Bringing the pieces together

Integrating cardiac and geriatric care in older patients with heart disease

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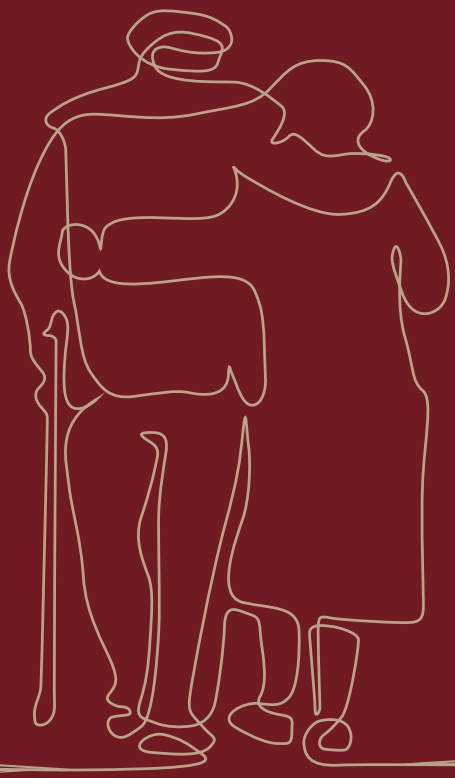

Patricia Jepma

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integrating cardiac and geriatric care in older patients with heart disease

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ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
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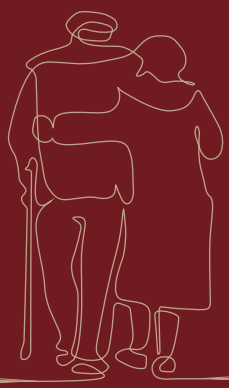
*Both authors equally contributed to this manuscript.

Chapter

1

General introduction



Due to an ageing population and increasing life expectancy, the number of older adults worldwide is expected to more than double in the next decades.[1] In the Netherlands, the number of adults of ≥ 65 years will increase from 2.5 million to 4.6 million between 2010 and 2040.[2] Higher age is an important risk factor for cardiac disease.[3] The incidence of cardiac disease will therefore grow significantly in the next decades,[4] with an expected increase of more than 100% in patients with heart failure and around 65% in patients with coronary artery disease.[5]

The treatment of older cardiac patients is complex due to comorbidities and geriatric conditions such as functional impairment, fall risk, malnutrition and the presence of polypharmacy.[6-8] However, the assessment of geriatric conditions is not part of the medical routine in cardiology and therefore these conditions are frequently unrecognized although they have a significant impact on treatment and on outcomes.[8,9] For example, cognitive impairment may lead to non-adherence to therapeutic regimes[9,10] and functional limitations can cause non-participation in center-based cardiac rehabilitation because of the intensity of the programs, disabling comorbidities and transportation problems.[11,12] In addition, treatments are mostly based on single disease-oriented guidelines and insufficiently take other conditions into account, which may result in conflicting recommendations and treatments.[13] Besides, guidelines currently do not address important outcomes for older patients such as daily functioning, symptom relief and quality of life. Thus, the care of older cardiac patients is suboptimal, which increases the risk of functional loss, readmission and mortality.[6,8] The integration of cardiac and geriatric care for older patients with heart disease is therefore needed.

Part 1: The identification of older hospitalized cardiac patients at high risk of adverse events

After hospital admission for cardiac disease, older patients are at high risk of readmission and mortality, especially in the first weeks post-discharge.[14] Approximately 20% of older patients with acute myocardial infarction or heart failure in the United States are readmitted within 30 days and 8% die in that first period.[14] These serious adverse events are associated with a high burden on patients and families,[13,15] on healthcare and costs.[4] The timely identification of high-risk patients is of great importance to provide early preventive interventions. Patient characteristics such as higher age,[16,17] comorbidities,[18,19] being single,[9,17] a hospital admission in the prior six months[20] and low socioeconomic status[17] are known to increase the risk of adverse events. However, if and how these risks vary by those risk factors during the first period post-discharge is unknown. This knowledge may contribute to the timely initiation of preventive intervention for patients with specific risk factors.

The need to identify hospitalized cardiac patients at risk of readmission has increased significantly in recent years. Many risk prediction models have been developed and systematic reviews have examined the performance of these models.[20-29] However, most reviews conclude that the discrimination of risk prediction models is poor to moderate and that there is a large variety in included predictors. In addition, most models are not readily applicable in daily practice as they lack a clinically useful presentation, such as a risk score or nomogram or use only administrative data.[22] As many new models have been developed and evaluated in recent years, a state-of-the-art overview is needed to examine the performance of clinical risk prediction models, identify characteristics that contribute to better predictions and to investigate predictors that are consistently associated with readmission.

In the Netherlands, the Dutch Safety Management System (DSMS), sponsored by the Ministry of Health, Welfare and Sport,[30] developed a clinically applicable screening tool to identify older patients at high risk of functional loss. This tool was implemented in 2012 and currently all Dutch hospitals are required to systematically screen hospitalized patients ≥ 70 years in four geriatric domains; delirium, falling, functional impairments and malnutrition. Functional loss is associated with a high risk of readmission and mortality.[31-34] Although this tool is currently used in daily practice to identify patients at high risk of functional loss, it is unknown if it is also applicable to identify older hospitalized cardiac patients at high risk for unplanned readmission and mortality.

Part 2: Lifestyle-related secondary prevention of cardiovascular complications in older cardiac patients

Nurse-coordinated interventions in the secondary prevention of cardiovascular complications have been proven to reduce the risk of recurrent cardiovascular events and to improve lifestyle-related risk factors such as weight reduction, physical activity and smoking cessation.[35-37] The Randomized Evaluation of Secondary Prevention by Outpatient Nurse SpEcialists (RESPONSE) trial[38,39] evaluated an outpatient nurse-coordinated intervention including lifestyle modification, biometric risk factors and medication adherence for patients after an acute coronary syndrome. This intervention was effective in reducing drug-treated cardiovascular risk factors and also improved quality of life.[37,38] However, room for improvement remained for the treatment of lifestyle-related risk factors. Therefore, the RESPONSE-2 trial[36,40] was developed, that investigated a community-based lifestyle intervention evaluating nurse-coordinated referral to a comprehensive set of three commercially available lifestyle interventions targeting weight reduction, physical activity and/or smoking cessation. Significant improvements were seen in lifestyle-related risk factors in the intervention group as compared with usual care.

Lifestyle-related interventions are also recommended in older patients and associated with improvements in functional status, cardiovascular risk, and reduced mortality.[3,41-44] However, treatment complexity in older patients is greater, due to polypharmacy, comorbidities, and functional loss, which may interfere with optimal secondary prevention.[8,42,45] In addition, the evidence in older patients is less conclusive as compared to younger patients as older adults are often excluded from clinical trials. This limits the generalizability of guideline recommendations to this population.[3,45] Furthermore, the impact of lifestyle-related interventions may be less in older patients compared to younger patients, due to their limited life expectancy and due to the fact that their unfavorable lifestyles have influenced their health over many decades.[41,46] The health-related consequences may be only partially reversible, in terms of life expectancy. However, other outcomes may still improve by lifestyle modification at later age such as functional independence and quality of life.[41,42,47]

More knowledge on the effectiveness of lifestyle-related secondary prevention in older cardiac patients is therefore needed. It is unknown whether the effects of the RESPONSE-2 trial are also applicable in older cardiac patients. Furthermore, the perspectives of older cardiac patients towards lifestyle-related secondary prevention in relation to their age and disease progression may be different from younger patients. Therefore, older cardiac patients' motivation for lifestyle modification after a hospital admission needs to be investigated.

Part 3: Development and evaluation of a transitional care intervention for older cardiac patients

Transitional care aims to improve continuity of care by multidisciplinary collaboration, structured post-discharge planning and early follow-up home-visits.[48-50] Transitional care was found to be effective in reducing readmission and mortality in several populations.[48,51,52] As older cardiac patients are at high risk of readmission and mortality, transitional care may also be effective in reducing adverse events in this population. We therefore developed the Cardiac Care Bridge program (CCB program) which was a nurse-coordinated, interdisciplinary complex intervention. The Medical Research Council (MRC) framework[53] for complex interventions was used to develop and evaluate the CCB program (figure 1).[54] Phases of d*evelopment, feasibility and piloting and evaluation* were used in the intervention development. The implementation phase is outside the scope of this thesis.

The inspiration for the development of the CCB program (figure 2) was formed by the positive outcomes of the *Transitional Care Bridge* study[52] and the *RESPONSE study*,[37] and on the importance of cardiac rehabilitation. The *Transitional Care Bridge study*[52,55] was a transitional care intervention for acutely hospitalized older patients providing a comprehensive geriatric assessment,

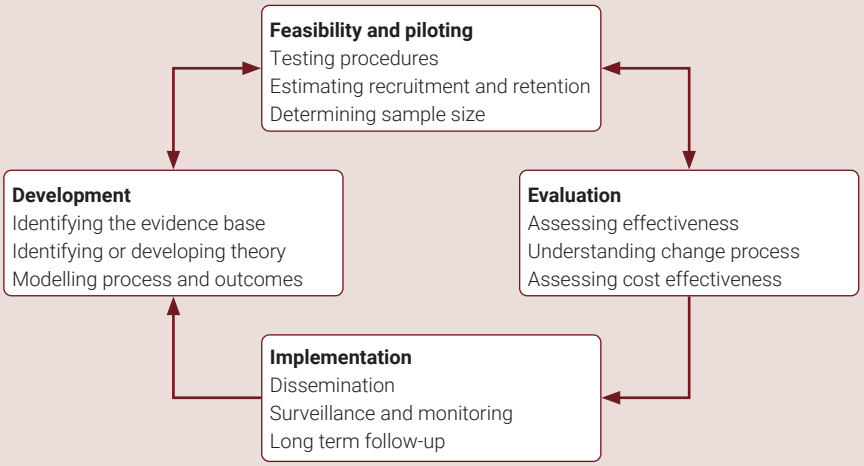


Figure 1. The Medical Research Council (MRC) framework for complex interventions[53]

an integrated care plan and a transitional care program. This program included visits during hospitalization and soon after discharge by a community care registered nurse with a focus on case management. The intervention was associated with a 25% reduction (HR 0.75, 95% CI 0.56-0.99, P=0.045) in mortality.[52] However, no impact was found on ADL-functioning and readmission. The previously mentioned *RESPONSE study*[37,39] evaluated an outpatient nurse-coordinated disease management intervention for patients after an acute coronary syndrome. A relative risk reduction of 17.4% (P=0.021) was found on the Systematic Coronary Risk Evaluation (SCORE) which is an integrated measure to estimate the risk of cardiovascular death in 10 years. In addition, a relative risk reduction of 34.8% (P=0.023) was found on readmission. Furthermore, cardiac rehabilitation is recommended after a recent cardiac event[3] and is also effective in older patients.[12] However, attendance and participation of these patients in center-based cardiac rehabilitation programs is low[11,56] which is associated with an increased risk for recurrent cardiovascular events and mortality.[3] In addition, older patients often suffer from functional loss during and after hospitalization.[33] This increases the risk for further functional deterioration and mortality post-discharge.[34] As reasons for non-participation are often related to the presence of functional limitations and transportation problems,[11,56] home-based cardiac rehabilitation under guidance of a physical therapist may have the potential to reduce adverse events and to improve physical functioning in patients' own environment.

Most transitional care interventions are currently nurse-coordinated and are provided from a *case management* perspective, delivering interventions with a broad view on patients' needs.[57,58] However, *disease management* interventions

are often lacking in transitional care. Although reasons for readmissions are heterogenous, many readmissions are disease-related[59] or caused by drug-related adverse events[60] suggesting that more attention is needed for disease-specific support in transitional care. The CCB program therefore integrated home-based cardiac rehabilitation and cardiac disease management into classic transitional care interventions, including early detection and monitoring of cardiac symptoms, medication management and monitoring of therapy adherence (figure 2).

The effectiveness of the CCB program[52] was evaluated in a multicenter randomized clinical trial that was conducted between June 2017 and March 2019 in six hospitals in the region of Amsterdam. In total, 306 patients ≥ 70 year at high risk of readmission and mortality participated in this study. The primary outcome was a composite of readmission and mortality within six months. In addition, also patients' experiences with the CCB program were examined.

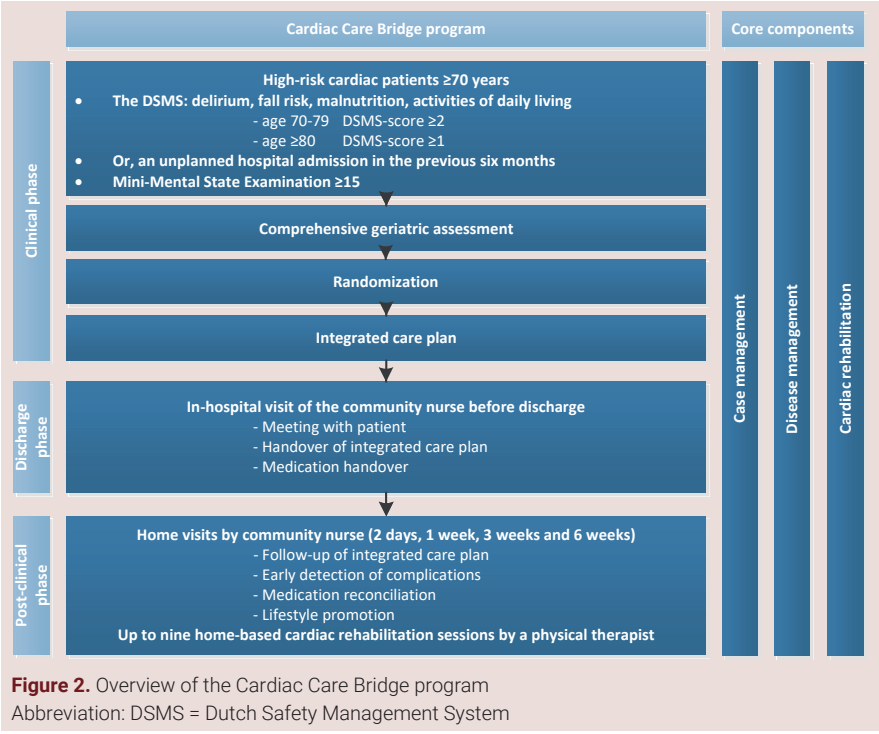


Figure 2. Overview of the Cardiac Care Bridge program
Abbreviation: DSMS = Dutch Safety Management System

Aims and outline of this thesis

The overall aim of the work described in this thesis is to explore the integration of cardiac and geriatric care for older patients with heart disease. Therefore, we first aimed to examine how hospitalized older cardiac patients at high risk for adverse events can be identified. Second, we aimed to examine lifestyle-related secondary prevention of cardiovascular complications by evaluating the effect of a lifestyle intervention in older cardiac patients after a hospital admission. We subsequently examined their motivation for lifestyle modification. Finally, our objective was to develop a transitional care intervention for older cardiac patients and to evaluate its effect on unplanned hospital readmission and mortality. Based on these aims, this thesis is divided into three parts.

In **Part 1**, we explored how hospitalized older cardiac patients at high risk for adverse events could be identified. **Chapter 2** describes the incidence of first unplanned all-cause readmission and mortality of patients ≥ 70 years with acute myocardial infarction or heart failure and explored the extent to which effects of risk factors varied over time. In **Chapter 3**, we provide an overview of clinical risk prediction models for unplanned hospital readmission in patients hospitalized for acute heart disease. **Chapter 4** describes the performance of the DSMS-tool alone and combined with other predictors in predicting all-cause unplanned hospital readmission or mortality within six months in acutely hospitalized older cardiac patients.

In **Part 2,** we evaluated lifestyle-related secondary prevention of cardiovascular complications in older cardiac patients. **Chapter 5** reports on the treatment effect of the RESPONSE-2 trial on lifestyle-related risk factors in older (≥ 65 years) versus younger (< 65 years) patients. **Chapter 6** presents older cardiac patients' perspectives toward lifestyle-related secondary prevention after a hospital admission.

In **Part 3**, we developed and examined the effectiveness of transitional care in older cardiac patients. **Chapter 7** describes the protocol of the nurse-coordinated CCB transitional care program for high-risk older hospitalized cardiac patients. **Chapter 8** presents the effects of the CCB program on unplanned hospital readmission and mortality within six months. **Chapter 9** describes the experiences of patients who participated in the intervention group of the CCB program.

Finally, **Chapter 10** and **Chapter 11** present a general discussion and summary of the main findings of this thesis.

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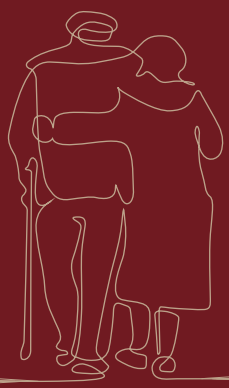
Part

1

The identification of older hospitalized cardiac patients at high risk of adverse events



Chapter

2

Readmission and mortality in patients ≥ 70 years with acute myocardial infarction or heart failure in the Netherlands: a retrospective cohort study of incidences' and changes in risk factors over time

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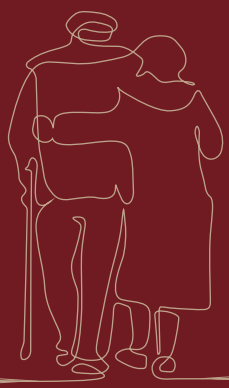

Abstract

Objectives: To determine the risk of first unplanned all-cause readmission and mortality of patients ≥ 70 years with acute myocardial infarction (AMI) or heart failure (HF) and to explore which effects of baseline risk factors vary over time.

Methods: A retrospective cohort study was performed on hospital and mortality data (2008) from Statistics Netherlands including 5,175 (AMI) and 9,837 (HF) patients. We calculated cumulative weekly incidences for first unplanned all-cause readmission and mortality during 6 months post-discharge and explored patient characteristics associated with these events.

Results: At 6 months, 20.4% and 9.9% (AMI) and 24.6% and 22.4% (HF) of patients had been readmitted or had died, respectively. The highest incidences were found in week 1. An increased risk for 14-day mortality after AMI was observed in patients who lived alone (hazard ratio (HR) 1.57, 95% confidence interval (CI) 1.01–2.44) and within 30 and 42 days in patients with a Charlson Comorbidity Index ≥ 3. In HF patients, increased risks for readmissions within 7, 30 and 42 days were found for a Charlson Comorbidity Index ≥ 3 and within 42 days for patients with an admission in the previous 6 months (HR 1.42, 95% CI 1.12–1.80). Non-native Dutch HF patients had an increased risk of 14-day mortality (HR 1.74, 95% CI 1.09–2.78).

Conclusion: The risk of unplanned readmission and mortality in older AMI and HF patients was highest in the 1st week post-discharge, and the effect of some risk factors changed over time. Transitional care interventions need to be provided as soon as possible to prevent early readmission and mortality.

Introduction

Older patients who have been recently discharged after hospital admission for cardiac events are at high risk of readmission and mortality.[1] Research has shown that factors such as higher age,[2,3] the presence of comorbidities,[4,5] being single,[2] low socioeconomic status,[2,6] and an admission in the previous 6 months[7] increase the risk of readmission and mortality.

Transitional care interventions (TCIs) aim to improve continuity of care after discharge through multidisciplinary collaboration, structured discharge planning and early follow-up home visits and have proven to lower the risk of readmission and mortality.[8-10] The start and duration of TCIs vary. Le Berre et al.[10] found that TCIs started after an average of 7.9 days (SD 6.2) post-discharge and lasted for an average of 179.7 days (SD 158.5), showing large diversity in duration of interventions. It is currently unclear what the optimal time window is for TCIs in (various subgroups of) older cardiac patients. Better delineation of which older cardiac patients would benefit most in which time windows would allow the most efficient deployment of TCIs.

Therefore, we determined the risk of a first unplanned all-cause readmission and mortality of patients ≥ 70 years with acute myocardial infarction (AMI) or heart failure (HF) and explored the extent to which effects of particular baseline risk factors vary over time.

Methods

Data sources

We used the National Medical Registration (LMR) of 2008 (and 2009 for the follow-up) from Statistics Netherlands[11] in which 88% of all hospital admissions in the Netherlands were registered anonymously. The LMR was linked to the Dutch Population Registry (GBA), which contains demographic characteristics. Record linkage was successful in 88.9% of hospital-admitted patients.[11] The dates of death were obtained from the Causes of Mortality registry. The Integrated Income Data of Household registry (IIDH) was used to retrieve additional information about residence, living circumstances and annual income.

Study population

Patients with an unplanned hospital admission in 2008 were included. Eligible patients were identified with help of the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM). Patients were eligible if they were ≥ 70 years old; had a discharge diagnosis of AMI (ICD-9 410) or HF (ICD-9 428) and

had a length of stay ≥ 1 day. The first cardiac admission that met these criteria was considered as the index admission. Transfers to other hospitals or wards during this admission were taken as part of the same admission. No approval of the Medical Ethics Committee was necessary as data were used from national registries with anonymous information.

Outcomes and risk factors

We examined the cumulative weekly incidence of a first unplanned all-cause readmission and mortality within 6 months. We identified potential risk factors at baseline and examined the extent to which their associations with the outcomes varied over time. An unplanned all-cause readmission was defined as any non-elective admission occurring at least 1 day after discharge from the index admission in any hospital. Risk factors were selected based on availability in the LMR, GBA and IIDH registries (Supplementary Material Table S1 - S4).

Statistical analysis

We described data using counts and percentages for categorical variables and means with standard deviations (SD) or medians with interquartile ranges (IQR) as appropriate.

We calculated the cumulative weekly incidence for unplanned all-cause readmission and mortality in AMI and HF patients until 6 months post-discharge. The number of events per week post-discharge was divided by the number of persons at risk at the start of that week. Follow-up ended if patients experienced the event of interest, died (in case of readmission) or at 6 months after the index admission if a target event did not occur.

Then, we examined by extended multivariable Cox regression analyses[12] to what extent the effects of baseline risk factors on unplanned all-cause readmission and mortality until 6 months post-discharge varied across five time points: 3, 7, 14, 30 and 42 days post-discharge. This modified Cox regression analysis is a time-to-event analysis to study if the association of a particular factor with the outcome varies over time. It involves risk factor-time interaction terms into the regression models (dummy variables for time were coded 0 = early and 1 = late).[12] To reduce the number of statistical tests, we performed chunk tests comparing models with and without all risk factor-time interaction terms based on the likelihood ratio test. Statistically non-significant chunk tests ($p \geq 0.05$) were interpreted as an indication that the extended model including the interaction terms did not lead to a better fit and standard multivariable Cox regression analysis was preferred. We took statistically significant chunk tests as an indication that the model with interactions fitted the data better. We performed a stepwise backward procedure with a *p*-value for entry and removal of 0.05 and 0.10, respectively. Statistically significant risk factor-time interactions

were interpreted as risk factors whose effect varied over time. We expressed all hazard ratios (HRs) such that values greater than 1 indicate higher risk at the earlier time point. HRs were displayed on a logarithmic scale to enhance compact visualisation of scattered estimates (Figs. 2, 3 and 4). Analyses were performed with SPSS Statistics 22.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 15,012 patients ≥ 70 years had an unplanned hospital admission and discharge diagnosis of AMI (*n*= 5,175; 35.5%) or HF (*n*= 9,837; 65.5%). During the index admission, 1,878 patients (12.5%) died: 576 AMI patients (11.1%) and 1,302 HF patients (13.2%). Thus, a total of 13,134 patients discharged with a diagnosis of AMI (*n*= 4,599) or HF (*n*= 8,535) were included. Table 1 shows the patient characteristics.

Cumulative incidence of a first unplanned all-cause readmission

Figure 1a shows the cumulative incidences of a first unplanned all-cause readmission within 6 months post-discharge. In total, 20.4% of AMI patients (*n*= 937) and 24.6% of HF patients (*n*= 2,103) had been readmitted. The highest incidences were found in week 1: 4.8% (AMI) and 3.7% (HF) were readmitted, respectively. After week 3, the cumulative weekly incidences were lower than 2%.

Cumulative incidence of mortality

Figure 1b shows the cumulative incidences of mortality within 6 months post-discharge. In total, 9.9% of AMI patients (*n*= 457) and 22.4% of HF patients (*n*= 1,914) had died. The highest cumulative incidences were found in week 1: 1.4% (AMI) and 2.1% (HF) died, respectively. After week 1, the cumulative incidence of mortality in AMI patients was lower than 1%. In HF patients, a more gradual decline in cumulative incidence was found with incidences between 1.5% and 0.5% from week 4 onward.

Risk factors of a first unplanned all-cause readmission

In AMI patients, the associations between risk factors and readmission did not vary over time. Therefore, the analyses resulted in the same model for all time windows (Table S1).

In HF patients, a higher Charlson Comorbidity Index (CCI) increased the risk of early readmission within 7, 30 and 42 days, e.g. patients with a CCI ≥ 3 had a 56% greater risk of readmission within 7 days (HR 1.56, 95% confidence interval (CI) 1.15-2.11) than patients with a CCI of 1 (reference category). Women had a 24% lower risk of readmission within 7 days (HR 0.76, 95% CI 0.60-0.97) than

Table 1. Baseline characteristics of included patients

	Acute myocardial infarction (*n*= 4,599)	**Heart failure** (*n*= 8,535)
Male, *n* (%)	2,464 (53.6%)	3,749 (43.9%)
Age, mean (SD)	79.2 (6.0)	81.8 (6.3)
Native Dutch, n (%)	4,123 (89.6%)	7,620 (89.3%)
Patients living alone[a], *n* (%)	1,999 (43.5%)	4,607 (54.0%)
Living in an institution, *n* (%)	314 (6.8%)	1,189 (13.9%)
Length of stay (days), median (IQR)	6.0 (4.0 - 10.0)	7.0 (5.0 - 12.0)
Admission in the previous 6 months, *n* (%)	158 (3.4%)	846 (9.9%)
CCI[b 28], *n* (%)		
Score 1	2,933 (63.8%)	5,379 (63.0%)
Score 2	1,200 (26.1%)	1,897 (22.2%)
Score ≥ 3	466 (10.1%)	1,259 (14.8%)
Annual income[c], *n* (%)		
≤ €16,801	2,538 (55.2%)	4,026 (47.2%)
> €16,801	2,059 (44.8%)	4,509 (52.8%)
Type of hospital, n (%)		
General hospital	1,874 (40.7%)	4,482 (52.5%)
Tertiary referral hospital	2,469 (53.7%)	4,776 (44.2%)
University hospital	256 (5.6%)	277 (3.2%)

IQR interquartile range, N number, SD standard deviation.
[a]Patients living alone or with children ≤ 18 years old
[b]Charlson Comorbidity Index (CCI)[28]: a weighted index to classify comorbid conditions based on their 1-year mortality prognosis. The index was categorised as above. A CCI of 1 was the reference category, because acute myocardial infarction and heart failure both score 1 point in the original CCI
[c]Dichotomised, based on median income in the dataset

men. Patients with an admission in the previous 6 months before the index hospitalization had no greater risk of readmission within 30 days (HR 1.23, 95% CI 0.97 - 1.57) than those without such previous admission, while a 42% greater risk was found for readmission within 42 days (HR 1.42, 95% CI 1.12-1.80) (Figure 2, Table S2).

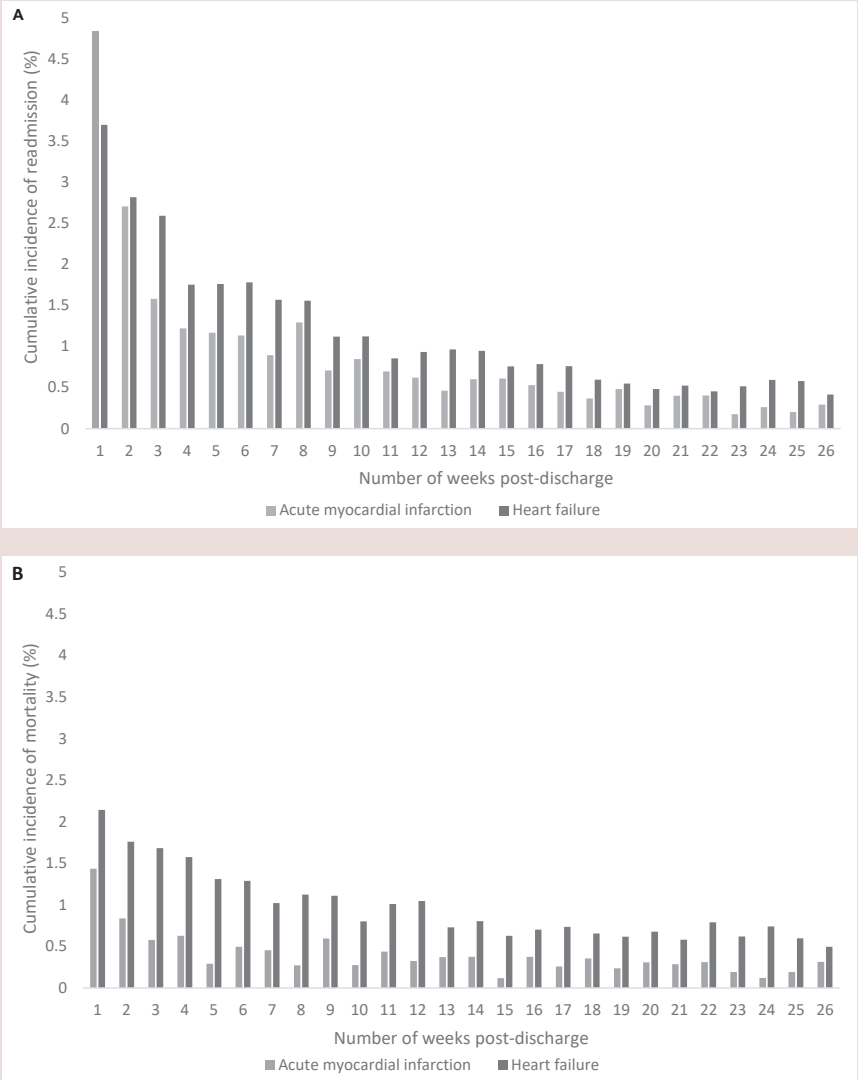

Figure 1 a The incidence rates of a first unplanned all-cause readmission within 6 months.
b The incidence rates of mortality within 6 months.
(The cumulative incidence was calculated for each week postdischarge by dividing the number of readmissions and deaths by the number of patients at risk for each week until 6 months post-discharge)

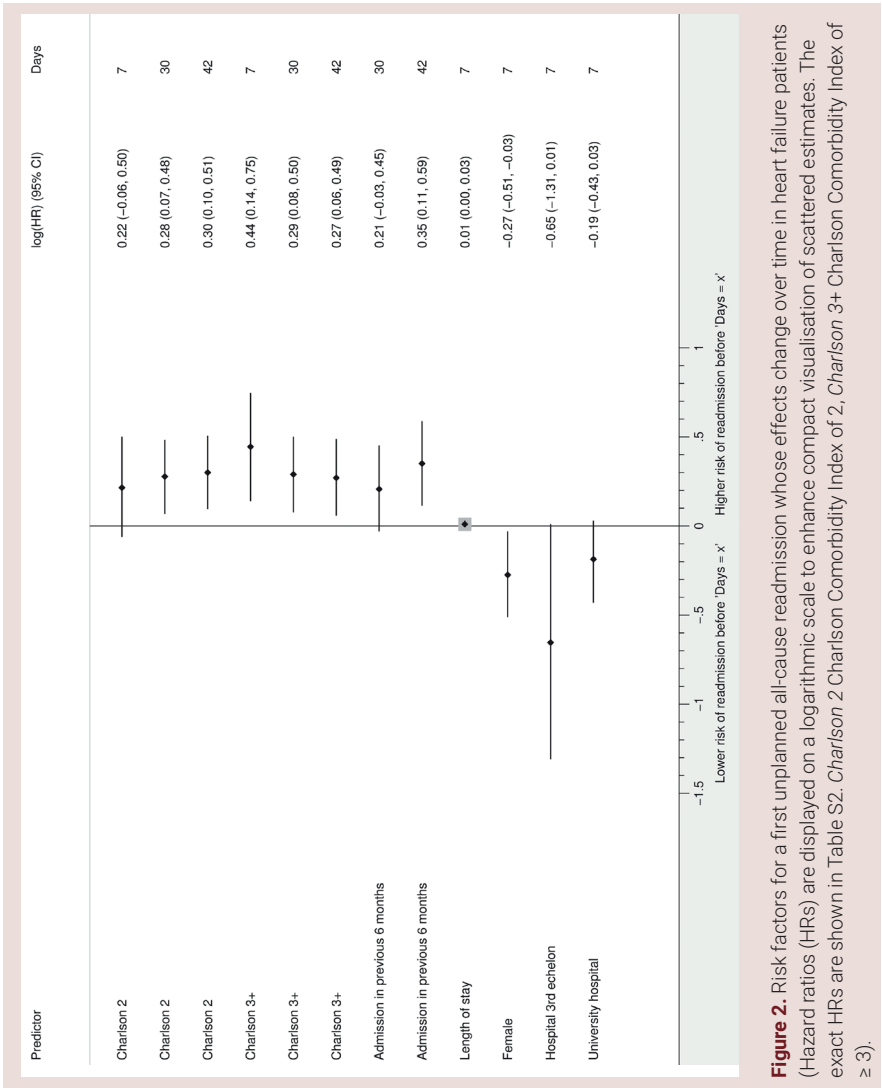

Figure 2. Risk factors for a first unplanned all-cause readmission whose effects change over time in heart failure patients (Hazard ratios (HRs) are displayed on a logarithmic scale to enhance compact visualisation of scattered estimates. The exact HRs are shown in Table S2. *Charlson 2* Charlson Comorbidity Index of 2, *Charlson 3+* Charlson Comorbidity Index of ≥ 3).

Risk factors for mortality

Figure 3 (and Table S3) shows the extended Cox regression analyses of early mortality post-discharge in AMI patients. Patients living alone had a 57% greater risk of mortality within 14 days (HR 1.57, 95% CI 1.01-2.44). Patients with a CCI ≥ 3 had a 121% greater risk of mortality within 42 days (HR 2.21, 95% CI 1.22-4.02) than those with a CCI of 1.

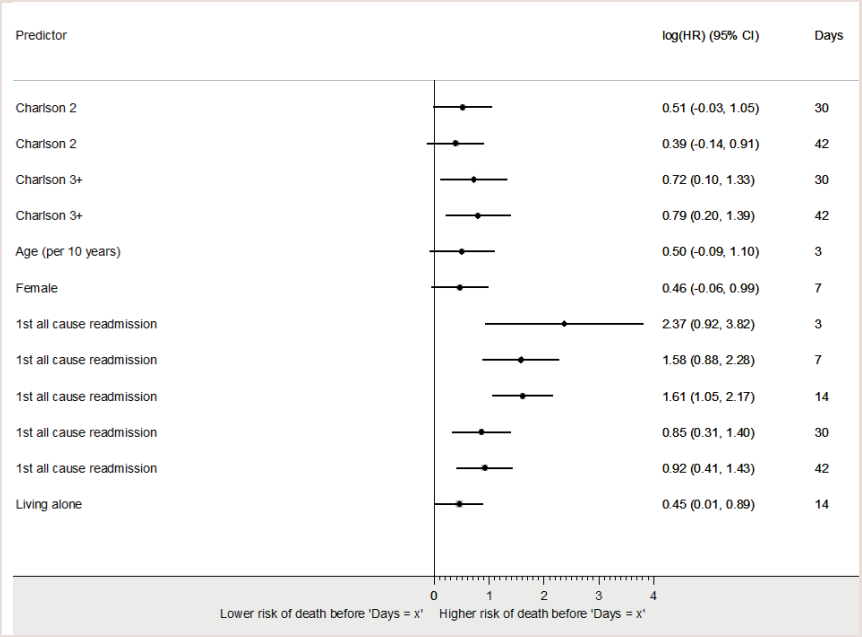

Figure 3. Risk factors for mortality whose effects change over time in acute myocardial infarction patients (HRs are displayed on a logarithmic scale to enhance compact visualisation of scattered estimates. The exact HRs are shown in Table S3. *Charlson 2* Charlson Comorbidity Index of 2, *Charlson 3+* Charlson Comorbidity Index of ≥ 3. *All-cause readmission*: This covariate indicates the first all-cause readmission after the index admission).

In HF patients, risk factor-time interactions were found for early mortality in all time windows (Figure 4, Table S4). The risk factor-time interaction for readmission indicated an increased risk of mortality in all time windows. Non-native Dutch patients, compared to native Dutch, had a 74% greater risk of early mortality within 14 days (HR 1.74, 95% CI 1.09-2.78). A 15% lower risk of early mortality within 42 days was found for every 10 years of age (HR 0.85, 95% CI 0.72-0.99). Lower risks of early mortality were also found for patients living in an institution or with an admission in the previous 6 months.

Discussion

In this retrospective cohort study of older cardiac patients after an unplanned hospital admission in the Netherlands, we found that 20.4% (AMI) and 24.6% (HF) had an unplanned all-cause readmission and 9.9% (AMI) and 22.4% (HF) had died within 6 months post-discharge. The highest incidences were found in

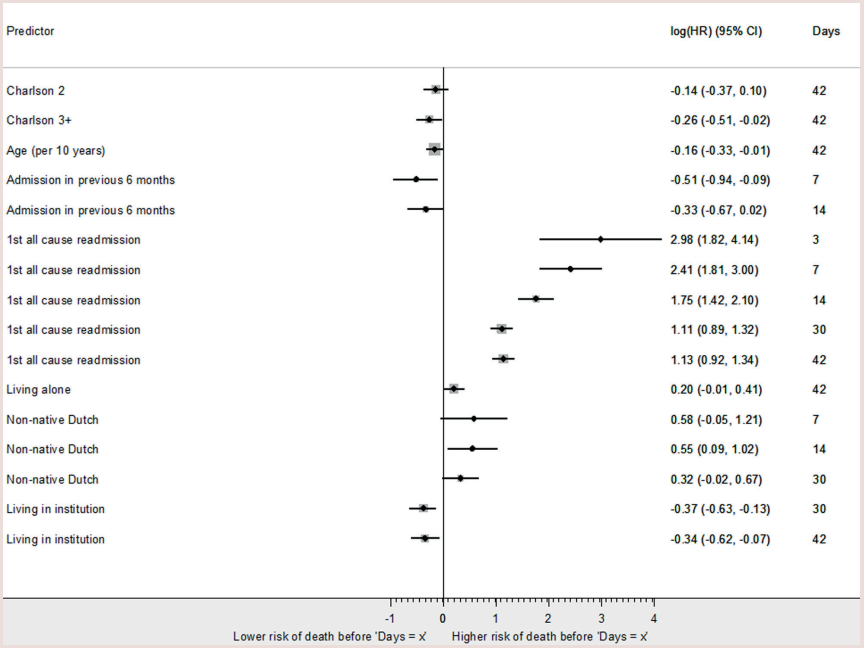

Figure 4. Risk factors for mortality whose effects change over time in older heart failure patients (HRs are displayed on a logarithmic scale to enhance compact visualisation of scattered estimates. The exact HRs are shown in Table S4. *Charlson 2* Charlson Comorbidity Index of 2, *Charlson 3+* Charlson Comorbidity Index of ≥ 3, *All-cause readmission*: This covariate indicates the first all-cause readmission after the index admission).

the 1st week post-discharge. Patients with comorbidities, an admission in the previous 6 months, patients living alone and non-native Dutch patients were at highest risk of early readmission and mortality.

Consistent with the literature from the United States,[13-15] this study on older Dutch cardiac patients confirms that the highest readmission and mortality rates were found right after discharge and that risks were higher and prolonged in HF patients compared to AMI patients.[15] These results suggest that the needs of older cardiac patients are insufficiently fulfilled in the early period post-discharge. The average start of TCIs after 8 days post-discharge[10] might already be too late to have a preventive effect on early readmission and mortality. Therefore, the timing of TCIs may need improvement.

We found that higher CCIs increased the risk of early readmission (HF) and mortality (AMI) at several time points. During hospital admission, older cardiac patients mainly receive disease-oriented treatments based on disease-specific guidelines, which are in turn based on studies that commonly exclude older and multimorbid patients.[16,17] However, older cardiac patients often suffer from

multiple comorbidities including diabetes, chronic pulmonary disease and renal failure.[4,5,18] Donzé et al.[19] found that the focus on acute illness during admission may lead to insufficient monitoring of comorbidities and increase the risk of exacerbations post-discharge. A broader assessment of older cardiac patients' needs during hospital admission might be required.[20]

Strengths and limitations

One of the strengths of our study is that we used a large nationwide database and had the opportunity to link and combine hospital and sociodemographic data with 1 year follow-up. This resulted in fairly rich data to examine risk factors for readmission and mortality. To our knowledge, our study is the first to examine change in those effects over time. While 11% of the cases were excluded because no linkage between hospital and sociodemographic data was possible, previous research from Statistics Netherlands showed that the number of linkable admissions were reliable for statistical analyses.[21]

This study also has limitations. First, we had access only to the registries of Statistics Netherlands in 2008 and 2009 for the follow-up. Due to national trends, the incidences of readmission and mortality might nowadays have increased in HF patients and decreased in AMI patients.[22] Although the incidences might be different, we expect that the highest incidences are still found in the 1st week post-discharge. Second, the LMR contained only administrative data which precluded adjustment for cardiovascular and geriatric risk factors that are known to increase the risk of readmission and mortality (e.g. history of cardiovascular disease, disability and polypharmacy). Third, we were unable to adjust for competing risk in patients that had died before experiencing an unplanned all-cause readmission which might have resulted in an underestimation for readmission.[23] Finally, the CCIs in our data may be too low because of the underreporting of comorbidities in medical files. This may have caused an underestimation of the effect on readmission and mortality.

Implications of findings

Hospitalised high-risk older cardiac patients need to be identified as soon as possible to guide them during care transitions. Instead of single disease-oriented treatments, a broad view on older cardiac patients' needs is necessary.[20] Around discharge, adequate communication between hospital and community care providers, e.g. accurate and timely discharge letters, and continuity of care after discharge have proven to reduce readmissions.[24] In addition, careful assessment of patients' readiness for discharge might be needed, as some high-risk patients might even be discharged before stable recovery.[25]

While single disease-oriented interventions during hospital admission are not suitable in older cardiac patients,[16,17,19] disease management interventions

might be integrated in TCIs. More disease-specific guidance after discharge, e.g. symptom monitoring, medication reconciliation and specific guidance in medication and lifestyle adherence, might also help to reduce the risk of readmission and mortality.[8,26] Personalised interventions might be required as HF patients were at higher and prolonged risk compared to AMI patients, and risk factors for readmission and mortality changed over time. Although readmission diagnoses are heterogeneous, early detection and proactive interventions might limit complications.[13,27]

Conclusion

The incidences of unplanned all-cause readmission and mortality in older AMI and HF patients were highest in the 1st week post-discharge, and the effects of several risk factors for these events at discharge changed over time. Transitional care interventions need to be provided as soon as possible in admitted high-risk older patients with AMI or HF to prevent early readmission and mortality.

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S1 Table. Extended Cox regression analysis of the first unplanned all-cause readmission in patients with acute myocardial infarction

	3-days		7-days		14-days		30-days		42-days	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Women	1.07 (0.93 - 1.23)	0.339	1.07 (0.93 - 1.23)	0.339	1.07 (0.93 - 1.23)	0.339	1.07 (0.93 - 1.23)	0.339	1.07 (0.93 - 1.23)	0.339
Age per 10 years	1.20 (1.06 - 1.33)	0.003	1.20 (1.06 - 1.33)	0.003	1.20 (1.06 - 1.33)	0.003	1.20 (1.06 - 1.33)	0.003	1.20 (1.06 - 1.33)	0.003
Non-native Dutch	1.12 (0.92 - 1.37)	0.260	1.12 (0.92 - 1.37)	0.260	1.12 (0.92 - 1.37)	0.260	1.12 (0.92 - 1.37)	0.260	1.12 (0.92 - 1.37)	0.260
Charlson comorbidity index[28]										
Score 1 (Ref)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Score 2	39.77 (30.09 - 52.56)	< 0.001	39.77 (30.09 - 52.56)	< 0.001	39.77 (30.09 - 52.56)	< 0.001	39.77 (30.09 - 52.56)	< 0.001	39.77 (30.09 - 52.56)	< 0.001
Score ≥ 3	44.87 (33.39 - 60.30)	< 0.001	44.87 (33.39 - 60.30)	< 0.001	44.87 (33.39 - 60.30)	< 0.001	44.87 (33.39 - 60.30)	< 0.001	44.87 (33.39 - 60.30)	< 0.001
Living alone	0.92 (0.79 - 1.07)	0.267	0.92 (0.79 - 1.07)	0.267	0.92 (0.79 - 1.07)	0.267	0.92 (0.79 - 1.07)	0.267	0.92 (0.79 - 1.07)	0.267
Living in an institution	0.71 (0.54 - 0.94)	0.016	0.71 (0.54 - 0.94)	0.016	0.71 (0.54 - 0.94)	0.016	0.71 (0.54 - 0.94)	0.016	0.71 (0.54 - 0.94)	0.016
Annual income < €16,801	0.98 (0.86 - 1.12)	0.789	0.98 (0.86 - 1.12)	0.789	0.98 (0.86 - 1.12)	0.789	0.98 (0.86 - 1.12)	0.789	0.98 (0.86 - 1.12)	0.789

S1 Table. *Continued*

	3-days		7-days		14-days		30-days		42-days	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Length of stay	0.99 (0.99 - 1.00)	0.123	0.99 (0.99 - 1.00)	0.123	0.99 (0.99 - 1.00	0.123	0.99 (0.99 - 1.00	0.123	0.99 (0.99 - 1.00	0.123
Admission in the previous 6 months	0.89 (0.67 - 1.18)	0.412	0.89 (0.67 - 1.18)	0.412	0.89 (0.67 - 1.18)	0.412	0.89 (0.67 - 1.18)	0.412	0.89 (0.67 - 1.18)	0.412
Type of hospital										
General hospital (ref)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Tertiary referral hospital	0.87 (0.76 - 0.99)	0.033	0.87 (0.76 - 0.99)	0.033	0.87 (0.76 - 0.99)	0.033	0.87 (0.76 - 0.99)	0.033	0.87 (0.76 - 0.99)	0.033
University hospital	0.67 (0.48 - 0.92)	0.014	0.67 (0.48 - 0.92)	0.014	0.67 (0.48 - 0.92)	0.014	0.67 (0.48 - 0.92)	0.014	0.67 (0.48 - 0.92)	0.014
Time-depended predictors	None		None		None		None		None	

S2 Table. Extended Cox regression analysis of the first unplanned all-cause readmission in patients with heart failure[a]

	3-days		7-days		14-days		30-days		42-days	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Women	0.99 (0.90 - 1.09)	0.835	0.95 (0.86 - 1.05)	0.325	0.99 (0.90 - 1.09)	0.835	0.99 (0.90 - 1.09)	0.838	0.99 (0.90 - 1.09)	0.837
Age per 10 years	1.06 (0.99 - 1.15)	0.103	1.06 (0.99 - 1.15)	0.103	1.06 (0.99 - 1.15)	0.103	1.06 (0.99 - 1.15)	0.102	1.06 (0.99 - 1.15)	0.104
Non-native Dutch	0.93 (0.81 - 1.07)	0.312	0.93 (0.81 - 1.07)	0.309	0.93 (0.81 - 1.07)	0.312	0.93 (0.81 - 1.07)	0.307	0.93 (0.81 - 1.07)	0.304
Charlson comorbidity index [28]										
Score 1 (Ref)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Score 2	2.69 (2.43 - 2.98)	< 0.001	2.78 (2.49 - 3.11)	< 0.001	2.69 (2.43 - 2.98)	< 0.001	3.03 (2.64 - 3.46)	< 0.001	3.15 (2.72 - 3.66)	< 0.001
Score ≥ 3	3.91 (3.51 - 4.36)	< 0.001	4.18 (3.72 - 4.70)	< 0.001	3.91 (3.51 - 4.36)	< 0.001	4.44 (3.84 - 5.12)	< 0.001	4.53 (3.86 - 5.31)	< 0.001
Living alone	0.95 (0.86 - 1.06)	0.369	0.96 (0.86 - 1.06)	0.377	0.95 (0.86 - 1.06)	0.369	0.95 (0.86 - 1.06)	0.370	0.96 (0.86 - 1.06)	0.373
Living in an institution	1.01 (0.88 - 1.16)	0.882	1.01 (0.88 - 1.16)	0.893	1.01 (0.88 - 1.16)	0.882	1.01 (0.88 - 1.16)	0.886	1.01 (0.88 - 1.16)	0.883
Annual income < €16,801	0.87 (0.80 - 0.96)	0.003	0.88 (0.80 - 0.96)	0.003	0.87 (0.80 - 0.96)	0.003	0.87 (0.80 - 0.96)	0.003	0.87 (0.80 - 0.96)	0.003

S2 Table. *Continued*

	3-days		7-days		14-days		30-days		42-days	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Length of stay	1.01 (0.997 - 1.006)	0.631	1.00 (0.998 - 1.01)	0.233	1.01 (0.997 - 1.006)	0.631	1.00 (0.997 - 1.006)	0.640	1.00 (0.997 - 1.006)	0.645
Admission in the previous 6 months	1.62 (1.44 - 1.82)	< 0.001	1.62 (1.44 - 1.83)	< 0.001	1.62 (1.44 - 1.82)	< 0.001	1.78 (1.52 - 2.07)	< 0.001	1.95 (1.65 - 2.30)	< 0.001
Type of hospital										
General hospital (ref)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Tertiary referral hospital	0.95 (0.87 - 1.04)	0.271	0.93 (0.84 - 1.02)	0.113	0.95 (0.87 - 1.04)	0.271	0.95 (0.87 - 1.04)	0.269	0.95 (0.87 - 1.04)	0.266
University hospital	0.60 (0.46 - 0.79)	< 0.001	0.54 (0.40 - 0.73)	< 0.001	0.60 (0.46 - 0.79)	< 0.001	0.60 (0.46 - 0.78)	< 0.001	0.60 (0.46 - 0.78)	< 0.001
Time-depended predictors	None				None					
Women			0.76 (0.60 - 0.97)	0.028						
Age per 10 years										
Non-native Dutch										
Charlson comorbidity index [28]										
Score 1 (Ref)			Ref	Ref			Ref	Ref	Ref	Ref

Score 2	1.24 (0.94 - 1.65)	0.128	1.32 (1.07 - 1.62)	0.009	1.35 (1.10 - 1.66)	0.004
Score ≥ 3	1.56 (1.15 - 2.11)	0.004	1.33 (1.08 - 1.65)	0.008	1.31 (1.06 - 1.63)	0.012
Living alone						
Living in an institution						
Annual income < €16,801						
Length of stay						
Admission in the previous 6 months			1.23 (0.97 - 1.57)	0.086	1.42 (1.12 - 1.80)	0.004
Type of hospital						
General hospital (ref)	Ref	Ref				
Tertiary referral hospital	0.52 (0.27 - 1.01)	0.128				
University hospital	0.83 (0.65 - 1.03)	0.053				

[a] Example of interpretation of the Extended Cox regression analysis: Heart failure patients with a Charlson comorbidity index ≥ 3 had a 1.56 times higher hazard of a first unplanned all-cause readmission within 7 days than heart failure patients with a Charlson comorbidity index of 1 (ref)

S3 Table. Extended Cox regression analysis of mortality in patients with acute myocardial infarction[a]

	3-days		7-days		14-days		30-days		42-days	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Women	0.91 (0.75 - 1.12)	0.369	0.97 (0.79 - 1.21)	0.807	0.91 (0.75 - 1.12)	0.369	0.91 (0.75 - 1.14)	0.366	0.91 (0.75 - 1.12)	0.368
Age per 10 years	2.52 (2.12 - 2.97)	< 0.001	2.43 (2.06 - 2.87)	< 0.001	2.43 (2.07 - 2.87)	< 0.001	2.43 (2.08 - 2.87)	< 0.001	2.43 (2.08 - 2.87)	< 0.001
Non-native Dutch	1.27 (0.96 - 1.67)	0.094	1.27 (0.96 - 1.67)	0.093	1.26 (0.96 - 1.67)	0.097	1.27 (0.96 - 1.67)	0.094	1.27 (0.96 - 1.67)	0.095
Charlson comorbidity index[28]										
Score 1 (Ref)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Score 2	1.26 (0.97 - 1.64)	0.082	1.26 (0.97 - 1.63)	0.085	1.26 (0.97 - 1.64)	0.082	1.56 (1.12 - 2.18)	0.009	1.55 (1.08 - 2.22)	0.017
Score ≥ 3	2.19 (1.65 - 2.92)	< 0.001	2.19 (1.65 - 2.92)	< 0.001	2.20 (1.65 - 2.93)	< 0.001	2.87 (2.01 - 4.10)	< 0.001	3.08 (2.11 - 4.49)	< 0.001
Living alone	1.00 (0.81 - 1.25)	0.976	1.00 (0.81 - 1.25)	0.981	1.11 (0.87 - 1.41)	0.396	1.00 (0.81 - 1.25)	0.984	1.00 (0.81 - 1.25)	0.986
Living in an institution	0.84 (0.60 - 1.17)	0.299	0.84 (0.60 - 1.17)	0.303	0.84 (0.60 - 1.17)	0.306	0.84 (0.60 - 1.17)	0.299	0.84 (0.60 - 1.17)	0.301
Annual income < €16,801	0.78 (0.64 - 0.94)	0.008	0.78 (0.64 - 0.94)	0.008	0.78 (0.64 - 0.94)	0.008	0.77 (0.64 - 0.94)	0.008	0.77 (0.64 - 0.94)	0.008
Length of stay	1.02 (1.01 - 1.03)	< 0.001	1.02 (1.01 - 1.03)	< 0.001	1.02 (1.01 - 1.03)	< 0.001	1.02 (1.01 - 1.03)	< 0.001	1.02 (1.01 - 1.03)	< 0.001

Admission in the previous 6 months	1.21 (0.82 - 1.79)	0.345	1.21 (0.82 - 1.79)	0.344	1.21 (0.82 - 1.79)	0.344	1.21 (0.81 - 1.79)	0.351	1.20 (0.81 - 1.79)	0.356
Type of hospital										
General hospital (ref)	Ref	Ref	Ref	Ref						
Tertiary referral hospital	0.84 (0.70 - 1.02)	0.077	0.84 (0.70 - 1.02)	0.077	0.84 (0.70 - 1.02)	0.074	0.84 (0.70 - 1.02)	0.074	0.84 (0.69 - 1.02)	0.073
University hospital	0.84 (0.53 - 1.31)	0.438	0.84 (0.53 - 1.32)	0.442	0.84 (0.53 - 1.32)	0.444	0.84 (0.53 - 1.32)	0.434	0.84 (0.53 - 1.32)	0.436
First all-cause readmission with 6 months	2.04 (1.59 - 2.61)	< 0.001	2.22 (1.72 - 2.86)	< 0.001	2.50 (1.93 - 3.25)	< 0.001	2.34 (1.77 - 3.19)	< 0.001	2.58 (1.89- 3.54)	< 0.001
Time-depended predictors										
Women	-		1.59 (0.94 - 2.70)	0.087	-		-		-	
Age per 10 years	1.65 (0.91 - 3.00)	0.101	-		-		-		-	
Non-native Dutch	-		-		-		-		-	
Charlson comorbidity index[28]	-		-		-		-		-	
Score 1 (Ref)	-		-		-		-		-	
Score 2	-		-		-		1.67 (0.97 - 2.87)	0.066	1.47 (0.87 - 2.49)	0.151
Score ≥ 3	-		-		-		2.05 (1.11 - 3.79)	0.022	2.21 (1.22 - 4.02)	0.009

S3 Table. *Continued*

	3-days		7-days		14-days		30-days		42-days	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Living alone	-		-		1.57 (1.01 - 2.44)	0.044	-		-	
Living in an institution	-		-		-		-		-	
Annual income < €16,801	-		-		-		-		-	
Length of stay	-		-		-		-		-	
Admission in the previous six months	-		-		-		-		-	
Type of hospital	-		-		-		-		-	
General hospital (ref)	-		-		-		-		-	
Tertiary referral hospital	-		-		-		-		-	
University hospital	-		-		-		-		-	
First all-cause readmission within 6 months	10.75 (2.51 - 45.45)	0.001	4.85 (2.40 - 9.80)	< 0.001	5.00 (2.86 - 8.77)	< 0.001	2.35 (1.37 - 4.05)	0.002	2.50 (1.50 - 4.17)	< 0.001

[a] Example of interpretation of the Extended Cox regression analysis: Acute myocardial infarction patients living alone had a 1.57 higher hazard of mortality within 14 days than patients not living alone.

