50 | 22,374 | 0.90 (0.83 to 0.99) | 0.49 | Low | High |
| qualt | 5 | 12,904 | 0.90 (0.83 to 0.98) | 0.49 | Low | High |
| exerc+incont+envir+ assist+qualt+brisk | 1 | 552 | 1.58 (1.01 to 2.48) | 0.05 | Low | High |
| **Number of repeated fallers[a]** | | | | | | |
| vibr | 1 | 710 | 0.33 (0.12 to 0.91) | 0.94 | Low | High |
| exerc+assist | 1 | 1,107 | 0.48 (0.25 to 0.93) | 0.88 | Low | High |
| exerc | 19 | 5,590 | 0.71 (0.53 to 0.95) | 0.71 | Low | Moderate[e] |
| **Falls rate[b]** | | | | | | |
| envir+assist+qualt +hypot+brisk | 1 | 397 | 0.42 (0.30 to 0.58) | 0.99 | NA | NA |
| exerc+assist | 2 | 1,188 | 0.68 (0.54 to 0.86) | 0.85 | NA | NA |
| exerc+med | 2 | 616 | 0.68 (0.47 to 0.98) | 0.81 | NA | NA |
| exerc+envir+assist+ hypot+brisk | 4 | 973 | 0.73 (0.59 to 0.92) | 0.78 | NA | NA |

| | | | | | | |
|---|---|---|---|---|---|---|
| exerc | 27 | 7,485 | 0.79 (0.73 to 0.87) | 0.70 | NA | NA |
| exerc+qualt+hypot+brisk | 1 | 298 | 2.08 (1.34 to 3.25) | 0.01 | NA | NA |
| exerc+nutr+envir+assist+brisk | 1 | 328 | 1.84 (1.14 to 2.97) | 0.03 | NA | NA |
| **Number of fall-related fractures[a]** | | | | | | |
| brisk | 2 | 3,046 | 0.60 (0.39 to 0.94) | 0.72 | Low | Moderate[d] |
| exerc | 10 | 5,678 | 0.62 (0.42 to 0.90) | 0.71 | Low | High |
| **Fracture rate[b]** | | | | | | |
| exerc | 5 | 2,511 | 0.49 (0.27 to 0.89) | 0.80 | NA | NA |
| exerc+qualt | 2 | 1,975 | 0.52 (0.28 to 0.96) | 0.70 | NA | NA |

[c] For the domains 'within-study bias' and 'reporting bias' there were major concerns for all comparisons. In order to still maintain distinctiveness, the evaluation of the confidence in the results of the NMA was based on the remaining four domains. Reason for downgrading CINeMA confidence rating: [d]indirectness, [e] heterogeneity

NA: characterization not applicable (NA) since CINeMA cannot address rate outcomes.

Abbreviations: **exerc**, exercise; **med**, medication; **surg**, surgery; **incont**, management of urinary incontinence; **nutr**, fluid or nutrition therapy; **psych**, psychological interventions; **envir**, environmental assessment and modifications; **assist**, assistive technology; **social**, social engagement; **qualt**, quality improvement strategies; **hypot**, management of orthostatic hypotension; **brisk**, basic falls risk assessment; **vibr**, whole-body vibration .

**Table 4.** Risk ratios with 95% confidence interval (CI), P-scores and CINeMA confidence ratings for the interventions with a statistically significant association versus usual care for the outcome number of fallers, subgroup age 75+

| Intervention | Studies (N) | Participants (N) | Effect size (95% CI) | P-score | CINeMA all domains[a] | CINeMA four domains[a] |
|---|---|---|---|---|---|---|
| exerc | 3 | 1,954 | 0.65 (0.50 to 0.85) | 0.91 | Low | High |
| qualt+brisk | 2 | 5,771 | 0.75 (0.64 to 0.87) | 0.80 | Low | High |
| exerc+qualt | 4 | 1,481 | 0.75 (0.67 to 0.83) | 0.81 | Low | High |
| exerc+envir+qualt | 1 | 3,182 | 0.76 (0.64 to 0.89) | 0.78 | Low | High |
| qualt | 5 | 9,681 | 0.85 (0.74 to 0.99) | 0.59 | Low | High |

[a] For the domains 'within-study bias' and 'reporting bias' there were major concerns for all comparisons. In order to still maintain distinctiveness, the evaluation of the confidence in the results of the NMA was based on the remaining four domains.

Abbreviations: **exerc**, exercise; **envir**, environmental assessment and modifications; **qualt**, quality improvement strategies; **brisk**, basic falls risk assessment.

## Discussion

In this SR and NMA, we updated current evidence on prevention of falls and fall-related fractures in older persons, with a focus on high risk subgroups of multimorbid older adults and aged ≥75 years. Compared to previous NMA by Tricco et al., we considered 57 new studies and added 4 interventions previously not considered.

Several single and multiple interventions were associated with a lower risk of falls (i.e. in keeping with Tricco et al.) and also with fall-related fractures (divergent from Tricco). Exercise (single intervention) was frequently investigated in included studies and associated with a lower risk of all primary and secondary outcomes in the primary analysis. This was no longer evident once disentangled down to the C-NMA level, where no effect of exercise on fracture outcomes was observed. The same applied to basic falls risk assessment. These findings did not alter after post-hoc inclusion of data from two recent major RCTs.[13,14]

Common components seen in significant multiple interventions were exercise, assistive technology, environmental assessment and modifications, quality improvement strategies and basic falls risk assessment. In agreement with a recent Cochrane review, multifactorial interventions were associated with a reduction in falls rate, but not in number of fallers.[5] One possible explanation is that falls rate may measure falls risk more accurately than number of fallers. While the latter counts persons who fall once or fall repetitively as one outcome event, the outcome falls rate counts each fall as a separate outcome event. Contrary to our findings above, Tricco et al. found that multifactorial intervention (comprised of exercise and quality improvement strategies) was associated with a reduction in number of fallers (OR 0.68; 95%-CI 0.49-0.94).[6]

We performed a meta-analysis on vitamin D supplementation versus placebo. We can corroborate previously published literature which showed no association of vitamin D with the risk of falls or fall-related fractures.[23,24] Although Tricco et al. found an effect on fallers and injurious falls when vitamin D is combined with calcium supplementation and other intervention components.[6]

Unexpectedly, considering that it is not widely used in clinical practice, whole-body vibration was associated with a lower risk of falls. This intervention was investigated in few studies (with small study populations and high summary risk of bias), so the clinical value is still unclear. The benefit we observed may be subject to publication bias.

This study has several strengths. (1) SR and NMA were performed in accordance with the EPOC tool and CINeMA approach. (2) Based on statistically significant effect estimates combined with high P-scores, we ranked interventions to draw conclusions. (3) By extracting information on the components forming the multifactorial interventions, we could also address which combination of components is most effective. (4) We investigated community-dwelling older adults, applied few exclusion criteria, and included interventions that complied with the transitivity assumption; thus our results

are widely generalizable. Moreover, whilst severe dementia was an exclusion criterion, we did allow studies with mild to moderate dementia participants as this reflects real-life and the increasing prevalence within the community-dwelling older population. (5) The large population size enabled subgroup analyses (aged 75+, multimorbidity).

This study has some limitations. (1) In contrast to Tricco and colleagues, we assigned a high risk of bias for domain blinding when falls and fractures were self-reported in a patient-diary, as it was often not possible to blind participants to their intervention. This may explain our larger percentage of studies deemed at high risk of bias for blinding, but is difficult to prevent due to the nature of the interventions. Furthermore, blinding participants to their assigned intervention could affect their willingness/probability of engaging with the intervention and their reporting of fall incidents. (2) Allocation concealment was unclear in half of the studies and this might affect the trust we can place in the estimates of intervention effect sizes. Whilst baseline characteristics and fall history were reasonably balanced (similar between the study arms in 85% and 77% of trials, respectively), it is possible that other influencing factors (e.g. willingness/probability of engaging with the interventions) were less balanced across the study arms. (3) Categorization of interventions into components allowed us to make inferences about the effect of these components as a whole (e.g. exercise), but not about specific subcategories within these components (e.g. strength training or tai chi). Where a component showed no significant effect, it could still be that subcategories within this component are effective, particularly so in cases with high 'within-component heterogeneity'. Many different interventions for fall prevention were evaluated and working with clustered intervention components was necessary to maintain sufficient power for the NMA. (4) Similarly, to avoid insufficient power we were unable to distinguish between different intervention dosages, durations of treatment, or between different lengths of follow-up durations in the NMAs. However, we expect the effect of the interventions to decrease with a longer follow-up duration, possibly reducing the overall effect estimates. Only 20% of included studies reported a follow-up longer than one year. Differences in dosage and length of interventions may also lead to 'within-component heterogeneity'. (5) CINeMA software cannot address rate outcomes. However, most studies reporting rates also provided data on dichotomous outcomes, for which CINeMA assessment was possible. Due to this overlap, the overall certainty in the evidence is expected to be similar across the dichotomous and rate outcomes. (6) Finally, most studies have similar baseline risk (e.g. falls rate) across interventions. When this is violated and large discrepancies are present, this limits our ability to draw indirect comparisons across the (C-)NMA. With few studies per comparison arm we cannot test with certainty whether baseline risk or other factors differ across intervention comparisons. Though we attempted to mitigate this risk with clinical (- compliance with transitivity assumption) and statistical (- heterogeneity assessments) judgements.

This NMA provides an extensive overview of current evidence for effective fall prevention interventions in older persons. Yet some questions remain unanswered.

More research is needed on fall prevention interventions in multimorbid older persons, since this subgroup analysis lacked sufficient power for the NMA. Additional studies are needed to clarify and confirm the effect of whole-body vibration, given the potential publication bias identified.

Further research is needed to evaluate effects of specific subcategories within the intervention components. For example, two recent studies performed by the research group of Tricco et al. explored effects of different quality improvement strategies and exercise interventions on falls.[25,26]

## Conclusion

Exercise is associated with a lower risk of falls and fall-related fractures. Common components of significant multiple interventions are exercise, assistive technology, environmental assessment and modifications, quality improvement strategies and basic falls risk assessment. A multifactorial intervention is associated with a reduction in falls rate, but not with a reduction in number of fallers. Over half of the studies included had methodological short comings (lack of allocation concealment and high risk of blinding). This points to a greater issue within the evidence base and highlights the need for more robust study procedures/reporting in which future policy can be based on. Few studies have investigated the effect of fall prevention interventions in multimorbid older people, which is highly recommended for future research.

## References


1. National Institute for Health and Care Excell. Falls in older people : assessing risk and prevention. *NICE Clin Guidel*. 2013;(June 2013):1-33. https://www.nice.org.uk/guidance/cg161/resources/falls-in-older-people-assessing-risk-and-prevention-35109686728645
2. Tinetti M, Speechley M, Ginter S. Risk factors for falls among elderly persons living in the community. *N Engl J Med*. 1988;319:1701–7.
3. Campbell A, Borrie M, Spears G, Jackson S, Brown J, Fitzgerald J. Circumstances and consequences of falls experienced by a community population 70 years and over during a prospective study. *Age Ageing*. 1990;19:136–41.
4. Deandrea S, Lucenteforte E, Bravi F, Foschi R, La Vecchia C, Negria E. Risk Factors for Falls in Community-dwelling Older People A Systematic Review and Meta-analysis. *Epidemiology*. 2010;21(5):658-668.
5. Hopewell S, Adedire O, Copsey BJ, et al. Multifactorial and multiple component interventions for preventing falls in older people living in the community (Review). *Cochrane Database Syst Rev*. Published online 2018. doi:10.1002/14651858.CD012221.pub2
6. Tricco A, Thomas S, Veroniki A, et al. Comparisons of interventions for preventing falls in older adults: A systematic review and meta-analysis. *J Am Med Assoc*. 2017;318(17):1687-1699. doi:10.1001/jama.2017.15006
7. Gillespie L, Robertson M, Gillespie W, et al. Interventions for preventing falls in older people living in the community (Review). *Cochrane database Syst Rev*. 2012;(9). doi:10.1201/b12752-36
8. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods*. 2012;3(2):80-97. doi:10.1002/jrsm.1037
9. Mavridis D, Giannatsi M, Cipriani A, Salanti G. A primer on network meta-analysis with emphasis on mental health. *Evid Based Ment Health*. 2015;18(2):40-46. doi:10.1136/eb-2015-102088
10. Streit S, Da Costa BR, Bauer DC, et al. Multimorbidity and quality of preventive care in Swiss University primary care cohorts. *PLoS One*. 2014;9(4):e96142. doi:10.1371/journal.pone.0096142
11. Grossman DC, Curry SJ, Owens DK, et al. Interventions to prevent falls in community-dwelling older adults us Preventive Services Task Force recommendation statement. *JAMA - J Am Med Assoc*. 2018;319(16):1696-1704. doi:10.1001/jama.2018.3097
12. Cheng P, Tan L, Ning P, et al. Comparative effectiveness of published interventions for elderly fall prevention: A systematic review and network meta-analysis. *Int J Environ Res Public Health*. 2018;15(3):498-511. doi:10.3390/ijerph15030498
13. Lamb SE, Bruce J, Hossain A, et al. Screening and Intervention to Prevent Falls and Fractures in Older People. *N Engl J Med*. 2020;383(19):1848-1859. doi:10.1056/nejmoa2001500
14. Bhasin S, Gill TM, Reuben DB, et al. A Randomized Trial of a Multifactorial Strategy to Prevent Serious Fall Injuries. *N Engl J Med*. 2020;383(2):129-140. doi:10.1056/nejmoa2002183
15. *Cochrane Effective Practice and Organisation of Care (EPOC). Suggested Risk of Bias Criteria for EPOC Reviews. EPOC Resources Fo r Review Authors, 2017. Available at: Http://Epoc.Cochrane.Org/Resources/Epoc-Resources-Review-Authors*.

16. Caldwell D, Welton N. Approaches for synthesising complex mental health interventions in meta-analysis. *Evid Based Ment Health*. 2016;19(1):16-21. doi:10.1136/eb-2015-102275
17. Rücker G, Petropoulou M, Schwarzer G. Network meta-analysis of multicomponent interventions. *Biometrical J*. 2020;62:808-821. doi:10.1002/bimj.201800167
18. Welton N, Caldwell D, Adamopoulos E, Vedhara K. Mixed treatment comparison meta-analysis of complex interventions: Psychological interventions in coronary heart disease. *Am J Epidemiol*. 2009;169(9):1158-1165. doi:10.1093/aje/kwp014
19. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol*. 2015;15(1):58. doi:10.1186/s12874-015-0060-8
20. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, et al. Cinema: An approach for assessing confidence in the results of a network meta-analysis. *PLoS Med*. 2020;17(4):e1003082. doi:10.1371/JOURNAL.PMED.1003082
21. Salanti G, Giovane C Del, Chaimani A, Caldwell DM, Higgins JPT. Evaluating the quality of evidence from a network meta-analysis. *PLoS One*. 2014;9(7):e99682. doi:10.1371/journal.pone.0099682
22. Jadad AR, To MJ, Emara M, Jones J. Consideration of multiple chronic diseases in randomized controlled trials. *J Am Med Assoc*. 2011;306(24):2670-2672.
23. Yao P, Bennett D, Mafham M, et al. Vitamin D and Calcium for the Prevention of Fracture: A Systematic Review and Meta-analysis. *JAMA Netw open*. 2019;2(12):e1917789. doi:10.1001/jamanetworkopen.2019.17789
24. Bolland M, Grey A, Avenell A. Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis. *Lancet Diabetes Endocrinol*. 2018;6(11):847-858. doi:10.1016/S2213-8587(18)30265-1
25. Tricco A, Thomas S, Veroniki AA, et al. Quality improvement strategies to prevent falls in older adults: A systematic review and network meta-Analysis. *Age Ageing*. 2019;48(3):337-346. doi:10.1093/ageing/afy219
26. Sibley KM, Thomas SM, Veroniki AA, et al. Comparative effectiveness of exercise interventions for preventing falls in older adults: A secondary analysis of a systematic review with network meta-analysis. *Exp Gerontol*. 2021;143:111151. doi:10.1016/j.exger.2020.111151

## Supplementary Content

Supplementary Appendix S1. Characteristics of the 220 included studies
Supplementary Appendix S2. Aggregate and individual risk of bias results
Supplementary Appendix S3. Additional results for number of fallers
Supplementary Appendix S4. Additional results for number of fallers, subgroup age 75+
Supplementary Appendix S5. Additional results for number of fallers, subgroup multimorbidity
Supplementary Appendix S6. Additional results for number of fall-related fractures
Supplementary Appendix S7. Additional results for number of repeated fallers
Supplementary Appendix S8. Additional results for number of hip fractures
Supplementary Appendix S9. Additional results for falls rate
Supplementary Appendix S10. Additional results for fracture rate
Supplementary Appendix S11. eMethods
- 1.1 Additional information regarding study population, interventions, comparators and outcomes
- 1.2 Electronic search strategy
- 1.3 Additional information on methods systematic review
- 1.4 Additional information on network meta-analysis
- 1.5 Additional information on CINeMA confidence rating

Supplementary Appendix S12. eReferences. List of 220 included studies and 3 companion reports

*The figures and tables below present the results of the data extraction, primary analyses and component network meta-analyses excluding post-hoc analyses. For results including post-hoc analyses, please contact the corresponding author.

**Supplementary Appendix S1.** Characteristics of the 220 included studies

**Supplementary Table S1.** Characteristics of the 220 included studies with community-dwelling participants

| First author, year[a] | Country | Comparison(s)[b] | Outcome(s)[c] | Sample size | Mean age (years) | Female (%) | Duration of treatment (weeks) | Duration of follow-up (weeks) | Fallers[d] (%) |
|---|---|---|---|---|---|---|---|---|---|
| Aloia, 2019[1] | United States | Med; ph_pbo | FALL, FX | 184 | 68.2 | 100 | 144 | 144 | 14 |
| Ansai, 2016[2] | Brazil | Exerc; exerc; uc | FALL | 69 | 82.4 | 68 | 16 | 16 | 44;30;35* |
| Arantes, 2015[3] | Brazil | Exerc; non-ph_pbo | FALL | 28 | 73.9;72.2* | 100 | 12 | 52 | 100 |
| Arkkukangas, 2019[4] | Sweden | Exerc+qualt; uc | FALL, FRATE | 107 | 83 | 70 | 12 | 12 | 42 |
| Ashari, 2016[5] | Malaysia | Exerc; uc | FALL | 68 | 63.7 | 57 | 16 | 16 | 21 |
| Ballard, 2004[6] | United States | Exerc; non-ph_pbo | FALL, FRATE | 39 | 73.4; 72.4* | 100 | 15 | 52 | 100 |
| Barker, 2016[7] | Australia | Exerc+brisk; brisk | FALL, FRATE | 49 | 69.3 | 88 | 12 | 24 | 65;52* |
| Barnett, 2003[8] | Australia | Exerc+qualt; qualt | FALL, RFALL | 163 | 74.9 | 67 | 52 | 52 | 43;41* |
| Barr, 2005[9] | United Kingdom | Brisk; uc | FALL, FX, HIP, FRATE | 2686 | 77.1 | 100 | 111 | 103 | 26;29* |
| Beck, 2010[10] | Australia | Vibr; uc | FALL, FRATE | 47 | 71.5 | 100 | 35 | 35 | NR |
| Beck 2016[11] | Denmark | Exerc+nutr+qualt; qualt | FALL, FRATE | 95 | 86.6 | 75 | 11 | 11 | NR |
| Beling, 2009[12] | United States | Exerc; uc | FRATE | 19 | 79; 87* | 36; 50* | 12 | 12 | 36;65* |
| Bernardelli, 2019[13] | Italy | Exerc; uc | FALL | 149 | 75.6 | 80 | 16 | 16 | NR |
| Bernocchi, 2019[14] | Italy | Exerc+qualt; qualt | FALL | 283 | 79 | 59 | 24 | 26 | 73;65* |
| Bischoff-Ferrari, 2006[15] | United States | Med; ph_pbo | FALL | 445 | 70.8 | 55 | 156 | 156 | NR |
| Blalock, 2010[16] | United States | Brisk+qualt; qualt | FALL, FRATE | 186 | 74.8 | 71 | NR | 42;47* | 43;48* |
| Boongird, 2017[17] | Thailand | Exerc+qualt; qualt | FALL, FRATE | 427 | 74.1; 73.9* | 84; 81* | 52 | 52 | NR |
| Boyé, 2016[18]91 (34% | The Netherlands | Brisk; uc | FALL | 580 | 76 | 62 | NA | 52 | 100 |
| Brown, 2002[19] | Australia | Social; exerc+qualte; uc | FALL | 149 | 80.7 | NR | 16 | 32 | 49;38;44* |
| Buchner, 1997[20] | United States | Exerc; uc | FALL, FRATE | 105 | 75 | 52;50* | 24 | 24 | 22 |
| Bunout, 2005[21] | Chile | Exerc; uc | FALL, FRATE | 298 | 75 | 71 | 52 | 52 | NR |
| Cameron, 2003[22] | Australia | Assist+qualt; uc | FX, RFALL, HIP, FXRATE, FRATE | 600 | NR | 100 | 104 | 104 | 100 |
| Cameron, 2011[23] | Australia | Assist+qualt; assist; qualt | FALL, FX, FRATE, FXRATE | 171 | 83;84;82* | 72;78; 72* | 26 | 26 | NR |
| Carpenter, 1990[24] | United Kingdom | Social; uc | FRATE | 539 | NR | 65 | 156 | 72 | NR |
| Chapuy, 2002[25] | France | Med; ph_pbo | FALL, FX, HIP | 583 | 85.2 | 100 | 104 | 104 | NR |
| Choi, 2005[26] | South Korea | Exerc; uc | FALL | 68 | 77.9 | 75 | 12 | 12 | 66;57* |
| Chu, 2017[27] | China | Envir+assist+brisk+ qualt; non-ph_pbo | FALL, RFALL | 204 | 78.3 | 71 | <1 | 52 | NR |
| Ciaschini, 2009[28] | Canada | Exerc+envir+qualt+ hypot+brisk; uc | FALL | 201 | 71.9 | 94 | NR | 52 | 43;40* |
| Clemson, 2004[29] | Australia | Exerc+brisk+qualt; social | FALL, RFALL, FRATE | 310 | 78.4 | 74 | 20 | 60 | 65;65* |
| Clemson, 2010[30] | Australia | Exerc+qualt; uc | FALL, RFALL, FRATE | 34 | 81.5 | 47 | 26 | 26 | 100 |
| Clemson, 2012[31] | Australia | Exerc; non-ph_pbo | FALL, FX, RFALL, FRATE | 317 | 83.4 | 55 | 52 | 52 | 100 |
| Close, 1999[32] | United Kingdom | Assist+envir+qualt+ hypot+brisk; uc | FALL, FRATE | 397 | 78.2 | 68 | NR | 52 | 100 |
| Cohen, 2015[33] | United States | Qualt+brisk; qualt | FALL | 5310 | 81 | 59 | 52 | 52 | NR |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Coleman, 1999[34] | United States | Qualt+brisk; uc | FALL | 169 | 77.3 | 49 | 104 | 104 | NR |
| Conroy, 2010[35] | United Kingdom | Exerc+envir+assist+ hypot+brisk; qualt | FALL, FRATE | 364 | 79 | 60 | NR | 52 | 59;56* |
| Cornillon, 2002[36] | France | Exerc+qualt+hypot+ brisk; uc | FALL, FRATE | 298 | 71.3;70.9* | 83 | 12 | 52 | 75; 76* |
| Cumming, 1999[37] | Australia | Envir; uc | FALL, FRATE | 530 | 76.8 | 57 | 2 | 52 | 39;39* |
| Cumming, 2007[38] | Australia | Envir+assist; uc | FALL, FX, HIP, FRATE | 616 | 80.6 | 68 | <1 | 52 | 54;55* |
| Dadgari, 2016[39] | Iran | Exerc; uc | FALL, RFALL | 317 | 70.3 | NR | 26 | 26 | NR |
| Dangour, 2011[40] | Chile | Exerc+nutr; exerc; nutr; uc | FALL, FX | 2002 | 66.2 | 68 | 104 | 104 | NR |
| Dapp, 2011[41] | Switzerland | Qualt+brisk; uc | RFALL | 1963 | 71.9;71.8* | 62;63* | 52 | 52 | NR |
| Davison, 2005[42] | United Kingdom | Exerc+envir+assist+ hypot+brisk; uc | FALL, FX, FRATE | 313 | 77 | 72 | NR | 52 | 100 |
| Day, 2015[43] | Australia | Exerc+qualt; non-ph_pbo | FALL, RFALL, FRATE | 503 | 77.7 | 70 | 48 | 48 | 29;30* |
| De Vries, 2010[44] | The Netherlands | Exerc+med+envir+assist+ hypot+brisk; uc | FALL, RFALL, FX | 217 | 79.8 | 71 | NR | 52 | 100 |
| Dhesi, 2004[45] | United Kingdom | Med; ph_pbo | FALL, FRATE | 139 | 76.8 | 78 | 26 | 26 | 100 |
| Dorresteijn, 2016[46] | The Netherlands | Psych+qualt; uc | FALL, RFALL, FRATE | 389 | 78.3 | 70 | 17 | 52 | NR |
| Dukas, 2004[47] | Switzerland | Med; ph_pbo | FALL, FRATE | 378 | 75.0 | 52 | 36 | 36 | 5;13* |
| Dyer, 2004[48] | United Kingdom | Exerc+assist+envir+ qualt+brisk; uc | FALL, FX, FRATE | 196 | 87.3 | 78 | 13 | 13 | NR |
| Ebrahim, 1997[49] | United Kingdom | Exerc+qualt; qualt | FALL, FX, FRATE | 165 | 67.2 | 100 | 104 | 104 | 59;56* |
| El-Khoury, 2015[50] | France | Exerc+qualt; qualt | FALL, FRATE | 706 | 79.7 | 100 | 104 | 104 | 39;45* |
| Elley, 2008[51] | New Zealand | Exerc+envir+assist+brisk; qualt | FALL, RFALL, FRATE | 312 | 80.8 | 69 | 52 | 52 | 100 |
| Fabacher, 1994[52] | United States | Envir+qualt+hypot+brisk; uc | FALL | 195 | 73.5;71.8* | 2 | 52 | 52 | 17;14* |
| Fairhall, 2014[53] | Australia | Exerc+incont+nutr+psych+ envir+qualt+brisk; uc | FALL, FX, FRATE | 241 | 83.3 | 68 | 52 | 52 | NR |
| Ferrer, 2014[54] | Spain | Exerc+nutr+envir+ assist+brisk; uc | FALL, FX, FRATE | 328 | 85 | 62 | 104 | 104 | 30;27* |
| Fitzharris, 2010[55] | Australia | Exerc+envir+assist; envir+ assist; exerc+envir; exerc+ assist; envir; assist; exerc; uc | FALL, RFALL, FRATE | 1107 | 76.1 | 60 | 15 | 76 | 6 |
| Fox, 2010[56] | United States | Exerc+incont+envir+assist+ qualt+brisk; brisk | FALL | 552 | 76.8 | 67 | NR | 52 | 58;42* |
| Freiberger, 2012[57] | Germany | Exerc+psych+qualt; exerc; exerc; uc | FRATE | 280 | 76.1 | 44 | 16 | 104 | NR |
| Gallagher, 2001[58] | United States | Med; uc | FX | 489 | 72 | 100 | 156 | 156 | NR |
| Gawler, 2016[59] | United Kingdom | Exerc; uc | FALL, FRATE | 791 | 73 | 62 | 24 | 104 | 22 |
| Giangregorio, 2018[60] | Canada, Australia | Exerc; non-ph_pbo | FALL | 141 | 76;77* | 100 | 52 | 52 | 37;30* |
| Gianoudis, 2014[61] | Australia | Exerc+qualt; qualt | FALL, RFALL, FX, FRATE | 162 | 67.5 | 73 | 52 | 52 | 100 |
| Gill, 2016[62] | United States | Exerc; exerc+qualt | HIP, FXRATE | 1635 | 78.9 | 67 | 104 - 183 | 180 | 50;49* |

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|---|---|---|---|---|---|---|---|---|---|
| Giusti, 2013[63] | Italy | Vibr; non-ph_pbo | FALL | 41 | 85.2 | 93 | <1 | 4 | NR |
| Glendenning, 2012[64] | Australia | Med+qualt; qualt | FALL, RFALL, FX | 686 | 76.7 | 100 | 36 | 36 | 33;25* |
| Grahn Kronhed, 2009[65] | Sweden | Exerc; uc | FALL | 65 | 71.4 | 100 | 17 | 52 | 23;44* |
| Grant, 2005[66] | United Kingdom | Med; ph_pbo | FALL | 5292 | NR | 85 | 194 | 268 | NR |
| Gschwind, 2015[67] | Germany, Spain, Australia | Exerc+qualt; qualt | FALL, FRATE | 153 | 74.7 | 61 | 16 | 16 | 33; 36* |
| Guse, 2015[68] | United States | Exerc+qualt; uc | FALL, FRATE | 516 | 79.2;78.8* | 87;79* | 104 | 104 | 13;18* |
| Haines, 2009[69] | Australia | Exerc+qualt; uc | FALL, FX, FRATE | 53 | 80.6 | 60 | 8 | 26 | NR |
| Halvarsson, 2013[70] | Sweden | Exerc; uc | FALL | 59 | 77 | 71 | 12 | 64 | 90 |
| Harper, 2017[71] | Australia | Qualt; uc | FALL, FRATE | 378 | 79.3;79.1* | 64;66* | 1 | 24 | 45;40* |
| Harwood, 2004[72] | United Kingdom | Med; uc | FALL | 150 | 81.2 | 100 | <1 | 52 | NR |
| Hendriks, 2008[73] | The Netherlands | Envir+assist+qualt+brisk; uc | FALL, RFALL | 333 | 74.9 | 68 | 15 | 52 | 100 |
| Hill, 2013[74] | Australia | Qualt; uc | FALL, FX, HIP, FRATE | 50 | 78.3 | 66 | 2 | 4 | NR |
| Hill, 2019[75] | Australia | Qualt; non-ph_pbo | FALL, RFALL, FX, FRATE | 382 | 77.4;78.1 | 60;63 | 1 | 24 | 73; 69* |
| Hin, 2017[76] | England | Med; ph_pbo | FALL | 305 | 72 | 49 | 52 | 52 | NR |
| Hogan, 2001[77] | Canada | Exerc+envir+assist+ hypot+brisk; social | FALL, FX, HIP, FRATE | 163 | 77.7 | 72 | NR | 52 | 100 |
| Holt, 2016[78] | New Zealand | Chiro; uc | FALL | 60 | 72 | 60 | 12 | 12 | 18 |
| Hornbrook, 1994[79] | United States | Exerc+envir+qualt; qualt | FALL, FX | 3182 | 73.4 | 62 | 4 | 104 | 14;15* |
| Houston, 2015[80] | United States | Med; ph_pbo | FALL, FRATE | 68 | 77.9 | 72 | 22 | 20 | 63;59* |
| Huang, 1998[81] | Taiwan | Envir+qualt+brisk; qualt | FALL | 120 | 72.4;71.6* | 38;53* | 16 | 8 | 17;15* |
| Huang, 2010[82] | Taiwan | Qualt; exerc; exerc+qualt; uc | FALL | 163 | 71.5 | 49 | 20 | 52 | 24;13;38;17 |
| Huang, 2011[83] | Taiwan | Exerc+psych+qualt; psych+qualt; qualt | FALL | 186 | NR | 59 | 8 | 20 | NR |
| Imhof, 2012[84] | Switzerland | Qualt+brisk; uc | FALL | 461 | 85 | 73 | 39 | 40 | 34;44 |
| Iwamoto, 2009[85] | Japan | Exerc; uc | FALL | 68 | 76.4 | 90 | 22 | 22 | NR |
| Kamei, 2015[86] | Japan | Exerc+envir+qualt+brisk; exerc+qualt+brisk | FALL | 130 | 75.7;75.8* | 84;86* | 4 | 52 | 28;29* |
| Kamide, 2009[87] | Japan | Exerc+qualt; uc | FALL | 57 | 71 | 100 | 26 | 52 | NR |
| Karinkanta, 2015[88] | Finland | Exerc; exerc; exerc; uc | FX, HIP, FXRATE | 149 | NR | 100 | 52 | 52 | NR |
| Kärkkäinen, 2010[89] | Finland | Med; uc | FALL, RFALL | 750 | 67.4 | 100 | 156 | 156 | NR |
| Kemmler, 2010[90] | Germany | Exerc+med; med | FX, FRATE | 246 | NR | 100 | 77 | 77 | NR |
| Kerse, 2005[91] | New Zealand | Exerc+qualt; uc | FALL | 270 | 71.6 | 63 | 52 | 52 | NR |
| Kerse, 2008[92] | New Zealand | Exerc+qualt; non-ph_pbo | FALL | 682 | 84.3 | 74 | 26 | 52 | NR |
| Khaw, 2017[93] | New Zealand | Med; ph_pbo | FALL, RFALL | 5056 | 65.9 | 42 | 177 | NR | NR |
| Kim, 2014[94] | Japan | Exerc; qualt | FALL, RFALL, FX | 105 | 77.8 | 100 | 13 | 52 | 100 |
| Kingston, 2001[95] | United Kingdom | Qualt+brisk; uc | FALL | 193 | 71.9 | 100 | 52 | 52 | 100 |
| Korpelainen, 2006[96] | Finland | Exerc; uc | FX, HIP, FRATE, FXRATE | 160 | NR | 100 | 129 | 128 | NR |
| Kovacs, 2013[97] | Hungary | Exerc; uc | FALL | 72 | 68.5;68.3 | 100 | 25 | 26 | NR |
| Lamb, 2018[98] | United Kingdom | Exerc; qualt | FALL, FX, FRATE, FXRATE | 418 | 78.4;76.9* | 36;41* | 16 | 52 | 32 |
| Lee, 2007[99] | Canada | Assist+qualt; uc | FALL | 86 | 79.7 | 72 | 9 | 9 | 100 |
| Lee, 2013[100] | Taiwan | Exerc+envir+assist+qualt+ brisk; qualt+brisk | FALL, FRATE | 616 | 75.7 | 55 | 13 | 52 | 41;29* |