S4 Table. Extended Cox regression analysis of mortality in patients with heart failure[a]

	3-days		7-days		14-days		30-days		42-days	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Women	0.78 (0.71 - 0.87)	< 0.001	0.78 (0.71 - 0.87)	< 0.001	0.78 (0.71 - 0.87)	< 0.001	0.79 (0.71 - 0.87)	< 0.001	0.78 (0.71 - 0.87)	< 0.001
Age per 10 years	1.97 (1.82 - 2.11)	< 0.001	1.97 (1.82 - 2.11)	< 0.001	1.97 (1.82 - 2.11)	< 0.001	1.97 (1.82 - 2.11)	< 0.001	1.84 (1.66 - 2.04)	< 0.001
Non-native Dutch	0.94 (0.81 - 1.09)	0.424	0.98 (0.84 - 1.15)	0.835	1.02 (0.86 - 1.20)	0.841	1.03 (0.86 - 1.23)	0.725	0.94 (0.80 - 1.09)	0.403
Charlson comorbidity index[28]										
Score 1 (Ref)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Score 2	1.04 (0.92 - 1.16)	0.545	1.04 (0.92 - 1.16)	0.555	1.04 (0.92 - 1.16)	0.563	1.04 (0.92 - 1.16)	0.574	0.97 (0.84 - 1.13)	0.717
Score ≥ 3	1.47 (1.30 - 1.66)	< 0.001	1.47 (1.30 - 1.66)	< 0.001	1.47 (1.30 - 1.66)	< 0.001	1.47 (1.30 - 1.66)	< 0.001	1.32 (1.12 - 1.55)	0.001
Living alone	0.88 (0.79 - 0.99)	0.027	0.89 (0.79 - 0.99)	0.029	0.89 (0.80 - 0.99)	0.030	0.89 (0.80 - 0.99)	0.032	0.97 (0.84 - 1.11)	0.612
Living in an institution	0.94 (0.82 - 1.08)	0.380	0.94 (0.82 - 1.08)	0.374	0.94 (0.82 - 1.08)	0.361	0.82 (0.69 - 0.97)	0.018	0.81 (0.67 - 0.97)	0.019
Annual income < €16,801	0.72 (0.66- 0.80)	< 0.001	0.73 (0.66- 0.80)	< 0.001	0.72 (0.66- 0.80)	< 0.001	0.72 (0.66- 0.80)	< 0.001	0.72 (0.66 - 0.80)	< 0.001
Length of stay	1.02 (1.02 - 1.03)	< 0.001	1.02 (1.02 - 1.03)	< 0.001	1.02 (1.02 - 1.03)	< 0.001	1.02 (1.02 - 1.03)	< 0.001	1.02 (1.02 - 1.03)	< 0.001

S4 Table. *Continued*

	3-days		7-days		14-days		30-days		42-days	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Admission in the previous 6 months	1.22 (1.07 - 1.40)	0.004	1.16 (1.01 - 1.34)	0.043	1.15 (0.99 - 1.34)	0.063	1.22 (1.06 - 1.39)	0.004	1.22 (1.06 - 1.40)	0.004
Type of hospital										
General hospital (ref)										
Tertiary referral hospital	0.99 (0.90 - 1.08)	0.742	0.98 (0.90 - 1.08)	0.732	0.98 (0.90 - 1.08)	0.730	0.99 (0.90 - 1.08)	0.740	0.99 (0.90 - 1.08)	0.766
University hospital	1.01 (0.78 - 1.30)	0.968	1.01 (0.78 - 1.30)	0.973	1.01 (0.78 - 1.30)	0.971	1.01 (0.78 - 1.30)	0.958	1.01 (0.78 - 1.30)	0.966
Readmission	1.90 (1.72 - 2.11)	< 0.001	2.05 (1.86 - 2.28)	< 0.001	2.24 (2.02 - 2.49)	< 0.001	2.47 (2.20 - 2.77)	< 0.001	2.77 (2.44 - 3.14)	< 0.001
Time-depended predictors										
Women	-				-		-			
Age per 10 years	-		-		-		-		0.85 (0.72 - 0.99)	0.042
Non-native Dutch	-		1.79 (0.95 - 3.36)	0.070	1.74 (1.09 - 2.78)	0.022	1.38 (0.98 - 1.95)	0.063		
Charlson comorbidity index[28]	-		-		-		-		-	
Score 1 (Ref)	-		-		-		-		-	

Score 2	-		-		-		-		0.87 (0.69 - 1.10)	0.237
Score ≥ 3	-		-		-		-		0.77 (0.60 - 0.98)	0.031
Living alone	-		-		-		-		1.22 (0.99 - 1.50)	0.060
Living in an institution	-		-		-		0.69 (0.53 - 0.88)	0.003	0.71 (0.54 - 0.93)	0.012
Annual income < €16,801	-		-		-		-		-	
Length of stay	-		-				-		-	
Admission in the previous 6 months	-		0.60 (0.39 - 0.91)	0.018	0.72 (0.51 - 1.02)	0.064	-		-	
Type of hospital	-		-		-		-		-	
General hospital (ref)	-		-		-		-		-	
Tertiary referral hospital	-		-		-		-		-	
University hospital	-		-		-		-		-	
First all-cause readmission within 6 months	19.61 (6.17 - 62.50)	< 0.001	11.11 (6.14 - 20.00)	< 0.001	5.78 (4.12 - 8.13)	< 0.001	3.03 (2.44 - 3.76)	< 0.001	3.11 (2.52 - 3.83)	< 0.001

[a] Example of interpretation of the Extended Cox regression analysis: Non-native Dutch heart failure patients had a 1.79 higher hazard of mortality within 7 days than native Dutch heart failure patients.

Chapter

3

Prediction models for hospital readmissions in patients with heart disease: a systematic review and meta-analysis

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Abstract

Objective: To describe the discrimination and calibration of clinical prediction models, identify characteristics that contribute to better predictions, and investigate predictors that are associated with unplanned hospital readmissions.

Design: Systematic review and meta-analysis.

Data source: Medline, EMBASE, ICTPR (for study protocols), and Web of Science (for conference proceedings) were searched up to 25 August 2020.

Eligibility criteria for selecting studies: Studies were eligible if they reported on 1) hospitalized adult patients with acute heart disease; 2) a clinical presentation of prediction models with c-statistic; 3) unplanned hospital readmission within six months.

Primary and secondary outcome measures: Model discrimination for unplanned hospital readmission within six months measured using concordance (c) statistics and model calibration. Meta-regression and sub-group analyses were performed to investigate predefined sources of heterogeneity. Outcome measures from models reported in multiple independent cohorts and similarly defined risk predictors were pooled.

Results: Sixty studies describing 81 models were included: 43 models were newly developed, and 38 were externally validated. Included populations were mainly heart failure (HF) patients (n=29). The average age ranged between 56.5 and 84 years. The incidence of readmission ranged from 3% till 43%. Risk of bias was high in almost all studies. The c-statistic was <0.7 in 72 models, between 0.7-0.8 in 16 models and >0.8 in 5 models. The study population, data source and number of predictors were significant moderators for the discrimination. Calibration was reported for 27 models. Only the GRACE-score had adequate discrimination in independent cohorts (0.78, 95% CI 0.63-0.86). Eighteen predictors were pooled.

Conclusion: Some promising models require updating and validation before use in clinical practice. The lack of independent validation studies, high risk of bias and low consistency in measured predictors limit their applicability.

Introduction

Hospital readmissions in patients with acute heart disease are associated with a high burden on patients, healthcare and costs.[1] The identification of high-risk hospitalized patients is important to provide timely interventions.

Numerous systematic reviews have previously investigated the prediction of unplanned hospital readmissions in several populations.[2-11] While some have included hospitalized patients in general,[10,11] others have focused specifically on patients with heart failure (HF)[2,4-7,9] or acute myocardial infarction (AMI).[3,8] The conclusion is generally the same, the discrimination is poor to adequate, and there is little consistency in the type of predictors included in the models.

The clinical applicability of risk prediction models in daily practice is currently limited. Statistical models are often not presented in a clinically useful way or models based on administrative data are considered.[3] These models therefore cannot be readily used in daily practice. In addition, prediction models are often developed for a very specific population, which asks from clinicians to be familiar with several models. Furthermore, patients may belong to multiple populations because of cardiac comorbidities.

We believe that the state of the art on risk prediction can be improved if more knowledge is available on the performance of clinical risk prediction models and risk predictors across different populations of patients with heart disease. Although heterogeneity in models and predictors is often considered as a limitation, it can inform effect moderators on how predictions can be improved.[12] For example, perhaps we can identify predictors who demonstrate a consistent association with hospital readmission regardless of the underlying disease. If this can be identified, a more general prediction model could be developed that is relevant for the heterogeneous group of patients on cardiac care units. This might contribute to the early recognition and onset of preventive interventions in patients with heart disease at risk of readmission.

We therefore performed a systematic review and meta-analysis on clinical risk prediction models for the outcome unplanned hospital readmission in patients hospitalized for acute heart disease. Our aim was to describe the discrimination and calibration of clinical prediction models, identify characteristics that contribute to better predictions, and to investigate predictors that are consistently associated with hospital readmissions.

Methods

A protocol was registered in PROSPERO (CRD42020159839). The results are reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[13]

Eligibility criteria

Studies were eligible if 1) the study population included hospitalized adult patients with (symptoms of) heart disease; 2) a prediction model with c-statistic was reported; 3) a clinically useful presentation of the model with risk factors was reported; 4) the outcome was unplanned hospital readmissions within six months; 5) the study design was appropriate, i.e. (nested) case-control study, (prospective and retrospective) cohort study, database and registry study, or secondary analysis of a trial; 6) they were reported in English.

Information sources

A search strategy was designed with an information specialist (PROSPERO protocol and Supplemental Text 1). We searched the Medline, EMBASE, WHO ICTPR search portal (for study protocols), and Web of Science (for conference proceedings) databases up to 25 August 2020 without any restrictions for eligible studies. We searched for full text manuscripts of the identified protocols. After selecting the full text manuscripts, we screened references lists and prospective citations (using Google Scholar) for additional eligible studies.

Study selection

Three reviewers were involved in the study selection process. Each reviewer independently screened two thirds of the titles, abstracts and full-text articles of potentially relevant references identified in the literature search. Disagreements were resolved through consensus. Sixteen authors were contacted and six delivered data for readmission when a composite outcome was used. Two authors were also contacted when data was reported combining multiple patient populations. However, no additional data was provided for the population with heart disease and these studies were excluded.

Data extraction

Data extraction was performed based on the 'Critical Appraisal and Data Extraction for Systematic Reviews' checklist using standardized forms in the Distiller Systematic Review Software (see Supplemental Text 2 for the data items).[14] One reviewer collected the data and the second reviewer verified the extracted data. Disagreements were resolved through consensus. Eight authors were contacted and two delivered data to resolve uncertainties or missing data.

Risk of bias

The PROBAST tool[15] was used to assess the risk of bias (RoB) for the participants, predictors, outcome and analysis for each model. One author assessed the RoB as low, high or unclear, and the second author verified the extracted data and

RoB conclusion. Disagreements were resolved through consensus. In addition, the applicability of the included studies based on our research question was assessed for the participants, predictors and outcome domains and rated as low concerns, high concerns or uncertain concerns regarding applicability.

Summary measures

The discrimination of the prediction models were described using the concordance (c)-statistic. Missing standard errors were derived from the sample data.[16] The calibration was described using the number of observed and expected events, the calibration slope, calibration in large, or the Hosmer-Lemeshow test.

The association between risk predictors and hospital readmission was described using regression coefficients. Missing standard errors for the coefficients were considered missing completely at random and were not imputed. A complete case analysis was performed.

Synthesis of results and analyses

Meta-analyses using random-effects models, with the Hartung-Knapp modification, were performed to describe the distribution of the between-study variance of the different prediction models and their predictors. Because we considered that there would be substantial heterogeneity, conclusions were not based on the precision of the pooled estimates.

The c-statistic from each model was pooled and a meta-regression was performed to investigate the moderation effect of age and the number of predictors on the discrimination. A subgroup analysis was performed to investigate the moderation effect of the different patient populations, design, outcome definition, and endpoint. The c-statistic of the validated model was used if available; otherwise the c-statistic from the development phase was used.

The c-statistics of specific prediction models that were evaluated in multiple studies were pooled for the endpoint 30 days follow-up.

Coefficients of predictors that were similarly defined in at least five studies were pooled for the endpoint 30 days follow-up. The patient populations were defined as subgroups to explore consistency and heterogeneity (I^2, tau) in the effect estimates.

Analyses were performed using the 'metan' package in STATA 15 IC and the 'metamisc package' in Rstudio.

Public and patient involvement

Because of the design of the study and because we did not collect primary date, we did not involve patients or the public in the design, conduct, or reporting of our research.

Results

A total of 8588 abstracts were reviewed and 60 studies describing 81 separate models were included (Figure 1). Table 1 provides an overview of the included studies and models, which were published between 2001 and 2020. The majority of the studies (n=40) was performed in the United States. The data sources used were mostly retrospective cohort studies (n=15), hospital databases (n=13) and registries (n=13). Included populations were mainly HF patients (n=29), surgical patients (n=14) and patients with an AMI or acute coronary syndrome (n=10). The average age was between 56.5 and 84 years. The sample size of development cohorts ranged from 182 till 193,899 patients and of the validation cohorts between 104 and 321,088 patients. The outcome of interest was mostly all-cause readmission (n=41) and measured on 30 days (n=55). The incidence of readmission per study ranged from 3% till 43%.

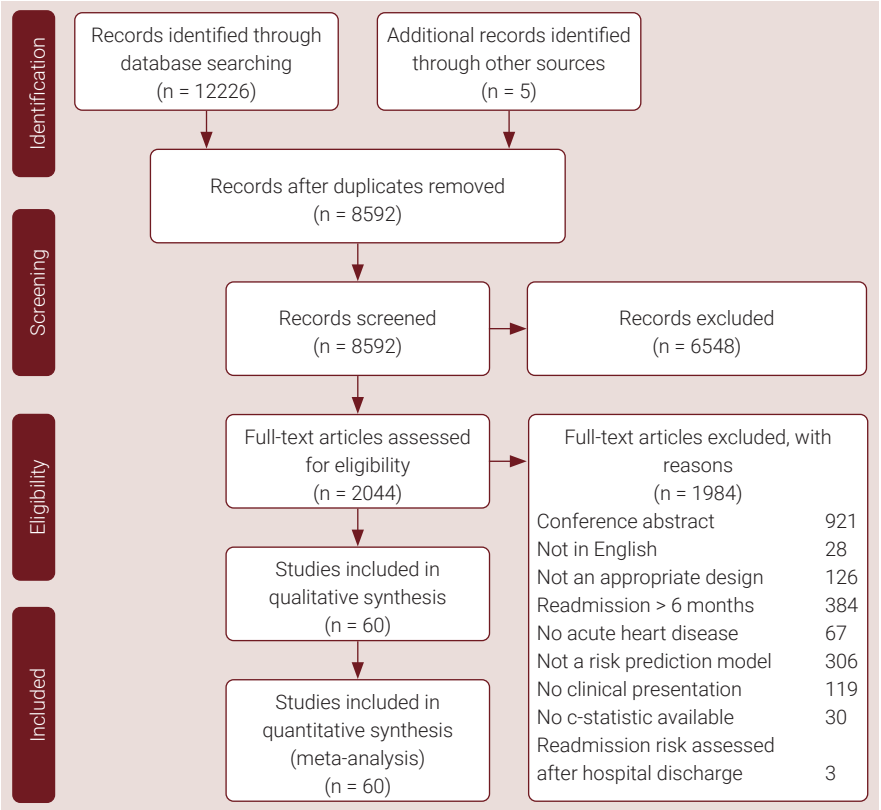

Figure 1. Flowchart
In total, 8592 records were screened and 60 studies with 81 prediction models were included.

Table 1. Study characteristics

Study	Model	Data source	Development	Validation	Sample size		Population	Average age	Outcome	Readmission (%)	
					Dev.	Val.				Dev.	Val.
Moretti et al.[17]	EuroHeart PCI score	Hospital database	NA	Ext	-	1192	ACS	71 (7)	30d		4.7
Asche et al.[18]	NR	Retrospective cohort	Yes	Split	2446	612	AMI	65 (15)	30d	8.9	
Cediel et al.[19]	TARRACO Risk Score	Retrospective cohort	Yes	No	611	401	AMI type 2, ischemia	D: 78 [17] V: 60 [21]	30d	2.6	
		Retrospective cohort	Yes	No	611	401	AMI type 2, ischemia	D: 78 [17] V: 60 [21]	180d	7.9	
Chote-chuang et al.[20]	GRACE	Retrospective cohort	NA	Ext	-	152	AMI	60.5 (6.3)	30d		5.3
	GRACE	Retrospective cohort	NA	Ext	-	152	AMI	60.5 (6.3)	180d		9.2
Hilbert et al.[21]	AMI decision tree	Registry	Yes	Ext	10848	10701	AMI	NR	30d	20.6	19.7
Dodson et al.[22]	SILVER-AMI 30-day readmission calculator	Prospective cohort	Yes	Split	2004	1002	AMI	81.5 (5.0)	30d	18.2	
Kini et al.[23]	NR	Registry	Yes	Split	60742	26107	AMI	76.5 (8.0)	90d	27.5	

Table 1. *Continued*

Study	Model	Data source	Development	Validation	Sample size		Population	Average age	Outcome	Readmission (%)	
					Dev.	Val.				Dev.	Val.
Nguyen et al.[24]	AMI READMITS score	Retrospective cohort	Yes	Split	661	165	AMI	65.5 (12.8)	30d	13	
	Full-stay AMI model	Retrospective cohort	Yes	Split	661	165	AMI	65.5 (12.8)	30d	13	
	CMS AMI administrative model	Retrospective cohort	NA	Ext	-	826	AMI	65.5 (12.8)	30d		13
Krumholz et al.[25]	CMS AMI administrative model	Registry	Yes	Split, Ext	100465	321088	AMI	78.7 (8.0)	30d	18.9	20.0 (Ext) NR (split)
	CMS AMI medical model	Registry	Yes	Split	130944	130944	AMI	76.2 (7.3)	30d	20	
Rana et al.[26]	Elixhauser index	Hospital database	NA	Ext	-	1660	AMI	67.9	30d		6.3
	HOSPITAL score	Hospital database	NA	Ext	-	1660	AMI	67.9	30d		6.3
Atzema et al.[27]	AFTER Part 2 scoring system	Retrospective cohort	Yes	Split	2343	1167	Arrhythmia, AF	D: 68.6 (14.7) V: 68.3 (15.1)	30d	7	7.6

Lahewala et al.[28]	CHADS2	Administrative	NA	Ext	-	116450	Arrhythmia, AF	<75	30d		15.8
	CHADS2	Administrative	NA	Ext	-	116450	Arrhythmia, AF	<75	90d		25.1
	CHA2DS-VASc	Administrative	NA	Ext	-	116450	Arrhythmia, AF	65-74	30d		15.8
	CHA2DS-VASc	Administrative	NA	Ext	-	116450	Arrhythmia, AF	65-74	90d		25.1
Benuzillo et al.[29]	CRSS	Hospital database	Yes	Boot, Ext	2589	896 (Ext) 500 (Boot)	CABG	66.7 (9.9)	30d	9.1	8.2 (Ext) 9.1 (Boot)
Deo et al.[30]	30-days CABG Readmission Calculator	Administrative	Yes	Boot	155054	1000	CABG	65.4 (10.4)	30d	12.5	
Engoren et al.[31]	NR	Hospital database	Yes	Split	2644	2711	CABG	NR	30d	7.6	8
Lancey et al.[32]	NR	Registry	Yes	Split	2341	2520	CABG	64.5 (10.5)	30d	8.8	9.5
Rosen-blum et al.[33]	The STS PROM score	Hospital database	NA	Ext	-	21719	CABG	63.5 (10.7)	30d		9.3
Zitser-Gurevich et al.[34]	NR	Prospective cohort	Yes	Split	2266,5	2266,5	CABG	65-74	30d	13.3	
	NR	Prospective cohort	Yes	Split	2266,5	2266,5	CABG	65-74	100d	24.1	

Table 1. *Continued*

Study	Model	Data source	Development	Validation	Sample size		Population	Average age	Outcome	Readmission (%)	
					Dev.	Val.				Dev.	Val.
Zywot et al.[35]	CABG Risk Scale	Administrative	Yes	Ext	126519	94318	CABG	D: 70-74 V: 70-74	30d	23	21
Ahmad et al.[36]	CMS HF administrative model	Prospective cohort	NA	Ext	-	183	HF	61 [18]	30d		22.4
Amaras-ingham et al.[37]	ADHERE	Hospital database	NA	Ext	-	1372	HF	56.5	30d		24.1
	CMS HF administrative model	Hospital database	NA	Ext	-	1372	HF	56.5	30d		24.1
	Tabak mortality score	Hospital database	NA	Ext	-	1372	HF	56.5	30d		24.1
Au et al.[38]	Administrative Claims Model: HF 30-day mortality	Administrative	NA	Ext	59652	59652	HF	75.8 (12.7)	30d		15.9
	Charlson Comorbidity Score	Administrative	NA	Ext	59652	59652	HF	75.8 (12.7)	30d		15.9
	CMS HF administrative model	Administrative	NA	Ext	59652	59652	HF	75.8 (12.7)	30d		15.9

	LACE	Administrative	NA	Ext	59652	59652	HF	75.8 (12.7)	30d		15.9
Bardhan et al.[39]	NR	Hospital database	Yes	No	40983	-	HF	69.2 (15.7)	30d	7	
Betihavas et al.[40]	NR	RCT secondary analysis	Yes	Boot	280	200	HF	74 [64 - 81]	28d	18	
Cox et al.[41]	CMS HF administrative model	Hospital database	No	Ext	-	1454	HF	75 (12)	30d		21.5
	CMS HF medical model	Hospital database	No	Ext	-	1454	HF	75 (12)	30d		21.5
Delgado et al.[42]	15-day CV readmission risk score	Prospective cohort	Yes	Boot	1831	500	HF	72.4 (12.1)	15d	7.1	
	30-day CV readmission risk score	Prospective cohort	Yes	Boot	1831	500	HF	72.4 (12.1)	30d	13.9	
Formiga et al.[43]	CMS HF medical model	Hospital database	NA	Ext	-	719	HF	78.1 (9)	30d		7.6
	CMS HF medical model	Hospital database	NA	Ext	-	719	HF	78.1 (9)	90d		14.4
Frizzell et al.[44]	CMS HF administrative model	Registry	NA	External	-	56477	HF	80 [2]	30d		21.2

Table 1. *Continued*

Study	Model	Data source	Development	Validation	Sample size		Population	Average age	Outcome	Readmission (%)	
					Dev.	Val.				Dev.	Val.
Hammill et al.[45]	CMS HF administrative model	Registry	NA	Ext	-	24163	HF	81	30d		21.9
Hilbert et al.[21]	HF decision tree	Registry	Yes	Ext	39682	38409	HF	NR	30d	25.5	25.2
Hummel et al.[46]	CMS HF medical model	Prospective cohort	NA	Ext	-	1807	HF	79.8 (7.6)	30d		27
Huynh et al.[47]	NR	Prospective cohort	Yes	Ext	430	1046	HF	D: 75 [19] V: 67 [17]	30d	21	24
Ibrahim et al.[48]	HOSPITAL score	Retrospective cohort	NA	Ext	-	692	HfpEF	68.3 (11.8)	30d		27.3
	LACE / LACE+ index	Retrospective cohort	NA	Ext	-	692	HfpEF	68.3 (11.8)	30d		27.3
Keenan et al.[49]	CMS HF administrative model	Registry	Yes	Split, Ext.	28319	845291	HF	79.9 (7.8)	30d	23.6	23.7 (Ext) NR (Split)
	CMS HF medical model	Registry	Yes	Split, Ext.	64329	64329	HF	75-84	30d	23.7	
Kitamura et al.[50]	FIM	Retrospective cohort	NA	Ext	-	113	HF	80.5 (6.7)	90d		20.4

Leong et al.[51]	30-day HF readmission risk score	Retrospective cohort	Yes	Split	888	587	HF	D: 70.0 (12.7) V: 69.1 (12.8)	30d	9.9	
Li et al.[52]	NR	Retrospective cohort	Yes	Split	51783	25887	HF	D: 84 [12] V: 84[11]	30d	24.2	
Lim et al.[53]	NR	Registry	Yes	No	4566	-	HF	70.5 (12.0)	30d	6.6 (car) 13 (all)	
Reed et al.[54]	AH model	Administrative	Yes	Split	NR	NR	HF	NR	30d	NR	
	CMS HF administrative model	Administrative	NA	Split	-	NR	HF	NR	30d		NR
	Hasan	Administrative	NA	Split	-	NR	HF	NR	30d		NR
	LACE	Administrative	NA	Split	-	NR	HF	NR	30d		NR
	PARR-30	Administrative	NA	Split	-	NR	HF	NR	30d		NR
Salah et al.[55]	ELAN-HF score	Prospective cohort secondary analysis	Yes	No	1301	-	HF	74 [16]	180d	36.1	
Sudhakar et al.56	CMS HF medical model	Hospital database	NA	Ext	-	1046	HF	65.2 (16.6)	30d		35.3
Tan et al.[57]	NR	Hospital database	Yes	Split	246	104	HF	D: 67.7 (12.3) V: 69.0 (12.9)	90d	24.5	11.7

Table 1. *Continued*

Study	Model	Data source	Development	Validation	Sample size		Population	Average age	Outcome	Readmission (%)	
					Dev.	Val.				Dev.	Val.
Wang et al.[58]	NR	Hospital database	Yes	No	4548	-	HF	68.5 [27.6]	30d	25.1	
Wang et al.[59]	LACE	Retrospective cohort	NA	Ext	-	253	HF	56.6 (11.5)	30d		24.5
Yazdan-Ashoori et al.[60]	CMS HF administrative model	Prospective cohort	NA	Ext	-	378	HF	73.1 (13.1)	30d		26
	LACE	Prospective cohort	NA	Ext	-	378	HF	73.1 (13.1)	30d		26
Disdier Moulder et al.[61]	NR	Prospective cohort	Yes	No	258		HF, ACS, NR	70.5 [23]	30d	17	
	NR	Prospective cohort	Yes	No	258		HF, ACS, NR	70.5 [23]	180d	38	
Raposeiras-Roubín et al.[62]	GRACE	Retrospective cohort	NA	Ext	-	4229	HF, ACS	68.2 [18.7]	30d		2.6
Burke et al.[63]	HOSPITAL score	Retrospective cohort	NA	Ext	-	HF: 3189 AMI: 767	HF, AMI	65.8 (16.8)	30d		HF: 18.2 AMI: 17.4
Minges et al.[64]	NR	Registry	Yes	Split	193899	194179	HF, PCI	65+	30d	11.4	

Pack et al.[65]	NR	Administrative	Yes	Split	30826	7706	HVD	64.9 (12.2)	90d	12.8	
Oliver-McNeil et al.[66]	ICD Readmission-Risk Score	Registry	Update	Ext	182	-	ICD	69 (11)	30d		17.6
Wasfy et al.[67]	Pre-PCI model	Registry	Yes	Split	24052	12008	NR	64.8 (12.5)	30d	10.4	
Barnett et al.[68]	NR	Registry	Update	Ext	19964	19964	Surgical	65.3 (12.4)	30d	11.4	
Brown et al.[69]	STS Augmented Clinical Model	Prospective cohort	Update	Boot	1046	NR	Surgical	65.4 (9.8)	30d	NR	
	STS 30-day Readmission Model	Prospective cohort	NA	Ext	-	1194	Surgical	73.3 (10.1)	30d		NR
Espinoza et al.[70]	30-day readmission score after cardiac surgery	Retrospective cohort	Yes	Split	2529	2567	Surgical	65.1 (11.5)	30d	11.9	
Ferraris et al.[71]	READMIT	Prospective cohort	Yes		2574		Surgical	63 (11)	30d	9.8	
Kilic et al.[72]	NR	Retrospective cohort	Yes	Split	3898	1295	Surgical	D:61.9 (14.7) V: 61.6 (15.1)	30d	10	11
Stuebe et al.[73]	NR	Hospital database	Yes	No	4800		Surgical	60-69	30d	12	

Table 1. *Continued*

Study	Model	Data source	Development	Validation	Sample size		Population	Average age	Outcome	Readmission (%)	
					Dev.	Val.				Dev.	Val.
Tam et al.[74]	NR	Retrospective cohort	Yes	Boot	63336	NR	Surgical	66.2 (10.7)	30d	11.3	
Khera et al.[75]	TAVR 30-Day Readmission Risk Model	Administrative	Yes	Boots, Ext	39305	40 (Boot) 885 (Ext)	TAVR	D: 81.3 V: 81.7	30d	16.2	16.2 (Boot) 18.9 (Ext)
Sanchez et al.[76]	NR	Registry	Yes	Split	6903	3442	TAVR	D: 81.1 (7.9) V: 81.3 (7.9)	30d	9.8	10.7

Abbreviations: ACS: acute coronary syndrome, AF: atrial fibrillation, AH: Adventist hositals, Boot: bootstrapping, CABG: coronary artery bypass grafting, Car: cardiac-related, CMS=centers for Medicare and Medicaid services, CRSS: CABG Readmission Risk Score, d: days, Dev: development, Ext: external validation, Fim: motor and cognitive Functional Independence Measure, HF: heart failure, HFpEF: heart failure with preserved ejection fraction, HVD: heart valve disease, ICD: implantable cardioverter defibrillator, NA: not applicable, NR: not reported, PARR-30: Patients at Risk of Re-admission within 30-days, PCI: percutaneous coronary intervention, SD: standard deviation, Split: random split, TAVR: transcatheter aortic valve replacement, Val: validation
Legend: Age is reported as mean (SD), median [IQR] or average age as reported in the study.

Risk of bias

Figure 2 summarizes the RoB and applicability assessment (Supplemental Table 1). The overall RoB was high in 98.9% of the models and only one study[22] showed low RoB in all four domains.

For the domain participants, 82.4% of studies was assessed as high RoB because most studies performed retrospective data analyses or used data from existing sources with large number of candidate predictors that were originally developed for other purposes, e.g. administrative databases or registries. The domain predictors was assessed as high RoB in 27.5% of the models, 24.2% as low RoB and 48.4% as unclear RoB. For the domain outcome, 41.8%, 34.1% and 24.2% were assessed as high, low and unclear RoB respectively.

The domain analysis was assessed as high RoB in 97.8%. Most studies did not use appropriate statistics for the development or validation of prediction models.

The domains participants and predictors were assessed as low concerns regarding applicability in all studies. For the domain outcome, 70.3% of studies used all-cause readmission as the outcome of interest and were therefore assessed as low concerns regarding applicability.

Prediction models

A total of 43 new models were developed for patients with HF (n=15), undergoing surgical procedures (n=12), AMI (n=9), transcatheter aortic valve replacement (TAVR) (n=2), a mixed sample with HF and coronary syndromes (n=2), arrhythmias (n=1), valvular disease (n=1), while one study did not specify the sample (table 1). The c-statistic was lower than 0.6 in five models, between 0.6 and 0.7 in 24 models, between 0.7 and 0.8 in six models, and between 0.8 and 0.9 in two models. In six models, the c-statistic was only reported for a validation cohort (table 2).

A total of 38 separate models were externally validated for patients with HF (n=26), AMI (n=4), surgical patients (n=3), acute coronary syndrome (n=2), arrhythmias (n=2), mixed sample with HF and coronary syndromes (n=1). The discrimination was lower than 0.6 in sixteen models, between 0.6 and 0.7 in fifteen models, between 0.7 and 0.8 in five models, and between 0.8 and 0.9 in two models (table 2).

The discrimination of six models was evaluated in multiple independent cohorts and was pooled in meta-analyses (Figure 3, Supplemental Figures 1-6): the CMS AMI administrative model[24,25] (0.65, 95% CI 0.56-0.73); the CMS HF administrative model[36-38,41,44,45,49,54,60] (0.60, 95% CI 0.58-0.62); the CMS HF medical model[41,43,46,49,56] (0.60, 95% CI 0.58-0.62); the HOSPITAL score[26,48,63] (0.64, 95% CI 0.58-0.70); the GRACE score[20,62] (0.78, 95% CI 0.63-0.86); and the LACE score[38,48,54,59,60] (0.62, 95% CI 0.53-0.70).

Figure 2. PROBAST Risk of bias and applicability
The PROBAST tool[15] was used to assess the risk of bias for the participants, predictors, outcome and analysis for each model. Only one study demonstrated low risk of bias on all domains.

On average, models for AMI patients had the best discrimination (0.67, n=16), followed by TAVR patients (0.65, n=2), HF patients (0.64, n=45), and surgical patients (0.63, n=17). The discrimination was highest in studies using secondary analysis (0.70, n=2) and retrospective cohort studies (0.69, n=23), and was lowest in studies using registries (0.61, n=17) and hospital databases (0.61, n=18). The discrimination decreased when the number of predictors increased (beta -0.002, n=90). There were no moderation effects based on the average age of the sample, outcome definition and endpoint of the prediction (Supplemental Figures 7–8 and Supplemental Table 2).

The calibration was reported for 27 models using multiple measures and could not be pooled (Table 2).

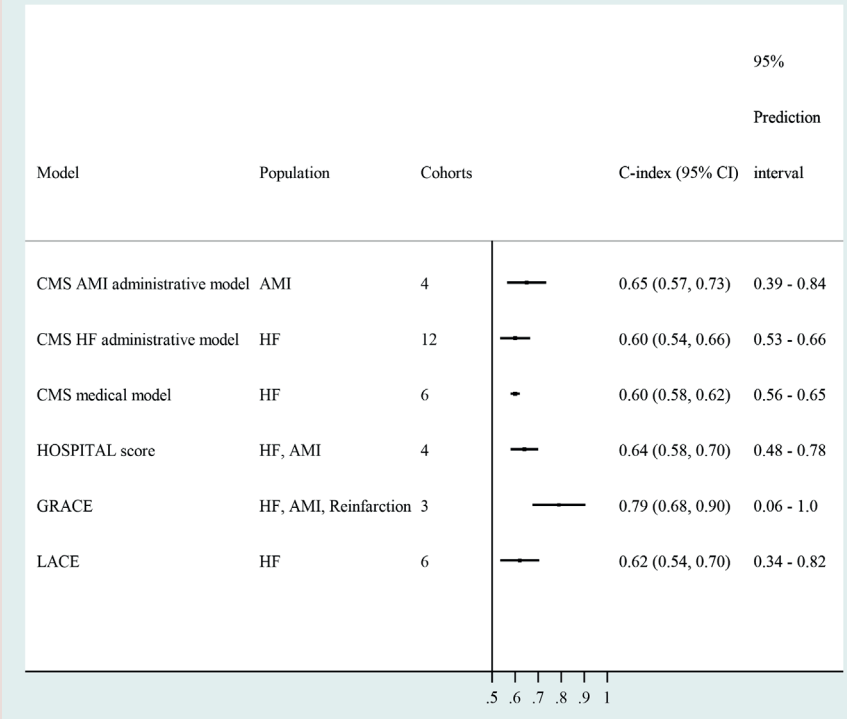

Figure 3. Meta-analysis of prediction models
Random-effect models were used to pool similar models reported in independent cohorts. For the HOSPITAL score, the discrimination for the HF and AMI samples were similar (0.65 and 0.64). For GRACE, the discrimination for the AMI and reinfarction samples were similar (0.77 and 0.74), and was higher for the HF sample (0.83). Only GRACE demonstrated adequate discrimination in external cohorts.

Table 2. Model discrimination and calibration

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
Moretti et al.[17]	EuroHeart PCI score	ACS	16	External	0.59 (0.48 - 0.71)	NA	
Asche et al.[18]	NR	AMI	19	Development, random split	0.74, NR	NA	
Cediel et al.[19]	TARRACO Risk Score	AMI type 2, ischemia	7	Development (30d)	0.71 (0.61 - 0.82)	NA	
		AMI type 2, ischemia	7	Development (180d)	0.71 (0.64 - 0.78)	NA	
Burke et al.[63]	HOSPITAL score	AMI	7	External	0.66 (0.61 - 0.71)	HLT	p=0.49
Chotechuang et al.[20]	GRACE	AMI	9	External (30d)	0.77 (0.65 - 0.88)	NA	
	GRACE	AMI	9	External (180d)	0.63 (0.49 - 0.77)	NA	
Hilbert et al.[21]	AMI decision tree	AMI	44	Development, External	0.65 (0.64 - 0.66), 0.61 (0.61 - 0.62)	NA	
Dodson et al.[22]	SILVER-AMI 30-day readmission calculator	AMI	10	Development, random split	0.65, 0.63	HLT	p>0.05, p=0.05
Kini et al.[23]	NR	AMI	12	Development, random split	NR, 0.66	Slope, in large, plot	0.973 (p=0.330), -0.038 (p=0.221)
Nguyen et al.[24]	AMI READMITS score	AMI	7	Development, random split	0.75 (0.70 - 0.80), 0.73 (0.71 - 0.74)	Plot, Plot	
	Full-stay AMI model	AMI	10	Development, random split	0.78 (0.74 - 0.83), 0.75 (0.74 - 0.76)	Plot	

	CMS AMI administrative model	AMI	32	External	0.74 (0.69 - 0.74)	Plot	
Krumholz et al.[25]	CMS AMI administrative model	AMI	32	Development, external, random split	0.63, 0.63, 0.62	In large, slope	
	CMS AMI medical model	AMI	45	Development, random split	0.58, 0.59	NA	0, 1 / 0.015, 0.997/ 0.015, 0.983
Rana et al.[26]	Elixhauser index	AMI	30	External	0.53 (0.42 - 0.65)	NA	
	HOSPITAL score	AMI	7	External	0.60 (0.47 - 0.73)	NA	
Atzema et al.[27]	AFTER Part 2 scoring system	Arrhythmia, AF	12	Development	0.69, NR	NA	
Lahewala et al.[28]	CHADS2	Arrhythmia, AF	5	External (30d)	0.64	NA	
	CHADS2	Arrhythmia, AF	5	External (90d)	0.63	NA	
	CHA2DS-VASc	Arrhythmia, AF	9	External (30d)	0.65	NA	
	CHA2DS-VASc	Arrhythmia, AF	9	External (90d)	0.63	NA	
Benuzillo et al.[29]	CRSS	CABG	5	Development, bootstrapping	0.63, 0.63	HLT	7.13 (p=0.52), 9.31 (p=0.32)
Deo et al.[30]	30-days CABG Readmission Calculator	CABG	20	Development	0.65	NA	

Table 2. *Continued*

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
Engoren et al.[31]	NR	CABG	6	Development, random split	0.68 (0.64 - 0.72), 0.68 (0.64 - 0.68)	NA	
Lancey et al.[32]	NR	CABG	8	Development, random split	0.64, 0.57	NA	
Rosenblum et al.[33]	The STS PROM score	CABG	40	External	0.59 (0.57 - 0.60)	NA	
Zitser-Gurevich et al.[34]	NR	CABG	17	Development, external (30d)	0.63, 0.66/0.63	HLT	7.91 (p=0.44)
	NR	CABG	13	Development (100d)	0.65	HLT	6.76 (p=0.56)
Zywot et al.[35]	CABG Risk Scale	CABG	27	Development, external	NR, 0.70	Plot	
Ahmad et al.[36]	CMS HF administrative model	HF	37	External	0.66 (0.57 - 0.76)	HLT	p=0.19
Amarasingham et al.[37]	ADHERE	HF	3	External	0.56 (0.54 - 0.59)	NA	
	CMS HF administrative model	HF	37	External	0.66 (0.63 - 0.68)	NA	
	Tabak mortality score	HF	18	External	0.61 (0.59 - 0.64)	NA	
Au et al.[38]	Administrative Claims Model: HF 30-day mortality	HF	17	External	0.58 (0.58 - 0.59)	NA	

	Charlson Comorbidity Score	HF	32	External	0.55 (0.55- 0.56)	NA	
	CMS HF administrative model	HF	37	External	0.59 (0.59 - 0.60)	NA	
	LACE	HF	18	External	0.58 (0.58 - 0.59)	NA	
Bardhan et al.[39]	NR	HF	30	Development	0.56	NA	
Betihavas et al.[40]	NR	HF	7	Development, bootstrapping	NR, 0.80	NA	
Burke et al.[63]	HOSPITAL score	HF	7	External	0.67 (0.65 - 0.70)	HLT	p=0.10
Cox et al.[41]	CMS HF administrative model	HF	37	External	0.61	NA	
	CMS HF medical model	HF	20	External	0.60	NA	
Delgado et al.[42]	15-day CV readmission risk score	HF	5	Development, bootstrapping	0.65, 0.63	Plot	
	30-day CV readmission risk score	HF	11	Development, bootstrapping	0.66, 0.64	Plot	
Formiga et al.[43]	CMS HF medical model	HF	19	External (30d)	0.65 (0.57 - 0.72)	NA	
	CMS HF medical model	HF	19	External (90d)	0.62 (0.56 - 0.68)	NA	
Frizzell et al.[44]	CMS HF administrative model	HF	37	External	0.60	NA	
Hammill et al.[45]	CMS HF administrative model	HF	37	External	0.59	Plot	
Hilbert et al.[21]	HF decision tree	HF	44	Development, External	0.59 (0.58 - 0.60), 0.58 (0.58 - 0.59)	NA	

Table 2. *Continued*

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
Hummel et al.[46]	CMS HF medical model	HF	28	External	0.61	NA	
Huynh et al.[47]	NR	HF	12	Development, external (30d)	0.82 (0.76 - 0.87), 0.73 (0.69 - 0.77)	NA	
	NR	HF	12	Development, external (90d)	NR, 0.65	NA	
Ibrahim et al.[48]	HOSPITAL score	HfpEF	7	External	0.60 (0.55 - 0.64)	NA	
	LACE	HfpEF	18	External	0.55 (0.50 - 0.60)	NA	
	LACE+ index	HfpEF	24	External	0.57 (0.52 - 0.62)	NA	
Keenan et al.[49]	CMS HF administrative model	HF	37	Development, external, random split	0.60, 0.60, 0.61	In large, slope	0, 1 / 0.02, 1.01/ 0.09, 1.05
	CMS HF medical model	HF	30	Development, random split	0.58, 0.61	In large, slope	0, 1 / 0, 1
Kitamura et al.[50]	FIM	HF	13	External	0.78	NA	
Leong et al.[51]	30-day HF readmission risk score	HF	7	Development, random split	0.76, 0.76	NA	
Li et al.[52]	NR	HF	10	Development, random split	0.63 (0.62 - 0.63) 0.63 (0.62 - 0.63)	HLT, plot	0.15 (p>0.005)
Lim et al.[53]	NR	HF	13	Development	0.68 (car), 0.62 (all)	HLT	27.5 (p=0.001) (car) 8.0 (p=0.429) (all)

Reed et al.[54]	AH model	HF	14	Development, random split	0.86 (0.85 - 0.86), 0.85 (0.84 - 0.86)	NA	
	CMS HF administrative model	HF	37	Random split	0.55 (0.54 - 0.56) 0.55 (0.54 - 0.57)	NA	
	Hasan	HF	9	Random split	0.80 (0.79 - 0.81) 0.80 (0.80 - 0.82)	NA	
	LACE	HF	18	Random split	0.75 (0.74 - 0.81) 0.74 (0.73 - 0.76)	NA	
Reed et al.[54]	PARR-30	HF	10	Random split	0.82 (0.81 - 0.83) 0.81 (0.80 - 0.82)	NA	
Salah et al.[55]	ELAN-HF score	HF	10	Development	0.60 (0.56 - 0.64)	NA	
Sudhakar et al.[56]	CMS HF medical model	HF	20	External	0.61 (0.57-0.64) ≥65y: 0.59 (0.53-0.64) Random patient-level: 0.58 (0.50-0.65)	NA	
Tan et al.[57]	NR	HF	3	Random split	0.73	HLT, plot	p=0.62
Wang et al.[58]	NR	HF	12	Development	0.65	NA	
Wang et al.[59]	LACE	HF	18	External	0.56 (0.48 - 0.64)	NA	
Yazdan-Ashoori et al.[60]	CMS HF administrative model	HF	37	External	0.61 (0.55 - 0.67)	NA	
	LACE	HF	18	External	0.59 (0.52 - 0.65)	HLT	p=0.73
Disdier Moulder et al.[61]	NR	HF, ACS, NR	4	Development (30d)	0.68	NA	

Table 2. *Continued*

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
	NR	HF, ACS, NR	5	Development (180d)	0.69	NA	
Raposeiras-Roubín et al.[62]	GRACE	HF, ACS	9	External	0.74 (0.73-0.80)	HLT	p=0.14
Minges et al.[64]	NR	HF, PCI	35	Development, random split	0.67, 0.66	NA	
Pack et al.[65]	NR	HVD	28	Development, random split	0.67 (full dev.)/ 0.65 (nomogram), 0.67 (full val.)	Harrell's E, O:E, Harrell's E, plot	0.1%, 1.9%, 1.6%
Oliver-McNeil et al.[66]	ICD Readmission-Risk Score	ICD	4	Update, External	0.69 (0.58 - 0.79)	HLT, plot	3.44 (p=0.49)
Wasfy et al.[67]	Pre-PCI model	NR	23	Development, random split	0.68, 0.67	HLT, plot	p=0.59
Barnett et al.[68]	NR validation	Surgical	15	External	0.59	NA	
	NR update	Surgical	18	Update	0.60 (0.59 - 0.62)	NA	
Brown et al.[69]	STS Augmented Clinical Model	Surgical	27	Update (bootstrap), random split, external (bootstrap)	0.66 (0.61 - 0.72), 0.56, 0.47 (0.42 - 0.53)	HLT	p=1.0

	STS 30-day Readmission Model	Surgical	21	Update (bootstrap), random split, external (bootstrap)	0.66 (0.62 - 0.71), 0.58, 0.47 (0.41 - 0.52)	HLT	p=0.492
Espinoza et al.[70]	0.47 (0.41 - 0.52)	HLT	p=0.492	Development, random split	0.66 (0.63 - 0.70), 0.64 (0.61 - 0.67)	NA	
Ferraris et al.[71]	READMIT	Surgical	9	Development	0.70	HLT	5.966 (p=0.651)
Kilic et al.[72]	NR	Surgical	15	Development, random split	NR, 0.64	HLT, plot	p=0.45, p=0.57
Stuebe et al.[73]	NR	Surgical	7	Development	0.63	NA	
Tam et al.[74]	NR	Surgical	29	Development, bootstrapping	0.63, 0.65	Plot	
Khera et al.[75]	TAVR 30-Day Readmission Risk Model	TAVR	11	Development, random split, external	NR, 0.63, 0.69	HLT, RMSE, RMSE, plot	p=0.33, 0.978, 0.928
Sanchez et al.[76]	NR	TAVR	10	Development, random split	0.61, 0.60	HLT	p=0.749, p=0.403

Abbreviations: ACS: acute coronary syndrome, AF: atrial fibrillation, AH: Adventist hospitals, CABG: coronary artery bypass grafting, Car: cardiac-related, CMS=centers for Medicare and Medicaid services, CRSS: CABG Readmission Risk Score, d: days, dev: development, Fim: motor and cognitive Functional Independence Measure, HF: heart failure, HFpEF: heart failure with preserved ejection fraction, HLT: Hosmer-Lemeshow test, HVD: heart valve disease, ICD: implantable cardioverter defibrillator, NA: not applicable, NR: not reported, O:E: observed:expected, PARR-30: Patients at Risk of Re-admission within 30-days, PCI: percutaneous coronary intervention, plot: calibration plot, TAVR: transcatheter aortic valve replacement, val: validation.

Predictors

A total of 766 predictor values were estimated in the included models. The median number of predictors per model was 15 (IQR=9–28). The predictors were mostly situated in the domains medical comorbidities (n=211), disease and hospital characteristics (n=128), demographic data (n=128), laboratory values (n=97), and medical history characteristics (n=51). Age (n=47), the presence of diabetes (n=26), insurance status (n=24), length of stay (n=28), and gender (n=23) were the most prevalent predictors. There was little consistency in the definition of predictors, and most studies did not report how they were measured.

Only 18 predictors were similarly defined in multiple studies and could be pooled for the outcome readmission at 30 days (Figure 4, Supplemental Table 3 and Supplemental Figures 9–26). The coefficients of four predictors demonstrated a consistent and significant association across the different samples: chronic obstructive pulmonary disease (COPD), history of HF, and valvular disease. The coefficients of eleven predictors demonstrated an overall significant association, i.e. age, female gender, arrhythmias, chronic lung disease, diabetes mellitus, cerebrovascular disease, cardiovascular accident, anemia, peripheral vascular disease, urgent admission, and infection, but this was not consistent across the samples and the prediction intervals were not significant. The effect of these predictors was mostly smaller in the HF samples.

The coefficients for most predictors could not be pooled because they had different definitions, cutoff values or reference categories. However, renal disease, including dialysis, a longer length of stay, creatinine, NT-proBNP, and previous hospital admissions demonstrated a consistent association with readmissions.

Discussion

In this systematic review, we included 60 studies that reported the results from 81 separate clinical risk prediction models and 766 risk predictors for unplanned readmission in patients with acute heart disease. No clinical model demonstrated good discrimination (i.e. c-statistic > 0.8) in independently externally validated cohorts, regardless of the underlying patient populations. GRACE was the only model that demonstrated adequate discrimination in multiple cohorts in patients with acute coronary syndromes[20,62] and HF,[62] but the RoB was high. There was little consistency in the measurement of risk predictors.

The results of our review are in line with previous systematic reviews which have mainly focused on samples of patients with HF, AMI or focused on generic prediction models. All reviews confirm that the discrimination is generally low. Our review confirms the importance of previous HF[4,5] and previous hospital

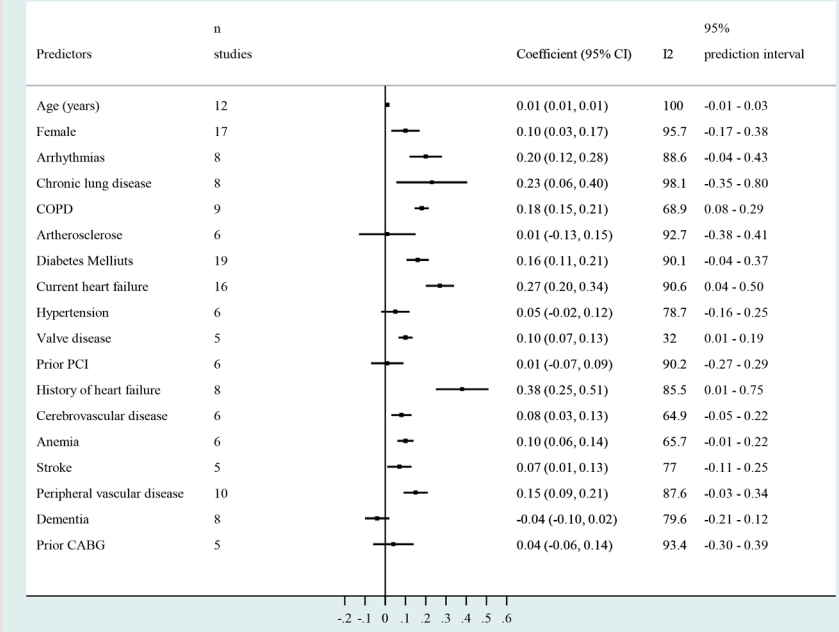

Figure 4. Predictors of unplanned hospital readmission
The plot provides an overview of the random-effects meta-analyses that were performed for predictors who were similarly defined for the outcome unplanned hospital readmission at 30 days follow-up. See Supplemental table 3 and Supplemental figures 9-26 for more details.

admissions[5,7] as consistent predictors for the risk of readmission. In addition two prevalent comorbidities, COPD and valve disease were also consistent predictors across the different populations. Other reviews also identified the importance of age, gender, comorbidities and certain laboratory values. These were also significant in our review but the association was not always consistent across the different populations or heterogeneously measured making comparisons difficult. As a result, no clinical risk prediction model or set of predictors that is relevant for different populations of heart disease could be identified.

Our review focused specifically on prediction models with a clinical presentation that can be used in daily practice, e.g. risk scores or nomograms. These simple models do not consider interactions between predictor values or nonlinear link functions in their predictions. This may partially explain the poor discrimination.[77] Using web applications or electronic patient records to run more complex prediction algorithms can likely offer a solution for future models. A recent systematic review observed an average c-statistic of 0.74 for models based using electronic patient records and machine learning algorithms.[10] Our

review included eleven studies[20,22,28,33,35,56,60,62,69,74,75] that developed or validated electronic tools for risk prediction and their discrimination ranged between 0.59 and 0.77. However, these electronic tools were mostly derived from score charts and nomograms.

There are also concerns about the generalizability of the prediction models. The median age of patients included in the samples was 68 years (IQR=65–75). However, older and frail patients suffer more multimorbidity and geriatric syndromes, and the distribution of predictor and outcome values will also be different than in younger samples. It is therefore unlikely that the majority of the current models will hold their value in daily clinical practice where there is a high prevalence of older patients. Only eight studies[18,22,25,27,47,49,52,76] included one or more geriatric risk factors (e.g. physical performance, dementia) as predictors for readmission. The performance of models including geriatric conditions was similar to models without these conditions. This might be explained by the relative young mean age of the samples in our review. Mahmoudi et al.[10] reported that functional and frailty status are important predictors, but were only included in a small number of studies. Frailty was not identified in any of the models in our review. It might be valuable to examine the additive value of these predictors in prediction models for patients with heart disease.

We observed high RoB in almost all clinical risk prediction models (98.8%). This was mainly because the calibration was lacking or not fully reported (e.g. only p-value of Hosmer-Lemeshow test). Furthermore, most studies performed retrospective data analyses or used data from existing sources. However, our results demonstrate that studies using these data sources had the lowest c-statistic, and that the c-statistic decreased when more predictors were tested. Databases often have missing data, misclassification bias, and random measurement error, which likely explains their average poor performance.[78] Only the SILVER-AMI study[22] demonstrated low RoB on all domains. However, their readmission risk calculator for older AMI patients only discriminated modestly (c-statistic = 0.65).

Our review included many recent published studies that were not included in previous reviews and added some new perspective to the literature. Our results show the current state-of-the art of risk prediction in patients with acute heart disease. The timely identification of patients with acute heart disease at risk of readmission remains challenging with the prediction models identified in this systematic review. Therefore, further research in risk prediction remains important and some recommendations for further research can be derived from this review. First, consistency is needed in the definition and measurement of predictors. More homogeneity might improve the identification of important predictors and their effect on readmission. Second, the results suggest that multiple predictors are associated with readmissions regardless of the underlying population. Therefore, attention might be shifted from developing new

risk prediction models to updating and externally validating existing prediction models in different populations with heart disease. Third, the applicability of current prediction models in daily practice is an important concern as most models had poor performance, were not replicated and had high RoB. More high-quality studies are needed that evaluate the discrimination, calibration and clinical usefulness. To limit the risk of bias as much as possible, future studies should adhere to the relevant reporting guidelines[79] and could use PROBAST[15] as a guidance to plan their study. Fourth, more complex models integrated in electronic patient records may results in better predictions.

Limitations

Although we performed an extensive literature search, we might have missed some eligible studies, particularly those published in non-English languages. We were able to perform meta-analysis for predictors that were often (≥ 5 models) reported. However, it might be possible that some less frequently mentioned predictors (e.g. geriatric predictors) are a valuable addition in clinical practice. The review included a large number of results and statistical tests which may result in an inflated alpha error. The meta-regression identified that models with less predictors had a better discrimination, but this could also be explained by overfitting models; this could not be tested.

Conclusion

A large number of clinical models have recently been developed. Although some models are promising as they demonstrated adequate to good discrimination, no model can currently be recommended for clinical practice. The lack of independently validated studies, high risk of bias and low consistency in measured predictors limit their applicability. Model updating and external validation is urgently needed.

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Supplemental materials

Supplemental Text 1. Search string

Ovid MEDLINE(R) ALL 1946 to November 21, 2019
Search date: 25 August 2020

#	Searches	Results
1	exp "predictive value of tests"/ or roc curve/ or exp Decision Support Techniques/	321482
2	("signal to noise" or roc curve or reiver operating or predict*).ab,kf,ti.	1644590
3	(decision adj2 (aid? or model* or clinical* or support or system? or tool?)).ab,kf,ti.	56262
4	decision?.ab,kf,ti.	381353
5	logistic models/	139814
6	(logistic model* or regression).ab,kf,ti.	758909
7	5 or 6	814876
8	4 and 7	23040
9	or/1-3,8	1861041
10	patient readmission/	17534
11	((readmission or readmitted or re-admission or re-admitted) and (hospital* or prehospital*)).ab,kf,ti.	20747
12	((readmission or readmitted or re-admission or re-admitted) adj2 (patient? or client)).ab,kf,ti.	4515
13	(rehospitali?ation? or re-hospitali?ation? or rehospitali?ed or re-hospitali?ed).ab,kf,ti.	7834
14	or/10-13	35723
15	exp cardiovascular system/ or exp cardiovascular diseases/	3001695
16	(cardiac* or cardio* or myocard* or coronary or heart).ab,jw,kf,ti.	2161260
17	(diastolic or systolic or edema or dyspnea or renocardiac or Stenocardia* or angor or angina* or atherioscleros* or atheroscleros* or arteroscleros* or Arterioscleros* or Kounis syndrome or ST elevation or STEMI or valve* or aortic or stenosis or Leopard Syndrome or Noonan Syndrome with Multiple Lentigines or Multiple Lentigines Syndrome or Obstructive Subaortic Conus or Absent Right Atrioventricular Connection or arrhythmia* or sinus or sinoatrial or atria* or auricular or atrioventricular or ventricular or bradycardia or Bradyarrhythmia* or tachycardia* or fibrillation* or flutter* or Right Bundle Branch Block or Brugada or extrasystole* or (commotion adj1 cordis) or Auriculo-Ventricular Dissociation or Auriculo Ventricular Dissociation or Atrioventricular Dissociation or A-V Dissociation or AV Dissociation or syncope or (Andersen adj2 Tawil) or QT Syndrome or (jervell adj2 lange) or Prolonged QT Interval or (romano adj1 ward) or parasystole or Pre-Excitation or Preexcitation or (Lown adj2 Ganong) or Short PR-Normal QRS Complex Syndrome or Short PR Normal QRS Complex Syndrome or Wolff-Parkinson-White or WPW Syndrome or Idioventricular Rhythm or Torsade de Pointes).ab,hw,kf,ti.	1642025

18	or/15-17	4136701
19	(predict* adj3 risk?).ab,kf,ti.	57669
20	retrospective.ab,hw,kf,ti.	1006259
21	(admission or hospitali?ation or discharge).ab,hw,kf,ti.	529444
22	and/18-21	692
23	and/9,14,18	3482
24	(ISRCTN96643197 or ChiCTR1900026250 or NCT04008914 or NCT03791541 or NCT03300791 or "CTRI/2016/10/007411" or "CTRI/2014/06/004690" or NCT03949439 or NCT03905226 or NCT00344513 or NCT01755052 or NCT02041585).ab,kf,ti.	9
25	((OPERA or REIC or FIgARO or PREDIC or optimize-hf or ten-hms or tele-hf or readmits or silver-ami or dc promis or KorAHF) adj3 (trial or study)).ab,kf,ti.	118
26	or/22-25	4209

Ovid Embase Classic+Embase <1947 to 2020 August 24>
Search date: 25 August 2020

#	Searches	Results
1	*predictive value/ or *receiver operating characteristic/ or exp *Decision Support system/	21786
2	("signal to noise" or roc curve or reiver operating or predict*).ab,kw,ti.	2224346
3	(decision adj2 (aid? or model* or clinical* or support or system? or tool?)).ab,kw,ti.	80866
4	decision?.ab,kw,ti.	531706
5	*logistic regression analysis/	1018
6	(logistic model* or regression).ab,kw,ti.	1107281
7	5 or 6	1107307
8	4 and 7	33059
9	or/1-3,8	2305864
10	*hospital readmission/	13570
11	((readmission or readmitted or re-admission or re-admitted) and (hospital* or prehospital*)).ab,kw,ti.	39681
12	((readmission or readmitted or re-admission or re-admitted) adj2 (patient? or client)).ab,kw,ti.	9596
13	(rehospitali?ation? or re-hospitali?ation? or rehospitali?ed or re-hospitali?ed).ab,kw,ti.	14392
14	or/10-13	56536
15	exp *cardiovascular system/	630584

16	(cardiac* or cardio* or myocard* or coronary or heart).ab,jw,kw,ti.	3123455
17	(diastolic or systolic or edema or dyspnea or renocardiac or Stenocardia* or angor or angina* or atherioscleros* or atheroscleros* or arteroscleros* or Arterioscleros* or Kounis syndrome or ST elevation or STEMI or valve* or aortic or stenosis or Leopard Syndrome or Noonan Syndrome with Multiple Lentigines or Multiple Lentigines Syndrome or Obstructive Subaortic Conus or Absent Right Atrioventricular Connection or arrhythmia* or sinus or sinoatrial or atria* or auricular or atrioventricular or ventricular or bradycardia or Bradyarrhythmia* or tachycardia* or fibrillation* or flutter* or Right Bundle Branch Block or Brugada or extrasystole* or (commotion adj1 cordis) or Auriculo-Ventricular Dissociation or Auriculo Ventricular Dissociation or Atrioventricular Dissociation or A-V Dissociation or AV Dissociation or syncope or (Andersen adj2 Tawil) or QT Syndrome or (jervell adj2 lange) or Prolonged QT Interval or (romano adj1 ward) or parasystole or Pre-Excitation or Preexcitation or (Lown adj2 Ganong) or Short PR-Normal QRS Complex Syndrome or Short PR Normal QRS Complex Syndrome or Wolff-Parkinson-White or WPW Syndrome or Idioventricular Rhythm or Torsade de Pointes).ab,hw,kw,ti.	2756334
18	or/15-17	4713190
19	(predict* adj3 risk?).ab,kw,ti.	90323
20	retrospective.ab,hw,kw,ti.	1280890
21	(admission or hospitali?ation or discharge).ab,hw,kw,ti.	1117031
22	and/18-21	991
23	and/9,14,18	6851
24	(ISRCTN96643197 or ChiCTR1900026250 or NCT04008914 or NCT03791541 or NCT03300791 or “CTRI/2016/10/007411” or “CTRI/2014/06/004690” or NCT03949439 or NCT03905226 or NCT00344513 or NCT01755052 or NCT02041585).ab,cn,kw,ti.	31
25	((OPERA or REIC or FIgARO or PREDIC or optimize-hf or ten-hms or tele-hf or readmits or silver-ami or dc promis or KorAHF) adj3 (trial or study)).ab,kw,ti.	285
26	or/22-25	8017

Supplemental Text 2. Data items

The following data was collected in accordance with the CHARMS checklist (Critical Appraisal and Data Extraction for Systematic Reviews): citation, source of data, country, study design, setting, participant description, sample characteristics, study dates, outcome definition, follow-up, number and type of predictors, definition and method for measurement of predictors, timing of predictor measurement, handling of predictors in the modelling, number of participants and number of outcomes/events, calibration, discrimination, classification, methods used for testing model performance, final multivariable model results (regression coefficients, intercept, baseline survival, model performance), and model presentation.