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|---|---|---|---|---|---|---|---|---|---|
| Lehtola, 2000[101] | Finland | Exerc; uc | FALL, FRATE | 131 | 72.3;72.4* | 80 | 26 | 42 | 10;9* |
| Leung, 2014[102] | China | Vibr; uc | FALL, RFALL, FX, FRATE | 710 | 72.9 | 100 | 78 | 78 | NR |
| Li, 2005[103] | United States | Exerc; non-ph_pbo | FALL, RFALL | 256 | 77.5 | 70 | 26 | 26 | NR |
| Li, 2018[104] | United States | Exerc; exerc; non-ph_pbo | FALL, RFALL, FRATE | 670 | 77.7 | 65 | 24 | 24 | 72 |
| Lightbody, 2002[105] | United Kingdom | Exerc+envir+assist+qualt+ hypot+brisk; uc | FALL, FRATE | 348 | 75 | 74 | 4 | 26 | 42 |
| Lips, 1996[106] | The Netherlands | Med; ph_pbo | FX, HIP | 2578 | NR | 74 | 208 | 208 | NR |
| Liu-Ambrose, 2005[107] | Canada | Exerc; exerc; non-ph_pbo | FALL, RFALL, FRATE | 97 | 79.6; 78.9; 79.5* | 100 | 25 | 52 | 16;18;19* |
| Liu-Ambrose, 2008[108] | Canada | Exerc+qualt+brisk; brisk | FALL, RFALL, FRATE | 59 | 82.2 | 69 | 52 | 52 | 100 |
| Logan, 2010[109] | United Kingdom | Exerc+envir+qualt+brisk; uc | FALL, FRATE | 204 | 82.5 | 65 | 6 | 52 | NR |
| Logghe, 2009[110] | The Netherlands | Exerc+qualt; qualt | FALL, FRATE | 269 | 77.2 | 71 | 13 | 52 | 64;60* |
| Lord, 1995[111] | Australia | Exerc; uc | FALL, RFALL | 197 | 71.6 | 100 | 52 | 52 | 28;29* |
| Lord, 2003[112] | Australia | Exerc; non-ph_pbo, uc | FALL, FRATE | 551 | 79.5 | 86 | 52 | 52 | 35;33;34* |
| Lord, 2005[113] | Australia | Exerc+surg+assist+qualt; uc | FALL, RFALL, FRATE | 403 | 80.4 | 66 | 52 | 52 | NR |
| Lurie, 2013[114] | United States | Exerc; exerc | FALL | 64 | 80.0 | 59 | 12 | 12 | NR |
| Luukinen, 2007[115] | Finland | Exerc+qualt+brisk; uc | FALL, FRATE | 437 | 88 | 79 | 69 | 68 | NR |
| MacRae, 1994[116] | United States | Exerc+qualt; qualt | FALL | 59 | 72.4;70.0* | 100 | 52 | 52 | 32;26* |
| Madureira, 2010[117] | Brazil | Exerc; qualt | FALL, FRATE | 66 | 74.0 | 100 | 52 | 52 | NR |
| Mahoney, 2007[118] | United States | Exerc+psych+envir+assist+ qualt+brisk; envir | FRATE | 282 | 79.6;80.3* | 79;78 | NA | 52 | 100 |
| Markle-Reid, 2010[119] | Canada | Qualt+brisk; qualt | FRATE | 109 | NR | 72 | 26 | 26 | NR |
| Matchar, 2017[120] | Singapore | Exerc+envir+assist+ qualt+brisk; qualt | FALL | 354 | 77.8 | 77 | 13 | 36 | 46;37* |
| McKiernan, 2005[121] | United States | Assist+qualt; qualt | FALL, FRATE | 109 | 74.2 | 60 | NR | 14 | 100 |
| McMurdo, 1997[122] | United Kingdom | Exerc; uc | FALL, FX | 118 | 65 | 100 | 104 | 104 | NR |
| McMurdo, 2000[123] | United Kingdom | Exerc+envir+assist+ hypot+brisk; social | FALL, FX, FRATE | 133 | 84 | 81 | 26 | 52 | NR |
| McMurdo, 2009[124] | United Kingdom | Nutr; ph_pbo | FALL | 253 | 81.8 | 61 | 16 | 16 | NR |
| Means, 2005[125] | United States | Exerc; social | FALL | 338 | 73.5 | 57 | 6 | 26 | NR |
| Merom, 2016[126] | Australia | Exerc+qualt; qualt | FALL, FRATE | 530 | 78 | 85 | 52 | 52 | 27;28* |
| Miko, 2018[127] | Hungary | Exerc; uc | FALL, FRATE | 97 | 69.3;69.1* | 100 | 52 | 52 | NR |
| Mikolaizak, 2017[128] | Australia | Exerc+envir+assist+ qualt+brisk; brisk | FRATE | 163 | 83.3 | 64 | 52 | 52 | 70;64* |
| Möller, 2014[129] | Sweden | Exerc+envir+qualt+ brisk; uc | FALL, RFALL, FRATE, FXRATE | 153 | 77.8 | 67 | 52 | 52 | NR |
| Morgan, 2004[130] | United States | Exerc; uc | FALL | 229 | 80.6 | 71 | 8 | 52 | 39;33* |
| Morris, 2008[131] | United States | Exerc; exerc; qualt | FALL, RFALL | 18 | 73.5;74.8; 81.4* | 100 | 8 | 25 | 50 |
| Mott, 2016[132] | United States | Brisk; qualt | FALL, RFALL | 80 | 74.9;76.3* | 77;81* | NA | 26 | NR |
| Newbury, 2001[133] | Australia | Brisk; uc | FALL | 100 | 79.3 | 63 | <1 | 52 | 27; 39* |

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|---|---|---|---|---|---|---|---|---|---|
| Ng, 2015[134] | Singapore | Exerc+psych+nutr; exerc; nutr; psych; ph_pbo | FALL | 246 | 70 | 61 | 24 | 52 | NR |
| Nikolaus, 2003[135] | Germany | Envir+assist+brisk; brisk | RFALL, FX, HIP, FRATE | 360 | NR | 73 | 52 | 52 | NR |
| Nowalk, 2001[136] | United States | Exerc+psych+qualt; exerc+ qualt; exerc+qualt | FALL | 110 | 84.7 | 87 | 89 | 104 | 61 |
| Ohtake, 2013[137] | Japan | Exerc+qualt; qualt | FALL | 182 | 83.6 | 84 | 8 | 9 | 27; 22* |
| Okubo, 2016[138] | Japan | Exerc+social+qualt; exerc+social+qualt | FRATE | 75 | 70.1 | 60;65* | 12 | 61 | 30;18* |
| Oliveira, 2019[139] | Australia | Qualt+brisk; qualt | FALL, FX, FRATE | 114 | 71;72* | 43;50 | 24 | 52 | 17;30* |
| Olsen, 2014[140] | Norway | Exerc+qualt; uc | FALL | 89 | 71.1 | 100 | 13 | 52 | 62;38* |
| Pai, 2014[141] | United States | Exerc; non-ph_pbo | FALL, RFALL, FX | 212 | 73.3 | 28 | NR | 52 | NR |
| Palvanen, 2014[142] | Finland | Exerc+med+surg+nutr+ envir+assist+qualt+brisk; qualt | FALL, FX, FRATE, FXRATE | 1314 | 77.5; 77.7* | 86 | 52 | 52 | NR |
| Pardessus, 2002[143] | France | Envir+qualt; qualt | FALL, FRATE | 60 | 83.2 | 78 | 52 | 52 | NR |
| Park, 2008[144] | Korea | Exerc; uc | FALL | 50 | 68.4 | 100 | 48 | 48 | 20;18* |
| Parry, 2016[145] | United Kingdom | Psych+qualt; uc | FALL, FRATE | 415 | 75.5 | NR | 26 | 26 | NR |
| Patil, 2015[146] | Finland | Exerc; uc | FALL, RFALL, FX, FRATE | 409 | 74.4;74.0* | 100 | 104 | 104 | 100 |
| Peel, 2000[147] | Australia | Envir; non-ph_pbo | FRATE | 195 | 69 | 79 | 52 | 52 | 34 |
| Pekkarinen, 2013[148] | Finland | Exerc+mde+qualt; uc | HIP | 2178 | 65.3 | 100 | 1 | 520 | NR |
| Perry, 2008[149] | Canada | Assist; uc | FALL | 40 | 69 | 48 | 12 | 12 | NR |
| Pérula, 2012[150] | Spain | Exerc+envir+qualt; qualt | FALL, FX | 404 | 76.4 | 53 | 52 | 52 | 33;30* |
| Pighills, 2011[151] | United Kingdom | Envir; uc | FALL, FRATE | 238 | 79 | 67 | 52 | 52 | 100 |
| Pit, 2007[152] | Australia | Qualt+brisk; uc | FALL | 849 | NR | 60 | NR | 52 | 22;29* |
| Porthouse, 2005[153] | United Kingdom | Med; qualt | FALL | 2838 | 77.0;76.7* | 100 | 100 | 100 | 34 |
| Rantz, 2017[154] | United States | Assist; uc | FALL | 171 | 83.6;86.0* | 74;73* | 55;50* | 52 | NR |
| Reinsch, 1992[155] | United States | Exerc+psych; exerc; psych; qualt | FALL, RFALL | 230 | 74.4 | 80 | 52 | 52 | 19;37;26;36* |
| Robertson, 2001[156] | New Zealand | Exerc+qualt; uc | FALL, FRATE | 240 | 80.9 | 100 | 52 | 52 | 36;38* |
| Robson, 2003[157] | Canada | Exerc+qualt+brisk; uc | FALL | 660 | 73 | 81 | 17 | 46;44* | 32;26* |
| Rubenstein, 2000[158] | United States | Exerc; uc | FALL | 59 | 75.5 | 0 | 12 | 12 | NR |
| Rubenstein, 2007[159] | United States | Incont+psych+assist+qualt; uc | FALL | 673 | 74.6;74.3* | 4;3* | NA | 156 | 40;39* |
| Russell, 2010[160] | Australia | Exerc+nutr+envir+assist+ qualt+brisk; qualt+brisk | FALL, FRATE | 712 | 75.4 | 70 | NR | 52 | 100 |
| Ryan, 1996[161] | United States | Qualt; uc | FALL, FRATE | 30 | 78 | 100 | 1 | 12 | NR |
| Sakamoto, 2013[162] | Japan | Exerc; uc | FALL, FX | 1788 | 80.4 | 81 | 26 | 26 | 35;31* |
| Sales, 2017[163] | Australia | Exerc; social | FALL | 48 | 71.4 | 70 | 18 | 52 | 62;63* |
| Salminen, 2009[164] | Finland | Exerc+psych+envir+assist+ qualt+brisk; qualt | FALL, FX, HIP, FRATE | 591 | 72.8 | 84 | 52 | 52 | 100 |
| Sambrook, 2012[165] | Australia | Med; qualt | FALL, FX, FRATE, FXRATE | 602 | 86.4 | 71 | 52 | 52 | 42;40* |
| Sanders, 2010[166] | Australia | Med; ph_pbo | FALL, RFALL, FX, HIP, FRATE, FXRATE | 2256 | 76.1 | 100 | 205 | 154 | NR |
| Sattin, 2005[167] | United States | Exerc; qualt | FALL, RFALL | 311 | 80.9 | 94 | 48 | 48 | 100 |
| Schoene, 2015[168] | Australia | Exerc+qualt; qualt | FALL | 90 | 81.5 | 67 | 16 | 16 | 38;28* |
| Schoon, 2018[169] | The Netherlands | Exerc; uc | FALL, FRATE | 78 | 80.3 | 65 | 24 | 24 | NR |
| Serra-Prat, 2017[170] | Spain | Exerc+nutr; uc | FALL | 133 | 77.9;78.8* | 57 | NR | 52 | NR |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sherrington, 2014[171] | Australia | Exerc+qualt; qualt | FALL, RFALL, FX FRATE, FXRATE | 340 | 81.2 | 74 | 52 | 52 | 72;69* |
| Shigematsu, 2008[172] | Japan | Exerc; exerc | FALL, FRATE | 68 | 69.1 | 63 | 12 | 32 | 26;15* |
| Shigematsu, 2008[173] | Japan | Exerc; exerc | FALL, FRATE | 39 | 69 | 46 | 12 | 60 | NR |
| Shimada, 2004[174] | Japan | Exerc; exerc | FALL, FRATE | 32 | 82.4 | 78 | 26 | 26 | 11;10* |
| Shumway-Cook, 2007[175] | United States | Exerc+qualt+brisk; qualt | FALL, RFALL, FRATE | 453 | 75.6 | 77 | 52 | 52 | NR |
| Siegrist, 2016[176] | Germany | Exerc+qualt; uc | FALL, FRATE | 378 | 78.1 | 75 | 16 | 52 | 54;51* |
| Sihvonen, 2004[177] | Finland | Exerc; uc | FALL, RFALL, FRATE | 27 | 81.3 | 100 | 4 | 52 | 35;29* |
| Skelton, 2005[178] | United Kingdom | Exerc+assist; non-ph_pbo | FALL, FRATE | 81 | 72.8 | 100 | 36 | 50 | 100 |
| Smith, 2007[179] | United Kingdom | Med; ph_pbo | FALL, FX, HIP FRATE, FXRATE | 9440 | 79.1 | 54 | 156 | 156 | NR |
| Smulders, 2010[180] | The Netherlands | Exerc+qualt; uc | FALL, FX, FRATE | 96 | 71 | 94 | 6 | 52 | 100 |
| Spice, 2009[181] | United Kingdom | Exerc+med+envir+assist+ qualt+hypot+brisk; uc | FALL, FX | 505 | 82.2 | 74 | NR | 52 | 100 |
| Stam, 2018[182] | The Netherlands | Exerc+psych+brisk; uc | FALL | 150 | 78.8 | 69 | 52 | 52 | 52;54* |
| Stanmore, 2019[183] | United Kingdom | Exerc; qualt | FALL, RFALL, FRATE | 92 | 77.9;77.8 * | 80;76* | 12 | 12 | 43;58* |
| Steadman, 2003[184] | United Kingdom | Exerc+qualt; exerc+qualt | FALL | 198 | 82.7 | 80 | 6 | 26 | NR |
| Stevens, 2001[185] | Australia | Envir+assist+qualt; non-ph_pbo | FALL, FRATE | 1615 | 76 | 54;52* | NA | 52 | 26;27* |
| Suttanon, 2013[186] | Australia | Exerc+social+qualt; qualt | FALL, FRATE | 40 | 81.9 | 63 | 26 | 26 | 53;19* |
| Suttanon, 2018[187] | Thailand | Exerc+envir+assist; uc | FALL, FRATE | 277 | 72.2;72.9* | 74;73 | 12 | 52 | 20;19* |
| Suzuki, 2004[188] | Japan | Exerc; qualt | FALL, FRATE | 52 | 78.0 | 100 | 26 | 84 | 14;17* |
| Tan, 2018[189] | Malaysia | Exerc+surg+envir+assist+ qualt+hypot+brisk; uc | FALL, FRATE | 268 | 75.3 | 67 | 52 | 52 | 100 |
| Taylor, 2012[190] | New Zealand | Exerc; non-ph_pbo | FALL, RFALL, FRATE | 684 | 74.5 | 73 | 20 | 20 | 60;61* |
| Tchalla, 2013[191] | France | Assist+brisk; brisk | FALL, RFALL | 96 | 86.6 | 77 | 52 | 52 | 74 |
| Thomas, 2018[192] | United States | Nutr; uc | FALL | 265 | 77.3;75.7* | NR | 15 | 15 | NR |
| Tinetti, 1994[193] | United States | Exerc+envir+hypot+brisk; social | FALL, FRATE | 301 | 77.9 | 69 | 26 | 52 | 41;44* |
| Tousignant, 2013[194] | Canada | Exerc+nutr+envir+brisk; exerc+nutr+envir | FALL, FRATE | 152 | 79.9 | 73 | 15 | 52 | NR |
| Trombetti, 2011[195] | Switzerland | Exerc; uc | FALL, RFALL, FRATE | 134 | 75.5 | 96 | 25 | 52 | 56;54* |
| Ueda, 2017[196] | Japan | Exerc+envir+qualt; exerc | FALL | 60 | 75.9 | 68 | 4 | 4 | 100 |
| Uusi-Rasi, 2015[197] | Finland | Med+exerc; ph_pbo+ exerc; Med; ph_pbo; | FRATE, FXRATE | 370 | 74.1;74.8; 74.1;73.8* | 100 | 104 | 104 | 100 |
| van der Meer, 2018[198] | The Netherlands | Brisk; uc | FALL | 136 | 75.7;76.6* | 69;72* | >1 | 12 | NR |
| van Haastregt, 2000[199] | The Netherlands | Psych+envir+brisk; uc | FALL, RFALL | 316 | 77.2 | 66 | 52 | 78 | 61;52* |
| Verrusio, 2017[200] | Italy | Exerc+assist; exerc | FALL | 150 | 64.8 | 47 | 52 | 52 | NR |
| Vetter, 1992[201] | United Kingdom | Exerc+nutr+envir+ qualt+brisk; qualt | FALL, FX | 674 | NR | NR | 208 | 208 | NR |
| Villar, 1998[202] | United Kingdom | Assist; uc | FALL | 141 | NR | 100 | 12 | 12 | NR |
| Vind, 2010[203] | Denmark | Exerc+assist+qualt+brisk; uc | FALL, FX, HIP | 392 | 74.4 | 74 | 13 | 52 | 100 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Vogler, 2009[204] | Australia | Exerc; exerc; social | FALL | 180 | 80 | 79 | 12 | 12 | 68;67;75* |
| von Stengel, 2011[205] | Germany | Exerc+vibr; exerc; non-ph_pbo | FRATE | 141 | 68.5 | 100 | 78 | 78 | NR |
| Voukelatos, 2007[206] | Australia | Exerc+qualt; uc | FALL, RFALL, FRATE | 702 | 69 | 84 | 16 | 26 | 31;36* |
| Voukelatos, 2015[207] | Australia | Exerc+qualt; uc | FALL, RFALL, FRATE | 386 | 73.2 | 74 | 48 | 48 | 23 |
| Wagner, 1994[208] | United States | Exerc+envir+assist+ qualt+brisk; qualt; uc | FALL | 924 | 72.5;72.6; 72.5* | 60;57; 59* | NA | 104 | 35;31;33* |
| Weber, 2008[209] | United States | Qualt+brisk; uc | FALL | 620 | 76.9 | 79 | NR | 64 | NR |
| Weerdesteyn, 2006[210] | The Netherlands | Exerc; uc | FALL, FRATE | 106 | 73.7;73.2; 74.9* | 82;77; 68* | 5 | 24 | 57;60;32* |
| Wesson, 2013[211] | Australia | Exerc+envir+social+ qualt; qualt | FALL, FRATE | 22 | 79.8 | 41 | 12 | 12 | 64;82* |
| Whitehead, 2003[212] | Australia | Exerc+envir+qualt+brisk; uc | FALL | 140 | 77.8 | 71 | 26 | 22 | 100 |
| Whitehead, 2016[213] | United Kingdom | Envir; uc | FALL | 22 | 82.9;82.0* | 73;40* | 24 | 24 | NR |
| Whitehead, 2018[214] | United Kingdom | Envir; uc | FALL, FRATE | 54 | 77 | 58 | 7-19 | 12 | 58;55* |
| Wolf, 2003[215] | United States | Exerc; qualt | FALL, RFALL | 311 | 80.9 | 94 | 48 | 48 | NR |
| Woo, 2007[216] | China | Exerc; exerc; uc | FALL | 180 | 68.9 | 50 | 52 | 52 | NR |
| Yokoi, 2015[217] | Japan | Exerc; uc | FALL | 105 | 80.2;78.5* | 65;56* | 26 | 52 | NR |
| Zieschang, 2017[218] | Germany | Exerc; non-ph_pbo | FALL, RFALL, FRATE | 96 | 82.1;82.2* | 73;75* | 12 | 52 | 58;64* |
| Zijlstra, 2009[219] | The Netherlands | Exerc+psych+qualt; uc | FALL, RFALL, FRATE | 540 | 77.9 | 72 | 8 | 60 | 56;55* |
| Zijlstra, 2012[220] | The Netherlands | Psych; uc | FALL, RFALL, FRATE | 540 | 77.9;77.8* | 73;71* | 8 | 54 | 54;56* |

[a] Citations correspond to the references of included studies

[b] Abbreviations: **exerc**, exercise; **med**, medication; **surg**, surgery; **incont**, management of urinary incontinence; **nutr**, fluid or nutrition therapy; **psych**, psychological interventions; **envir**, environmental assessment and modifications; **assist**, assistive technology; **social**, social engagement; **qualt**, quality improvement strategies; **hypot**, management of orthostatic hypotension; **brisk**, basic falls risk assessment; **vibr**, whole-body vibration; **chiro**, chiropractic care; **uc**, usual care; **ph_pbo**, pharmacological placebo; **non-ph_pbo**, non-pharmacological placebo.

[c] Outcomes abbreviations:

FALL = Number of fallers, FX = Number of fractures, RFALL = Number of repeated fallers, HIP = Number of hip fractures

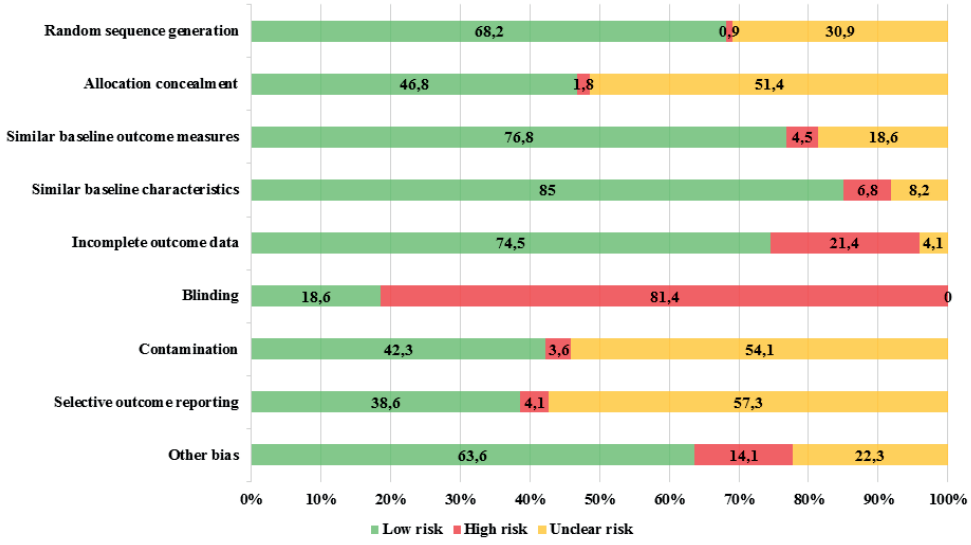
FRATE = Falls rate, FXRATE = Fracture rate

[d] Percentage of participants who suffered a fall in the preceding 12 months

* Data reported per study arm

NR = not reported, NA = not applicable

**Supplementary Appendix S2.** Aggregate and individual risk of bias results




**Supplementary Figure S1.** Aggregate risk of bias results according to the Effective Practice and Organisation of Care (EPOC) version of Cochrane's Risk of Bias tool (n = 220 studies)

**Supplementary Table S2.** Risk of bias assessment of the 220 included studies

| First author, year[a] | Random sequence generation | Allocation concealment | Similar baseline outcome measures | Similar baseline characteristics | Incomplete outcome data | Blinding | Contamination | Selective outcome reporting | Other bias |
|---|---|---|---|---|---|---|---|---|---|
| Aloia, 2019[1] | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk | Unclear risk |
| Ansai, 2016[2] | Low risk | Low risk | High risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Unclear risk |
| Arantes, 2015[3] | Low risk | Unclear risk | High risk | Low risk | Low risk | Low risk | Low risk | High risk | Low risk |
| Arkkukangas, 2019[4] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | High risk | Low risk |
| Ashari, 2016[5] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk |
| Ballard, 2004[6] | Low risk | Unclear risk | Low risk | Unclear risk | Low risk | Low risk | Low risk | Unclear risk | Low risk |
| Barker, 2016[7] | Low risk | Low risk | Low risk | Low risk | High risk | High risk | High risk | Low risk | Low risk |
| Barnett, 2003[8] | Unclear risk | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Low risk |
| Barr, 2005[9] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Beck, 2010[10] | Low risk | Unclear risk | Unclear risk | Unclear risk | Low risk | High risk | Unclear risk | Unclear risk | High risk |
| Beck 2016[11] | Unclear risk | Low risk | Unclear risk | High risk | Unclear risk | High risk | Low risk | Unclear risk | Low risk |
| Beling, 2009[12] | Unclear risk | Unclear risk | High risk | Low risk | High risk | High risk | Low risk | Unclear risk | Low risk |
| Bernardelli, 2019[13] | Low risk | Low risk | Unclear risk | Low risk | High risk | High risk | Low risk | Unclear risk | Low risk |
| Bernocchi, 2019[14] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Bischoff-Ferrari, 2006[15] | Unclear risk | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | Unclear risk | Unclear risk | Low risk |
| Blalock, 2010[16] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | High risk | Low risk |
| Boongird, 2017[17] | Low risk | Low risk | Unclear risk | Low risk | Unclear risk | High risk | Low risk | Low risk | Low risk |
| Boyé, 2016[18] | low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk |
| Brown, 2002[19] | Low risk | Unclear risk | Low risk | Unclear risk | Low risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Buchner, 1997[20] | Unclear risk | Unclear risk | Low risk | Low risk | High risk | High risk | Low risk | Unclear risk | Low risk |
| Bunout, 2005[21] | Low risk | Unclear risk | Unclear risk | Unclear risk | High risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Cameron, 2003[22] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Unclear risk |
| Cameron, 2011[23] | Low risk | Low risk | Unclear risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Carpenter, 1990[24] | Low risk | Unclear risk | Low risk | Low risk | High risk | High risk | Unclear risk | Unclear risk | Low risk |
| Chapuy, 2002[25] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | Low risk | Unclear risk | Unclear risk | Unclear risk |
| Choi, 2005[26] | Low risk | Unclear risk | Unclear risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Unclear risk |
| Chu, 2017[27] | Low risk | Low risk | Unclear risk | Low risk | Low risk | Low risk | Unclear risk | Unclear risk | Low risk |
| Ciaschini, 2009[28] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Unclear risk |
| Clemson, 2004[29] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Clemson, 2010[30] | Low risk | Unclear risk | Low risk | Low risk | High risk | High risk | Unclear risk | Unclear risk | High risk |
| Clemson, 2012[31] | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | Unclear risk | Low risk | Low risk |
| Close, 1999[32] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Cohen, 2015[33] | Unclear risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Coleman, 1999[34] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Low risk |
| Conroy, 2010[35] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Cornillon, 2002[36] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Low risk |
| Cumming, 1999[37] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Cumming, 2007[38] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | High risk | High risk | Unclear risk | Low risk |
| Dadgari, 2016[39] | Low risk | Low risk | Low risk | Low risk | High risk | High risk | Low risk | Low risk | Low risk |
| Dangour, 2011[40] | Unclear risk | Low risk | Unclear risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk |
| Dapp, 2011[41] | Unclear risk | Low risk | Unclear risk | Low risk | Low risk | High risk | High risk | Low risk | Unclear risk |
| Davison, 2005[42] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | High risk | Unclear risk | Low risk |
| Day, 2015[43] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear risk | Unclear risk | Low risk |
| De Vries, 2010[44] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Unclear risk |
| Dhesi, 2004[45] | Low risk | Unclear risk | Low risk | Low risk | Low risk | Low risk | Unclear risk | Unclear risk | Low risk |
| Dorresteijn, 2016[46] | Low risk | High risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk |
| Dukas, 2004[47] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear risk | Low risk |
| Dyer, 2004[48] | Low risk | Low risk | Low risk | Unclear risk | Low risk | High risk | Low risk | Unclear risk | Low risk |
| Ebrahim, 1997[49] | Low risk | Low risk | Low risk | Low risk | High risk | High risk | Unclear risk | Unclear risk | Low risk |
| El-Khoury, 2015[50] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Elley, 2008[51] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk |
| Fabacher, 1994[52] | Low risk | Low risk | Low risk | Low risk | High risk | High risk | Low risk | Unclear risk | Low risk |
| Fairhall, 2014[53] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Ferrer, 2014[54] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Fitzharris, 2010[55] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Fox, 2010[56] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Unclear risk |
| Freiberger, 2012[57] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Gallagher, 2001[58] | Unclear risk | Unclear risk | Unclear risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Gawler, 2016[59] | Low risk | Low risk | Low risk | Low risk | High risk | High risk | Low risk | Low risk | Low risk |
| Giangregorio, 2018[60] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Gianoudis, 2014[61] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Gill, 2016[62] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Giusti, 2013[63] | Low risk | Low risk | Unclear risk | Low risk | Low risk | Low risk | Low risk | Unclear risk | High risk |
| Glendenning, 2012[64] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk |
| Grahn Kronhed, 2009[65] | Unclear risk | Unclear risk | High risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Grant, 2005[66] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Gschwind, 2015[67] | Low risk | Unclear risk | Low risk | High risk | Low risk | High risk | Unclear risk | Low risk | Unclear risk |
| Guse, 2015[68] | Unclear risk | Unclear risk | High risk | Low risk | Low risk | High risk | Low risk | Low risk | Unclear risk |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Haines, 2009[69] | Low risk | Low risk | High risk | High risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Halvarsson, 2013[70] | Unclear risk | Unclear risk | Low risk | High risk | High risk | High risk | Unclear risk | Unclear risk | Low risk |
| Harper, 2017[71] | Low risk | High risk | Low risk | Low risk | Low risk | High risk | High risk | Low risk | High risk |
| Harwood, 2004[72] | Low risk | Low risk | Low risk | Low risk | High risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Hendriks, 2008[73] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Low risk |
| Hill, 2013[74] | Low risk | Low risk | Low risk | Unclear risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Hill, 2019[75] | Low risk | Low risk | Low risk | Low risk | Unclear risk | Low risk | Low risk | Low risk | Unclear risk |
| Hin, 2017[76] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Hogan, 2001[77] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Holt, 2016[78] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | High risk | Low risk |
| Hornbrook, 1994[79] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Low risk |
| Houston, 2015[80] | Low risk | Unclear risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Huang, 1998[81] | Unclear risk | Unclear risk | Low risk | Low risk | Unclear risk | High risk | Low risk | Unclear risk | Unclear risk |
| Huang, 2010[82] | Unclear risk | Unclear risk | High risk | High risk | High risk | High risk | Low risk | Unclear risk | Unclear risk |
| Huang, 2011[83] | Low risk | Low risk | Low risk | High risk | Low risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Imhof, 2012[84] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Iwamoto, 2009[85] | Unclear risk | Unclear risk | Low risk | High risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Kamei, 2015[86] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Low risk |
| Kamide, 2009[87] | Low risk | Unclear risk | Low risk | Low risk | High risk | High risk | Unclear risk | Unclear risk | Low risk |
| Karinkanta, 2015[88] | Low risk | Unclear risk | Unclear risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Kärkkäinen, 2010[89] | Unclear risk | Unclear risk | Unclear risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Kemmler, 2010[90] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Unclear risk |
| Kerse, 2005[91] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Low risk |
| Kerse, 2008[92] | Low risk | Unclear risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk | Low risk |
| Khaw, 2017[93] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Kim, 2014[94] | Low risk | Unclear risk | Low risk | Unclear risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Kingston, 2001[95] | Unclear risk | Unclear risk | Unclear risk | Unclear risk | High risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Korpelainen, 2006[96] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Kovacs, 2013[97] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Lamb, 2018[98] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | Unclear risk |
| Lee, 2007[99] | Low risk | Unclear risk | Low risk | Low risk | High risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Lee, 2013[100] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Lehtola, 2000[101] | Unclear risk | Unclear risk | Low risk | Unclear risk | Low risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Leung, 2014[102] | Unclear risk | Low risk | Unclear risk | Low risk | Low risk | High risk | Low risk | High risk | Low risk |
| Li, 2005[103] | Low risk | Unclear risk | Low risk | Low risk | Low risk | Low risk | Unclear risk | Unclear risk | Unclear risk |
| Li, 2018[104] | Low risk | Unclear risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Lightbody, 2002[105] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Lips, 1996[106] | Low risk | Low risk | Unclear risk | Low risk | Low risk | Low risk | Unclear risk | Unclear risk | Unclear risk |
| Liu-Ambrose, 2005[107] | Unclear risk | Unclear risk | High risk | Low risk | Low risk | Low risk | Low risk | Unclear risk | Low risk |
| Liu-Ambrose, 2008[108] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Logan, 2010[109] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Logghe, 2009[110] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Lord, 1995[111] | Unclear risk | Unclear risk | Low risk | Low risk | High risk | High risk | Unclear risk | Unclear risk | Low risk |
| Lord, 2003[112] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Unclear risk |
| Lord, 2005[113] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Lurie, 2013[114] | Unclear risk | Low risk | Unclear risk | High risk | High risk | Low risk | Unclear risk | Low risk | High risk |
| Luukinen, 2007[115] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| MacRae, 1994[116] | Unclear risk | Unclear risk | Unclear risk | Unclear risk | Unclear risk | High risk | Low risk | Unclear risk | Low risk |
| Madureira, 2010[117] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Mahoney, 2007[118] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Low risk |
| Markle-Reid, 2010[119] | Low risk | Low risk | Low risk | Low risk | High risk | High risk | Unclear risk | Low risk | Unclear risk |
| Matchar, 2017[120] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk |
| McKiernan, 2005[121] | Unclear risk | Unclear risk | Unclear risk | Unclear risk | Low risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| McMurdo, 1997[122] | Unclear risk | Unclear risk | Low risk | Low risk | High risk | High risk | Unclear risk | Unclear risk | High risk |
| McMurdo, 2000[123] | Unclear risk | Unclear risk | Unclear risk | Low risk | Low risk | High risk | Low risk | Unclear risk | High risk |
| McMurdo, 2009[124] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear risk | Low risk | Low risk |
| Means, 2005[125] | Low risk | Unclear risk | Low risk | Low risk | High risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Merom, 2016[126] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk |
| Miko, 2018[127] | Unclear risk | Unclear risk | Unclear risk | Unclear risk | Low risk | High risk | Low risk | Unclear risk | Low risk |
| Mikolaizak, 2017[128] | Low risk | Low risk | Low risk | Low risk | High risk | High risk | Low risk | Low risk | Low risk |
| Möller, 2014[129] | Unclear risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | High risk |
| Morgan, 2004[130] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | High risk |
| Morris, 2008[131] | Unclear risk | Unclear risk | Unclear risk | Unclear risk | High risk | High risk | Unclear risk | Unclear risk | High risk |
| Mott, 2016[132] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | High risk |
| Newbury, 2001[133] | Low risk | Unclear risk | Unclear risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Ng, 2015[134] | Low risk | Low risk | Unclear risk | High risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Nikolaus, 2003[135] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Nowalk, 2001[136] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | Low risk | Unclear risk | Unclear risk | Low risk |
| Ohtake, 2013[137] | Unclear risk | Unclear risk | Low risk | Low risk | High risk | High risk | Low risk | Unclear risk | Low risk |
| Okubo, 2016[138] | Low risk | Unclear risk | High risk | Low risk | Low risk | Low risk | Low risk | Unclear risk | Low risk |
| Oliveira, 2019[139] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk |
| Olsen, 2014[140] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |

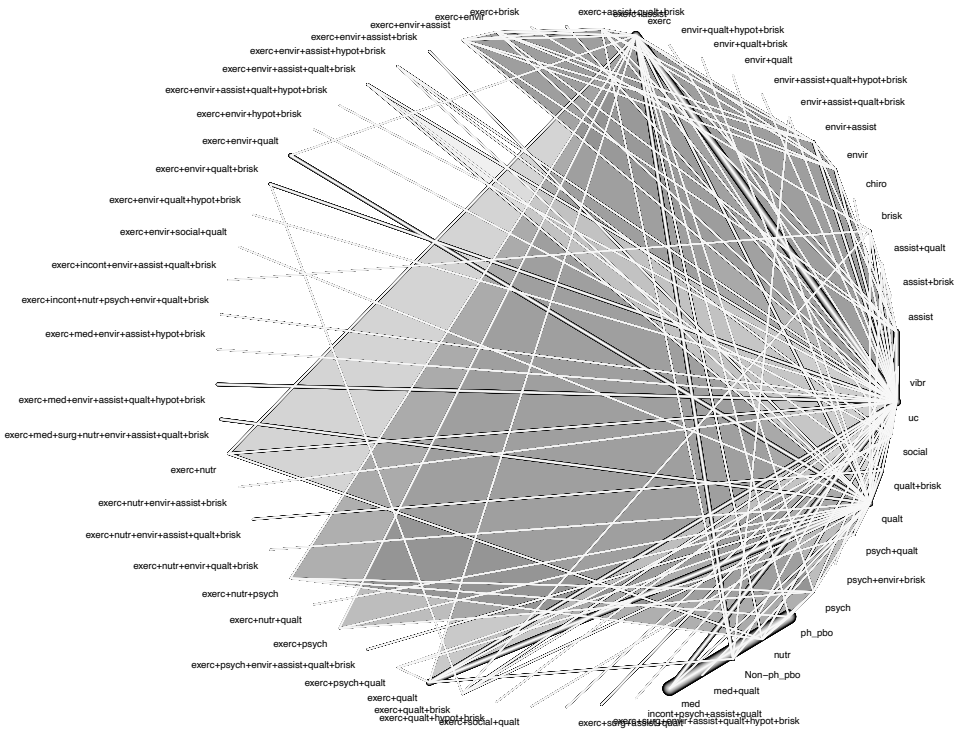
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Pai, 2014[141] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | Low risk | Unclear risk | High risk | Unclear risk |
| Palvanen, 2014[142] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Pardessus, 2002[143] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Park, 2008[144] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Parry, 2016[145] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Patil, 2015[146] | Unclear risk | Unclear risk | Unclear risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Peel, 2000[147] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear risk | Low risk |
| Pekkarinen, 2013[148] | Unclear risk | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Unclear risk |
| Perry, 2008[149] | Unclear risk | Unclear risk | Unclear risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | High risk |
| Pérula, 2012[150] | Low risk | Low risk | Low risk | High risk | Low risk | High risk | Low risk | Low risk | High risk |
| Pighills, 2011[151] | Low risk | Low risk | Low risk | High risk | Low risk | High risk | Unclear risk | Low risk | High risk |
| Pit, 2007[152] | Low risk | Unclear risk | Low risk | Low risk | High risk | High risk | Low risk | Low risk | Low risk |
| Porthouse, 2005[153] | Low risk | Low risk | Low risk | Low risk | Unclear risk | High risk | Low risk | Unclear risk | High risk |
| Rantz, 2017[154] | Unclear risk | Unclear risk | Unclear risk | Unclear risk | Unclear risk | High risk | Low risk | Unclear risk | High risk |
| Reinsch, 1992[155] | Unclear risk | Unclear risk | Low risk | Low risk | High risk | High risk | Low risk | Unclear risk | High risk |
| Robertson, 2001[156] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Low risk |
| Robson, 2003[157] | Unclear risk | Unclear risk | Low risk | Low risk | High risk | High risk | Low risk | Unclear risk | Unclear risk |
| Rubenstein, 2000[158] | Low risk | Unclear risk | Low risk | Low risk | Unclear risk | High risk | Unclear risk | Unclear risk | Low risk |
| Rubenstein, 2007[159] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | High risk |
| Russell, 2010[160] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | High risk | Low risk | Low risk |
| Ryan, 1996[161] | Unclear risk | Unclear risk | High risk | Unclear risk | Low risk | High risk | Unclear risk | Unclear risk | High risk |
| Sakamoto, 2013[162] | Low risk | Low risk | Low risk | Low risk | High risk | High risk | Low risk | Unclear risk | High risk |
| Sales, 2017[163] | Low risk | High risk | Low risk | High risk | High risk | High risk | Low risk | Low risk | Low risk |
| Salminen, 2009[164] | Unclear risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Sambrook, 2012[165] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk |
| Sanders, 2010[166] | Low risk | Low risk | Unclear risk | Low risk | Low risk | Low risk | Unclear risk | Low risk | Low risk |
| Sattin, 2005[167] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Low risk |
| Schoene, 2015[168] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | High risk | Low risk |
| Schoon, 2018[169] | Low risk | Low risk | Unclear risk | Low risk | High risk | High risk | Low risk | Low risk | High risk |
| Serra-Prat, 2017[170] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | High risk | Low risk | Low risk |
| Sherrington, 2014[171] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Shigematsu, 2008[172] | Low risk | Unclear risk | Low risk | Low risk | Low risk | Low risk | Unclear risk | Unclear risk | Unclear risk |
| Shigematsu, 2008[173] | Unclear risk | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | Unclear risk | Unclear risk | High risk |
| Shimada, 2004[174] | Unclear risk | Unclear risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Unclear risk | High risk |
| Shumway-Cook, 2007[175] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Siegrist, 2016[176] | Low risk | Low risk | Low risk | High risk | High risk | High risk | Low risk | Low risk | Low risk |
| Sihvonen, 2004[177] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | High risk |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Skelton, 2005[178] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | Low risk | Unclear risk | Unclear risk | Low risk |
| Smith, 2007[179] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear risk | Unclear risk | Unclear risk |
| Smulders, 2010[180] | Unclear risk | Low risk | Unclear risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Spice, 2009[181] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk |
| Stam, 2018[182] | Low risk | Low risk | Low risk | Low risk | High risk | High risk | Low risk | Low risk | Low risk |
| Stanmore, 2019[183] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk |
| Steadman, 2003[184] | Low risk | High risk | Low risk | Low risk | Low risk | Low risk | Unclear risk | Unclear risk | Low risk |
| Stevens, 2001[185] | High risk | Low risk | Low risk | Unclear risk | Low risk | Low risk | Low risk | Unclear risk | High risk |
| Suttanon, 2013[186] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | High risk |
| Suttanon, 2018[187] | Low risk | Low risk | Low risk | Low risk | High risk | High risk | Low risk | Unclear risk | Low risk |
| Suzuki, 2004[188] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Tan, 2018[189] | Low risk | Low risk | Low risk | Low risk | High risk | High risk | Low risk | Low risk | Low risk |
| Taylor, 2012[190] | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Low risk | Low risk |
| Tchalla, 2013[191] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Thomas, 2018[192] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk |
| Tinetti, 1994[193] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | High risk |
| Tousignant, 2013[194] | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Low risk | Low risk |
| Trombetti, 2011[195] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Ueda, 2017[196] | Low risk | Low risk | Unclear risk | Low risk | High risk | High risk | Low risk | Unclear risk | Unclear risk |
| Uusi-Rasi, 2015[197] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| van der Meer, 2018[198] | Low risk | Low risk | Unclear risk | Low risk | Low risk | High risk | High risk | Low risk | Low risk |
| van Haastregt, 2000[199] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Verrusio, 2017[200] | Low risk | Unclear risk | Unclear risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Vetter, 1992[201] | Low risk | Unclear risk | Low risk | Unclear risk | Low risk | High risk | Low risk | Unclear risk | Unclear risk |
| Villar, 1998[202] | Unclear risk | Unclear risk | Unclear risk | Unclear risk | High risk | High risk | Unclear risk | Unclear risk | Unclear risk |
| Vind, 2010[203] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Vogler, 2009[204] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | High risk | Low risk |
| von Stengel, 2011[205] | Low risk | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | Unclear risk | Unclear risk | Low risk |
| Voukelatos, 2007[206] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Voukelatos, 2015[207] | Low risk | Low risk | Low risk | Low risk | High risk | High risk | Unclear risk | Low risk | Low risk |
| Wagner, 1994[208] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | High risk |
| Weber, 2008[209] | Unclear risk | Unclear risk | Low risk | Low risk | Unclear risk | High risk | Low risk | Unclear risk | High risk |
| Weerdesteyn, 2006[210] | High risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Low risk |
| Wesson, 2013[211] | Low risk | Low risk | Unclear risk | Low risk | Low risk | High risk | Unclear risk | Low risk | High |
| Whitehead, 2003[212] | Unclear risk | Low risk | Low risk | Low risk | High risk | High risk | Unclear risk | Unclear risk | Low risk |
| Whitehead, 2016[213] | Low risk | Low risk | Unclear risk | High risk | High risk | High risk | Low risk | Low risk | Low risk |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Whitehead, 2018[214] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | High risk |
| Wolf, 2003[215] | Unclear risk | Unclear risk | Unclear risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Low risk |
| Woo, 2007[216] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Unclear risk | Low risk |
| Yokoi, 2015[217] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Unclear risk | Low risk |
| Zieschang, 2017[218] | Low risk | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk | Low risk |
| Zijlstra, 2009[219] | Low risk | Unclear risk | Low risk | Low risk | Low risk | High risk | Unclear risk | Low risk | Low risk |
| Zijlstra, 2012[220] | Unclear risk | Unclear risk | Low risk | Low risk | High risk | High risk | Low risk | High risk | Low risk |

[a] Citations correspond to the references of included studies

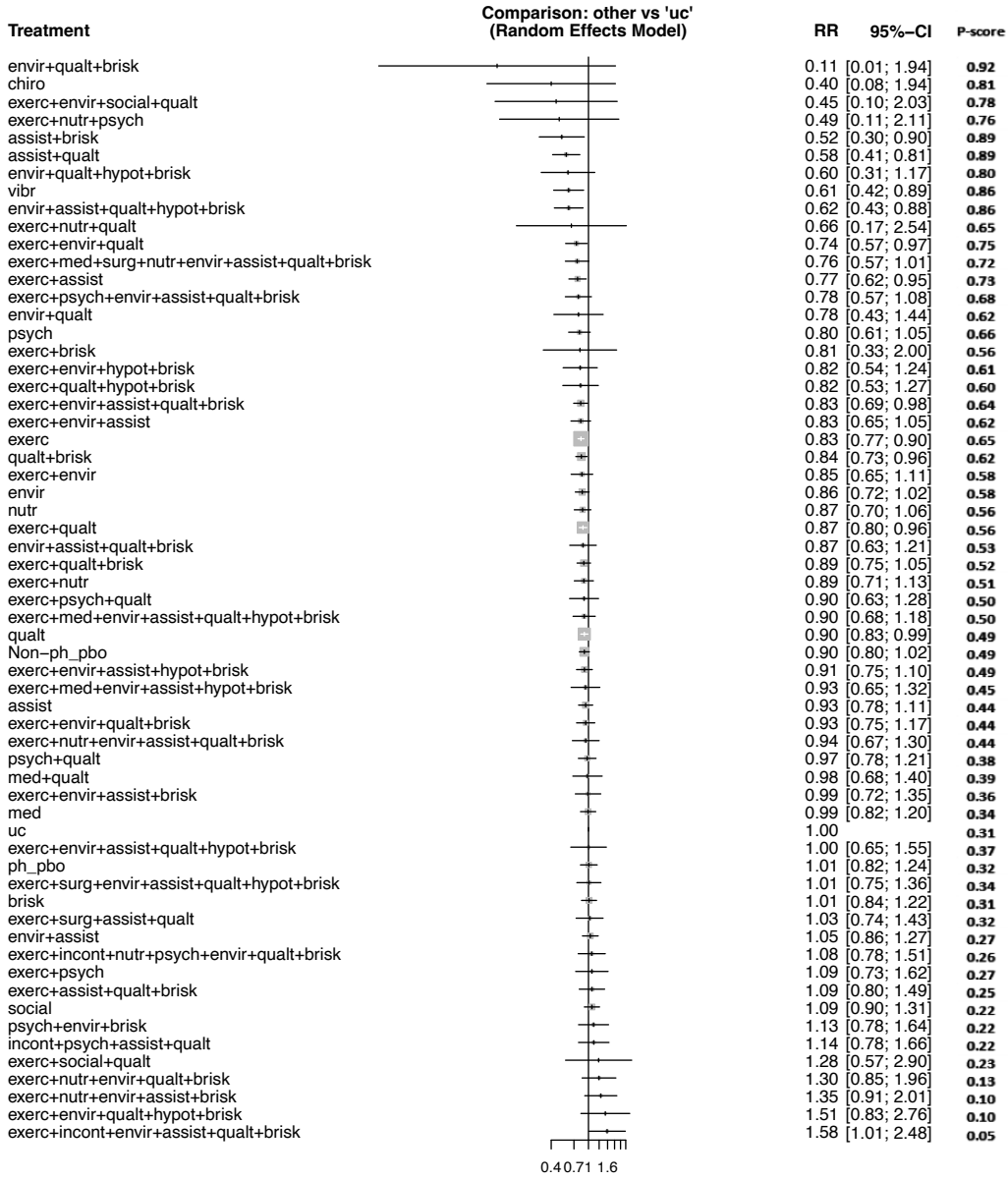
**Supplementary Appendix S3.** Additional results for number of fallers




Abbreviations: **exerc**, exercise; **med**, medication; **surg**, surgery; **incont**, management of urinary incontinence; **nutr**, fluid or nutrition therapy; **psych**, psychological interventions; **envir**, environmental assessment and modifications; **assist**, assistive technology; **social**, social engagement; **qualt**, quality improvement strategies; **hypot**, management of orthostatic hypotension; **brisk**, basic falls risk assessment; **vibr**, whole-body vibration; **chiro**, chiropractic care; **uc**, usual care; **ph_pbo**, pharmacological placebo; **non-ph_pbo**, non-pharmacological placebo.

A network plot provides an overview of the interventions investigated in all included randomized control trials. Interventions connected by a line were directly compared in one or more studies (direct evidence), e.g. exercise + nutrition versus usual care. Each node represents an intervention addressed in the included studies. The nodes are sized according to the number of participants who have received this intervention. The thickness of the line is according to the number of studies addressing this comparison.

**Supplementary Figure S2.** Connected network plot for number of fallers including 189 studies and 61 interventions




Abbreviations: **exerc**, exercise; **med**, medication; **surg**, surgery; **incont**, management of urinary incontinence; **nutr**, fluid or nutrition therapy; **psych**, psychological interventions; **envir**, environmental assessment and modifications; **assist**, assistive technology; **social**, social engagement; **qualt**, quality improvement strategies; **hypot**, management of orthostatic hypotension; **brisk**, basic falls risk assessment; **vibr**, whole-body vibration; **chiro**, chiropractic care; **uc**, usual care; **ph_pbo**, pharmacological placebo; **non-ph_pbo**, non-pharmacological placebo.

The boxes and error bars represent the risk ratios and its 95% confidence interval.

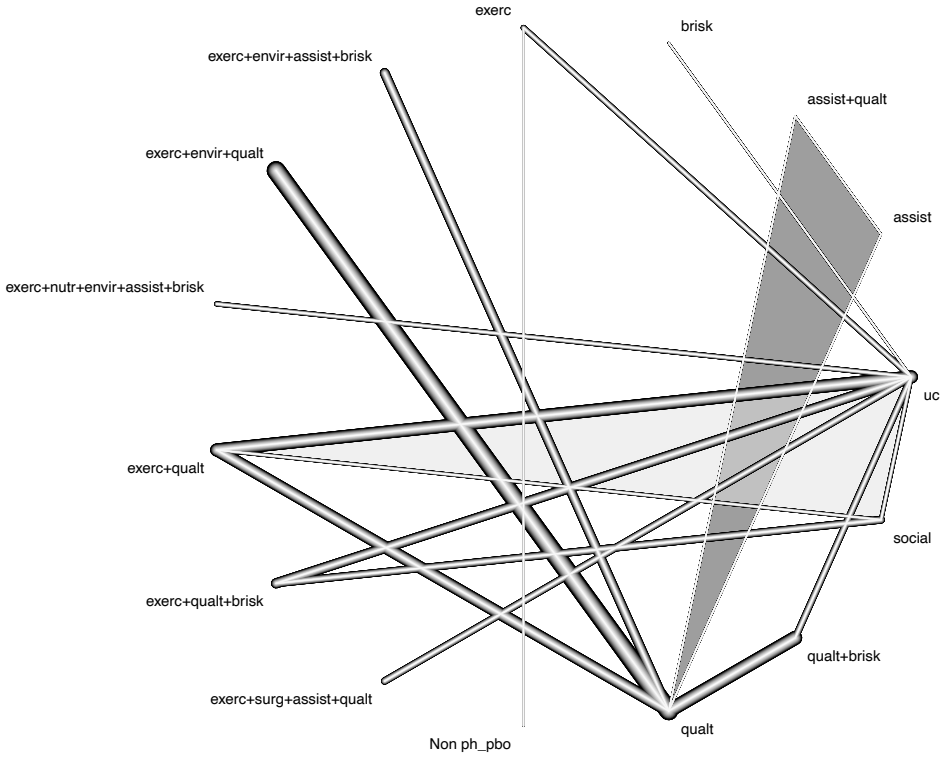
**Supplementary Figure S3.** Summary risk ratios (RR) with 95% confidence intervals (95%-CI) and P-scores resulting from the network meta-analysis for every intervention consisting of one or more components versus usual care for the outcome number of fallers

**Supplementary Table S3.** Risk ratios with 95% confidence intervals (95% CI) resulting from the component network meta-analysis for every intervention component versus usual care for the outcome number of fallers

| Component | Risk ratio | 95% CI |
|---|---|---|
| assist | 0.98 | 0.90-1.06 |
| brisk | 1.03 | 0.94-1.12 |
| chiro | 0.40 | 0.08-1.95 |
| envir | 1.01 | 0.92-1.11 |
| vibr | 0.61 | 0.42-0.90 |
| exerc | 0.92 | 0.88-0.97 |
| nutr | 1.02 | 0.90-1.16 |
| med | 1.00 | 0.88-1.15 |
| hypot | 0.97 | 0.84-1.12 |
| incont | 1.39 | 1.08-1.79 |
| non_ph_pbo | 0.98 | 0.87-1.11 |
| ph_pbo | 1.03 | 0.88-1.22 |
| psych | 0.96 | 0.84-1.09 |
| qualt | 0.94 | 0.89-1.01 |
| social | 1.14 | 0.97-1.34 |
| surg | 1.06 | 0.86-1.31 |

Abbreviations: **exerc**, exercise; **med**, medication; **surg**, surgery; **incont**, management of urinary incontinence; **nutr**, fluid or nutrition therapy; **psych**, psychological interventions; **envir**, environmental assessment and modifications; **assist**, assistive technology; **social**, social engagement; **qualt**, quality improvement strategies; **hypot**, management of orthostatic hypotension; **brisk**, basic falls risk assessment; **vibr**, whole-body vibration; **chiro**, chiropractic care; **ph_pbo**, pharmacological placebo; **non-ph_pbo**, non-pharmacological placebo.

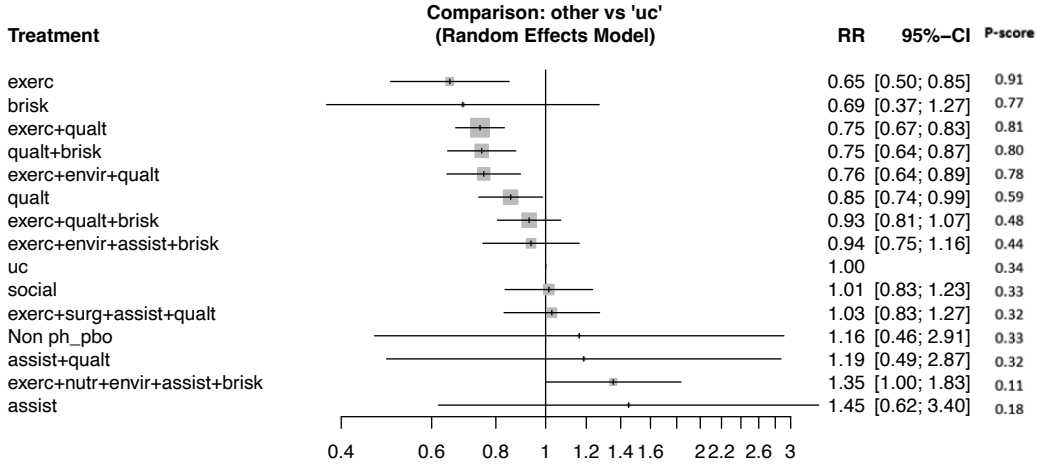
**Supplementary Appendix S4.** Additional results for number of fallers, subgroup age 75+




Abbreviations: **exerc**, exercise; **surg**, surgery; **nutr**, fluid or nutrition therapy; **envir**, environmental assessment and modifications; **assist**, assistive technology; **social**, social engagement; **qualt**, quality improvement strategies; **brisk**, basic falls risk assessment; **uc**, usual care; **non-ph_pbo**, non-pharmacological placebo.

A network plot provides an overview of the interventions investigated in all included randomized control trials. Interventions connected by a line were directly compared in one or more studies (direct evidence), e.g. exercise + nutrition versus usual care. Each node represents an intervention addressed in the included studies. The nodes are sized according to the number of participants who have received this intervention. The thickness of the line is according to the number of studies addressing this comparison.

**Supplementary Figure S4.** Network plot for number of fallers, subgroup age 75+




Abbreviations: **exerc**, exercise; **surg**, surgery; **nutr**, fluid or nutrition therapy; **envir**, environmental assessment and modifications; **assist**, assistive technology; **social**, social engagement; **qualt**, quality improvement strategies; **brisk**, basic falls risk assessment; **uc**, usual care; **non-ph_pbo**, non-pharmacological placebo.

The boxes and error bars represent the risk ratios and its 95% confidence interval.

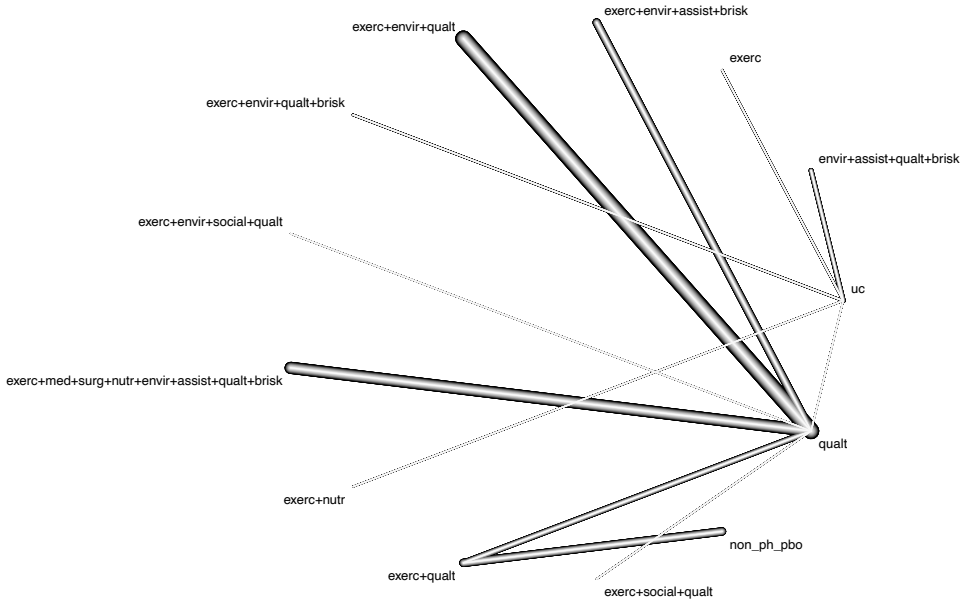
**Supplementary Figure S5.** Summary risk ratios (RR) with 95% confidence intervals (95%-CI) and P-scores resulting from the network meta-analysis for every intervention consisting of one or more components versus usual care for the outcome number of fallers, subgroup age 75+

**Supplementary Table S4.** Risk ratios with 95% confidence intervals (95% CI) resulting from the component network meta-analysis for every intervention component versus usual care for the outcome number of fallers, subgroup age 75+

| Component | Risk ratio | 95% CI |
|---|---|---|
| assist | 1.31 | 0.86-1.99 |
| brisk | 0.93 | 0.79-1.09 |
| envir | 1.04 | 0.79-1.36 |
| exerc | 0.85 | 0.72-1.00 |
| nutr | 1.27 | 0.78-2.06 |
| med | 1.00 | 0.92-1.08 |
| non_ph_pbo | 1.51 | 0.60-3.78 |
| ph_pbo | 1.00 | 0.93-1.09 |
| qualt | 0.96 | 0.78-1.17 |
| social | 0.90 | 0.70-1.16 |
| surg | 0.97 | 0.54-1.75 |

Abbreviations: **exerc**, exercise; **med**, medication; **surg**, surgery; **nutr**, fluid or nutrition therapy; **envir**, environmental assessment and modifications; **assist**, assistive technology; **social**, social engagement; **qualt**, quality improvement strategies; **brisk**, basic falls risk assessment; **uc**, usual care; **ph_pbo**, pharmacological placebo**; non-ph_pbo**, non-pharmacological placebo

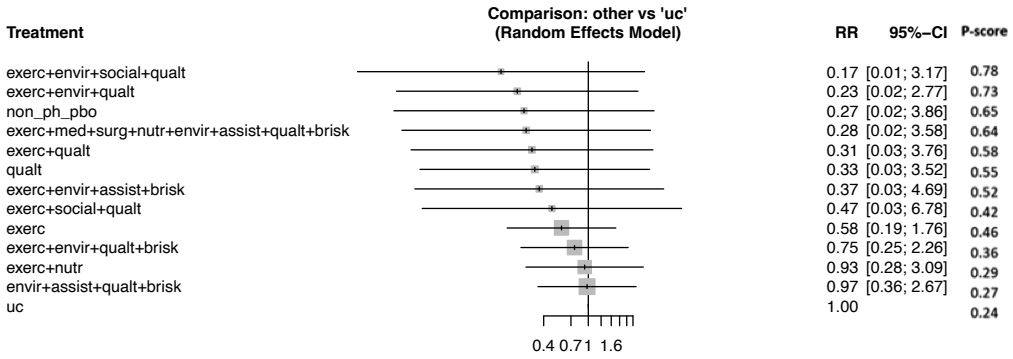
**Supplementary Appendix S5.** Additional results for number of fallers, subgroup multimorbidity




Abbreviations: **exerc**, exercise; **med**, medication; **surg**, surgery; **nutr**, fluid or nutrition therapy; **envir**, environmental assessment and modifications; **assist**, assistive technology; **social**, social engagement; **qualt**, quality improvement strategies; **brisk**, basic falls risk assessment; **uc**, usual care; **non-ph_pbo**, non-pharmacological placebo.

A network plot provides an overview of the interventions investigated in all included randomized control trials. Interventions connected by a line were directly compared in one or more studies (direct evidence), e.g. exercise + nutrition versus usual care. Each node represents an intervention addressed in the included studies. The nodes are sized according to the number of participants who have received this intervention. The thickness of the line is according to the number of studies addressing this comparison.

**Supplementary Figure S6.** Network plot for number of fallers, subgroup multimorbidity




Abbreviations: **exerc**, exercise; **med**, medication; **surg**, surgery; **nutr**, fluid or nutrition therapy; **envir**, environmental assessment and modifications; **assist**, assistive technology; **social**, social engagement; **qualt**, quality improvement strategies; **brisk**, basic falls risk assessment; **uc**, usual care; **non-ph_pbo**, non-pharmacological placebo.

The boxes and error bars represent the risk ratios and its 95% confidence interval.

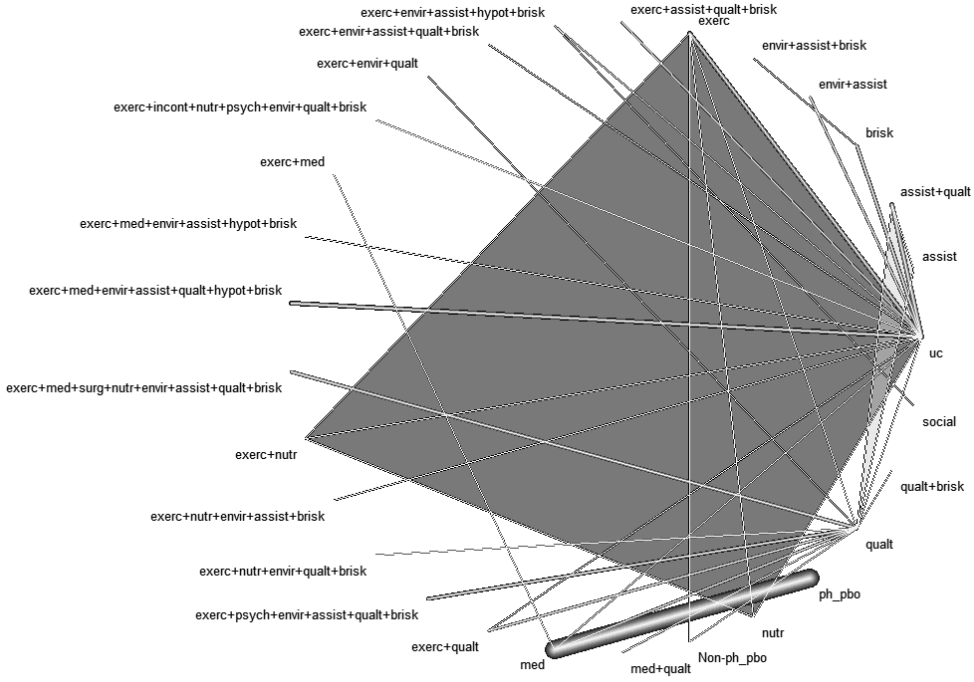
**Supplementary Figure S7.** Summary risk ratios (RR) with 95% confidence intervals (95%-CI) and P-scores resulting from the network meta-analysis for every intervention consisting of one or more components versus usual care for the outcome number of fallers, subgroup multimorbidity

**Supplementary Table S5.** Risk ratios with 95% confidence intervals (95% CI) resulting from the component network meta-analysis for every intervention component versus usual care for the outcome number of fallers, subgroup multimorbidity

| Component | Risk ratio | 95% CI |
|---|---|---|
| assist | 1.00 | 0.21-4.74 |
| brisk | 1.48 | 0.33-6.55 |
| envir | 0.76 | 0.32-1.85 |
| exerc | 0.83 | 0.46-1.52 |
| nutr | 1.11 | 0.29-4.19 |
| med | 0.89 | 0.38-2.09 |
| non_ph_pbo | 0.57 | 0.13-2.43 |
| qualt | 0.80 | 0.39-1.63 |
| social | 1.32 | 0.44-4.02 |
| incont | 0.89 | 0.38-2.09 |

Abbreviations: **exerc**, exercise; **med**, medication; **incont**, management of urinary incontinence; **nutr**, fluid or nutrition therapy; **envir**, environmental assessment and modifications; **assist**, assistive technology; **social**, social engagement; **qualt**, quality improvement strategies; **brisk**, basic falls risk assessment; **non-ph_pbo**, non-pharmacological placebo.

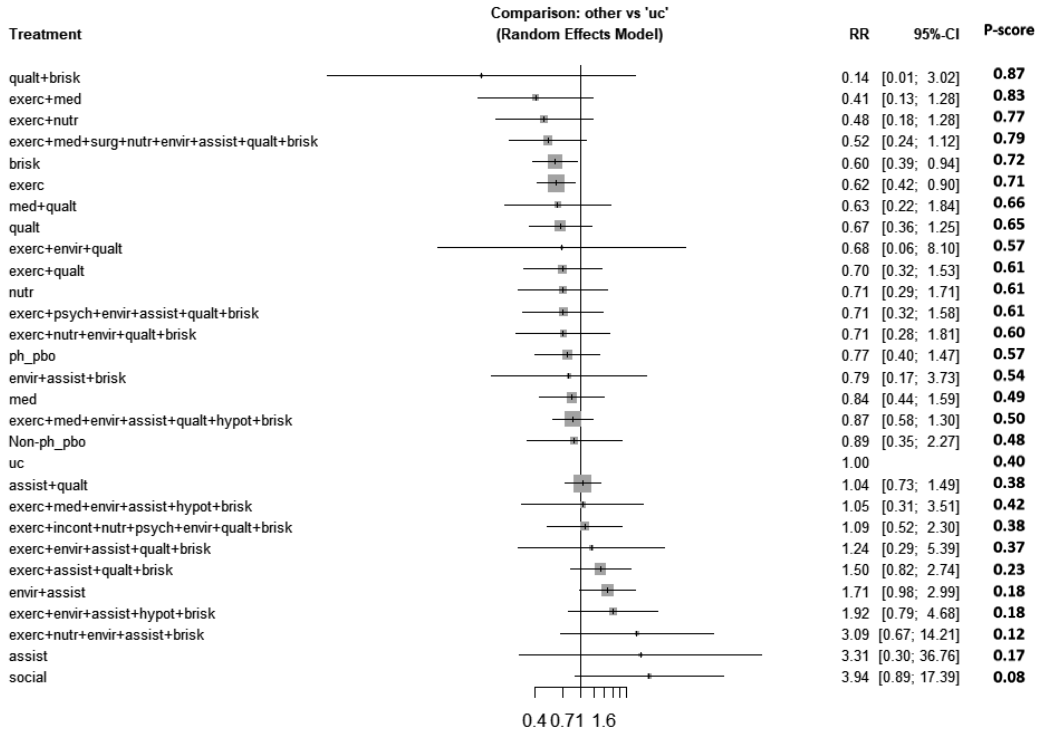
**Supplementary Appendix S6.** Additional results for number of fall-related fractures




Abbreviations: **exerc**, exercise; **med**, medication; **surg**, surgery; **incont**, management of urinary incontinence; **nutr**, fluid or nutrition therapy; **psych**, psychological interventions; **envir**, environmental assessment and modifications; **assist**, assistive technology; **social**, social engagement; **qualt**, quality improvement strategies; **hypot**, management of orthostatic hypotension; **brisk**, basic falls risk assessment; **uc**, usual care; **ph_pbo**, pharmacological placebo; **non-ph_pbo**, non-pharmacological placebo.

A network plot provides an overview of the interventions investigated in all included randomized control trials. Interventions connected by a line were directly compared in one or more studies (direct evidence), e.g. exercise + nutrition versus usual care. Each node represents an intervention addressed in the included studies. The nodes are sized according to the number of participants who have received this intervention. The thickness of the line is according to the number of studies addressing this comparison.

**Supplementary Figure S8.** Connected network plot for number of fall-related fractures




Abbreviations: **exerc**, exercise; **med**, medication; **surg**, surgery; **incont**, management of urinary incontinence; **nutr**, fluid or nutrition therapy; **psych**, psychological interventions; **envir**, environmental assessment and modifications; **assist**, assistive technology; **social**, social engagement; **qualt**, quality improvement strategies; **hypot**, management of orthostatic hypotension; **brisk**, basic falls risk assessment; **uc**, usual care; **ph_pbo**, pharmacological placebo; **non-ph_pbo**, non-pharmacological placebo.

The boxes and error bars represent the risk ratios and its 95% confidence interval.