Supplemental Table 1. Risk of Bias

Study	Model	Risk of bias					Applicability			
		Participants	Predictors	Outcome	Analysis	Overall Risk of bias	Participants	Predictors	Outcome	Overall Applicability
Barnett et al.	Model validation	-	?	+	-	-	+	+	+	+
	Model update	-	?	+	-	-	+	+	+	+
Sanchez et al.	NR	-	?	?	-	-	+	+	+	+
Deo et al.	30-days CABG Readmission Calculator	-	-	-	-	-	+	+	?	?
Tan et al.	NR	-	-	-	-	-	+	+	-	-
Wang et al.	NR	-	?	?	-	-	+	+	+	+
Rosenblum et al.	The STS PROM score	-	?	-	-	-	+	+	+	+
Dodson et al.	SILVER-AMI 30-day readmission calculator	+	+	+	+	+	+	+	+	+
Lim et al.	NR	+	?	-	-	-	+	+	-	-
Kini et al.	NR	-	-	-	?	-	+	+	+	+
Nguyen et al.	AMI READMITS score	-	-	+	-	-	+	+	+	+
	Full-stay AMI model	-	-	+	-	-	+	+	+	+
	CMS AMI administrative model	-	?	+	-	-	+	+	+	+
Cediel et al.	TARRACO Risk Score	-	-	-	-	-	+	+	-	-

Supplemental Table 1. *Continued*

Study	Model	Risk of bias				Overall	Applicability			Overall
		Participants	Predictors	Outcome	Analysis	Risk of bias	Participants	Predictors	Outcome	Applicability
Brown et al.	STS 30-day Readmission Model	+	?	?	-	-	+	+	?	?
	STS Augmented Clinical Model	-	?	+	-	-	+	+	?	?
Khera et al.	TAVR 30-Day Readmission Risk Model	-	-	?	-	-	+	+	?	?
Tam et al.	NR	-	-	?	-	-	+	+	?	?
Atzema et al.	AFTER Part 2 scoring system	-	-	-	-	-	+	+	-	-
Stuebe et al.	NR	-	+	-	-	-	+	+	+	+
Huynh et al.	NR	-	-	?	-	-	+	+	+	+
Zywot et al.	CABG Risk Scale	-	?	?	-	-	+	+	+	+
Cox et al.	CMS HF medical model	-	+	+	-	-	+	+	+	+
	CMS HF administrative model	-	?	+	-	-	+	+	+	+
Zitser-Gurevich et al.	NR	?	+	+	-	-	+	+	+	+
Ahmad et al.	CMS HF administrative model	-	+	+	-	-	+	+	+	+
Minges et al.	NR	-	+	+	-	-	+	+	+	+
Pack et al.	NR	-	-	-	-	-	+	+	+	+
Benuzillo et al.	CRSS	-	-	+	-	-	+	+	+	+
Kitamura et al.	FIM	-	?	-	-	-	+	+	+	+

Lahewala et al.	CHADS2	-	?	+	-	-	+	+	+	+
	CHA2DS-VASc	-	?	+	-	-	+	+	+	+
Formiga et al.	CMS HF medical model	-	?	-	-	-	+	+	+	+
Leong et al.	30-day HF readmission risk score	-	+	-	-	-	+	+	-	-
Burke et al.	HOSPITAL score	-	-	-	-	-	+	+	+	+
Kilic et al.	NR	-	?	-	-	-	+	+	+	+
Moulder et al.	NR	+	+	-	-	-	+	+	+	+
Chotechuang et al.	GRACE	-	-	-	-	-	+	+	-	-
Yazdan-Ashoori et al.	LACE	?	?	+	-	-	+	+	+	+
	CMS HF administrative model	?	?	+	-	-	+	+	+	+
Oliver-McNeil et al.	ICD Readmission-Risk Score	-	?	-	-	-	+	+	+	+
Sudhakar et al.	CMS HF medical model	-	+	-	-	-	+	+	+	+
Raposeiras-Roubín et al.	GRACE	-	-	-	-	-	+	+	-	-
Betihavas et al.	NR	-	?	-	-	-	+	+	-	-
Lancey et al.	NR	-	?	-	-	-	+	+	+	+
Moretti et al.	EuroHeart PCI score	-	+	-	-	-	+	+	-	-
Hilbert et al.	HF decision tree	-	+	+	-	-	+	+	+	+
	AMI decision tree	-	+	+	-	-	+	+	+	+
Wang et al.	LACE	-	?	-	-	-	+	+	+	+
Rana et al.	HOSPITAL score	-	?	-	-	-	+	+	-	-

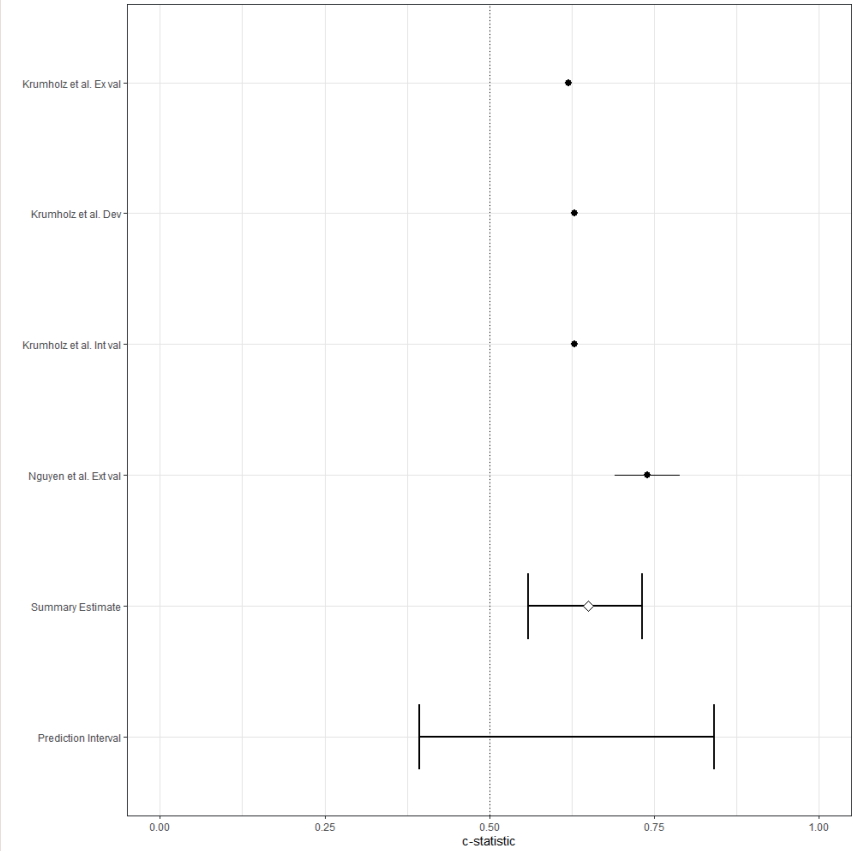
Supplemental Table 1. *Continued*

Study	Model	Risk of bias				Overall	Applicability			Overall
		Participants	Predictors	Outcome	Analysis	Risk of bias	Participants	Predictors	Outcome	Applicability
	Elixhauser index	-	?	-	-	-	+	+	-	-
Hummel et al.	CMS HF medical model	?	+	+	-	-	+	+	+	+
Salah et al.	ELAN-HF score	-	?	-	-	-	+	+	-	-
Wasfy et al.	Pre-PCI model	-	+	?	-	-	+	+	+	+
Engoren et al.	NR	-	?	+	-	-	+	+	+	+
Au et al.	Administrative Claims Model: HF 30-day mortality	-	?	?	-	-	+	+	?	?
	Charlson Comorbidity Score	-	?	?	-	-	+	+	?	?
	CMS HF administrative model	-	?	?	-	-	+	+	?	?
	LACE	-	?	?	-	-	+	+	?	?
Krumholz et al.	CMS AMI medical model	+	-	+	-	-	+	+	+	+
	CMS AMI administrative model	-	-	+	-	-	+	+	+	+
Amarasingham et al.	Tabak mortality score	-	?	?	-	-	+	+	+	+
	CMS HF administrative model	-	?	?	-	-	+	+	+	+
	ADHERE	-	?	?	-	-	+	+	+	+
Keenan et al.	CMS HF administrative model	-	-	+	-	-	+	+	+	+

	CMS HF medical model	+	-	-	-	-	+	+	+	+
Ferraris et al.	READMIT	?	+	+	-	-	+	+	+	+
Delgado et al.	15-day CV readmission risk score	?	+	-	-	-	+	+	-	-
	30-day CV readmission risk score	?	+	-	-	-	+	+	-	-
Espinoza et al.	30-day readmission score after cardiac surgery	+	?	?	-	-	+	+	+	+
Reed et al.	CMS HF administrative model	-	?	?	-	-	+	+	+	+
	PARR-30	-	?	?	-	-	+	+	+	+
	LACE	-	?	?	-	-	+	+	+	+
	Hasan	-	?	?	-	-	+	+	+	+
	AH model	-	?	?	-	-	+	+	+	+
Ibrahim et al.	HOSPITAL score	-	+	-	-	-	+	+	+	+
	LACE	-	+	-	-	-	+	+	+	+
	LACE+ index	-	+	-	-	-	+	+	+	+
Bardhan et al.	NR	-	-	-	-	-	+	+	-	-
Asche et al.	NR	-	?	-	-	-	+	+	?	?
Li et al.	NR	-	?	+	-	-	+	+	+	+
Hammill et al.	CMS HF administrative model	-	-	+	?	-	+	+	+	+
Frizzell et al.	CMS HF administrative model	-	-	+	-	-	+	+	+	+

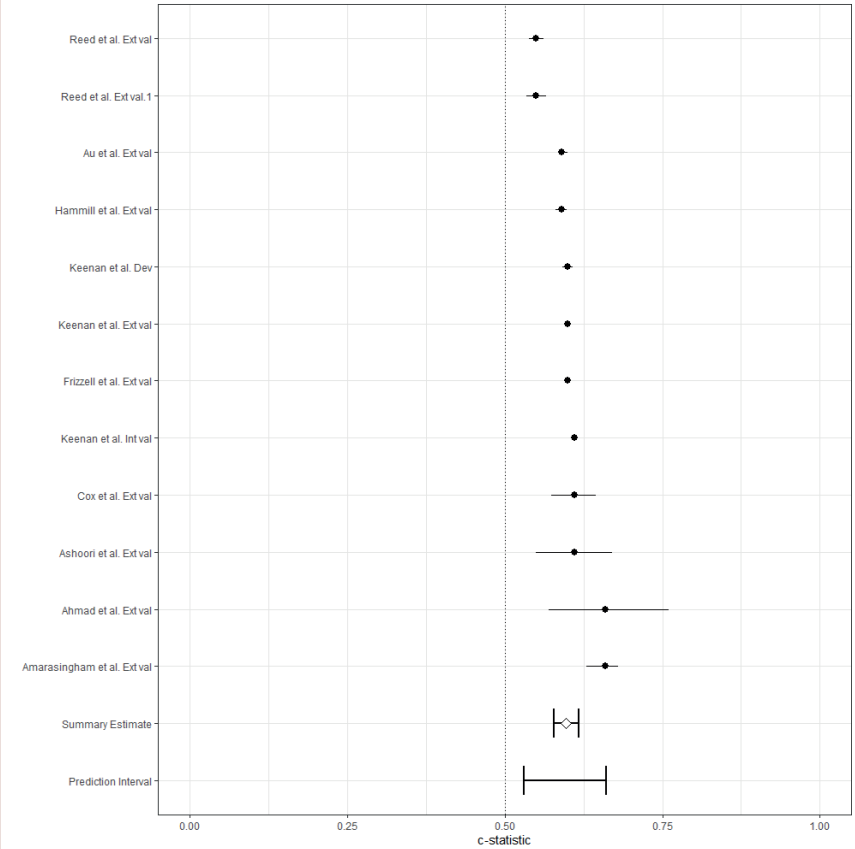
Legend: the overall risk of bias assessment is located in the main paper.
Abbreviations: AH: Adventist hositals, CABG: coronary artery bypass grafting, CMS=centers for Medicare and Medicaid services, CRSS: CABG Readmission Risk Score, Fim: motor and cognitive Functional Independence Measure, HF: heart failure, ICD: implantable cardioverter defibrillator, NR: not reported, PARR-30: Patients at Risk of Re-admission within 30-days, PCI: percutaneous coronary intervention, TAVR: transcatheter aortic valve replacement

Supplemental Figure 1. Meta-analysis of CMS AMI administrative model



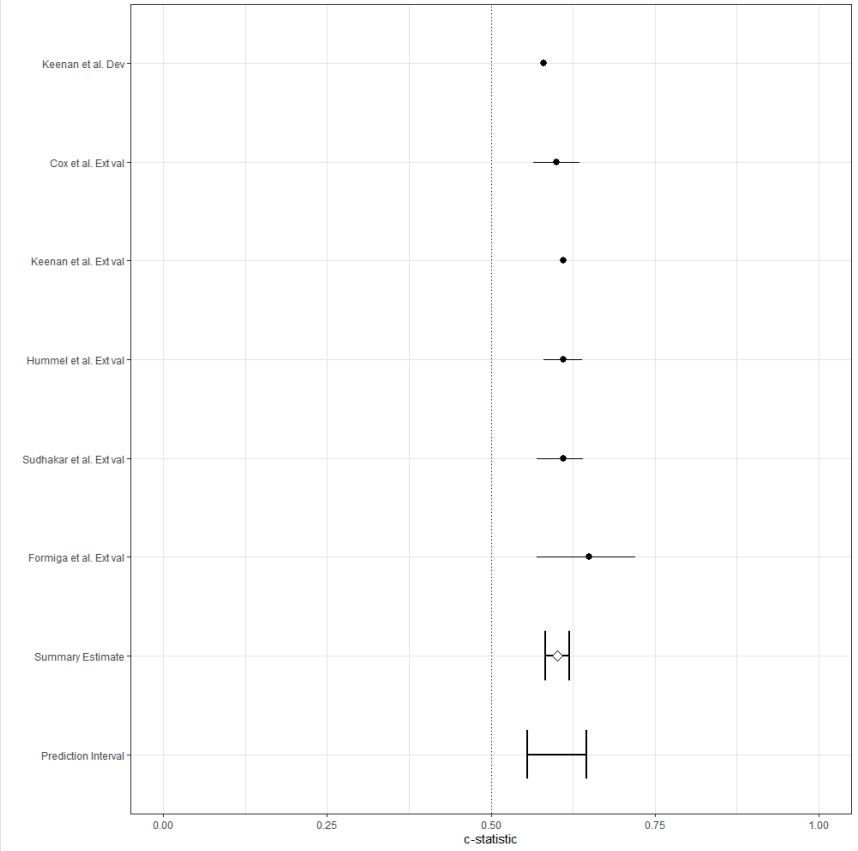
Legend: The CMS acute myocardial infarction (AMI) administrative model was evaluated in four independent cohorts in two studies: 0.65, 95% CI 0.56 to 0.73, 95% prediction interval 0.39 to 0.84. Standard errors were derived from the reported c-statistics, sample size and observed events. The readmission rate was missing for the internal validation cohort in the Krumholz et al. study, and this data was needed to derive the observed events. The development and validation cohort in the Krumholz et al. study were similar samples and we used the average readmission rate from these two cohorts to impute the missing readmission rate for the internal validation.
Abbreviations: Ext val: external validation, Int val: internval validation, Dev: Development

Supplemental Figure 2. Meta-analysis of CMS HF administrative model



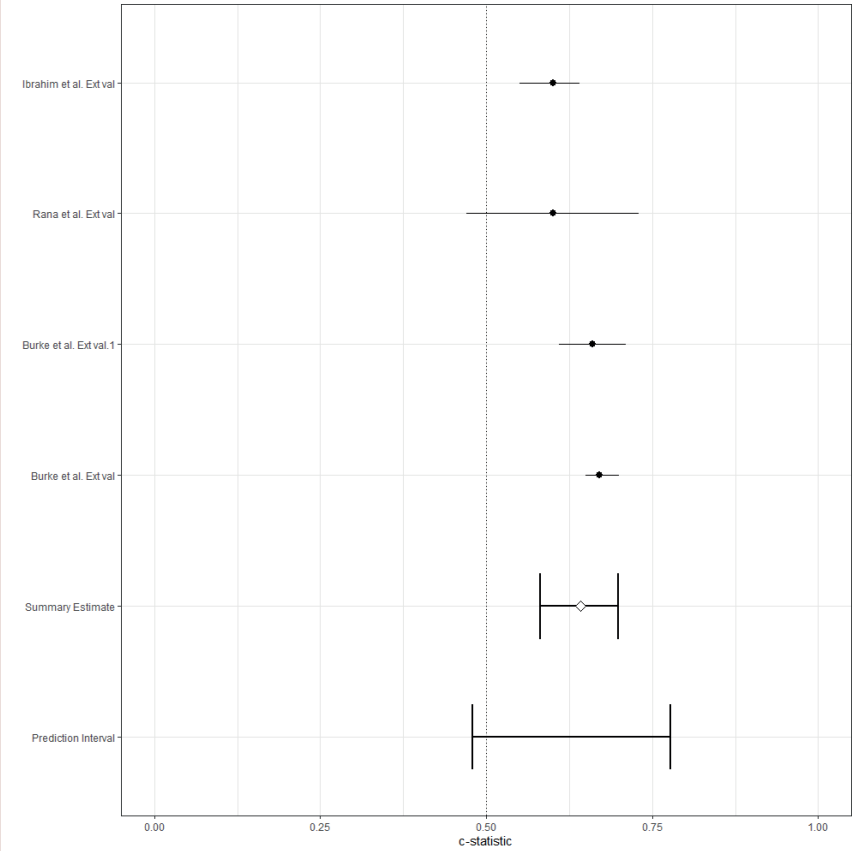
Legend: The CMS heart failure (HF) administrative model was evaluated in twelve independent cohorts in nine studies: 0.60, 95% CI 0.58 to 0.62, 95% prediction interval 0.53 to 0.66. Standard errors were derived from the reported c-statistics, sample size and observed events. The readmission rate was missing for the internal validation cohort in the Keenan et al. study, and this data was needed to derive the observed events. The development and validation cohort in the Keenan et al. study were similar samples and we used the average readmission rate from these two cohorts to impute the missing readmission rate for the internal validation.
Abbreviations: Ext val: external validation, Int val: internval validation, Dev: Development

Supplemental Figure 3. Meta-analysis of CMS medical model



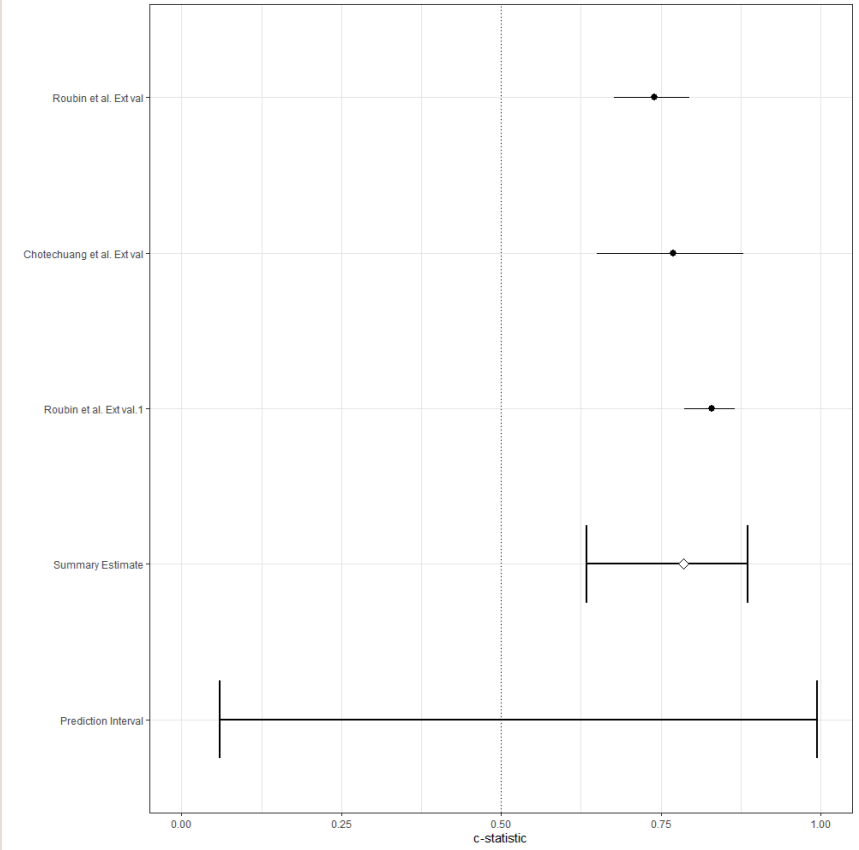
Legend: The CMS medical model was evaluated in six independent cohorts in five studies: 0.60, 95% CI 0.58 to 0.62, 95% prediction interval 0.56 to 0.65. Standard errors were derived from the reported c-statistics, sample size and observed events.
Abbreviations: Ext val: external validation, Int val: internval validation, Dev: Development

Supplemental Figure 4. Meta-analysis of HOSPITAL score



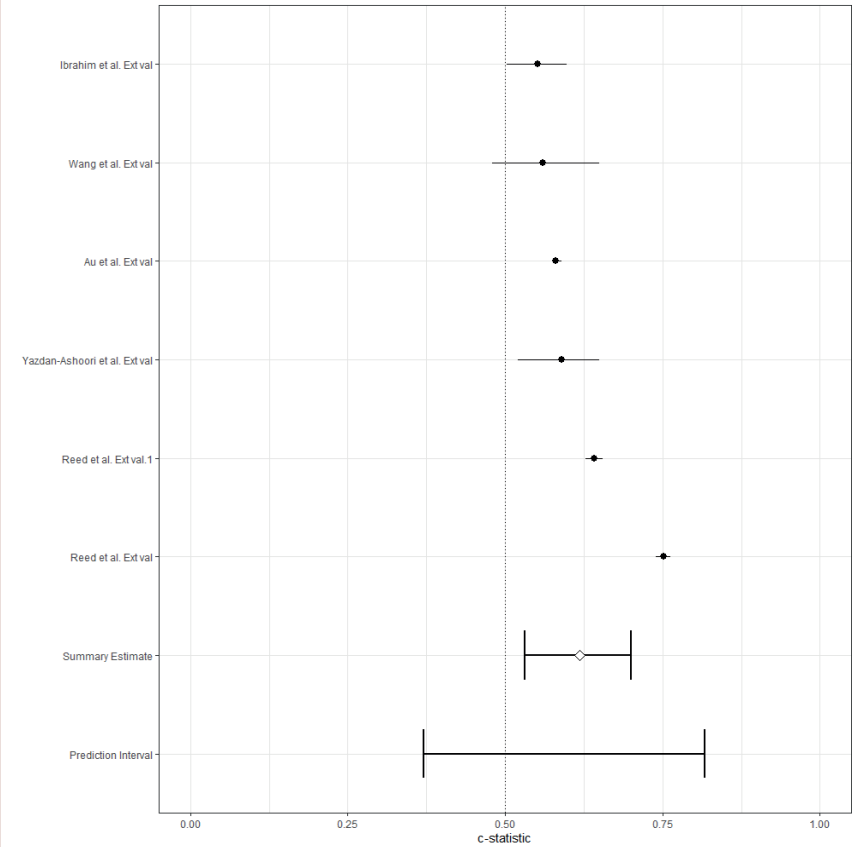
Legend: The HOSPITAL score was evaluated in four independent cohorts in three studies: 0.64, 95% CI 0.58 to 0.70, 95% prediction interval 0.48 to 0.78. Standard errors were derived from the reported c-statistics, sample size and observed events.
Abbreviations: Ext val: external validation, Int val: internval validation, Dev: Development

Supplemental Figure 5. Meta-analysis of GRACE



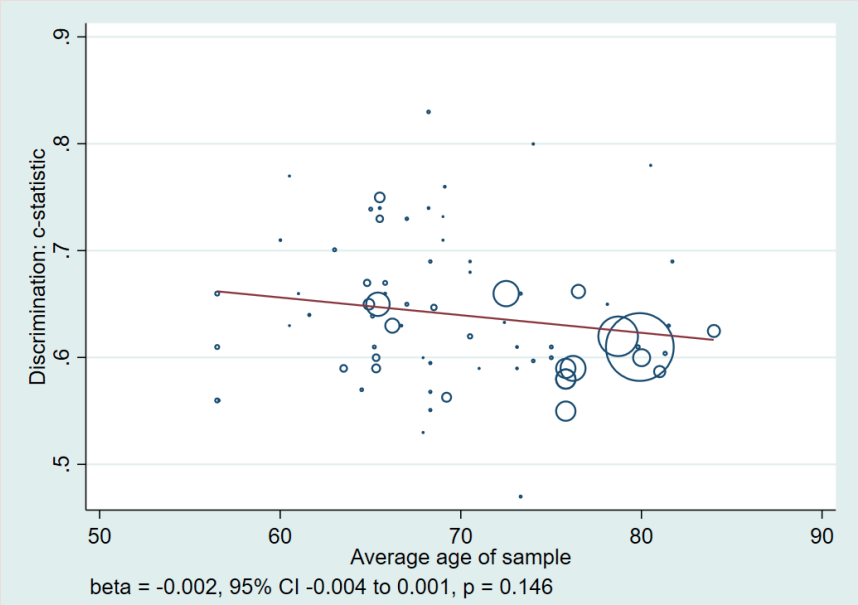
Legend: GRACE was evaluated in four independent cohorts in three studies: 0.79, 95% CI 0.63 to 0.86, 95% prediction interval 0.06 to 1.00. Standard errors were derived from the reported c-statistics, sample size and observed events.
Abbreviations: Ext val: external validation, Int val: internval validation, Dev: Development

Supplemental Figure 6. Meta-analysis of LACE



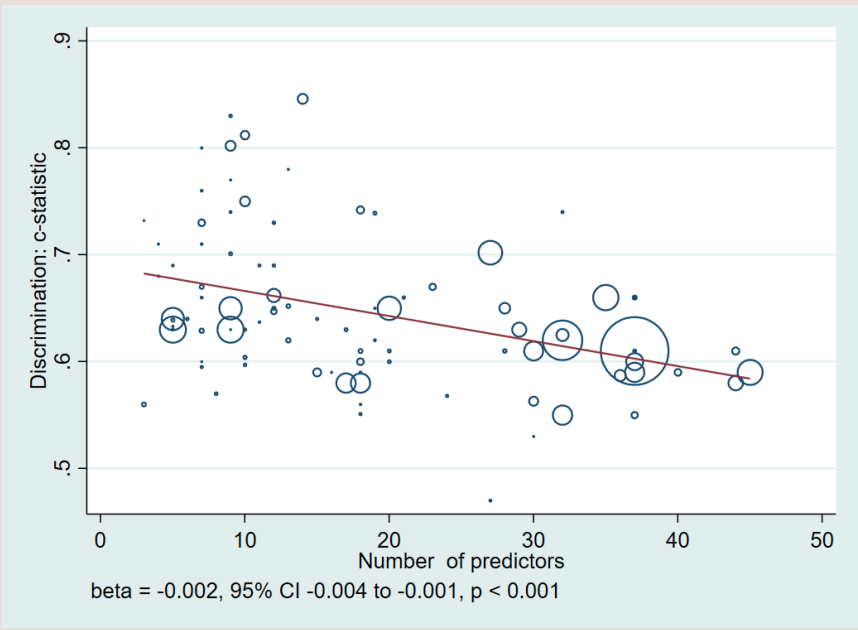
Legend: LACE was evaluated in six independent cohorts in five studies: 0.62, 95% CI 0.53 to 0.70, 95% prediction interval 0.37 to 0.82. Standard errors were derived from the reported c-statistics, sample size and observed events.
Abbreviations: Ext val: external validation, Int val: internval validation, Dev: Development

Supplemental Figure 7. Age as moderator



Legend: A meta-regression with average sample age as covariate was performed. The outcome was the discrimination (c-statistic). There is no association between the sample age and the discrimination.

Supplemental Figure 8. Number of predictors as moderator



Legend: A meta-regression with the number of predictors as covariate was performed. The outcome was the discrimination (c-statistic). The discrimination increases with the number of predictors decreases. This association is significant.

Supplemental Table 2. Subgroup analyses

Moderators	N	C-statistic	95% CI	Test for subgroup difference
Population				p = 0.835
- Surgical	17	0.627	0.605 – 0.649	
- TAVR	2	0.645	0.560 – 0.729	
- Heart failure	45	0.641	0.623 – 0.658	
- Acute myocardial infarction	16	0.671	0.644 – 0.697	
- Arrhythmias	5	0.640	0.630 – 0.649	
- Valve disease	1	0.650	0.641 – 0.659	
- ICD implantation	1	0.710	0.605 – 0.815	
- Reinfarction	1	0.740	0.681 – 0.799	
- Acute coronary syndrome	1	0.590	0.475 – 0.705	
- Mixed	3	0.660	0.656 – 0.664	
Data source				p = 0.014
- Registry	17	0.613	0.602 – 0.624	
- Administrative database	17	0.664	0.635 – 0.693	
- Hospital database	18	0.612	0.593 – 0.632	
- Prospective cohort	16	0.640	0.613 – 0.667	
- Retrospective cohort	23	0.682	0.653 – 0.710	
- Secondary analysis	2	0.695	0.497 – 0.894	
Endpoint				p = 0.589
- 15 days	1	0.633	0.539 – 0.727	
- 28 days	1	0.800	0.720 – 0.880	
- 30 days	78	0.642	0.631 – 0.654	
- 90 days	8	0.645	0.632 – 0.657	
- 100 days	1	0.652	0.626 – 0.678	
- 180 days	4	0.656	0.591 – 0.721	
Outcome definition				p = 0.144
- All cause	65	0.644	0.633 – 0.656	
- Cardiac related	18	0.676	0.628 – 0.723	

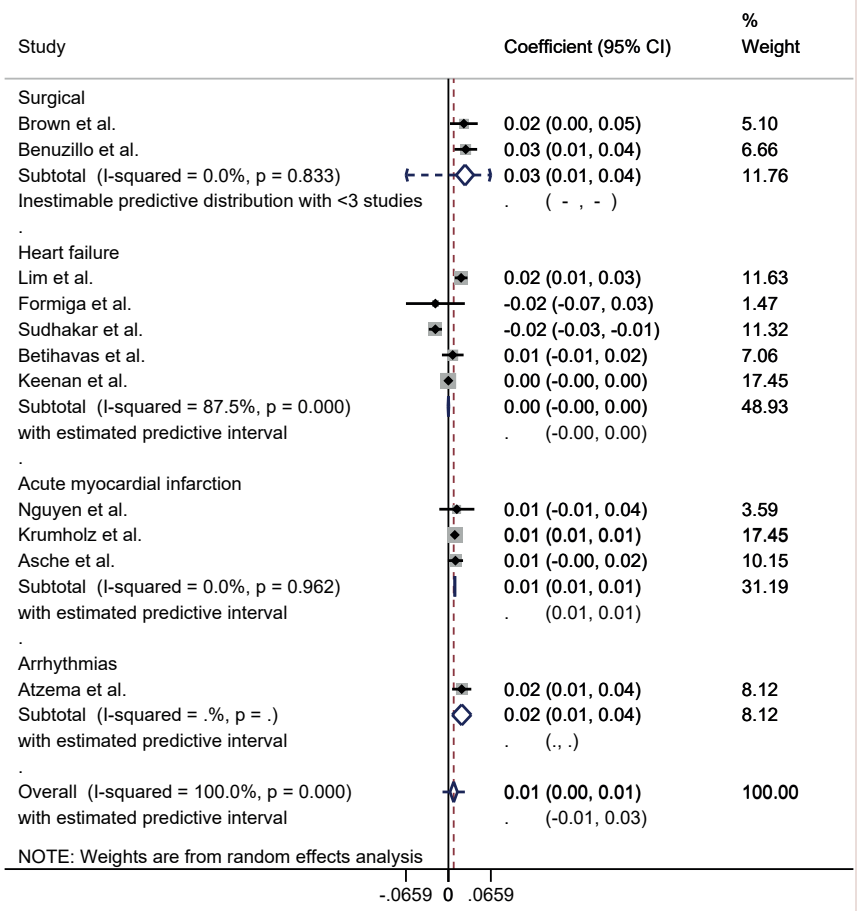
Legend: Subgroup analyses were performed. The outcome was the discrimination (c-statistic). The discrimination is moderator by the data source that was used in the study, but not by the population, outcome definition and endpoint.

Supplemental Table 3. Summary of meta-analyses predictors

Predictor	Coefficient, 95% CI	Prediction interval
Age (years)	0.01, 0.00 - 0.01	-0.01 - 0.03
Female	0.10, 0.03 - 0.17	-0.17 - 0.38
Arrhythmias	0.20, 0.12 - 0.28	-0.04 - 0.43
Chronic lung disease	0.23, 0.05 - 0.40	-0.35 - 0.80
Chronic obstructive pumonary disease	0.18, 0.15 - 0.22	0.08 - 0.29
Artherosclerose	0.01, -0.13 - 0.15	-0.38 - 0.41
Diabetes mellitus	0.16, 0.11 - 0.22	-0.04 - 0.37
Current heart failure	0.27, 0.20 - 0.34	0.04 - 0.50
Hypertension	0.05, -0.02 - 0.12	-0.16 - 0.25
Valve disease	0.10, 0.06 - 0.13	0.01 - 0.19
Prior percutaneous coronary intervention	0.01, -0.07 - 0.09	-0.27 - 0.29
History of heart failure	0.38, 0.25 - 0.51	0.01 - 0.75
Cerebrovascular disease	0.08, 0.03 - 0.13	-0.05 - 0.22
Anemia	0.10, 0.06 - 0.14	-0.01 - 0.22
Stroke	0.07, 0.01 - 0.13	-0.11 - 0.25
Peripheral vascular disease	0.15, 0.09 - 0.21	-0.03 - 0.34
Dementia	-0.04, -0.10 - 0.02	-0.21 - 0.12
Prior Coronary Artery Bypass Graft	0.04, -0.06 - 0.14	-0.30 - 0.39

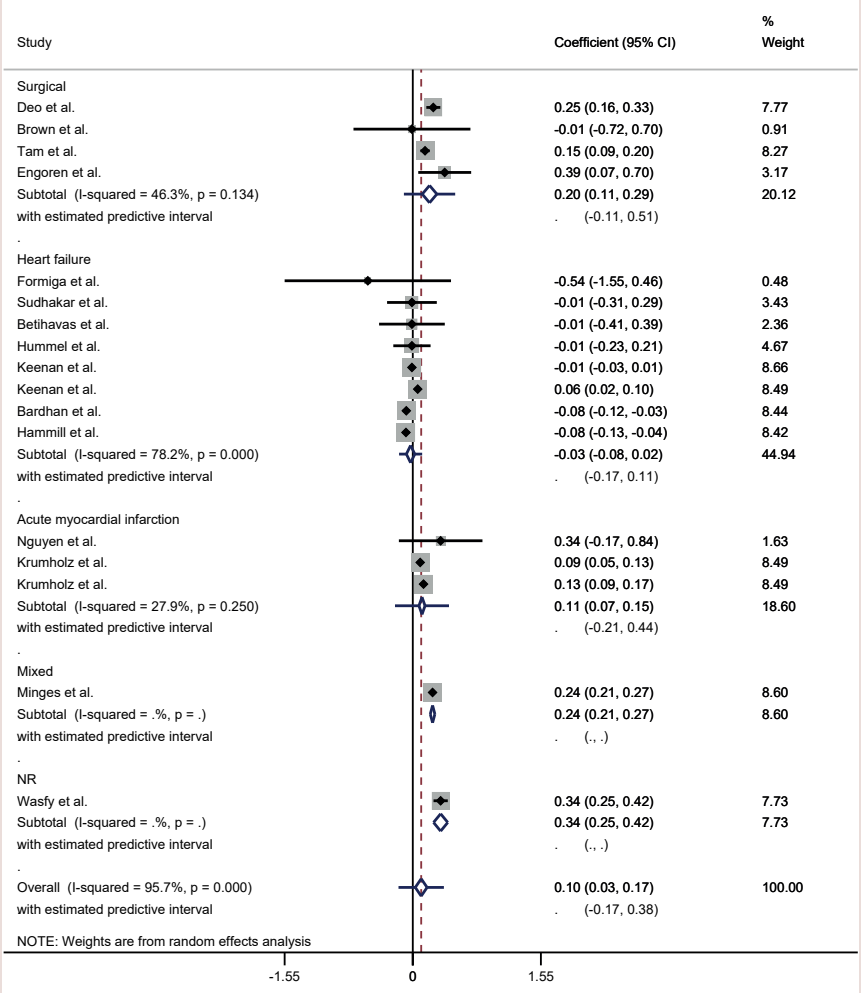
Legend: A meta-analyses was performed with the outcome 30 day unplanned hospital readmissions. The forest plots are detailed below. Please note that there are some small differences with the data reported in Figure 4 in the main manuscript. This is because of a difference in rounding the decimal points by the software.

Supplemental Figure 9. Age as predictor



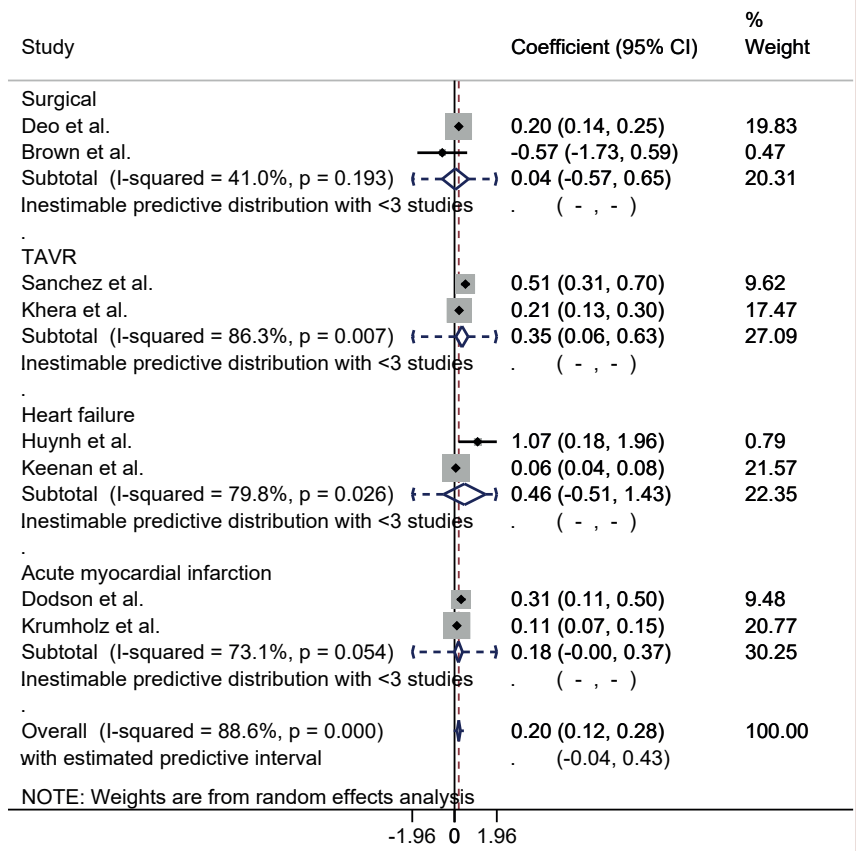
Legend: Two studies were not included in the analysis. One study had a missing standard error and one study reported transformed values. The values of their coefficients were: -0.001, and log(0,502).

Supplemental Figure 10. Female as predictor



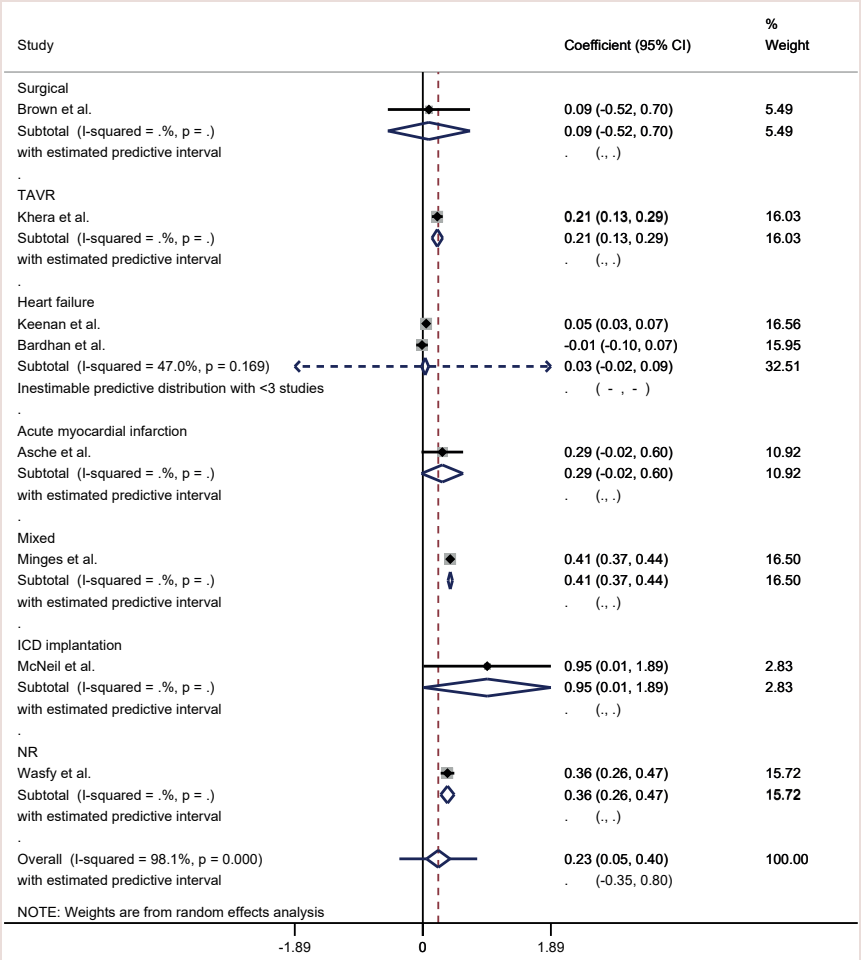
Legend: Two studies were not included in the analysis because the standard errors were missing. The values of their coefficients were: -0.28 and 0.206.

Supplemental Figure 11. Arrhythmias as predictor



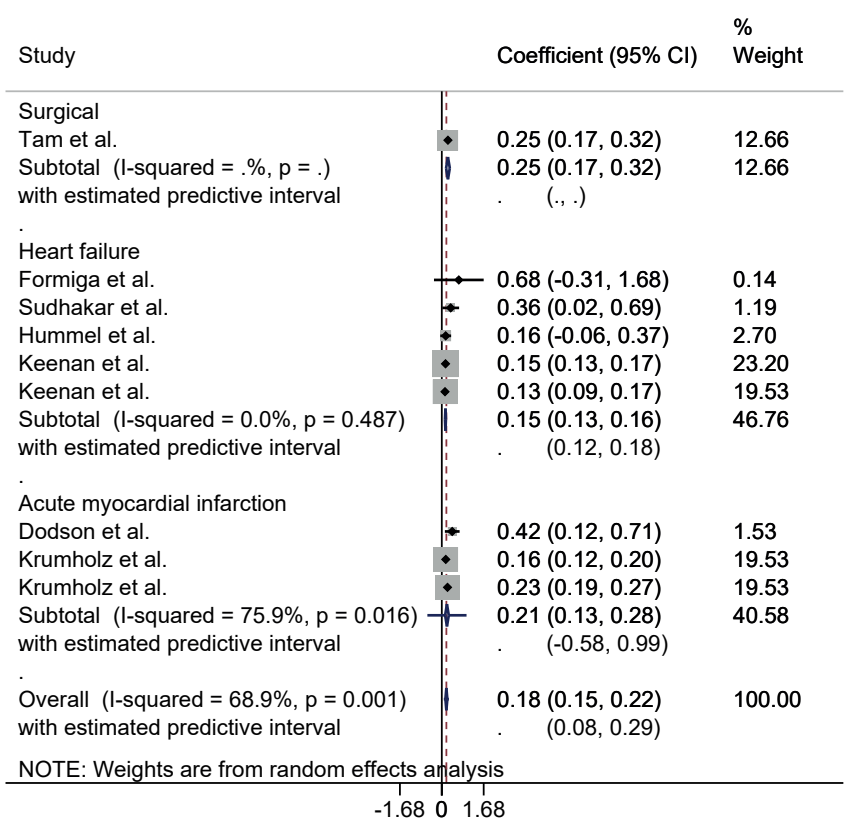
Legend: There was no missing data in the analysis.

Supplemental Figure 12. Chronic lung disease as predictor



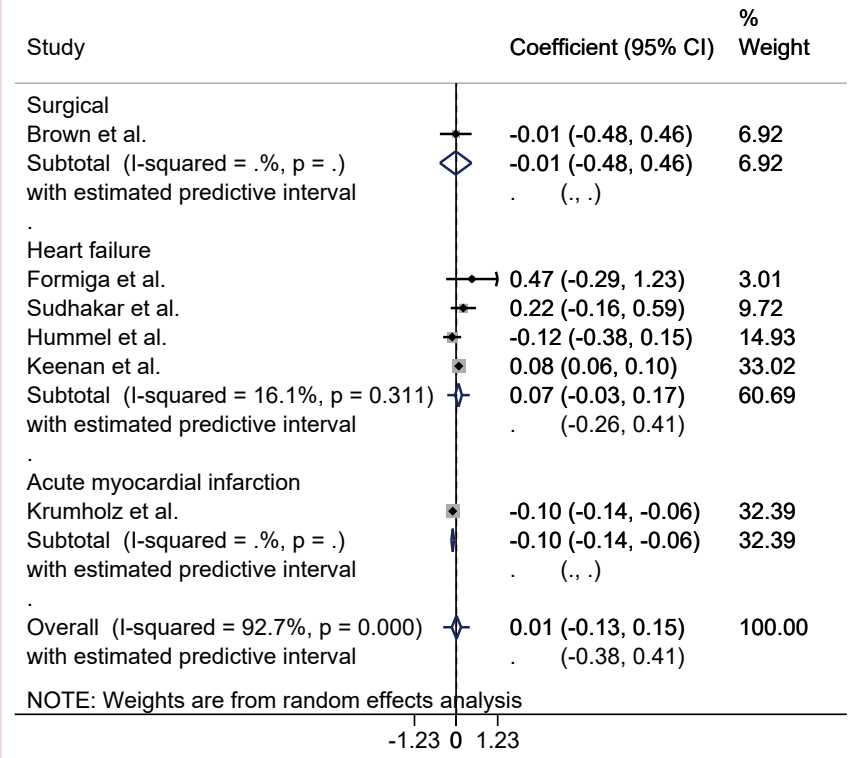
Legend: There was no missing data in the analysis.

Supplemental Figure 13. Chronic Obstructive Pulmonary Disease as predictor



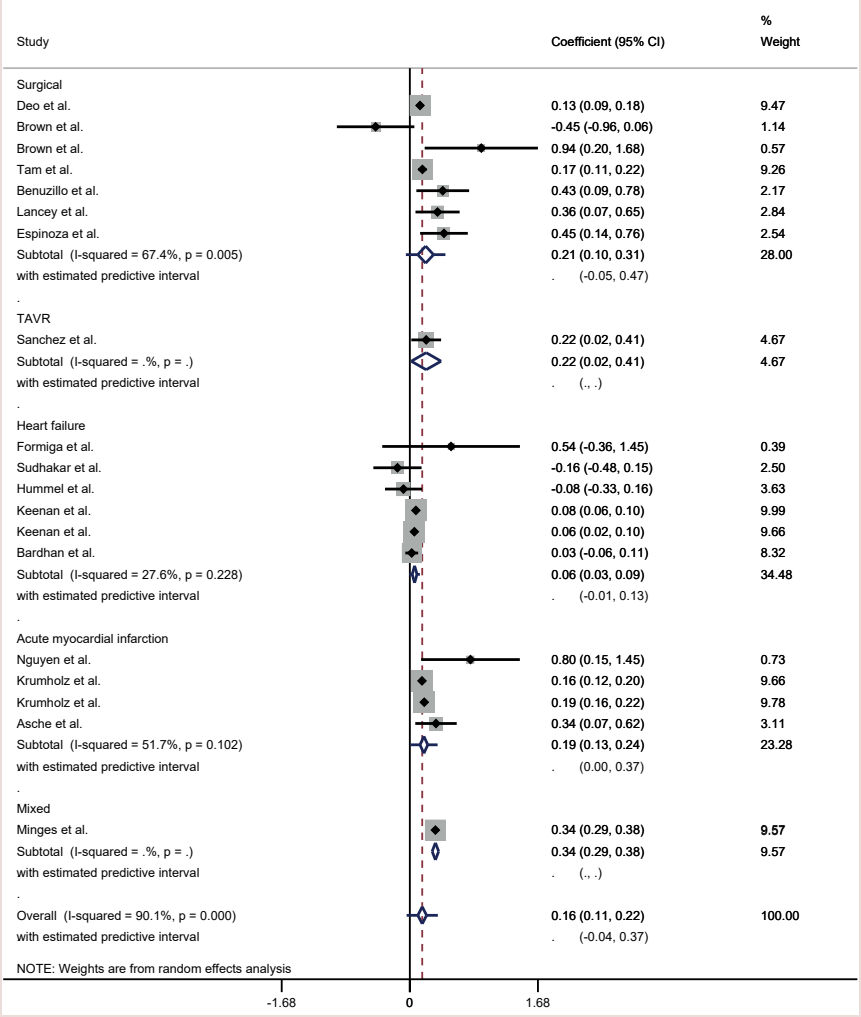
Legend: Two studies were not included in the analysis because the standard errors were missing. The values of their coefficients were: 0.053 and 0.677.

Supplemental Figure 14. Artherosclerose as predictor



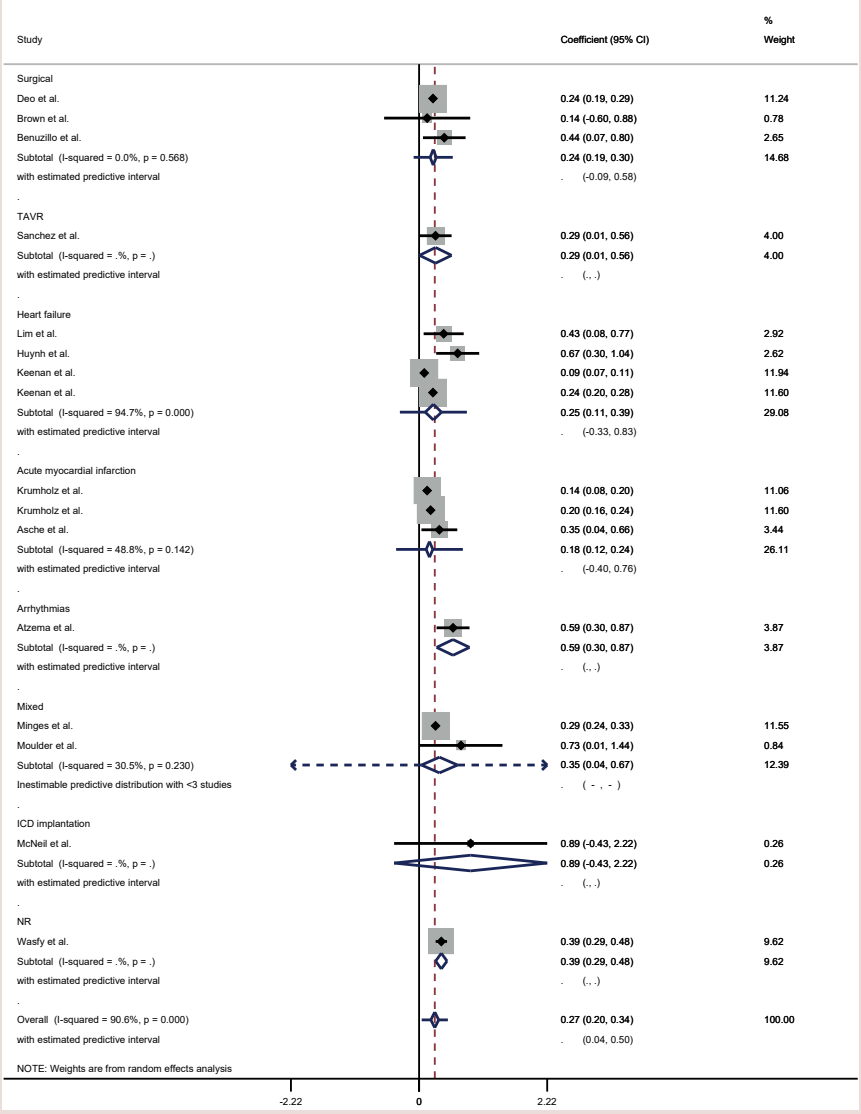
Legend: One study was not included in the analysis because the standard error were missing. The values of their coefficient was: 0.11.

Supplemental Figure 15. Diabetes Mellitus as predictor



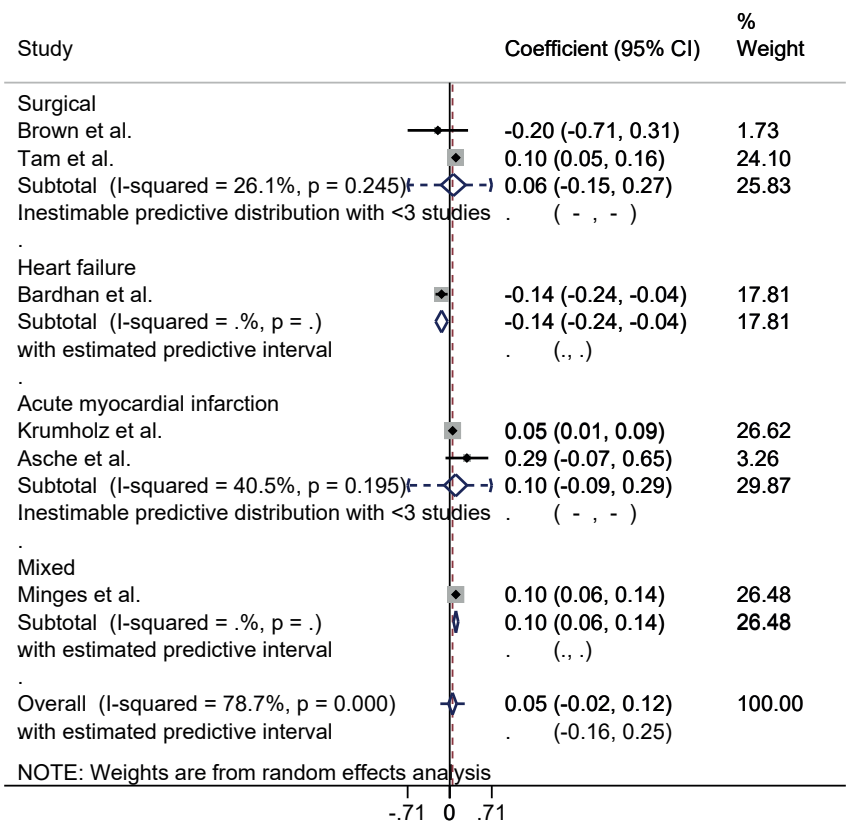
Legend: Two studies were not included in the analysis because the standard errors were missing. The values of their coefficients were: -0.068 and 0.639.

Supplemental Figure 16. Current heart failure as predictor



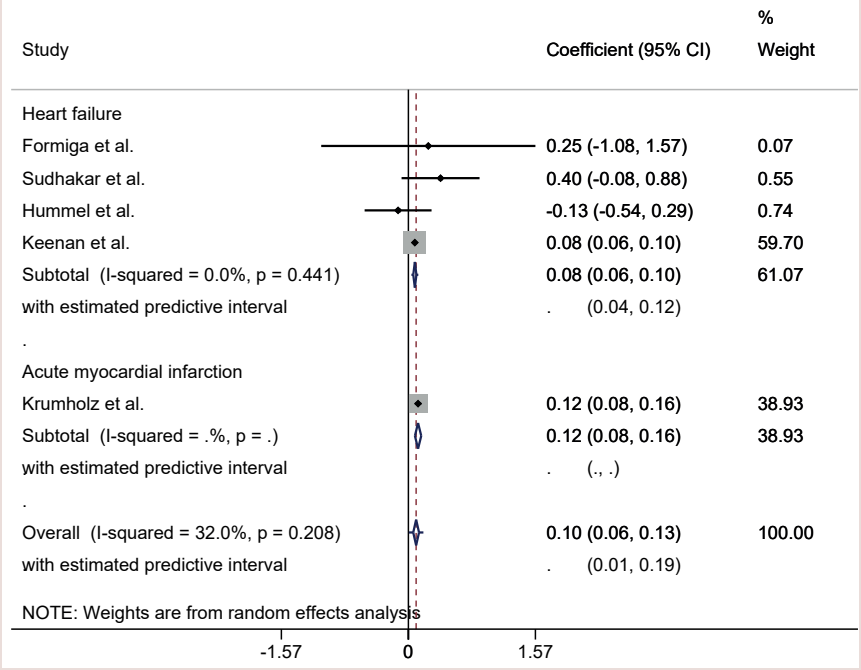
Legend: There was no missing data.