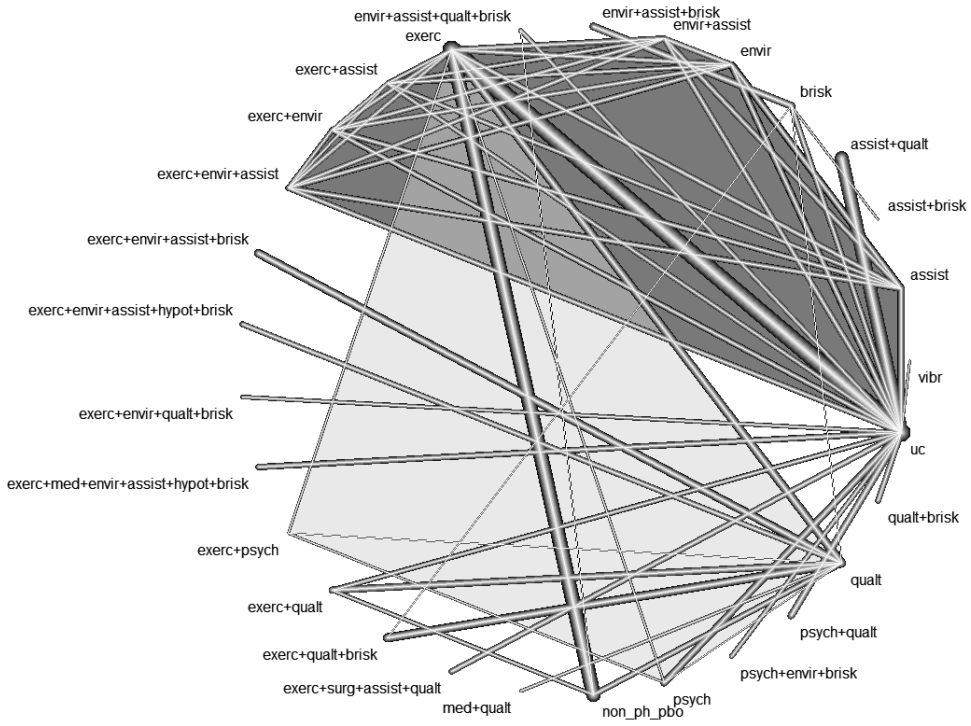
**Supplementary Figure S9.** Summary risk ratios (RR) with 95% confidence intervals (95%-CI) and P-scores resulting from the network meta-analysis for every intervention consisting of one or more components versus usual care for the outcome number of fall-related fractures

**Supplementary Table S6.** Risk ratios with 95% confidence intervals (95% CI) resulting from the component network meta-analysis for every intervention component versus usual care for the outcome number of fall-related fractures

| Component | Risk ratio | 95% CI |
|---|---|---|
| assist | 1.66 | 1.07-2.59 |
| brisk | 0.88 | 0.61-1.26 |
| envir | 1.19 | 0.68-2.07 |
| exerc | 0.83 | 0.64-1.07 |
| nutr | 1.07 | 0.60-1.90 |
| med | 0.85 | 0.56-1.27 |
| hypot | 1.01 | 0.48-2.10 |
| incont | 2.20 | 0.64-7.57 |
| non_ph_pbo | 1.00 | 0.44-2.30 |
| ph_pbo | 0.77 | 0.51-1.17 |
| psych | 0.73 | 0.36-1.50 |
| qualt | 0.73 | 0.50-1.07 |
| social | 2.98 | 0.79-11.31 |
| surg | 0.60 | 0.26-1.34 |

Abbreviations: **exerc**, exercise; **med**, medication; **surg**, surgery; **incont**, management of urinary incontinence; **nutr**, fluid or nutrition therapy; **psych**, psychological interventions; **envir**, environmental assessment and modifications; **assist**, assistive technology; **social**, social engagement; **qualt**, quality improvement strategies; **hypot**, management of orthostatic hypotension; **brisk**, basic falls risk assessment; **uc**, usual care; **ph_pbo**, pharmacological placebo; **non-ph_pbo**, non-pharmacological placebo.

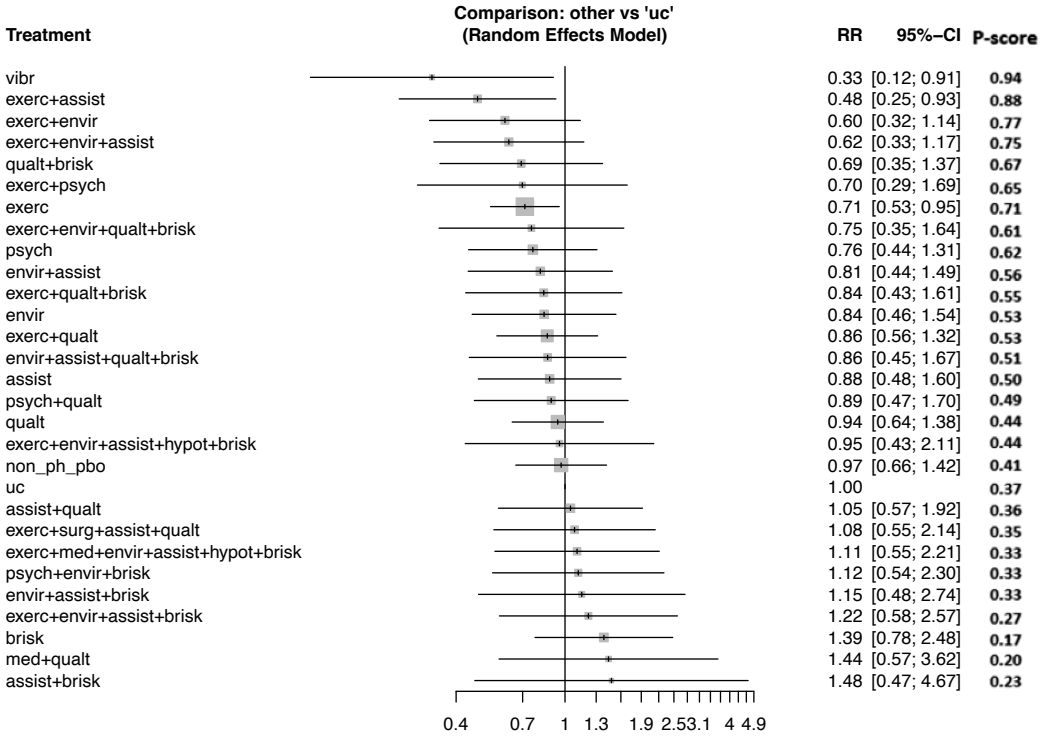
**Supplementary Appendix S7. Additional results for number of repeated fallers**




Abbreviations: **exerc**, exercise; **med**, medication; **surg**, surgery; **psych**, psychological interventions; **envir**, environmental assessment and modifications; **assist**, assistive technology; **qualt**, quality improvement strategies; **hypot**, management of orthostatic hypotension; **brisk**, basic falls risk assessment; **vibr**, whole-body vibration; **uc**, usual care; **non-ph_pbo**, non-pharmacological placebo.

A network plot provides an overview of the interventions investigated in all included randomized control trials. Interventions connected by a line were directly compared in one or more studies (direct evidence), e.g. exercise + nutrition versus usual care. Each node represents an intervention addressed in the included studies. The nodes are sized according to the number of participants who have received this intervention. The thickness of the line is according to the number of studies addressing this comparison.

**Supplementary Figure S10.** Network plot for number of repeated fallers




Abbreviations: **exerc**, exercise; **med**, medication; **surg**, surgery; **psych**, psychological interventions; **envir**, environmental assessment and modifications; **assist**, assistive technology; **qualt**, quality improvement strategies; **hypot**, management of orthostatic hypotension; **brisk**, basic falls risk assessment; **vibr**, whole-body vibration; **uc**, usual care; **non-ph_pbo**, non-pharmacological placebo.

The boxes and error bars represent the risk ratios and its 95% confidence interval.

**Supplementary Figure S11.** Summary risk ratios (RR) with 95% confidence intervals (95%-CI) and P-scores resulting from the network meta-analysis for every intervention consisting of one or more components versus usual care for the outcome number of repeated fallers

**Supplementary Table S7.** Risk ratios with 95% confidence intervals (95% CI) resulting from the component network meta-analysis for every intervention component versus usual care for the outcome number of repeated fallers

| Component | Risk ratio | 95% CI |
|---|---|---|
| assist | 0.99 | 0.82-1.18 |
| brisk | 1.17 | 0.93-1.47 |
| envir | 0.97 | 0.79-1.19 |
| vibr | 0.33 | 0.13-0.81 |
| exerc | 0.79 | 0.69-0.90 |
| med | 1.36 | 0.82-2.26 |
| hypot | 0.99 | 0.59-1.66 |
| non_ph_pbo | 1.01 | 0.80-1.29 |
| ph_pbo | 1.33 | 0.75-2.34 |
| psych | 0.87 | 0.67-1.14 |
| qualt | 0.92 | 0.78-1.07 |
| surg | 1.53 | 0.87-2.69 |

Abbreviations: **exerc**, exercise; **med**, medication; **surg**, surgery; **psych**, psychological interventions; **envir**, environmental assessment and modifications; **assist**, assistive technology; **qualt**, quality improvement strategies; **hypot**, management of orthostatic hypotension; **brisk**, basic falls risk assessment; **vibr**, whole-body vibration; **ph_pbo**, pharmacological placebo**; non-ph_pbo**, non-pharmacological placebo.

**Supplementary Appendix S8.** Additional results for number of hip fractures

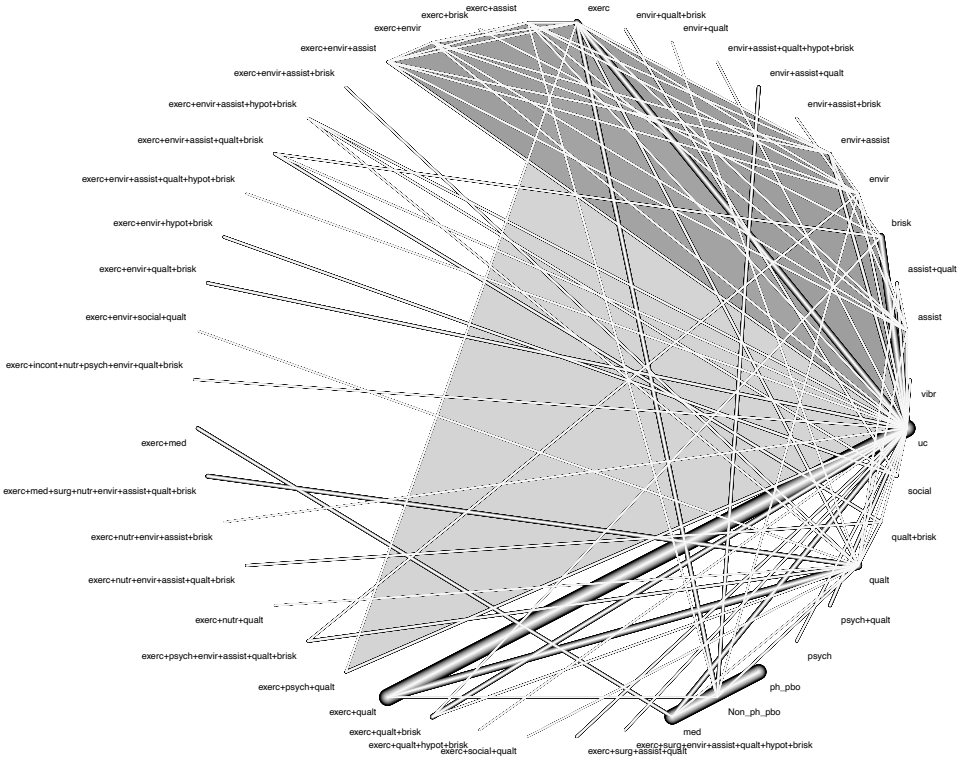
For the outcome of number of hip fractures, the performance of primary analysis was not possible due to the lack of a connected network. Analysis at the component level (C-NMA) was possible.

**Supplementary Table S8.** Risk ratios with 95% confidence intervals (95% CI) resulting from the component network meta-analysis for every intervention component versus usual care for the outcome number of hip fractures

| Component | Risk ratio | 95% CI |
|---|---|---|
| assist | 1.16 | 0.44-3.12 |
| brisk | 0.83 | 0.28-2.48 |
| envir | 1.48 | 0.30-7.26 |
| exerc | 0.79 | 0.21-3.02 |
| med | 0.79 | 0.14-4.33 |
| hypot | 0.79 | 0.23-2.67 |
| ph_pbo | 0.69 | 0.12-3.89 |
| psych | 0.89 | 0.10-7.87 |
| qualt | 0.78 | 0.37-1.65 |
| social | 1.27 | 0.37-4.29 |

Abbreviations: **exerc**, exercise; **med**, medication; **psych**, psychological interventions; **envir**, environmental assessment and modifications; **assist**, assistive technology; **social**, social engagement; **qualt**, quality improvement strategies; **hypot**, management of orthostatic hypotension; **brisk**, basic falls risk assessment; **ph_pbo**, pharmacological placebo.

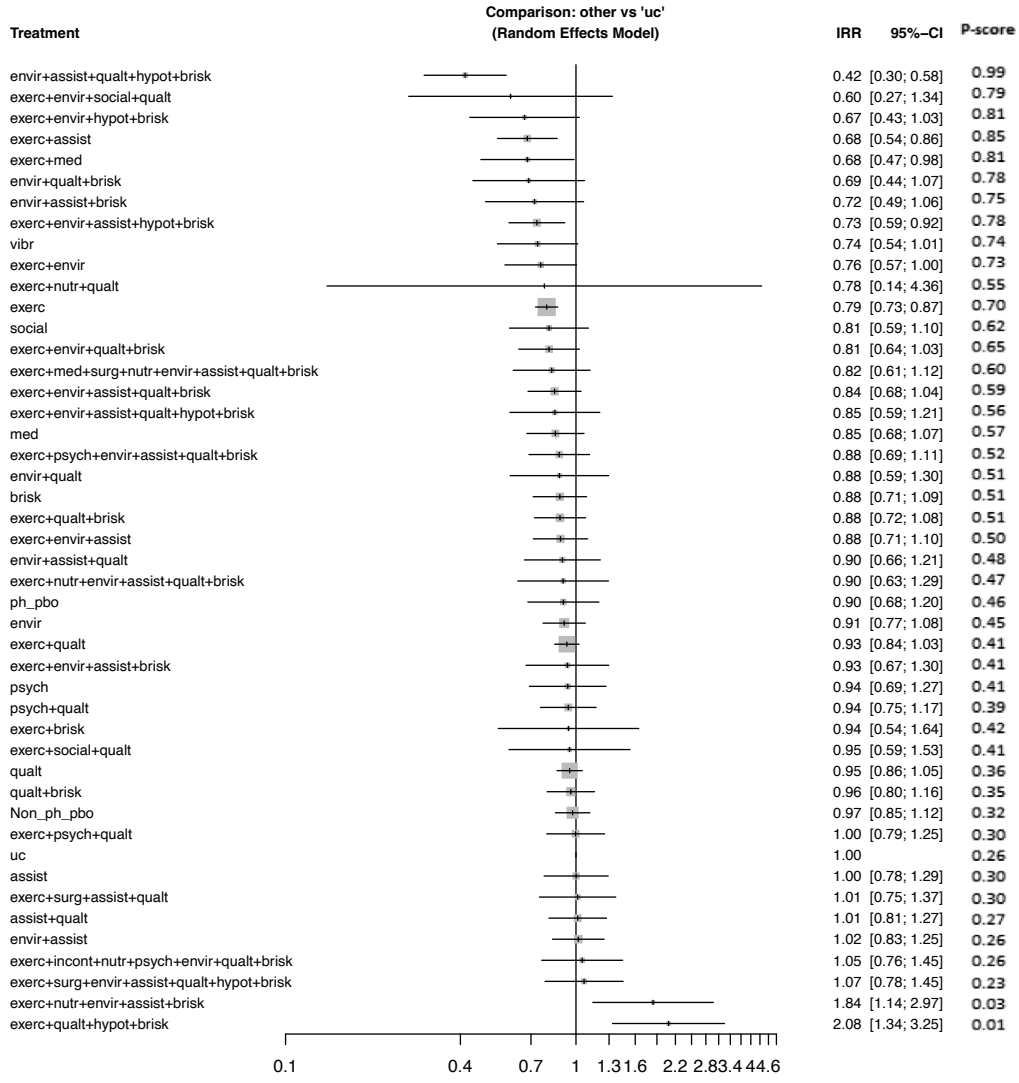
**Supplementary Appendix S9.** Additional results for falls rate




Abbreviations: **exerc**, exercise; **med**, medication; **surg**, surgery; **incont**, management of urinary incontinence; **nutr**, fluid or nutrition therapy; **psych**, psychological interventions; **envir**, environmental assessment and modifications; **assist**, assistive technology; **social**, social engagement; **qualt**, quality improvement strategies; **hypot**, management of orthostatic hypotension; **brisk**, basic falls risk assessment; **vibr**, whole-body vibration; **chiro**, chiropractic care; **uc**, usual care; **ph_pbo**, pharmacological placebo; **non-ph_pbo**, non-pharmacological placebo.

A network plot provides an overview of the interventions investigated in all included randomized control trials. Interventions connected by a line were directly compared in one or more studies (direct evidence), e.g. exercise + nutrition versus usual care. Each node represents an intervention addressed in the included studies. The nodes are sized according to the number of participants who have received this intervention. The thickness of the line is according to the number of studies addressing this comparison.

**Supplementary Figure S12.** Network plot for falls rate




Abbreviations: **exerc**, exercise; **med**, medication; **surg**, surgery; **incont**, management of urinary incontinence; **nutr**, fluid or nutrition therapy; **psych**, psychological interventions; **envir**, environmental assessment and modifications; **assist**, assistive technology; **social**, social engagement; **qualt**, quality improvement strategies; **hypot**, management of orthostatic hypotension; **brisk**, basic falls risk assessment; **vibr**, whole-body vibration; **chiro**, chiropractic care; **uc**, usual care; **ph_pbo**, pharmacological placebo; **non-ph_pbo**, non-pharmacological placebo.

The boxes and error bars represent the rate ratios and its 95% confidence interval.

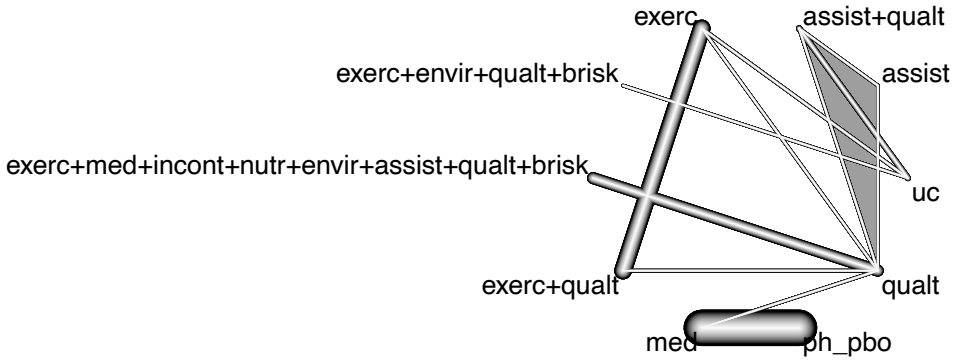
**Supplementary Figure S13.** Summary rate ratios (IRR) with 95% confidence intervals (95%-CI) and P-scores resulting from the network meta-analysis for every intervention consisting of one or more components versus usual care for the outcome falls rate

**Supplementary Table S9.** Rate ratios with 95% confidence intervals (95% CI) resulting from the component network meta-analysis for every intervention component versus usual care for the outcome falls rate

| Component | Rate ratio | 95% CI |
|---|---|---|
| assist | 1.00 | 0.91-1.10 |
| brisk | 0.99 | 0.90-1.09 |
| envir | 0.94 | 0.85-1.03 |
| vibr | 0.74 | 0.53-1.02 |
| exerc | 0.90 | 0.86-0.95 |
| nutr | 1.24 | 0.97-1.58 |
| med | 0.81 | 0.66-1.00 |
| hypot | 0.94 | 0.80-1.11 |
| incont | 0.98 | 0.63-1.50 |
| non_ph_pbo | 1.08 | 0.96-1.21 |
| ph_pbo | 0.87 | 0.66-1.14 |
| psych | 1.02 | 0.90-1.17 |
| qualt | 1.01 | 0.95-1.08 |
| social | 0.95 | 0.80-1.14 |
| surg | 1.14 | 0.92-1.42 |

Abbreviations: **exerc**, exercise; **med**, medication; **surg**, surgery; **incont**, management of urinary incontinence; **nutr**, fluid or nutrition therapy; **psych**, psychological interventions; **envir**, environmental assessment and modifications; **assist**, assistive technology; **social**, social engagement; **qualt**, quality improvement strategies; **hypot**, management of orthostatic hypotension; **brisk**, basic falls risk assessment; **vibr**, whole-body vibration; **ph_pbo**, pharmacological placebo; **non-ph_pbo**, non-pharmacological placebo.

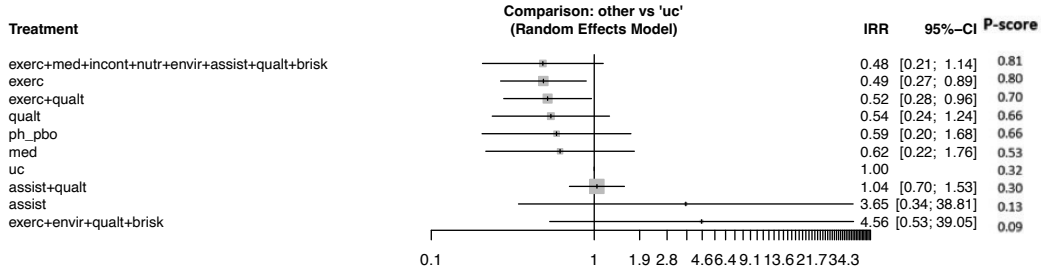
**Supplementary Appendix S10. Additional results for fracture rate**




Abbreviations: **exerc**, exercise; **med**, medication; **incont**, management of urinary incontinence; **nutr**, fluid or nutrition therapy; **envir**, environmental assessment and modifications; **assist**, assistive technology; **qualt**, quality improvement strategies; **brisk**, basic falls risk assessment; **ph_pbo**, pharmacological placebo.

A network plot provides an overview of the interventions investigated in all included randomized control trials. Interventions connected by a line were directly compared in one or more studies (direct evidence), e.g. exercise + nutrition versus usual care. Each node represents an intervention addressed in the included studies. The nodes are sized according to the number of participants who have received this intervention. The thickness of the line is according to the number of studies addressing this comparison.

**Supplementary Figure S14.** Network plot for fracture rate




Abbreviations: **exerc**, exercise; **med**, medication; **incont**, management of urinary incontinence; **nutr**, fluid or nutrition therapy; **envir**, environmental assessment and modifications; **assist**, assistive technology; **qualt**, quality improvement strategies; **brisk**, basic falls risk assessment; **uc**, usual care; **ph_pbo**, pharmacological placebo.

The boxes and error bars represent the rate ratios and its 95% confidence interval.

**Supplementary Figure S15.** Summary rate ratios (IRR) with 95% confidence intervals (95%-CI) and P-scores resulting from the network meta-analysis for every intervention consisting of one or more components versus usual care for the outcome fracture rate

**Supplementary Table S10.** Rate ratios with 95% confidence intervals (95% CI) resulting from the component network meta-analysis for every intervention component versus usual care for the outcome fracture rate

| Component | Rate ratio | 95% CI |
|---|---|---|
| assist | 1.06 | 0.65 - 1.74 |
| brisk | 2.56 | 0.85 - 7.78 |
| envir | 2.56 | 0.85 - 7.78 |
| exerc | 0.69 | 0.44 - 1.06 |
| nutr | 0.40 | 0.13 - 1.29 |
| med | 1.15 | 0.56 - 2.36 |
| hypot | 0.40 | 0.13 - 1.29 |
| ph_pbo | 1.05 | 0.50 - 2.19 |
| qualt | 1.01 | 0.80 - 1.28 |

Abbreviations: **exerc**, exercise; **med**, medication; **nutr**, fluid or nutrition therapy; **envir**, environmental assessment and modifications; **assist**, assistive technology; **qualt**, quality improvement strategies; **hypot**, management of orthostatic hypotension**; brisk**, basic falls risk assessment; **ph_pbo**, pharmacological placebo.

**Supplementary Appendix S11.** eMethods

## 1.1 Additional information regarding study population, interventions, comparators and outcomes

**Supplementary Table S11.** Additional information regarding study population, interventions, comparators and outcomes

| | |
|---|---|
| **Population** | Community-dwelling (living at home or in residential facilities) adults aged ≥65 years.<br>Included: - Minimal dependence was allowed (e.g. home assistance with housework or showering, delivery of meals)<br>- Patients recruited in hospital and then discharged home for follow-up<br>Excluded: - Nursing home or rehabilitation center setting<br>- Studies on specific conditions (e.g. stroke, Parkinson's Disease, severe dementia, spinal cord injury, multiple sclerosis, amputations), where the effects of the interventions cannot be generalized to most community-dwelling older people |
| **Intervention** | Any intervention aimed at preventing falls:<br>- single<br>- multiple (>2 interventions, fixed combination)<br>- multifactorial (>2 interventions, personalized according to the results of a pre-executed falls risk assessment)<br>Included: - Fourteen individual intervention components were identified (manuscript Table 1).<br>Excluded: - Interventions violating the transitivity assumption (i.e. intervention not applicable to all participants in all studies included in the NMA) |
| **Comparator** | One of the following control groups: usual care, pharmacological placebo, non-pharmacological placebo (a sham intervention), and any other type of intervention to prevent falls. |

| | |
|---|---|
| **Outcomes** | *Primary outcomes*:<br>1. Number of fallers (participants who sustained one or more falls)<br>2. Number of fall-related fractures<br><br>*Secondary outcomes:*<br>1. Number of repeated fallers (one individual sustaining at least two falls)<br>2. Number of hip fractures<br>3. Falls rate (number of falls per person-year of follow-up)<br>4. Fracture rate (number of fall-related fractures per person-year of follow-up) |

## 1.2 Electronic search strategy

General limits applied to the search of the updated literature included:
- Studies published between 2015 – 2019
- Human studies only, i.e. no animal studies

The search strategy for PubMed is presented below. The search strategy for the other databases can be requested from the corresponding author.

Search PubMed:

1. "Accidental Falls"[Mesh]
2. fall[Title/Abstract]
3. falls[Title/Abstract]
4. faller*[Title/Abstract]
5. fallen[Title/Abstract]
6. falling[Title/Abstract]
7. fall-related[Title/Abstract]
8. near-fall*[Title/Abstract]
9. or/1-8
10. "Adult"[Mesh]
11. "Health Services for the Aged"[Mesh]
12. elder*[Title/Abstract] OR geriatric*[Title/Abstract] OR gerontolog*[Title/Abstract] OR old-age*[Title/Abstract] OR senior*[Title/Abstract]
13. ((older[Title/Abstract] OR adult*[Title/Abstract] OR age[Title/Abstract] OR aged[Title/Abstract]) AND (man[Title/Abstract] OR men[Title/Abstract] OR woman*[Title/Abstract] OR women*[Title/Abstract] OR patient[Title/Abstract] OR patients[Title/Abstract] OR person*[Title/Abstract] OR people*[Title/Abstract] OR population*[Title/Abstract]))
14. or/10-13
15. 9 and 14
16. controlled clinical trial[Publication Type] OR randomized controlled trial[Publication Type]

17. "Clinical Trials as Topic"[Mesh]
18. randomised[Title/Abstract] OR randomized[Title/Abstract] OR randomly[Title/Abstract] OR RCT*[Title/Abstract] OR placebo*[Title/Abstract]
19. (singl*[Title/Abstract] OR doubl*[Title/Abstract] OR trebl*[Title/Abstract] OR tripl*[Title/Abstract]) AND (mask*[Title/Abstract] OR blind*[Title/Abstract] OR dumm*[Title/Abstract])
20. trial[Title]
21. or/16-20
22. 15 AND 21
23. 22 NOT (animals[MeSH] NOT humans[MeSH])
24. "Urinary Incontinence"[Mesh]
25. "Enuresis"[Mesh]
26. Urinary Incontinence[Title/Abstract]
27. Urine Incontinence[Title/Abstract]
28. or/24-27
29. "Hypotension, Orthostatic"[Mesh]
30. Postural hypotension [Title/Abstract]
31. Orthostatic Hypotension [Title/Abstract]
32. or/29-31
33. "Shoes"[Mesh]
34. "Braces"[Mesh]
35. "Canes"[Mesh]
36. "Walkers"[Mesh]
37. "Mobility Limitation"[Mesh]
38. walking aid* [Title/Abstract]
39. walking stick* [Title/Abstract]
40. rollator* [Title/Abstract]
41. walking frame* [Title/Abstract]
42. or/33-41
43. 28 OR 32 OR 42
44. 23 AND 43

## 1.3 Additional information on methods systematic review

**Screening:** Studies from author Yoshihiro Sato were excluded, because a large part of his studies have been officially retracted from PubMed.

**Data extraction:** When multiple follow-up time points were reported, we chose the time point where we expected the highest clinical impact, e.g. in case of an exercise intervention, we chose the time point closest to the end of the exercise intervention.

When only data on fall frequency was available, we combined data on fall frequency and the general follow-up time duration to estimate falls rates, assuming that each participant was followed for the entire follow-up period.

## 1.4 Additional information on network meta-analysis

***Simplifications***

Originally, we had planned to include all the different types of exercise as subgroups (e.g balance, strength, flexibility, endurance training). However, after completion of data extraction, the sample sizes for the subgroups were too small and thus had to be merged into one exercise component. For example, in RCTs with similar intervention arms: exercise (balance training) vs. exercise (strength training) vs. medication, exercise was merged (balance & strength training) vs. medication. For the merging process, the two exercise sample sizes were added together, and for dichotomous outcomes the number of events were added together but for continuous outcomes we computed weighted means and pooled standard deviations.

RCTs where all intervention arms belonged to the same overall component were disregarded, e.g exercise (balance) vs. exercise (strength) vs. exercise (flexibility), since no comparisons could be drawn for the efficacy of one intervention over another.

***Data synthesis***

At first, we conducted a random-effects meta-analysis using inverse variance weighting for each pairwise comparison.[1] We conducted the analysis in R using the 'meta' package.[2] DerSimonian-Laird estimator was used for estimating the between-study variance.

Many studies compared interventions consisting of multiple interacting components. The primary NMA followed the standard approach where each distinct combination of components is treated as a separate intervention. To disentangle the effect of each component, we additionally employed statistical models to obtain relative effects for each separate component (component-NMA (C-NMA). For both analyses (standard NMA and (C-NMA),[3,4] we used the *netmeta* package[5] in R software (version 3.6.1) which handles the within multi-arm trials correlation by reducing the weight given to each effect size.[2] A prerequisite for standard NMA is that the network is connected (you can go from any node to any other one). The C-NMA approach allows disconnected networks to be analyzed jointly as long as they include some common components. However, we performed NMA only for connected networks in which the number of studies exceeded the number of treatment nodes. We excluded from the analysis studies comparing identical treatments in the study arms, e.g. exercise (balance) vs. exercise (strength), or not having the necessary arm-level data.

We encountered studies in which participants were randomized to multiple or multifactorial interventions. The main challenge in such a network was to disentangle the

effects of each component. We conducted a series of network meta-analyses. We followed the models (below) described in Welton et al. 2009 to estimate relative effects.[3]
More specifically,

**Model A**, **pairwise meta-analysis:** Some of the trials compared an active intervention to usual care. Model A lumps all interventions together and compares to the reference treatment (e.g. usual care). Such a model answers the question whether interventions work as a whole.

**Model B, standard NMA:** Each possible combination of components is considered to be a separate intervention and has its own effect. This was the primary analysis.

**Model C, component NMA, additive model:** Assumes that each component has a separate effect. The total effect of an intervention is equal to the sum of the relative component effects (additivity assumption).

**Model D, component NMA, interaction model:** Extension of Model C with extra terms for combinations of pairs of components. Allows pairs of components to have a bigger or smaller effect than would be expected from the sum of their individual components

In the network meta-analysis, we used models A, B and where appropriate model C.
For models A and B, we presented relative effects for each treatment, whereas for model C we placed emphasis on the absolute effects of components. Along with effects we also ranked interventions using P-scores.[6]

***Assessment of heterogeneity***

For each comparison we assessed statistical heterogeneity by visually inspecting the forest plot. We computed the chi-square test for heterogeneity, the  index and the actual estimated value of heterogeneity ($I^2$) both in each pairwise comparison and in the network.[7] For dichotomous outcomes, magnitude of heterogeneity variance was compared with the empirical distribution as derived by Turner et al 2012.[8] Both in standard pairwise meta-analyses and in network meta-analysis we assumed that heterogeneity is the same for all treatment comparisons to increase power in estimation. We estimated heterogeneity using restricted maximum likelihood both in pairwise and network meta-analysis.

***Assessment of Inconsistency***

**Assessment of statistical inconsistency**

A key assumption in NMA is that of transitivity. This assumption implies that the distribution of effect modifiers is similar across treatment comparisons. In order to get a valid indirect estimate for B vs C via A, the distribution of all characteristics that may influence the relative effect for B vs C must be similar in A vs B and A vs C studies. Alternative interpretations of transitivity can be found in Salanti 2012.[9] Intransitivity may manifest itself statistically through large discrepancies between direct and indirect evidence. This is called inconsistency.

**Local approaches for evaluating inconsistency**

We applied the node-splitting approach to evaluate if direct evidence for a treatment comparison is in agreement with the indirect evidence estimated from the entire network after studies involving this treatment comparison were omitted.[10]

**Global approaches for evaluating inconsistency**

To check the assumption of consistency in the entire network we used the "design-by treatment" model as described by Higgins and colleagues.[11] This method accounts for different sources of inconsistency that can occur when studies with different designs (two-arm trials vs. three-arm trials) give different results as well as disagreement between direct and indirect evidence. Using this approach, we inferred the presence of inconsistency from any source in the entire network based on a chi-square test. Inconsistency and heterogeneity are interweaved; to distinguish between these two sources of variability we employed the $I^2$ for inconsistency that measures the percentage of variability that cannot be attributed to random error or heterogeneity (within comparison variability).

**1.5 Additional information on CINeMA confidence rating**

**Methods:**

A semi-automated assessment of the confidence in the results of the NMA was performed using CINeMA for every possible pairwise comparison of interventions. CINeMA makes judgements about six domains (within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence) and scores each NMA treatment effect estimate as "no concerns", "some concerns" and "major concerns". Regarding within-study biases and indirectness, we summarized these domains for each network estimate using the average risk of bias and indirectness respectively. For reporting bias we summarized each network estimate as having "major concerns" as there are no established statistical methods to explore that and we did not have other information on whether such biases exist. For imprecision, we considered that relative effect estimates below 0.8 or above 1.25 are clinical important and we followed the CINeMA strategy for exploring whether statistical significance and clinical importance coincide for each outcome. Incoherence (inconsistency) was checked by the node-split method[10] and a global test for inconsistency.[11] We additionally checked the net-heat plot.[12] For heterogeneity we followed the standard CINeMA approach. A key characteristic of the CINeMA approach is the use of the percentage contribution matrix that shows how information flows in the network and more specifically, how each study and/or direct comparison informs the effect estimates.

**Results**

For the domains 'within-study bias' and 'reporting bias', there were major concerns for all comparisons, resulting in low confidence in the results for every comparison. Major

concerns for the domain 'within-study bias' were mainly the result of the lack of blinding of personnel and participants, due to the nature of the fall prevention interventions. For reporting bias we summarized each network estimate as having "major concerns" as there are no established statistical methods to explore that. In order to still maintain distinctiveness, the evaluation of the confidence in the results of the NMA was based on the remaining 4 domains. The results of the assessments and the reasons for downgrading are presented in manuscript Table 3 and 4 for the 23 interventions with statistically significant associations versus usual care. Based on the assessment without consideration of the domains 'within-study bias' and 'reporting bias', for 20 of the 23 comparisons the confidence in the treatment effect was considered high.

## References


1. Nikolakopoulou A, Mavridis D, Salanti G. Demystifying fixed and random effects meta-analysis. Evid Based Ment Health 2014;17:53-57.
2. Rücker G, Schwarzer G. Reduce dimension or reduce weights? Comparing two approaches to multi-arm studies in network meta-analysis. Stat Med 2014;33:4353-4369. doi:10.1002/sim.6236
3. Caldwell D, Welton N. Approaches for synthesising complex mental health interventions in meta-analysis. Evid Based Ment Health 2016;19:16-21. doi:10.1136/eb-2015-102275
4. Rücker G, Petropoulou M, Schwarzer G. Network meta-analysis of multicomponent interventions. Biometrical J 2020;62:808-821. doi:10.1002/bimj.201800167
5. Rücker G, Krahn U, König J, Efthimiou O, Schwarzer G. netmeta: Network Meta-Analysis using Frequentist Methods. R package version 1.0-1. Published online 2019. https://cran.r-project.org/package=netmeta
6. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol 2015;15:58. doi:10.1186/s12874-015-0060-8
7. Higgins JP, Thompson SG. Controlling the risk of spurious findings from meta-regression. Stat Med 2004;23:1663-1682. doi:10.1002/sim.1752
8. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. Int J Epidemiol 2012;41:818-827. doi:10.1093/ije/dys041
9. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Res Synth Methods 2012;3:80-97. doi:10.1002/jrsm.1037
10. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med 2010;29:932-944. doi:10.1002/sim.3767
11. Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods 2012;3:98-110. doi:10.1002/jrsm.1044
12. Krahn U, Binder H, König J. A graphical tool for locating inconsistency in network meta-analyses. BMC Med Res Methodol 2013;13:35. doi:10.1186/1471-2288-13-35

## Supplementary Appendix S12. eReferences. List of 220 included studies and 3 companion reports


1. Aloia JF, Rubinova R, Fazzari M, Islam S, Mikhail M, Ragolia L. Vitamin D and Falls in Older African American Women: The PODA Randomized Clinical Trial. J Am Geriatr Soc 2019;67:1043-1049. doi:10.1111/jgs.15760
2. Ansai JH, Aurichio TR, Gonçalves R, Rebelatto JR. Effects of two physical exercise protocols on physical performance related to falls in the oldest old: A randomized controlled trial. Geriatr Gerontol Int 2016;16:492-499. doi:10.1111/ggi.12497
3. Arantes PMM, Dias JMD, Fonseca FF et al. Effect of a Program Based on Balance Exercises on Gait, Functional Mobility, Fear of Falling, and Falls in Prefrail Older Women: A Randomized Clinical Trial. Top Geriatr Rehabil 2015;31:113-120. doi:10.1097/TGR.0000000000000056
4. Arkkukangas M, Söderlund A, Eriksson S, Johansson AC. Fall Preventive Exercise with or Without Behavior Change Support for Community-Dwelling Older Adults: A Randomized Controlled Trial with Short-Term Follow-up. J Geriatr Phys Ther 2019;42:9-17. doi:10.1519/JPT.0000000000000129
5. Ashari A, Hamid TA, Hussain MR, Hill KD. Effectiveness of Individualized Home-Based Exercise on Turning and Balance Performance among Adults Older than 50 yrs: A Randomized Controlled Trial. Am J Phys Med Rehabil 2016;95:355-365. doi:10.1097/PHM.0000000000000388
6. Ballard JE, McFarland C, Wallace LS, Holiday DB, Roberson G. The effect of 15 weeks of exercise on balance, leg strength, and reduction in falls in 40 women aged 65 to 89 years. J Am Med Womens Assoc 2004;59:255-261.
7. Barker AL, Talevski J, Bohensky MA, Brand CA, Cameron PA, Morello RT. Feasibility of Pilates exercise to decrease falls risk: A pilot randomized controlled trial in community-dwelling older people. Clin Rehabil 2016;30:984-996. doi:10.1177/0269215515606197
8. Barnett A, Smith B, Lord SR, Williams M, Baumand A. Community-based group exercise improves balance and reduces falls in at-risk older people: A randomised controlled trial. Age Ageing 2003;32:407-414. doi:10.1093/ageing/32.4.407
9. Barr RJ, Stewart A, Torgerson DJ, Seymour DG, Reid DM. Screening elderly women for risk of future fractures - Participation rates and impact on incidence of falls and fractures. Calcif Tissue Int 2005;76:243-248. doi:10.1007/s00223-004-0101-5
10. Beck BR, Norling TL. The effect of 8 mos of twice-weekly low- or higher intensity whole body vibration on risk factors for postmenopausal hip fracture. Am J Phys Med Rehabil 2010;89:997-1009. doi:10.1097/phm.0b013e3181f71063
11. Beck AM, Christensen AG, Hansen BS, Damsbo-Svendsen S, Kreinfeldt Skovgaard Møller T. Multidisciplinary nutritional support for undernutrition in nursing home and home-care: A cluster randomized controlled trial. Nutrition 2016;32:199-205. doi:10.1016/j.nut.2015.08.009
12. Beling J, Roller M. Multifactorial intervention with balance training as a core component among fall-prone older adults. J Geriatr Phys Ther 2009;32:125-133. doi:10.1519/00139143-200932030-00008

13. Bernardelli G, Roncaglione C, Damanti S, Mari D, Cesari M, Marcucci M. Adapted physical activity to promote active and healthy ageing: the PoliFIT pilot randomized waiting list-controlled trial. Aging Clin Exp Res 2019;31:511-518. doi:10.1007/s40520-018-1002-1
14. Bernocchi P, Giordano A, Pintavalle G et al. Feasibility and Clinical Efficacy of a Multidisciplinary Home-Telehealth Program to Prevent Falls in Older Adults: A Randomized Controlled Trial. J Am Med Dir Assoc 2019;20:340-346. doi:10.1016/j.jamda.2018.09.003
15. Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: A 3-year randomized controlled trial. Arch Intern Med 2006;166:424-430. doi:10.1001/.424
16. Blalock SJ, Casteel C, Roth MT, Ferreri S, Demby KB, Shankar V. Impact of enhanced pharmacologic care on the prevention of falls: A randomized controlled trial. Am J Geriatr Pharmacother 2010;8:428-440. doi:10.1016/j.amjopharm.2010.09.002
17. Boongird C, Keesukphan P, Phiphadthakusolkul S, Rattanasiri S, Thakkinstian A. Effects of a simple home-based exercise program on fall prevention in older adults: A 12-month primary care setting, randomized controlled trial. Geriatr Gerontol Int 2017;17:2157-2163. doi:10.1111/ggi.13052
18. Boyé NDA, van der Velde N, de Vries OJ et al. Effectiveness of medication withdrawal in older fallers: Results from the improving medication prescribing to reduce risk of falls (IMPROveFALL) trial. Age Ageing 2016;46:142-146. doi:10.1093/ageing/afw161
19. Brown AI. Functional adaptation to exercise in elderly subjects: Physiotherapy, Curtin University of Technology; 2002.
20. Buchner DM, Cress ME, De Lateur BJ et al. The effect of strength and endurance training on gait, balance, fall risk, and health services use in community-living older adults. Journals Gerontol - Ser A Biol Sci Med Sci 1997;52:218-224. doi:10.1093/gerona/52A.4.M218
21. Bunout D, Barrera G, Avendano M et al. Results of a community-based weight-bearing resistance training programme for healthy Chilean elderly subjects. Age Ageing 2005;34:80-83. doi:10.1093/ageing/afi005
22. Cameron ID, Cumming RG, Kurrle SE et al. A randomised trial of hip protector use by frail older women living in their own homes. Inj Prev 2003;9:138-141. doi:10.1136/ip.9.2.138
23. Cameron ID, Kurrle S, Quine S et al. Increasing adherence with the use of hip protectors for older people living in the community. Osteoporos Int 2011;22:617-626. doi:10.1007/s00198-010-1334-y
24. Carpenter GI, Demopoulos GR. Screening the elderly in the community: Controlled trial of dependency surveillance using a questionnaire administered by volunteers. Br Med J 1990;300:1253-1256. doi:10.1136/bmj.300.6734.1253
25. Chapuy MC, Pamphile R, Paris E et al. Combined calcium and vitamin D3 supplementation in elderly women: Confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: The decalyos II study. Osteoporos Int 2002;13:257-264. doi:10.1007/s001980200023

26. Choi JH, Moon JS, Song R. Effects of Sun-style Tai Chi exercise on physical fitness and fall prevention in fall-prone older adults. J Adv Nurs 2005;51:150-157. doi:10.1111/j.1365-2648.2005.03480.x
27. Chu MML, Fong KNK, Lit ACH et al. An Occupational Therapy Fall Reduction Home Visit Program for Community-Dwelling Older Adults in Hong Kong After an Emergency Department Visit for a Fall. J Am Geriatr Soc 2017;65:364-372. doi:10.1111/jgs.14527
28. Ciaschini PM, Straus SE, Dolovich LR et al. Community-based intervention to optimise falls risk management: A randomised controlled trial. Age Ageing 2009;38:724-730. doi:10.1093/ageing/afp176
29. Clemson L, Cumming RG, Kendig H, Swann M, Heard R, Taylor K. The effectiveness of a community-based program for reducing the incidence of falls in the elderly: A randomized trial. J Am Geriatr Soc 2004;52:1487-1494. doi:10.1111/j.1532-5415.2004.52411.x
30. Clemson L, Singh MF, Bundy A et al. LiFE Pilot Study: A randomised trial of balance and strength training embedded in daily life activity to reduce falls in older adults. Aust Occup Ther J 2010;57:42-50. doi:10.1111/j.1440-1630.2009.00848.x
31. Clemson L, Fiatarone Singh MA, Bundy A et al. Integration of balance and strength training into daily life activity to reduce rate of falls in older people (the LiFE study): Randomised parallel trial. BMJ 2012;345:e4547. doi:10.1136/bmj.e4547
32. Close J, Ellis M, Hooper R, Glucksman E, Jackson S, Swift C. Prevention of falls in the elderly trial (PROFET): A randomized controlled trial: Commentary. Lancet 1999;353:93-97. doi:10.1111/j.1532-5415.1999.tb02587.x
33. Cohen MA, Miller J, Shi X, Sandhu J, Lipsitz LA. Prevention program lowered the risk of falls and decreased claims for long-term services among elder participants. Health Aff 2015;34:971-977. doi:10.1377/hlthaff.2014.1172
34. Coleman EA, Grothaus LC, Sandhu N, Wagner EH. Chronic Care Clinics: A randomized controlled trial of a new model of primary care for frail older adults. J Am Geriatr Soc 1999;47:775-783. doi:10.1111/j.1532-5415.1999.tb03832.x
35. Conroy S, Kendrick D, Harwood R et al. A multicentre randomised controlled trial of day hospital-based falls prevention programme for a screened population of community-dwelling older people at high risk of falls. Age Ageing 2010;39:704-710. doi:10.1093/ageing/afq096
36. Cornillon E, Blanchon MA, Ramboatsisetraina P et al. Effectiveness of falls prevention strategies for elderly subjects who live in the community with performance assessment of physical activities (before–after). Ann Readapt Med Phys 2002;45:493-504. doi:10.1016/S0168-6054(02)00302-1
37. Cumming RG, Thomas M, Szonyi G et al. Home visits by an occupational therapist for assessment and modification of environmental hazards: a randomized trial of falls prevention. J Am Geriatr Soc 1999;47:1397-1402. doi:10.1111/j.1532-5415.1999.tb01556.x
38. Cumming RG, Ivers R, Clemson L et al. Improving vision to prevent falls in frail older people: A randomized trial. J Am Geriatr Soc 2007;55:175-181. doi:10.1111/j.1532-5415.2007.01046.x

39. Dadgari A, Hamid TA, Hakim MN et al. Randomized control trials on Otago Exercise Program (OEP) to reduce falls among elderly community dwellers in Shahroud, Iran. Iran Red Crescent Med J 2016;18:e26340. doi:10.5812/ircmj.26340
40. Dangour AD, Albala C, Allen E et al. Effect of a nutrition supplement and physical activity program on pneumonia and walking capacity in chilean older people: A factorial cluster randomized trial. PLoS Med 2011;8:e1001023. doi:10.1371/journal.pmed.1001023
41. Dapp U, Anders JAM, Von Renteln-Kruse W et al. A randomized trial of effects of health risk appraisal combined with group sessions or home visits on preventive behaviors in older adults. Journals Gerontol - Ser A Biol Sci Med Sci 2011;66A:591-598. doi:10.1093/gerona/glr021
42. Davison J, Bond J, Dawson P, Steen IN, Kenny RA. Patients with recurrent falls attending Accident & Emergency benefit from multifactorial intervention - A randomised controlled trial. Age Ageing 2005;34:162-168. doi:10.1093/ageing/afi053
43. Day L, Hill KD, Stathakis VZ et al. Impact of Tai-Chi on falls among preclinically disabled older people: A randomized controlled trial. J Am Med Dir Assoc 2015;16:420-426. doi:10.1016/j.jamda.2015.01.089
44. de Vries OJ, Peeters GMEEG, Elders PJM et al. Multifactorial Intervention to Reduce Falls in Older People at High Risk of Recurrent Falls - A Randomized Controlled Trial. Arch Intern Med 2010;170:1110-1117. doi:10.1001/archinternmed.2010.169
45. Dhesi JK, Jackson SHD, Bearne LM et al. Vitamin D supplementation improves neuromuscular function in older people who fall. Age Ageing 2004;33:589-595. doi:10.1093/ageing/afh209
46. Dorresteijn TAC, Zijlstra GAR, Ambergen AW, Delbaere K, Vlaeyen JWS, Kempen GIJM. Effectiveness of a home-based cognitive behavioral program to manage concerns about falls in community-dwelling, frail older people: Results of a randomized controlled trial. BMC Geriatr 2016;16:2. doi:10.1186/s12877-015-0177-y
47. Dukas L, Bischoff HA, Lindpaintner LS et al. Alfacalcidol Reduces the Number of Fallers in a Community-Dwelling Elderly Population with a Minimum Calcium Intake of More Than 500 Mg Daily. J Am Geriatr Soc 2004;52:230-236. doi:10.1111/j.1532-5415.2004.52060.x
48. Dyer CAE, Taylor GJ, Reed M, Dyer CA, Robertson DR, Harrington R. Falls prevention in residential care homes: A randomised controlled trial. Age Ageing 2004;33:596-602. doi:10.1093/ageing/afh204
49. Ebrahim S, Thompson PW, Baskaran V, Evans K. Randomized placebo-controlled trial of brisk walking in the prevention of postmenopausal osteoporosis. Age Ageing 1997;26:253-260. doi:10.1093/ageing/26.4.253
50. El-Khoury F, Cassou B, Latouche A, Aegerter P, Charles M-A, Dargent-Molina P. Effectiveness of two year balance training programme on prevention of fall induced injuries in at risk women aged 75-85 living in community: Ossébo randomised controlled trial. BMJ 2015;351:h3830. doi:10.1136/bmj.h3830
51. Elley CR, Robertson MC, Garrett S et al. Effectiveness of a falls-and-fracture nurse coordinator to reduce falls: A randomized, controlled trial of at-risk older adults. J Am Geriatr Soc 2008;56:1383-1389. doi:10.1111/j.1532-5415.2008.01802.x

52. Fabacher D, Josephson K, Pietruszka F, Linderborn K, Morley JE, Rubenstein LZ. An In-Home Preventive Assessment Program for Independent Older Adults: A Randomized Controlled Trial. J Am Geriatr Soc 1994;42:630-638. doi:10.1111/j.1532-5415.1994.tb06862.x
53. Fairhall N, Sherrington C, Lord SR et al. Effect of a multifactorial, interdisciplinary intervention on risk factors for falls and fall rate in frail older people: A randomised controlled trial. Age Ageing 2014;43:616-622. doi:10.1093/ageing/aft204
54. Ferrer A, Formiga F, Sanz H, de Vries OJ, Badia T, Pujol R. Multifactorial assessment and targeted intervention to reduce falls among the oldest-old: A randomized controlled trial. Clin Interv Aging 2014;9:383-394. doi:10.2147/CIA.S57580
55. Fitzharris MP, Day L, Lord SR, Gordon I, Fildes B. The Whitehorse NoFalls trial: Effects on fall rates and injurious fall rates. Age Ageing 2010;39:728-733. doi:10.1093/ageing/afq109
56. Fox PJ, Vazquez L, Tonner C, Stevens JA, Fineman N, Ross LK. A Randomized Trial of a Multifaceted Intervention to Reduce Falls Among Community-Dwelling Adults. Heal Educ Behav 2010;37:831-848. doi:10.1177/1090198110366003
57. Freiberger E, Häberle L, Spirduso WW, Zijlstra GAR. Long-term effects of three multicomponent exercise interventions on physical performance and fall-related psychological outcomes in community-dwelling older adults: A randomized controlled trial. J Am Geriatr Soc 2012;60:437-446. doi:10.1111/j.1532-5415.2011.03859.x
58. Gallagher JC, Fowler SE, Detter JR, Sherman SS. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. J Clin Endocrinol Metab 2001;86:3618-3628. doi:10.1210/jcem.86.8.7703
59. Gawler S, Skelton DA, Dinan-Young S et al. Reducing falls among older people in general practice: The ProAct65+ exercise intervention trial. Arch Gerontol Geriatr 2016;67:46-54. doi:10.1016/j.archger.2016.06.019
60. Giangregorio LM, Gibbs JC, Templeton JA et al. Build better bones with exercise (B3E pilot trial): results of a feasibility study of a multicenter randomized controlled trial of 12 months of home exercise in older women with vertebral fracture. Osteoporos Int 2018;29:2545-2556. doi:10.1007/s00198-018-4652-0
61. Gianoudis J, Bailey CA, Ebeling PR et al. Effects of a targeted multimodal exercise program incorporating high-speed power training on falls and fracture risk factors in older adults: A community-based randomized controlled trial. J Bone Miner Res 2014;29:182-191. doi:10.1002/jbmr.2014
62. Gill TM, Pahor M, Guralnik JM et al. Effect of structured physical activity on prevention of serious fall injuries in adults aged 70-89: Randomized clinical trial (LIFE study). BMJ 2016;352:i245. doi:10.1136/bmj.i245
63. Giusti A, Giovale M, Ponte M et al. Short-term effect of low-intensity, pulsed, electromagnetic fields on gait characteristics in older adults with low bone mineral density: A pilot randomized-controlled trial. Geriatr Gerontol Int 2013;13:393-397. doi:10.1111/j.1447-0594.2012.00915.x
64. Glendenning P, Zhu K, Inderjeeth C, Howat P, Lewis JR, Prince RL. Effects of three-monthly oral 150,000 IU cholecalciferol supplementation on falls, mobility, and muscle strength in older

postmenopausal women: A randomized controlled trial. J Bone Miner Res 2012;27:170-176. doi:10.1002/jbmr.524

65. Grahn Kronhed AC, Hallberg I, Ödkvist L, Möller M. Effect of training on health-related quality of life, pain and falls in osteoporotic women. Adv Physiother 2009;11:154-165. doi:10.1080/14038190902896659
66. Grant AM. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium or vitamin D, RECORD): A randomised placebo-controlled trial. Lancet 2005;365:1621-1628. doi:10.1016/S0140-6736(05)63013-9
67. Gschwind YJ, Eichberg S, Ejupi A et al. ICT-based system to predict and prevent falls (iStoppFalls): Results from an international multicenter randomized controlled trial. Eur Rev Aging Phys Act 2015;12:10. doi:10.1186/s11556-015-0155-6
68. Guse CE, Peterson DJ, Christiansen AL, Mahoney J, Laud P, Layde PM. Translating a fall prevention intervention into practice: A randomized community trial. Am J Public Health 2015;105:1475-1481. doi:10.2105/AJPH.2014.302315
69. Haines TP, Russell T, Brauer SG et al. Effectiveness of a video-based exercise programme to reduce falls and improve health-related quality of life among older adults discharged from hospital: A pilot randomized controlled trial. Clin Rehabil 2009;23:973-985. doi:10.1177/0269215509338998
70. Halvarsson A, Franzén E, Farén E, Olsson E, Oddsson L, Ståhle A. Long-term effects of new progressive group balance training for elderly people with increased risk of falling - A randomized controlled trial. Clin Rehabil 2013;27:450-458. doi:10.1177/0269215512462908
71. Harper KJ, Barton AD, Arendts G, Edwards DG, Petta AC, Celenza A. Controlled clinical trial exploring the impact of a brief intervention for prevention of falls in an emergency department. Emerg Med Australas 2017;29:524-530. doi:10.1111/1742-6723.12804
72. Harwood RH, Sahota O, Gaynor K, Masud T, Hosking DJ. A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: The Nottingham Neck of Femur (NoNOF) study. Age Ageing 2004;33:45-51. doi:10.1093/ageing/afh002
73. Hendriks MRC, Bleijlevens MHC, Van Haastregt JCM et al. Lack of effectiveness of a multidisciplinary fall-prevention program in elderly people at risk: A randomized, controlled trial. J Am Geriatr Soc 2008;56:1390-1397. doi:10.1111/j.1532-5415.2008.01803.x
74. Hill A-M, Etherton-Beer C, Haines TP. Tailored Education for Older Patients to Facilitate Engagement in Falls Prevention Strategies after Hospital Discharge-A Pilot Randomized Controlled Trial. PLoS One 2013;8:e63450. doi:10.1371/journal.pone.0063450
75. Hill A-M, McPhail SM, Haines TP et al. Falls after Hospital Discharge: A Randomized Clinical Trial of Individualized Multimodal Falls Prevention Education. Journals Gerontol - Ser A Biol Sci Med Sci 2019;74:1511-1517. doi:10.1093/gerona/glz026
76. Hin H, Tomson J, Newman C et al. Optimum dose of vitamin D for disease prevention in older people: BEST-D trial of vitamin D in primary care. Osteoporos Int 2017;28:841-851. doi:10.1007/s00198-016-3833-y

77. Hogan DB, MacDonald FA, Betts J et al. A randomized controlled trial of a community-based consultation service to prevent falls. CMAJ 2001;165:537-543.
78. Holt KR, Haavik H, Lee ACL, Murphy B, Elley CR. Effectiveness of Chiropractic Care to Improve Sensorimotor Function Associated with Falls Risk in Older People: A Randomized Controlled Trial. J Manipulative Physiol Ther 2016;39:267-278. doi:10.1016/j.jmpt.2016.02.003
79. Hornbrook MC, Stevens VJ, Wingfield DJ, Hollis JF, Greenlick MR, Ory MG. Preventing falls among community-dwelling older persons: Results from a randomized trial. Gerontologist 1994;34:16-23. doi:10.1093/geront/34.1.16
80. Houston DK, Tooze JA, Demons JL et al. Delivery of a Vitamin D Intervention in Homebound Elderly Adults Using a Meals-on-Wheels Program: A Pilot Study. J Am Geriatr Soc 2015;63:1861–1867. doi:10.1111/jgs.13610
81. Huang T. Fall-prevention in Taiwanese elderly adults. University of Texas at Austin; 1998.
82. Huang H-C, Liu C-Y, Huang Y-T, Kernohan WG. Community-based interventions to reduce falls among older adults in Taiwan - long time follow-up randomised controlled study. J Clin Nurs 2010;19:959-968. doi:10.1111/j.1365-2702.2009.02834.x
83. Huang T-T, Yang L-H, Liu C-Y. Reducing the fear of falling among community-dwelling elderly adults through cognitive-behavioural strategies and intense Tai Chi exercise: A randomized controlled trial. J Adv Nurs 2011;67:961-971. doi:10.1111/j.1365-2648.2010.05553.x
84. Imhof L, Naef R, Wallhagen MI, Schwarz J, Mahrer-Imhof R. Effects of an advanced practice nurse in-home health consultation program for community-dwelling persons aged 80 and older. J Am Geriatr Soc 2012;60:2223-2231. doi:10.1111/jgs.12026
85. Iwamoto J, Suzuki H, Tanaka K et al. Preventative effect of exercise against falls in the elderly: A randomized controlled trial. Osteoporos Int 2009;20:1233-1240. doi:10.1007/s00198-008-0794-9
86. Kamei T, Kajii F, Yamamoto Y et al. Effectiveness of a home hazard modification program for reducing falls in urban community-dwelling older adults: A randomized controlled trial. Japan J Nurs Sci 2015;12:184-197. doi:10.1111/jjns.12059
87. Kamide N, Shiba Y, Shibata H. Effects on balance, falls, and bone mineral density of a home-based exercise program without home visits in community-dwelling elderly women: A randomized controlled trial. J Physiol Anthropol 2009;28:115-122. doi:10.2114/jpa2.28.115
88. Karinkanta S, Kannus P, Uusi-Rasi K, Heinonen A, Sievänen H. Combined resistance and balance-jumping exercise reduces older women's injurious falls and fractures: 5-year follow-up study. Age Ageing 2015;44:784-789. doi:10.1093/ageing/afv064
89. Kärkkäinen MK, Tuppurainen M, Salovaara K et al. Does daily vitamin D 800 IU and calcium 1000 mg supplementation decrease the risk of falling in ambulatory women aged 65-71 years? A 3-year randomized population-based trial (OSTPRE-FPS). Maturitas 2010;65:359-365. doi:10.1016/j.maturitas.2009.12.018
90. Kemmler W, Von Stengel S, Engelke K, Häberle L, Kalender WA. Exercise effects on bone mineral density, falls, coronary risk factors, and health care costs in older women: The randomized

controlled senior fitness and prevention (SEFIP) study. Arch Intern Med 2010;170:179-185. doi:10.1001/archinternmed.2009.499

91. Kerse N, Elley CR, Robinson E, Arroll B. Is physical activity counseling effective for older people? A cluster randomized, controlled trial in primary care. J Am Geriatr Soc 2005;53:1951-1956. doi:10.1111/j.1532-5415.2005.00466.x
92. Kerse N, Peri K, Robinson E et al. Does a functional activity programme improve function, quality of life, and falls for residents in long term care? Cluster randomised controlled trial. BMJ 2008;337:a1445. doi:10.1136/bmj.a1445
93. Khaw KT, Stewart AW, Waayer D et al. Effect of monthly high-dose vitamin D supplementation on falls and non-vertebral fractures: secondary and post-hoc outcomes from the randomised, double-blind, placebo-controlled ViDA trial. Lancet Diabetes Endocrinol 2017;5:438-456. doi:10.1016/S2213-8587(17)30103-1
94. Kim H, Yoshida H, Suzuki T. Falls and fractures in participants and excluded non-participants of a fall prevention exercise program for elderly women with a history of falls: 1-year follow-up study. Geriatr Gerontol Int 2014;14:285-292. doi:10.1111/ggi.12095
95. Kingston P, Jones M, Lally F, Crome P. Older people and falls: A randomized controlled trial of a health visitor (HV) intervention. Rev Clin Gerontol 2001;11:209-214. doi:10.1017/S0959259801011327
96. Korpelainen R, Keinänen-Kiukaanniemi S, Heikkinen J, Väänänen K, Korpelainen J. Effect of impact exercise on bone mineral density in elderly women with low BMD: A population-based randomized controlled 30-month intervention. Osteoporos Int 2006;17:109-118. doi:10.1007/s00198-005-1924-2
97. Kovacs E, Prokai L, Meszaros L, Gondos T. Adapted physical activity is beneficial on balance, functional mobility, quality of life and fall risk in community-dwelling older women: A randomized single-blinded controlled trial. Eur J Phys Rehabil Med 2013;49:301-310.
98. Lamb SE, Mistry D, Alleyne S et al. Aerobic and strength training exercise programme for cognitive impairment in people with mild to moderate dementia: The DAPA RCT. Health Technol Assess (Rockv) 2018;22:1-201. doi:10.3310/hta22280
99. Lee JS, Hurley MJ, Carew D, Fisher R, Kiss A, Drummond N. A Randomized Clinical Trial to Assess the Impact on an Emergency Response System on Anxiety and Health Care Use among Older Emergency Patients after a Fall. Acad Emerg Med 2007;14:301-308. doi:10.1197/j.aem.2006.11.017
100. Lee H-C, Chang K-C, Tsauo J-Y, Hung J-W, Huang Y-C, Lin S-I. Effects of a multifactorial fall prevention program on fall incidence and physical function in community-dwelling older adults with risk of falls. Arch Phys Med Rehabil 2013;94:606-615. doi:10.1016/j.apmr.2012.11.037
101. Lehtola S, Hänninen L, Päätaloi M. The Incidence of Fall During Six-Months Exercise Intervention and Four-Months Follow-Up Among Home-Dwelling Persons Aged 70-75 Years. Liik T 2000;6:41-47.

102. Leung KS, Li CY, Tse YK et al. Effects of 18-month low-magnitude high-frequency vibration on fall rate and fracture risks in 710 community elderly - A cluster-randomized controlled trial. Osteoporos Int 2014;25:1785-1795. doi:10.1007/s00198-014-2693-6
103. Li F, Harmer P, Fisher KJ et al. Tai Chi and fall reductions in older adults: A randomized controlled trial. Journals Gerontol - Ser A Biol Sci Med Sci 2005;60A:187-194. doi:10.1093/gerona/60.2.187
104. Li F, Harmer P, Fitzgerald K et al. Effectiveness of a Therapeutic Tai Ji Quan Intervention vs a Multimodal Exercise Intervention to Prevent Falls among Older Adults at High Risk of Falling: A Randomized Clinical Trial. JAMA Intern Med 2018;178:1301-1310. doi:10.1001/jamainternmed.2018.3915
105. Lightbody E, Watkins C, Leathley M, Sharma A, Lye M. Evaluation of a nurse-led falls prevention programme versus usual care: A randomized controlled trial. Age Ageing 2002;31:203-210. doi:10.1093/ageing/31.3.203
106. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons: A randomized, placebo-controlled clinical trial. Ann Intern Med 1996;124:400-406. doi:10.7326/0003-4819-124-4-199602150-00003
107. Liu-Ambrose TYL, Khan KM, Eng JJ, Gillies GL, Lord SR, McKay HA. The beneficial effects of group-based exercises on fall risk profile and physical activity persist 1 year postintervention in older women with low bone mass: Follow-up after withdrawal of exercise. J Am Geriatr Soc 2005;53:1767-1773. doi:10.1111/j.1532-5415.2005.53525.x
108. Liu-Ambrose T, Donaldson MG, Ahamed Y et al. Otago home-based strength and balance retraining improves executive functioning in older fallers: A randomized controlled trial. J Am Geriatr Soc 2008;56:1821-1830. doi:10.1111/j.1532-5415.2008.01931.x
109. Logan PA, Coupland CAC, Gladman JRF et al. Community falls prevention for people who call an emergency ambulance after a fall: Randomised controlled trial. BMJ 2010;340:c2102. doi:10.1136/bmj.c2102
110. Logghe IHJ, Zeeuwe PEM, Verhagen AP et al. Lack of effect of tai chi chuan in preventing falls in elderly people living at home: A randomized clinical trial. J Am Geriatr Soc 2009;57:70-75. doi:10.1111/j.1532-5415.2008.02064.x
111. Lord SR, Ward JA, Williams P, Strudwick M. The effect of a 12 month exercise trial on balance, strenght and falls in older women: a randomised controlled trial. J Am Geriatr Soc 1995;43:1198-1206. doi:10.1111/j.1532-5415.1995.tb07394.x
112. Lord SR, Castell S, Corcoran J et al. The Effect of Group Exercise on Physical Functioning and Falls in Frail Older People Living in Retirement Villages: A Randomized, Controlled Trial. J Am Geriatr Soc 2003;51:1685-1692. doi:10.1046/j.1532-5415.2003.51551.x
113. Lord SR, Tiedemann A, Chapman K, Munro B, Murray SM, Sherrington C. The effect of an individualized fall prevention program on fall risk and falls in older people: A randomized, controlled trial. J Am Geriatr Soc 2005;53:1296-1304. doi:10.1111/j.1532-5415.2005.53425.x
114. Lurie JD, Zagaria AB, Pidgeon DM, Forman JL, Spratt KF. Pilot comparative effectiveness study of surface perturbation treadmill training to prevent falls in older adults. BMC Geriatr 2013;13:49. doi:10.1186/1471-2318-13-49

115. Luukinen H, Lehtola S, Jokelainen J, Väänänen-Sainio R, Lotvonen S, Koistinen P. Pragmatic exercise-oriented prevention of falls among the elderly: A population-based, randomized, controlled trial. Prev Med (Baltim) 2007;44:265-271. doi:10.1016/j.ypmed.2006.09.011
116. MacRae PG, Feltner ME, Reinsch S. A 1-Year Exercise Program for Older Women: Effects on Falls, Injuries, and Physical Performance. J Aging Phys Act 1994;2:127-142. doi:10.1123/japa.2.2.127
117. Madureira MM, Bonfá E, Takayama L, Pereira RMR. A 12-month randomized controlled trial of balance training in elderly women with osteoporosis: Improvement of quality of life. Maturitas 2010;66:206-211. doi:10.1016/j.maturitas.2010.03.009
118. Mahoney JE, Shea TA, Przybelski R et al. Kenosha County falls prevention study: A randomized, controlled trial of an intermediate-intensity, community-based multifactorial falls intervention. J Am Geriatr Soc 2007;55:489-498. doi:10.1111/j.1532-5415.2007.01144.x
119. Markle-Reid M, Browne G, Gafni A et al. The effects and costs of a multifactorial and interdisciplinary team approach to falls prevention for older home care clients "at risk" for falling: A randomized controlled trial. Can J Aging 2010;29:139-161. doi:10.1017/S0714980809990377
120. Matchar DB, Duncan PW, Lien CT et al. Randomized Controlled Trial of Screening, Risk Modification, and Physical Therapy to Prevent Falls Among the Elderly Recently Discharged From the Emergency Department to the Community: The Steps to Avoid Falls in the Elderly Study. Arch Phys Med Rehabil 2017;98:1086-1096. doi:10.1016/j.apmr.2017.01.014
121. McKiernan FE. A simple gait-stabilizing device reduces outdoor falls and nonserious injurious falls in fall-prone older people during the winter. J Am Geriatr Soc 2005;53:943-947. doi:10.1111/j.1532-5415.2005.53302.x
122. McMurdo MET, Mole PA, Paterson CR. Controlled trial of weight bearing exercise in older women in relation to bone density and falls. Br Med J 1997;314:569. doi:10.1136/bmj.314.7080.553
123. McMurdo MET, Millar AM, Daly F. A randomized controlled trial of fall prevention strategies in old peoples' homes. Gerontology 2000;46:83-87. doi:10.1159/000022139
124. McMurdo MET, Price RJG, Shields M, Potter J, Stott DJ. Should oral nutritional supplementation be given to undernourished older people upon hospital discharge? A controlled trial. J Am Geriatr Soc 2009;57:2239-2245. doi:10.1111/j.1532-5415.2009.02568.x
125. Means KM, Rodell DE, O'Sullivan PS. Balance, mobility, and falls among community-dwelling elderly persons: Effects of a rehabilitation exercise program. Am J Phys Med Rehabil 2005;84:238-250. doi:10.1097/01.PHM.0000151944.22116.5A
126. Merom D, Mathieu E, Cerin E et al. Social Dancing and Incidence of Falls in Older Adults: A Cluster Randomised Controlled Trial. PLoS Med 2016;13:e1002112. doi:10.1371/journal.pmed.1002112
127. Miko I, Szerb I, Szerb A, Bender T, Poor G. Effect of a balance-training programme on postural balance, aerobic capacity and frequency of falls in women with osteoporosis: A randomized controlled trial. J Rehabil Med 2018;50:542-547. doi:10.2340/16501977-2349
128. Mikolaizak AS, Lord SR, Tiedemann A et al. A multidisciplinary intervention to prevent subsequent falls and health service use following fall-related paramedic care: A randomised controlled trial. Age Ageing 2017;46:200-208. doi:10.1093/ageing/afw190