Supplemental Figure 17. Hypertension as predictor



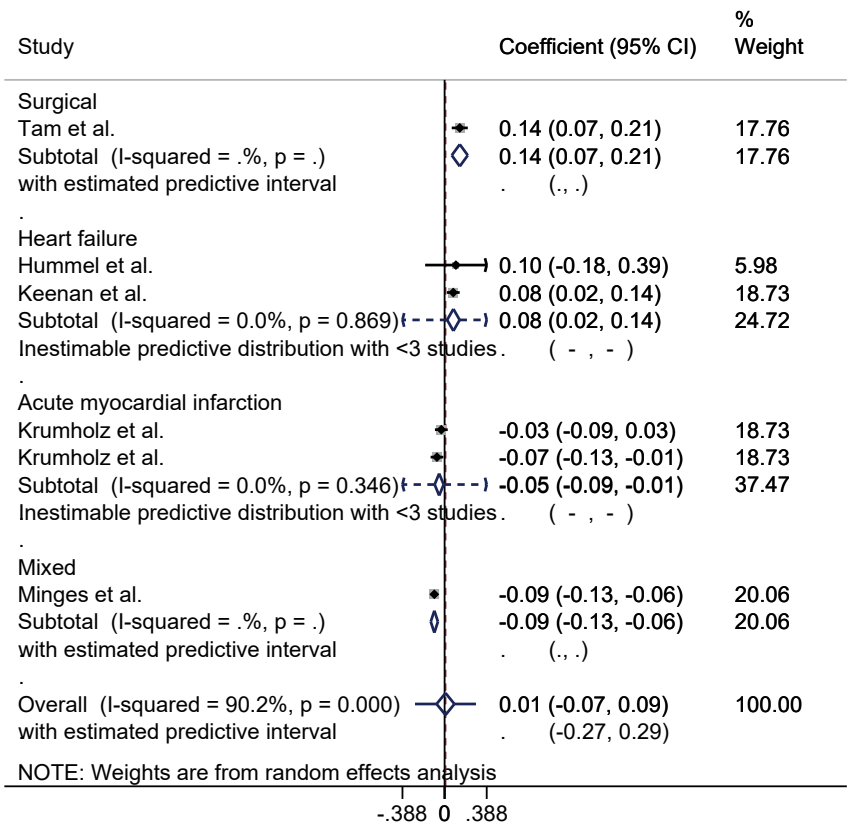
Legend: One study was not included in the analysis because the standard error were missing. The values of their coefficient was: -0.28.

Supplemental Figure 18. Valve disease as predictor



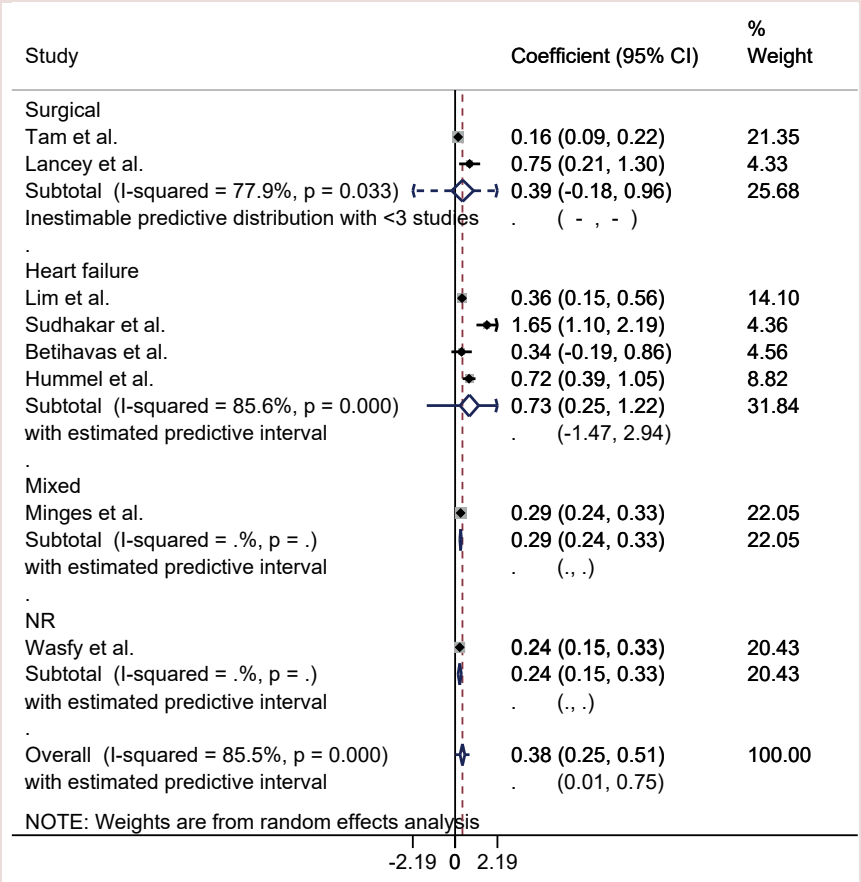
Legend: There was nog missing data.

Supplemental Figure 19. Prior percutaneous coronary intervention as predictor



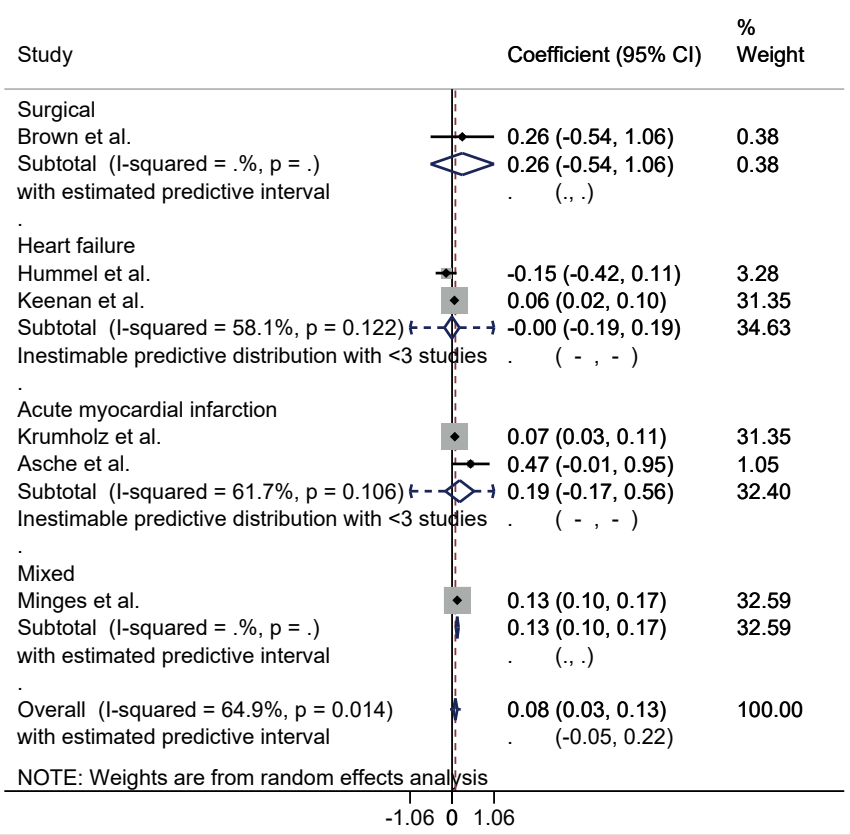
Legend: There was no missing data.

Supplemental Figure 20. History of heart failure as predictor



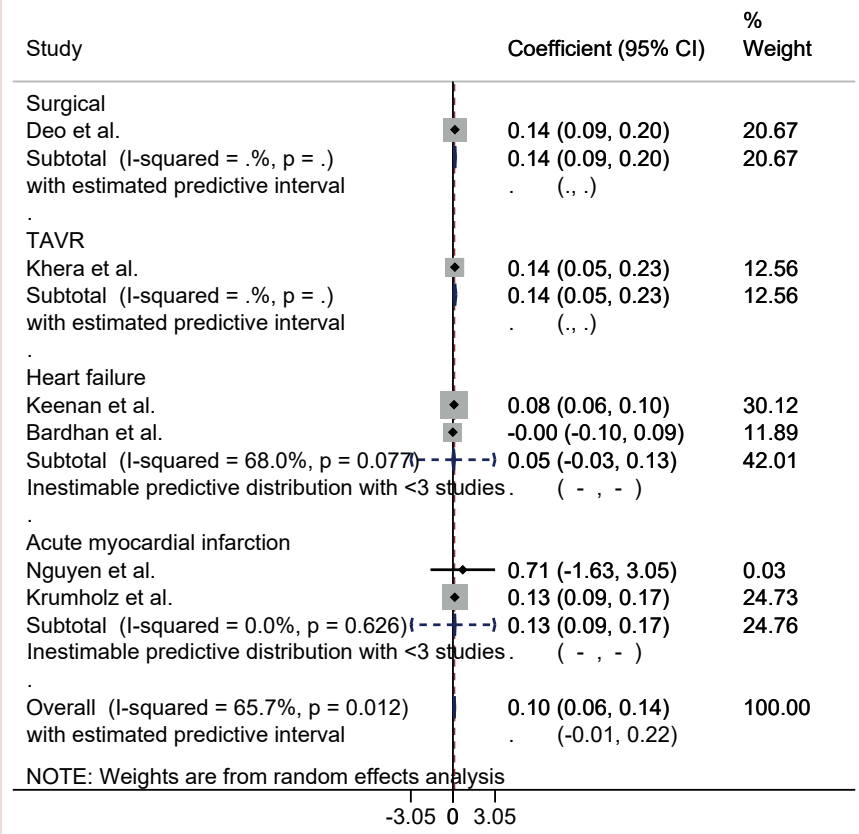
Legend: There was no missing data.

Supplemental Figure 21. Cerebrovascular disease as predictor



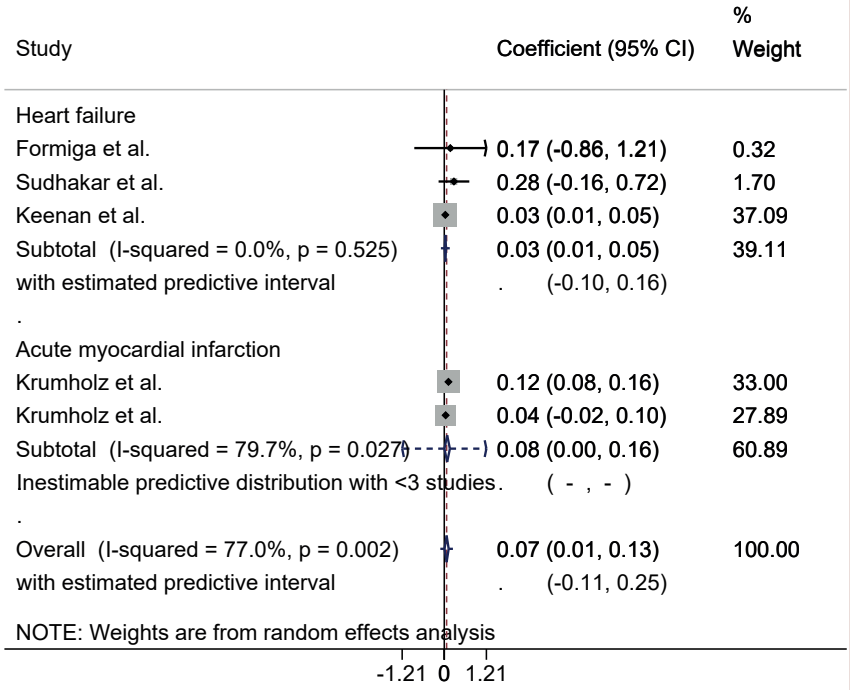
Legend: There was no missing data.

Supplemental Figure 22. Anemia as predictor



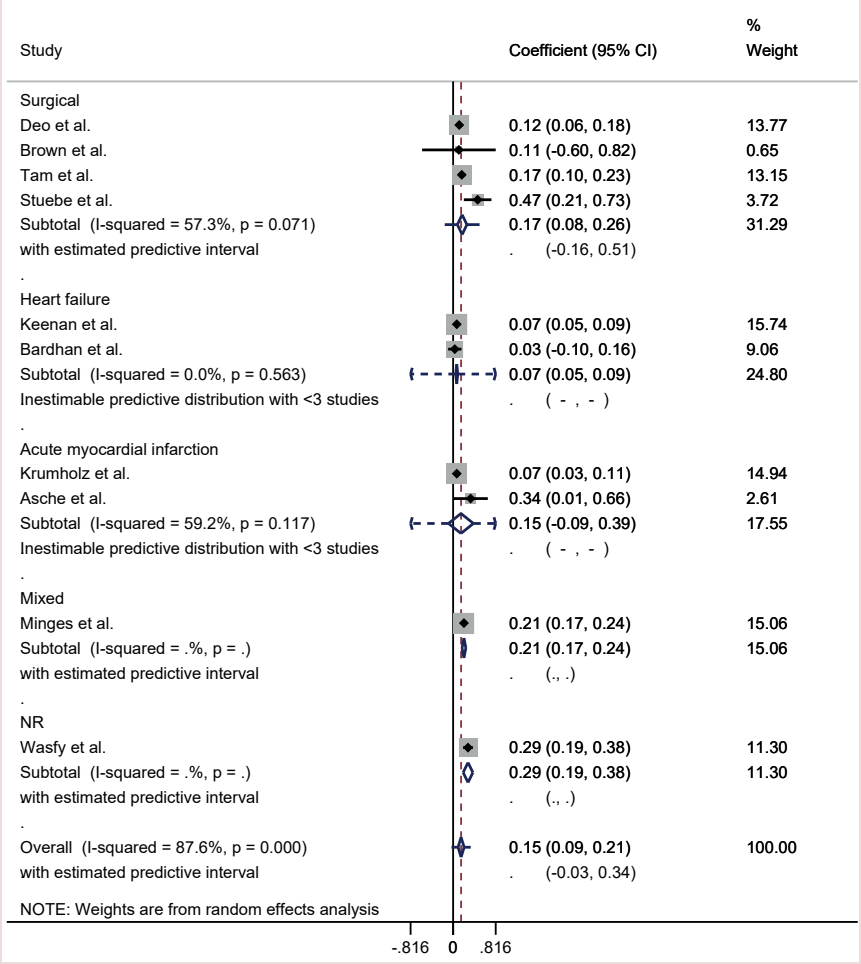
Legend: There was no missing data.

Supplemental Figure 23. Stroke as predictor



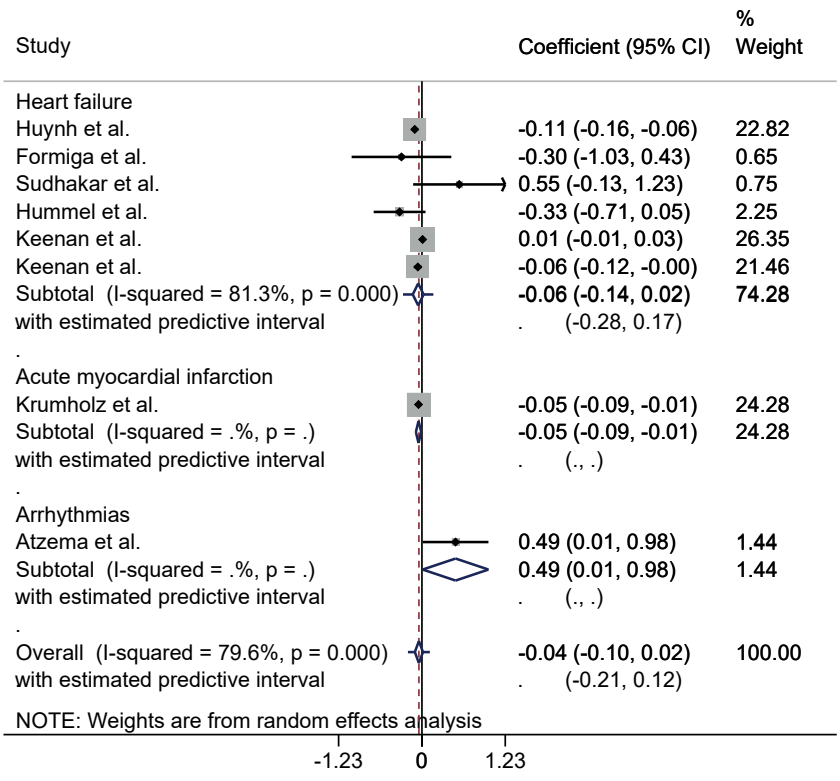
Legend: There was no missing data.

Supplemental Figure 24. Peripheral vascular disease as predictor



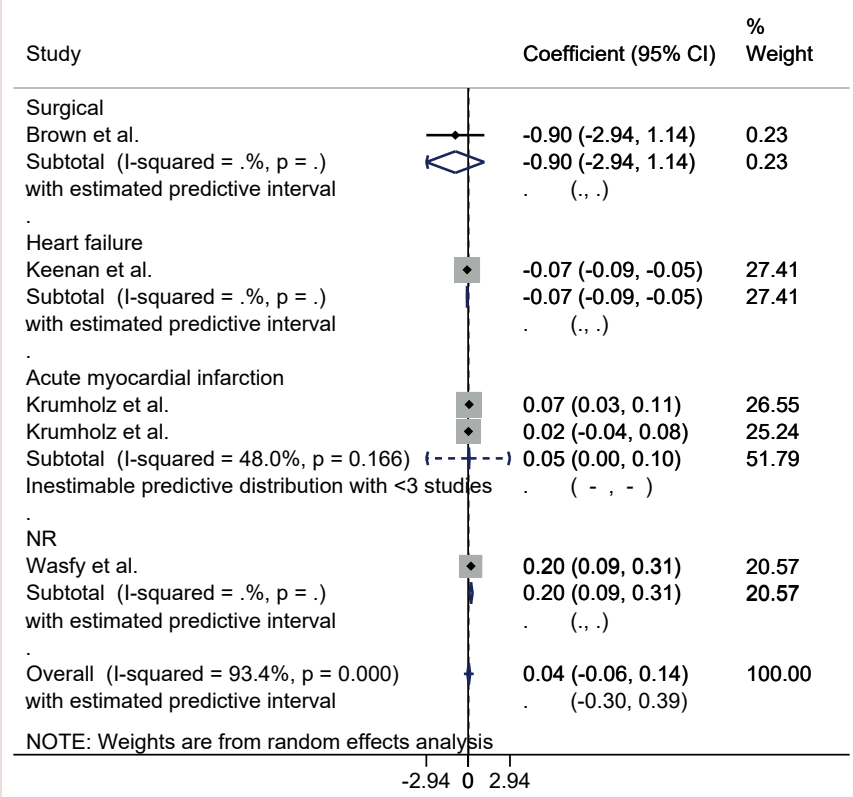
Legend: There was no missing data.

Supplemental Figure 25. Dementia as predictor



Legend: There was no missing data.

Supplemental Figure 26. Prior Coronary Artery Bypass Graft as predictor



Legend: There was no missing data.

Chapter

4

The performance of the Dutch Safety Management System frailty tool to predict the risk of readmission or mortality in older hospitalised cardiac patients

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Abstract

Background: Early identification of older cardiac patients at high risk of readmission or mortality facilitates targeted deployment of preventive interventions. In the Netherlands, the frailty tool of the Dutch Safety Management System (DSMS-tool) consists of (the risk of) delirium, falling, functional impairment, and malnutrition and is currently used in all older hospitalised patients. However, its predictive performance in older cardiac patients is unknown.

Aim: To estimate the performance of the DSMS-tool alone and combined with other predictors in predicting hospital readmission or mortality within six months in acutely hospitalised older cardiac patients.

Methods: An individual patient data meta-analysis was performed on 529 acutely hospitalised cardiac patients ≥ 70 years from four prospective cohorts. Missing values for predictor and outcome variables were multiply imputed. We explored discrimination and calibration of: (1) DSMS-tool alone; (2) the four components of the DSMS-tool and adding easily obtainable clinical predictors; (3) a model based on step 2 and adding more difficult to obtain predictors. Predictors in model 2 and 3 were selected using backward selection using a threshold of p=0.157. We used shrunk c-statistics, calibration plots, regression slopes and Hosmer-Lemeshow p-values (P_{HL}) to describe predictive performance in terms of discrimination and calibration.

Results: The population mean age was 82 years, 52% were males and 51% were admitted for heart failure. DSMS-tool was positive in 45% for delirium, 41% for falling, 37% for functional impairments and 29% for malnutrition. The incidence of hospital readmission or mortality gradually increased from 37% to 60% with increasing DSMS scores. Overall, the DSMS-tool discriminated limited (c-statistic 0.61, 95% 0.56-0.66). The final model included the DSMS-tool, diagnosis at admission and Charlson Comorbidity Index and had a c-statistic of 0.69 (95% 0.63-0.73; P_{HL} was 0.658).

Discussion: The DSMS-tool alone has limited capacity to accurately estimate the risk of readmission or mortality in hospitalised older cardiac patients. Adding disease-specific risk factor information to the DSMS-tool resulted in a moderately performing model. To optimise the early identification of older hospitalised cardiac patients at high risk, the combination of geriatric and disease-specific predictors should be further explored.

Background

Hospitalisation of older cardiac patients is associated with increased risk of functional loss, readmission or mortality.[1-3] Geriatric conditions such as malnutrition, tendency to fall and functional impairment are common in older cardiac patients and contribute to these adverse health outcomes.[2,4,5]

Measurement of risk in older cardiac patients facilitates early initiation of targeted interventions to delay or prevent complications such as (further) functional loss, readmission or mortality in those patients susceptible to such interventions.[6] Risk stratification may help to determine in which patients guideline-recommended treatments may be deployed and for which patients harms outweigh benefits.[4,7]

The Dutch Safety Management System (VeiligheidsManagementSysteem, DSMS) of the Ministry of Health, Welfare and Sport, developed the DSMS-screening tool to detect hospitalised older patients at high risk of functional loss.[8] The DSMS-tool has been in use since 2012 and all Dutch hospitals are required to screen hospitalised older patients on (their risk of) four geriatric domains; delirium, falling, functional impairment and malnutrition. Functional loss is associated with a high risk of readmission and mortality.[9-12] As the DSMS detects frail older patients at high risk of functional loss, the tool may also be capable of identifying patients at high risk of these adverse outcomes and if so, would enable timely targeted deployment of preventive interventions. Therefore, the aim of this study is to estimate the performance of the DSMS-tool alone and combined with other predictors in predicting all-cause unplanned hospital readmission or mortality within six months in acutely hospitalised older cardiac patients.

Methods

An individual patient data meta-analysis was performed on 529 acutely hospitalised cardiac patients ≥ 70 years from four prospective cohort studies: 1) The Hospital-ADL study[11] examined the development and course of geriatric conditions during and after hospitalisation; 2) the Surprise Question Cohort[13] examined to what extent a negative answer of healthcare professionals to the question "would I be surprised if this patient died in the next year?", corresponded to mortality within the next year; 3) the Transitional Care Bridge study,[14] a multi-centre randomised trial (RCT) on nurse-coordinated transitional care. Only patients of the control group were included in this study because the intervention was found to have a statistically significant effect on mortality; 4) the Cardiac Care Bridge,[15] a multi-centre RCT. All patients were included in the current study

because the interventions proved to be ineffective.

Patients were eligible for the current study if they 1) had been admitted with a cardiac disease, 2) had been acutely hospitalised for ≥ 48 hours, and 3) were aged ≥ 70 years.

The DSMS-screening tool

Table 1 shows the content of the DSMS-tool.[8] The tool consists of single yes/no questions that assess the four geriatric conditions to identify patients at high risk of functional loss. The answers to the questions can also be added up to form the total score. Based on the number of geriatric conditions, the DSMS-score therefore ranges between 0-4.

Table 1. Screening tool for vulnerable elderly of the Dutch Safety Management System

Domain	Instrument	Questions	Cut-off	Score
Delirium risk	Single questions	Assessing whether: 1) the patient has memory problems; 2) the patient needed help with self-care in the last 24 hours; 3) the patient has previously had a delirium	≥ 1 point	1
Fall risk	Single question	Have you fallen in the last six months?	yes	1
Functional impairment	KATZ-6[16]	Assessing whether the patient currently needs help with 1) bathing, 2) dressing, 3) toileting, 4) transferring from bed to a chair, 5) eating, and 6) whether the patient uses incontinence material	≥ 2 points	1
Malnutrition	SNAQ[17]	Assessing whether the patient: 1) lost weight unintentionally in the last month (>3kg) or last six months (>6kg) and/or 2) has poor appetite in the last month and 3) used supplemental drinks or tube feeding in the last month.	Question 1 = yes and/ or question 2 + 3 = yes	1
Total score				0-4

KATZ-6[16]: Modified KATZ-6 index, kg: kilogram, *SNAQ*[17]: Short Nutritional Assessment Questionnaire.

Outcome

The primary outcome was the performance of the DSMS-tool in predicting six-month all-cause unplanned readmission or mortality. Readmission data were collected from medical files in the participating hospitals and supplemented with patients' and family members' self-reported readmissions in other hospitals. Mortality was registered within the original cohorts and originates from medical files, the Dutch National Personal Records Database,[18] or information from family members at follow-up.

Statistical analyses

Missing data

Additional file 1 shows the frequency of missing data in the four cohorts. Missing values for predictor and outcome variables were imputed 20 times using the MICE package in R-Studio (version 3.6.1), involving 19 variables, including 3 indicator variables to identify the 4 cohorts.[19] The only continuous variable with missing values, length of stay (days), was log-transformed before imputation. We used predictive mean matching throughout. The complete datasets (m=20) were analysed separately and the results pooled using the pooled sampling variance method.[20]

Descriptive statistics

Descriptive statistics are reported as means with standard deviation (SD) for normally distributed continuous variables and medians with interquartile range (IQR) for non-normally distributed data. Categorical variables are reported as frequencies and percentages. The incidence of all-cause unplanned readmission or mortality at six months is reported per DSMS-score. DSMS-scores 3 and 4 were merged to indicate high-risk patients due to the limited numbers with score 4.

Regression models

The prediction model for readmission or mortality within six months was developed and tested by using an individual patient data meta-analysis of prediction models. Both geriatric and disease-specific candidate predictors associated with readmission or mortality were selected. We explored discrimination and calibration of: 1) DSMS alone (delirium, falling, functional impairment and malnutrition); 2) clinical candidate predictors easily obtainable from medical files or by short questions: age, sex, educational level, living arrangement, polypharmacy (≥ 5 medicines), admission in the previous six months and cardiac diagnosis at admission, first without and then including the items of the DSMS; 3) a model based on step 2 and adding more difficult to obtain candidate predictors: Charlson comorbidity index, Mini-Mental State Examination (MMSE), handgrip strength, Short Physical Performance Battery (SPPB) and Geriatric Depression Scale-15 and forcing the DSMS-items into the model. In steps 2 and 3, a backward selection procedure was performed. Predictors were retained in the model if their p-value was < 0.157, corresponding with Akaike's information criterion.[21] No dummy variables were included for the included cohorts. We internally validated the models using 250 bootstrap samples, which were drawn from the original dataset with missing values and missing values filled in by multiple imputation (m=20) in every single bootstrap sample. We used shrunk c-statistics, calibration plots (figure 3, additional files 2-4), regression

slopes and Hosmer-Lemeshow p-values (P_{HL}) to describe discrimination and calibration. Regression coefficients were shrunk by a single shrinkage factor to reduce over-optimism of model performance in new populations.[22] Since two of the data sets were from randomised trials, that used frailty instruments as an inclusion criterion, we tested model calibration on the combined data of the two observational cohorts to ensure application to a more natural target population. We used the psfmi package in R-studio (version 3.6.1) for these analyses. The psfmi package is fully described elsewhere.[23]

Results

Population characteristics

In total, 529 patients were included in this study (figure 1, table 2). The mean age was 82 years and 52% were males. Most patients had been admitted for heart failure (51%), 38% had been admitted to the hospital in the previous six months and 25% of the included patients had cognitive impairment (MMSE < 24). Regarding the DSMS-score, a positive screening was observed in 45% for the risk of delirium, 41% for fall risk, 37% for functional impairment and 29% for malnutrition. The prevalence's were 21, 31, 30 and, 19 percent for a DSMS-score of 0, 1, 2 and 3 or 4, respectively. The crude incidences of readmission or mortality at six months were 37, 42, 48 and 60 percent in patients with DSMS score 0, 1, 2 and 3 or 4, respectively.

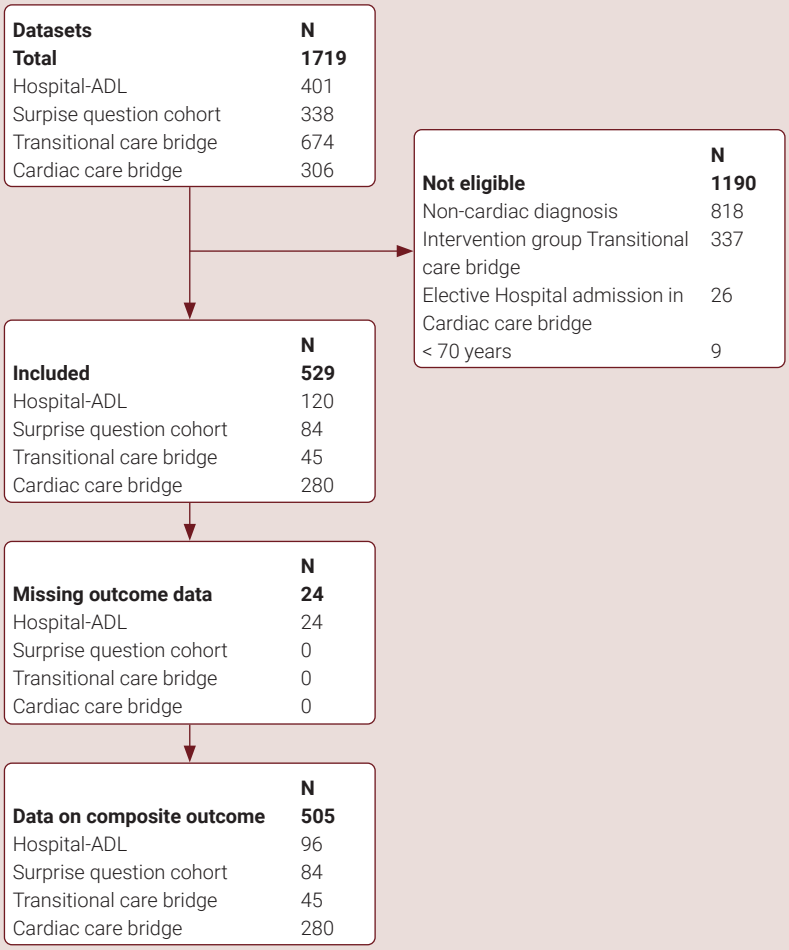

Figure 1. Flowchart

Table 2. Baseline characteristics

		Hospital-ADL (n=120)	Surprise question cohort (n=84)	Transitional care bridge study (n=45)	Cardiac care bridge (n=290)
Sociodemographics					
Age		79.3 ± 6.1	82.8 ± 6.4	81.8 ± 7.6	82.3 ± 6.3
70-79 years		65 (45.2)	28 (33.3)	22 (48.9)	86 (30.7)
≥ 80 years		55 (45.8)	56 (66.7)	23 (51.1)	194 (69.3)
Gender	Female	65 (54.2)	45 (54.8)	17 (37.8)	145 (51.8)
Educational level[a]	Primary school or less	31 (25.8)	35 (40.5)	37 (82.2)	112 (40.0)
	Secondary education	68 (56.6)	34 (40.5)	5 (11.1)	92 (32.9)
	College or university	21 (17.5)	16 (19.0)	3 (6.7)	75 (26.8)
Living arrangement	Living alone	48 (40.0)	44 (52.4)	16 (35.6)	160 (57.1)
Hospital admission					
Diagnosis on admission	Heart failure	48 (40.0)	26 (31.0)	25 (55.6)	173 (61.8)
	Acute coronary syndrome	28 (23.3)	33 (39.3)	10 (22.2)	42 (15.0)
	Other	44 (36.7)	25 (29.8)	10 (22.2)	65 (23.2)
Length of stay	Days	5.1 [3.3 - 8.5]	7.0 [4.0 - 12.0]	8.0 [5.0 - 16.5]	7.0 [4.3 - 10.0]
Hospital admission ≤ six months prior to index event		37 (30.8)	20 (23.8)	17 (37.8)	128 (45.7)
Geriatric conditions					
Polypharmacy	≥ 5 medicines	79 (65.8)	62 (73.8)	40 (88.9)	225 (80.4)

Charlson Comorbidity Index		1 [1 - 3]	2 [1 - 4]	4 [2 - 5]	3 [1 - 4]
MMSE		26.5 ± 2.9	25.3 ± 1.8	25.7 ± 3.6	24.7 ± 3.6
Depression	GDS-15	3.4 ± 2.5	4.7 ± 1.5	4.7 ± 1.6	3.4 ± 2.5
Handgrip strength[b]	kg	27.6 ± 10.4	23.7 ± 2.4	18.4 ± 7.3	21.4 ± 8.8
Functional status	SPPB	7.0 ± 3.5	5.5 ± 2.1	5.4 ± 1.8	4.8 ± 2.8
DSMS-items[c]					
Delirium risk score	DSMS at risk of delirium	19 (15.8)	24 (28.6)	37 (82.2)	159 (56.8)
Fall ≤ six months	DSMS risk of falling	39 (32.5)	21 (25.0)	21 (46.7)	133 (47.5)
Functional impairment (KATZ-6)	DSMS impairment in ADL	38 (31.7)	22 (26.2)	23 (51.1)	112 (40.0)
Malnutrition risk (SNAQ)	DSMS risk of malnutrition	32 (26.7)	5 (6.0)	21 (46.7)	94 (33.6)
DSMS score 0		43 (35.8)	43 (51.2)	2 (4.4)	21 (7.5)
DSMS score 1		42 (35.0)	17 (20.2)	9 (20.0)	97 (34.6)
DSMS score 2		24 (20.0)	20 (23.8)	16 (35.6)	97 (34.6)
DSMS score 3 or 4		12 (10.0)	5 (6.0)	18 (40.0)	66 (23.6)

Mean ± standard deviation, median [25-75 centile], N (%). [a]Primary education: elementary or primary school. Secondary education: pre-vocational, senior general or pre-university. Higher education: higher professional or university, [b]Dominant hand highest value, [c]Dutch Safety Management System8: the score between 0-4 points, based on four domains of frailty: (risk of) delirium, falling, functional impairment, and malnutrition.

Abbreviations: ADL: Activities of Daily Living; DSMS=Dutch Safety and Management System; GDS=Geriatric Depression Scale; KATZ-6[16]:Modified KATZ-6 index; kg: kilogram; MMSE=Mini-Mental State Examination; *SNAQ*[17]: Short Nutritional Assessment Questionnaire; SPPB=Short Physical Performance Battery.

Performance of the DSMS-tool

Figure 2 and table 3 show the predictive performance of the three models in predicting readmission or mortality within six months. In model 1, including the DSMS only, malnutrition was the strongest predictor (OR 2.29, 95% CI 1.47 – 3.56). The model discriminated limited (c-statistic 0.61, 95% CI 0.56 – 0.66) and after internal validation discrimination decreased (c-statistic 0.55). In model 2a (without the DSMS-items) only sex, admission in the previous six months and diagnosis at admission remained in the model. In model 2b, the DSMS-items were added to the predictors in 2a which slightly improved discrimination (c-statistic 0.66, 95% CI 0.61 – 0.71). In the observational cohorts, the c-statistic of model 2b was 0.57 (95% CI 0.48 – 0.65), however, the model was well calibrated (corrected slope 0.71, P_{HL}=0.89) (additional files 2-3). In model 3, the admission diagnosis and Charlson comorbidity index were selected, which yielded a model c-statistic of 0.69 (95% CI 0.63 – 0.73), which fell to 0.66 after internal validation. The calibration plot is shown in additional file 4. In the observational cohorts, the discriminative performance was lower (c-statistic 0.58, 95% CI 0.47-0.68) but well calibrated (corrected slope 0.76, P_{HL}=0.66) as shown in figure 3.

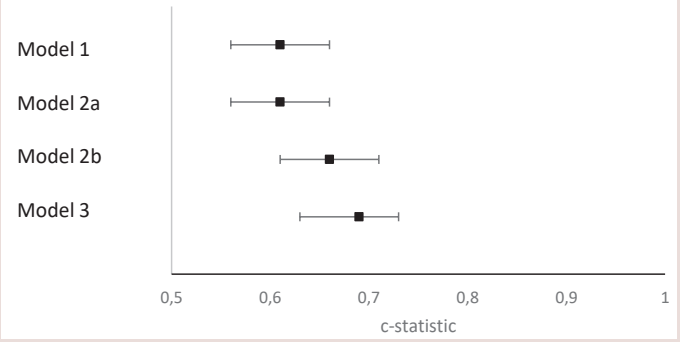

Figure 2. Areas under the curve and 95% confidence intervals for predictors of six-month readmission or mortality

Model 1: DSMS delirium, DSMS fall risk, DSMS functional impairment, DSMS malnutrition
Model 2a: sex, admission in the previous six months and cardiovascular diagnosis
Model 2b: sex, admission in the previous six months and cardiovascular diagnosis + model 1
Model 3: Charlson comorbidity index,[24] cardiovascular diagnosis + model 1

Table 3. Multivariable analyses and predictive performance for readmission or mortality at six-months[a]

	Model 1			Model 2a			Model 2b			Model 3		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
DSMS												
Delirium	1.39	(1.29 - 1.50)	<0.001				1.29	(0.93 - 1.79)	0.127	1.06	(0.76 - 1.46)	0.740
Fall risk	1.09	(0.77 - 1.55)	0.642				1.1	(0.81 - 1.49)	0.551	1.07	(0.80 - 1.44)	0.664
Functional impairment	1.24	(0.91 - 1.69)	0.174				1.23	(0.88 - 1.74)	0.236	1.18	(0.77 - 1.81)	0.457
Malnutrition	2.21	(1.45 - 3.38)	<0.001				1.89	(1.31 - 2.72)	<0.001	1.79	(1.26 - 2.53)	0.001
Female				0.80	(0.61 - 1.06)	0.113	0.73	(0.54 - 1.00)	0.045			
Admission previous six months				1.33	(0.97 - 2.13)	0.156	1.34	(0.97 - 1.84)	0.073			
Admission diagnosis												
Heart failure				Reference		0.004	Reference		0.026	Reference		0.102
Acute coronary syndrome				0.74	(0.52 - 1.06)		0.84	(0.56 - 1.24)		0.90	(0.62 - 1.31)	
Other				0.57	(0.40 - 0.79)		0.60	(0.42 - 0.87)		0.68	(0.48 - 0.97)	
Charlson comorbidity Index												
Score 0										Reference		0.002
Score 1										1.12	(0.64 - 1.96)	
Score 2										1.06	(0.59 - 1.90)	
Score 3										1.71	(0.95 - 3.07)	
Score 4										1.93	(1.02 - 3.66)	
Score ≥ 5										2.72	(1.42 - 5.27)	

Table 3. *Continued*

[a]No dummy variables for the four cohorts were included in the multivariable analyses
Abbreviations: DSMS=Dutch Safety Management System

Model 1: DSMS delirium, DSMS fall risk, DSMS functional impairment, DSMS malnutrition
Model 2a: sex, admission in the previous six months and cardiovascular diagnosis
Model 2b: sex, admission in the previous six months and cardiovascular diagnosis + model 1
Model 3: Charlson comorbidity index,[24] cardiovascular diagnosis + model 1

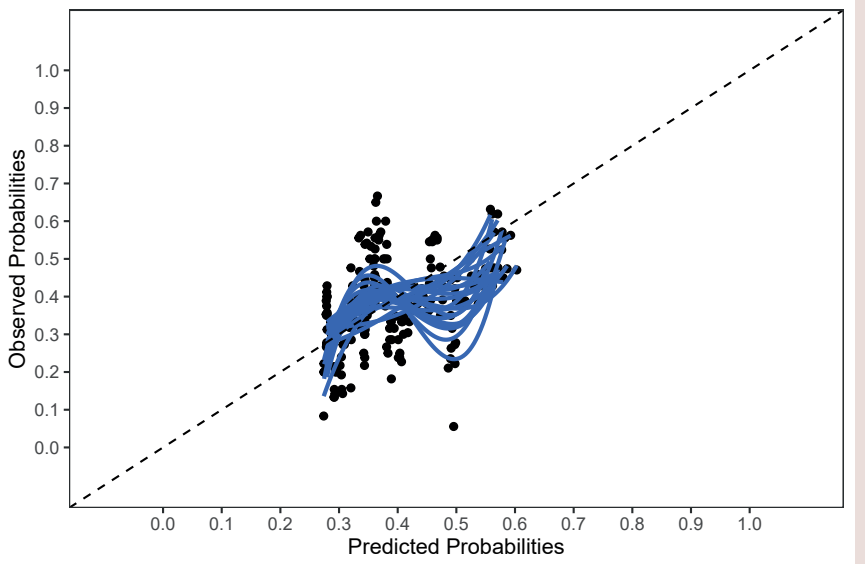

Figure 3. Calibration plot of readmission or mortality within six months (model 3) in the two observational cohorts.

Discussion

We examined the performance of the DSMS-tool, alone and combined with other predictors, on all-cause unplanned hospital readmission or mortality within six months in older patients acutely hospitalised for a cardiac reason. Our results show that the DSMS-tool's performance is limited in this population. However, in combination with the diagnosis on admission and the Charlson comorbidity index, reasonable predictions could be made.

Originally, the DSMS-items were introduced into Dutch hospitals to assess the risk of functional loss in older patients on admission and to selectively deploy interventions to prevent functional loss early.[8] However, the predictive

performance has not been studied before implementation in 2012. Heim et al.[25] studied discrimination of the DSMS-tool in predicting the occurrence of a composite outcome of death, high healthcare demand or at least one additional dependency in activities of daily living within 3 months follow-up among acutely and electively hospitalised patients ≥ 70 years at departments of neurology, urology, surgery and orthopaedics. On external validation in 812 patients (of which 105 only had data on healthcare demand), they found a sensitivity of 0.61 and a specificity of 0.75 (c-statistics 0.68) for the DSMS-tool reinforced by information on age (cut-off at 80 years). Using different methods (cardiac patients, all acutely admitted, six-month composite outcome of readmission or death, multiple imputation of missing values, bootstrapping and shrinkage), we found that discrimination of the DSMS-tool to predict the occurrence of six-month hospital readmission or mortality was much lower (shrunk c-statistic=0.55). Although the contrasting c-statistics may be explained by the different outcome measures and time window, it could also be explained by differences between the study populations. For example, Heim et al.[25] included both acutely as electively hospitalised patients including a high percentage of surgical and orthopaedic patients, whereas we focussed solely on the acutely hospitalised cardiac population in which a high prevalence of geriatric conditions and comorbidities were found. In addition, more patients in our study were cognitively impaired (MMSE ≤23 21.3% versus 15.9%).[25] Surprisingly, and despite a fairly wide range of ages in our study, age was not a strong predictor and was not selected in any of the models.

Hermans et al.[26] studied, in a retrospective analysis of routine data, the association between the DSMS-score and the occurrence of mortality or a composite of various complications after a percutaneous coronary intervention within 30 days in patients with ST-elevated myocardial infarction ≥ 70 years. They found an OR of 9.6 (95%CI 1.6-56.9) for a DSMS-score (≥ 1) to predict 30-day mortality. However, the authors were hindered by the low incidence of mortality (n=11, 5%) which may have led to severe overfitting of their regression model.

Until now, only few studies have studied the performance of the DSMS-tool. These studies vary in study population, time window, outcomes and methods and are therefore difficult to compare. As a result, more research is needed to study the performance of the DSMS-tool, especially since in the Netherlands its use is compulsory in all patients ≥70 years who are hospitalised. In addition, it is important to not only identify patients at risk but also act on it, that is, initiate early preventive interventions in those patients indicated by their predicted risk. As far as we are aware, treatment thresholds, in terms of predicted risk, are seldom specified. Within the DSMS-tool, attention is payed to practical hospital-based interdisciplinary interventions in patients with one or more risk factors present.[8] However, it is known that common geriatric syndromes are often still present three months post-discharge.[11] The DSMS recommends transferring

risk information to caregivers in primary care. However, more attention may be needed to continue interventions from hospital to home. For example, transitional care interventions contribute to continuity of care across care settings and have been shown to reduce the risk of readmission and mortality in several populations.[27,28]

We conclude that a combination of variables reflecting geriatric conditions (the DSMS-items and the Charlson comorbidity index) and a disease-related factor (diagnosis at admission), led to better predictive performance than a model of the DSMS-items alone. A recent systematic review of risk prediction models in cardiac patients showed that only few studies use geriatric predictors, such as physical performance or dementia, to estimate patients' probabilities of experiencing an unplanned readmission (van Grootven, submitted). However, models containing geriatric predictors did not seem to predict much different than those without. This may be explained by the relatively low mean age in the underlying studies as most studies included patients ≤ 70 years. This lowers the presence of geriatric syndromes, which may hinder accurate detection of potential predictive capabilities. The SILVER-AMI study included patients ≥ 75 years and developed risk prediction models for 30 and 180-day readmission.[2,29] In accordance with our results, they found that a combination of geriatric as well as disease-specific risk factors best predicted the risk of readmission.

Strengths and limitations

In this study we combined data of older cardiac patients of four studies to examine the performance of the DSMS-tool and the contribution of additional variables using rigorous statistical methods. Our study contributes to the evidence on how to identify older cardiac patients at risk of readmission or mortality.

Some limitations should however be considered. First, we examined the performance of the DSMS-tool on the risk estimation of hospital readmission or mortality in older cardiac patients. However, the tool has originally been developed to identify older patients at risk of functional loss. Since functional loss is strongly related to hospital readmission or mortality, testing the performance of the DSMS-tool on these outcomes is considered plausible.[9,10] Second, while we were able to select a broad range of geriatric predictors, some important medical (disease-specific) predictors (e.g. left ventricular ejection fraction, and stage of disease (NYHA)) may have been missed. Information on these tests is usually not available on hospital admission (and in our four cohorts) and were therefore not included in our model which focusses on the early admission phase. However, data about the disease history and comorbidities may be available at hospital admission. For example, the presence of specific comorbidities such as renal failure, diabetes[30,31] or chronic obstructive pulmonary disease[2,29] are known to increase the risk of adverse outcomes and may be of additional value in future

risk prediction models for older cardiac patients. Third, in the two intervention cohorts a selected subgroup of 87% frail older cardiac patients according to the DSMS-tool was included, compared to 44% in the two observational cohorts. We therefore performed a second internal validation process on the two observational cohorts to reflect model performance in a hospitalised older cardiac patient population representative of that encountered in clinical practice. Last, despite rigorous steps taken to assess the internal validity of our models, an additional external validation in independent datasets is recommended to examine the generalisability of our results.

Conclusion

The DSMS-tool alone has limited capacity to accurately estimate the risk of readmission or mortality in hospitalised older cardiac patients. Adding disease-specific risk factor information to the DSMS-tool resulted in a moderately performing model. To optimise the early identification of older hospitalised cardiac patients at risk, the combination of geriatric and disease-specific predictors should be further explored.

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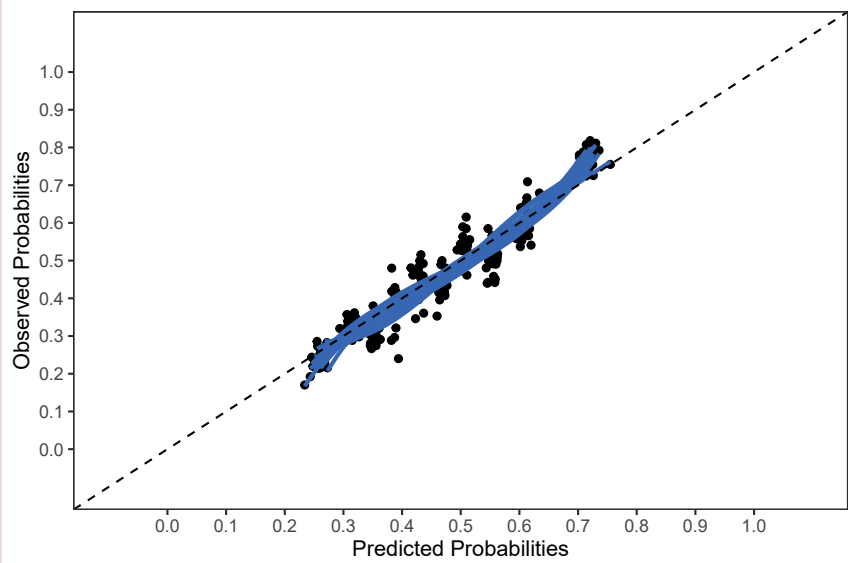
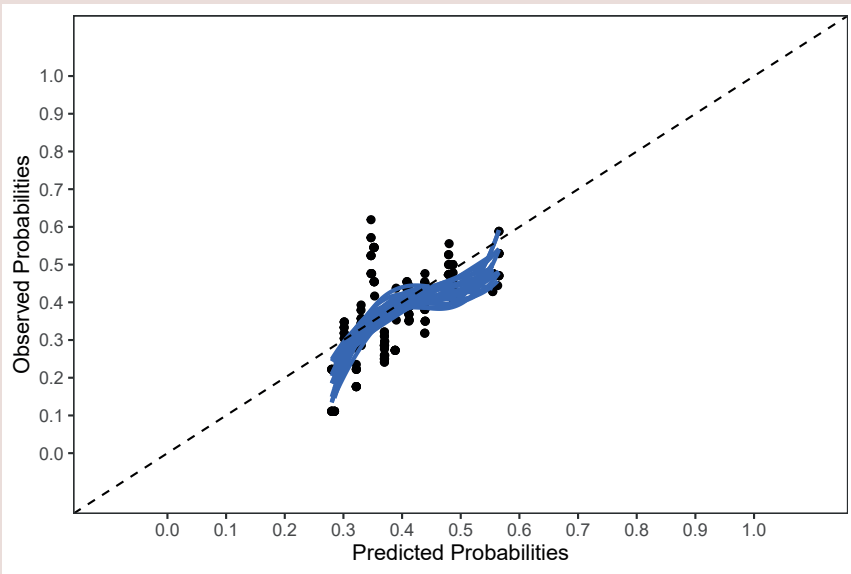
Additional file 1. Frequency of missing data per variable in the four cohorts

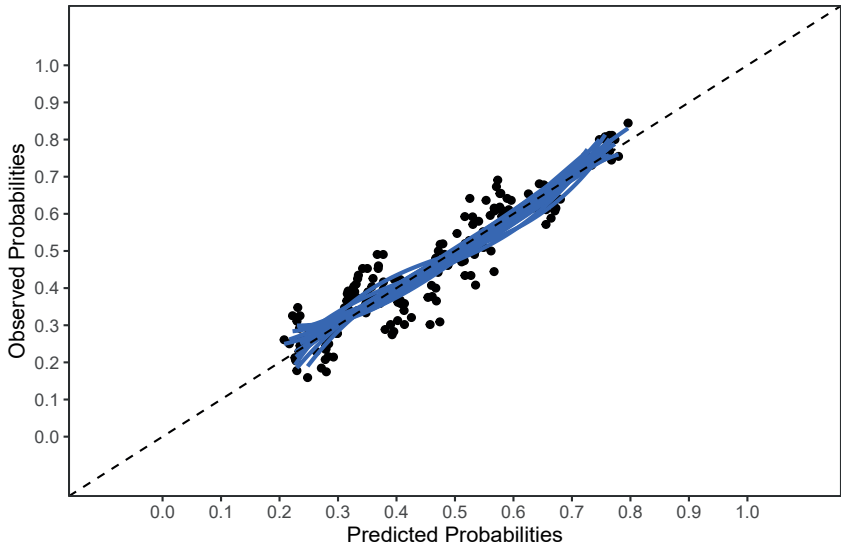
	Hospital-ADL (n=120)	Surprise question cohort (n=84)	Transitional care bridge study (n=45)	Cardiac care bridge study (n=280)
Sociodemographics				
Age	0	0	0	0
Gender	0	0	0	0
Educational level	0	84	0	1
Living arrangement	0	0	0	0
Hospital admission				
Diagnosis on admission	0	0	0	0
Length of stay	4	1	0	0
Hospital admission ≤6 months prior to index event	0	1	45	0
Geriatric conditions				
Polypharmacy	2	3	2	6
Charlson Comorbidity Score	0	0	1	0
MMSE	7	84	1	0
Depression	2	84	45	2
Handgrip strength	26	84	21	33
Functional status	36	84	45	92
DSMS-items				
Delirium risk score	0	5	1	0
Activities of Daily Living (KATZ-6)	0	2	0	0
Malnutrition risk (SNAQ)	1	2	2	0
Fall ≤6 months	0	6	1	0
Outcome				
Composite outcome on 6 months	24	0	0	0



Supplemental figure 1. Calibration plot of readmission or mortality within six months (model 2b) in 250 bootstrapped samples.



Supplemental figure 2. Calibration plot of readmission or mortality within six months (model 2b) in the two observational cohorts.



Supplemental figure 3. Calibration plot of readmission or mortality within six months (model 3), in 250 bootstrapped samples.

Part

2

Lifestyle-related secondary prevention of cardiovascular complications in older cardiac patients

Chapter

5

Lifestyle modification in older versus younger coronary artery disease patients

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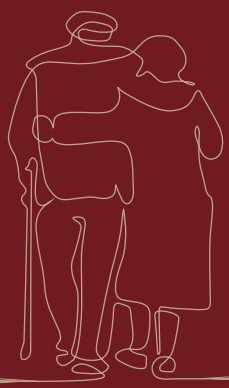
Heart 2020:106(14);1066-1072



Abstract

Objective: To compare the treatment effect on lifestyle-related risk factors (LRFs) in older (≥65 years) versus younger (<65 years) patients with coronary artery disease (CAD) in The Randomised Evaluation of Secondary Prevention by Outpatient Nurse SpEcialists 2 (RESPONSE-2) trial.

Methods: The RESPONSE-2 trial was a community-based lifestyle intervention trial (N=824) comparing nurse-coordinated referral with a comprehensive set of three lifestyle interventions (physical activity, weight reduction and/or smoking cessation) to usual care. In the current analysis, our primary outcome was the proportion of patients with improvement at 12 months follow-up (n=711) in ≥1 LFR stratified by age.

Results: At baseline, older patients (n=245, mean age 69.2±3.9 years) had more adverse cardiovascular risk profiles and comorbidities than younger patients (n=579, mean age 53.7±6.6 years). There was no significant variation on the treatment effect according to age (p value treatment by age=0.45, OR 1.67, 95% CI 1.22 to 2.31). However, older patients were more likely to achieve ≥5% weight loss (OR old 5.58, 95% CI 2.77 to 11.26 vs. OR young 1.57, 95% CI 0.98 to 2.49, p=0.003) and younger patients were more likely to show non-improved LRFs (OR old 0.38, 95% CI 0.22 to 0.67 vs. OR young 0.88, 95% CI 0.61 to 1.26, p=0.01).

Conclusion: Despite more adverse cardiovascular risk profiles and comorbidities among older patients, nurse-coordinated referral to a community-based lifestyle intervention was at least as successful in improving LRFs in older as in younger patients. Higher age alone should not be a reason to withhold lifestyle interventions in patients with CAD.

Introduction

The prevalence of coronary artery disease (CAD) increases with age,[1] and due to increasing life expectancies expected to further increase in the coming decades.[2] Interventions to reduce lifestyle-related risk factors (LRFs) such as overweight, physical inactivity and smoking have proven to be effective in secondary prevention of cardiovascular events and are also recommended in older patients.[3,4] However, treatment complexity in older patients is greater, due to polypharmacy, comorbidities, and functional decline, which may interfere with secondary prevention.[2,5,6] Therefore, accessible and individualised programmes are needed, particularly in older patients.[7] However, evidence for the efficacy of various lifestyle prevention programmes in older patients is less conclusive than in younger patients.[3,4]

The Randomised Evaluation of Secondary Prevention by Outpatient Nurse SpEcialists 2 (RESPONSE-2) trial was a community-based lifestyle intervention trial evaluating nurse-coordinated referral to a comprehensive set of three lifestyle interventions (weight reduction, physical activity and/or smoking cessation).[8,9] In the overall population significant improvements were seen in LRFs in the intervention group as compared with usual care. However, it is unclear whether these effects differ according to age. We therefore performed a secondary analysis in the RESPONSE-2 trial comparing the treatment effect on LRFs in older (≥65 years) vs younger (<65 years) patients. We hypothesised that the treatment effect on LRFs in the overall RESPONSE-2 population was comparable in older and younger patients.

Methods

Study design

We used data from the RESPONSE-2 trial (n=824), a multicentre, randomised controlled trial conducted in 15 hospitals in the Netherlands.[8] The trial was designed to examine the effect of nurse-coordinated referral to a comprehensive set of up to three community-based interventions to improve LRFs in patients with CAD. Written informed consent was obtained from all patients. The methods and outcomes are described in detail elsewhere[8,9] and are briefly summarised below. In the current study, we compared improvements in LRFs at 12 months follow-up in older (65-84 years) versus younger (32-65 years) patients.

Patient population

In the RESPONSE-2 trial, patients aged 18 years or older were eligible <8 weeks

after hospitalisation for acute coronary syndrome (ACS), and/or coronary revascularisation, if they had at least one of the following lifestyle risk factors: (1) body mass index (BMI) ≥27 kg/m^2, (2) self-reported physical inactivity (<30 min of physical activity of moderate intensity five times per week), (3) self-reported current smoking or stopped ≤6 months before hospital admission, and if they reported to be motivated to attend at least one lifestyle programme.

Exclusion criteria were: planned revascularisation after discharge; life expectancy ≤2 years; congestive heart failure New York Heart Association class III or IV; visits to outpatient clinic and/or lifestyle programme not feasible; no internet access; and anxiety or depressive symptoms (Hospital Anxiety and Depression Scale (HADS) >14), as this was expected to impede lifestyle changes.[10]

All patients received usual care, including visits to the cardiologist, cardiac rehabilitation according to national and international guidelines[3,11] and up to four visits to a nurse-coordinated secondary prevention programme addressing healthy lifestyles, biometric risk factors and medication adherence.

Public and patient involvement

The RESPONSE-2 trial was based on the evaluation of the RESPONSE-1 trial, including involvement from participating nurses and patients.12,13 During the study, patients were filmed for the training of participating nurses and were asked about their experiences with the lifestyle programme(s). The nurses contributed to the development and implementation of the study and spread a leaflet with study results among patients.

Nurse-coordinated care and referral to lifestyle programmes

Patients in the intervention group were referred to up to three lifestyle programmes by registered nurses with experience in cardiovascular care. The number and sequence of the lifestyle programmes was determined by patient's risk profile/preferences. Nurses were trained in a systematic referral approach, consisting of risk status assessment, discussing the current risk status with patients, and assessing levels of motivation to sustain or improve LRFs. Depending on levels of motivation, participation in relevant lifestyle programme(s) was advised, followed by referral.