129. Möller UO, Kristensson J, Midlöv P, Ekdahl C, Jakobsson U. Effects of a one-year home-based case management intervention on falls in older people: A randomized controlled trial. J Aging Phys Act 2014;22:457-464. doi:10.1123/JAPA.2013-0101
130. Morgan RO, Virnig BA, Duque M, Abdel-Moty E, DeVito CA. Low-Intensity Exercise and Reduction of the Risk for Falls Among At-Risk Elders. Journals Gerontol Ser A Biol Sci Med Sci 2004;59A:1062–1067. doi:10.1093/gerona/59.10.m1062
131. Morris DM. An evaluation of yoga for the reduction of fall risk factors in older adults: Department of Educational Psychology and Learning Systems Florida State University; 2008.
132. Mott DA, Martin B, Breslow R et al. Impact of a medication therapy management intervention targeting medications associated with falling: Results of a pilot study. J Am Pharm Assoc 2016;56:22-28. doi:10.1097/CCM.0b013e31823da96d.Hydrogen
133. Newbury JW, Marley JE, Beilby JJ. A randomised controlled trial of the outcome of health assessment of people aged 75 years and over. Med J Aust 2001;175:104-107. doi:10.5694/j.1326-5377.2001.tb143541.x
134. Ng TP, Feng L, Nyunt MSZ et al. Nutritional, Physical, Cognitive, and Combination Interventions and Frailty Reversal among Older Adults: A Randomized Controlled Trial. Am J Med 2015;128:1225-1236. doi:10.1016/j.amjmed.2015.06.017
135. Nikolaus T, Bach M. Preventing falls in community-dwelling frail older people using a home intervention team (HIT): Results from the randomized falls-HIT trial. J Am Geriatr Soc 2003;51:300-305. doi:10.1046/j.1532-5415.2003.51102.x
136. Nowalk MP, Prendergast JM, Bayles CM, D'Amico FJ, Colvin GC. A randomized trial of exercise programs among older individuals living in two long-term care facilities: The fallsFREE program. J Am Geriatr Soc 2001;49:859-865. doi:10.1046/j.1532-5415.2001.49174.x
137. Ohtake M, Morikagi Y, Suzuki I, Kanoya Y, Sato C. Effects of exercise on the prevention of conditions leading to the need for long-term care. Aging Clin Exp Res 2013;25:49-57. doi:10.1007/s40520-013-0016-y
138. Okubo Y, Osuka Y, Jung S et al. Walking can be more effective than balance training in fall prevention among community-dwelling older adults. Geriatr Gerontol Int 2016;16:118-125. doi:10.1111/ggi.12444
139. Oliveira JS, Sherrington C, Paul SS et al. A combined physical activity and fall prevention intervention improved mobility-related goal attainment but not physical activity in older adults: a randomised trial. J Physiother 2019;65:16-22. doi:10.1016/j.jphys.2018.11.005
140. Olsen CF, Bergland A. The effect of exercise and education on fear of falling in elderly women with osteoporosis and a history of vertebral fracture: Results of a randomized controlled trial. Osteoporos Int 2014;25:2017-2025. doi:10.1007/s00198-014-2724-3
141. Pai Y-C, Bhatt T, Yang F, Wang E. Perturbation training can reduce community-dwelling older adults' annual fall risk: A randomized controlled trial. Journals Gerontol - Ser A Biol Sci Med Sci 2014;69:1586-1594. doi:10.1093/gerona/glu087

142. Palvanen M, Kannus P, Piirtola M, Niemi S, Parkkari J, Järvinen M. Effectiveness of the Chaos Falls Clinic in preventing falls and injuries of home-dwelling older adults: A randomised controlled trial. Injury 2014;45:265-271. doi:10.1016/j.injury.2013.03.010
143. Pardessus V, Puisieux F, Di Pompeo C, Gaudefroy C, Thevenon A, Dewailly P. Benefits of home visits for falls and autonomy in the elderly: A randomized trial study. Am J Phys Med Rehabil 2002;81:247-252. doi:10.1097/00002060-200204000-00002
144. Park H, Kim KJ, Komatsu T, Park SK, Mutoh Y. Effect of combined exercise training on bone, body balance, and gait ability: A randomized controlled study in community-dwelling elderly women. J Bone Miner Metab 2008;26:254-259. doi:10.1007/s00774-007-0819-z
145. Parry SW, Bamford C, Deary V, et al. Cognitive–behavioural therapy-based intervention to reduce fear of falling in older people: Therapy development and randomised controlled trial – the strategies for increasing independence, confidence and energy (STRIDE) study. Health Technol Assess (Rockv) 2016;20:1-206. doi:10.3310/hta20560
146. Patil R, Uusi-Rasi K, Tokola K, Karinkanta S, Kannus P, Sievänen H. Effects of a multimodal exercise program on physical function, falls, and injuries in older women: A 2-year community-based, randomized controlled trial. J Am Geriatr Soc 2015;63:1306-1313. doi:10.1111/jgs.13489
147. Peel N, Steinberg M, Williams G. Home safety assessment in the prevention of falls among older people. Aust N Z J Public Health 2000;24:536-539. doi:10.1111/j.1467-842X.2000.tb00506.x
148. Pekkarinen T, Löyttyniemi E, Välimäki M. Hip fracture prevention with a multifactorial educational program in elderly community-dwelling Finnish women. Osteoporos Int 2013;24:2983-2992. doi:10.1007/s00198-013-2381-y
149. Perry SD, Radtke A, McIlroy WE, Fernie GR, Maki BE. Efficacy and Effectiveness of a Balance-Enhancing Isole. J Gerontol Med Sci 2008;63A:595-602. doi:10.1093/gerona/63.6.595
150. Pérula LA, Varas-Fabra F, Rodríguez V et al. Effectiveness of a multifactorial intervention program to reduce falls incidence among community-living older adults: A randomized controlled trial. Arch Phys Med Rehabil 2012;93:1677-1684. doi:10.1016/j.apmr.2012.03.035
151. Pighills AC, Torgerson DJ, Sheldon TA, Drummond AE, Bland JM. Environmental assessment and modification to prevent falls in older people. J Am Geriatr Soc 2011;59:26-33. doi:10.1111/j.1532-5415.2010.03221.x
152. Pit SW, Byles JE, Henry DA, Holt L, Hansen V, Bowman DA. A Quality Use of Medicines program for general practitioners and older people: A cluster randomised controlled trial. Med J Aust 2007;187:23-30. doi:10.5694/j.1326-5377.2007.tb01110.x
153. Porthouse J, Cockayne S, King C, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3 ) for prevention of fractures in primary care. BMJ. 2005;330:1-6.
154. Rantz M, Phillips LJ, Galambos C et al. Randomized Clinical Trial of Technology to Automatically Detect Early Signs of Illness in Senior Housing. J Am Med Dir Assoc 2017;18:860-870.
155. Reinsch S, MacRae P, Lachenbruch PA, Tobis JS. Attempts to Prevent Falls and Injury: A Prospective Community Study. Gerontologist 1992;32:450-456. doi:10.1093/geront/32.4.450

156. Robertson MC, Devlin N, Gardner MM, Campbell AJ. Effectiveness and economic evaluation of a nurse delivered home exercise programme to prevent falls. 1: Randomised controlled trial. Br Med J 2001;322:1-6. doi:10.1136/bmj.322.7288.701
157. Robson E, Edwards J, Gallagher E, Baker D. Steady as you go (SAYGO): A falls-prevention program for seniors living in the community. Can J Aging 2003;22:207-216.
158. Rubenstein LZ, Josephson KR, Trueblood PR, et al. Effects of a group exercise program on strength, mobility, and falls among fall-prone elderly men. Journals Gerontol - Ser A Biol Sci Med Sci 2000;55A:M317-M321. doi:10.1093/gerona/55.6.M317
159. Rubenstein LZ, Alessi CA, Josephson KR, Trinidad Hoyl M, Harker JO, Pietruszka FM. A randomized trial of a screening, case finding, and referral system for older veterans in primary care. J Am Geriatr Soc 2007;55:166-174. doi:10.1111/j.1532-5415.2007.01044.x
160. Russell MA, Hill KD, Day LM et al. A randomized controlled trial of a multifactorial falls prevention intervention for older fallers presenting to emergency departments. J Am Geriatr Soc 2010;58:2265-2274. doi:10.1111/j.1532-5415.2010.03191.x
161. Ryan JW, Spellbring AM. Implementing strategies to decrease risk of falls in older women. J Gerontol Nurs 1996;22:25-31. doi:10.3928/0098-9134-19961201-10
162. Sakamoto K, Endo N, Harada A et al. Why not use your own body weight to prevent falls? A randomized, controlled trial of balance therapy to prevent falls and fractures for elderly people who can stand on one leg for ≤15 s. J Orthop Sci 2013;18:110-120. doi:10.1007/s00776-012-0328-3
163. Sales M, Polman R, Hill KD, Levinger P. A Novel Exercise Initiative for Seniors to Improve Balance and Physical Function. J Aging Health 2017;29:1424-1443. doi:10.1177/0898264316662359
164. Salminen MJ, Vahlberg TJ, Salonoja MT, Aarnio PTT, Kivela S-L. Effect of a risk-based multifactorial fall prevention program on the incidence of falls. J Am Geriatr Soc 2009;57:612-619.
165. Sambrook PN, Cameron ID, Chen JS et al. Does increased sunlight exposure work as a strategy to improve vitamin D status in the elderly: A cluster randomised controlled trial. Osteoporos Int 2012;23:615-624. doi:10.1007/s00198-011-1590-5
166. Sanders KM, Stuart AL, Williamson EJ et al. Annual high-dose oral vitamin D and falls and fractures in older women: A randomized controlled trial. JAMA 2010;303:1815-1822. doi:10.1001/jama.2010.594
167. Sattin RW, Easley KA, Wolf SL, Chen Y, Kutner MH. Reduction in fear of falling through intense tai chi exercise training in older, transitionally frail adults. J Am Geriatr Soc 2005;53:1168-1178. doi:10.1111/j.1532-5415.2005.53375.x
168. Schoene D, Valenzuela T, Toson B et al. Interactive cognitive-motor step training improves cognitive risk factors of falling in older adults - A randomized controlled trial. PLoS One 2015;10:e0145161. doi:10.1371/journal.pone.0145161
169. Schoon Y, Bongers KTJ, Olde Rikkert MGM. Feasibility study by a single-blind randomized controlled trial of self-management of mobility with a gait-speed feedback device by older persons at risk for falling. Assist Technol Published online 2018:1-7. doi:10.1080/10400435.2018.1529004

170. Serra-Prat M, Sist X, Domenich R et al. Effectiveness of an intervention to prevent frailty in pre-frail community-dwelling older people consulting in primary care: A randomised controlled trial. Age Ageing 2017;46:401-407. doi:10.1093/ageing/afw242
171. Sherrington C, Lord SR, Vogler CM et al. A post-hospital home exercise program improved mobility but increased falls in older people: A randomised controlled trial. PLoS One 2014;9:e104412. doi:10.1371/journal.pone.0104412
172. Shigematsu R, Okura T, Nakagaichi M et al. Square-stepping exercise and fall risk factors in older adults: A single-blind, randomized controlled trial. Journals Gerontol - Ser A Biol Sci Med Sci 2008;63A:76-82. doi:10.1093/gerona/63.1.76
173. Shigematsu R, Okura T, Sakai T, Rantanen T. Square-stepping exercise versus strength and balance training for fall risk factors. Aging Clin Exp Res 2008;20:19-24. doi:10.1007/BF03324743
174. Shimada H, Obuchi S, Furuna T, Suzuki T. New intervention program for preventing falls among frail elderly people: The effects of perturbed walking exercise using a bilateral separated treadmill. Am J Phys Med Rehabil 2004;83:493-499. doi:10.1097/01.PHM.0000130025.54168.91
175. Shumway-Cook A, Silver IF, LeMier M, York S, Cummings P, Koepsell TD. Effectiveness of a community-based multifactorial intervention on falls and fall risk factors in community-living older adults: A randomized, controlled trial. Journals Gerontol - Ser A Biol Sci Med Sci 2007;62A:1420-1427. doi:10.1093/gerona/62.12.1420
176. Siegrist M, Freiberger E, Geilhof B et al. Fall Prevention in a Primary Care Setting: The Effects of a Targeted Complex Exercise Intervention in a Cluster Randomized Trial. Dtsch Arztebl Int 2016;113:365-372. doi:10.3238/arztebl.2016.0365
177. Sihvonen S, Sipilä S, Taskinen S, Era P. Fall incidence in frail older women after individualized visual feedback-based balance training. Gerontology 2004;50:411-416. doi:10.1159/000080180
178. Skelton D, Dinan S, Campbell M, Rutherford O. Tailored group exercise (Falls Management Exercise — FaME) reduces falls in community-dwelling older frequent fallers (an RCT). Age Ageing 2005;34:636-636. doi:10.1093/ageing/afi174
179. Smith H, Anderson F, Raphael H, Maslin P, Crozier S, Cooper C. Effect of annual intramuscular vitamin D on fracture risk in elderly men and women - A population-based, randomized, double-blind, placebo-controlled trial. Rheumatology 2007;46:1852-1857. doi:10.1093/rheumatology/kem240
180. Smulders E, Weerdesteyn V, Groen BE et al. Efficacy of a short multidisciplinary falls prevention program for elderly persons with osteoporosis and a fall history: A randomized controlled trial. Arch Phys Med Rehabil 2010;91:1705-1711. doi:10.1016/j.apmr.2010.08.004
181. Spice CL, Morotti W, George S et al. The Winchester falls project: A randomised controlled trial of secondary prevention of falls in older people. Age Ageing 2009;38:33-40. doi:10.1093/ageing/afn192
182. Stam H, Van Der Wouden JC, Hugtenburg JG, Twisk JWR, Van Der Horst HE, Maarsingh OR. Effectiveness of a multifactorial intervention for dizziness in older people in primary care: A cluster randomised controlled trial. PLoS One 2018;13:e0204876. doi:10.1371/journal.pone.0204876

183. Stanmore EK, Mavroeidi A, De Jong LD et al. The effectiveness and cost-effectiveness of strength and balance Exergames to reduce falls risk for people aged 55 years and older in UK assisted living facilities: A multi-centre, cluster randomised controlled trial. BMC Med 2019;17:1-14. doi:10.1186/s12916-019-1278-9
184. Steadman J, Donaldson N, Kalra L. A randomized controlled trial of an enhanced balance training program to improve mobility and reduce falls in elderly patients. J Am Geriatr Soc 2003;51:847-852. doi:10.1046/j.1365-2389.2003.51268.x
185. Stevens M, Holman CDJ, Bennett N, de Klerk N. Preventing Falls in Older People: Outcome Evaluation of a Randomized Controlled Trial. J Am Geriatr Soc 2001;49:1448–1455. doi:10.1046/j.1532-5415.2001.4911236.x.
186. Suttanon P, Hill KD, Said CM et al. Feasibility, safety and preliminary evidence of the effectiveness of a home-based exercise programme for older people with Alzheimer's disease: A pilot randomized controlled trial. Clin Rehabil 2013;27:427-438. doi:10.1177/0269215512460877
187. Suttanon P, Piriyaprasarth P, Krootnark K, Aranyavalai T. Effectiveness of falls prevention intervention programme in community-dwelling older people in Thailand: Randomized controlled trial. Hong Kong Physiother J 2018;38:1-11. doi:10.1142/S1013702518500014
188. Suzuki T, Kim H, Yoshida H, Ishizaki T. Randomized controlled trial of exercise intervention for the prevention of falls in community-dwelling elderly Japanese women. J Bone Miner Metab 2004;22:602-611. doi:10.1007/s00774-004-0530-2
189. Tan PJ, Khoo EM, Chinna K et al. Individually-tailored multifactorial intervention to reduce falls in the Malaysian Falls Assessment and Intervention Trial (MyFAIT): A randomized controlled trial. PLoS One 2018;13:e0199219. doi:10.1371/journal.pone.0199219
190. Taylor D, Hale L, Schluter P et al. Effectiveness of tai chi as a community-based falls prevention intervention: A randomized controlled trial. J Am Geriatr Soc 2012;60:841-848. doi:10.1111/j.1532-5415.2012.03928.x
191. Tchalla AE, Lachal F, Cardinaud N et al. Preventing and managing indoor falls with home-based technologies in mild and moderate Alzheimer's disease patients: Pilot study in a community dwelling. Dement Geriatr Cogn Disord 2013;36:251-261. doi:10.1159/000351863
192. Thomas KS, Parikh RB, Zullo AR, Dosa D. Home-delivered meals and risk of self-reported falls: Results from a randomized trial. J Appl Gerontol 2018;37:41-57. doi:10.1177/0733464816675421
193. Tinetti ME, Baker DI, McAvay G et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. N Engl J Med 1994;331:821-827. doi:10.1056/NEJM199409293311301
194. Tousignant M, Corriveau H, Roy P-M, Desrosiers J, Dubuc N, Hébert R. Efficacy of supervised Tai Chi exercises versus conventional physical therapy exercises in fall prevention for frail older adults: A randomized controlled trial. Disabil Rehabil 2013;35:1429-1435. doi:10.3109/09638288.2012.737084
195. Trombetti A, Hars M, Herrmann FR, Kressig RW, Ferrari S, Rizzoli R. Effect of music-based multitask training on gait, balance, and fall risk in elderly people: A randomized controlled trial. Arch Intern Med 2011;171:525-533. doi:10.1001/archinternmed.2010.446

196. Ueda T, Higuchi Y, Imaoka M, Todo E, Kitagawa T, Ando S. Tailored education program using home floor plans for falls prevention in discharged older patients: A pilot randomized controlled trial. Arch Gerontol Geriatr 2017;71:9-13. doi:10.1016/j.archger.2017.02.010
197. Uusi-Rasi K, Patil R, Karinkanta S, et al. Exercise and vitamin D in fall prevention among older women: a randomized clinical trial. JAMA Intern Med 2015;175:703-711. doi:10.1001/jamainternmed.2015.0225
198. Van Der Meer HG, Wouters H, Pont LG, Taxis K. Reducing the anticholinergic and sedative load in older patients on polypharmacy by pharmacist-led medication review: A randomised controlled trial. BMJ Open 2018;8:e019042. doi:10.1136/bmjopen-2017-019042
199. van Haastregt JCM, Diederiks JPM, van Rossu E, de Witte LP, Voorhoeve PM, Crebolder HFJM. Effects of a programme of multifactorial home visits on falls and mobility impairments in elderly people at risk: randomised controlled trial. Br Med J 2000;321:994-998. doi:10.1136/bmj.321.7267.994
200. Verrusio W, Gianturco V, Cacciafesta M, Marigliano V, Troisi G, Ripani M. Fall prevention in the young old using an exoskeleton human body posturizer: a randomized controlled trial. Aging Clin Exp Res 2017;29:207-214. doi:10.1007/s40520-016-0540-7
201. Vetter NJ, Lewis PA, Ford D. Can health visitors prevent fractures in elderly people? Br Med J 1992;304:888-890. doi:10.1136/bmj.304.6831.888
202. Villar MTA, Hill P, Inskip H, Thompson P, Cooper C. Will elderly rest home residents wear hip protectors? Age Ageing 1998;27:195-198. doi:10.1093/ageing/27.2.195
203. Vind AB, Andersen HE, Pedersen KD, Joergensen T, Schwarz P. Effect of a program of multifactorial fall prevention on health-related quality of life, functional ability, fear of falling and psychological well-being. A randomized controlled trial. Aging Clin Exp Res 2010;22:249-254. doi:10.3275/6628
204. Vogler CM, Sherrington C, Ogle SJ, Lord SR. Reducing Risk of Falling in Older People Discharged From Hospital: A Randomized Controlled Trial Comparing Seated Exercises, Weight-Bearing Exercises, and Social Visits. Arch Phys Med Rehabil 2009;90:1317-1324. doi:10.1016/j.apmr.2009.01.030
205. Von Stengel S, Kemmler W, Engelke K, Kalender WA. Effects of whole body vibration on bone mineral density and falls: Results of the randomized controlled ELVIS study with postmenopausal women. Osteoporos Int 2011;22:317-325. doi:10.1007/s00198-010-1215-4
206. Voukelatos A, Cumming RG, Lord SR, Rissel C. A randomized, controlled trial of tai chi for the prevention of falls: The central sydney tai chi trial. J Am Geriatr Soc 2007;55:1185-1191. doi:10.1111/j.1532-5415.2007.01244.x
207. Voukelatos A, Merom D, Sherrington C, Rissel C, Cumming RG, Lord SR. The impact of a home-based walking programme on falls in older people: The easy steps randomised controlled trial. Age Ageing 2015;44:377-383. doi:10.1093/ageing/afu186
208. Wagner EH, LaCroix AZ, Grothaus L et al. Preventing disability and falls in older adults: A population-based randomized trial: Commentary. Am J Public Health 1994;84:1800-1806. doi:10.2105/ajph.84.11.1800

209. Weber V, White A, McIlvried R. An electronic medical record (EMR)-based intervention to reduce polypharmacy and falls in an ambulatory rural elderly population. J Gen Intern Med 2008;23:399-404. doi:10.1007/s11606-007-0482-z
210. Weerdesteyn V, Rijken H, Geurts ACH, Smits-Engelsman BCM, Mulder T, Duysens J. A five-week exercise program can reduce falls and improve obstacle avoidance in the elderly. Gerontology 2006;52:131-141. doi:10.1159/000091822
211. Wesson J, Clemson L, Brodaty H et al. A feasibility study and pilot randomised trial of a tailored prevention program to reduce falls in older people with mild dementia. BMC Geriatr 2013;13:89. doi:10.1186/1471-2318-13-89
212. Whitehead C, Wundke R, Crotty M, Finucane P. Evidence-based clinical practice in falls prevention: a randomised controlled trial of a falls prevention service. Aust Heal Rev 2003;26:88-97. doi:10.1071/AH030088
213. Whitehead PJ, Walker MF, Parry RH, Latif Z, McGeorge ID, Drummond AER. Occupational Therapy in HomEcare Re-ablement Services (OTHERS): results of a feasibility randomised controlled trial. BMJ Open 2016;6:e011868. doi:10.1136/bmjopen-2016-011868
214. Whitehead PJ, Golding-Day MR, Belshaw S, Dawson T, James M, Walker MF. Bathing adaptations in the homes of older adults (BATH-OUT): Results of a feasibility randomised controlled trial (RCT). BMC Public Health 2018;18:1293. doi:10.1186/s12889-018-6200-4
215. Wolf SL, Sattin RW, Kutner M, O'Grady M, Greenspan AI, Gregor RJ. Intense Tai Chi Exercise Training and Fall Occurrences in Older, Transitionally Frail Adults: A Randomized, Controlled Trial. J Am Geriatr Soc 2003;51:1693-1701. doi:10.1046/j.1532-5415.2003.51552.x
216. Woo J, Hong A, Lau E, Lynn H. A randomised controlled trial of Tai Chi and resistance exercise on bone health, muscle strength and balance in community-living elderly people. Age Ageing 2007;36:262-268. doi:10.1093/ageing/afm005
217. Yokoi K, Yoshimasu K, Takemura S, Fukumoto J, Kurasawa S, Miyashita K. Short stick exercises for fall prevention among older adults: A cluster randomized trial. Disabil Rehabil 2015;37:1268-1276. doi:10.3109/09638288.2014.961660
218. Zieschang T, Schwenk M, Becker C, Uhlmann L, Oster P, Hauer K. Falls and Physical Activity in Persons with Mild to Moderate Dementia Participating in an Intensive Motor Training Randomized Controlled Trial. Alzheimer Dis Assoc Disord 2017;31:307-314. doi:10.1097/WAD.0000000000000201
219. Zijlstra GAR, Van Haastregt JCM, Ambergen T et al. Effects of a multicomponent cognitive behavioral group intervention on fear of falling and activity avoidance in community-dwelling older adults: Results of a randomized controlled trial. J Am Geriatr Soc 2009;57:2020-2028. doi:10.1111/j.1532-5415.2009.02489.x
220. Zijlstra GAR, Van Haastregt JCM, Kempen GIJM. Zicht op Evenwicht': Een effectieve interventie om bezorgdheid om te vallen en gerelateerd vermijdingsgedrag bij ouderen te verminderen. Tijdschr Gerontol Geriatr 2012;43:164-175. doi:10.1007/s12439-012-0026-9

Companion reports:

1. Huang T-T, Acton GJ. Effectiveness of home visit falls prevention strategy for Taiwanese community-dwelling elders: Randomized trial. Public Health Nurs 2004;21:247-256.
2. Liu-Ambrose T, Khan KM, Eng JJ, Janssen PA, Lord SR, McKay HA. Both Resistance and Agility Training Reduce Fall Risk in 75–85 Year Old Women with Low Bone Mass: A Six-Month Randomized Controlled. J Am Geriatr Soc 2004;52:657-665. doi:10.1111/j.1532-5415.2004.52200.x
3. Uusi-Rasi K, Patil R, Karinkanta S et al. A 2-Year Follow-Up After a 2-Year RCT with Vitamin D and Exercise: Effects on Falls, Injurious Falls and Physical Functioning Among Older Women. J Gerontol A Biol Sci Med Sci 2017;72:1239-1245. doi:10.1093/gerona/glx044

CHAPTER 9

9

# General discussion

Cardiovascular disease is the most common cause of death in Europe with annually 3.8 million deaths and more than 60 million potential life years lost.[1] In 2020, the average age of death from cardiovascular disease in the Netherlands was 78 years for men and 84 years for women.[2] New cardiac interventions have improved survival in cardiovascular disease.[3–5] In the older population, there is strong variability in health and functional status, which is partly due to the presence of frailty and geriatric impairments.[6,7] Therefore, besides age, factors such as cognitive and functional status, frailty and comorbidity are important predictors of mortality and input for the shared decision-making process.[8] A comprehensive geriatric assessment (CGA) is a multidisciplinary assessment that systematically examines a patient's medical, mental, functional and social capabilities and limitations.[9,10] It is an effective instrument to identify geriatric impairments and frailty. In this thesis, first we assessed the prevalence of geriatric impairments and frailty resulting from CGA in different populations with cardiovascular disease, and the association of these impairments and frailty with post-operative adverse events (Part 1). Next, we studied the impact of medication, in particular statin therapy, and of polypharmacy on postoperative outcomes in patients with cardiovascular disease (Part 2). Finally, we explored the effectiveness of (multicomponent) interventions on geriatric impairments. In Part 2 of this thesis, we investigated whether medication review interventions are associated with improved outcomes in older persons. In Part 3, we examined which fall prevention interventions are associated with a decrease in falls and fall-related fractures in older persons. In this general discussion, we will discuss and interpret the main findings of this thesis, and elaborate on the implications and future perspectives.

## Main findings, interpretation and implications

### Part 1. Geriatric impairments in patients with cardiovascular disease

In Chapter 2 of this thesis, we presented the prevalence of frailty and (geriatric) impairments in 73 patients aged ≥40 years who underwent CGA as part of the patient selection procedure for heart transplantation (HTx) and left ventricular assist devices (LVAD). HTx and LVAD are advanced therapies which may be indicated in case of chronic end-stage heart failure that remains refractory despite individualized optimal medical and conventional device therapy. In 97% of patients, at least 1 impairment resulted from CGA. The most common impairments were polypharmacy, high morbidity burden, reduced renal function, osteopenia, depression, poor quality of life, reduced functionality, (risk of) malnutrition, reduced grip strength and high caregiver burden. A small proportion (7% according to Fried's frailty criteria, 6% according to the Edmonton Frail Scale) of the potential LVAD and HTx candidates were frail and 39% were pre-frail. Most recommendations were made regarding 1. education (about the intervention and expected clinical course postoperatively), patient counselling, shared decision making

and advance care planning; 2. delirium risk and prevention; 3. mobility and fall prevention; and 4. malnutrition or weight reduction. The domains for which most impairments were found and the domains for which most treatment recommendations were given matched well, with the functional domain as the frontrunner. This study has demonstrated that, despite the relatively young population already informally pre-selected by cardiologists, impairments are common in all four domains of CGA.

To our knowledge, there are no previous studies in which CGA has been performed in potential candidates for LVAD and HTx. Some studies have been conducted on the prevalence of individual components of CGA, such as multimorbidity, polypharmacy, malnutrition, frailty, sleep quality, depression, cognitive impairment, anxiety, quality of life, and caregiver burden. The results of those studies are difficult to compare with the present study, given the heterogeneity with regard to heart failure severity, age of the study population, definitions used for geriatric impairments, and the timing within the pathway of LVAD implantation or HTx (ranging from pre-intervention screening to many years after surgery and everything in between.)[11–17] The studies in which impairments were measured just before LVAD implantation or HTx showed higher rates of malnutrition (using a different measurement tool than in the current study)[18] and approximately equal rates of depression.[19] At discharge after LVAD implantation, the prevalence of hyperpolypharmacy was found to be higher than at screening prior to LVAD and HTx as in the current study, which is quite conceivable since LVAD implantation and HTx involve starting new medication.[20]

In Chapter 3 and 4, we evaluated the prevalence of frailty and geriatric impairments in TAVI candidates, and the association with post-operative adverse events. In Chapter 3, 431 TAVI candidates who visited the geriatric outpatient clinic for preoperative screening were included. In this study, we focused on frailty status, which was assessed according to the Groningen Frailty Indicator. Frailty was present in 36% of the patients. Frailty was associated with a higher risk of the composite outcome of postoperative complications (odds ratio (OR) 1.55; 95% confidence interval (CI) 1.03 to 2.34), 30-day mortality (OR 4.84; 95% CI 1.62 to 14.49)], 3-month mortality (OR 2.52; 95% CI 1.00 to 6.28) and 1-year mortality (OR 2.96; 95% CI 1.46 to 6.00), when compared to non-frailty. In Chapter 4, we determined the prevalence and prognostic value of a more comprehensive set of geriatric impairments in 490 patients who underwent TAVI. Geriatric impairments were found to be common in this population. A third of these patients (35%) were frail and over 50% had a high comorbidity burden. Polypharmacy (≥5 medications) was present in 83% of patients and hyperpolypharmacy (≥10 medications) in 33%. Frequently present geriatric impairments were cognitive impairment, dependence in instrumental activities of daily living (IADL) and ADL, (a risk of) malnutrition, reduced walking speed and handgrip strength. In multivariate analyses, cognitive impairment was identified as an independent predictor of major postoperative complications during hospitalisation (OR 2.16; 95% CI 1.14 to 4.19) and the composite outcome of mortality and hospital readmissions within

three months of TAVI and major postoperative complications during hospitalisation (OR 2.40; 95% CI 1.21 to 4.79).

In recent years, a number of studies have included older adults who underwent CGA prior to TAVI.[21–23] As in Chapter 4, these studies found high prevalences of multimorbidity, cognitive impairment, malnutrition, limitations in (i)ADL and impaired gait, but a direct comparison is limited due to heterogeneity in instruments used and cut-off values applied. Baritello and colleagues conducted a review of pre-intervention frailty assessments in older patients undergoing TAVI and identified 49 different frailty assessments, which leads to a wide range of frailty prevalence estimates for TAVI recipients, ranging from 6% to 90% for single indicators and 15% to 85% for multidimensional frailty instruments.[24] The association of frailty with an increased risk of short- and long-term mortality in older patients undergoing TAVI found in Chapter 3 is consistent with the previous literature.[25] In Chapter 4, frailty was not found to be an independent predictor of the composite outcome consisting of mortality, hospitalisation and postoperative complications. This is probably due to multicollinearity, as the multivariate analysis included variables that (indirectly) indicate frailty (multimorbidity, cognitive impairment, disability in iADL and gait speed) and thus are highly correlated with frailty. In the univariate analysis, the association between frailty and the composite outcome was borderline significant (OR 1.47; 95% CI 0.99 to 2.19), p=0.06. The independent association found in Chapter 4 between cognitive impairment and postoperative adverse events is confirmed in a recent systematic review and meta-analysis on the impact of pre-existing cognitive impairment on outcomes after TAVI.[26] The explanation for this association is not yet clear. It is possible that the increased risk of delirium in patients with cognitive decline contributes to the increased risk of postoperative complications. Also, it is likely that in a proportion of the patients with cognitive impairment, the aetiology is vascular. The presence of vascular risk factors may explain the increased risk of postoperative morbidity in patients with cognitive impairment.[27]

In conclusion, the studies from Chapters 2 to 4 demonstrate that geriatric impairments and frailty are highly prevalent in (older) adults undergoing various cardiac interventions. The studies in TAVI candidates (Chapter 3 and 4) confirm the available literature on the prevalence of geriatric impairments in this population, and the study of geriatric impairments in potential LVAD and HTx candidates (Chapter 2) adds new information to the current body of evidence. The geriatric impairments and frailty in TAVI candidates have also been found to be associated with adverse outcomes, and are therefore an important input in the shared decision-making process regarding the proportionality of cardiac interventions. Also, frailty and geriatric impairments identified through CGA can be indicators of interventions to improve the pre-operative level of fitness and reduce the risk of adverse outcomes. However, studies have shown that geriatric impairments in older adults with CVD are often not well recognised by involved physicians (e.g. cardiologists) in daily practice.[28,29] The CGA is ideally suited to systematically diagnose

geriatric impairments in all four domains of a person's health, making this instrument an important contribution to optimising patient care and the shared decision-making process in older and/or frail patients.

Usually, CGA is applied to adults aged 65 years and older. In the studies of this thesis, CGA was for the first time and successfully applied to potential candidates for LVAD and HTx aged at least 40 years. A number of measurement tools related to CGA are validated in patients with heart failure.[30,31] Yet, these tools related to CGA are not validated in younger adults. If longitudinal studies confirm that (geriatric) impairments have a predictive value on adverse outcomes in candidates for LVAD or HTx, and CGA is applied to detect these impairments and improve the quality of patient selection and patient care, it would be recommended to validate this instrument in this younger population with end-stage heart failure. It is important to conduct further longitudinal research to investigate the prognostic value of frailty and (geriatric) impairments assessed with CGA. Patient selection for LVAD and HTx is complex, and this information can improve the quality of the patient selection process. This requires more understanding of the pre- and postoperative reversibility of impairments, also through longitudinal studies. In case of reversibility, HTx or LVAD intervention will be considered to be more suitable than in case of irreversible impairments. Only one pilot study evaluated the effect of an individual multimodal pre-habilitation programme in 19 patients awaiting heart transplantation. They found significant increases in functional capacity, exercise capacity, quality of life and emotional well-being in 11 patients who were re-evaluated before heart transplantation.[32] However, no formal assessment of frailty or other impairments was performed before and after the intervention.[32] No cardiovascular or other exercise-related events occurred during the supervised training. There is preliminary evidence from another study that frailty is (partially) reversible after LVAD or HTx.[33] It is known that frailty status is dynamic, and one possible explanation for decrease in frailty after LVAD or HTx is that frailty and heart failure share common pathological pathways of low-grade inflammation and metabolic stress that decreases after the intervention.[34]

Many different conceptual definitions of frailty are in use. However, the tools available to evaluate frailty are based on two basic concepts of frailty: the physical frailty phenotype and the multidimensional cumulative deficit model. In Chapter 2 of this thesis, we used both Fried's physical frailty criteria and the multidomain Edmonton Frail Scale to assess frailty. It was found that four out of five patients with an ambiguous advice for LVAD or HTx resulting from CGA were rated as non-frail by the Edmonton Frails scale. According to Fried's criteria, one patient was assessed as non-frail and 4 patients as pre-frail. One in three patients with a negative advice for LVAD or HTx was assessed as non-frail by both the Edmonton Frail scale and Fried's frailty criteria. Thus, relative high proportions of patients with an ambiguous or negative advice were not identified as frail. Although the multidomain components of the Edmonton Frail Scale nicely reflect CGA, subtle deficits

in cognition, social support, anxiety, or nutritional status are not detected with this instrument. Comorbidity is also not assessed in either instrument. These subtle deficits and comorbidity may have contributed to the ambiguous or negative advices. Our expert-based experience in determining frailty in potential LVAD and HTx candidates is that CGA is the most appropriate assessment to determine frailty, given the wide range of geriatric impairments and the subtle abnormalities it identifies.

Given the high prevalence and proven negative effect of geriatric impairments on adverse outcomes in patients with CVD, interventions that can have a beneficial effect on these outcomes should be explored. Parts 2 and 3 of the general discussion address various interventions, including medication review and fall prevention interventions in older patients.

## Part 2. Medication use in patients with cardiovascular disease and the impact of medication review interventions in older adults

Despite the emergence of multiple intervention options in recent decades, medication-based treatment is still the cornerstone of CVD treatment.[35] For instance, randomised controlled trials (RCTs) have shown a significant protective effect of statins on adverse outcomes in patients with coronary heart disease.[36] The effect of statins in patients undergoing TAVI implantation is less clear. The combination of several medications, termed polypharmacy in the case of the concomitant use of ≥5 medications,[37] can also have adverse effects, especially in multimorbid (older) adults with CVD. In this part of the discussion, we elaborate on the potential protective effect of statins in patients undergoing TAVI and on the prevalence and impact of polypharmacy in patients with an LVAD. Finally, we discuss interventions to improve polypharmacy and medication appropriateness.

In Chapter 6, we assessed whether statin treatment is associated with 90-day mortality, 90-day readmissions, and major postoperative complications during hospitalisation, and the composite of these outcomes in older patients undergoing TAVI. In 584 patients, of whom 56% were treated with a statin, we found no significant association between statin use and the aforementioned outcomes. This finding on short-term outcomes is consistent with previous observational studies on cardiovascular complications and mortality in TAVI patients.[38–41] However, multiple observational studies and two meta-analyses showed a protective effect of statin use on long-term outcomes of TAVI.[42,43] Available studies indicated that the beneficial effect of statins in reducing the risk of all-cause mortality was more evident with high-intensity statin treatment (HIS) than low or moderate-intensity treatment.[39] Because our study had a relatively small number of patients treated with HIS, this probably has resulted in too little power to demonstrate whether there are significant associations between HIS and the outcomes. Apart from this, there is no clear explanation for the discrepancy in the effect of statin use on short-term and long-term outcomes. Some studies have suggested a direct nonatherosclerotic or pleiotropic effect

of statins (amongst others anti-inflammatory) during the postoperative period following TAVI. Yet, the studies on short-term outcomes did not confirm this. Available studies are all observational and in a large proportion of the studies there is no information on statin adherence in the period after TAVI. It should be considered that the protective effect of statins on long-term outcomes could be the result of residual confounding (e.g. statin use could reflect an increased health awareness) or a reduction in cardiovascular events due to coronary heart disease (CHD), since concomitant CHD disease is common in patients undergoing TAVI.[44] In the study presented in Chapter 6, we found no significant effect of statin use on cardiovascular events. Results of studies on whether the effect of statins is greatest in TAVI patients with or without (risk of) CHD disease are conflicting.[41,45] Ideally, a randomised controlled double-blind trial dividing TAVI patients into different statin intensity groups, in which medication adherence is explored, might eliminate bias. This will be ethically challenging as a proportion of patients have a clear indication for a statin given relevant comorbidities. In addition, when improved outcomes in statin users are found, this could also result from an effect on CHD. A possible answer to both issues is to choose a study population without (an increased risk of) CHD. It is also important to properly analyse outcomes (mortality and morbidity) for whether or not they are related to CHD.

Polypharmacy is often the result of an attempt to comply with single-disease oriented (cardiovascular) clinical guidelines. A recent literature review found that the prevalence of polypharmacy in patients with heart failure ranges from 17 to 99%.[46] In the general older population, polypharmacy is related to an increased risk of adverse drug reactions, drug–drug interactions, drug–disease interactions, non-adherence, cognitive impairment, malnutrition, urine incontinence, decline in physical functioning, and increased risk of falls and delirium.[47–49] A number of factors account for the high incidence of drug related problems in the older population with polypharmacy. The process of biological ageing is often accompanied by changes in pharmacokinetics and pharmacodynamics leading to increased drug sensitivity.[50] Moreover, older patients with multimorbidity often involve multiple medical specialists. These specialists all prescribe the best evidence-based therapy for the condition in question, but often do not adequately consider the patient's multimorbidity and consequences of complex pharmacotherapy. Lack of consideration of characteristics of older patients, such as cognitive impairment, depressed mood, reduced manual dexterity and swallowing ability, may lead to reduced adherence.
The negative effects of polypharmacy are also recognised in patients with heart failure.[51] However, little is known about the prevalence and impact of (hyper)polypharmacy in patients with an LVAD. In Chapter 5, we assessed the impact of total medication use on outcomes in 210 patients aged ≥40 years on LVAD support. The prevalence of patients with 5-9 medications (polypharmacy) and ≥10 medications (hyperpolypharmacy) was 63% and 35%, respectively. Over a quarter of patients (27%) died after a median of 828

days following LVAD implantation. The prescription of ≥10 medications was significantly associated with a higher risk of mortality (adjusted for comorbidity burden) when compared to the use of <10 medications.

A remarkable fact of the association found in Chapter 5 between hyperpolypharmacy and increased mortality risk is the median time to death of more than 2 years. This leads to the hypothesis that the association found is not the direct result of the aforementioned consequences of polypharmacy, but that hyperpolypharmacy may be strongly related to another confounding factor. Potentially important confounding factors for this association are frailty and comorbidity. In the study of Chapter 5, the association between hyperpolypharmacy and mortality remained significant after adjusting for comorbidity burden, age, sex and device type. No adjustment was made for frailty as there were no data available on frailty status in this retrospective study. There are no other studies available on polypharmacy in patients with LVAD to compare our results with. A recent study in a more general population of adults aged ≥70 years in the emergency department strengthens the hypothesis that the association between (hyper)polypharmacy and short-term mortality is at least partly explained by the presence of frailty.[52] The question is whether frailty contributes to the development of (hyper)polypharmacy or vice versa. A systematic review found that longitudinally, non-frail persons with polypharmacy were at significantly higher odds for developing prefrailty compared to those not exposed to polypharmacy, even after adjustment for comorbidities.[53] To our knowledge, only one study has examined the longitudinal association between frailty and polypharmacy. This study found that frail women aged ≥ 77 years had an increased risk of developing persistent polypharmacy compared with non-frail women.[54] This suggests a potential bi-directional association between frailty and polypharmacy.[53,55] Contrary to the above, another cohort study consisting of patients aged 70 years and older found that polypharmacy in (pre-)frail older adults is associated with mortality, disability, hospitalisation and emergency room visits, but not in non-frail older adults.[56] This latter suggests that frailty may act as modulator of the negative impact of polypharmacy on health outcomes.[57] In conclusion, it is plausible that the association found in Chapter 5 between hyperpolypharmacy and mortality in patients on LVAD support is at least partly explained by the confounding effect of frailty. This substantiates that it is important for clinicians to recognise hyperpolypharmacy as a red flag in the treatment of these patients. It is likely that hyperpolypharmacy in itself leads to increased morbidity and mortality risk, but it also indicates the probable presence of frailty. In the heart failure population and specifically in the LVAD population, frailty is a well-known predictor of adverse outcomes.[58,59] There is a need to further investigate whether frailty and polypharmacy can be improved and whether this affects outcomes in this population.

In recent years, there has been a shift from a focus on reducing polypharmacy to a focus on reducing medication inappropriateness. Polypharmacy and medication inappropriateness

are highly correlated. Polypharmacy is associated with both prescribing drugs that may be inappropriate for (older) people, known as potentially inappropriate drugs (PIMs), and not prescribing appropriate drugs, known as potential prescribing omissions (PPOs).[60] The OPERAM (optimising therapy to prevent avoidable hospital admission in the multimorbid elderly) substudy on potentially preventable drug-related hospital admissions found that exacerbation of heart failure was the most common cause of potentially preventable drug-related hospital admissions, due to both overtreatment (e.g. NSAIDs) and undertreatment (angiotensin-converting enzyme inhibitors, B-blockers and diuretics).[61] Different approaches are available to screen for PIMs and PPOs, yet we tend to overestimate the effectiveness of medication and underestimate the potential harm of medication, especially in frail patients.[62–64] Realising this, recent years there is a less-is-more attitude towards medication use. Therefore, deprescribing is recommended when possible to optimise medication therapy.[65] Yet, relatively few RCTs have been conducted on deprescribing-related interventions specifically targeting cardiovascular medications.[66] A small RCT in patients with recovered dilated cardiomyopathy found that medication for heart failure (loop diuretics, mineralocorticoid receptor antagonists, B-blockers) cannot simply be discontinued given the high risk of heart failure relapse after treatment withdrawal.[67] A study of statin discontinuation in patients with a life expectancy ≤ 1 year and a history of CVD in most participants found no difference in mortality between the groups that discontinued statins and those that continued. Discontinuation of statins may even improve quality of life.[68] A study of antihypertensive drug discontinuation in patients with mild cognitive impairment found that antihypertensive drug discontinuation did not lead to an improvement in cognitive, psychological or general daily functioning, but also did not lead to an increase in adverse events.[69]

A medication review is a potential approach to improve medication appropriateness and deprescribe medication. Available evidence indicate that 8-13% of hospital admissions are associated with drug related problems, of which 50% are preventable.[70] In Chapter 7 of this thesis, we investigated the efficacy of medication review interventions for preventing hospital readmissions through a systematic review and network meta-analysis. Twenty-five RCTs evaluating the effectiveness of medication review with or without co-interventions in adults aged ≥65 were included. Medication review in combination with (a) medication reconciliation and patient education and (b) medication reconciliation, patient education, professional education and transitional care were associated with a lower risk of all-cause hospital readmission within 30 days compared to usual care. Medication review combined with medication reconciliation, patient education, professional education and transitional care resulted in a reduction of hospital readmissions at any time compared to usual care. Medication review without co-interventions did not significantly influence hospital readmissions. A recent Cochrane review update of RCTs of medication reviews for hospitalised older patients confirmed this association with a decline in hospital

readmissions.[71] A subgroup analysis within the Cochrane review found no difference in effect between trials including medication review with co-interventions (e.g. written information to the patient, primary care physician or community pharmacy) and trials with basic medication reviews. However, there was heterogeneity within the group of medication review with co-interventions. A number of previous studies have highlighted the importance of co-interventions.[72–74] Medication review combined with co-interventions is effective to reduce the risk of hospital readmissions in hospitalised or recently discharged adults ≥ 65 years.

In conclusion, we found that statin treatment is not associated with an improved short-term risk of mortality, readmissions, and major postoperative complications, and the composite of these outcomes in older patients undergoing TAVI. Furthermore, we showed that hyperpolypharmacy is associated with an increased mortality risk in patients on LVAD support. This finding substantiates that it is important for clinicians to recognise hyperpolypharmacy as a red flag in the treatment of these patients. Furthermore, it is important to perform a multicomponent medication review intervention to reduce the risk of hospital readmissions. In addition to medication review, medication reconciliation, patient education, healthcare professional education and transitional care are essential components that need to be implemented in clinical practice to reach this positive effect on hospital readmissions.

## Part 3. Fall prevention interventions in older adults

In part 3 of the general discussion, we explore the effect of interventions on the geriatric impairments falls and fall-related fractures. Falling is a relevant geriatric impairment because it occurs often in adults aged 65 and older and can have far-reaching consequences.[75,76] Various cardiovascular diseases and in some cases their medical treatment lead to an increased risk of falls.[77,78] In Chapter 8, we compared the effectiveness of single, multiple, and multifactorial interventions to prevent falls and fall-related fractures in community-dwelling persons aged ≥65 years through a systematic review and network meta-analysis of 220 RCTs. Fall prevention interventions can be divided into three main groups: 1) single interventions (participants receive one type of intervention), 2) multiple interventions (participants receive the same, fixed combination of two or more types of interventions), and 3) multifactorial interventions (participants receive a personalized selection out of two or more types of interventions, according to the results of a pre-executed, personal falls risk assessment).

The single interventions exercise and quality improvement strategies (e.g. patient education) were associated with reductions in number of fallers, compared with usual care. Exercise as a single intervention was associated with a reduction in falls rate. Common components of multiple interventions significantly associated with a reduction in number of fallers and falls rate were exercise, assistive technology, environmental assessment

and modifications, quality improvement strategies, and basic falls risk assessment (e.g., medication review). When ranking interventions by effectiveness, multicomponent interventions were generally found to be more effective than single interventions. Multifactorial interventions were also associated with a reduction in falls rate, but not with a reduction in the numbers of fallers.

The following single interventions, compared with usual care, were associated with reductions in number of fall-related fractures: basic falls risk assessment and exercise. Multiple interventions were not significantly associated with less fall-related fractures. For the outcome fall-related fractures, we did not analyse the effect of multifactorial interventions because of a lack of power due to the limited size of the network.

In 2017 Tricco et al. presented the first network meta-analysis on fall prevention.[79] They concluded that exercise as a single intervention and various multicomponent interventions were associated with lower risk of injurious falls compared with usual care. Chapter 8 updated this study. To the best of our knowledge, since the publication of Chapter 8 of this thesis, no (network) meta-analysis has been conducted on the effectiveness of the full range of fall prevention interventions in community-dwelling older people. Since publication, several new studies have examined the effectiveness of single interventions and multifactorial interventions, and our findings were further confirmed in these studies.[80–82] The study by Lee et al.[82] involved a meta-analysis of the effect of multifactorial interventions and found a lowering effect on the number of fallers, which was not found in our study and the most recent Cochrane review on this topic.[83]

Over half of the studies included in Chapter 8 had methodological short comings (lack of allocation concealment and blinding). This points to a major limitation within the current evidence base and highlights the need for more robust study procedures/reporting methods on which future fall prevention policy can be based on.

In conclusion, some single interventions, with exercise being the most studied, are associated with a reduction in number of fallers, falls rate and number of fall-related fractures. Yet, multicomponent interventions in particular are effective in reducing number of fallers and falls rate. Important components of multicomponent interventions include exercise, assistive technology, environmental assessment and modifications, quality improvement strategies, and basic falls risk assessment. In case it is preferred or only feasible to implement one intervention, an exercise intervention is recommended to reduce falls. Given the multifactorial nature of falls, a multicomponent intervention is preferable to a single intervention in routine fall prevention care for community-dwelling older adults.

## Conclusion and future perspectives

This thesis revealed that geriatric impairments (e.g. polypharmacy, reduced functionality and malnutrition) and frailty are common in patients with CVD, in particular those screened for LVAD, HTx and TAVI. These geriatric impairments and frailty are associated with adverse outcomes. Since cognitive impairment was identified as an independent predictor of adverse outcomes in patients undergoing TAVI, it is important to screen for cognitive impairment in potential candidates for TAVI. As mentioned in the introduction, it is well known that geriatric impairments are usually multifactorial conditions. In line with this, both network meta-analyses we conducted showed that multicomponent interventions in particular are effective in preventing adverse outcomes. Multicomponent medication review interventions including medication reconciliation, patient education, education of healthcare professional and transitional care have a positive effect on hospital readmissions. Multicomponent fall prevention interventions including exercise, assistive technology, environmental assessment and modifications, quality improvement strategies, and basic falls risk assessment are effective in reducing fall risk. The network meta-analysis on medication review interventions showed the importance of paying attention to transitional care. Future studies are needed to assess the effect, feasibility and challenges of implementation of these interventions. In the Netherlands, the recently initiated trial 'Less Is More: Optimised pharmacotherapy with improved coNtinuity of CarE in hospitaLised oLder peOple (LIMONCELLO) will investigate the effect of a medication review in hospitalised patients, including cardiac patients. This study will focus on patient involvement and transitional care with involvement of relevant hospital specialists, the general practitioner and community pharmacist. This transitional care is important, as previous large multicentre studies on the effect of improving medication appropriateness have shown that a relatively low percentage of medication recommendations were implemented.[84,85]

Future research should also confirm and further explore the impact of geriatric impairments and frailty on outcomes in specific cardiovascular populations, amongst others potential LVAD and HTx candidates. Knowledge of the prognostic value of these impairments provides a better understanding of the potential risks of intervention and therefore can improve shared decision-making. Further research is also needed on which multicomponent interventions are most effective in reducing geriatric impairments and frailty in this cardiovascular population and the effect on clinical outcomes.

## References


1. Townsend N, Kazakiewicz D, Wright F., et al. Epidemiology of cardiovascular disease in Europe. *Nat Rev Cardiol*. 2022;19(2):133-143.
2. Koop Y, Wimmers RH, Bots ML, Vaartjes I. Jaarcijfers Hart- en Vaatziekten 2021: sterfte door hart- en vaatziekten. 2021.
3. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2022;43(7):561-632.
4. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med*. 2001;345(20):1435-1443.
5. Khush KK, Cherikh WS, Chambers DC, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult heart transplantation report — 2019; focus theme: Donor and recipient size match. *J Hear Lung Transplant*. 2019;38(10):1056-1066.
6. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric Syndromes: Clinical, Research and Policy Implications of a Core Geriatric Concept. *J Am Geriatr Soc*. 2007;55(5):780-791.
7. Ferrucci L, Kuchel GA. Heterogeneity of Aging: Individual Risk Factors, Mechanisms, Patient Priorities, and Outcomes. *J Am Geriatr Soc*. 2021;69(3):610-612.
8. Landi F, Liperoti R, Russo A, et al. Disability, more than multimorbidity, was predictive of mortality among older persons aged 80 years and older. *J Clin Epidemiol*. 2010;63(7):752-759.
9. Stuck A, Siu A, Wieland G, Adams J, Rubenstein L. Comprehensive geriatric assessment: a meta-analysis of controlled trials. *Lancet*. 1993;342(8878):1032-1036.
10. Devons CAJ. Comprehensive geriatric assessment: making the most of the aging years. *Curr Opin Clin Nutr Metab Care*. 2002;5(1):19-24.
11. Atila N, Ozsaker E. Depression, anxiety, stress levels, and coping styles of caregivers of patients with left ventricular assist device. *Perspect Psychiatr Care*. 2022;58(4):2414-2422.
12. Choi JJ, Oldham MA, Pancharovski T, et al. Cognitive Change After Left Ventricular Assist Device Implantation: A Case Series and Systematic Review. *J Acad Consult Psychiatry*. 2022;63:599-606.
13. Gomis-Pastor M, Roig Mingell E, Mirabet Perez S, et al. Multimorbidity and medication complexity: New challenges in heart transplantation. *Clin Transplant*. 2019;33(10):e13682.
14. Grady KL, Okwuosa I, Andrei AC, et al. Patient and Caregiver Health-related Quality of Life and Caregiver Burden While Awaiting Heart Transplantation: Findings From the Sustaining Quality of Life of the Aged: Heart Transplant or Mechanical Support (SUSTAIN-IT) Study. *Transplant Direct*. 2021;7(12):E796.
15. Macdonald P. Frailty of the heart recipient. *Transplantation*. 2021;105(11):2352-2361.
16. Mols RE, Bakos I, Christensen B, Horváth-Puhó E, Løgstrup BB, Eiskjær H. Influence of multimorbidity and socioeconomic factors on long-term cross-sectional health care service utilization in heart transplant recipients: A Danish cohort study. *J Hear Lung Transplant*. 2022;41(4):527-537.

17. Yost G, Bhat G, Mahoney E, Tatooles A. Reduced Anxiety and Depression in Patients With Advanced Heart Failure After Left Ventricular Assist Device Implantation. *Psychosomatics*. 2017;58(4):406-414.
18. Aggarwal A, Kumar A, Gregory MP, et al. Nutrition assessment in advanced heart failure patients evaluated for ventricular assist devices or cardiac transplantation. *Nutr Clin Pract*. 2013;28(1):112-119.
19. D'Aoust RF, Antonsdottir I, Budhathoki C, Casida J. Sleep quality and depression in adults with durable left-ventricular assist devices. *Int J Artif Organs*. 2021;44(8):574-579.
20. Dautzenberg L, Numan L, Knol W, et al. Hyperpolypharmacy is a predictor of mortality after left ventricular assist device (LVAD) implantation. *Am Hear J Plus Cardiol Res Pract*. 2022;24:100233.
21. Yu Z, Zhao Q, Ye Y, et al. Comprehensive Geriatric Assessment and Exercise Capacity in Cardiac Rehabilitation for Patients Referred to Transcatheter Aortic Valve Implantation. *Am J Cardiol*. 2021;158:98-103.
22. Roca F, Durand E, Eltchaninoff H, Chassagne P. Predictive Value for Outcome and Evolution of Geriatric Parameters after Transcatheter Aortic Valve Implantation. *J Nutr Heal Aging*. 2020;24(6):598-605.
23. Bobet AS, Brouessard C, Le Tourneau T, Manigold T, De Decker L, Boureau AS. Length of Stay in Older Patients Undergoing Transcatheter Aortic Valve Replacement: Value of a Geriatric Approach. *Gerontology*. 2022;68(7):746-754.
24. Baritello O, Salzwedel A, Sündermann SH, Niebauer J, Völler H. The pandora's box of frailty assessments: Which is the best for clinical purposes in TAVI patients? a critical review. *J Clin Med*. 2021;10(19):4506.
25. Anand A, Harley C, Visvanathan A, et al. The relationship between preoperative frailty and outcomes following transcatheter aortic valve implantation: A systematic review and meta-analysis. *Eur Hear J - Qual Care Clin Outcomes*. 2017;3(2):123-132.
26. Sim JJL, Ling RR, Neo VSQ, et al. The Impact of Cognitive Impairment on Clinical Outcomes After Transcatheter Aortic Valve Implantation (from a Systematic Review and Meta-Analysis). *Am J Cardiol*. 2022;185:63-70.
27. Yanagisawa R, Tanaka M, Yashima F, et al. Frequency and Consequences of Cognitive Impairment in Patients Underwent Transcatheter Aortic Valve Implantation. *Am J Cardiol*. 2018;122(5):844-850.
28. Flood KL, Rohlfing A, Le CV, Carr DB, Rich MW. Geriatric syndromes in elderly patients admitted to an inpatient cardiology ward. *J Hosp Med*. 2007;2(6):394-400.
29. Naylor MD, Stephens C, Bowles KH, Bixby MB. Cognitively impaired older adults: from hospital to home. *Am J Nurs*. 2005;105(2):52-61.
30. Haworth JE, Moniz-Cook E, Clark AL, Wang M, Cleland JGF. An evaluation of two self-report screening measures for mood in an out-patient chronic heart failure population. *Int J Geriatr Psychiatry*. 2007;22(11):1147-1153.

31. Hawkins MAW, Gathright EC, Gunstad J, et al. The MoCA and MMSE as screeners for cognitive impairment in a heart failure population: A study with comprehensive neuropsychological testing. *Hear Lung*. 2014;43(5):462-468.
32. Gimeno-Santos E, Coca-Martinez M, Arguis MJ, et al. Multimodal prehabilitation as a promising strategy for preventing physical deconditioning on the heart transplant waiting list. *Eur J Prev Cardiol*. 2020;27(19):2367-2370.
33. Aili SR, Villanueva JE, Joshi Y, Emmanuel S, Macdonald P. Prevention and Reversal of Frailty in Heart Failure. *Circ J*. 2022;86(1):14-22.
34. DeFilippis EM, Nakagawa S, Maurer MS, Topkara VK. Left Ventricular Assist Device Therapy in Older Adults: Addressing Common Clinical Questions. *J Am Geriatr Soc*. 2019;67(11):2410-2419.
35. Aïdoud A, Gana W, Poitau F, et al. High Prevalence of Geriatric Conditions Among Older Adults With Cardiovascular Disease. *J Am Heart Assoc*. 2023;12(2):e026850.
36. Cheung BMY, Lauder IJ, Lau C-P, Kumana CR. Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes. *Br J Clin Pharmacol*. 2004;57(5):640-651.
37. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC Geriatr*. 2017;17(1):230.
38. Merdler I, Rozenbaum Z, Finkelstein A, et al. Effect of Statin Therapy and Long-Term Mortality Following Transcatheter Aortic Valve Implantation. *Am J Cardiol*. 2019;123(12):1978-1982.
39. Huded CP, Benck LR, Stone NJ, et al. Relation of Intensity of Statin Therapy and Outcomes After Transcatheter Aortic Valve Replacement. *Am J Cardiol*. 2017;119(11):1832-1838.
40. Klinkhammer B. Statin therapy is not associated with improved overall survival after transcatheter aortic valve replacement (TAVR). *J Cardiovasc Dis Res*. 2018;9(2):54-58.
41. Yashima F, Hara M, Inohara T, et al. Statin therapy for patients with aortic stenosis who underwent transcatheter aortic valve implantation: A report from a Japanese multicentre registry. *BMJ Open*. 2021;11(6):e044319.
42. Takagi H, Hari Y, Nakashima K, Kuno T, Ando T. Meta-Analysis for Impact of Statin on Mortality After Transcatheter Aortic Valve Implantation. *Am J Cardiol*. 2019;124(6):920-925.
43. Yarahmadi P, Kabiri A, Forouzannia SM, Yousefifard M. Statins and Mortality of Patients After Transcatheter Aortic Valve Implantation: A Systematic Review and Meta-analysis. *Angiology*. Published online 2022:1-13.
44. Kumar A, Sammour Y, Reginauld S, et al. Adverse clinical outcomes in patients undergoing both PCI and TAVR: Analysis from a pooled multi-center registry. *Catheter Cardiovasc Interv*. 2021;97(3):529-539.
45. Fischer-Rasokat U, Renker M, Bänsch C, et al. Effects of Statins After Transcatheter Aortic Valve Implantation in Key Patient Populations. *J Cardiovasc Pharmacol*. 2021;78(5):669-674.
46. Beezer J, Al Hatrushi M, Husband A, Kurdi A, Forsyth P. Polypharmacy definition and prevalence in heart failure: a systematic review. *Heart Fail Rev*. 2022;27(2):465-492.
47. Seppala LJ, van de Glind EMM, Daams JG, et al. Fall-Risk-Increasing Drugs: A Systematic Review and Meta-analysis: III. Others. *J Am Med Dir Assoc*. 2018;19(4):372.e1-372.e8.

48. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf*. 2014;13(1):57-65.
49. Nobili A, Pasina L, Tettamanti M, et al. Potentially severe drug interactions in elderly outpatients: Results of an observational study of an administrative prescription database. *J Clin Pharm Ther*. 2009;34(4):377-386.
50. Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: Basic principles and practical applications. *Br J Clin Pharmacol*. 2003;57(1):6-14.
51. Sukumar S, Orkaby AR, Schwartz JB, et al. Polypharmacy in Older Heart Failure Patients: a Multidisciplinary Approach. *Curr Heart Fail Rep*. 2022;19(5):290-302.
52. van Dam CS, Labuschagne HA, van Keulen K, et al. Polypharmacy, comorbidity and frailty: a complex interplay in older patients at the emergency department. *Eur Geriatr Med*. 2022;13(4):849-857.
53. Palmer K, Villani ER, Vetrano DL, et al. Association of polypharmacy and hyperpolypharmacy with frailty states: a systematic review and meta-analysis. *Eur Geriatr Med*. 2019;10(1):9-36.
54. Thiruchelvam K, Byles J, Hasan SS, Egan N, Kairuz T. Prevalence and association of continuous polypharmacy and frailty among older women: A longitudinal analysis over 15 years. *Maturitas*. 2021;146:18-25.
55. Cesari M. How polypharmacy affects frailty. *Expert Rev Clin Pharmacol*. 2020;13(11):1179-1181.
56. Bonaga B, Sánchez-Jurado PM, Martínez-Reig M, et al. Frailty, Polypharmacy, and Health Outcomes in Older Adults: The Frailty and Dependence in Albacete Study. *J Am Med Dir Assoc*. 2018;19(1):46-52.
57. Herr M, Robine JM, Pinot J, Arvieu JJ, Ankri J. Polypharmacy and frailty: Prevalence, relationship, and impact on mortality in a French sample of 2350 old people. *Pharmacoepidemiol Drug Saf*. 2015;24(6):637-646.
58. Yang X, Lupón J, Vidán MT, et al. Impact of frailty on mortality and hospitalization in chronic heart failure: A systematic review and meta-analysis. *J Am Heart Assoc*. 2018;7(23):e008251.
59. Meece LE, Yu J, Winchester DE, et al. Prognostic Value of Frailty for Heart Failure Patients Undergoing Left Ventricular Assist Device Implantation: A Systematic Review. *Cardiol Rev. 2023;* Mar 7.
60. Steinman MA, Landefeld CS, Rosenthal GE, Berthenthal D, Sen S, Kaboli PJ. Polypharmacy and prescribing quality in older people. *J Am Geriatr Soc*. 2006;54(10):1516-1523.
61. Sallevelt BTGM, Egberts TCG, Huibers CJA, et al. Detectability of Medication Errors With a STOPP/START-Based Medication Review in Older People Prior to a Potentially Preventable Drug-Related Hospital Admission. *Drug Saf*. 2022;45(12):1501-1516.
62. Ioannidis JPA, Lau J. Completeness of Safety Reporting in Randomized Trials. An Evaluation of 7 Medical Areas. *JAMA*. 2001;285:437-443.
63. Tinetti ME, Bogardus ST, Agostini J V. Potential Pitfalls of Disease-Specific Guidelines for Patients with Multiple Conditions. *N Engl J Med*. 2004;351(27):2870-2874.
64. Fried TR, Mecca MC. Medication Appropriateness in Vulnerable Older Adults: Healthy Skepticism of Appropriate Polypharmacy. *J Am Geriatr Soc*. 2019;67(6):1123-1127.

65. Mangin D, Bahat G, Golomb BA, et al. International Group for Reducing Inappropriate Medication Use & Polypharmacy (IGRIMUP): Position Statement and 10 Recommendations for Action. *Drugs and Aging*. 2018;35(7):575-587.
66. Krishnaswami A, Steinman MA, Goyal P, et al. Deprescribing in Older Adults With Cardiovascular Disease. *J Am Coll Cardiol*. 2019;73(20):2584-2595.
67. Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet*. 2019;393(10166):61-73.
68. Kutner JS, Blatchford PJ, Taylor DH, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. *JAMA Intern Med*. 2015;175(5):691-700.
69. Moonen JEF, Foster-Dingley JC, De Ruijter W, et al. Effect of discontinuation of antihypertensive treatment in elderly people on cognitive functioning-the DANTE Study Leiden: A randomized clinical trial. *JAMA Intern Med*. 2015;175(10):1622-1630.
70. Somers A, Robays H, Vander Stichele R, van Maele G, Bogaert M, Petrovic M. Contribution of drug related problems to hospital admission in the elderly. *J Nutr Health Aging*. 2010;14(6):477-482.
71. Bülow C, Clausen SS, Lundh A, Christensen M. Medication review in hospitalised patients to reduce morbidity and mortality. *Cochrane Database Syst Rev*. 2023;2023(1).
72. Ensing HT, Stuijt CCM, Van Den Bemt BJF, et al. Identifying the Optimal Role for Pharmacists in Care Transitions: A Systematic Review. *J Manag Care Spec Pharm*. 2015;21(8):614-638.
73. Mekonnen AB, Mclachlan AJ, Brien J-AE. Effectiveness of pharmacist-led medication reconciliation programmes on clinical outcomes at hospital transitions: a systematic review and meta-analysis. *BMJ Open*. 2016;6:e010003.
74. Rodrigues DA, Plácido AI, Mateos-Campos R, Figueiras A, Herdeiro MT, Roque F. Effectiveness of Interventions to Reduce Potentially Inappropriate Medication in Older Patients: A Systematic Review. *Front Pharmacol*. 2022;12:777655.
75. National Institute for Health and Care Excell. Falls in older people : assessing risk and prevention. *NICE Clin Guidel*. 2013;June:1-33.
76. Hartholt KA, Van Beeck EF, Polinder S, et al. Societal consequences of falls in the older population: Injuries, healthcare costs, and long-term reduced quality of life. *J Trauma - Inj Infect Crit Care*. 2011;71(3):748-753.
77. de Vries M, Seppala LJ, Daams JG, et al. Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: I. Cardiovascular Drugs. *J Am Med Dir Assoc*. 2018;19(4):371.e1-371.e9.
78. Jansen S, Bhangu J, de Rooij S, Daams J, Kenny RA, van der Velde N. The Association of Cardiovascular Disorders and Falls: A Systematic Review. *J Am Med Dir Assoc*. 2016;17(3):193-199.
79. Tricco AC, Thomas SM, Veroniki AA, et al. Comparisons of interventions for preventing falls in older adults: A systematic review and meta-analysis. *JAMA*. 2017;318(17):1687-1699.

80. Sherrington C, Fairhall NJ, Wallbank GK, et al. Exercise for preventing falls in older people living in the community. *Cochrane database Syst Rev*. 2019;1:CD012424.
81. Yang F, Su X, Sanchez MC, Hackney ME, Butler AJ. Vibration training reducing falls in community-living older adults: a pilot randomized controlled trial. *Aging Clin Exp Res*. Published online 2023:1-12.
82. Lee SH, Yu S. Effectiveness of multifactorial interventions in preventing falls among older adults in the community: A systematic review and meta-analysis. *Int J Nurs Stud*. 2020;106:103564.
83. Hopewell S, Adedire O, Copsey BJ, et al. Multifactorial and multiple component interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev*. 2018;2018(7).
84. O'Mahony D, Gudmundsson A, Soiza RL, 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.
85. Blum MR, Sallevelt BTGM, Spinewine A, et al. Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults (OPERAM): Cluster randomised controlled trial. *BMJ*. 2021;374:n1585.