The three lifestyle programmes (Weight Watchers, Philips DirectLife and Luchtsignaal smoking cessation) were offered in their existing format. In short, the weight loss programme (Weight Watchers) was provided as a programme for weight reduction by addressing diet patterns, unhealthy behaviour and physical activity. Weekly group-based sessions were provided. The physical activity programme (Philips DirectLife) was offered as an internet-based programme with an accelerometer and personalised feedback by an online coach to monitor

and improve physical activity. Luchtsignaal provided a telephone counselling-based smoking cessation programme based on motivational interviewing by trained professionals, and pharmacological treatments for smoking cessation were prescribed, as appropriate. More details about the nurse-coordinated care and lifestyle programmes have been described elsewhere.[8,9,14]

Data collection and measurements

Data were collected at baseline (first visit within 8 weeks after hospital discharge) and at 12 months, and included cardiovascular history and risk factors, dietary status, physical activity, smoking status and medication use. Body weight, height and waist circumference were measured and BMI was calculated. Physical activity was measured by the 6 min walking distance (6MWD).[15] Smoking status was assessed by a urinary cotinine test (UltiMed one step, Dutch Diagnostic, Zutphen, the Netherlands; detection limit 200 ng/mL).

Outcomes

We compared the treatment effect in older (65-84 years) versus younger (32-64 years) patients. The primary outcome was improvement in ≥1 LRF(s) without deterioration in the other two LRFs at 12 months follow-up. Improvement was defined as: (1) weight loss of ≥ 5%[11]; (2) a urine cotinine level <200 ng/m; and/or (3) ≥10% increase in 6MWD.[16] Deterioration was defined as: (1) any weight gain in combination with a BMI >25 kg/m^2; (2) a positive cotinine test (>200 ng/mL) in non-smokers at baseline and (3) any decrease in 6MWD compared with baseline. Two exceptions were made: in patients who stopped smoking and/or improved their 6MWD, an increase of 2.5% in BMI was classified as no deterioration. Secondary outcomes included differences in isolated LRFs (weight, smoking and physical activity) and an LRFs analysis of no improvement. We analysed non-improved patients defined as patients with ≥1 LRF(s) not on target at baseline and who had remained not on target 12 months later.[8,9]

Statistical methods

Continuous variables are described using means with SD for normally distributed data and medians with IQR for non-normally distributed data. Categorical variables are presented using frequencies and percentages.

The variation in treatment effect by age was first investigated using unadjusted logistic regression analyses (OR) with 95% CI including treatment, age (dichotomised at 65 years) and an interaction term of treatment by age. We considered p values <0.10 indicative of variation in treatment effect and then reported separate ORs. Statistically non-significant interaction terms (p≥0.10) were interpreted as an indication that there was no variation in treatment effect by age. In these outcomes, we reported the OR of the analyses in the overall

population (figure 1, table 1).

The baseline measurements of the variables age, sex, marital status, educational level, BMI ≥ 27 kg/m^2, self-reported physical inactivity, self-reported current smoking or stopped ≤ 6 months before hospital admission, low-density lipoprotein cholesterol LDL cholesterol, systolic blood pressure, diabetes mellitus and no history of cardiovascular disease (CVD) were identified as potential confounders. Then, we performed adjusted logistic regression analyses to examine if there were any discrepancies between the unadjusted and adjusted regression analyses regarding treatment by age interactions. As a sensitivity analysis, we investigated (in unadjusted analyses) how the treatment effect varied across the whole age spectrum (from 32 to 84 years) with age as a continuous variable, using the non-parametric method as described by Bonetti and Gelber[17] and the parametric method as described by Royston and Sauerbrei.[18,19]

Statistical analyses were performed using SPSS V.24.0 (IBM, Armonk, New York, USA) and Stata V.13.1 (StataCorp. 2013).

Results

Patient characteristics

A total of 824 participants were randomised in the RESPONSE-2 trial. In 711 patients, outcome data were complete and these patients were included in the primary analysis (figure 1). Mean age was 69.2±3.9 years in older patients and 53.7±6.6 in younger patients (table 2). Overall, 20.4% of older patients and 22.1% of younger patients were female. Older patients more frequently had a history of CVD (45.3% vs. 30.6%, p<0.001) and more comorbid conditions, such as hypertension (52.5% vs 34.2%, p<0.001), diabetes mellitus (24.1 % vs 11.9%, p<0.001) and peripheral artery disease (9.8% vs 2.6%, p<0.001) compared with younger patients (table 2 and 3). There were no significant differences in medication prescriptions between older and younger patients at baseline.

Overall, 86.9% was overweight (BMI ≥ 25 kg/m^2) and 63.3% did not meet the target for adequate physical activity (≥5 times per week 30 min/day moderate physical activity) at baseline (table 3). Younger patients were more often current smokers (26.1% vs 14.7%, p<0.001) and more frequently had quit smoking within 6 months before or during hospital admission (31.6% vs. 14.3%, p<0.001) than older patients. Both older and younger patients chose most frequently to attend a single lifestyle programme (50.5% vs. 47.5%, p=0.64), of whom 52.0% and 48.4% participated in the physical activity programme (Appendix table S1).

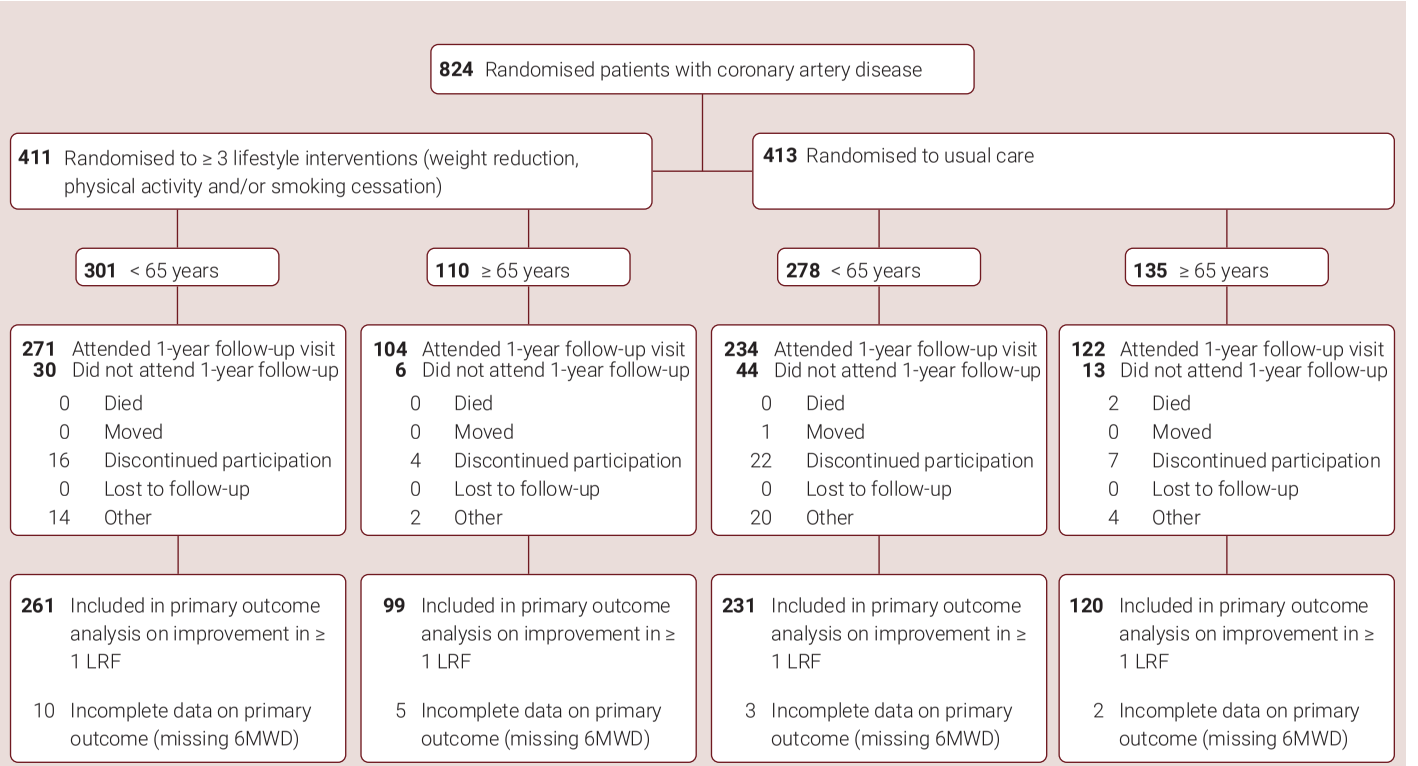


Figure 1. Study population flow chart
Abbreviations: 6MWD = 6 min walking distance; LRF = lifestyle-related risk factor

Table 1. Primary and secondary outcomes

	Age ≥65 years		Age <65 years		Age ≥65 years	Age <65 years	Treatment by age
	Intervention	**Control**	**Intervention**	**Control**	**OR (95% CI)**	**OR (95% CI)**	**P value**
Primary outcome, n (%)							
Success*	41/99 (41.4)	31/120 (25.8)	92/261 (35.2)	60/231 (26.0)	1.67 (1.22 to 2.31)		0.45
Secondary outcomes, n (%)							
No improvement	37/99 (37.4)	73/120 (60.8)	108/261 (41.4)	103/231 (44.6)	0.38 (0.22 to 0.67)	0.88 (0.61 to 1.26)	0.01
Weight reduction, n (%)							
≥ 5% weight reduction	40/99 (40.4)	13/120 (10.8)	57/261 (21.8)	35/231 (15.2)	5.58 (2.77 to 11.26)	1.57 (0.98 to 2.49)	0.003
≥ 5% weight reduction in patients with baseline BMI ≥ 27 kg/m2	38/72 (52.8)	12/87 (13.8)	50/197 (25.4)	27/166 (16.3)	6.99 (3.25 to 15.01)	1.75 (1.04 to 2.95)	0.003
Smoking status, n (%)							
Urine cotinine <200 ng/mL	86/99 (86.9)	95/120 (79.2)	186/261 (71.3)	163/231 (70.6)	2.28 (0.99 to 5.24)	0.90 (0.60 to 1.34)	0.05
Urine cotinine <200 ng/mL in smokers <6 months before admission	17/29 (58.6)	10/34 (29.4)	69/143 (48.3)	66/132 (50.0)	3.40 (1.20 to 9.66)	0.93 (0.58 to 1.50)	0.03
Physical activity, n (%)							
≥10% improvement on 6MWD	45/98 (45.9)	45/120 (37.5)	118/261 (45.2)	94/231 (40.7)	1.27 (0.94 to 1.71)		0.62
≥10% improvement on 6MWD in baseline physically inactive	30/67 (44.8)	27/74 (36.5)	76 / 160 (47.5)	63/143 (44.4)	1.14 (0.72 to 1.79)		0.60

Values are n/N (%). *Success is defined as improvement in ≥1 LRF without deterioration of the other 2.
Abbreviations: BMI, body mass index; LRFs, lifestyle-related risk factors; 6MWD, 6 min walking distance.

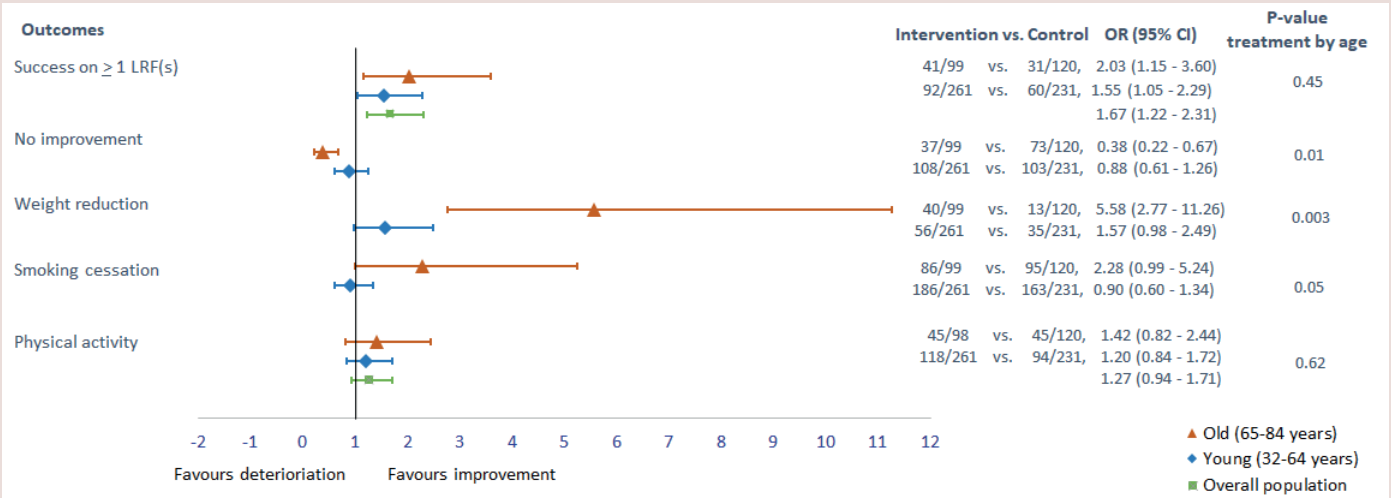


Figure 2. Outcomes in lifestyle-related risk factors after 12 months

Treatment effect in older and younger patients

In older patients, 41.4% patients (41/99) in the intervention group compared with 25.8% patients (31/120) in the control group were successful in improving ≥1 LRFs at 12 months without deterioration in the other LRFs (ie, the primary outcome, table 1). In younger patients, 35.2% patients (92/261) in the intervention group compared with 26.0% patients (60/231) in the control group improved ≥1 LRFs. In the univariable analyses, older patients in the intervention group were numerically more successful in improving LRFs, however, no variation in treatment effect by age was found (p=0.45, OR overall 1.67, 95% CI 1.22 to 2.31) (figure 2).

Older patients were less likely to show non-improved LRFs at all (interventions: 37.4% vs. controls: 60.8%) compared with younger patients (interventions: 41.4% vs. controls: 44.6%) (table 1). Furthermore, older patients in the intervention group (OR 0.38, 95% CI 0.22 to 0.67) were less likely to have non-improved LRFs as compared with younger patients in the intervention group (OR 0.88, 95% CI 0.61 to 1.26, 1.49) (p value treatment by age=0.01) (figure 2).

Older patients were more successful in achieving weight reduction of ≥ 5% (40.4% interventions vs 10.8% controls, OR 5.58, 95% CI 2.77 to 11.26) compared with younger patients (21.8% interventions vs. 15.2% controls, OR 1.57, 95% CI 0.98 to 2.49) (p value treatment by age=0.003) (table 1, figure 2). In addition, in patients with a BMI ≥ 27 kg/m^2 at baseline, higher rates of ≥ 5% weight reduction were observed in older patients (52.8% interventions vs. 13.8% controls, OR 6.99, 95% CI 3.25 to 15.01) as compared with younger patients (25.4% interventions vs. 16.3 controls, OR 1.75, 95% CI 1.04 to 2.95) (p value treatment by age=0.003) (table 1). Older patients attended more sessions in the weight reduction programme compared with younger patients (median 30 vs. 10, p<0.001) (Appendix table S1). In patients attending >30 sessions, 91.3% of older patients and 57.9% of younger patients achieved ≥ 5% weight reduction (p=0.03).

Numerically more older patients had negative cotinine tests (interventions: 86.9% vs. controls: 79.2%, OR 2.28, 95% CI 0.99 to 5.24) compared with younger patients (interventions: 71.3% vs. controls: 70.6%, OR 0.90, 95% CI 0.60 to 1.34) (p value treatment by age=0.05) (table 1, figure 2). In addition, more older pre-event smokers in the intervention quit smoking at 12 months follow-up (58.6% interventions vs. 29.4% controls, OR 3.40, 95% CI 1.20 to 9.66) while in younger smokers no difference was found in smoking cessation rates (48.3% interventions vs. 50.0% controls, OR 0.93, 95% CI 0.58 to 1.50) (p value treatment by age=0.03) (table 1).

No differences were observed on improvement on the 6MWD in both older (interventions: 45.9% vs. controls: 37.5%) and younger patients (interventions: 45.2% vs. controls: 40.7%) (p value treatment by age=0.62, overall OR 1.27, 95% CI 0.94 to 1.71) (table 1, figure 2).

Table 2. Baseline characteristics

	Age ≥65 years (n = 245)	Age <65 years (n = 579)	P value
Demographics and medical history			
Age, years	69.2±3.9	53.7±6.6	<0.001
Female	50 (20.4)	128 (22.1)	0.59
Caucasian	234 (95.5)	529 (91.4)*	0.04
Higher education (>13 years)	95 (38.8)	236 (40.8)	0.64
Relationship (married or cohabiting)	198 (80.8)	471 (81.3)	0.85
Index event			
ST-segment elevation myocardial infarction	77 (31.4)	266 (45.9)	<0.001
Non-ST-segment elevation myocardial infarction	91 (37.1)	200 (34.5)	0.47
Unstable angina	28 (11.4)	40 (6.9)	0.04
Stable angina requiring revascularisation	49 (20.0)	73 (12.6)	0.01
Treatment			
Percutaneous coronary intervention	180 (73.5)	459 (79.3)	0.08
Coronary artery bypass surgery	35 (14.3)	52 (9.0)	0.03
Medication only	30 (12.2)	68 (11.7)*	0.82
Medication prescription			
Antiplatelet/anticoagulation agents	244 (99.6)	578 (99.8)	0.51
Beta-blockers	209 (85.3)	493 (85.1)	1.00
ACE inhibiter/ARB	190 (77.6)	423 (73.1)	0.19
Lipid-lowering drugs	239 (97.6)	559 (96.5)	0.52
Previous cardiovascular disease			
Myocardial infarction	62 (25.3)	121 (20.9)	0.17
Percutaneous coronary intervention	49 (20.0)	79 (13.6)	0.03
Coronary artery bypass surgery	19 (7.8)	12 (2.1)	<0.001
Stroke	12 (4.9)	14 (2.4)	0.08
Peripheral artery disease	24 (9.8)	15 (2.6)	<0.001
No known history of cardiovascular disease	134 (54.7)*	402 (69.4)	<0.001

Values are mean±SD or n (%).
*Difference between intervention and control group after randomisation, p<0.05.
Abbreviations: ACE, Angiotensin-converting enzyme; ARB, Angiotensin II receptor blockers.

We did not find any discrepancies between the non-adjusted and adjusted regression analyses regarding the treatment by age interactions.

Sensitivity analysis

When age was analysed as a continuous variable (Appendix figures S1-S5), we found that the treatment effect increased with age for the outcomes *non-improved LRFs* (p values ranging from 0.05 to 0.13), *weight reduction* (p values ranging from 0.001 to 0.005) and *smoking cessation* (p values ranging from 0.03 to 0.94). There were no strong indications that treatment effects varied by age for *successful improvement on LRFs* (p values ranging from 0.07 to 0.15) and *physical activity* (p values ranging from 0.23 to 0.28).

Table 3. Risk profiles and lifestyle-related risk factors at baseline

	Age ≥65 years (N=245)	**Age <65 years (N=579)**	**P value**
Risk profiles			
BMI, mean (SD), kg/m2	29.9 ± 4.6	29.6 ± 4.4	0.35
Overweight (BMI ≥25 kg/m2)	216 (88.2)	500 (86.4)	0.57
Overweight (BMI ≥27 kg/m2)	182 (74.3)	427 (73.7)	0.93
Quit smoking ≤6 months (baseline)	35 (14.3)	183 (31.6)	<0.001
Physically inactive	158 (64.5)	364 (62.9)	0.69
Systolic blood pressure ≥140 mmHg	124 (50.6)	171 (29.5)	<0.001
LDL cholesterol ≥1.8 mmol/L	155 (63.3)	408 (70.5)	0.02
Waist circumference, cm	108.5±12.1	106.0±11.9*	0.01
6MWD, m	433±103	506±107	<0.001
History of hypertension	128 (52.5)	198 (34.2)*	<0.001
History of diabetes mellitus	59 (24.1)	69 (11.9)	<0.001
History of dyslipidaemia	69 (28.2)	115 (19.9)	0.01
Eligibility for lifestyle programmes, n (%)			
Eligble Weightwatchers	182 (74.3)	427 (73.7)	0.93
Eligible Luchtsignaal	71 (29.0)	334 (57.7)	<0.001
Eligible Direct life	158 (64.5)	364 (62.9)	0.69

Values are mean±SD or n (%).
*Difference between intervention and control group after randomisation, p<0.05
Abbreviations: BMI, body mass index; LDL, low-density lipoprotein; 6MWD, 6 min walking distance.

Discussion

Our findings suggest that despite more adverse cardiovascular risk profiles and comorbidities, nurse-coordinated referral to a community-based lifestyle intervention was at least as successful in improving LRFs in older compared with younger patients. While levels of physical activity did not improve in both groups, older patients in the intervention group were more successful in weight reduction and smoking cessation as compared with younger patients.

At baseline, older patients more frequently had a history of CVD, adverse cardiovascular risk profiles and more comorbidities such as hypertension, diabetes mellitus and peripheral artery disease. In older patients the risk of recurrent events is higher due to age alone, but comorbidities and risk factors not on target can further increase this risk.[3,20] Despite these higher risks, older patients are underrepresented in clinical trials, resulting in poor generalisability of interventions in this population.[6] Our study shows that suboptimal risk profiles in older patients can be modified by easily accessible and widely available community-based prevention programmes. Conversely, success rates in the control groups at 12 months were identical for the two age groups. A considerable percentage of older patients in the control group (61%) showed no improvement in LRFs, demonstrating that risk modification in older patients is suboptimal in the context of usual secondary preventive care, but can be facilitated using lifestyle prevention programmes. However, we observed comparable non-improved LRFs at 12 months follow-up in younger patients in both study groups (intervention 41.4% vs. control 44.6%, p=0.47). This suggests that both younger and older patients are in need for other lifestyle interventions. Further research is needed to evaluate how secondary preventive care could be customised in this population as younger patients will commonly have many years of being at increased risk of subsequent events. The weight reduction component was the most effective intervention in the overall RESPONSE-2 trial.[8] In our age-specific analysis, older patients in the intervention group were more successful in weight reduction than younger patients. This might be explained by the higher attendance rate of older patients to the weight reduction programme. Our findings are in line with previous reports that identified older age as an important determinant for dietary adherence in lifestyle modification programmes.[21,22] Although long-term effects of weight reduction on mortality in older adults remain to be established, weight loss has shown to be associated with increased functional independence and higher quality of life.[23,24] both important outcomes for older patients.[4] However, caution is required in older patients with unintended weight loss as it can be a sign of underlying pathology or deconditioning.[25,26]

Previous research has shown that older patients are more successful in smoking cessation if they have recently been hospitalised for an ACS or

revascularisation,[27] have previously experienced multiple cardiac events or procedures[28] or associate health-related complaints with smoking.[29,30] This is in line with our findings, as we found more successful quitters among the older patients in the intervention group as compared with younger patients, and older patients more frequently had a history of CVD and more comorbidities. Interestingly, only 7/29 (24.1%) of the eligible older patients in the intervention group attended the smoking cessation programme (Appendix table S1). Presumably, the longer duration of smoking in patients at higher age contributes to the difficulties in quitting. We have previously shown that patients who quit smoking immediately during or directly after hospital admission are more successful in long-term smoking abstinence.[14,31] Therefore, healthcare providers should use the opportunity of hospitalisation to discuss smoking cessation with patients.

In the RESPONSE-2 trial, the attendance rates to the physical activity and smoking cessation programmes were comparable between older and younger patients, except for the weight reduction programme, which was more frequently visited by older patients. Retirement has been shown to be associated with successful lifestyle modification, presumably because retired adults have more time to implement lifestyle changes in their daily life.[32] In addition, the nurse-coordinated lifestyle programmes in the RESPONSE-2 trial were community-based and easily accessible, potentially removing barriers which normally might have contributed to non-participation.

Strengths and limitations

There are several strengths to our study. First, we examined the effect of a large multicentre randomised trial on lifestyle modification in older patients. Second, the community-based lifestyle interventions were uniformly offered in their existing format which facilitates implementation in daily practice for older as well as for younger patients. Third, all lifestyle outcomes were objectively measured.

Some aspects our study warrant consideration. First, our study population included a relatively healthy group of older patients. Patients were eligible if they were able to visit the outpatient clinic and lifestyle programmes and had little no anxiety or depression disorders (HADS ≤14). Therefore, our findings cannot readily be extrapolated to older and sicker patients with multimorbid conditions and a high level of frailty. Such patients might benefit more from cardiac rehabilitation programmes or functional interventions rather than lifestyle modification aimed at long-term secondary prevention.

Second, assessing effect modification by age after dichotomising age at 65 years can be attractive from a clinical decision-making perspective. To some extent the cut-off is arbitrary, as other cut-offs may also be considered. The current cut-off of 65 years was based on the current European guidelines that

still use 65 years as a cut-off point for older patients[3] in combination with the limited sample of patients ≥70 years in our study. However, a dichotomised cut-off point can be problematic as it entails some statistical inefficiency. In addition, it is biologically implausible that a sudden change in effect exists at the age of 65 years. Therefore, to supplement our main analysis we performed extensive parametric and non-parametric analyses using age as a continuous variable, which supported our finding that the treatment effect was at least of the same magnitude in older as in younger patients.

Conclusion

Despite the higher prevalence of risk factors and comorbidities, nurse-coordinated referral to a community-based lifestyle intervention appears to be at least as successful in improving lifestyle in older as in younger patients. These results suggest that age alone should not be a reason to withhold lifestyle interventions in older patients with CAD.

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Appendix

Table S1. Attendance and intensity of followed lifestyle programmes

	Age ≥65 years (n=99)	Age <65 years (n=261)	P value
Followed 0 programmes	19 (19.2)	36 (13.8)	0.25
Followed 1 programme	50 (50.5)	124 (47.5)	0.64
Physical activity	26 (52.0)	60 (48.4)	
Weight reduction	21 (42.0)	44 (35.5)	
Smoking cessation	3 (6.0)	20 (16.1)	
Followed 2 programmes	29 (29.3)	92 (35.2)	0.32
Physical activity and weight reduction	26 (89.7)	78 (84.8)	
Physical activity and smoking cessation	3 (10.3)	8 (8.7)	
Weight reduction and smoking cessation	0 (0.0)	6 (6.5)	
Followed 3 programmes	1 (1.0)	9 (3.4)	0.30
Intensity Direct Life	56 (56.6)	155 (59.4)	
12 weeks (completed)	49 (87.5)	127 (81.9)	0.41
7 - 11 weeks	1 (1.8)	13 (8.4)	
<7 weeks	4 (7.1)	10 (6.5)	
Only assessment	2 (3.6)	5 (3.2)	
Intensity Weight Watchers (in sessions)	47 (47.4)	136 (52.1)	
Median no. of sessions [IQR]	30 [12-40]	10 [2-20]	<0.001
> 30	23 (48.9)	19 (14.0)	
20-30	6 (12.8)	14 (10.3)	
11-20	7 (14.9)	26 (19.1)	
3-10	7 (14.9)	39 (28.7)	
1-2	4 (8.5)	33 (24.3)	
0	0 (0.0)	5 (3.7)	

Table S1. *Continued*

	Age ≥65 years (n=99)	Age <65 years (n=261)	P value
Intensity LuchtSignaal	7 (7.1)	43 (16.5)	
Completed	5 (71.4)	29 (67.4)	0.96
Half of the sessions (3-4 sessions)	1 (14.3)	8 (18.6)	
Less than half of the sessions (<3 sessions)	1 (14.3)	6 (14.0)	

Values are n/N (%)

Legend for figures S1-S5

The panel shows how the treatment effect, that is, the difference between (the natural logarithms of the) odds ratios, varies as age increases, for each of the five outcomes. The top graphs, for each outcome, show the results of the non-parametric subgroup treatment effect pattern plot (STEPP, tail method) approach.[1] The straight middle graphs show the results of linear models,[2] while the bottom graphs show fractional polynomial-2 models with intermediate flexibility (flex3) [flex option in Stata's user-written mfpi command].[3] The p-values below each graph are for the interaction of treatment with age. As always, p-values should not be interpreted too rigidly, and these p-values are no exception. We interpret these graphs as strong evidence of a stronger treatment effect with increasing age for body mass index (BMI); moderate to weak evidence for overall success and unchanged lifestyle-related risk factors; and no evidence for a different treatment effect at different ages for smoking and exercise. Grey areas are 95% confidence intervals. All graphs were based on data from 711 patients. Models were not adjusted for confounders.

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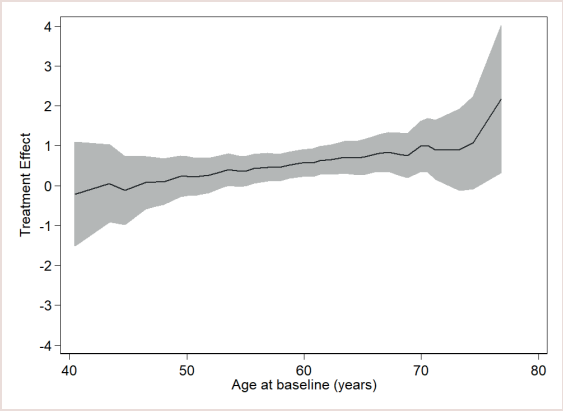
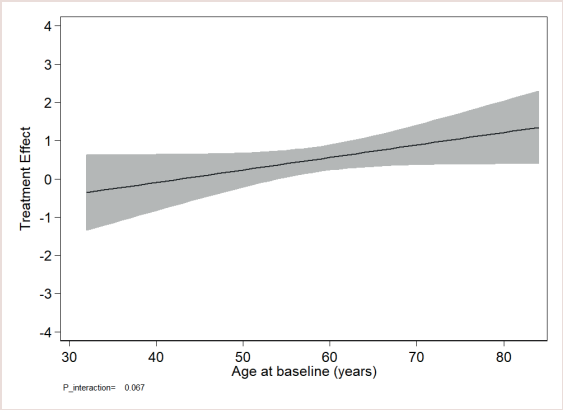




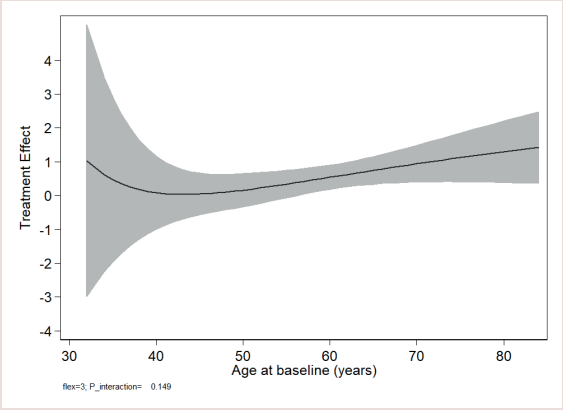
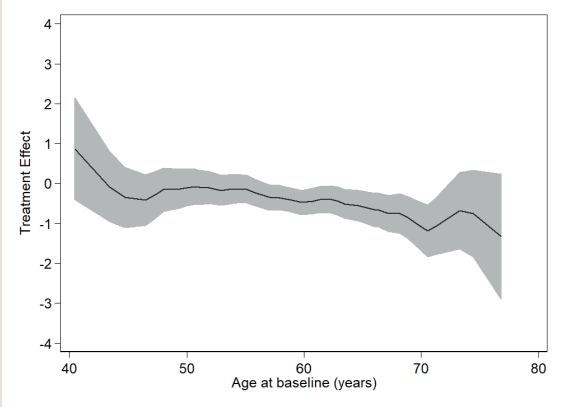
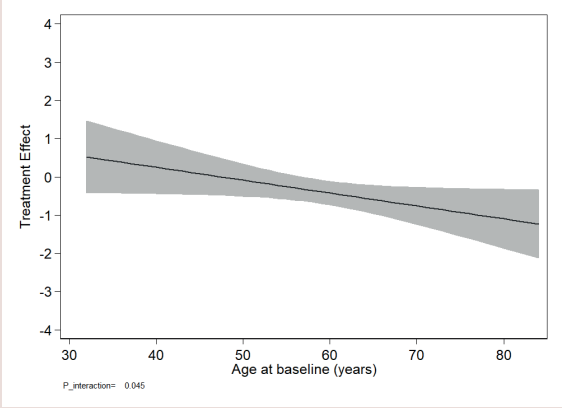


Figure S1. Treatment effect by age as a continuous variable for success on lifestyle-related risk factors





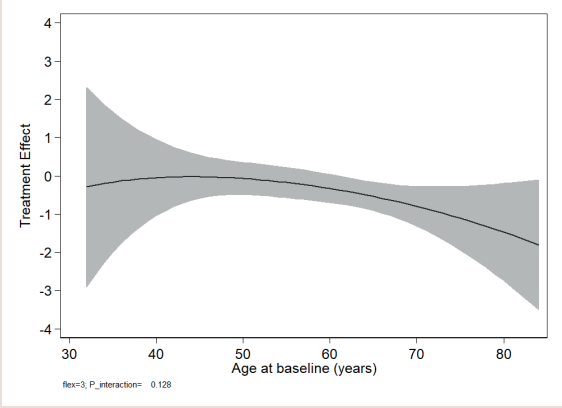
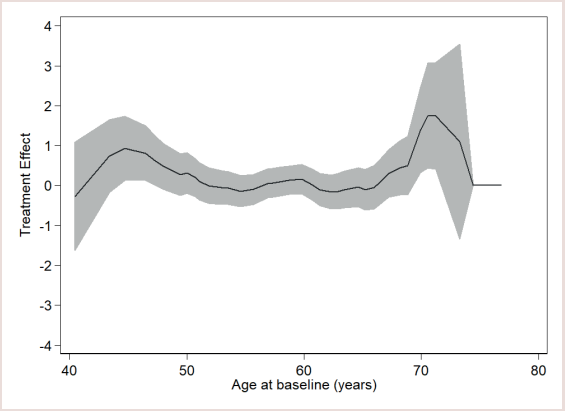
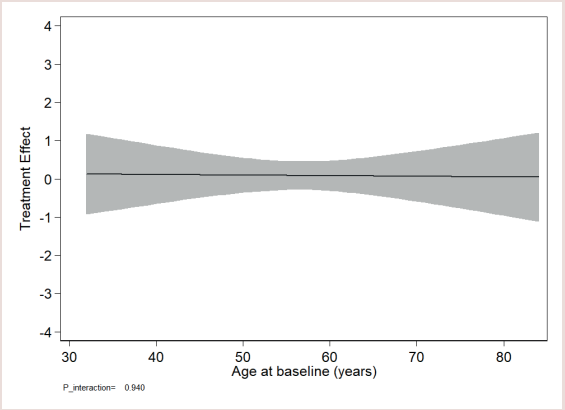


Figure S2. Treatment effect by age as a continuous variable for non-improved lifestyle-related risk factors





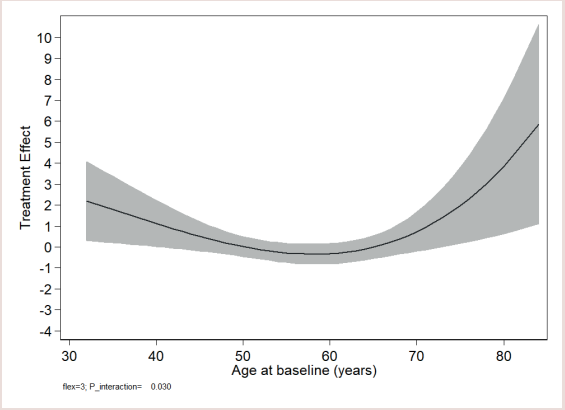
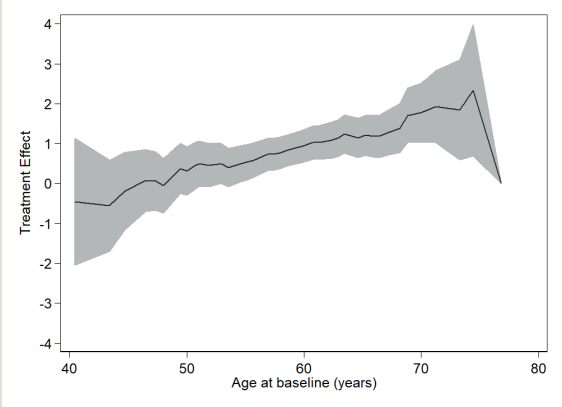
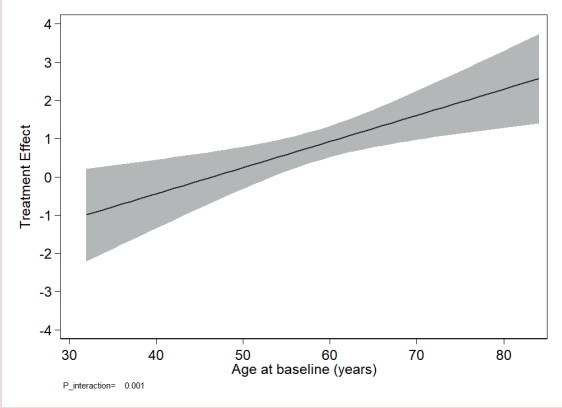


Figure S3. Treatment effect by age as a continuous variable for smoking cessation





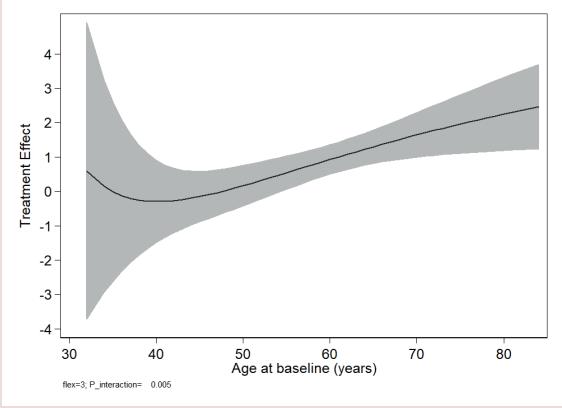
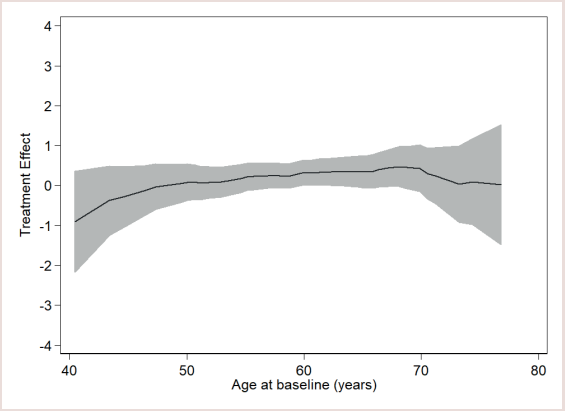
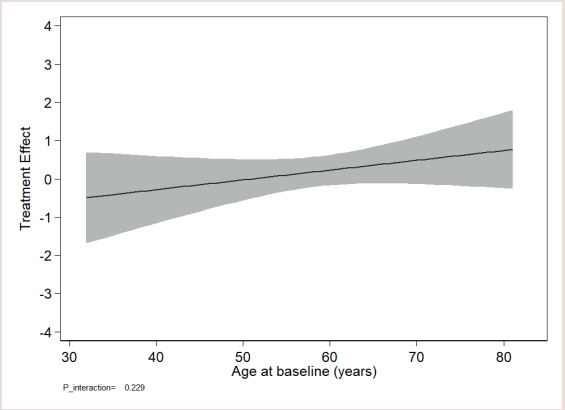


Figure S4. Treatment effect by age as a continuous variable for weight loss





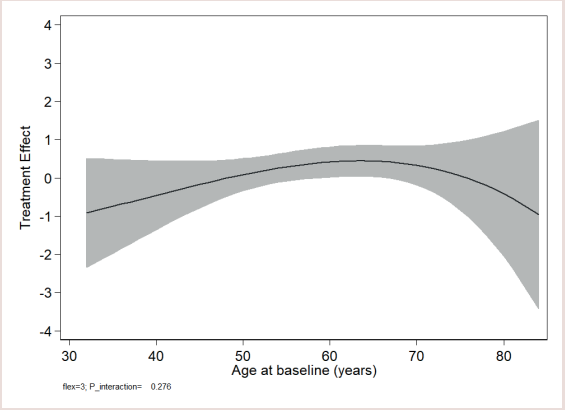


Figure S5. Treatment effect by age as a continuous variable for physical activity

Chapter

6

Older patients' perspectives toward lifestyle-related secondary cardiovascular prevention after a hospital admission – a qualitative study

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Abstract

Background: lifestyle-related secondary prevention reduces cardiac events and is recommended irrespective of age. However, motivation may be influenced by age and disease progression.

Objective: to explore older cardiac patients' perspectives toward lifestyle-related secondary prevention after a hospital admission.

Methods: a generic qualitative design was used. Semi-structured interviews were performed with cardiac patients ≥ 70 years within 3 months after a hospital admission. The interview guide was based on the Attitude, Social influence and self-Efficacy (ASE) model. All interviews were analysed using thematic analysis.

Results: eight themes emerged which were linked to the determinants of the ASE-model. The 3 themes (i) Perspectives are determined by general health and habits, (ii) feeling the threat as a motivator, and (iii) balancing between health benefits and quality of life (QoL), were linked to attitude. Regarding *social influence*, the themes (iv) feeling both encouraged and hindered by family members, and (v) the healthcare professional says so, were identified. For the *self-efficacy* determinant, (vi) experiences from previous lifestyle changes, (vii) integrating advice in daily life and (viii) feeling limited by functional impairments, emerged as themes.

Conclusion: most older cardiac patients made no lifestyle modifications after the last hospital admission and balanced possible benefits against their QoL. Functional impairments frequently limit implementation, in particular of physical activity. Patients' preferences and patient-centred outcomes focusing on QoL and functional independence may be the starting point when healthcare professionals discuss lifestyle modification in older patients. The involvement of family members may help patients to integrate lifestyle-related secondary prevention in daily life.

Introduction

Due to an aging population, the incidence and prevalence of cardiac disease in older adults is rising.[1,2] Lifestyle-related risk factors (LRFs) such as physical inactivity, overweight and smoking are associated with the development of cardiac events.[3-5] Interventions to reduce these LRFs have proven to be effective in the secondary prevention of these events.[3,6]

Lifestyle-related secondary prevention in older patients is associated with benefits in functional status, cardiovascular risk and mortality.[3,6-9] However, the evidence is less conclusive when compared with younger patients as older patients are often excluded from clinical trials. This limits the generalisability of guideline recommendations to this population.[3,10] Furthermore, guidelines mainly focus on disease-specific outcomes such as the prevention of recurrent cardiovascular events and mortality,[3] whereas the treatment goals in older patients include more patient-centred outcomes such as symptom relief, and the prevention of disease deterioration and readmissions.[11,12] In addition, lifestyle-related secondary prevention among older adults is often suboptimal due to functional impairment, malnutrition and multimorbidity.[7]

Current guidelines recommend to discuss (lifestyle-related) secondary prevention during hospital admission[3] as the event creates a window of opportunity for lifestyle modification. However, this recommendation may be less applicable toward older, chronic cardiac patients in whom an acute hospital admission may be less unexpected when compared with (younger) patients with a first cardiac event. Subsequently, this may also impact older patients' perspectives toward lifestyle-related secondary prevention.

The aim of this qualitative study was to explore older cardiac patients' perceptions toward lifestyle-related secondary prevention after a hospital admission. We explored their perspectives using the Attitude, Social influence and self-Efficacy (ASE) model.[13,14] This is a Dutch theoretical framework that contributed to an in-depth understanding of the underlying factors that explain older cardiac patients' intention and actual behaviour in lifestyle-related secondary prevention.

Methods

Design

We used a generic qualitative approach[15] to study the perspectives of older cardiac patients toward lifestyle-related secondary prevention. COREQ-guidelines have been used for transparency reporting.[16]

Participants

Participants were cardiac patients ≥ 70 years who participated in the Cardiac Care Bridge transitional care programme (CCB-programme).[17] This was a Dutch multicentre randomised controlled trial (RCT, N=306) between June 2017 and March 2019 on nurse-coordinated transitional care that aimed to reduce hospital readmission and mortality within 6 months by combining case management, disease management and home-based cardiac rehabilitation. Details of this study have been published.[17] Participants were recruited from the control group of the RCT and received care as usual. They were eligible for this qualitative study if they had a cardiac hospital admission in the past 3 months and were living at home. Participants were purposively selected by one of the researchers (PJ or SP) to provide maximum variation in age and gender as much as possible and were subsequently invited by telephone to participate. Recruitment stopped when no new codes and themes emerged from the data and the research question could be answered.[18]

Data collection

The interviews were conducted between January and June 2019 at participants' home. The interviews were performed by two investigators (PJ or SP) who followed training in qualitative research. Both were interested in disease management for older cardiac patients. PJ and SP have a bachelor's degree in nursing. PJ also has a master's degree in health sciences. SP followed a master's programme in nursing sciences during the time of the interviews and worked as a community nurse. Both researchers did not have prior relations with the participants.

A semi-structured interview guide was developed using the ASE-model (Appendix A1).[13,14] At the start of the interview, we asked participants if they knew which LRFs for heart disease were currently relevant to their condition. Participants' answers were the starting point of the interview. Data collection and analysis of the interviews were performed iteratively, which meant that the researchers moved back and forth between sampling, data collection and analysis. The interview guide was adjusted during the data collection phase based on new findings in order to create an in-depth insight on the perspectives of participants. The interviews were audio recorded fully and field notes were made during and after the interviews. Information regarding disease characteristics and LRFs was available from previously collected data for the RCT during hospitalisation (Table 1).

Data analysis

Two researchers (PJ and SP) were involved in the data analysis. Data were analysed by the assumption that lifestyle-related secondary prevention in older

patients was influenced by their disease history, presence of geriatric conditions, experienced symptoms and prevention of deterioration and readmission.[7,11,12,15]

The six phases of thematic analysis according to Braun and Clarke[19] were used to analyse the data. First, all interviews were transcribed verbatim. PJ and SP familiarised themselves with the data by re-reading the transcripts (phase 1). Then, both researchers independently coded the first five transcripts using open coding. These initial codes were compared and discussed until consensus was reached. The remaining interviews were coded by one researcher (SP) and discussed with PJ (phase 2).The initial codes were then sorted in the ASE-model. We subsequently searched for themes within these three components (phase 3). All themes were reviewed and restructured and the definitive themes were discussed with the research team until agreement was reached (phases 4 and 5). Subsequently, corresponding quotes were selected, the research question was answered, and the findings were compared with the literature (phase 6).

Ethical issues

The Medical Research Ethics Committee of the Amsterdam University Medical Centres approved this study (Reference number W_15_299 # 15.0354). Prior to the interview, participants received oral and written information and informed consent was obtained.

Results

In total, 13 interviews were performed. The mean age was 80.0 years (± 6.4) and 11 of 13 (85%) of them were male (Table 1). In total, 10 of 13 (77%) of the participants were admitted for heart failure (HF) and 3 of 13 (23%) were admitted for acute myocardial infarction (AMI). During six interviews (46%), a spouse was present. The mean duration of the interviews was 45 min (range 20-85 min). The ASE-model resulted in 8 themes that represented older cardiac patients' perspectives on lifestyle-related secondary prevention after a hospital admission (Table 2).

Attitude

Perspectives are determined by general health and habits

Most participants had been diagnosed with cardiac disease for years (median: 5 years, interquartile range [3–18]). None mentioned LRFs as possible cause, but some believed that their age or familial risk factors had contributed to their disease:

Table 1. Participant characteristics

Participant	Age	Sex	Ethnicity	Primary cardiac diagnosis	Cardiac disease history in years	Living together	Educational level
P01	77	M	Dutch	HF	5	Yes	Primary school or less
P02	72	M	Dutch	HF	24	Yes	Secondary education
P03	73	M	Dutch	HF	1	No	College or university
P04	81	M	Dutch	AMI	5	Yes	Primary school or less
P05	74	M	Dutch	AMI	0	Yes	College or university
P06	89	M	Dutch	HF	3	Yes	College or university
P07	88	M	Dutch	HF	42	Yes	College or university
P08	87	M	Dutch	HF	0	Yes	Primary school or less
P09	87	M	Surinamese	HF	4	No	Primary school or less
P10	73	M	Dutch	HF	27	Yes	College or university
P11	81	F	Dutch	AMI	16	No	College or university
P12	83	F	Dutch	HF	10	No	Primary school or less
P13	75	M	Dutch	HF	18	Yes	Secondary education

Abbreviations: P: patient, M: men, F: female, HF: heart failure, AMI: acute myocardial infarction.

Charlson comorbidity index [a]	KATZ-6 [b]	Fall in past 6 months	(At risk of) malnutrition [c]	Body Mass Index	Diet	Smoking status	Fluid restriction
1	0	No	Yes	22.9	Salt-restricted, high-calorie	Former smoker	No
2	0	No	No	23.8	Salt-restricted	Former smoker	No
2	0	No	Yes	N/A	Salt-restricted, high-calorie	Former smoker	Yes
2	0	Yes	No	N/A	No	Former smoker	No
2	0	No	No	N/A	Carbohydrate-restricted	Never smoked	No
1	0	Yes	No	26.4	Salt-restricted	Former smoker	Yes
4	2	No	No	26.2	Salt-and carbohydrate-restricted	Former smoker	No
1	0	Yes	No	N/A	No	Never smoked	No
3	0	Yes	No	18.0	Salt- and carbohydrate-restricted	Current smoker	Yes
4	0	No	No	21.8	Salt-restricted	Former smoker	No
3	0	Yes	Yes	N/A	Salt- and cholesterol-restricted	Never smoked	No
1	0	No	Yes	23.4	Salt- and cholesterol-restricted, high-calorie	Never smoked	Yes
3	0	No	No	32.4	No	Former smoker	No

N/A: Not applicable
[a] Charlson Comorbidity Index[20]: a weighted index to classify comorbid conditions based on their 1-year mortality prognosis. [b] KATZ[21]: Index of Independence in Activities of Daily Living (KATZ-6): Scores range from zero to six points with higher scores indicating more dependence. [c] SNAQ[22]: Short Nutritional Assessment Questionnaire to assess (the risk of) malnutrition.

Table 2. Identified themes within the ASE-model

	Themes
Attitude	Perspectives are determined by general health and habits
	Feeling the threat as a motivator
	Balancing between health benefits and QoL
Social influence	Feeling both encouraged and hindered by family members
	The healthcare professional says so
Self-efficacy	Experiences from previous lifestyle changes
	Integrating advice in daily life
	Feeling limited by functional impairments

'Well, you are getting older and that is how it goes. Things are going through your mind, like 'does it run in the family?' I asked my brothers and sisters and they told me that family members on my mother's side have died because of heart failure.' (P3, Male, 73, HF)

Most participants reported that their attitude toward their lifestyle had not changed since the last admission. They mentioned that they have made diet modifications after a previous diagnosis, e.g. diabetes mellitus or hypertension which resulted in a low carbohydrate or salt-restricted diet. Their attitude was thus formed by their general health and not specifically by their current cardiac condition:

'Yes, because otherwise my kidneys will be struggling. It is no fun… it's not as good as before [salt-restricted diet]. But you got to do it all just for yourself. Or you will die.' (P10, Male, 73, HF)

'We almost always ate without salt, so not much has changed [since the last admission]. We started with salt-free food when I was diagnosed with hypertension forty years ago. I am used to it.' (P6, Male, 89, HF)

In some participants, it was necessary to adapt previously made lifestyle modifications because of the presence of new conditions. For example, a malnourished participant understood that she had to increase her calorie intake:

I (interviewer): 'And you told us that before you got into the hospital, you paid a lot of attention to your cholesterol, why did you think that was important?'
R (respondent): 'Blood pressure, just eating fibers, for your intestines. Yeah, I have to let go of that now, because I have to eat whipped cream [laughs].

Eat lots of meat, but I like meat, you know. It's not a matter of appetite.' (P12, Female, 83, HF)

Participants perceived physical activity as important to prevent weight gain or because they just felt better by being active. Several participants chose the stairs instead of the elevator or practiced regularly on an exercise bike at home:

'You could say I'm like really addicted to it [cycling]. (…) And at the same time I watch TV. And when something good is on, I forget the time. Then I just keep on cycling. And it feels good.' (P08, Male, 87, HF)

Feeling the threat as a motivator

The perceived threat was formed by participants' experiences during hospitalisation and symptoms post-discharge. This affected their opinion about lifestyle modification. Participants who experienced symptoms felt more urgency to adhere to lifestyle-related regimes. One participant was admitted because of decompensated HF and experienced severe dyspnea. Adherence to a salt-restricted diet was important to her as she felt that this might contribute to the prevention of a new episode:

'The misery with the dyspnea.. That was so bad, especially in the last period [before the admission]. I really had to hold the wall to get from the couch to the kitchen. I never want that feeling again. You cannot completely rule it out, but that is the reason why we are very strict with salt.' (P12, Female, 83, HF)

Participants with a higher perceived threat were more willing to compromise on their quality of life (QoL), if they felt that this might contribute to the prevention of a hospital admission:

'Yes, really unappealing [salt-restricted diet]. It is insipid, tasteless. But I want to make sure that I don't end up in the hospital again. And at the same time I realise that this could be the final stage of my life. And it is much more meagre because of this kind of food.' (P09, Male, 87, HF)

However, some participants were unsure if they were able to prevent a readmission but their attitude toward lifestyle modification was still positive as it helped them to have control over the situation:

'He [cardiologist] said, 'unfortunately we experience that a number of people come back to the hospital with exactly the same symptoms'. Well, I am not sure that it would not happen to me. But I can say that I will do everything I can to prevent it. I will not go back because of my own stupidity.' (P12, Female, 83, HF)

It was observed that the perceived threat of recurrent events was lower in participants without symptoms post-discharge. Furthermore, some participants were anxious during the hospital admission but were still critical about lifestyle advices they received:

> *'During that cardiac catheterization, it really went through my mind that this could be the end. But later I was thinking about the recommended diet. I am not going to fully adjust while I'm already 74. Such as the cholesterol and things like that.' (P05, Male, 74, AMI)*

Balancing between health benefits and QoL

We observed that participants questioned if lifestyle modification would yield any health benefit at their age and some preferred QoL above possible health gains:

> *'Just imagine, I'm totally changing my diet. Healthier, even more fruit and all that (…). What is it going to get me? How many more years will I be given and what's the QoL in those additional years? Well, I don't think that it will be much good to me.' (P05, Male, 74, AMI)*

Participants seemed to have a more negative attitude toward lifestyle-related secondary prevention when the positive effects of these modifications were not perceptible on the short term, as for example in lowering alcohol and fat consumption. In view of their age, they doubted if modification of these LRFs would contribute to their health:

> *'You know, salting things just a bit less. I don't know. But I will be 82 next July. And, I think, if I have to deny myself everything, than I don't want to get that old. But I do want to enjoy my life.' (P11, Female, 81, AMI)*

Some participants also realised that lifestyle modifications could actually contribute to a better QoL. For example, participants' believed that physical activity helped them to remain independent:

> *I: 'And how did you come up with the idea of doing this [walking back and forth through the living room]?'*
> *R: 'Well, use your brains, thinking I want to get better. Or maybe hoping that I could still return to my own home. Being independent.' (P12, Female, 83, HF, temporarily living with her daughter at home)*

Social influence

Feeling both encouraged and hindered by family members

Spouses played an important role in participants' health habits. For example, cohabiting participants reported that they did the groceries and the cooking together. In most cases, spouses joined participants when a salt-restricted diet was imposed. Therefore, diet modifications were easily made and participants felt supported by their spouse. Children also had an important supportive influence on their diet:

> *'When we're eating, I'd say, we will eat fresh vegetables as much as possible and not a lot of meat. These are the things that they [kids] told us. I always used to bring a bowl of yoghurt. Now they say: why don't you put some blue berries in it? So then I do that.' (P04, Male, 81, AMI)*

Family members encouraged participants to be physically active. However, some participants with physical limitations experienced that they were unable to meet the expectations, which sometimes led to frustration:

> *'Then I have to gather the courage [go walking outside]. And I'm honest with you.(…) I'm being told every time [by spouse and kids]. But then I think, yeah whatever, it's OK.(...) It goes in one ear and out the other [laughter]. And I say it every time..You don't feel my body. I would like to [walk], but I can't do it all the time.' (P01, Male, 77, HF)*

Other participants experienced that family members slowed them down in physical activity because they were concerned that the participant went beyond their limits:

> *'My wife too, she's always like: 'She [physical therapist] said, do it 15 times, so why do you do more?' But that is probably my perfectionist nature. One time I would accept it and another time I'd think, woman, what do you know!' (P04, Male, 81, AMI)*

The healthcare professional says so

Participants with chronic heart disease received advice from many healthcare professionals through the years. In general, patients found it important to adhere to these advices.

> *'When I get instructions and do things the wrong way, I will blame myself. I can't go like, I got advice and just put it aside. That isn't right, is it? You'd best do as you're told, otherwise you might as well not have gotten admitted.' (P03, Male, 73, HF)*

However, participants were sometimes critical about the different advices they received, especially when these advices were contradictory or when advices changed over time. As a result, participants were then making their own considerations or where searching for someone who could help to determine what advice they had to follow:

> *I: 'I actually hear you say that of a lot of different healthcare professionals advice you [about diet]. How do you determine your own path in this?'*
> *R: 'Well, by making an appointment with the dietitian. We need some kind of external authority. We have to separate the wheat from the chaff. And how do you determine what is wright? We are getting a little tired of it [all different advices].' (P09, Male, 87, HF)*

Some participants mentioned that the physician took their age into consideration when giving lifestyle advices. This, for example, led to more flexible advice regarding alcohol consumption:

> *I: 'So, what do you think when they say that one glass is better than two, and how is that for your heart?'*
> *R: 'Well, I haven't noticed anything, no changes. But I once talked to one of them cardiologists. He said: you know, you're 90 years old. What's the difference between reaching 100 or 98? And I agree with that.' (P06, Male, 89, HF)*

Self-Efficacy

Experiences from previous lifestyle changes

The majority of participants made lifestyle modifications earlier in life, mostly related to smoking cessation and diet modification. Self-efficacy was based on these attempts. Previous successful experiences gave people the confidence that they were able to maintain these lifestyle modifications:

> *'No, that's no problem at all [to maintain smoking cessation]. If they offer me one, I'll just say no, even at birthday parties.' (P03, Male, 73, HF)*

However, some former smokers also reported several failed cessation attempts and mentioned that the cardiac event (e.g. AMI) was an important life event that gave them the perseverance to finally quit.

Integrating advice in daily life

Participants sometimes perceived struggles on how to incorporate lifestyle advice in their daily life, for example regarding a fluid restriction or a salt-restricted diet. During hospitalisation, participants were supported by healthcare professionals

as their daily intake was registered and low-salt meals were provided. However, participants experienced that they had not developed skills during the admission on how to integrate these restrictions in daily life.