CHAPTER 10

# 10

# English summary

## Background

The prevalence of cardiovascular disease (CVD) is increasing globally. Many patients with CVD belong to the group of patients aged 75 years and older. New cardiac interventions have improved survival in CVD. However, older age is associated with increased geriatric impairments and complications. Frailty and geriatric impairments such as cognitive impairment, falls and decreased functionality are clinical conditions that are most prevalent in the older population, and often do not fit into separate disease categories because of their multifactorial basis. Frailty is defined as a syndrome of decreased physiological reserve and resistance to stressors. In recent years, evidence has grown that frailty and geriatric impairments may help identify patients at increased risk of adverse postoperative outcomes. Comprehensive geriatric assessment (CGA) is a well-known method that can be used for identification of these high risk patients. CGA is a multidisciplinary assessment that systematically examines a patient's capabilities and limitations regarding the medical, mental, functional and social domains. Frailty and geriatric impairments can be diagnosed through CGA. A medication review is also part of CGA, which is particularly important in patients with polypharmacy. The prevalence of polypharmacy increases with age and is higher in particular patient groups, including patients with CVD. Polypharmacy is associated with a higher risk of adverse outcomes, such as mortality, adverse drug reactions, hospital readmissions and falls. Several recommendations for interventions to decrease the risk of geriatric impairments and complications follow from CGA and medication review. A significant part of these recommendations involve fall prevention interventions.

In this thesis, we assessed the prevalence of geriatric impairments resulting from CGA in different populations with CVD, and the association of these impairments with post-operative adverse events (Part 1). Next, we examined the effect of medication on postoperative outcomes in patients undergoing various cardiac interventions. In addition, we investigated whether medication review interventions are associated with improved outcomes in older persons (Part 2). Finally, we examined which fall prevention interventions are associated with a decrease in falls and fall-related fractures in older persons (Part 3).

### Part 1. Geriatric impairments in patients with cardiovascular disease

Patients with chronic end-stage heart failure that remains refractory despite individualised optimal medical and conventional device therapy may be selected for advanced therapies, including heart transplantation (HTx) and left ventricular assist devices (LVAD). In **Chapter 2**, the prevalence of frailty and (geriatric) impairments was assessed in a cross-sectional study including 73 patients aged ≥40 years who received a CGA as part of the patient selection procedure for LVAD and HTx. In every patient, a conclusion comprising frailty

and other impairments was formulated on the medical, mental, functional, and social domains, and recommendations were made, amongst others to improve the preoperative level of fitness. Frailty was assessed by Fried's frailty criteria and the Edmonton Frail Scale. The mean age of the participants was 58 years (range 40-71). Half of the patients (52%) were screened for HTx, 45% for LVAD, and in two patients both options were still open at the moment of CGA. In 97% of patients, at least 1 impairment resulted from CGA. The most common impairments were polypharmacy, high morbidity burden, reduced renal function, osteopenia, depression, poor quality of life, reduced functionality, (risk of) malnutrition, reduced grip strength and high caregiver burden. A small proportion (6-7%) of the potential LVAD and HTx candidates were frail and 39% were pre-frail. Most recommendations were made regarding 1. education (about the intervention and expected clinical course postoperatively), patient counselling, shared decision making and advance care planning; 2. delirium risk and prevention; 3. mobility and fall prevention; and 4. malnutrition or weight reduction. The domains for which most impairments were found and the domains for which most treatment recommendations were given matched well, with the functional domain as the frontrunner.

This study has demonstrated that, despite the relatively young population already informally pre-selected by cardiologists, impairments are common in all four domains of CGA. Decision making regarding patient selection for LVAD and HTx is complex and unique for each patient. The comprehensive information regarding impairments and associated risks obtained through CGA can be incorporated into this decision making, allowing better consideration of potential risks and benefits. Yet, the prognostic value of the impairments resulting from CGA needs further investigation by means of longitudinal studies.

In recent years, transcatheter aortic valve implantation (TAVI) has become the treatment of choice for patients with severe symptomatic aortic valve stenosis considered to be at increased or high surgical risk. In Chapter 3 and 4, we investigated the prevalence of frailty and geriatric impairments in TAVI candidates, and the association with post-operative adverse events.

In **Chapter 3**, we focused on the association of frailty with outcomes following TAVI. We conducted a cohort study, including all TAVI candidates who visited the geriatric outpatient clinic for preoperative screening. Frailty status was assessed according to the Groningen Frailty Indicator. A total of 431 patients were included. The mean age of the study population was 81 years. Frailty was present in 36% of the patients. Frailty was associated with a higher risk of the composite outcome of postoperative complications (odds ratio (OR) 1.55; 95% confidence interval (CI) 1.03 to 2.34), 30-day mortality (OR 4.84; 95% CI 1.62 to 14.49), 3-month mortality (OR 2.52; 95% CI 1.00 to 6.28) and 1-year mortality (OR 2.96; 95% CI 1.46 to 6.00). Since frailty is common in TAVI candidates and associated with an increased risk of postoperative morbidity and mortality, it is recommended that

the screening and management of frailty will be optimised in guidelines for valvular heart disease.

In **Chapter 4**, we performed a cohort study of patients who were referred to the geriatric outpatient clinic for CGA prior to TAVI. This cohort included 490 patients who underwent TAVI. The mean age was 81 years. A third of these patients (35%) were frail. Polypharmacy (≥5 medications) was present in 83% of patients and hyperpolypharmacy (≥10 medications) in 33%. Geriatric impairments that were often identified were cognitive impairment, dependence in instrumental activities of daily living (IADL) and ADL, (a risk of) malnutrition, reduced walking speed and handgrip strength. In multivariate analyses, cognitive impairment was identified as an independent predictor of major postoperative complications during hospitalisation (OR 2.16; 95% CI 1.14 to 4.19) and the composite outcome of mortality and hospital readmissions within three months of TAVI and major postoperative complications during hospitalisation (OR 2.40; 95% CI 1.21 to 4.79). Therefore, it is important to screen for cognitive impairment prior to TAVI and it is recommended to include this in current TAVI guidelines.

## Part 2. Medication use in patients with cardiovascular disease and the impact of medication review interventions in older adults

In Chapter 5 and 6 we investigated the association between medication use and outcomes in patients undergoing LVAD and TAVI implantation.

Patients with heart failure have a greater comorbidity burden compared to patients of similar age without heart failure. The pharmacological treatment of these cardiac and non-cardiac comorbidities in patients with end-stage heart failure generates polypharmacy, which is associated with a higher risk of overtreatment, undertreatment, medication errors, poor adherence, adverse drug-reactions and drug-drug interactions. No studies are available on the prevalence of polypharmacy and hyperpolypharmacy in patients on LVAD support and the association with adverse outcomes after LVAD implantation. Therefore, in **Chapter 5**, we aimed to determine the prevalence of polypharmacy (5-9 medications) and hyperpolypharmacy (≥10 medications) in patients after primary LVAD implantation and evaluate the association of hyperpolypharmacy with overall mortality and complications while on LVAD support. We performed a retrospective cohort study including 210 patients aged ≥40 years who received a primary LVAD implantation between 2011 and 2019. The median age of the patients was 58 years. The prevalence of patients with 5-9 medications and ≥10 medications was 63% and 35%, respectively. The median follow-up duration was 948 days. The prescription of ≥10 medications was significantly associated with a higher risk of mortality (HR 2.03; 95% CI 1.15-3.6 adjusted for sex, age, comorbidity and stratified for device type) when compared to the use of <10 medications. The prescription of ≥10 medications was not associated with a higher risk of major bleeding, cardiac arrhythmia or driveline infection. Future research is needed to assess the efficacy of individual risk-

benefit profiling of (cardiovascular) medication to ensure appropriate polypharmacy and decrease negative health outcomes.

Previous studies demonstrated that statin treatment is associated with improved one-year survival after TAVI, both in patients with and without coronary artery disease, suggesting pleiotropic effects of statins on preventing perioperative complications. Available studies on short-term outcomes have only focused on cardiovascular outcomes and mortality and not on other complications. Our aim was therefore to determine whether statin treatment is associated with short-term risk of mortality, readmissions, and major postoperative complications, and the composite of these outcomes in older patients undergoing TAVI. In **Chapter 6**, we performed a cohort study including patients aged 65 years and older who underwent CGA prior to TAVI between 2014 and 2021. In total, 584 patients, of whom 56% were treated with a statin, were included. Preoperative statin treatment during TAVI was common, but not associated with decreased risks of short-term outcomes after a TAVI including 90-day mortality, 90-day readmissions, major postoperative complications, and the composite of these outcomes. Additional analysis showed no significant association between statin treatment intensity and any of the short-term outcomes. Because this study had a relatively small number of patients treated with high intensity statin therapy (20% of the patients with a statin), further research is needed to determine whether or not high intensity statin treatment has an effect on short-term outcomes in patients that can tolerate high statin dosages.

Because of the negative effects of (hyper)polypharmacy, we investigated whether medication review leads to improved outcomes in older adults. Previous research showed that medication review leads to improved medication appropriateness, reduced polypharmacy and reduced adverse drug reactions, however, there is little evidence for an effect on clinical outcomes. In **Chapter 7**, we assessed the efficacy of medication review as an isolated intervention and with several co-interventions for preventing hospital readmissions in older adults through a systematic review and network meta-analysis. Twenty-five randomised controlled trials evaluating the effectiveness of medication review interventions with or without co-interventions to prevent hospital readmissions in hospitalised or recently discharged adults aged ≥65 were included. Of these, 11 studies (7,318 participants) contributed to the network meta-analysis on the outcome of all-cause hospital readmission within 30 days. Medication review in combination with (a) medication reconciliation and patient education (risk ratio (RR) 0.45; 95% CI 0.26 to 0.80) and (b) medication reconciliation, patient education, professional education and transitional care (RR 0.64; 95% CI 0.49 to 0.84) were associated with a lower risk of all-cause hospital readmission compared to usual care. Medication review without co-interventions did not significantly influence hospital readmissions (RR 1.06; 95% CI 0.45 to 2.51). The network meta-analysis on the outcome of all-cause hospital readmission at any time included 24

studies (11,677 participants). Medication review combined with medication reconciliation, patient education, professional education and transitional care resulted in a reduction of hospital readmissions (RR 0.82; 95% CI 0.74–0.91) compared to usual care. When the quality of the studies included in this systematic review was appraised, this raised some concerns, mainly regarding allocation concealment, blinding and contamination. Future trials of higher quality are needed in this field.

## Part. 3 Fall prevention interventions in older adults

In **Chapter 8**, we compared the effectiveness of single, multiple, and multifactorial interventions to prevent falls and fall-related fractures in community-dwelling persons aged ≥65 years through a systematic review and network meta-analysis. Fall prevention interventions can be divided into three main groups: 1) single interventions (participants receive one type of intervention), 2) multiple interventions (participants receive the same, fixed combination of two or more types of interventions), and 3) multifactorial interventions (participants receive a personalised selection out of two or more types of interventions, according to the results of a pre-executed, personal falls risk assessment). In total, 220 randomised controlled trials evaluating the effectiveness of fall prevention interventions were included. Network meta-analysis including 192 studies revealed that the following single interventions, compared with usual care, were associated with reductions in number of fallers: exercise (RR 0.83; 95% CI 0.77 to 0.89) and quality improvement strategies (e.g., patient education) (RR 0.90; 95% CI 0.83 to 0.98). Exercise as a single intervention was associated with a reduction in falls rate (RR 0.79; 95% CI 0.73 to 0.86). Common components of multiple interventions significantly associated with a reduction in number of fallers and falls rate were exercise, assistive technology, environmental assessment and modifications, quality improvement strategies, and basic falls risk assessment (e.g., medication review). Multifactorial interventions were associated with a reduction in falls rate (RR 0.87; 95% CI 0.80 to 0.95), but not with a reduction in number of fallers (RR 0.95; 95% CI 0.89 to 1.01). The following single interventions, compared with usual care, were associated with reductions in number of fall-related fractures: basic falls risk assessment (RR 0.60; 95% CI 0.39 to 0.94) and exercise (RR 0.62; 95% CI 0.42 to 0.90). Over half of the studies included had methodological short comings (lack of allocation concealment and high risk of blinding). This points to a major limitation within the current evidence base and highlights the need for more robust study procedures/reporting methods on which future fall prevention policy can be based on.

In **Chapter 9**, we discussed the results of the aforementioned studies and the implications for clinical practice, as well as recommendations for future research. We concluded that geriatric impairments and frailty are common in patients with CVD, in particular those screened for LVAD, HTx and TAVI. Geriatric impairments (amongst others cognitive impairment and hyperpolypharmacy) and frailty were associated with adverse outcomes

in patients with CVD. Knowledge of the prognostic value of these impairments provides a better understanding of the potential risks of intervention and therefore can improve shared decision-making. Hence, future research should further explore the impact of geriatric impairments and frailty on outcomes in specific cardiovascular populations, amongst others potential LVAD and HTx candidates. Further research is also needed on which multicomponent interventions are most effective in reducing geriatric impairments and frailty in this cardiovascular population and the effect on clinical outcomes. In line with the multifactorial nature of geriatric impairments, both network meta-analyses we conducted showed that multicomponent interventions in particular are effective in preventing adverse outcomes. Future studies are needed to assess the effect, feasibility and challenges of implementation of these interventions.

# Addenda

# Nederlandse samenvatting

Hart- en vaatziekten (HVZ) komen wereldwijd steeds meer voor. Veel patiënten met HVZ zijn 75 jaar of ouder. Nieuwe hartinterventies hebben de overleving van HVZ verbeterd. Een hogere leeftijd gaat echter ook gepaard met een hoger risico op het optreden van complicaties. Kwetsbaarheid en geriatrische aandoeningen zoals cognitieve stoornissen, vallen en een verminderde functionaliteit komen met name voor bij de oudere patiënt. Het betreft aandoeningen die vaak niet in afzonderlijke ziektecategorieën passen doordat deze geriatrische aandoeningen multifactorieel bepaald zijn. Kwetsbaarheid wordt gedefinieerd als een syndroom van verminderde fysiologische reserves en een verminderende weerstand tegen stressfactoren. In de afgelopen jaren is aangetoond dat kwetsbaarheid en geriatrische aandoeningen een rol kunnen spelen bij het identificeren van patiënten met een verhoogd risico op ongunstige uitkomsten van een interventie. Het comprehensive geriatric assessment (CGA) is een uitgebreid klinisch geriatrisch onderzoek waarmee de mogelijkheden en beperkingen van een patiënt onderzocht worden op medisch, psychisch, functioneel en sociaal gebied. Doordat kwetsbaarheid en geriatrische aandoeningen gediagnosticeerd kunnen worden door middel van CGA, kan het CGA gebruikt worden om patiënten met een groter risico op nadelige uitkomsten van interventies te identificeren. Een medicatiebeoordeling maakt ook deel uit van het CGA, wat vooral belangrijk is bij patiënten die veel medicatie tegelijkertijd gebruiken (polyfarmacie). Polyfarmacie komt vaker voor op hogere leeftijd en bij patiënten met HVZ. In het geval van polyfarmacie is er een groter risico op onder andere sterfte, bijwerkingen, heropnames in ziekenhuizen en vallen. Uit het CGA en een medicatiebeoordeling volgen verschillende aanbevelingen voor interventies om het risico op geriatrische aandoeningen en complicaties te verminderen. Een deel van deze aanbevelingen betreft valpreventieve interventies.

In dit proefschrift onderzochten we hoe vaak geriatrische aandoeningen voorkomen bij verschillende patiëntgroepen met HVZ, vastgesteld door middel van een CGA. Tevens onderzochten we of deze geriatrische aandoeningen geassocieerd zijn met negatieve uitkomsten van interventies (deel 1). Vervolgens onderzochten we het effect van medicatie op uitkomsten van interventies bij patiënten die verschillende soorten hartinterventies ondergaan. Daarnaast onderzochten we of een medicatiebeoordeling geassocieerd is met verbeterde uitkomsten bij ouderen (deel 2). Tot slot onderzochten we welke valpreventieve interventies geassocieerd zijn met een afname van vallen en valgerelateerde fracturen bij ouderen (deel 3).

## Deel 1. Geriatrische aandoeningen bij patiënten met hart- en vaatziekten

Patiënten met ernstig hartfalen wat onvoldoende reageert op een optimale persoonsgerichte (medicamenteuze) behandeling kunnen worden geselecteerd voor geavanceerde therapieën, waaronder harttransplantatie of een steunhart. Bij een harttransplantatie wordt het hart van een patiënt met ernstig hartfalen vervangen door een donorhart. Een steunhart is een mechanische pomp die de functie van het hart ondersteunt en gedeeltelijk overneemt. In hoofdstuk 2 onderzochten we hoe vaak kwetsbaarheid en (geriatrische) aandoeningen werden vastgesteld door middel van een CGA bij 73 patiënten van 40 jaar of ouder. Deze patiënten werden onderzocht omdat ze mogelijk een harttransplantatie of steunhart-implantatie zouden ondergaan. Voor elke patiënt werd een conclusie geformuleerd met betrekking tot de aanwezigheid van kwetsbaarheid en andere aandoeningen op medisch, mentaal, functioneel en sociaal gebied. Ook werden behandeladviezen gegeven om de conditie voorafgaand aan de ingreep te verbeteren. Kwetsbaarheid werd beoordeeld aan de hand van de kwetsbaarheidscriteria van Fried en de Edmonton Frail Scale. De gemiddelde leeftijd van de deelnemers was 58 jaar. Bij 97% van de patiënten werd ten minste één aandoening gevonden tijden het CGA. De meest voorkomende aandoeningen waren polyfarmacie, het hebben van meerdere ziektes tegelijk (multimorbiditeit), een achteruitgang in nierfunctie, botontkalking, depressie, slechte kwaliteit van leven, verminderde functionaliteit, (risico op) ondervoeding, een verminderde knijpkracht van de hand en een hoge zorglast voor mantelzorgers. Een klein deel (6 tot 7%) van de potentiële kandidaten voor steunhart en harttransplantatie was kwetsbaar en 39% had een voorstadium van kwetsbaarheid. De meeste behandeladviezen werden gedaan met betrekking tot 1). educatie (over de interventie en het verwachte klinische beloop na de interventie), counseling van patiënten, gedeelde besluitvorming en advance care planning; 2). delierrisico en preventie; 3). mobiliteit en valpreventie; en 4). ondervoeding of gewichtsreductie. De domeinen (medisch, psychisch, functioneel en sociaal) waarvoor de meeste aandoeningen werden gevonden en de domeinen waarvoor de meeste behandeladviezen werden gegeven, kwamen goed overeen. Voor het functionele domein werden de meeste aandoeningen gevonden en behandeladviezen gegeven.

Uit dit onderzoek kan geconcludeerd worden dat aandoeningen in alle vier de domeinen veelvuldig voorkomen, ondanks de relatief jonge leeftijd van de patiënten. Tevens heeft er al een informele selectie plaatsgevonden door de betrokken cardioloog waarbij ernstig kwetsbare patiënten niet werden verwezen voor een CGA. De besluitvorming over de selectie van patiënten voor steunhart en harttransplantatie is complex. De uitgebreide informatie over (geriatrische) aandoeningen en daaraan gerelateerde risico's die door het CGA wordt verkregen, kan worden meegenomen in deze besluitvorming, waardoor potentiële risico's en voordelen beter kunnen worden afgewogen. Welke risico's er precies gerelateerd zijn aan de gevonden aandoeningen dient verder onderzocht te worden door middel van longitudinale studies.

Een aortaklepstenose is een vernauwing van de aortaklep en de meest voorkomende hartklepaandoening op hogere leeftijd. Tijdens een Transkatheter Aortaklep Implantatie (TAVI) wordt een klep via een katheter ingebracht en in de aangedane aortaklep geplaatst. De afgelopen jaren is een TAVI de eerste keus behandeling geworden voor patiënten met een ernstige symptomatische aortaklepstenose, waarbij een chirurgische aortaklepvervanging als riskant wordt ingeschat. In hoofdstuk 3 en 4 onderzochten we hoe vaak kwetsbaarheid en geriatrische aandoeningen voorkomen bij TAVI-kandidaten. Ook onderzochten we of dit geassocieerd is met slechte uitkomsten van TAVI.
In hoofdstuk 3 richtten we ons op de associatie tussen kwetsbaarheid en uitkomsten na TAVI. Alle TAVI-kandidaten die de geriatrische polikliniek bezochten voor een CGA als onderdeel van de preoperatieve screening werden in deze studie geïncludeerd. Kwetsbaarheid werd beoordeeld volgens de Groningen Frailty Indicator. In totaal werden 431 patiënten geïncludeerd. De gemiddelde leeftijd van de onderzoekspopulatie was 81 jaar. Kwetsbaarheid werd vastgesteld bij 36% van de patiënten. Kwetsbaarheid was geassocieerd met een hoger risico op postoperatieve complicaties (odds ratio (OR) 1,55; 95% betrouwbaarheidsinterval (CI) 1,03 tot 2,34), 30-dagen mortaliteit (OR 4,84; 95% CI 1,62 tot 14,49), 3-maanden mortaliteit (OR 2,52; 95% CI 1,00 tot 6,28) en 1-jaars mortaliteit (OR 2,96; 95% CI 1,46 tot 6,00). Aangezien kwetsbaarheid veel voorkomt bij TAVI-kandidaten en geassocieerd is met een verhoogd risico op postoperatieve complicaties en overlijden, wordt aanbevolen om de screening naar kwetsbaarheid en de behandeling hiervan te optimaliseren in richtlijnen voor hartkleplijden.
In hoofdstuk 4 voerden we een opnieuw een studie uit naar patiënten die voorafgaand aan een TAVI naar de geriatrische polikliniek waren verwezen voor een CGA. Deze studie omvatte 490 patiënten en de gemiddelde leeftijd was 81 jaar. Een derde van deze patiënten (35%) was kwetsbaar. Polyfarmacie (het gelijktijdig gebruik van ≥5 medicijnen) was aanwezig bij 83% van de patiënten en hyperpolyfarmacie (≥10 medicijnen) bij 33%. Geriatrische aandoeningen die vaak werden gevonden betroffen cognitieve stoornissen, afhankelijkheid in (instrumentele) activiteiten van het dagelijks leven, (een risico op) ondervoeding, verminderde loopsnelheid en handknijpkracht. Cognitieve stoornissen werden geïdentificeerd als een onafhankelijke voorspeller van ernstige postoperatieve complicaties tijdens ziekenhuisopname (OR 2,16; 95% CI 1,14 tot 4,19) en de samengestelde uitkomst van overlijden of heropnames in het ziekenhuis binnen drie maanden na TAVI en ernstige postoperatieve complicaties tijdens ziekenhuisopname (OR 2,40; 95% CI 1,21 tot 4,79). Het is daarom van belang om voorafgaand aan TAVI te screenen op cognitieve stoornissen en het wordt aanbevolen om dit op te nemen in de huidige TAVI-richtlijnen.

## Deel 2. Medicatiegebruik bij patiënten met hart- en vaatziekten en de impact van een medicatiebeoordeling bij oudere volwassenen

In hoofdstuk 5 en 6 onderzochten we de associatie tussen medicatiegebruik en uitkomsten bij patiënten die een steunhart-implantatie en TAVI ondergingen.

Patiënten met hartfalen lijden vaker ook aan andere aandoeningen (comorbiditeit) dan patiënten van vergelijkbare leeftijd zonder hartfalen. De medicamenteuze behandeling van deze cardiale en niet-cardiale comorbiditeit bij patiënten met hartfalen leidt vaak tot polyfarmacie. Polyfarmacie gaat gepaard met een hoger risico op overbehandeling, onderbehandeling, medicatiefouten, slechte therapietrouw, bijwerkingen en interacties tussen medicijnen. Er zijn geen studies beschikbaar over hoe vaak polyfarmacie en hyperpolyfarmacie voorkomen bij patiënten met een steunhart. Ook niet over de associatie tussen polyfarmacie en ongunstige uitkomsten na steunhart-implantatie. Daarom onderzochten we in hoofdstuk 5 hoe vaak polyfarmacie (5-9 medicamenten) en hyperpolyfarmacie (≥10 medicamenten) voorkomt bij patiënten na steunhart-implantatie. Tevens onderzochten we de associatie tussen hyperpolyfarmacie en het optreden van complicaties en overlijden na steunhart-implantatie. We includeerden 210 patiënten van ≥ 40 jaar die tussen 2011 en 2019 een steunhart-implantatie ondergingen. De mediane leeftijd van de patiënten was 58 jaar. Van de 210 patiënten gebruikten 63% 5-9 medicamenten en 35% ≥10 medicamenten. Hyperpolyfarmacie was geassocieerd met een hoger sterfterisico (hazard ratio 2,03; 95% CI 1,15 tot 3,6) in vergelijking met het gebruik van <10 medicamenten. Hyperpolyfarmacie was niet geassocieerd met een hoger risico op complicaties als grote bloedingen, hartritmestoornissen of driveline-infecties. Toekomstig onderzoek is nodig om te achterhalen of een geïndividualiseerde aanpassing na afweging van voor- en nadelen van (cardiovasculaire) medicatie zinvol is om negatieve gezondheidsuitkomsten te verminderen.

Eerdere studies hebben aangetoond dat behandeling met cholesterolverlagers geassocieerd is met een betere overleving één jaar na TAVI, zowel bij patiënten mét een atherosclerotische aandoening van de kransslagaders als zonder. Dit suggereert dat cholesterolverlagers naast het verlagen van cholesterol, mogelijk ook andere positieve effecten hebben die het risico op complicaties na TAVI zouden kunnen verlagen.
Reeds verrichte onderzoeken naar korte termijn effecten van cholesterolverlagers na TAVI hebben zich enkel gericht op specifieke cardiovasculaire uitkomsten en overlijden. Ons doel was daarom om te bepalen of behandeling met cholesterolverlagers bij oudere patiënten die een TAVI ondergaan geassocieerd is met korte termijn effecten op een breder scala aan uitkomsten. Deze uitkomsten betreffen overlijden, ziekenhuisheropnames en postoperatieve complicaties, en de samenstelling van deze uitkomsten. In hoofdstuk 6 includeerden we patiënten van 65 jaar en ouder die tussen 2014 en 2021 een CGA ondergingen voorafgaand aan een TAVI. In totaal werden 584 patiënten geïncludeerd,

waarvan 56% voorafgaand aan de TAVI een cholesterolverlager gebruikte. Het gebruik van een cholesterolverlager voorafgaand aan TAVI bleek niet geassocieerd te zijn met lagere risico's op overlijden of ziekenhuisheropname 90 dagen na implantatie, belangrijke postoperatieve complicaties en de samenstelling van deze uitkomsten. Aanvullende analyse liet ook geen verband zien tussen de dosering van de cholesterolverlager en één van de uitkomsten. In dit onderzoek werd een relatief klein aantal patiënten (20% van alle gebruikers van een cholesterolverlager) behandeld met een hoge dosering cholesterolverlager. Daarom is verder onderzoek nodig om te bepalen of een hogere dosering een gunstig effect heeft op de korte termijn uitkomsten bij patiënten die een hoge dosering kunnen verdragen.

Vanwege de bekende negatieve effecten van (hyper)polyfarmacie, hebben we onderzocht of een medicatiebeoordeling leidt tot beterde uitkomsten bij oudere volwassenen. Een medicatiebeoordeling is een beoordeling van de gebruikte medicatie bij voorkeur door een arts en apotheker op basis van een gestructureerde, kritische evaluatie van de medische-, medicamenteuze- en gebruiksinformatie met als doel het optimaliseren van de effectiviteit van de medicamenteuze behandeling en het verminderen van de kans op gerelateerde problemen (bijvoorbeeld bijwerkingen). Eerder onderzoek toonde aan dat medicatiebeoordeling leidt tot het beter gebruiken van geschikte medicatie, minder polyfarmacie en minder bijwerkingen, maar er is weinig bewijs voor een positief effect op klinische uitkomsten. In hoofdstuk 7 hebben we door middel van een systematische beoordeling van de literatuur en een netwerkmeta-analyse de effectiviteit van een medicatiebeoordeling beoordeeld, zowel als geïsoleerde interventie als in combinatie met verschillende co-interventies. Er werden 25 gerandomiseerde onderzoeken geïncludeerd die de effectiviteit evalueerden van een medicatiebeoordeling met of zonder co-interventies om ziekenhuisheropnames te voorkomen bij opgenomen of recent ontslagen volwassenen van 65 jaar of ouder. Hiervan droegen 11 studies (7.318 deelnemers) bij aan de netwerk meta-analyse naar de uitkomst 'ziekenhuisheropname binnen 30 dagen'. Medicatiebeoordeling in combinatie met (a) medicatiereconciliatie en patiëntvoorlichting (risk ratio (RR) 0,45; 95% CI 0,26 tot 0,80) en (b) medicatiereconciliatie, patiëntvoorlichting, educatie aan de professional en zorg rondom ontslag naar een andere instelling of zorglijn (RR 0,64; 95% CI 0,49 tot 0,84) werden geassocieerd met een lager risico op ziekenhuisheropname binnen 30 dagen in vergelijking met gebruikelijke zorg. Medicatiebeoordeling zonder co-interventies had geen significante invloed op ziekenhuisheropnames binnen 30 dagen (RR 1,06; 95% CI 0,45 tot 2,51). De netwerkmeta-analyse naar de uitkomst 'ziekenhuisheropname op enig moment' omvatte 24 onderzoeken (11.677 deelnemers). Medicatiebeoordeling in combinatie met medicatiereconciliatie, patiëntvoorlichting, educatie aan de professional en zorg rondom ontslag naar een andere instelling of zorglijn resulteerde in een afname van ziekenhuisheropnames op enig moment (RR 0,82; 95% CI 0,74 tot 0,91), vergeleken met gebruikelijke

zorg. Er waren zorgen over de kwaliteit van de studies die in deze systematische literatuur beoordeling waren opgenomen, bijvoorbeeld omdat de toewijzing van patiënten aan een interventiegroep of een controlegroep niet geblindeerd verliep. In de toekomst zijn studies t.a.v. medicatiebeoordeling van hogere kwaliteit nodig.

## Deel 3. Valpreventie bij oudere volwassenen

In hoofdstuk 8 hebben we de effectiviteit onderzocht van enkelvoudige, meervoudige en multifactoriële interventies ter preventie van vallen en val-gerelateerde fracturen onder thuiswonende personen ≥65 jaar door middel van een systematische beoordeling van de literatuur en een netwerkmeta-analyse. Valpreventieve interventies kunnen worden onderverdeeld in drie hoofdgroepen: 1) enkelvoudige interventies: deelnemers ontvangen één soort interventie, 2) meervoudige interventies: deelnemers ontvangen dezelfde, vaste combinatie van twee of meer soorten interventies, en 3) multifactoriële interventies: deelnemers ontvangen een gepersonaliseerde selectie uit twee of meer soorten interventies, gebaseerd op de resultaten van een vooraf uitgevoerde, persoonlijke beoordeling van het valrisico. In totaal werden 220 gerandomiseerde onderzoeken naar de effectiviteit van valpreventieve interventies geïncludeerd. Netwerkmeta-analyse met 192 studies toonde aan dat de volgende enkelvoudige interventies, in vergelijking met gebruikelijke zorg, geassocieerd waren met een vermindering van het aantal mensen dat valt: lichaamsbeweging (RR 0,83; 95% CI 0,77 tot 0,89) en strategieën voor kwaliteitsverbetering (o.a. patiënteducatie) (RR 0,90; 95% CI 0,83 tot 0,98). Lichaamsbeweging als enkelvoudige interventie was ook geassocieerd met een afname van het aantal valincidenten (RR 0,79; 95% CI 0,73 tot 0,86). Veel voorkomende componenten van meervoudige interventies die geassocieerd waren met een vermindering van het aantal mensen dat valt en het aantal valincidenten waren lichaamsbeweging, ondersteunende technologie (hulpmiddelen voor persoonlijke zorg, bescherming, mobiliteit en communicatie), veiliger maken van de woonomgeving, strategieën voor kwaliteitsverbetering en basisevaluatie van het valrisico (bijv. cardiovasculair onderzoek, medicatiebeoordeling). Multifactoriële interventies werden geassocieerd met een afname van het aantal valincidenten (RR 0,87; 95% CI 0,80 tot 0,95), maar niet met een afname van het aantal mensen dat valt (RR 0,95; 95% CI 0,89 tot 1,01). De volgende enkelvoudige interventies, vergeleken met gebruikelijke zorg, waren geassocieerd met reducties in het aantal val-gerelateerde fracturen: basisevaluatie van het valrisico (RR 0,60; 95% CI 0,39 tot 0,94) en lichaamsbeweging (RR 0,62; 95% CI 0,42 tot 0,90). Meer dan de helft van de geïncludeerde onderzoeken had methodologische tekortkomingen. Dit wijst op een belangrijke tekortkoming in het huidige bewijsmateriaal en benadrukt de noodzaak voor robuustere onderzoeksprocedures/rapportagemethoden waarop toekomstig valpreventiebeleid kan worden gebaseerd.

In hoofdstuk 9 bespraken we de resultaten van de bovengenoemde onderzoeken en de implicaties voor de klinische praktijk, evenals aanbevelingen voor toekomstig onderzoek.

We concludeerden dat geriatrische aandoeningen en kwetsbaarheid veel voorkomen bij patiënten met HVZ, in het bijzonder bij patiënten die worden gescreend voor een steunhart, harttransplantatie en TAVI. In deze onderzoeken werd een CGA gebruikt om de kwetsbaarheid te bepalen bij potentiële kandidaten voor steunhart en harttransplantatie. Geriatrische aandoeningen (onder andere cognitieve stoornissen en hyperpolyfarmacie) en kwetsbaarheid werden in verband gebracht met ongunstige uitkomsten bij patiënten met HVZ. Kennis van de prognostische betekenis van deze aandoeningen zorgt voor een beter begrip van de potentiële risico's van een interventie en kan daarom de gezamenlijke besluitvorming verbeteren. Toekomstig onderzoek moet de invloed van geriatrische aandoeningen en kwetsbaarheid op de uitkomsten in specifieke cardiovasculaire populaties verder onderzoeken, onder andere bij potentiële kandidaten voor steunhart en harttransplantatie. Zo is er aanvullend onderzoek nodig naar welke interventies het meest effectief zijn in het verminderen van geriatrische aandoeningen en kwetsbaarheid in deze cardiovasculaire populatie en het effect op klinische uitkomsten.

In lijn met de multifactoriële aard van geriatrische aandoeningen, toonden beide netwerkmeta-analyses die we uitvoerden aan dat met name interventies met meerdere componenten effectief zijn in het voorkomen van ongunstige uitkomsten. Toekomstige studies zijn nodig om het effect, de haalbaarheid en de uitdagingen van de implementatie van deze interventies te onderzoeken.

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# Curriculum vitae

Lauren Dautzenberg was born on July 3, 1992, in Schijndel, the Netherlands. She attended secondary school at 'het Elde college' in Schijndel, from which she graduated in 2010. In 2016, Lauren obtained her medical degree from Erasmus University Rotterdam. A few months later, she started her residency training in Geriatric Medicine, which she will complete in 2026. From 2019 to 2022, Lauren interrupted her residency training to work full-time on PhD research.

Lauren lives with her husband Job Gevers and her children Pieter and Olivia in Schijndel.