> *'That is the hard part [restricting fluids]. How do you schedule that? And they say you must also count the yoghurt and pudding. (…) I found it hard to make sure to stay below that level. Measuring glasses and things like that.' (P03, Male, 73, HF)*

The internet was frequently mentioned as a source of additional information and tips on how to integrate advices in their daily life as this patient with a fluid restriction stated:

> *'But I surf on the internet a lot, looking for advice (...). If you're really thirsty, then you think, don't cross the limit, because you got to save this amount for tonight.. And then I take one of the candy balls.' (P12, Female, 83, HF)*

Feeling limited by functional impairments

Participants experienced many functional impairments or comorbidities, e.g., fatigue, balance problems, fear of falling, and intermitted claudication which hampered their physical activity. In many participants, lower levels of self-efficacy were observed due to these symptoms and comorbidities:

> *'I should exercise more. I should go outdoors more. But I was really tired for weeks. And I've been home for nearly two months now. I took the grandchildren out once, but I felt very insecure [because of muscle weakness in the legs].' (P12, Female, 83 HF)*

Only one participant reported that he followed a cardiac rehabilitation programme after the last admission. He mentioned that it helped him to safely explore his physical limits. However, many patients experienced that they lost confidence in their body and were insecure if their heart could handle physical activity:

> *'And I did become anxious, like: am I forcing myself? (…) I find that hard to get over and same with exercising, maybe. It took a while before I had the courage to go out again.' (P09, Male, 87, HF)*

Despite these functional impairments, participants' daily routine stimulated them to stay active post-discharge. For example, being able to do groceries contributed to increased confidence in their abilities which stimulated them to go outside.

Discussion

This qualitative study aimed to explore older cardiac patients' perceptions toward lifestyle-related secondary prevention after a hospital admission.

Related to the ASE-component *attitude*, participants' perspectives regarding lifestyle were determined by their general health and habits. The last cardiac hospital admission did therefore not lead to new attitudes in most participants. Participants who experienced a higher health threat, for example because of symptoms post-discharge, felt more urgency to adhere to lifestyle-recommended regimes in the hope to prevent complications or a readmission. This is in line with health behavioural change theories, which describe that someone's perceived susceptibility to a threat, i.e. risk perception, is an important motivator for behavioural change.[23]

Participants often questioned if lifestyle modifications at their age would yield any health benefit and mentioned that they preferred their QoL above some lifestyle recommendations. Although the current guidelines mainly focus on the prevention of recurrent cardiovascular events and mortality,[3] the time-to-benefit of some lifestyle changes might indeed exceed the life expectancy in older patients.[24] Therefore, healthcare professionals need to explore older patients' preferences and consider if lifestyle modifications would yield any advantages. This might lead to the shared decision that no new changes would be implemented in daily life. However, regardless of life expectancy, some lifestyle factors such as physical activity and weight management, have shown to improve QoL and reduce the risk of functional loss in older patients.[6,7,25] These more short-term and patient-centred outcomes are important for older patients and may be a starting point when healthcare professionals discuss lifestyle modifications.

The ASE-component *social influence* indicated that participants felt encouraged by family members, especially in relation to their diet. However, mixed results were found regarding to physical activity. Although participants experienced that their children were mostly supportive, they sometimes experienced tensions when they were unable to meet these expectations. Furthermore, some tensions were caused by overconcerned spouses who restricted participants in physical activity. Previous studies showed the importance of social support from family members and friends in lifestyle modification and maintenance.[26-28] Therefore, healthcare professionals may consider involving the social system when discussing lifestyle modification with older patients. Patients' needs and barriers in lifestyle modification should also be discussed to reduce (the risk of) social pressure.

In relation to the last component of the ASE-model, *self-efficacy*, previous successes in lifestyle modifications (e.g. regarding diet or smoking cessation)

contributed to higher levels of self-efficacy for new adjustments. However, participants also experienced barriers that reduced their self-efficacy. Some participants received new treatment regimens during hospitalisation, e.g. a fluid restriction, but had difficulties to integrate these advices at home. In accordance with Nicolai et al.[28], participants also experienced barriers such as comorbidities, physical impairments and geriatric conditions (e.g. fatigue and fear of falling) that lowered their self-efficacy and limited them in their daily life. This suggests that older cardiac patients might need more guidance post-discharge to help them continue prescribed regimes at home. For example, they may benefit from interventions that improve continuity of care, such as transitional care interventions.[29] Furthermore, functional support post-discharge, e.g. by (home-based) physical therapy, may contribute to improve patients' functional status.[30]

Strengths and limitations

This qualitative study provides data on older cardiac patients' perceptions toward lifestyle-related secondary prevention. Evidence in this population is limited and their perspectives are even less examined. By use of the ASE-model, we were able to identify important themes for older cardiac patients. We explored their perspectives toward lifestyle-related secondary prevention and our findings may help to improve care in this population.

Several limitations should be considered. First, a low number of women participated in this study. Gender differences are associated with other LRFs, other manifestations of cardiovascular disease and other treatments.[31] However, the outcomes in our study might be generalisable as, regardless of gender, patient-centred outcomes as QoL, symptom relief and functional independence are important to all older patients.[11] Second, our interview guide followed the LRFs that were mentioned by participants. We did not discuss motivation toward non-reported LRFs and it is possible that they did not consider or recognise them as important. Although this may limit our results, participants' perspectives were leading during the interview which resulted in minimal direction of the interview by the researchers. Finally, we did not select participants on the presence of one or more LRFs. This has led to a study population that in general reported that they already had adopted a healthy lifestyle. Although we aimed to have a non-judgmental attitude during the interviews and participants were told that their answers were confidential, socially desirable answers could not be fully excluded and may have influenced their answers.

Conclusion

Most older cardiac patients made no lifestyle modifications after the last hospital admission and balanced possible health benefits against their QoL. Functional impairments frequently limit implementation, in particular of physical activity.

Patients' preferences and patient-centred outcomes focusing on QoL and functional independence may be the starting point when healthcare professionals discuss lifestyle in older patients. The involvement of family members may help patients to integrate lifestyle-related secondary prevention in daily life.

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Appendix 1: Interview guide

Introductory questions

1. You were recently admitted to the Cardiology ward because of (…).
   Can you tell me what happened please?
   a. How serious did you think your reason for hospital admission was?
2. What could have made you suffer from (…)/being diagnosed with (...)?
   a. Can you tell me how you feel about being diagnosed with (…)?
   b. Do you worry about suffering from (…)?
3. How likely do you think it is that what happened to you (….) can happen again?
4. Do you think that there are habits in your lifestyle (now or previously) that may have affected the development of (…)?
   a. If so, what effect do you think this has on the development of (…)?
   b. If not, how do you think that this (…) has happened?
5. How much effort do you spend on working on your health?
   Do you see this as important?

If no lifestyle factor is mentioned:
You indicated *(in question 4)* that you do not really think working on your health as being important.

- Can you tell me a bit more about that please?
- How do you try to work on your health?

Probing (after introductory questions)

Okay, you think that these lifestyle factors (…) have contributed to the problem. I would like to find out more about that. Is it okay with you if we talk about these things some more now?

6. You answered (in question 2) that you think lifestyle factor (…) may have had something to do with the problem. Is this something that is on your mind?
   a. What are your thoughts about this?
   b. How do you feel about this?

7. Have you ever received information about (…)?
   a. Can you tell me more about this?
   b. What did you think about this information?
   c. Who gave you this information?

8. We now know that it can be quite difficult for people to work on their health

because it is sometimes difficult to chance everyday habits. Do you find it difficult to work on your (...)?

a. Can you tell me more about that?

We just talked about lifestyle factor (...). You said that (...) is important to you.
We know that the environment can be important in maintaining or changing everyday living habits. Sometimes other people are very helpful and supportive while in other cases it may well be that other people can make the changes more difficult.

9. How involved are the people around you (for instance, your partner, children or others nearby) with you when it comes to (…)?
    a. Can you tell me more about that?

10. Do you feel supported by the people around you when it comes to (…)?
    a. Can you tell me more about that? How do you feel about this? What makes you aware of this?
    b. How does this affect you (…)?

11. Are there other people around you also who do not really support you when it comes to (…)? If so:
    a. Can you explain this more? What makes you aware of this?
    b. How does this affect you (…)?
    c. How do you cope with this?

12. We just talked about what you would like to work on (or what you might already be working on). We know that some people find it very difficult to get started on this.
    a. How is that for you?
        i. Positive: apart from the factors mentioned earlier, are there any other factors that help you do well?
        ii. Negative: apart from the factors mentioned earlier, are there any other factors that make (…) more difficult?

13. Do you think you are able to make lifestyle changes related to (…)?

If yes:

a. How would you do this? Or, how have you done this?
b. What (else) do you need?

If no:

c. Why do you think that you are unable to make lifestyle changes related to (…)?
d. What would you need/what would help you to be able to do (…)?

14. Have you made previous efforts in relation to (…)?
    If yes:
    a. Can you tell me more about these?
    b. What made them work/not work at that time?
    c. Can you mention specific times when they did/did not work?
    d. Do you know why you relapsed with (…)?
    If no: go to question 15.

15. You just mentioned in (…) that you feel able to make lifestyle changes related to (…) and that you will start (…) to make them.
    a. How does that look to you now?
    b. What timeframe do you have for your plan?

16. How much effect do you think that (…) has on your health?
    a. What expectations do you have about this?
    b. Are there any other advantages to you that could play a role?

17. Apart from focusing on (…), are there other things that you do for your health on a daily basis?
    If yes:
    a. Can you tell me more about these?
    → Go back to questions 5-16 about other mentioned lifestyle factor
    If no: go to question 18

18. Are there other changes that you would rather not do anything about?
    a. Can you tell me more about these?
    b. What makes you not want to change these?
    c. Have you thought differently about this in the past?

19. Do you do anything else to prevent ending up in hospital again?
    a. Can you tell me more about these?
    b. What makes you see this as important/not important?

20. Are you taking any medications?
    a. Can you tell me more about these?

21. Are there any medications that you deliberately forget to take at times?
    a. What causes you to do this/not do this?

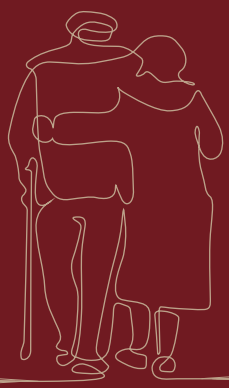
Conclusion

22. Are there any other lifestyle improvements that we have not discussed yet but that you would like to address?

Part

3

Development and evaluation of a transitional care intervention for older cardiac patients



Chapter

7

The Cardiac Care Bridge program: design of a randomized trial of nurse-coordinated transitional care in older hospitalized cardiac patients at high risk of readmission and mortality

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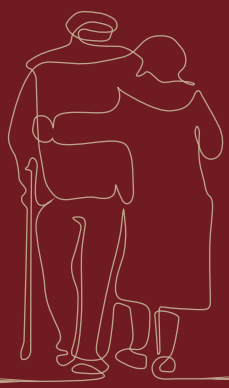

Abstract

Background: After hospitalization for cardiac disease, older patients are at high risk of readmission and death. Although geriatric conditions increase this risk, treatment of older cardiac patients is limited to the management of cardiac diseases. The aim of this study is to investigate if unplanned hospital readmission and mortality can be reduced by the Cardiac Care Bridge transitional care program (CCB program) that integrates case management, disease management and home-based cardiac rehabilitation.

Methods: In a randomized trial on patient level, 500 eligible patients ≥ 70 years and at high risk of readmission and mortality will be enrolled in six hospitals in the Netherlands. Included patients will receive a Comprehensive Geriatric Assessment (CGA) at admission. Randomization with stratified blocks will be used with pre-stratification by study site and cognitive status based on the Mini-Mental State Examination(15-23 vs ≥ 24). Patients enrolled in the intervention group will receive a CGA-based integrated care plan, a face-to-face handover with the community care registered nurse (CCRN) before discharge and four home visits post-discharge. The CCRNs collaborate with physical therapists, who will perform home-based cardiac rehabilitation and with a pharmacist who advices the CCRNs in medication management The control group will receive care as usual.

The primary outcome is the incidence of first all-cause unplanned readmission or mortality within 6 months post-randomization. Secondary outcomes at 3, 6 and 12 months after randomization are physical functioning, functional capacity, depression, anxiety, medication adherence, health-related quality of life, healthcare utilization and care giver burden.

Discussion: This study will provide new knowledge on the effectiveness of the integration of geriatric and cardiac care.

Background

Cardiac disease is the leading cause of hospitalization and mortality.[1] In the population of older hospitalized cardiac patients, 20% are readmitted and 10% die within 1 month post-discharge.[2] In addition to cardiac disease, geriatric conditions such as impaired activities of daily living (ADL) (77%), cognitive impairment (42%) and fall risk (30%) are highly prevalent.[3] The assessment of geriatric conditions is not currently part of routine medical evaluation in cardiology. As a result, these conditions are often unrecognized[4,5] leading to an increased risk of new disabilities, readmission and death.[3,6]

The transition of care in which patients transfer between different settings increases the risk for adverse health outcomes due to inadequate attention to patients' healthcare needs.[7,8] For example, the failure to recognize geriatric conditions in older cardiac patients negatively impacts treatments post-discharge, e.g. because of nonadherence to (pharmacological) treatment in cognitively impaired patients[4] or poor participation in cardiac rehabilitation programs because of disabilities, the high intensity of these programs,[9,10] fatigue[11] and difficulties traveling to and from cardiac rehabilitation centers.[12,13] This is unfortunate since cardiac rehabilitation has been shown to reduce cardiovascular risk factors, readmission and mortality in older cardiac patients.[14]

Adequate guidance during hospitalization, during the transition from hospital to home and in the early post-discharge period may potentially reduce the risk of adverse events. Transitional care is a model that aims to continue care when patients transfer between different care settings, with a focus on patients' needs.[15,16] Recently, the Transitional Care Bridge program resulted in a 25% (HR 0.75, 95% CI 0.56-0.99, P = 0.045) reduction in mortality in acutely hospitalized older patients, by combining a Comprehensive Geriatric Assessment (CGA), an integrated care plan and a transitional care program, including visits during hospitalization and soon after discharge by a community care registered nurse (CCRN).[17] However, with this case-management approach no effects were found on readmission rates and ADL-functioning. We hypothesize that this may be caused by a main focus on case management within the care transition program with a lack of attention for disease management and rehabilitation after discharge.

The RESPONSE study of Jorstad et al.[18] involved a nurse-coordinated outpatient intervention that included guidance on lifestyle factors, biometric risk factors and therapy adherence in patients after an acute coronary syndrome. In this disease management approach, a relative risk reduction of 17.4% (P = 0.021) was found on the Systematic Coronary Risk Evaluation (SCORE), which is an integrated measure to estimate the risk of cardiovascular death in 10 years. In addition, a relative risk reduction of 34.8% (P = 0.023) was found on readmission.

Combining case management, disease management and home-based rehabilitation may have the potential to reduce readmission and mortality. Therefore, we developed the nurse-coordinated Cardiac Care Bridge transitional care program (CCB program) aiming to reduce unplanned hospital readmission and mortality in the first 6 months in comparison to usual care in older hospitalized cardiac patients at high risk of readmission and mortality. In this paper we report on the design of this program.

Methods/Design

This study follows the Standard Protocol Items for Interventional Trials (SPIRIT) checklist.[19] The next paragraphs describe the Cardiac Care Bridge program, the study design and research methods.

Design and setting

A single-blinded multi-center parallel group superiority trial with randomization at patient level will be performed in six hospitals in the Amsterdam region of the Netherlands: 1) Academic Medical Center (AMC), Amsterdam, 2) Amstelland Medical Center, Amstelveen, 3) BovenIJ Medical Center, Amsterdam, 4) Medical Center Slotervaart, Amsterdam, 5) Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam, 6) Tergooi Medical Center, Blaricum. In the transitional and post-clinical phase, five community nursing care organizations will participate: 1) Amstelring, 2) Buurtzorg Nederland, 3) Cordaan Home Care, 4) Evean, 5) Vivium Care Group. In the post-clinical phase, several community based physical therapists (PT) will participate. The recruitment for the study started on June 5, 2017 and will end after the last patient has been followed-up for 12 months, which is expected in December, 2019.

Study population

Potential participants are all cardiac patients 70 years and older, acutely or electively admitted to the departments of cardiology or cardiothoracic surgery and admitted ≥ 48 h. They are eligible for inclusion if they are at high risk of functional decline according to screening instrument for frail elderly of the Dutch Safety Management Program (VMS instrument, Table 1). Four geriatric conditions (ADL, falls, malnutrition and delirium) are part of this screening. Oud et al.[20] also found a positive association between an increase of the number of risk factors with the VMS instrument and risk of death. Heim et al.[21] studied the optimal predictive value of frailty on adverse outcomes (death, functional decline and high healthcare use) with the VMS instrument. The strongest predictive value was found by a positive score on ≥ 3 risk factors in patients aged 70-79

and a positive score on ≥ 1 risk factor in patients aged ≥ 80 years. However, the screening of malnutrition may not be sensitive in cardiac patients because of an increased risk of weight gain due to decompensated heart failure.[22] Therefore, we considered patients aged 70-79 years with ≥ 2 risk factors and patients aged ≥ 80 years with ≥ 1 risk factor eligible for inclusion. In addition, patients at high risk of readmission and mortality are eligible to participate if they have had an unplanned hospital admission in the previous 6 months. This risk factor is associated with an increased risk of further readmissions and mortality.[23,24]

Exclusion criteria are the following: 1) severe cognitive impairment, assessed with the Mini-Mental State Examination (MMSE < 15), 2) congenital heart disease, 3) terminal illness, defined as a life expectancy of less than 3 months as estimated by the treating physician, 4) transfer from or a planned discharge to a nursing home, 5) planned discharge to another department or another hospital not participating in this study, 6) inability to communicate in Dutch, 7) delirium as confirmed by patient's physician and not resolved within 4 days after hospital admission.

Table 1. Screening tool for vulnerable elderly of the Dutch Safety Management Program

Risk domain	Instrument	Questions	Cut-off	Score*
Fall risk	Single question	Did you fall in the last 6 months?	yes	1
Malnutrition	SNAQ[25]	Assessing whether the patient: 1) lost weight unintentionally in the last 3-6 months and/or 2) experiences a decreased appetite and 3) used supplemental drinks or tube feeding	Question 1 = yes or Question 2 + 3 = yes	1
Delirium	Single questions	Assessing whether: 1) the patient has cognitive impairment; 2) the patient needed help with self-care in the last 24 h; 3) the patient has previously undergone a delirium	≥ 1 point	1
ADL-functioning	KATZ-6[26]	Assessing whether the patient needs help with: 1) bathing, 2) dressing, 3) toileting, 4) transferring from bed to a chair, 5) eating, and 6) whether the patient uses incontinence material	≥ 2 points	1
Total score				0-4

Abbreviations: SNAQ: Short Nutritional Assessment Questionnaire, ADL-functioning: Activities of Daily Living-functioning, KATZ-6: Modified KATZ-6 index.
*Patients are at high risk of functional decline if aged 70-79 years and score ≥ 2 or aged ≥ 80 years and score ≥ 1.

Randomization and blinding

After patients are screened for eligibility and have provided informed consent to a cardiac research nurse (CRN), the baseline assessment will be performed. After the baseline assessment patients will be randomized to the intervention or control group. Stratified block randomization (1:1) will be used with pre-stratification by study site and cognitive status based on the MMSE (15-23 vs ≥ 24). To ensure allocation concealment, a web-based data management program (Research Manager, https://my-researchmanager.com/en/home-2/)[27] and random permuted blocks of variable sizes will be used.

Group assignment will be blinded to patients. They will be informed that the study aim is to study different forms of post-discharge care and will receive only general information about the study protocol according to the postponed informed consent procedure of Boter et al.[28] Patients will be blinded to the aim of the intervention to prevent a potential Hawthorne effect.[29,30] At the end of follow-up, patients (or their caregivers) will be fully informed about the content of the study intervention and the allocated treatment they received. Healthcare practitioners who execute the intervention cannot be blinded. Outcome assessments will be performed by research nurses who are blinded to the allocated treatment. Statistical analyses will be performed according to a predefined statistical analysis plan (see Statistical Analysis paragraph) by investigators blinded to group assignment.

Due to the minimal expected side effects related to the intervention of the CCB care program a data monitoring committee is not mandatory for this trial.

Hospital care for all included patients

Table 2 shows the time frame and components of the CCB program in the intervention and control groups. All included patients will receive a CGA within 72 h after admission by a CRN, which will also serve as the baseline study measurement (Table 3). The CGA identifies health issues in the somatic, psychological, social and functional domains, including problems related to polypharmacy, malnutrition, fall risk, delirium, depression and quality of life. Cardiovascular risk factors (e.g. body mass index, smoking, alcohol use and physical performance) will also be assessed. Following assessment, consenting patients will be randomized to the intervention or control group.

Table 2. Time frame and components of the Cardiac Care Bridge program and the control group

Time Frame	Intervention component	Baseline – outcome measures	Professionals involved	Intervention	Control
Clinical phase					
≤ 72 h after hospital admission	CGA*	Baseline	CRN†	X	X
≤ 72 h after hospital admission	Integrated care plan		CRN†	X	
During hospital stay	Geriatric team consultation in case of ≥ 5 identified health issues or ≥ 1psychological issue		CRN†, CNS‡, geriatrician	X	
Discharge phase					
Before hospital discharge	In-person handover of the CGA*, integrated care plan and medical treatment plan		CRN†, CCRN§	X	
Before hospital discharge	Visit of CCRN§ to participant		CCRN§	X	
At discharge	Medical discharge letter		Cardiologist, GP‖, CCRN§	X	X
Post-clinical phase					
≤ 3 days after hospital discharge	Home visit 1. Medication reconciliation and integrated care plan		CCRN§	X	
≤ 1 week	Home visit 2. Intake home based cardiac rehabilitation and integrated care plan		CCRN§, PT¶	X	
Week 1	Two home-based cardiac rehabilitation sessions		PT¶	X	
Week 2	Two home-based cardiac rehabilitation sessions		PT¶	X	

Table 2. *Continued*

Week 3	Home visit 3. lifestyle promotion and self-management Two home-based cardiac rehabilitation sessions		CCRN[§] PT[¶]	X X	
Week 4	Two home-based cardiac rehabilitation sessions		PT[¶]	X	
Week 5	Two home-based cardiac rehabilitation sessions		PT[¶]	X	
Week 6	Home visit 4. Evaluation of integrated care plan and home-based cardiac rehabilitation Two home-based cardiac rehabilitation sessions		CCRN[§] PT[¶]	X X	
≤ 12 weeks	Home visit 5. If indicated by the CCRN[b]				
3 months		Follow-up telephone	Research Nurse	X	X
6 months		Follow-up home visit	Research Nurse	X	X
12 months		Follow-up telephone	Research Nurse	X	X

*Comprehensive Geriatric Assessment (CGA), [†]Cardiac Research Nurse (CRN), [‡]Clinical Nurse Specialist in geriatrics (CNS), [§]Community Care Registered Nurse (CCRN), [‖]General Practitioner (GP), [¶]Physical therapist (PT)

Intervention

The CCB program encompasses three phases of the care process: 1) clinical phase, 2) discharge phase from hospital to home and 3) post-clinical phase after hospital discharge. The intervention consists of three components: 1) case management, 2) disease management and 3) home-based cardiac rehabilitation. Medication management is an important topic in the three phases of the CCB intervention and is part of all three components.

Phase 1: Clinical phase

Patients randomized to the intervention group will receive an integrated care plan based on geriatric and cardiac conditions identified by the CGA. This plan will be

developed by the CRN together with the patient as follows. The CRN discusses identified health issues, asks if the patient recognizes them and what issues they prioritize for treatment. The integrated care plan is used to prioritize care during the three phases of the intervention. In case of ≥ 1 health issue in the psychological domain or ≥ 5 potential health issues in total, the geriatrician will be consulted. If indicated, the CRN also consults with other disciplines.

Phase 2: Discharge phase

At least one day before discharge, the CCRN visits the patients to discuss and prepare discharge to home. A personalized face-to-face handover between the CRN and the CCRN is completed using a standardized discharge checklist. In case of logistical difficulties the handover is performed by video call via tablet. The CGA, integrated care plan and ongoing interventions are discussed. In addition, the current medical condition, medication prescriptions and therapy advices a patient needs to adhere to (e.g. fluid restrictions in case of heart failure) are discussed. Finally, the CRN contacts the primary care PT by telephone to arrange home-based cardiac rehabilitation.

Phase 3: Post-clinical phase

After discharge home, the CCRN and PT continue care at home. The focus of these visits is in the first month post-discharge since this is when patients are at highest risk for readmission, mortality and functional decline[2,3] The CCRN visits the patient four times post-discharge; within 3 days, at 1, 3 and 6 weeks and if needed one more visit within 12 weeks post-discharge. During all home visits, the CGA, the integrated care plan and patients' current medical condition is evaluated. During the first home visit medication reconciliation is performed by the CCRN to obtain the most accurate possible list of a patient's current medications.[31,32] This is done by comparing all the medications that the patient is taking (including over-the-counter drugs, herbals and vitamins) to those listed in the provided medication records (medication overview from the community pharmacy and the discharge summary from the hospital). Within 48 h after discharge the discharge summary, which contains an overview of the medications at discharge, reasons for changes in medication and results of diagnostic tests is sent from the hospital to the CCRN and pharmacist who is part of the research team.

In Table 2, the home visit schedule is presented, including specific themes during the home visits. The CCRN is allowed to deviate from the home visit schedule if indicated, for example because of changes in patients' health status. During the home visits, the CCRN will indicate and refer if there is a need for additional care (domiciliary or otherwise) during or after the intervention period. For specific questions related to patients' health status or medication discrepancies identified during medication reconciliation, the CCRN has access

to the cardiac team of the hospital, the general practitioner (GP), pharmacist according to local communication routes or protocols of the hospitals. During the home visits the CCRN observes signs and symptoms of actual or potential drug-related problems (DRP), such as side-effects and inappropriate medication use (e.g. nonadherence) by using a recently developed instrument (Supplementary file 1. Adapted Red Flag instrument) based on the Red Flag instrument by Sino et al.[33] The observed problems are documented by the CCRN in the Adapted Red Flag instrument and evaluated by the pharmacist-investigator who has identified DRP and proposed suitable solutions. Subsequently the CCRN discusses these DRP and proposed solutions with the responsible healthcare providers.

The PT provides two home-based cardiac rehabilitation sessions per week during the first 6 weeks post-discharge. This program is based on therapy advices according to the Dutch multidisciplinary guideline of cardiac rehabilitation.[34] Depending on the patient's functional status a stepwise graded exercise approach will be followed, starting with low intensity functional rehabilitation (class IV or higher on the Specific Activity Scale[35]) to the Metabolic Equivalent of Task level[36] (MET-level) needed for their goals and desired activities, as described in the rehabilitation plan. Exercise therapy will be adapted to comorbid diseases according to current guidelines. Within the last 2 weeks of the rehabilitation program, patient's functional status will be evaluated. The CCRN and PT work in close collaboration during the intervention to tailor care and to evaluate progress. They have a joint home visit in the first week after discharge to verify and agree on the integrated care plan in relation to patients' priorities.

In case of readmissions to participating hospitals and wards during the study follow-up of 12 months, patients will repeatedly receive the CCB program with exception of the rehabilitation exercise component. This is due to the limit on physical therapy sessions funded by Dutch healthcare insurance policies.

Usual care

Patients in the control group will receive usual care during hospitalization and after discharge. During hospitalization, other disciplines are consulted as needed. The control group may receive geriatric care if the patients' treating physician consults the geriatric team. All participating hospitals have a geriatric consultation team that can be consulted by the patients' treating physician on indication. After discharge, care as usual may include medical care by a cardiologist according to the national cardiovascular guidelines and a cardiac nurse specialist, if available. Also, control group patients can be referred to center-based cardiac rehabilitation. According to the Dutch multidisciplinary guideline of cardiac rehabilitation, center-based cardiac rehabilitation consists two one-hour exercise sessions per week during 6 weeks.[34] However, it is expected that only a small number of patients in the control group will receive center-based

cardiac rehabilitation due to their age, illness and clinical complexity.

Standard primary care will be provided in both the intervention and the control group. For non-cardiovascular problems, the GP is the primary healthcare provider. Optional care provision in the GP practice includes secondary prevention, medication titration, regular evaluations of physical health status and referral to other disciplines. In both groups the GP will be informed about the hospitalization by a discharge letter from the medical specialist. In the intervention group the GP is informed about the patients' study participation by letter. During the intervention, the CCRN will be an extra liaison between care providers in case of medical, mental or social issues.

In the Netherlands virtually all citizens have basic healthcare insurance, which includes coverage of primary care visits, hospital outpatient visits, hospitalizations and prescribed medication. Dutch citizens can also purchase optional supplementary insurance, which includes physical therapy and other services.

Training for healthcare providers and implementation

The CCB program combines case management, disease management and home-based cardiac rehabilitation, which require additional skills of healthcare providers. The participating CRNs and CCRNs will therefore follow a 5-day training program focussing on case management and disease management which addresses geriatric conditions, the performance of the CGA, development of an integrated care plan, pathophysiology of common cardiac diseases, early detection of physical deterioration and complications, pharmaceutical treatments and cardiac rehabilitation, including lifestyle counselling.[9-13] The participating PTs followed 2,5 day of the 5-day training program together with the CRNs and CCRNs, focussing on pathophysiology of common cardiac diseases, early detection of physical deterioration and complications, pharmaceutical treatments and cardiac rehabilitation, including lifestyle counselling.

We performed a feasibility process in six participating hospitals from June 2016 until May 2017 to check for potential inclusion rates to implement the study protocol and to train CRNs in data collection. In total 45 patients were included in this pilot phase. After successful implementation, we started the official inclusion stepwise per hospital with the first hospitals starting in June 2017.

Sample size calculation

The sample size calculation is based on findings in a relevant subpopulation (101/674) of cardiac patients of the Transitional Care Bridge program,[17] a comparable study including hospitalized patients ≥ 65 years at high risk of functional decline. Based on a six-month incidence rate of 44% (readmission and mortality combined) in the usual care subpopulation of the Transitional

Care Bridge program and a minimal important difference of 12.5% in absolute risk reduction (from 44% to 31.5%) in patients in the intervention arm, (2-sided alpha of 0.05; power of 80%), a sample size of 235 patients per group is required. To compensate for an assumed 5% loss to follow-up, the total sample size per group will be 250 (Figure 1).

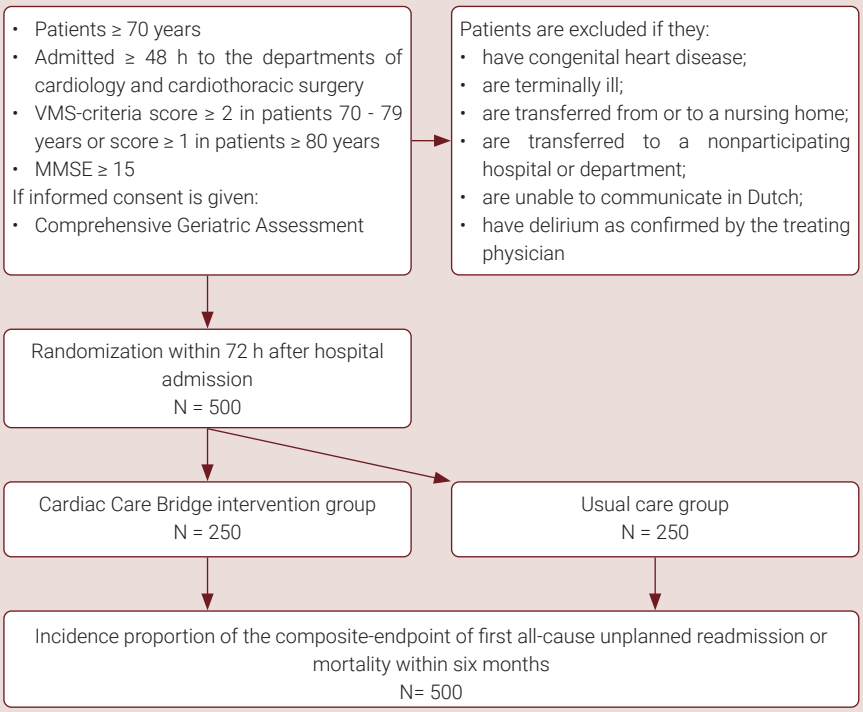

Figure 1. Flowchart of patient selection and randomization

Outcomes and measurements

Primary outcome

The primary outcome is the incidence of first all-cause unplanned readmission or mortality within 6 months post-randomization.

Secondary outcomes

Secondary outcomes will be measured at three, 6 and 12 months. Data will be collected by telephone at three and 12 months and at 6 months by a home visit of a blinded research nurse. Table 3 provides an overview of the data collection

on different time points. The secondary outcomes are the following:

- The incidence of the first all-cause unplanned hospital readmission or mortality within 3 months and 12 months after randomization (triangulated by self-reporting and hospital data management system)
- Activities of Daily Living (ADL)- / instrumental ADL-functioning at 3, 6 and 12 months after randomization (the AMC Linear Disability Score)[37]
- Functional capacity at 6 months after randomization (Short Physical Performance Battery[38] and 2-minute step test[39])
- Medication adherence (questionnaire and pharmacy dispensing records) at 3, 6 and 12 months after randomization
- Anxiety and depression at 6 months after randomization (HADS-anxiety[40] and Geriatric Depression Scale-15[41])
- Health-related quality of life at 6 and 12 month after randomization (EuroQol-5D-5L)[42]
- Healthcare utilization at 3, 6 and 12 months after randomization (extension of *The Older Persons and Informal Caregivers Survey - Minimum Data Set (TOPIC-MDS)*[43] including readmission, emergency visits, GP visits, physical therapy and cardiac rehabilitation)
- Caregiver burden, at 6 and 12 months after randomization (TOPIC-MDS)[43]

Statistical analyses

All analyses will be performed according to a predefined statistical analysis plan, which is published in the Netherlands Trial Register (NTR6316). The primary analyses will be performed according to the intention-to-treat principle. Outcomes will be reported as unadjusted risk differences and their 95% confidence intervals. Adjusted analyses using multivariable logistic or linear regression models, as appropriate, will focus on the incidence proportion of the composite endpoint of readmission and mortality up to 6 months. All analyses will be adjusted for the following potential confounders: age, sex, Charlson Comorbidity Score, MMSE, cardiovascular diagnosis, length of stay and living arrangement. In addition, subgroup analyses will be performed for cardiac diagnosis, frailty status with the VMS screening tool, cognitive status with the MMSE and social economic status. Data will be collected by an electronic Case Record Form in Research Manager,[27] a web-based data management program. Multiple imputation will be used as a sensitivity analysis to assess the impact of missing values.

Table 3. Baseline assessment, outcome measures and time points in the Cardiac Care Bridge

	CGA	Question or instrument	T0*	T0+†	T1‡	T2§	T3‖
Sociodemographic data							
Age		Date of birth	X¶				
Gender			X¶				
Postal code			X				
Living arrangement			X				
Marital status			X				
Ethnicity		Patients' country of birth	X				
Education			X				
Mortality		Date of death	X¶		X¶	X¶	X¶
Medical data							
Diagnosis (and history) of cardiac disease			X¶				
Comorbidities		CCI[55]	X¶				
Date of hospitalization			X¶				
Hospitalization department			X				
Functional domain							
ADL- and iADL-functioning	+	ALDS[37]	X		X	X	X
Functional status		Specific Activity Scale[35]	X			X	

Hearing impairment	+	Do you experience difficulties with hearing, despite the use of a hearing aid?	X			
Visual impairment	+	Do you experience difficulties with your vision, despite the use of glasses?	X			
Fatigue	+	NRS	X		X	
Falls	+	Frequency	X	X	X	X
Fear of falling	+	NRS	X	X	X	X
Physical domain						
Nutritional status	+	SNAQ[25]	X	X	X	X
Pain	+	NRS[56]	X		X	
Dizziness	+	Do you currently suffer from dizziness If yes, does this affect your daily living?	X		X	
Shortness of breath	+	Do you currently suffer from shortness of breath? If yes, does this affect your daily living?	X		X	
Angina pectoris	+	Do you currently suffer from angina pectoris If yes, does this affect your daily living?	X		X	
Heart palpitations	+	Do you currently suffer from heart palpitations? If yes, does this affect your daily living?	X		X	
Incontinence	+	Do you suffer from incontinence? If yes, do you suffer from incontinence of urine and/or defecation?	X		X	
Presence of urinary catheter	+	Do you have a urinary catheter? If yes, did you have the urinary catheter before hospitalization?	X		X	
Nycturia	+	Do you currently suffer from nycturia? If yes, does this affect your daily living?	X		X	
Handgrip strength	+	Jamar[57]	X		X	

Table 3. *Continued*

	CGA	Question or instrument	T0*	T0+†	T1‡	T2§	T3‖
Psychological domain							
Cognitive status	+	MMSE[58]	X			X	
Depression & apathy	+	GDS-15[41]	X			X	
Anxiety	+	HADS-A[40]	X		X	X	X
Quality of life	+	EQ-5D-5L[42]	X		X	X	X
Smoking status		Do you smoke or did you smoke in the past? If yes, how many cigarettes per day and for how many years?	X		X	X	X
Alcohol use		AUDIT-C[59]	X		X	X	X
Social domain							
Caregiver burden		TOPIC-MDS[43]	X			X	X
Medication use							
Polypharmacy	+	Do you use five or more different medications?	X			X	
Medication adherence	+	Medication Adherence Questionnaire	X		X	X	X
Side effect of medication	+	Do you experience difficulties or side effects with medication use?	X			X	
Type of medication		Type, frequency and dose of medication	X¶		X¶	X¶	X¶
Physical performance							
Physical performance		30-second chair stand test[60]		X		X	
Mobility		SPPB[38]	X			X	

Physical capacity	2 MST[39]	X	X		X	
Perceived exertion	Borg RPE scale[61]	X	X		X	
Dyspnoea	MRC dyspnoea scale[62]		X		X	
Parameters						
BMI	Weight and length	X			X	
Waist circumference		X			X	
Blood pressure	mmHg	X			X	
Heart frequency	BPM	X			X	
Respiratory rate		X			X	
Blood parameters	Hemoglobin	X¶		X¶	X¶	X¶
	Albumin	X¶		X¶	X¶	X¶
	Creatinine	X¶		X¶	X¶	X¶
	Total cholesterol	X¶		X¶	X¶	X¶
	LDL-cholesterol	X¶		X¶	X¶	X¶
	HDL-cholesterol	X¶		X¶	X¶	X¶
	Triglyceride	X¶		X¶	X¶	X¶
	Glucose / HbA1C	X¶		X¶	X¶	X¶
Healthcare utilization	**TOPIC-MDS**[43]					
Readmission	Have you been hospitalized in the last 6 months? If yes, what was the hospitalization diagnosis and in what hospital were you readmitted?			X¶	X¶	X¶

Table 3. *Continued*

	CGA	Question or instrument	T0*	T0+†	T1‡	T2§	T3‖
Emergency visits		Have you visited the emergency or cardiac emergency room in the last 6 months? If yes, how many times and for what reason?			X*	X*	X*
Nursing home admission		Have you been admitted to a nursing home in the last months? If yes, for how many weeks?			X	X	X
General practice consult		Have you had a consult with your general practitioner in the last month? If yes, was this during office hours or during the evening, night or weekend and how many times in total?			X	X	X
Home visit of GP		Have you had a home visit from your GP in last month? If yes, was this during office hours or during the evening, night or weekend, and how many times in total?			X	X	X
Home care		Do you receive home care? If yes, is this care assistance and/or domestic help, and how many hours per week?			X	X	X
Day care		Do you have day care? If yes, how many days per week?			X	X	X
Cardiac rehabilitation use		Do you participate in cardiac rehabilitation in a rehabilitation center or outpatient clinic?			X	X	X
Physical therapy		Do you participate in cardiac rehabilitation in a rehabilitation center or outpatient clinic?			X	X	X

Abbreviations: CCI Charlson Comorbidity Index, ALDS Amsterdam Linear Disability Scale, NRS Numeric Rating Scale, SNAQ Short Nutritional Assessment Questionnaire, MMSE Mini Mental State Examination, GDS-15 Geriatric Depression Scale-15, HADS-A Hospital Anxiety and Depression Scale-Anxiety subscale, EuroQol-5D Euroqol quality of life, MDS Minimal Dataset, SPPB Short Physical Performance Battery, 2MST 2 Minute Step Test, Borg RPE scale Ratings of Perceived Exertion scale, MRC Dyspnea Scale Medical Research Council Dyspnea Scale, mmHg millimetre of mercury, BPM beats per minute.
*T0: baseline, ≤ 48 h after admission; †T0+: within 2 weeks after hospitalization during home-based cardiac rehabilitation intake; ‡T1: 3 months after hospitalization, follow-up by telephone; §T2: 6 months after hospitalization, follow-up by home visit; ‖T3: 12 months after hospitalization, follow-up by telephone.
¶Data will be obtained from the medical record

Cost effectiveness analysis

We will perform a cost-effectiveness analysis from a societal perspective. Incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the difference in total costs between the intervention group and the control care group by difference in readmission/mortality rates and Quality Adjusted Life Years (QALYs). The uncertainty surrounding the ICERS will be estimated with non-parametric bootstrapping (5000 replications). The intention to treat principle will be applied to analyse the data. Missing values for cost and effect data will be predicted by multiple imputation.

Process evaluation

Quantitative data will be collected by using pre-defined process indicators to measure study performance and adherence to the intervention by the patient, CRN, CCRN and PT. Process indicators will be used to study fidelity and adherence to the study protocol. Process indicators are focussed on documentation, communication between healthcare providers, consultation of disciplines, referral to healthcare providers and medication issues. All process indicators will be quantified by nominator and denominator and collected through existing resources. Usual care will be documented to be able to assess the difference between the intervention and control group. In addition, qualitative data will be collected during the intervention by focus groups with healthcare providers and in semi-structured interviews with patients and informal caregivers to evaluate satisfaction with the intervention. These data will be analysed to identify factors that promote or impede future implementation of the CCB care program.

(Serious) adverse events

Study related adverse events (AE) will be reported when the AE occurs during the comprehensive geriatric assessment and baseline data collection or after discharge when the AE occurs during the home visits by the CCRN or during the physical therapy sessions / self-practice physical therapy sessions by the patients within the intervention period (till 12 weeks post-discharge). After 12 weeks, the intervention has stopped. Therefore, serious adverse events after this period are not expected to be caused by the study and will only be recorded during the annual security reports.

Discussion

This protocol for a multi-center randomized controlled trial is designed to prevent hospital readmission and mortality after hospitalization in cardiac patients ≥ 70 years old who have been admitted to the department of cardiology or

cardiothoracic surgery. Older patients who are discharged after hospitalization for a cardiac disease are at high risk of adverse outcomes, in particular early readmission and mortality.[44,45] This vulnerable patient population is currently underrepresented in medical research, resulting in a lack of evidence on how to improve their outcomes.[46-48]

In this paper we describe the study protocol of the CCB care program in which we combine three care components: case management, disease management and home-based cardiac rehabilitation that will be provided during and after hospitalization for cardiac disease. Multidisciplinary collaboration between the in-hospital cardiac team, including the CRN and the cardiologist, the clinical nurse specialist in geriatrics and the pharmacist, CCRN and PT in primary care, is an important part of the study intervention. By introducing face-to-face ('warm') handovers before discharge and a joint home visit of the CCRN and PT and support from a pharmacist, we expect to reduce information loss, improve the continuity of treatment, leading to a decrease in readmission and mortality.

Current literature on transitional care and cardiac rehabilitation in older high risk patients focuses mainly on the separate components of case management, disease management and home-based cardiac rehabilitation. In the recent Transitional Care Bridge program, a nurse-coordinated transitional intervention in acutely hospitalized high-risk older patients led to a 25% reduction in mortality, HR 0.75; 95% CI 0.56-0.99. However, there was less impact on time to first hospitalization, HR 1.21; 95% CI 0.91-1.60.[17] The RESPONSE trial, a nurse-coordinated disease management intervention after a coronary syndrome led to a 35% reduction in readmission rates and 17.5% reduction in cardiovascular risk factors in a general cardiac patient population aged < 80 years.[18] Studies on cardiac rehabilitation in the elderly found positive trends on patients' functional ability.[9,49] However, most of these were pilot studies with limited power. In addition to the heterogeneity of the study effects of these studies, the components do not fully meet patients' needs in the care continuum.[50] Therefore, we expect that a combination of care components focusing on patients' needs has a greater likelihood of being effective. The Korinna trial[51] combined both case management and disease management in older patients after a myocardial infarction, but did not find a relevant effect on hospital readmission (HR 1.01; 95% CI 0.72-1.41). Compared to the intervention in the Korinna trial,[51] the CCB program is focussed on a broader cardiac patient population instead of patients after acute myocardial infarction only. Other differences are the emphasis of the CCB program on the first period after hospitalization with a first home visit within 3 days after discharge and the additional home based cardiac rehabilitation program.

Strengths and limitations

The first strength of this study is that it includes a wider variety of the cardiac patient population than previous studies. This is because it selects patients based on their risk of readmission and mortality, instead of diagnosis, and because it selects from six hospitals in both an urban and a rural area. Second, this study has a robust design and includes a postponed informed consent procedure, which assures high internal validity. Third, a comprehensive geriatric assessment is used to develop a personalized care plan, including cardiac and geriatric care, that is transferrable across settings and healthcare providers. Fourth, due to the comprehensive nature of the intervention, it will not be possible to evaluate separate intervention components on their effectiveness but by use of process indicators we will collect data on the execution of the components of the intervention and performance of the involved healthcare providers to support interpretation of the study results. Finally, the intervention has been designed in multi-disciplinary collaboration between nurses, physical therapists, pharmacists and physicians.

This study also has some limitations. First, we exclude patients with delirium and dementia. These patients are at risk for readmission[52] and mortality[53,54] and therefore could potentially benefit from this intervention. However, it is not possible to include these patients in the CCB program because of ethical considerations. Secondly, the face-to-face handover between de CRN and CCRN is a promising intervention but also challenging due to logistical difficulties as, for example, the sometimes unpredictable discharges from the hospital. An alternative handover was introduced by video call via tablets.

In summary, the CCB program aims to significantly reduce the primary composite endpoint of unplanned hospital readmission and mortality in older cardiac patients.

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Supplementary file 1. Adapted Red Flag Instrument

Does the patient currently experiences one of the symptoms listed below? If the answer is yes, write YES in column 'SYMPTOM PRESENT' and ask the following questions: 'Did the symptom appear suddenly?' **(YES/NO)**, 'Is the symptom acceptable/not bothersome?' **(YES/NO)** and '**Does** the patient think the symptom is caused by medication?' **(YES/NO)**. If yes, write down the name of the medication. If the patient has a symptom which is not listed below, write the symptom down in the row 'Other symptom'.

CAUTION: Always call 112 in case of a sudden onset of a symptom

	SYMPTOM PRESENT?	SUDDEN?	ACCEPTABLE?	NAME MEDICINE?
Cardiology				
- Tightness of chest				
- Extreme high/low* blood pressure compared to normal				
- Weight gain of 2 kg or more in 2-3 days and/or increased swelling of the legs, ankles, abdomen*				
- (Exacerbation of) shortness of breath/ waking up in the night, suddenly breathless*				
- Sudden rapid/irregular* heartbeat				
- Dizziness when standing up				
- Red-glossy and/or painful legs (Deep venous thrombosis)				
Bleedings				
- Black stool color				
- Easy bruising/repeated episodes of nosebleeds*				
Neurology				
- Recently fainted				

- Paralysis (facial / on one side of the body and difficulty with speaking				
- Confusion (delirium)				
- Altered level of consciousness (drowsy)				
- Frequent headaches				
Gastrointestinal disorders,				
- No bowel movement in 5 days				
- Nausea, vomiting and/or loss of appetite*				
- Acid reflux				
- Stomach ache				
Other				
- Fatigue (listlessness)				
- Excessive thirst				
- Dry mouth and/or decreased urinary frequency compared to normal*				
- Severe muscle ache				
- Dry and hacking cough				
- Other symptom, such as:				

*Circle the applicable answer.

Adapted version of 'Red flag instrument' by Sino et al.[33]

Does the patient have any problems with medication use, medication adherence and/or adjusting the medication regimen to the daily schedule? Observe and assess problems with medication use by asking the questions listed below. Please tick the box "YES" if applicable. Additional comments concerning a symptom or problems with medication use can be specified in the comments field.

ASSESSMENT OF MEDICATION MANAGEMENT	YES?
- The patient keeps old (unused) medication around (*e.g. because multi-dose drug dispensing is not adjusted with changed medication*)	O
- The patient has medication from previous days in the pill box or multi-dose drug dispensing	O
- The patient does not store medication properly (*e.g. medication is stored in different places and/or different containers*)	O
- The patient uses expired medication (*e.g. due to functional illiteracy expiration or vision problems*)	O
- The patient does not store medication in the original containers and/or at the recommended storage conditions (*e.g. cool, dry, dark*)	O

QUESTIONS MEDICATION USE	YES?
- Does the patient have difficulty with ordering medication and therefor regularly runs out of medication?	O
- Does the patient have trouble telling mediation apart? (*e.g. when using multiple medication*)	O
- Does the patient experiences difficulty with adjusting the medication regimen to the daily schedule?	O
- Does the patient experiences problems with reading and/or understanding the instructions for use? (*e.g. due to functional illiteracy or vision problems*)	O
- Does the patient experiences difficulty with handling the immediate packaging and pressing the medication out?	O
- Does the patient experiences difficulty with completing preparation of medication before use and administration? (*e.g. administration of insulin, inhalation and anti-coagulant medication, applying medication patches and eye ointment, or instilling eye drops and ear drops*)	O
- Does the patient encounter difficulty with taking medication? (*e.g. lodging of medication in the mouth or throat, problems with the flavor of medication, or no motivation to take medication*)	O
- Does the patient drink more than 3 glasses of alcohol a day?	O

QUESTIONS MEDICATION ADHERENCE
"Almost everyone occasionally misses one or more doses of their medicines. Each person has its own way of taking medication. Sometimes this can deviate from the doctor's prescription. I would like to ask you some questions regarding your medication intake. There is no right or wrong answer." • From the moment you were admitted to the hospital for your heart, which medicine(s) did you forget to take? Explanation: _____ • From the moment you were admitted to the hospital for your heart, how often did you forget to take the medicine(s)? Explanation: _____ • From the moment you were admitted to the hospital for your heart, which medicine(s) did you consciously not take as prescribed by the doctor? (e.g. more, less, skipped, stopped) Explanation: _____

COMMENTS

*Circle the applicable answer.

Adapted version of 'Red flag instrument' by Sino et al.[33]

Chapter

8

The Nurse-Coordinated Cardiac Care Bridge Transitional Care Programme: A Randomised Clinical Trial

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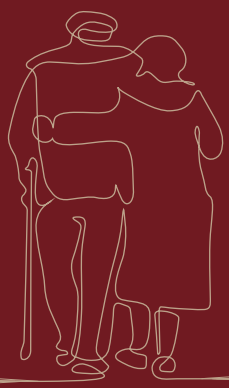
Submitted



Abstract

Background: After hospitalisation for cardiac disease, older patients are at high risk of readmission and death.

Objective: The Cardiac Care Bridge (CCB) transitional care programme evaluated the impact of combining case management, disease management and home-based cardiac rehabilitation (CR) on hospital readmission and mortality.

Design: Single-blind, randomised clinical trial.

Setting: The trial was conducted in six hospitals in the Netherlands between June 2017 and March 2020. Community-based nurses and physical therapists continued care post-discharge.

Subjects: Cardiac patients ≥70 years were eligible if they were at high risk of functional loss or if they had an unplanned hospital admission in the previous six months.

Methods: The intervention group received a comprehensive geriatric assessment-based integrated care plan, a face-to-face handover with the community nurse before discharge and follow-up home visits. The community nurse collaborated with a pharmacist and participants received home-based CR from a physical therapist. The primary composite outcome was first all-cause unplanned readmission or mortality at six months.

Results: 306 participants were included. Mean age was 82.4 (SD 6.3), 58% had heart failure and 92% were acutely hospitalised. 67% of the intervention key-elements were delivered. The composite outcome incidence was 54.2% (83/153) in the intervention group and 47.7% (73/153) in the control group (RR 1.14, 95% CI 0.91-1.42, p=0.253). At 12 months, similar results were found.

Conclusion: The CCB programme in high-risk older cardiac patients did not reduce hospital readmission or mortality within six months. We hypothesise that the selected patient population may not be responsive to high-intensity preventive strategies.

Introduction

The incidence and prevalence of cardiovascular disease in older adults are rising, leading to high risk of adverse events such as readmission and mortality.[1,2] Hospital treatment of older cardiac patients is commonly disease-oriented with interventions based on disease-specific guidelines. However, geriatric conditions such as functional impairment, fall risk and malnutrition[3] often go unrecognised although they increase the risk of adverse events.[4,5]

The transitional phase, when patients transfer from hospital to home, is a high-risk period for adverse events.[6] Medication-related problems are common[7] and symptoms of physical deterioration often stay unrecognised.[8] Furthermore, participation in cardiac rehabilitation (CR) programmes is low.[9] As CR is effective in older patients,[9] non-participation could increase the risk of recurrent cardiovascular events and mortality.[10]

Transitional care has been shown effective in reducing hospital readmission and mortality.[11-13] However, results are inconclusive in older cardiac patients.[14-17] Most transitional care interventions are provided from a *case* management perspective, delivering interventions with a broad focus on patients' needs.[6,17] The integration of disease management and tailored home-based CR into transitional care interventions may be necessary.

The purpose of this study was to evaluate the effects on unplanned hospital readmission and mortality of the nurse-coordinated 'Cardiac Care Bridge (CCB) transitional care programme' which combines case management, disease management and home-based CR in high-risk older hospitalised cardiac patients.

Methods

Study design and setting

We tested the CCB programme in a parallel single-blind multicentre randomised trial, performed between June 5, 2017 and March 31, 2020 in six hospitals surrounding Amsterdam, the Netherlands. Community nurses (CNs) and community-based physical therapists (PT) continued care post-discharge. The trial design has been published.[18] The study was approved by the Medical Ethics Committee of the Amsterdam University Medical Centre (Protocol ID: MEC2016_024) and registered in the Dutch Trial Register (NTR6316, April 6, 2017).

Study population

Cardiac patients of ≥70 years, admitted to the departments of cardiology or

cardiothoracic surgery and admitted ≥48 hours were eligible if they were at high risk of functional loss according to the screening instrument for frail elderly of the Dutch Safety Management System (DSMS).[19] Four geriatric conditions (limitation in Activities of Daily Living (ADL), falls, malnutrition and delirium) are part of this frailty tool, and the DSMS-score ranges between 0-4. Patients were considered at high risk with a DSMS-score ≥2 in patients aged 70-79 years or DSMS-score ≥1 in patients aged ≥80 years.[20] Regardless of the DSMS-score, we also included patients with an unplanned hospital admission in the prior six months as this is associated with increased risk for adverse events.[21]

Exclusion criteria were 1) inability to provide consent and follow instructions due to severe cognitive impairment (Mini-Mental State Examination, MMSE <15) or delirium as confirmed by the treating physician, 2) congenital heart disease, 3) life expectancy of ≤3months as estimated by the treating physician, 4) transfer from or planned discharge to a nursing home, 5) planned discharge to another department or hospital not participating in this study, 6) inability to communicate.

Randomisation

The consent procedure and randomisation were performed ≤72 hours after admission. According to the postponed informed consent procedure of Boter et al.,[22] study participants were blinded to the specific study aims to prevent a potential Hawthorne effect.[23] At the end of the study, participants were fully informed about the intervention and treatment allocation. Stratified block randomisation to the intervention or control group (1:1) was used with pre-stratification by study site and cognitive status (MMSE 15-23 vs ≥24). Allocation concealment was ensured by a web-based data management programme (Research Manager, https://my-researchmanager.com/en/) and random permuted blocks of two, four and six were used.

Usual Care

All patients received a comprehensive geriatric assessment (CGA) at baseline. The control group continued with usual care including consultation by other disciplines during hospitalisation, outpatient visits to the cardiologist and cardiac nurse specialist, and centre-based CR if indicated. In addition, standard care was provided by the family physician. The Dutch healthcare system is described in Appendix 1.

Intervention

The CCB programme was performed in three phases (Appendix 2): the clinical, discharge and post-clinical phase. The intervention consisted of three care components: 1) case management, 2) disease management and 3) home-based CR. The intervention key-elements are described below. All involved healthcare

professionals received a post-Bachelor-level training in case management, disease management and CR (Appendix 3). Informal caregivers were involved in the intervention if they were present.

In the clinical phase, health issues identified by the CGA were discussed and prioritised by the cardiac nurse and the participant. An integrated care plan based on patients' goals was formulated which was leading during the intervention. A geriatrician and other disciplines (e.g. dietician) were consulted based on CGA findings.

The discharge phase started when the discharge date was set. The cardiac nurse contacted the CN and PT to arrange the post-clinical phase. In hospital, the CN visited the participant and the cardiac nurse for a handover of the integrated care plan, and information about participants' medical condition and treatments. In addition, the medical discharge letter was sent to all post-discharge CCB healthcare professionals.

The CN planned home visits within three days, and one, three and six weeks after discharge and an additional home visit within twelve weeks if necessary. During home visits, the CN reviewed the integrated care plan, participants' health status, medication and potential drug-related problems (DRPs) including side-effects and inappropriate use. Together with the CCB pharmacist, medication reconciliation was performed during the first home visit. DRPs were signalled by the CN using the Red Flag instrument.[24] Issues were discussed with the pharmacist who proposed adjustments. For questions regarding participants' health status, the CN contacted e.g. the general practitioner or cardiologist based on indication.

The PT provided one or two home-based CR sessions per week, with a maximum of nine sessions during the first six weeks post-discharge according to the Dutch CR guideline.[25] The first home visit by the PT was a joint intake with the CN and the participant to discuss goals and desired activities, which led to a rehabilitation plan. Depending on participants' functional status a stepwise graded exercise approach was followed, including improving functional activities (e.g. rising from chair, walking, climbing stairs) and increasing muscle strength.

Primary and secondary outcomes

The primary outcome was a composite of first all-cause unplanned readmission or mortality within six months after randomisation. We defined an unplanned readmission as a non-elective admission ≥ one night. Secondary outcomes included the composite outcome at three and twelve months after randomisation and the incidence of the first all-cause unplanned hospital readmission and mortality separate at three, six and twelve months. Mortality data were collected from medical files and the Dutch National Personal Records Database.[26] Data on readmissions were collected from medical files in the participating hospitals and

supplemented with participants' self-reported readmissions to other hospitals. Data collection was performed by research nurses who were blinded to the treatment allocation.

Sample size calculation

The sample size calculation was based on a comparable study of 101/674 hospitalised cardiac patients ≥65 years at high risk of functional loss.[13] Based on a six month incidence of 44% (readmission and mortality combined) in the usual care group and a minimal important difference of 12.5% in absolute risk reduction (from 44% to 31.5%) in participants in the intervention arm (2-sided alpha of 0.05; power of 80%), a sample size of 235 participants per group was required. To compensate for an assumed 5% loss to follow-up, the total intended sample size per group was 250.

Statistical analyses

Analyses were performed according to a predefined statistical analyses plan based on the intention-to-treat principle (Appendix 4).

We reported univariable outcomes and presented the multivariable models in the appendices as both analyses revealed comparable results. The treatment effect of the primary and secondary outcomes was expressed as risk ratio (RR) and the corresponding 95% confidence intervals (CIs) based on a chi-square test, and as risk differences and number needed to treat.[27] In addition, we also reported hazard ratios (HR) and corresponding 95% CIs, plotted the Kaplan-Meier curves and used logrank statistics.

Multivariable logistic and Cox regression analyses were performed and resulting adjusted OR were transformed into RRs.[28] We adjusted for frailty status, study site, age, sex, any admissions in the previous six months, Charlson comorbidity score, MMSE, cardiovascular diagnosis and living arrangement. In addition, we checked for treatment interaction with the following predefined subgroup analyses: age, frailty status, any unplanned hospital admission in the previous six months, cognitive impairment and diagnosis at index admission. Correction for (semi-)competing risk was performed by a unidirectional transition multistate model (illness-deceased model) (Appendix 5).

All statistical tests were 2-sided. P-values <0.05 were considered statistically significant. Analyses were performed with SPSS 25.0 (SPSS Inc., Chicago, IL, USA) and Stata Statistical Software: Release 13 (College Station, TX: StataCorp LP).

Intervention fidelity

Fidelity to key-elements of the intervention was registered by CCB healthcare professionals and evaluated by quality indicators (Appendix 6). For each

participant, the denominator of the intervention key-elements was set to the number of feasible key-elements. Key-elements missed due to e.g. hospital readmission, death or disabilities that precluded participants from taking part in any key-element, were not deemed feasible and not counted in the denominator. The mean fidelity rate was calculated per intervention key-element and in addition for each participant, we calculated the mean fidelity percentage across all key-elements that a participant was entitled to. The overall adherence percentage across all 153 participants, was calculated by an unweighted average of the participant-specific percentages.

Results

We screened 6,857 patients for enrolment, 623 patients (9%) were eligible for participation (Figure 1). Most exclusions were due to low DSMS-scores (59%). In total, 306 eligible patients provided informed consent (49%) and were randomised (153/153). Inclusion was prematurely halted on March 31, 2019 caused by increasing implementation activities of CCB key-elements by CNs in usual care, such as home-based follow-up and the Red Flag instrument.[24] Outcome data were complete for all included participants (follow-up until March 31, 2020).

Both groups were well balanced in baseline characteristics (p>0.05) except for the risk of delirium (p=0.050) and the DSMS-score of 3 (p=0.033) (Table 1). On average, participants were 82.4 years old (SD 6.3) and 51% were male. Participants were mostly admitted for HF (58%) and 45% had had an unplanned hospital admission in the previous six months. In total, 56% were at risk of delirium, 47% had fallen in the six months prior to admission, 39% had ADL-limitations and 33% had malnutrition (Table 1).

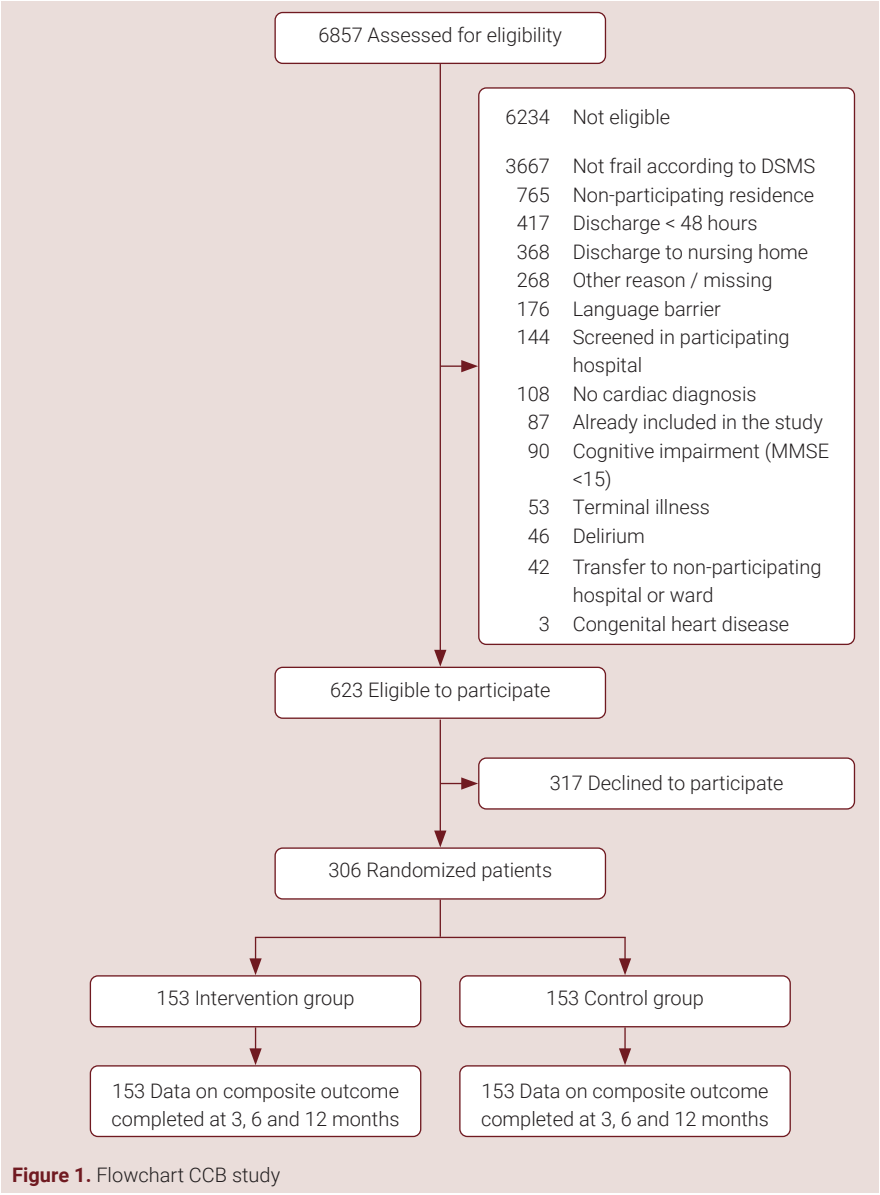


Figure 1. Flowchart CCB study

Table 1. Baseline characteristics

		Intervention (n=153)		Control (n=153)	
Sociodemographics	**Measurement**				
Age		82.5	(6.1)	82.3	(6.5)
	70-79 years	40	26.1%	51	33.3%
	≥ 80 years	113	73.9%	102	66.7%
Sex	Male	70	45.8%	86	56.2%
Country of origin	Netherlands	135	88.2%	138	90.2%
Level of education[a]	Primary education	66	43.1%	61	39.9%
	Secondary education	52	34.0%	44	28.8%
	Higher education	35	22.9%	47	30.7%
Cohabitating		66	43.1%	68	44.4%
Socioeconomic status[b]	Low (< 1 SD)	25	16.3%	27	17.6%
	Intermediate	83	54.2%	81	52.9%
	High (> 1 SD)	45	29.4%	45	29.4%
Index hospitalisation					
Acute hospitalisation		139	90.8%	141	92.2%
Length of stay	Days	7	[4-10]	7	[4.5-10]
Diagnosis on admission	Heart failure	86	56.2%	91	59.5%
	Rhythm or conduction disorder	27	17.6%	20	13.1%
	Acute coronary syndrome	19	12.4%	24	15.7%
	Valve deficits	14	9.2%	12	7.8%
	Other	7	4.6%	6	3.9%
Treatment during admission	Medical treatment only	115	75.2%	116	75.8%
	PCI	13	8.5%	15	9.8%
	TAVR	15	9.8%	11	7.2%
	Device implantation	12	7.8%	10	6.5%
	Other	1	0.7%	4	2.6%
Inclusion criteria	**Measurement**				
Previous hospital admission	≤ 6 months prior to index event	66	43.1%	73	47.7%

Table 1. *Continued*

		Intervention (n=153)		Control (n=153)	
Delirium	DSMS delirium risk score	94	61.4%	77	50.3%
Activities of Daily Living	DSMS impairment in ADL (KATZ-6)	65	42.5%	54	35.3%
Activities of Daily Living	Median (KATZ-6)	1	[0-3]	0	[0-2]
ADL-functioning	ALDS-score (0-100)	72	[58-84]	76	[63-86]
Malnutrition	DSMS malnutrition (SNAQ)	57	37.3%	43	28.1%
Fall risk	DSMS fall ≤ 6 months	67	43.8%	78	51.0%
Fear of falling	NRS ≥ 4	63	41.2%	66	43.1%
DSMS score[c]	DSMS 0	13	8.5%	13	8.5%
	DSMS 1	49	32.0%	59	38.6%
	DSMS 2	50	32.7%	57	37.3%
	DSMS 3	33	21.6%	19	12.4%
	DSMS 4	8	5.2%	5	3.3%
Medical history					
Heart failure		105	68.6%	110	71.9%
Hypertension		95	62.1%	94	61.4%
Acute coronary syndrome		57	37.3%	53	34.6%
Atrial fibrillation		54	35.3%	59	38.6%
Diabetes mellitus		52	34.0%	47	30.7%
Renal failure		51	33.3%	59	38.6%
Chronic obstructive pulmonary disease		29	19.0%	24	15.7%
Peripheral vascular disease		29	19.0%	21	13.7%
Cerebrovascular accident		23	15.0%	27	17.6%
Lifestyle factors	**Measurement**				
Current smoker	Self-reported	16	10.5%	14	9.2%
Body Mass Index	Kg/m^2	26.8	(5.9)	25.8	(4.6)
Geriatric conditions	**Measurement**				
Cognitive impairment	MMSE 15-23	47	30.7%	48	31.4%

Table 1. *Continued*

		Intervention (n=153)		Control (n=153)	
Comorbidities	Charlson Comorbidity Score	3	[1-4]	3	[1-4]
Depressive symptoms	GDS ≥ 6	22	14.6%	18	11.8%
Anxiety	HADS-A ≥ 8	18	11.9%	24	15.7%
Dyspnoea	Self-reported	125	81.7%	123	80.4%
Fatigue	NRS ≥ 4	114	74.5%	114	74.5%
Dizziness	Self-reported	65	42.5%	76	49.7%
Urine incontinence	Self-reported	42	27.5%	41	26.8%
Polypharmacy	≥ 5 (from medication overview)	141	92.2%	144	94.1%
Medication side effects	Self-reported	34	22.2%	35	22.9%
Functional status	SPPB	4	[2-6]	5	[3-7]
Handgrip strength[d]	Male (norm >30 kg)	26.4	9.2	27.0	(7.8)
	Female (norm >18kg)	16.1	(5.8)	15.3	(4.7)

(SD), [25-75 percentile]. [a]Primary education: elementary or primary school. Secondary education: pre-vocational, senior general or pre-university. Higher education: higher professional or university. [b]Socioeconomic status score was calculated from the postal code of patients' residence by the Netherlands Institute for Social Research (SCP) and based on income, employment and educational level. [c]Dutch Safety Management System[19]: the score between 0-4 points, based on four domains of frailty (malnutrition, risk of impairments in daily functioning, risk on delirium and fall risk). A higher score on the DSMS indicates a higher risk of functional loss. [d]Dominant hand highest value.
Abbreviations: ALDS=Amsterdam Linear Disability Scale; CABG=Coronary Artery Bypass Grafting; DSMS=Dutch Safety and Management System; GDS=Geriatric Depression Scale; HADS-A=Hospital Anxiety and Depression Scale-Anxiety; MMSE=Mini-Mental State Examination; NRS=numeric rating scale; PCI=Percutaneous Coronary Intervention; SNAQ=Short Nutritional Assessment Questionnaire; SPPB=Short Physical Performance Battery; TAVR=Transcatheter Aortic Valve Replacement

Primary outcome

The incidence of the six-month composite outcome of first all-cause readmission or mortality was 54.2% (83/153) in the intervention group and 47.7% (73/153) in the control group (RR 1.14, 95% CI 0.91-1.42, p=0.253, HR 1.17, 95% CI 0.85-1.60, p=0.341) (Table 2, Figure 2). The multivariable analysis showed similar results (Appendix 7). The number needed to treat for harm was 15.3 (95% CI number needed to harm (22; infinity), number needed to benefit (6; infinity).

In the univariable subgroup analyses of the primary outcome, the intervention

effect was less favourable in participants admitted with an acute coronary syndrome (RR 2.53, 95% CI 1.26-3.46, p=0.014, p for interaction=0.026) and for participants who had been admitted in the previous six months (RR 1.27, 95% CI 1.04-1.43, p=0.023, p for interaction=0.040). No treatment interactions were found for age, DSMS-score and cognitive impairment on the composite outcome (Appendix 8).

Table 2. Primary and secondary outcomes in the CCB study[a]

	Intervention n=153 (%)	Control n=153 (%)	Risk difference (%) (95% CI)	Risk ratio (95% CI)	P-value risk ratio	Hazard ratio (95% CI)	P-value hazard ratio
Composite outcome							
3 months	63 (41.2)	59 (38.6)	2.6% (-8.4 - 13.6)	1.07 (0.81 - 1.41)	0.641	1.09 (0.76 - 1.55)	0.652
6 months	83 (54.2)	73 (47.7)	6.5% (-4.7 - 18.0)	1.14 (0.91 - 1.42)	0.253	1.17 (0.85 - 1.60)	0.341
12 months	101 (66.0)	88 (57.5)	8.5% (-2.4 - 19.3)	1.15 (0.96 - 1.37)	0.126	1.21 (0.91 - 1.61)	0.192
Unplanned readmission							
3 months	45 (29.4)	48 (31.4)	-1.9% (-12.2 - 8.3)	0.94 (0.67 - 1.32)	0.709	0.93 (0.62 - 1.39)	0.706
6 months	60 (39.2)	59 (38.6)	0.7% (-10.3 - 11.6)	1.02 (0.77 - 1.35)	0.907	1.00 (0.70 - 1.43)	0.995
12 months	73 (47.7)	70 (45.8)	1.9% (-0.2 - 13.1)	1.04 (0.82 - 1.32)	0.731	0.98 (0.70 - 1.36)	0.886
Mortality							
3 months	26 (17.0)	20 (13.1)	3.9% (-4.1 - 12.0)	1.30 (0.76 - 2.23)	0.337	1.34 (0.75 - 2.40)	0.329
6 months	36 (23.5)	28 (18.3)	5.2% (-3.9 - 14.3)	1.29 (0.83 - 2.00)	0.261	1.33 (0.81 - 2.17)	0.262
12 months	59 (38.6)	41 (26.8)	11.8% (1.3 - 22.2)	1.44 (1.04 - 2.00)	0.028	1.55 (1.04 - 2.31)	0.031

[a]Results are not corrected for (semi-)competing risk. Appendix 5 presents the for (semi-)competing risk corrected outcomes in a multi-state (illness-deceased) model.

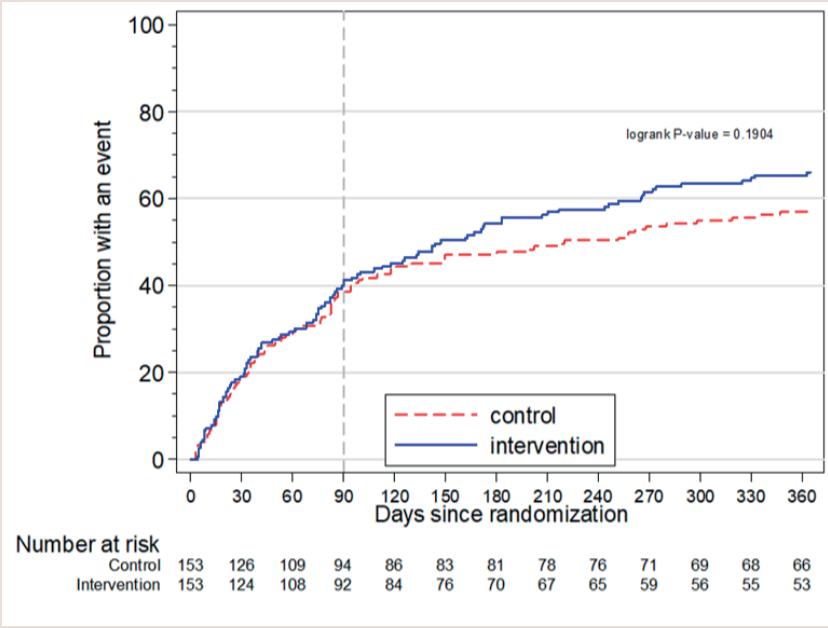


Figure 2. Kaplan-Meier curve of the composite outcome within 12 months
Legend: Dashed line at 90 days marks the end of the intervention period. The curves of the intervention and control group in the primary outcome diverged after the intervention was completed at 90 days follow-up.

Secondary outcomes

At three and twelve months after randomisation, non-significant differences were found on the composite outcome (Table 2). In addition, we did not find statistically significant differences on readmission (three, six and twelve months) and mortality (on three and six months). However, at twelve months follow-up, 38.6% of participants in the intervention group and 26.8% participants in the control group died (RR 1.44, 95% CI 1.04-2.00, p=0.028, HR 1.55, 95% CI 1.04-2.31, p=0.031)). Multivariable regression analyses of all secondary outcomes showed comparable results (Appendix 7). Results of the multi-state illness-deceased models up to twelve months, are presented in Appendix 5.

Intervention fidelity

In total, the mean participant fidelity percentage across all key-elements that a participant entitled to was 67%. However, the fidelity rates varied widely across the various key-elements (median 60%, IQR [41-69], range (17-100)). Table 3 presents the measures of intervention fidelity per key-element. In total, 75% of all intervention key-elements in the clinical phase were performed, 37% in the discharge phase and 64% in the post-clinical phase.

Table 3. Intervention fidelity

Intervention key-elements	N[a]	%
Clinical phase		
CGA and CGA-based integrated care plan	153/153	100
Geriatric consultation based on indication[b]	11/66	17
Discharge phase		
Handover		
Face-to-face	49/134	37
Telephone	19/134	14
Written	66/134	49
Post-clinical phase		
Community nurse home visits[c]	82/133	62
First home visit within 72h after discharge	76/133	57
Number of community nurse home visits	Median 3	IQR 2-4
Medication reconciliation including the Red Flag instrument[24]	118/133	89
Follow-up of the integrated care plan	71/132	54
Lifestyle promotion	91/132	69
Joint home-visit of the physical therapist and community nurse	33/81	41
Home-based cardiac rehabilitation[d]	70/116	60
Number of home-based rehabilitation sessions	Median 4	IQR 2-6
Mean participant-specific fidelity percentage	**153**	**67**

[a] The denominator is set on the number of eligible patients per intervention key-element.
[b] Geriatric team consultation was indicated in case of ≥1 problem within the psychological domain or ≥5 geriatric problems in total.
[c] Four home visits, according to the CCB protocol.
[d] Max. nine home-based rehabilitation session, according to the CCB protocol.
Abbreviations: CGA comprehensive geriatric assessment, IQR interquartile range

Discussion

The CCB programme did not reduce the (time-to-event) rates of hospital readmission or mortality in six months following hospitalisation. Similarly, for the secondary outcome of unplanned hospital readmission alone, no significant difference was found. In the analysis of mortality, we found a statistically significant difference at twelve months follow-up in favour of the control group.

Systematic reviews on transitional care interventions in patients with HF

found that high intensity interventions and (nurse) home visiting programmes reduced the incidence of readmission,[11,14,15] mortality,[11] and the composite endpoint of all-cause readmission and mortality.[15] The discrepancy of these reviews[11,15] with our findings may be related to a higher mean age (82.4 years versus 70-74 years) and the frail older cardiac population in our trial. In line with our findings, two recent randomised trials in patients with HF[16] and patients with AMI[17] reported no significant differences on readmission and mortality.

To our knowledge, our study is the first that combined case management, disease management and home-based CR in frail older cardiac patients. However, we could not confirm that integration of these intervention components improves outcomes. Several factors may have contributed to the results. First, we included a severely frail study population with a high mean age, many disabling comorbidities and geriatric conditions and an extensive medical history. In both groups, mortality rates were high. These factors suggest that the included population may have been beyond the reach of prevention programmes such as the CCB programme. Second, within the high-quality Dutch standard healthcare system many services are being offered to frail older patients which possibly diminished the contrast between groups (Appendix 1). Third, we observed that real-world circumstances were of influence of the fidelity of this intervention. Our intervention fidelity may have contributed to the lack of effect. A higher fidelity on the intervention key-elements could have resulted in a greater contrast between the intervention and control group. However, we cannot exclude the possibility that full fidelity would have led to even more deleterious effects on mortality due to the detrimental trend in the intervention group, through yet unexplained mechanisms.

An extended process evaluation was performed parallel to the trial and addresses the barriers and facilitators for intervention fidelity.[29] In brief, low fidelity rates in healthcare professionals were mostly associated with time limits. For example, the short hospital stay and ad hoc discharge planning reduced the opportunity for geriatric consultation or an in-hospital handover of the integrated care plan to the community nurse. For future purpose, geriatric co-management interventions could be considered during hospitalization in which the responsibility for the treatment is shared between the treating physician and the geriatric team. This kind of intervention intensifies collaboration and has proven to reduce mortality post-discharge.[30,31] Furthermore, alternative communication routes such as a video call handover between the patient, the hospital and community nurse, may ensure continuity of care while less time-consuming than an in-hospital handover. We explored the unexpectedly higher mortality rates in the intervention group. Baseline differences in the population regarding e.g. level of frailty were explored statistically. However, correction in the multivariable analysis yielded essentially the same results. Alternatively, our findings may be due to the play of chance. Previously, Fan et al.[32] performed a comprehensive

care programme to reduce hospitalisation in patients with pulmonary disease and found unexplained higher mortality rates among intervention patients.

In this frail older cardiac patients, other interventions with more focus on quality of life may be needed.[33] For example, advance care planning (ACP) may be more suitable as the CCB population seemed unresponsive to high intensity preventive interventions and event rates were high. ACP focus on patient-centred preferences to increase comfort, quality of life and reduce readmission.[34] Future studies should carefully consider the population eligible for preventive interventions versus those who are eligible for palliative interventions.

Study limitations

The following limitations should be considered. First, only 9% (623/6857) of screened patients were considered eligible for the CCB programme. Most patients were excluded because of low DSMS-scores and non-participating residential areas. In total, 49% of eligible patients provided informed consent which may affect the external validity of the results. Patients more often refuse study participation when their health exceed their coping capacities.[35] Second, we were unable to continue the study until the planned 500 participants due to the quickly (and prematurely) developing regular transitional care for older cardiac patients in our region, This development illustrates that the high rates of readmission and mortality in this high-risk population were being recognised and that professionals seek effective preventive interventions. Due to the high incidence rate of the primary outcome, we had sufficient power to answer the study question. Last, we performed a complex intervention according to a standardised intervention protocol. We invested in an intensive training programme and organised regular follow-up meetings, however, variation in the intervention performance turned out to be inevitable. Our findings reflect the effectiveness and working mechanisms of the intervention under real circumstances and the perceived barriers and facilitators showed some important lessons on organizing care for frail older cardiac patients.[29]

Conclusion

The CCB nurse-coordinated transitional care programme, did not reduce the high rates of unplanned hospital readmission or mortality six months following hospitalisation compared to usual care, in high-risk older cardiac patients. We hypothesise that the selected patient population may not be responsive to high-intensity preventive strategies.

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Appendix 1. The healthcare system in the Netherlands

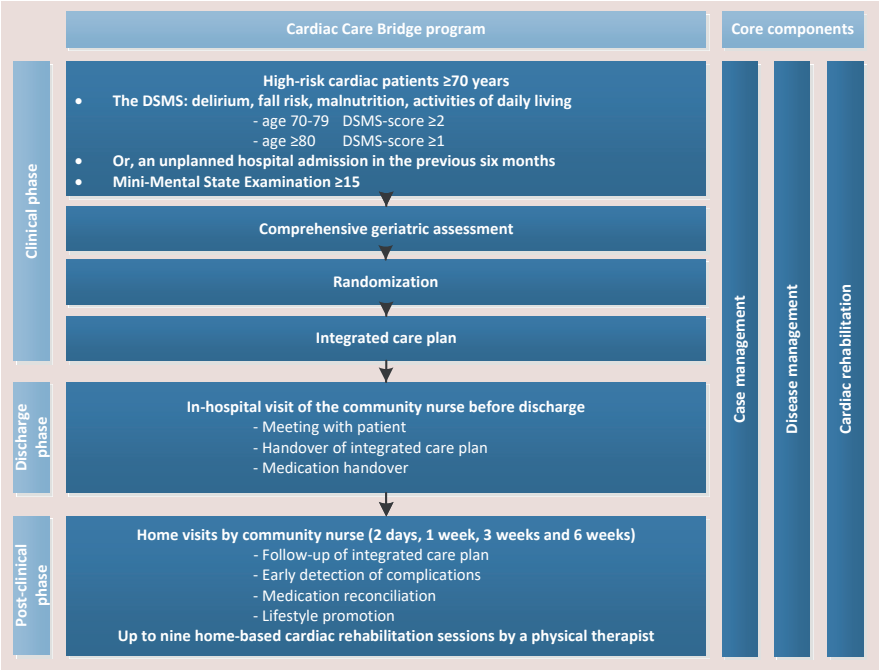
All Dutch citizens have an obligated health care insurance including coverage of primary care visits, hospital outpatient visits, hospital admissions, center-based cardiac rehabilitation (CR) and prescribed medication. In addition, Dutch citizens can purchase supplemental insurance for e.g. additional primary care physical therapy. All patients pay an annual excess (deductible) of 385 euros, which is payed for visits to the hospital, emergency department visits and medications.[36] For homecare, this deductible fee is income-dependent. Family physician (FP) care is excluded from this deductible fee.

All Dutch citizens have an FP who indicates if referral to the hospital for specialised care is necessary (gate-keeper system). Only in case of emergencies, patients are allowed to access the hospital emergency department directly.

In total, there are 108 hospitals in the Netherlands of which eight are university teaching hospitals. In 2012, all hospitals implemented a programme called 'Care for Vulnerable Older Persons' within the Dutch Safety Management Programme (DSMS),[19] which is part of the Ministry of Health, Welfare and Sport. In practice, hospitals are obligated to screen every patient of 70 years and older on (risk of) falls, delirium, limitations in activities of daily living and malnutrition to increase the awareness among hospital staff regarding the risk of functional loss. Many of the Dutch hospitals have a geriatric team which may be consulted.

After cardiac hospitalisation, patients can be referred by the physician to an outpatient CR programme. According to the international guidelines, the rehabilitation programme consists of standard modules for physical rehabilitation (FIT), a psycho-educative prevention module (PEP) and an information module (INFO) about the disease, symptoms and pharmacological and non-pharmacological treatment. A geriatric rehabilitation programme is available in the Dutch nursing homes in case cardiac patients need inpatient rehabilitation on an adjusted level due to their condition and age. If inpatient rehabilitation is not indicated, but outpatient CR is too intensive or infeasible, patients often do not undergo a rehabilitation programme. If indicated, patients can be referred to home care services and primary care physical therapy.

Appendix 2. Overview of the Cardiac Care Bridge programme



Appendix 3. Training of Cardiac Care Bridge healthcare professionals

All involved healthcare professionals in the Cardiac Care Bridge programme (CCB programme) received a training programme focusing on two modules, 1) geriatric case management and 2) cardiac disease management including cardiac rehabilitation in older patients. The training programme was provided interdisciplinary to encourage contact between healthcare professionals and promote collaboration during the CCB programme. The training was developed by the Faculty of Health of the Amsterdam University of Applied Sciences. All involved healthcare professionals followed the programme. In case of absence during one training, participants received an alternative assignment or followed the training in a following course. After course completion with a final exam for module 1, participants received an acknowledged certificate and received educational accreditation points for module 1 and 2 from the professional organisation.

Module 1. Geriatric case management (15 hours)

This module included an introduction to transitional care models and was provided to the cardiac hospital nurses and the community nurses within the CCB programme. Furthermore, the identification of frail elderly in the clinical setting, information on the comprehensive geriatric assessments and the interpretation of identified health problems on the functional, physical, psychological and social domains were part of the programme. The hospital nurses and community nurses were instructed to develop an integrated care plan based on the comprehensive geriatric assessment. Furthermore, healthcare professionals were educated on how to involve informal caregivers and the social network in patients' care and support.

Module 2. Cardiac disease management including cardiac rehabilitation in older patients (15 hours)

This module was interdisciplinary provided to the cardiac hospital nurses, the community nurses and the physical therapists within the CCB programme. The content of this module included an introduction to geriatric cardiology and the complex interaction between cardiac and geriatric conditions. Features of frequently occurring disease symptoms or deterioration e.g. atrial fibrillation and heart failure decompensation, were taught. Furthermore, cardiac-related pharmacotherapy and polypharmacy in relation to early signs and symptoms of deterioration and the performance of medication reconciliation were part of the programme. Non-pharmacological secondary prevention including motivational

interviewing, and home-based CR in older cardiac patients were part of the programme. During the programme, nurses and physical therapists were also trained in separate groups with a specific focus on their tasks within the CCB programme, e.g. cardiogeriatric training principles for physical therapists. In addition, all participants received a CPR training.

Appendix 4. Statistical analysis plan

	Outcomes	Timepoint (months)	Data type	Statistical model	Covariates	Subgroup analysis
	Primary					
1	Incidence proportion of the composite endpoint (all-cause unplanned readmission or mortality)	6	Dichotomous	1, 2, 3, 4	1 - 9	1, 2, 3, 4, 5
	Secondary outcomes					
2	(Time to) composite endpoint (all-cause unplanned readmission or mortality)	3, 6, 12	Dichotomous / time-to-event	1, 2, 3, 4	1 - 9	NA
3	(Time to) first unplanned readmission*	3, 6, 12	Dichotomous / time-to-event	1, 3, 4, 6	1 - 9	NA
4	(Time to) death	3, 6, 12	Dichotomous / time-to-event	1, 2, 3, 4, 6	1 - 9	NA

*An unplanned readmission is defined as a non-elective admission with a length of stay of > 1 night

	Statistical models	Command
1.	Crude models dichotomous: Relative risk (RR), risk difference (RD), Number Needed to Treat (NNT=1/RD)	SPSS Command = frequencies, crosstabs (Chi2)
2.	Crude model: Kaplan Meier survival analysis	SPSS Command = Analyze -> Survival -> Kaplan-Meier
3.	Adjusted models: Logistic regression model (OR)	SPSS Command = Analyze-> Regression-> Binary Logistic. Recalculation of OR into RR32 and RD
4.	Adjusted model: Cox regression model (HR)	SPSS Command = Analyze -> Survival -> Cox Regression
5.	Crude and adjusted: Multistate model	STATA Command = illdprep and stmp2illd

	Covariates, based on baseline differences	Data type
1.	Frailty status according to VMS criteria	Ordinal (range 0-4, categories VMS=0, VMS=1, VMS=2, VMS=3 or 4)
2.	Study site	Categorical , 6 categories (6 sites)
3.	Age	Continuous
4.	Sex	Dichotomous (male or female)
5.	Charlson comorbidity score	Categorical , 6 categories (score 0, score 1, score 2, score 3, score 4, score >= 5)
6.	MMSE	Continuous
7.	Cardiovascular diagnosis	Categorical, 3 categories (heart failure, acute coronary syndrome or other)
8.	Living arrangement	Dichotomous (living together or living alone)
9.	Admission in the previous six months	Dichotomous (yes or no)

	Predefined subgroups	
1.	70-79 years vs ≥ 80 years	Dichotomous (70-79 or ≥ 80)
2.	Frailty status according to VMS criteria (0-4)	Ordinal (range 0-4, categories VMS=0, VMS=1, VMS=2, VMS=3 or 4)
3.	Any unplanned hospital admission in the previous six months (yes/no)	Dichotomous (yes or no)
4.	MMSE (15-23 vs ≥ 24)	Dichotomous (15-23 or ≥ 24)
5.	Cardiovascular admission diagnosis (heart failure, acute coronary syndrome vs other)	Ordinal (categories heart failure, acute coronary syndrome and other)

Abbreviations: DSMS=Dutch Safety Management Programme; HR=Hazard Ratio; MMSE=Mini-Mental State Examination (MMSE); OR=Odds Ratio; RD=Risk Difference; RR=Relative Risk.

Appendix 5. Multistate illness-deceased model

5.1 Methods

A unidirectional transition multistate model (illness-deceased model) was used to estimate the three transition hazards (at home→deceased (absorbing state); at home→first readmission (intermediary state); first readmission→deceased (absorbing state) (Appendix 5.2). Such a model can tackle the (semi-)competing risk situation posed by decease-prevented readmissions, but not vice versa. The three proportions add up to 1 (unity) at any particular time point. We allowed the intervention effects to differ between the three transitions by using interaction terms. The graph for deceased was produced by combining deceased occurring at home with those during readmissions. We used the *illdprep* and *stmp2illd* commands in Stata 13. The time-to-event analyses were fit using a flexible parametric survival model that allowed the effect of treatment to vary across the three transitions.

5.2 Results

Figure A shows the unadjusted multi-state model results up to twelve months. The graphs show that the between-trial arm differences in the proportions of participants at home mainly arose through the effects on mortality, not so much those on readmissions. The results from an adjusted model are shown in Figure B.

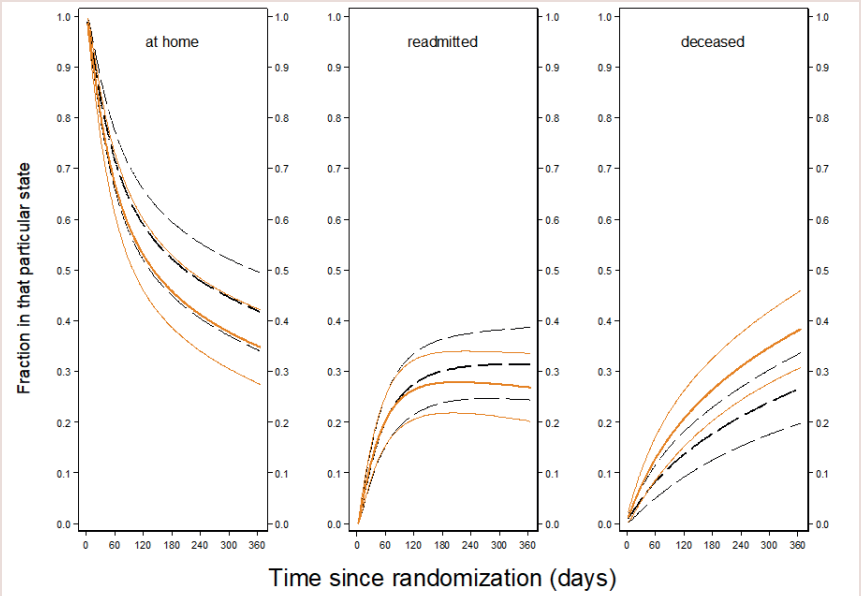


Figure A. Results of the unadjusted illness-deceased model up to 12 months follow-up
Legend: Solid (orange) lines indicate fractions of the participants in the intervention group in the three respective states at any time point. Long dashed (black) lines indicate fractions of the participants in the control group in the three respective states at any time point. The outer lines of each colour indicate the 95% confidence bands.

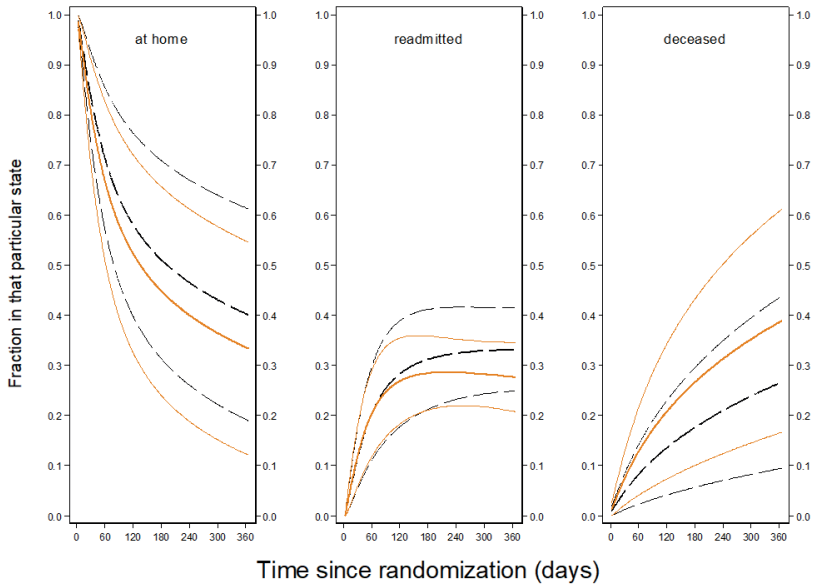


Figure B. Results of the adjusted illness-deceased model up to 12 months follow-up
Legend: Model adjusted for centre and diagnostic group. Solid (orange) lines indicate fractions of the participants in the intervention group in the three respective states at any time point. Long dashed (black) lines indicate fractions of the participants in the control group in the three respective states at any time point. The outer lines of each colour indicate the 95% confidence bands.

Appendix 6. Example of Cardiac Care Bridge quality indicator*

Face -to-face handover	
Aim	All participants in the intervention group of the Cardiac Care Bridge (CCB) programme received a face-to-face handover before hospital discharge between the cardiac nurse and the community nurse.
Operationalisation	Percentage of intervention participants that received an in-hospital face-to-face handover between the cardiac nurse and the community nurse.
Numerator	All participants receiving a face-to-face handover
Denominator	All participants eligible to receive a face-to-face handover
Definition	A participant received a face-to-face handover if: - The community nurse visited the participant and the cardiac nurse in the hospital - The log contained a notification of the hospital visit.
In-/exclusion criteria	Inclusion: - All CCB intervention participant who were discharged home Exclusion: - Participants who would be transferred to an inpatient care facility post-discharge or who died during hospitalisation
Type of indicator	Process indicator
Source numerator	Log
Source denominator	Data management programme Research Manager
Measurement frequency	Once per participant
Measurement level	Participant level

*Other examples are available upon request

Appendix 7. Results from multivariable logistic and time-to-event regression analyses at three, six and twelve months

	Intervention	Control	Risk difference (%) (95% CI)	Risk ratio[a] (95% CI)	P-value risk ratio	Hazard ratio (95% CI)	P-value hazard ratio
Composite outcome							
3 months	63 (41.2%)	59 (38.6%)	4.0% (-7.7% - 16.6%)	1.10 (0.80 - 1.43	0.52	1.10 (0.76 - 1.58)	0.62
6 months	83 (54.2%)	73 (47.7%)	7.3% (-5.2% - 19.1%)	1.15 (0.89 - 1.40)	0.25	1.17 (0.85 - 1.60)	0.37
12 months	101 (66.0%)	88 (57.5%)	10.2% (-2.0% - 20.5%)	1.18 (0.96 - 1.36)	0.10	1.20 (0.89 - 1.61)	0.23
Unplanned redmission[b]							
3 months	45 (29.4%)	48 (31.4%)	-2.4% (-12.1% - 9.6%)	0.92 (0.61 - 1.31)	0.67	0.86 (0.57 - 1.32)	0.50
6 months	60 (39.2%)	59 (38.6%)	0.0% (-11.2% - 12.3%)	1.00 (0.71 - 1.32)	0.99	0.94 (0.65 - 1.36)	0.74
12 months	73 (47.7%)	70 (45.8%)	1.1% (10.0% - 13.9%)	1.04 (0.78 - 1.31)	0.77	0.92 (0.65 - 1.29)	0.61
Mortality							
3 months	26 (17.0%)	20 (13.1%)	8.4% (-2.5% - 23.6%)	1.49 (0.85 - 2.39)	0.15	1.62 (0.88 - 2.99)	0.12
6 months	36 (23.5%)	28 (18.3%)	7.3% (-2.6% - 20.7%)	1.40 (0.90 - 1.91)	0.17	1.48 (0.88 - 2.49)	0.14
12 months	59 (38.6%)	41 (26.8%)	14.6% (2.3% - 28.1%)	1.54 (1.09 - 2.05)	0.018	1.65 (1.09 - 2.50)	0.019

Analyses were adjusted for frailty according to the DSMS criteria (4 categories), study site (6 categories), age (continuous), sex, any admissions in the previous six months (yes/no), Charlson comorbidity score (5 categories), MMSE (continuous), cardiovascular diagnosis (heart failure, acute coronary syndrome or other), living arrangement (alone/not alone).

[a] Multivariable logistic regression analyses were performed and resulting adjusted ORs were transformed into RRs.[28]

[b] Results are not corrected for (semi-)competing risk. Appendix 8 presents the for (semi-)competing risk corrected outcomes in an illness-deceased multi-state model.

Appendix 8. Results from uni- and multivariable subgroup analyses on the composite outcome at six months

		Intervention n/N (%)	Control n/N (%)	Unadjusted risk ratio[a] (95% CI)	P-value	P-value interaction	Adjusted risk ratio[a] (95% CI)	P-value	P-value interaction
Age	70-79 years	21/40 (52.5)	31/51 (60.8)	1.12 (0.93 - 1.29)	0.20	0.56	1.14 (0.93 - 1.32)	0.18	0.45
	≥ 80 years	62/113 (54.9)	42/102 (41.2)	1.04 (0.62 - 1.51)	0.86		1.01 (0.55 - 1.53)	0.98	
VMS-score	Score 0	4/13 (30.8)	6/13 (46.2)	0.67 (0.18 - 1.49)	0.42	0.27	0.62 (0.14 - 1.58)	0.41	0.16
	Score 1 (ref)	25/49 (51.0)	25/59 (42.4)	1.20 (0.77 - 1.63)	0.37	ref	1.36 (0.91 - 173)	0.12	ref
	Score 2	27/50 (54.00)	28/57 (49,.1)	1.10 (0.72 - 1.46)	0.62	0.78	0.96 (0.56 - 1.37)	0.81	0.22
	Score 3 or 4	27/41 (65.9)	14/24 (58.3)	1.13 (0.70 - 1.45)	0.55	0.97	1.27 (0.82 - 1.55)	0.22	0.95
Diagnosis	Heart failure (ref)	51/86 (59.3)	54/91 (59.3)	1.00 (0.75 - 1.22)	1.00	ref	0.99 (0.72 - 1.123)	0.95	ref
	Acute coronary syndrome	12/19 (63.2)	6/24 (25.0)	2.53 (1.26 - 3.46)	0.014	0.026	2.51 (1.15 - 3.50)	0.03	0.041
	Other diagnoses	20/48 (41.7)	13/38 (34.2)	1.22 (0.67 - 1.85)	0.48	0.56	1.24 (0.64 - 1.92)	0.48	0.54
Cognition	MMSE < 24	26/47 (55.3)	21/48 (43.8)	1.17 (0.87 - 1.46)	0.28	0.89	1.16 (0.83 - 1.49)	0.34	0.97
	MMSE ≥ 24	57/106 (53.8)	52/105 (49.5)	1.12 (0.76 - 1.45)	0.53		1.15 (0.76 - 1.51)	0.45	
Admission in the previous six months	Yes	35/66 (53.0)	43/73 (58.9)	1.27 (1.04 - 1.43)	0.023	0.040	1.28 (1.03 - 1.45)	0.033	0.052
	No	48/87 (55.2)	30/80 (37.5)	0.86 (0.52 - 1.28)	0.486		0.84 (0.47 - 1.32)	0.482	

Analyses were adjusted for frailty according to the DSMS criteria (4 categories), study site (6 categories), age (continuous), sex, any admissions in the previous six months (yes/no), Charlson comorbidity score (5 categories), MMSE (continuous), cardiovascular diagnosis (heart failure, acute coronary syndrome or other), living arrangement (alone/not alone). Abbreviations: MMSE=Mini-Mental State Examination; ref=reference group

[a] Multivariable logistic regression analyses were performed and resulting adjusted ORs were transformed into RRs.[28]

Chapter

9

Experiences of frail older cardiac patients with a nurse-coordinated transitional care intervention - a qualitative study

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Abstract

Background: The Cardiac Care Bridge (CCB) program was a randomized nurse-coordinated transitional care program combining case management, disease management and home-based rehabilitation for hospitalized frail older cardiac patients. This qualitative study explored the experiences of patients' participating in this nurse-coordinated transitional care intervention, as part of a larger process evaluation, in order to support interpretation of the neutral trial outcomes and the contribution of the intervention components from participants' point of view.

Methods: A generic qualitative approach was used. Semi-structured interviews were performed with sixteen patients ≥ 70 years who participated in the intervention group. Participants were selected by gender, diagnosis, living arrangement and hospital of inclusion. Data were analysed using thematic analysis. In addition, quantitative data about intervention delivery were analysed.

Results: Three themes emerged from the data: 1) appreciation of care continuity; 2) varying experiences with recovery and, 3) the presence of an existing care network. Participants felt supported by the transitional care intervention as they experienced post-discharge caregiver support and continuity of care. The perceived contribution of the program in participants' recovery varied. Some participants reported physical improvements while others felt impeded by comorbidities or frailty. The home visits by the community nurse were appreciated, although some participants did not recognize the added value. Participants with an existing formal caregiver network preferred to consult these professionals instead of the caregivers who were involved in the transitional care intervention.

Conclusion: Our results contribute to an explanation of the neutral study of a nurse-coordinated transitional care intervention. For future purpose, the intervention intensity and content of the intervention could be more individualized by tailoring interventions to older cardiac patients' needs, considering their frailty, self-management skills and existing formal and informal caregiver networks.

Background

Older cardiac patients are at high risk of hospital readmission and mortality, especially in the first weeks after hospitalization for a cardiac event.[1,2] Transitional care interventions (TCIs) aim to improve continuity of care in patients transitioning between care settings and are usually provided by a case management approach with a broad focus on patients' needs.[3] These interventions have been proven to reduce hospital readmission and mortality in older and chronically ill patients.[4,5] However, the results of transitional care interventions in cardiac patients show mixed results on these outcomes.[6-8] Besides case management, (older) cardiac patients also need disease-specific guidance post-discharge regarding symptom monitoring, medication and lifestyle-related adherence and cardiac rehabilitation (CR).

The Cardiac Care Bridge program was a nurse-coordinated TCI combining case management, disease management and home-based CR for frail hospitalized cardiac patients ≥ 70 years. No statistically significant difference was found on the main composite outcome of readmission and mortality within six months after randomization (Jepma et al., submitted).

The CCB program was a complex intervention as it included multiple interacting components, stakeholders and organisational levels.[9] Besides analysing trial outcomes, we performed a process evaluation to examine the mechanisms and contextual factors that influenced these outcomes. As part of this evaluation, we explored the experiences of participants receiving this TCI. Their perspectives support the interpretation of the trial outcomes and the contribution of intervention components from the participants' point of view.

Methods

Aim

The aim of this study was to explore the experiences of participants receiving a nurse-coordinated TCI in order to support interpretation of the trial outcomes and the contribution of the intervention components from participants' point of view.

Design

We used a generic qualitative approach to understand participants' experiences with a nurse-coordinated TCI.[10] This design was considered suitable as the research question did not fit any of the established methodologies (e.g. grounded theory, phenomenology and ethnography).[11] The generic qualitative

approach allowed us to use the strengths of these methodologies and the flexibility to gather a rich and in-depth description of participants' experiences. Participants were interviewed parallel to the performance of the intervention. To prevent potential bias, we analysed their experiences before the study results on effectiveness of the TCI were known. COREQ-guidelines have been used for transparency reporting.[12]

The CCB transitional care program

The CCB program was a Dutch multi-center randomized controlled trial (RCT) on nurse-coordinated, interdisciplinary transitional care in frail, older (≥70 years) hospitalized cardiac patients. In total, 306 patients were recruited in six hospitals. The primary outcome was a composite endpoint of unplanned hospital readmission and mortality within six months after randomization.

The CCB program was a complex intervention combining case management, disease management and CR in three phases; the clinical, discharge and post-clinical phase (Figure 1). In the clinical phase, a comprehensive geriatric assessment (CGA) was performed to identify geriatric conditions and to develop an integrated care plan which was leading during and after hospitalization. In the discharge phase, a community-care registered nurse (CN) visited the patient and clinical caregivers in the hospital for a personal handover of the integrated care plan and to prepare the discharge phase. In the post-clinical phase, the CN performed four home visits within the first six weeks. These home visits included among others medication reconciliation, early signalling of health deterioration or complications and an evaluation of the integrated care plan. On indication, an extra home visit was performed within the first three months post-discharge. In addition, a physical therapist (PT) performed nine home-based CR sessions at patients' home. Details of this study have been published.[13]

Participants

Participants of this qualitative study were frail cardiac patients ≥ 70 years who were included in the intervention group within the last three months.[13] Participants were purposively selected by gender, diagnosis, living arrangement (alone/together) and hospital of inclusion to ensure a maximum variation of experiences. They were invited by phone to participate in an interview after the intervention was completed. Recruitment stopped when no new codes and themes emerged from the data and the research question could be answered.[14]

Data collection

The interviews were conducted between December 2017 and June 2018 at participants' home. The interviews were performed by two researchers (PJ RN, MSc) and (SdP RN, BSc) who followed additional training in qualitative research.

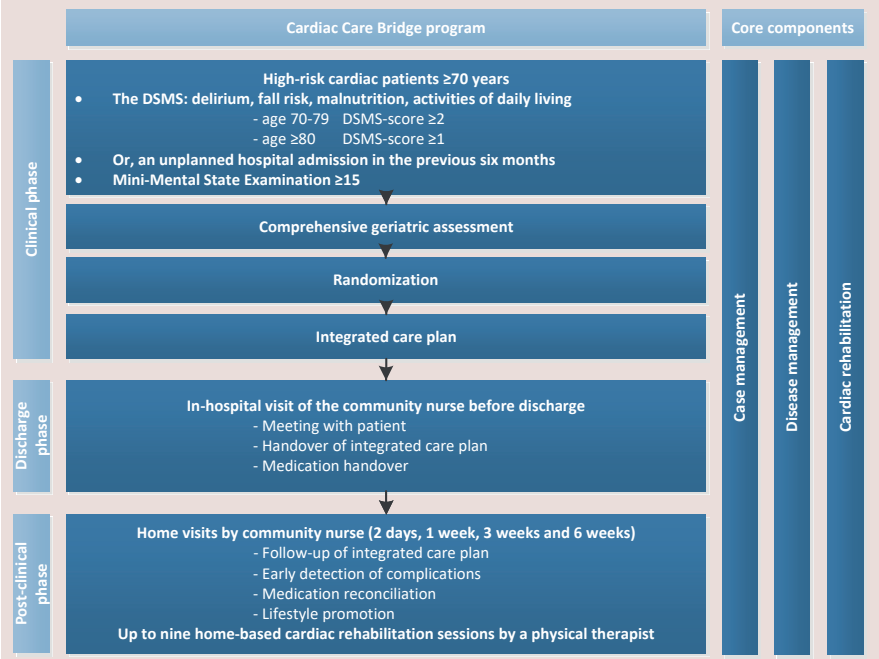

Figure 1. Overview of the CCB transitional care program

Both have a bachelor's degree in nursing. PJ also has a master's degree in health sciences. SdP followed a nursing master's program during the time of the interviews and worked as a quality nurse in an organization for nursing homes. Both researchers did not had prior relations with the included participants. A semi-structured interview guide [see Additional file 1] was developed based on the clinical, discharge and post-clinical phase of the intervention. Small adjustments have been made during the data collection process to ensure that all key elements of the intervention were fully questioned. The complete interviews were audio recorded and field notes were made during and after the interview. The interviews lasted between 25 and 70 minutes.

Data regarding participants sociodemographic and disease characteristics were collected for the RCT during hospitalization (table 1). Furthermore, data about the intervention delivery was registered in medical hospital files and logbooks which were filled out by the participating healthcare providers during the intervention. A process evaluation of the intervention delivery is reported.[15]

Ethical consideration

The CCB study was approved by the Medical Research Ethics Committee of the AMC (Protocol ID: MEC2016_024) (Netherlands Trial Register number: NTR6316, 06/04,2017) and conforms with the principles outlined in the declaration of Helsinki.[16] Prior to the interview, participants received oral and written information about this qualitative study and written informed consent was obtained.

Data analysis

Data were analysed using the six phases of thematic analysis according to Braun and Clarke.[17] All interviews were transcribed verbatim. PJ and IB familiarized themselves with the data by reading the transcripts (phase 1). The coding process started with open coding using the coding program MAXQDA 12. Per two coded transcripts, consensus about codes was reached before coding the next two transcripts (phases 2). During this process, PJ and IB discussed emerging themes (phase 3) which were reviewed repeatedly and discussed with the research team (phase 4). All codes were analysed and structured, which led to the final themes (phase 5). Corresponding quotes were selected, the research question was answered and findings were compared with literature (phase 6).

We also analysed quantitative data about the intervention delivery in interviewed participants from medical hospital files and logbooks (table 2). This contributed to a complete view of participants perspectives in the context of the delivered intervention.

Results

Data saturation was reached after sixteen interviews. Participants' partner or a child participated in eight interviews. The mean age of included participants was 82.4 years (SD 5.3), 50% was female, 56.3% was admitted due to heart failure and 56.3% lived together with a partner (Table 1). Table 2 shows the intervention delivery in interviewed participants. In total, three themes were identified from the interviews: 1) appreciation of care continuity; 2) varying experiences with recovery and, 3) the presence of an existing care network.

Theme 1: appreciation of care continuity

Participants experienced that healthcare providers during all three phases of care (clinical, discharge and post-clinical phase) looked after them. During the clinical phase, participants reported that they met many different healthcare providers and most participants were unable to distinguish usual hospital care from the care delivered in the TCI. Some participants who did remember the CGA, indicated that they understood that it was necessary to additionally address

Table 1. Baseline characteristics of interviewed participants in the CCB program

Patient	Age	Sex	Residency status	Educational level	MMSE[a]	DSMS[b]	Hospitali-zation ≤ 6 months	Primary diagnosis	Charlson comorbidity index[c]
1	87	Female	With partner	Primary	21	1	No	Valve deficit	2
2	86	Female	Alone	Primary	29	1	No	Acute coronary syndrome	2
3	81	Male	With partner	Primary	27	1	No	Heart failure	4
4	85	Female	Alone	Secondary	24	2	No	Acute coronary syndrome	0
5	76	Male	With partner	Higher	27	3	Yes	Rhytm or conduction disorder	4
6	87	Male	Alone	Secondary	29	1	No	Heart failure	4
7	84	Female	Alone	Higher	28	3	No	Heart failure	2
8	82	Male	With partner	Higher	28	1	No	Rhytm or conduction disorder	6
9	89	Male	With child	Higher	27	1	No	Heart failure	4
10	82	Female	With partner	Primary	29	2	Yes	Heart failure	1
11	79	Male	With partner	Higher	29	2	No	Rhytm or conduction disorder	1
12	87	Female	Alone	Primary	29	1	Yes	Valve deficit	3
13	73	Male	Alone	Primary	24	1	Yes	Heart failure	5
14	86	Male	Alone	Secondary	27	4	No	Heart failure	2
15	84	Female	Alone	Primary	24	1	No	Heart failure	4
16	71	Female	With partner	Primary	24	3	Yes	Heart failure	5

[a] Mini-Mental State Examination[18]: the score ranges between 0-30 points. In the CCB program, only patients with a MMSE ≥ 15 were included. A MMSE-score < 24 indicates cognitive impairment. [b] Dutch Safety Management System[19]: the score between 0-4 points, based on four domains of frailty (malnutrition, risk of impairments in daily functioning, risk on delirium and fall risk). A higher score on the DSMS indicates a higher risk of functional loss. [c] Charlson comorbidity index[20]: a weighted index to classify comorbid conditions based on their 1-year mortality prognosis.

their health. Together with the identified problems from the CGA, participants' personal goals were incorporated in an integrated care plan. However, most participants reported that they had no personal goals and were awaiting the care being delivered by the community nurse and physical therapist at home.

> *Interviewer (I): 'But has she also discussed with you what you would want to do when you were at home again?'*
> *Respondent (R): 'I also believe in going upstairs [going up the stairs again], I believe that. But now and then I was not altogether there either. Then I was so tired and then I thought ... Oh, I wish I could sleep well.' (P16, female, 71 years)*

The CGA-based integrated care plan was discussed by the cardiac research nurse in the discharge phase during a face-to-face handover with the community nurse, in the presence of the patient. The community nurse visited 10/16 participants in-hospital and in 4/16 participants a handover by phone was performed (table 2). Not all participants who received an in-hospital visit of the community nurse were able to remember this. Participants who did, highly appreciated it to meet the community nurse before discharge to be prepared for who would visit them at home:

> *'She said this is the nursing service that comes to your home, (…). Well I think that is neat. (…) Look, you know who you are dealing with and not that umm there suddenly is one at the door and you think hey… This feels good.' (P13, male, 73 years)*

In the post-clinical phase, participants reported that they were satisfied about the relationship with the caregivers because they felt healthcare providers were experienced, adequately informed about their health and kept an extra eye on them post-discharge. As the following participant stated, this also led to more motivation to the home-based CR exercises:

> *'Yes, above all that, you get guidance and a helping hand to keep doing it [physical exercises]. Look, if you throw in at the deep end now and you have to do exercises, then it will either happen or not. But she [the physical therapist] was really adamant that "well you have to do it". Well then you simply just did. I was happy with it [with the TCI]. That gives you some certainty.' (P5, male, 76 years)*

Regarding the community nurse, participants experienced support in checking their health status by measurement of vital signs. They also felt supported in medication management. For example, one participant had specific goals about her medication adherence and the community nurse arranged a multi-dose drug

Table 2. Intervention delivery in interviewed participants

	Clinical phase			Discharge phase	Post-clinical phase						
Patient	**CGA**	**Geriatric consultation**	**Geriatric consultation indicated?**[a]	**Handover**	**Number of home visits CN**[b]	**First home visit CN within median of 3 days**	**Medication verification**	**Evaluation of care plan**	**Lifestyle discussed**	**Number of home visits PT**[c]	**Joint intake CN/PT**
1	Yes	No	Yes	Face to face	4	No	Yes	No	Yes	4	Yes
2	Yes	No	Yes	Face to face	4	Yes	Yes	No	No	9	No
3	Yes	No	Yes	Face to face	4	Yes	Yes	No	Yes	9	No
4	Yes	No	Yes	Telephone	3	No	Yes	Yes	Yes	6	Yes
5	Yes	No	Yes	Face to face	5	No	Yes	Yes	Yes	7	No
6	Yes	No	Yes	Unknown	4	Yes	Yes	Yes	Yes	9	No
7	Yes	No	Yes	Telephone	4	Yes	Yes	Yes	Yes	9	No
8	Yes	No	Yes	Unknown	5	No	Yes	Yes	Yes	8	No
9	Yes	No	No	Face to face	4	Yes	Yes	No	Yes	9	Yes
10	Yes	No	No	Telephone	3	No	Yes	No	No	9	No
11	Yes	No	No	Face to face	4	Yes	Yes	Yes	Yes	1	NA
12	Yes	No	No	Face to face	4	Yes	Yes	Yes	No	0	NA
13	Yes	No	No	Face to face	4	Yes	Yes	Yes	Yes	4	No
14	Yes	No	No	Telephone	5	Yes	Yes	Yes	Yes	7	No
15	Yes	Yes	Yes	Face to face	5	Yes	Yes	No	Yes	7	No

Table 2. *Continued*

	Clinical phase			Discharge phase	Post-clinical phase						
Patient	**CGA**	**Geriatric consultation**	**Geriatric consultation indicated?**[a]	**Handover**	**Number of home visits CN**[b]	**First home visit CN within median of 3 days**	**Medication verification**	**Evaluation of care plan**	**Lifestyle discussed**	**Number of home visits PT**[c]	**Joint intake CN/PT**
16	Yes	No	Yes	Face to face	3	Yes	Yes	No	Yes	2	No

Abbreviations: CGA=comprehensive geriatric assessment, CN=community nurse, NA=not applicable, PT=physical therapist.
[a] Geriatric team consultation was indicated in case of ≥ 5 geriatric problems of which ≥ 1 problem had to be within the psychological domain. [b] Four home visits, according to the intervention protocol. An extra home visit was performed on indication, assessed by the CN. [c] Max. nine home-based rehabilitation session, according to the intervention protocol.

dispenser for her:

> *'I say, I do need that [the community nurse] every now and then. There is a big stick behind the door (...) That it was said and now you should do that. And now you really have to make sure you take your pills on time.' (P16, female, 71 years)*

Participants had some difficulties to fully describe the care that was delivered by the community nurse. Additional information from the logbooks showed that the community nurse performed medication reconciliation in all participants. Furthermore, in 9/16 participants the integrated care plan was evaluated and in 13/16 participants lifestyle promotion was discussed (table 2). Furthermore, in 3/15 participants a joint home visit of the community nurse and physical therapist was performed to coordinate care together.

Theme 2: varying experiences with recovery

The majority of participants were satisfied about their recovery in the post-clinical phase. Participants reasoned that, as part of aging, recovery took time or understood that recovery was not fully feasible.

All participants received home visits of the community nurse post-discharge. The number of home visits by the community nurse ranged from three to five (mean = 4, SD 0.7) and by the physical therapist from zero to nine (median = 7, [IQR: 4-9]) (table 2). Many participants indicated that the number of home visits by the community nurse and physical therapist

were sufficient, and more care would not have contributed to their recovery.

Regarding the home visits by the community nurse, some participants reported interventions by the community nurse, but not recognized the importance in relation to the prevention of further complications:

> *'That [the community nurse] also took the blood pressure and then she wrote a note to the doctor. And so, I had to go to the doctor, yes. At first, I did not even know I had it [high blood pressure]. But then she noticed that my blood pressure was a little high. But yes, previously, I had been suffering from it for years, a little too high blood pressure.' (P1, female, 87 years)*

Therefore, it was difficult for participants to recall if and how the community nurse had contributed to their recovery:

> *'Yes, I do not really know [whether the community nurses contributed]. No, as I am now, I actually feel good physically, except for that wound and my feet. But they cannot do anything about that anymore. I like it when she visits. But whether it contributes [home visits of the community nurse] that I doubt.' (P9, male, 89 years)*

In general, participants considered the home-based CR as an opportunity to work on their daily functioning. Participants with personal goals were motivated to achieve progress in their recovery:

> *'Because I also say last time, "I have set a goal, I want to be able to walk for an hour and I want to be able to cycle a bit again", and then he says [physical therapist] "well for the last couple of times we will try to cycle together".' (P10, female, 82 years).*

Participants experienced progress in their recovery mainly in improved muscle strength and condition:

> *'Look, I can do all those exercises, and, in the beginning, you were uhm well then you really had to catch up. But now I just recover in a minute, two minutes and then it is back to normal. So, then you see, you feel that you are building up something and that is important.' (P5, male, 76 years)*

However, most participants were severe frail or were limited duo to comorbidities. One participant therefore ended the home-based CR prematurely. In other participants, the experienced symptoms (e.g. dyspnoea, tiredness, joint problems) impeded them during the physical exercises:

'Yes, and that did not work [the exercises], it is too tiring for me, for my legs. (…). For a young guy, the suggested exercises were good, you have to be of the right age. But my whole body will be gone in a minute.' (P3, male, 81 years)

In addition to the rehabilitation sessions, most participants received exercises to practice on a daily basis without the presence of the physical therapist. Participants indicated that they often forgot to practise or found it hard to fit these exercises in their daily routine:

'You do not get to it when you are alone. Then we have, when I remember that I have to do it [exercises of the physical therapist], I have something again, then I had to turn off the gas for example. Look of course I have a terrible disability, meaning that my short-term memory is unbelievably bad.' (P6, male, 87 years)

Theme 3: the presence of an existing care network

Most participants had a large formal care network including the general practitioner (GP), cardiologist or a hospital-based cardiac nurse specialist. Participants reported that the community nurse and physical therapist collaborated together and with other involved healthcare providers. Participants remembered that the community nurse consulted the GP, cardiologist or the pharmacist to discuss abnormal vital signs, increased weight or medication-related problems which often resulted in medication changes.

R2: 'Those medicines were changed several times (…).'
I: 'Was it difficult for you that they were changed so frequently?'
R1: No, actually, but I do not know which medicines I should have then, then everything is just all let loose [in multi-dose drug dispenser].
I: 'Okay and the community nurse helped with that, I understand?'
R1: 'Yes, the hospital told her [community nurse] which ones had to get out.' (P3, male, 81 years)

Participants with an extended formal caregiver network experienced the TCI as an extra appointment within an already busy schedule of care-related appointments:

'Once [number of sessions of the physical therapist per week], I think that is enough, yes, I am terribly busy this week. Yesterday I saw the physical therapist, today you are here [interview], tomorrow I have to go to radiology, on Thursday I will see the thrombosis service… The following week, then I have to go back to umm, the surgeon. Yes, I mean you still have so many appointments.' (P10, female, 82 years).

In addition, some participants preferred the familiar relationships with formal caregivers instead of the short-term involvement of the community nurse and physical therapist. For example, one participant already had physical therapy before admission and did not accept additional home-based CR from the TCI. Another chronic heart failure participant had easily accessible contact with the hospital-based heart failure nurse specialist and consulted her instead of the community nurse in case of deviant symptoms:

> *'I must have a systolic pressure of 100 and no higher. (…). So, then I contacted A. [cardiac nurse specialist] when my blood pressure was too high. Because of course she obviously knows that too. (…) Then it turned out that she had passed a medication to the doctor, and from the doctor it went to the ward, but there had been a hitch when they forgot about this medicine.' (P6, male, 87 years)*

Besides the formal caregiver network, most participants also had informal caregivers nearby. Informal caregivers who were present during the interviews reported that they were involved in the TCI. They felt supported as they could ask questions about the care and discussed worries about their loved ones.

> *'Yes, I then asked for [advice]. About the quantity of syringes and [umm], but she also told you where is the best place to inject (…). She gave some good advice.' (Partner P8, male, 82 years)*

The presence of informal caregivers also had a strengthening effect on participants' therapy adherence. They often reminded the participant to perform the exercises from the physical therapist on a daily basis:

> *'I think it is incredibly good. I am also always attending so that I see what exercises he has to do. So then at least once a day I call "and now it is for all those exercises".' (Partner P8, male, 82 years)*

In participants with a small or no informal caregiver network, the CCB program was also experienced as additional support:

> *'Well, because I have that big stick behind the door. (…) And my husband thinks so too. He is away a lot. He also works now and then. It helps that there is still a little control [over the medicines].' (P16, female, 71 years).*

Discussion

This study explored frail older cardiac patients' experiences with a nurse-coordinated TCI. In general, participants appreciated the care they received within this intervention, and especially felt supported by the home visits in the post-clinical phase. However, participants with severe comorbidities did not always recognized the TCI as a personalized program. Participants with an extended (in)formal caregiver network were satisfied with the TCI, although they preferred their existing network. The results of this qualitative study contribute to an understanding on how the trial participants responded to the intervention and help to interpret the neutral study outcomes on hospital readmission and mortality within six months (Jepma et al, submitted). Three themes emerged from the data: 1) appreciation of care continuity; 2) varying experiences with recovery, and 3) the presence of an existing care network.

Regarding the first theme *appreciation of care continuity*, participants were positive about the delivered care in the clinical, discharge and post-clinical phase although they had some difficulties to distinguish the TCI from usual care. Participants who were able to remember the face-to-face handover of the integrated care plan in the clinical phase were positive about this visit from the community care nurse. Previous research showed that communication (e.g. effective handovers) between care settings contributes to patient satisfaction and is essential to ensure care continuity.[21,22] Furthermore, participants mainly appreciated the home visits of the community care nurse and physical therapist. Especially, interventions such as the measurement of vital signs, medication management and home-based rehabilitation were mentioned as of great value. Participants felt that the community nurse and physical therapist kept an extra eye on them post-discharge, which contributed to medication adherence and a sense of security to perform CR exercises. Previous studies also reported that patients felt safe when preventive home visits were delivered.[23,24] However, participants had some difficulties to mention the specific role of the community care nurse which was primary to prevent health deterioration. Darby et al.[25] previously examined the experiences of geriatric hospitalized patients and also described that patients did not recognize that observing and monitoring their health was part of the actual treatment. Therefore, it is possible that participants mostly experienced that the community nurse visited them without realizing that prevention of health deterioration was the main goal.

Regarding the second theme *varying experiences with recovery*, participants positively valued the home-based CR by the physical therapist and experienced that this has contributed to their functional recovery and self-confidence in their own abilities. This is in line with other studies that examined participants' experiences regarding rehabilitation.[26,27] However, some participants with severe

comorbidities experienced the physical therapy as too intensive. Although not measured, it is possible that these patients experienced apathy and therefore were less motivated. Apathy is a common geriatric condition around hospital admission[28] and independently associated with an increased risk of functional decline, frailty and cardiovascular disease.[29,30] These participants had less personalized rehabilitation goals and seemed less motivated for physical therapy. We observed that participants who were able to formulate personal rehabilitation goals were motivated to achieve progress in rehabilitation. Goal setting is essential in rehabilitation as it helps to evaluate the rehabilitation progress and is associated with increased patient motivation and satisfaction with care delivery.[31-33] Therefore, more attention on goal setting and recognition of apathy in frail older cardiac patients may be needed in the education of physical therapists for home-based CR. However, we hypothesize that some patients in this TCI were beyond the reach of preventive strategies because of their high age in combination with comorbidities and frailty, and improvement in functional status was no longer feasible. It is important to consider what participants could benefit from home-based CR and for what patients palliative interventions focussing on quality of life[34] would be more suitable.

Participants in this nurse-coordinated TCI were unsure if the home visits by the community nurse contributed to their recovery. It was observed during the interviews that participants reported nurses' interventions (e.g. consultation with the GP about the blood pressure) during the home visits but not recognized their importance to prevent complications. Bleijenberg et al.[35] previously described that older patients appreciated proactive nurse-led home visits when the timing was in line with their needs. It is possible that, after early signalling of health deterioration by the community nurse, proactive interventions were applied before participants noticed that action was needed. This is in line with the experiences of community nurses within this TCI who reported that they contributed to the prevention of complications by early signalling health deteriorations (e.g. heart failure decompensation).[15] In addition, one of the community nurses experienced that patients thought that they were able to recognize their heart failure deterioration early. However, her experience was that patients overlook the first signals of health deterioration and that early observation and intervening by the community nurse was important to prevent adverse events. This might explain why participants only reported that the community nurse consulted the hospital about the medication while the actual action might have been the prevention of a hospital readmission.

The third theme *the presence of an existing care network* showed that the participants in this TCI mostly had a large formal and informal caregiver network. Participants experienced that the community nurse and physical therapist collaborated with other healthcare professionals. Also, the informal caregivers were sufficiently involved in the intervention, for example in education by the

community nurse. A protocol for the content of the intervention was used within this TCI which was individualized as much as possible. However, we observed that participants with a large and more familiar formal caregiver network experienced the intervention as intensive and additional to their already busy schedule of care-related appointments. Therefore, the home visits might also be proactively performed by a familiar healthcare professional such as a nurse practitioner working at the general practice. Furthermore, some chronically ill participants seemed to have well self-management skills and were able to easily consult the heart failure nurse specialist themselves in case of a deteriorating health situation. It is known that care coordination across care transitions is important to ensure safe and efficient transitions in care and to reduce the risk of adverse outcomes.[3,36] As all included patients were at high risk of readmission and mortality,[13] also older cardiac patients with an existing care network and participants with self-management skills might contributed from a transitional care program. However, for future purpose, this nurse-coordinated TCI could personalize the intervention intensity and content more to participants' needs to improve patient satisfaction and efficiency of care.

Strengths and limitations

We were able to provide important insights into the experiences of older cardiac patients within a nurse-coordinated TCI to better understand the trial outcomes and the contribution of the intervention components. As this population is often excluded from clinical trials, their perspectives on participation in research are of added value. The identified themes in this qualitative study contribute to the further development of transitional care interventions for older cardiac patients.

This study also had some limitations. First, this qualitative study was performed within the first three months after the intervention was completed. Participants had difficulties to recall their experiences with the TCI, especially in the clinical and discharge phase. Therefore, it was difficult for patients to specifically recall their experiences regarding some key elements of the intervention and to distinguish usual care from care they received within the intervention. We were able to supplement participants' experiences with data from the logbooks in which involved healthcare providers reported the intervention delivery. This contributed to a more complete view of the intervention delivery in interviewed participants and put the qualitative results in perspective. Second, socially desirable answers could not be fully excluded and may have influenced participants' answers on their experience with the TCI. Third, selection bias might have occurred as we were unable to examine the experiences of participants whom were deceased soon after inclusion, had withdrawn informed consent in the TCI or did not consent to participate in this qualitative study (n=4). It is possible that their opinions would have resulted in

other experiences. Nevertheless, we believe the current selection of patients are representative for the study population in this study.

Conclusion

The results of this qualitative study contribute to an explanation of the neutral study. For future purpose, the intervention intensity and content of this nurse-coordinated TCI could be more individualized by tailoring interventions to older cardiac patients' needs, considering their frailty, self-management skills and existing formal and informal caregiver networks.

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Additional file 1: Interview guide

This interview will be about your experiences with the care you received after being admitted to the [name of hospital] at [name of ward] because of problems with your heart.

Opening question:

1. I understand that you were admitted for (designate the diagnosis)? Is that true?
   a. How are you now?

Clincal phase:

While at the ward in the hospital, you started participating in a scientific study referred to as the XXX study. To this end, you signed an informed consent form and a study nurse asked you a number of questions about the condition of your health prior to and during hospital admission. Can you still remember this? {If yes, continue to question 2}

No? It was a rather long questionnaire that was administered to you by a study nurse who completed the answers on a small computer screen that she had with her. For example, you were asked questions about your daily functioning (whether you could still wash yourself, change your clothes, runs errands) and about fatigue, your fear of falling, your appetite, the medicines you are taking and whether you are satisfied with your life. Do you still remember this? {Yes, go further to question 2} {No, skip to question 3}

2. Do you know why this questionnaire was administered to you?
   a. Yes? Can you explain that?
3. Did you get the feeling that you could also tell your own story during this interview?
   a. Can you tell us a bit more about that?
4. How stressful did you find this questionnaire?

In addition to the questionnaire, you also had to do some physical exercises, such as… Can you still remember that? {Yes, go further to question 5} {No, skip to question 7}

5. Do you know why these physical tests were done on you?
   a. Yes? Can you explain that?
   b. No?
6. How stressful did you find these physical tests?

Using the questionnaire and some physical tests, the study nurse assessed which health symptoms needed further attention during and after hospitalisation and a treatment plan was accordingly drawn up.

7. Have you discussed the results of the questionnaires and tests?
    a. Yes? Do you remember what was discussed with you?
        i. Can you say what you thought about that?
    b. No? Did you want the results of the tests to be discussed with you?

Using the treatment plan with goals, we wanted to see if we could facilitate your recovery.

8. Were there things you wanted to achieve yourself when you got back home?
    a. Yes? Can you explain that?
    b. Were these goals taken into consideration when drawing up the integrated care plan?
        i. Yes? Can you tell us a bit more about that?
        ii. No? Can you indicate exactly what you missed or how you would have wanted it differently?

Discharge phase

9. At one point you were almost allowed to go home. Can you tell us how the preparations for the discharge went and how you experienced this?
    a. Were there any other things that needed to be arranged for you before you went home?
        i. Yes? Can you tell us about everything that had to be arranged?
    b. Did you feel involved in everything that needed to be arranged for discharge and were you consulted?
        i. Yes? Can you tell us a bit more about that?
        ii. No? Can you indicate how you would have wanted to be more involved?

10. Did the community nurse visit you in the hospital?
    a. Yes? How did you feel about the community nurse visiting you in the hospital before? (Deepening; what exactly was nice or not?)
        i. Can you tell us what you thought of the conversation with the community nurse in the hospital?
        ii. Were there other things you would have wanted to discuss during this visit from the community nurse in the hospital?
    b. No? How would you have felt if you had already met the community nurse in the hospital?
        i. Yes? Can you explain that?

11. Can you tell me if you were confident to go home, were you ready for discharge?
    a. Yes? Can you tell us what you had confidence in?
    b. No? Can you tell us what you dreaded?

Post-clinical phase:

I now want to talk to you about the period back at home:

12. Can you tell us how you experienced the first period at home?
    a. Did you still need care at that time?
        i. Yes, what care did you need and who helped you with that?
    b. Can you tell us whether you were confident that this care was properly arranged?
    c. Can you tell us what was most difficult for you when you returned home?
        i. Did you discuss that with someone? (for example, the community nurse? With family or relatives? Or other caregivers?)
    d. Can you also tell us what was not so bad for you when you returned home?

We know that people are sometimes uncertain about their health status after being admitted to hospital. Such as symptoms that you may still have because of the hospitalisation, your condition, or things that you were able to do independently before admission but that are now more difficult.

13. Do you recognise that you have ever been unsure about something after being discharged from hospital?
    a. Yes? Can you tell us a bit more about that?
    b. Have you ever discussed these uncertainties with someone?

14. Did you have any other symptoms (physical or otherwise) when you were at home?
    a. Yes? Can you tell us about this?
    b. Have you ever discussed these symptoms with someone? (for example, the community nurse? With family or relatives? Or other caregivers?)
        i. Yes? With whom and how could they support you?
        ii. No? Why not?

15. Were there any family or relatives who were involved in the support when you returned home?
    a. Yes? Can you tell us about the role they play in the support?
    b. How do you experience the involvement of your family or relatives?

Community nurse

As I mentioned to you earlier, a community nurse [name] should have visited you during the first few weeks after discharge and she came to discuss how you were doing after your hospitalisation. Is that correct and do you remember it? {Yes? Go to question 16} {No? Go to question 17}?

16. Can you tell us a bit about the visits of the community nurse; and what you were talking about?

17. The community nurse visits patients to support their recovery after hospitalisation, for example by looking at your medicines with you, or discussing your fluid and diet intake and often your blood pressure is also monitored.
    a. Did she talk to you about the medicines, for example?
        i. Yes? Could you tell us more about what she then discussed with you?
        ii. No? What do you think about that? Would you have wanted the community nurse to have discussed this with you?
    b. b. Did you talk about, for example, your lifestyle (healthy food, exercise in daily life)?
        i. Yes? Could you tell us more about what she then discussed with you?
        ii. No? What do you think about that? Would you have wanted the community nurse to have discussed this with you?
    c. c.(If possible) You just said that you sometimes had… complaints at home. Is that also something that you have discussed with the community nurse?
        i. If so, what did she do about your complaints?
        ii. If not, do you know why you did not discuss this with her?

18. Did you feel that the community nurse took your wishes into consideration?
    a. Yes? Can you tell us a bit more about that?
    b. No? Can you tell us whether and how he/she could have had more due consideration to your wishes?
    c. To what extent did the community nurse encourage you to remain independent?

19. Did you trust the expertise of the community nurse?
    a. Can you say why or why not?

20. Do you know approximately how frequently the community nurse has visited your home?
    a. Was the number of visits sufficient for you, or did you think the number of visits was too many or too few?

b. Was the number of visits spread nicely over the time for you? Was there too much or too little time in between?

Physical therapist

In the first few weeks, a physical therapist [name] had also visited you a number of times. Can you still remember that? {*No? The physical therapist has probably worked with you on your condition and given you exercises to perform on your own, such as getting up from a chair several times, and perhaps doing squats, is that correct?*} {No: go to question 22, Yes: go to question 17}

21. Can you tell us about the visits of the physical therapist to your home, what exactly did he/she do?

The physical therapist sometimes helps people set goals to return to activities that may have been made more difficult by the hospital admission. Sometimes the physical therapist exercises together to facilitate doing this independently again.

22. Was it jointly discussed with you what you would like to achieve with the visits of the physical therapist?
    a. Yes? Can you tell us a bit more about that?
    b. No? Can you tell us how he/she could have had more due consideration to your wishes here?

23. Did the physical therapist give you exercises that you could perform yourself when the physical therapist was not present?
    a. No? Do you know why you did not get any exercises?
        i. What do you think about that?
    b. Yes? What did you think of the exercises?
    c. Were the exercises too difficult, exactly right or too easy?
    d. Were you successful in performing these exercises even when the physical therapist was not there?
    e. Did the physical therapist encourage you to get started with the exercises yourself?
        i. Yes? Can you tell us how he/she did that?
        ii. No? How could the physical therapist have stimulated you more?
    f. Were you confident that these exercises also contributed to your recovery?
        i. Can you say why or why not?
    g. Have you ever found it exciting to exercise, even when the physical therapist was with you?
        i. Can you say why/why not?

24. Did you trust the expertise of the physical therapist?
    a. Can you say why or why not?

25. Do you know approximately how frequently the physical therapist has visited your home?
    a. Was the number of visits sufficient for you, or did you think the number of visits was too many or too few?
    b. How many times a week did the physical therapist visit you? Was the number of visits spread nicely over the time for you? Was there too much or too little time in between?

26. Did the community nurse and the physical therapist also visit you home together/at the same time?
    a. Yes? Can you tell us how this visit came about?
    b. Do you also know why they visited your home together?
        i. What has this visit contributed to for you?
        ii. How were you involved in this joint visit?

27. Did the community nurse or physical therapist ever have contact with the hospital or your general practitioner?
        i. Yes? Do you know what this was for?
        ii. How did you feel about them doing that and then involving you with it?

28. I understand that many caregivers visited you. What do you think about that?

Closure:

29. Are you satisfied with the current condition of your health and what you have achieved since your discharge from the hospital?
    a. Yes? Do you feel that the support of the community nurse has contributed to this? And the physical therapist?
        i. Which support has contributed something for you and which support has not?
    b. No? Can you indicate why?

30. Have you been readmitted to hospital recently?
    a. Yes? What was the reason for this readmission?
    b. How did that go?
    c. Were any more caregivers involved in the readmission?
        i. Yes? Which caregivers were involved and how?
        (Emphasis on the community nurse and physical therapist at home)

(Only ask this question if appropriate)
I hear you say that xxx went wrong, but is it true that this gives you the impression that the readmission was unnecessary?

31. Could the admission have been prevented in your opinion?
    i. If so, how do you think it could have been prevented?

32. Are there any aspects you missed in this interview, which you think are important for me to know?

May I thank you very much for this interview. You have told me a lot in a short time, we will deal with the information xxx as follows and we will use it xxx.

Chapter

10

General discussion

The overall aim of the work described in this thesis was to explore the integration of cardiac and geriatric care for older patients with heart disease. First, by examining how hospitalized older cardiac patients at high risk for adverse events can be identified. Second, by investigating lifestyle-related secondary prevention of cardiovascular complications in older cardiac patients. And third, by the development and evaluation of a transitional care intervention for older cardiac patients. This chapter will reflect on the main findings and provides recommendations for research, clinical practice, and education.

Main findings

The identification of high-risk patients remains challenging. In **Chapter 2**, we found that the incidence of readmission and mortality in patients ≥ 70 years is the highest in the first week post-discharge. The risk factors presence of comorbidities, an admission in the previous six months, living alone, and non-native Dutch origin increased the risk of readmission and mortality, and we found that these risks varied across different time points. We concluded that preventive interventions need to start as soon as possible to prevent early readmission and mortality.

Chapter 3 provides an overview of clinical risk prediction models than can help to identify hospitalized cardiac patients at high risk of readmission. We found that current models do not perform well, have low consistency in the measurement of predictors, cannot be replicated and carry a high risk of bias. Although many clinical models have been developed, no model can currently be recommended for clinical practice. Model updating and external validation of existing models is therefore urgently needed.

In **Chapter 4** we examined the performance of the Dutch Safety Management System (DSMS) screening tool, alone and in combination with other predictors, to estimate all-cause unplanned hospital readmission and mortality in older hospitalized cardiac patients. We found that this tool had limited capacity to accurately estimate the risk of readmission and mortality in this population. Involving other clinical information, including both geriatric and disease-specific risk factors, resulted in a moderately performing prediction model. Further research on adequate identification of older high-risk cardiac patients is warranted.

We also examined lifestyle-related secondary prevention of cardiovascular complications in older cardiac patients. In **Chapter 5**, we analyzed the treatment effect of the RESPONSE-2 trial on lifestyle-related risk factors in older (≥ 65 years) versus younger (< 65 years) patients. This chapter demonstrates that despite more adverse cardiovascular risk profiles and comorbidities, nurse-coordinated referral to a community-based lifestyle intervention was at least as successful in

improving lifestyle-related risk factors in older as in younger patients. Older age alone should not be a reason to withhold lifestyle interventions in patients with coronary artery disease.

In **Chapter 6**, we examined older cardiac patients' perspectives regarding lifestyle modification after a hospital admission using the Attitudes, Social influence and self-Efficacy model. In most older patients, their *attitude* was formed by general health and habits. Experiencing a health threat (e.g. presence of severe symptoms) was observed as a motivator for lifestyle modification. However, patients balanced health benefits and quality of life when considering lifestyle modifications. Regarding *social influence*, it was observed that patients felt both encouraged and hindered by family members and that older patients valued the opinion of healthcare professionals. Within the determinant *self-efficacy*, it was found that older cardiac patients had difficulties to integrate lifestyle advices in their daily life and that some patients were limited by functional impairments. We concluded that short-term and patient-centered outcomes, such as functional independence, are important for older patients and may be a useful starting point when healthcare professionals discuss lifestyle modification. Furthermore, the involvement of family members may help patients to integrate lifestyle-related secondary prevention in daily life.

Third, we developed (**Chapter 7**) and evaluated (**Chapter 8** and **Chapter 9**) the effect of the Cardiac Care Bridge program (CCB program): a nurse-coordinated, interdisciplinary transitional care intervention for older cardiac patients combining case management, disease management and home-based cardiac rehabilitation. **Chapter 8** reports that no beneficial effect on the composite primary outcome of readmission and mortality was found. We hypothesized that the selected patient population may not be responsive to high-intensity preventive strategies. In future research, one should carefully consider the population eligible for this type of interventions and those who are in the advanced stage of disease and move towards end-of-life interventions.

In **Chapter 9**, we examined the experiences of participating patients in the CCB program. They appreciated the home visits and care continuity post-discharge, but some questioned the contribution of the CCB program to their recovery. Furthermore, the CCB program was experienced as too intensive by some patients and as an extra burden on top of an already busy schedule of care-related appointments. We concluded that the intervention intensity and content of this nurse-coordinated transitional care intervention should be more individualized in the future by tailoring interventions to older cardiac patients' needs, considering their frailty, self-management skills and existing (in)formal caregiver network.

Implications

The results of this thesis have several implications for research, clinical practice, and education.

Implications for research

The use of clinical prediction models to identify high-risk older cardiac patients could be helpful to target interventions to the appropriate group. However, we found that most studies were of low quality and that the current models are not applicable in clinical practice (**Chapter 3**). More high-quality studies are needed to evaluate the discrimination, calibration and clinical usefulness, and to be able to identify high-risk patients in a phase when preventive interventions may be effective. Furthermore, only eight of the sixty included studies[1-6] in our systematic review included geriatric risk factors such as physical performance and dementia, which are known to increase the risk for adverse events. It is therefore unlikely that most of the current models will hold their value in daily clinical practice where there is a high prevalence of older patients. This might be explained by the relatively low mean age in the underlying studies as most studies included patients ≤ 70 years which lowers the risk for the presence of geriatric syndromes.

Our results on the DSMS-tool (**Chapter 4**) showed that this tool alone had limited capacity (0.61, 95% 0.56-0.66) to estimate the risk of all-cause unplanned readmission and mortality in older cardiac patients. Previously, Heim et al.[7] studied the performance of the DSMS-tool among hospitalized patients ≥ 70 years with a variety of non-cardiac diagnoses on functional loss, high healthcare demand and mortality within three months. They found a sensitivity of 0.61 and a specificity of 0.75 (c-statistics 0.68). Furthermore, Hermans et al.[8] found an odds ratio of 9.6 (95%CI 1.6-56.9) for a DSMS-score (≥ 1) to predict 30-day mortality. Until now, only few studies have studied the performance of the DSMS-tool. These studies vary in study population, time window, methods, and outcomes and are therefore difficult to compare. As a result, more research is needed to study the performance of the DSMS-tool, especially since in the Netherlands its use is compulsory in all patients ≥70 years who are hospitalized.[9]

The evidence on secondary prevention of cardiovascular complications is less conclusive in older as compared to younger patients.[10,11] Older cardiac patients are underrepresented in clinical trials which results in poor generalizability of effective interventions in this population.[12] Furthermore, single disease-oriented guidelines inadequately take patients with multimorbidity and geriatric conditions into account.[13] The ageing cardiac population will grow significantly in the coming decades,[14] and therefore more research is needed on optimal treatment strategies for these patients.

The CCB program (**Chapter 8**) was a high-intensity preventive intervention and was not effective in reducing readmission and mortality rates in severely frail older cardiac patients. This suggest that these patients may have been beyond the reach of preventive interventions. It is currently unknown what patients may benefit from high-intensity preventive interventions such as the CCB program and in what patients advance care planning interventions with more focus on comfort and quality of life may be more effective. More research is needed on how to distinguish these types of high-risk older cardiac patients to be able to better target interventions to their needs. Furthermore, some other outcomes within the CCB program are currently analyzed such as medication adherence, activities of daily living and quality of life. These secondary outcomes may provide additional insights on the effectiveness of this intervention.

Implications for clinical practice

We found that the DSMS-tool alone had limited capacity to detect older cardiac patients at risk of all-cause unplanned readmission or mortality within six months after hospitalization (**Chapter 4**). Several models were developed, and we found that the performance of the model was at best moderate when both geriatric and disease-specific risk factors (admission diagnosis and the Charlson comorbidity index) were assessed (c-statistic of 0.69, 95% 0.63-0.73). The SILVER-AMI study included patients ≥ 75 years and developed risk prediction models for 30 and 180-day readmission.[2,15] In accordance with our results, they found a combination of geriatric as well as disease-specific risk factors that best estimated the risk of readmission (c-statistic validation cohort=0.65). To detect older cardiac patients at risk, both geriatric and disease-specific risk factors should therefore be identified to be able to start early preventive interventions in those in need. As the performance of prediction models remain only modest, it possibly should be accepted that accurate risk stratification between patient at risk and patients at very high risk might not be possible.

It is important that healthcare professionals consider secondary prevention of cardiovascular complications in older cardiac patients. We found that easily accessible community-based lifestyle interventions were also effective in this population (**Chapter 5**). Remarkably, a considerable percentage of older patients in the control group (61%) showed no improvement in lifestyle-related risk factors, demonstrating that risk modification in older patients is suboptimal in current secondary preventive care. This may be partly due to the less conclusive evidence in this population.[10,11] In addition, our qualitative analyses demonstrated patients' perspectives that influenced their motivation for lifestyle modification. For example, patients sometimes had difficulties to adapt lifestyle modifications in their daily life or where hindered by physical limitations (e.g. in physical activity). After a hospital admission, older patients need more help to integrate advices

in their daily life, for example by guidance in their own environment and by the involvement of relatives and friends. Furthermore, we found that older patients sometimes questioned whether lifestyle modification at their age would yield any health benefit. The time-to-benefit of some lifestyle changes may indeed exceed the life expectancy in older patients.[16] Healthcare professionals therefore need to explore older patients' preferences and consider if lifestyle modifications would yield any advantages at their age (**Chapter 6**). This may lead to the shared decision that no new lifestyle changes are to be implemented. However, some lifestyle-related interventions are associated with increased quality of life and functional independence[11,17,18] and older cardiac patients' need to be given the opportunity to consider these interventions.

In part 3 of this thesis, we developed and evaluated the nurse-coordinated CCB transitional care program for older cardiac patients (**Chapter 7-9**). This intervention was unable to reduce the risk of readmission and mortality for this frail older population (**Chapter 8**) and we therefore do not recommend implementation in its current design. Furthermore, the fidelity of some intervention components was low.[19] This may have influenced our outcomes and some recommendations could be made, independent of the neutral study findings on readmission and mortality.

In the CCB program (**Chapter 7** and **8**), we aimed to integrate cardiac and geriatric care during and after hospitalization which partly succeeded. For example, all patients received a comprehensive geriatric assessment during the clinical phase. However, this was an extensive additional anamnesis on top of the usual anamnesis which sometimes was a burden for very ill and fatigued patients. Further integration of components of the comprehensive geriatric assessment in the usual anamnesis may contribute to less burden for patients, the timely recognition of geriatric conditions and the early deployment of interventions.

The geriatric consultation within the CCB program was performed in only 17% of patients with an indication. However, we found a high prevalence of geriatric conditions such as (risk of) delirium (56%), falling (47%), physical disabilities (39%), malnutrition (33%) and cognitive impairment (31%). Our process evaluation showed that a short hospital stay was one of the main reasons for the lack of geriatric consultation.[19] Geriatric conditions were therefore not adequately addressed during hospitalization which deprived the opportunity to prevent further deterioration and adverse event. As we found that the incidence of readmission and mortality in cardiac patients ≥ 70 years was the highest in the first week post-discharge (**Chapter 2**), we hypothesize that prevention of adverse events may already be needed during hospitalization. The Transitional Care Bridge study,[20] on which the CCB program was inspired, found a positive result on mortality within six months post-discharge. A possible explanation may be that the clinical component of the intervention was performed by the geriatric

hospital team. Previous research also showed that this was associated with reduced mortality in the first six months post-discharge.[21] This indicates that more intensive collaboration with the geriatric team is needed in hospitalized older cardiac patients. In addition, to better integrate disease-specific and geriatric care, also geriatric co-management interventions may be more suitable during hospitalization. Within geriatric co-management interventions, the responsibility for the treatment is shared between the medical specialty of patients' diagnosis and the geriatric team.[22] Both teams collaborate intensively in the prevention and treatment of geriatric care. Previous research in geriatric patients found that multidisciplinary geriatric co-management is associated with recovery in activities of daily living and mobility, and a reduction of complications and length of stay.[23] A shared interdisciplinary collaboration in the treatment of older cardiac patients during hospitalization may contribute to the integration of cardiac and geriatric care and may prevent complications post-discharge.

The transitional phase in which patients moved from hospital to home is experienced as a period in which patients are at high risk of readmission and mortality. In the CCB program,[24] we aimed to improve this transition by a personal handover of the treatment and integrated care plan from the cardiac hospital nurse to the community care nurse. This component was only performed in 35% of the cases. The process evaluation of the CCB program suggested that a short hospital stay and ad hoc discharge planning reduced the opportunity for the in-hospital handover of the integrated care plan to the community care nurse.[19] Previous research showed the importance of a clear transfer of information in the transition of care.[25,26] Therefore, more feasible options may be considered such as digital resources (e.g. tablet) to perform a handover. This may contribute to the continuity of care from hospital to home while it is less time-consuming.

In the post-clinical phase, the home visits in the CCB program by the community care nurse and physical therapist were appreciated by patients. However, due to their frailty and comorbidities, most patients already had a large (in)formal caregiver network. These patients experienced the CCB program as intensive and additional to their already busy schedule of care-related appointments. However, it is known that care coordination across care transitions is important to ensure safe and efficient transitions in care and to reduce the risk of adverse outcomes.[27,28] Therefore, transitional care interventions may be more integrated in patients' already existing network, for example by a nurse practitioner working at the general practice. This may increase the continuity of care and reduces the intensity of care for the patient.

Implications for education

Care during hospitalization is mainly delivered from a *disease management* approach, focusing on a disease-specific treatment. As a result, geriatric conditions remain often unrecognized, although they increase the therapy complexity and the risk for adverse events.[27,29] More attention for geriatrics in the curricula of medical, paramedic and nursing students is needed to be able to recognize and treat geriatric conditions in time. In addition, traditional curricula commonly address single complaints and diseases. Although this is a logical initial approach, it should probably be expanded by education on multimorbidity and complex cases. In addition, interprofessional education is needed to prepare students for interdisciplinary collaboration. This may contribute to adequate treatments of frail and multimorbid cardiac patients.

In primary care, care is mostly provided from a *case management* approach, focusing on treatments with a broad view of patients' needs.[28] After hospitalization, more disease-specific guidance e.g. symptom monitoring, medication reconciliation and specific guidance in medication and lifestyle adherence is required to reduce disease-specific adverse events post-discharge.[30,31] We therefore recommend to educate healthcare professionals in primary care (e.g. community nurse and physical therapist) in disease-specific knowledge such as the early signs of deterioration in heart failure.[32]

In the CCB program, we educated all participating healthcare professionals in disease management, case management and home-based cardiac rehabilitation at the start of the study. For future trials, we suggest to create a continuous learning environment[33] in which professionals are educated and instructed on an ongoing base. From an educational perspective, the transfer of knowledge does not automatically lead to the required competence to perform the tasks as outlined in the study protocol.[34] We observed that some early signals of deterioration were not recognized in time which was associated with readmissions that might have been avoidable.[35] Therefore, interprofessional training on a regular basis may be needed in which healthcare professionals could bring their own case reports and discuss with specialists what interventions may be applied and what could be done differently in the future.

Conclusion

This thesis explored the integration of cardiac and geriatric care for older cardiac patients and shows that this should be a priority in the coming years. Based on this thesis, recommendations can be made. First, most current risk prediction models are unable to adequately identify older cardiac patients at risk for adverse events. Further research is needed to investigate if prediction

models combining disease-specific and geriatric risk factors could improve risk assessment in this high-risk population. As long as accurate models are absent, a distinction between high risk and very high risk cannot be made in older cardiac patients and is therefore not recommended for clinical purposes. Second, age alone should not be a reason to withhold lifestyle-related secondary prevention in older cardiac patients. Their treatment preferences and important outcomes, such as quality of life and functional independence, need to be considered when discussing lifestyle modification. Third, the high-intensity Cardiac Care Bridge program in older cardiac patients did not reduce their risk of readmission and mortality. Other, effective interventions for this population could be developed. Alternatively, our research might show that frail older cardiac patients need more palliative interventions focusing on comfort and quality of life and should no longer be exposed to high-intensity preventive interventions. More research is needed on how to distinguish patients who may benefit from high-intensity preventive interventions from those who may benefit more from palliative interventions.

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Chapter

11

Summary
Nederlandse samenvatting

Summary

Bringing the pieces together
integrating cardiac and geriatric care in older patients with heart disease

Due to the increasing aging population, the number of older cardiac patients is also expected to rise in the next decades. The treatment of older cardiac patients is complex due to the simultaneously presence of comorbidities and polypharmacy, and geriatric conditions such as functional impairment, fall risk and malnutrition. However, the assessment of geriatric conditions is not part of the medical routine in cardiology and therefore these conditions are frequently unrecognized although they have a significant impact on treatment and on outcomes. In addition, treatments are mostly based on single-disease oriented guidelines and inadequately take other conditions into account. This may lead to conflicting recommendations and treatments that do not address important outcomes for older patients such as daily functioning, symptom relief and quality of life. Thus, the care of older cardiac patients is currently suboptimal which increases the risk of functional loss, readmission and mortality.

The overall aim of the work described in this thesis is to explore the integration of cardiac and geriatric care for older patients with heart disease. First, by examining how hospitalized older cardiac patients at high risk for adverse events could be identified. Second, by investigating lifestyle-related secondary prevention of cardiovascular complications in older cardiac patients. And third, by developing a transitional care intervention for older cardiac patients and evaluating the effect on unplanned hospital readmission and mortality.

Part 1: The identification of older hospitalized cardiac patients at high risk of adverse events

Chapter 2 describes the incidence of first unplanned all-cause readmission and mortality of Dutch patients ≥ 70 years after hospitalization for acute myocardial infarction (AMI: n=5,175) or heart failure (HF: n=9,837) and explores which effects of baseline risk factors vary over time. In total, 20.4% of patients with AMI and 24.6% of patients with HF had an unplanned all-cause readmission and 9.9% (AMI) and 22.4% (HF) had died within six months post-discharge. The incidence of these adverse events was the highest in the first week post-discharge and were higher and prolonged in HF patients in comparison to AMI patients. Patients with comorbidities, an admission in the previous six months, patients living alone, and non-native Dutch patients were at highest risk of early readmission and mortality.

Chapter 3 provides an overview of clinical risk prediction models for unplanned hospital readmission in acutely hospitalized cardiac patients. We identified 60 studies that reported the results of 81 separate clinical risk prediction models and a total of 766 predictors for unplanned readmission. Most clinical models performed poor to modest and the risk of bias was high in almost all studies (98.9%). In addition, there was little consistency in the measurement of predictors. Also, in independently externally validated cohorts, none of the clinical models demonstrated good discrimination (i.e. c-statistic > 0.8). GRACE was the only model that demonstrated adequate discrimination in multiple cohorts including patients with acute coronary syndromes and HF. However, the risk of bias was also high in these studies.

Chapter 4 presents the results of the discriminative performance of the DSMS screening tool, alone and in combination with other predictors, on a six-month composite outcome of hospital readmission and mortality in hospitalized older cardiac patients. The DSMS-tool was unable to accurately estimate the risk of readmission and mortality in hospitalized older cardiac patients (c-statistic 0.61, 95% 0.56-0.66). The addition of the Charlson comorbidity index and admission diagnosis resulted in a moderate model performance (c-statistic 0.69, 95% CI 0.63-0.73; P_{HL} 0.658). To optimize the early identification of older hospitalized cardiac patients at high risk, the combination of geriatric and disease-specific predictors should be further explored.

Part 2: Lifestyle-related secondary prevention of cardiovascular complications in older cardiac patients

Chapter 5 reports on lifestyle modification in older older (≥ 65 years, n=245) versus younger (< 65 years, n=579) patients with coronary artery disease in the RESPONSE-2 trial. This study investigated the treatment effect of nurse-coordinated referral to a comprehensive set of up to three community-based lifestyle interventions that focused on weight reduction, physical activity and/or smoking cessation. Within the current study, a secondary analysis was performed on the proportion of older versus younger patients with improvement at 12 months follow-up in ≥ 1 lifestyle-related risk factor. At baseline, older patients (mean age 69.2 ± 3.9 years) had more adverse cardiovascular risk profiles and comorbidities than younger patients (mean age 53.7 ± 6.6 years). There was no statistically significant variation on the proportion of patients with improvement in ≥ 1 lifestyle-related risk factor according to age (p-value effect modification improvement by age=0.45, OR 1.67, 95% CI 1.22-2.31). However, older patients were more likely to achieve ≥ 5% weight loss (OR old 5.58, 95% CI 2.77-11.26 vs. OR young 1.57, 95% CI 0.98-2.49, p=0.003) and younger patients were more likely to show non-improved lifestyle-related risk factors (OR old 0.38, 95% CI 0.22-

0.67 vs. OR young 0.88, 95% CI 0.61-1.26, p=0.01). We concluded that despite older patients' adverse cardiovascular risk profiles and comorbidities, nurse-coordinated referral to a community-based lifestyle intervention was at least as successful in improving lifestyle-related risk factors in older as compared to younger patients.

Chapter 6 reports on the findings of a qualitative study in cardiac patients ≥ 70 years to examine their perspectives toward lifestyle-related secondary prevention within three months after a hospital admission. Eight themes emerged which were linked to the determinants of the Attitudes, Social influence and self-Efficacy model (ASE-model). Within the determinant *attitude*, three themes were identified: 1) perspectives are determined by general health and habits, 2) feeling the threat as a motivator, and 3) balancing between health benefits and quality of life. Regarding *social influence*, two themes emerged: 4) feeling both encouraged and hindered by family members, and 5) the healthcare professional says so. For the *self-efficacy* determinant, the following three themes were identified: 6) experiences from previous lifestyle changes, 7) integrating advice in daily life and, 8) feeling limited by functional impairments. We concluded that patients' preferences and patient-centred outcomes focusing on quality of life and functional independence can be a good starting point for healthcare professionals to discuss lifestyle modification with older patients. The involvement of family members may help to integrate lifestyle-related secondary prevention in daily life.

Part 3: Development and evaluation of a transitional care intervention for older cardiac patients

Chapter 7 describes the design of the Cardiac Care Bridge program which was a multicentre randomized clinical trial in hospitalized cardiac patients ≥ 70 years at high risk of readmission and mortality. This nurse-coordinated, interdisciplinary transitional care program combined case management, disease management and home-based cardiac rehabilitation in frail older cardiac patients. All patients received a comprehensive geriatric assessment and the intervention group received an additional integrated care plan, a face-to-face handover with the community nurse before discharge and follow-up home visits within two days, one, three and six weeks. The community nurse collaborated with a pharmacist and patients received home-based cardiac rehabilitation from a physical therapist. The primary composite outcome was first all-cause unplanned readmission or mortality within six months.

Chapter 8 describes the effects of the CCB program on the primary outcome of unplanned readmission and mortality within six months following

hospitalization. In total, 306 patients were included (51% male, mean age 82.4 years ± 6.3 years). Nearly 50% were hospitalized or had fallen in the previous six months, 31% were cognitively impaired and 39% had functional impairments. 67% of the intervention components were delivered: 75% of key-elements in the clinical phase, 37% in the discharge phase and 64% in the post-clinical phase. The primary outcome incidence was 54.2% (83/153) in the intervention group and 47.7% (73/153) in the control group (RR 1.14, 95% CI 0.91-1.42, p=0.253). At twelve months, comparable results on the composite outcome were found. No statistically significant differences were observed for the outcome readmission at three, six and twelve months and for mortality on three and six months. Within twelve months follow-up, 38.6% of patients in the intervention group and 26.8% patients in the control group died (RR 1.44, 95% CI 1.04-2.00, p=0.028). These results demonstrate that the CCB program in high-risk older cardiac patients did not reduce the high rates of hospital readmission or mortality. We hypothesize that the selected patient population may not be responsive to high-intensity preventive strategies. Other interventions with a focus on comfort and quality of life might be more suitable in this population.

Chapter 9 reports on participants' experiences with the CCB program. Three themes emerged from the data: 1) appreciation of care continuity; 2) varying experiences with recovery; and 3) the presence of an existing care network. Participants felt supported by the CCB program due to the post-discharge caregiver support which contributed to the perceived continuity of care. The perceived contribution of the program in participants' recovery varied. Some participants reported physical improvements while others felt impeded by comorbidities or frailty. The home visits by the community nurse were appreciated, although some participants did not recognize the added value. Participants with an existing formal caregiver network preferred to consult this network instead of the caregivers who were involved in the transitional care intervention. We concluded that the intervention intensity and content of the CCB program should be more individualized in the future by tailoring interventions to older cardiac patients' needs, considering their frailty, self-management skills and existing (in)formal caregiver network.

Chapter 10 presents a general discussion on the main findings and presents implications for research, clinical practice and education. This thesis explored the integration of cardiac and geriatric care for older cardiac patients and shows that this should be a priority in the coming years. Based on this thesis, recommendations can be made. First, most current risk prediction models are unable to adequately identify older cardiac patients at risk for adverse events. Further research is needed to investigate if prediction models combining disease-specific and geriatric risk factors could improve risk assessment in

this high-risk population. As long as accurate models are absent, a distinction between high risk and very high risk cannot be made in older cardiac patients and is therefore not recommended for clinical purposes. Second, age alone should not be a reason to withhold lifestyle-related secondary prevention in older cardiac patients. Their treatment preferences and important outcomes, such as quality of life and functional independence, need to be considered when discussing lifestyle modification. Third, the high-intensity Cardiac Care Bridge program in older cardiac patients did not reduce their risk of readmission and mortality. Other, effective interventions for this population could be developed. Alternatively, our research might show that frail older cardiac patients need more palliative interventions focusing on comfort and quality of life and should no longer be exposed to high-intensity preventive interventions. More research is needed on how to distinguish patients who may benefit from high-intensity preventive interventions from those who may benefit more from palliative interventions.

Samenvatting

Het samenbrengen van de puzzelstukjes
integratie van cardiologische en geriatrische zorg voor oudere hartpatiënten

Door de groeiende populatie ouderen, wordt in de komende decennia ook een toename van het aantal oudere hartpatiënten verwacht. De behandeling van deze populatie is complex door de gelijktijdige aanwezigheid van meerdere ziekten en geriatrische problemen zoals functionele beperkingen, valrisico en ondervoeding. De screening van geriatrische problemen is in de cardiologie nog geen onderdeel van de medische anamnese met als gevolg dat deze problemen vaak niet worden herkend. Zij hebben echter wel een negatieve invloed op de cardiologische behandeling.

De cardiologische behandeling is voornamelijk gebaseerd op aanbevelingen uit richtlijnen die zich op een enkele ziekte richten en die andere ziekten buiten beschouwing laten. Dit leidt vaak tot tegenstrijdige aanbevelingen en tot behandelingen die onvoldoende rekening houden met uitkomsten die voor oudere patiënten belangrijk zijn, zoals het dagelijks functioneren, symptoomverlichting, zelfredzaamheid en kwaliteit van leven. De zorg voor oudere hartpatiënten is momenteel dus niet optimaal, wat het risico verhoogt op functieverlies, heropname en overlijden.

Het doel van dit proefschrift is om de integratie van cardiologische en geriatrische zorg voor oudere hartpatiënten te onderzoeken. Ten eerste, door te onderzoeken hoe in het ziekenhuis opgenomen oudere hartpatiënten met een hoog risico op ongewenste uitkomsten kunnen worden geïdentificeerd. Ten tweede, door het onderzoeken van leefstijlgerelateerde secundaire preventie bij oudere hartpatiënten. En ten derde, door het ontwikkelen en evalueren van een transmurale interventie voor oudere hartpatiënten met als doel het voorkomen van ongeplande heropname en overlijden.

Deel 1: De identificatie van in het ziekenhuis opgenomen oudere hartpatiënten met een hoog risico op ongewenste uitkomsten

Hoofdstuk 2 beschrijft hoe vaak een eerste ongeplande heropname en overlijden binnen zes maanden optreden bij Nederlandse patiënten ≥ 70 jaar na een ziekenhuisopname voor een acuut myocardinfarct (AMI, n=5175) of hartfalen (HF, n=9837). In totaal werd 20% van de patiënten met een AMI en 25% van de patiënten met HF ten minste één keer ongepland heropgenomen binnen zes maanden. Daarnaast overleden binnen deze tijdsperiode 10% van de patiënten met een AMI een 22% van de patiënten met HF na ontslag. De

frequentie van deze ongewenste uitkomsten was het hoogst in de eerste week na ontslag. In vergelijking met patiënten met een AMI, hadden patiënten met HF een groter risico op ongewenste uitkomsten en dit risico was ook langer aanwezig. Hoofdstuk 2 onderzocht daarnaast of én welke risicofactoren het risico over de tijd beïnvloedden. Patiënten hadden het grootste risico op vroege heropname en overlijden wanneer er ook sprake was van de aanwezigheid van andere ziekten, een eerdere ziekenhuisopname in de afgelopen zes maanden, een niet-Nederlandsche achtergrond of wanneer zij alleen woonden.

Hoofdstuk 3 geeft een overzicht van modellen voor het voorspellen van ongeplande heropnames in acuut opgenomen hartpatiënten. We identificeerden 60 studies die de resultaten beschreven van 81 verschillende 'klinische predictiemodellen', dat wil zeggen modellen die van toepassing zijn op opgenomen patiënten, en 766 voorspellers voor ongeplande heropname. De meeste van de klinische predictiemodellen presteerden matig tot slecht and bijna alle studies hadden een hoog risico op vertekening ('bias') (98,9%). Daarnaast was er weinig consistentie in de manier waarop de voorspellers werden gemeten. In de extern gevalideerde cohorten werd bij geen enkel predictiemodel een goed onderscheidend vermogen voor ongeplande heropname gevonden. GRACE was het enige predictiemodel dat voldoende onderscheidend vermogen liet zien in meerdere cohorten van patiënten met een acuut coronair syndroom of HF.

Hoofdstuk 4 presenteert gegevens over het onderscheidend vermogen van het screeningsinstrument van het Veiligheidsmanagementsysteem (VMS) op heropname of overlijden binnen zes maanden bij oudere hartpatiënten die zijn opgenomen in het ziekenhuis. De VMS was maar beperkt in staat om het risico op heropname of overlijden accuraat te schatten (c-statistic 0.61, 95% betrouwbaarheidsinterval (BI) 0.56-0.66). Het toevoegen van andere risicofactoren (Charlson comorbidity index en opnamediagnose) resulteerde in een redelijk onderscheidend vermogen (c-statistic 0.69, 95% BI 0.63-0.73). Om het tijdig identificeren van oudere hartpatiënten met een hoog risico op ongewenste uitkomsten mogelijk te maken, is meer onderzoek nodig naar de toegevoegde waarde van zowel ziekte-specifieke als geriatrische risicofactoren in klinische predictiemodellen voor deze patiëntengroep.

Deel 2: Leefstijlgerelateerde secundaire preventie van cardiovasculaire complicaties bij oudere hartpatiënten

Hoofdstuk 5 beschrijft leefstijlverandering bij oudere (≥ 65 jaar, n=245) versus jongere (< 65 jaar, n=579) patiënten met een coronaire hartziekte in de RESPONSE-2 studie. Dit was een onderzoek waarin drie laagdrempelig toegankelijke leefstijlprogramma's werden aangeboden die gericht waren op

gewichtsvermindering, beweging en/of stoppen met roken. Deze zorg werd door verpleegkundigen gecoördineerd. Met de gegevens van het onderzoek werd een secundaire analyse uitgevoerd waarin het verbeteren van leefstijlgerelateerde risicofactoren werd vergeleken tussen oudere (≥ 65 jaar) en jongere patiënten (<65 jaar) in de eerste 12 maanden na ziekenhuisopname. Bij aanvang van de studie hadden oudere patiënten (gemiddelde leeftijd 69 jaar) meer ongunstige cardiovasculaire risicoprofielen en bijkomende aandoeningen ten opzichte van jongere patiënten (gemiddelde leeftijd 54 jaar). Na 12 maanden werd er tussen oudere en jongere patiënten geen statistisch significant verschil gevonden in verbetering van één of meer leefstijlgerelateerde risicofactoren (p-waarde effectmodificatie= 0,45, OR 1,67, 95% BI 1,22-2,31). Oudere patiënten hadden wel meer kans om 5% (of meer) gewichtsverlies te bereiken (OR oud 5,58, 95% BI 2,77-11,26 vs. OR jong 1.57, 95% BI 0,98-2,49, p=0.003). Jongere patiënten hadden meer kans om niet te verbeteren op leefstijlgerelateerde risicofactoren (OR oud 0,38, 95% BI 0,22-0,67 vs. OR jong 0.88, 95% BI 0,61-1,26, p=0,01). We concludeerden dat oudere patiënten, ondanks de ongunstigere cardiovasculaire risicoprofielen en de aanwezigheid van bijkomende aandoeningen, minstens evenveel succes kunnen bereiken als jongere patiënten op het verbeteren van leefstijlgerelateerde risicofactoren, wanneer zij een laagdrempelig toegankelijk leefstijlprogramma volgen.

Hoofdstuk 6 beschrijft de bevindingen van een kwalitatief onderzoek bij hartpatiënten van 70 jaar en ouder, naar hun perspectieven op leefstijlgerelateerde preventie in de eerste drie maanden na een ziekenhuisopname. In totaal kwamen acht thema's naar voren die konden worden onderverdeeld in de determinanten Attitude, Social Influence en Self-Efficacy van het ASE-model. Binnen de determinant *attitude* werden drie thema's gevonden: 1) perspectieven worden bepaald door de algehele gezondheid en gewoontes, 2) het voelen van dreiging als een drijfveer, en 3) het afwegen van de gezondheidsvoordelen ten opzichte van de kwaliteit van leven. Met betrekking tot de determinant *sociale invloed* werden twee thema's gevonden: 4) zich zowel aangemoedigd als belemmerd voelen door familieleden, en 5) 'de zorgprofessional zegt het'. Ten slotte werden voor de determinant *self-efficacy* drie thema's gevonden, 6) ervaringen met eerdere leefstijlveranderingen, 7) het integreren van leefstijladviezen in het dagelijks leven, en 8) het gevoel beperkt te worden door functionele achteruitgang. We concludeerden dat de voorkeuren van patiënten en uitkomsten die gericht zijn op kwaliteit van leven en functionele onafhankelijkheid een goed uitgangspunt kunnen zijn wanneer zorgverleners leefstijlverandering met oudere patiënten bespreken. Het betrekken van de familieleden kan daarnaast bijdragen aan leefstijlgerelateerde preventie in het dagelijks leven van oudere hartpatiënten.

Deel 3: De ontwikkeling en evaluatie van een transmurale interventie voor oudere hartpatiënten

Hoofdstuk 7 beschrijft de opzet van de Cardiologische Zorgbrug studie, een multicenter gerandomiseerd onderzoek bij in het ziekenhuis opgenomen hartpatiënten van 70 jaar en ouder, met een hoog risico op heropname en overlijden na ontslag. We ontwikkelden een interdisciplinaire transmurale interventie waarbij er zorg tijdens ziekenhuisopname en na ontslag thuis werd aangeboden. Hierbij werden drie vormen van zorg gecombineerd. Allereerst *casemanagement*, generalistische zorg waarbij de zorgvraag van de patiënt op lichamelijk, psychisch, sociaal en functioneel gebied in kaart wordt gebracht. Ten tweede, *diseasemanagement* ofwel ziekte-specifieke zorg, dat onder andere gericht is op vroegtijdig signaleren van achteruitgang in de (cardiologische) gezondheid, begeleiding bij medicatie en bij leefstijl. En ten derde, *hartrevalidatie* aan huis, dat onder andere gericht is op het revalideren in spierkracht, conditie, inspanningsvermogen en vertrouwen in het lichaam. De zorg werd gecoördineerd door verpleegkundigen. Alle patiënten kregen een uitgebreide geriatrische anamnese en de interventiegroep ontving aanvullend een geïntegreerd zorgplan, een 'warme' overdracht met de wijkverpleegkundige in het ziekenhuis, en huisbezoeken binnen twee dagen, één, drie en zes weken. De wijkverpleegkundige werkte samen met een apotheker om de juiste medicatie te verstrekken en medicatiefouten te voorkomen én met een fysiotherapeut die hartrevalidatie aan huis uitvoerde. De gecombineerde primaire uitkomst van het onderzoek was het aantal ongeplande heropnames of overlijden binnen zes maanden na ziekenhuisopname.

Hoofdstuk 8 beschrijft de resultaten van de Cardiologische Zorgbrug studie op de primaire gecombineerde uitkomst (ongeplande heropname of overlijden binnen zes maanden). In totaal werden 306 patiënten geïncludeerd (51% man, gemiddelde leeftijd 82 jaar). 67% van de interventiecomponenten werd in de praktijk uitgevoerd: 75% van de interventiecomponenten tijdens ziekenhuisopname, 35% in de ontslagfase en 64% in de thuisfase. Het optreden van de primaire uitkomst (heropname of overlijden) was hoog in beide groepen: 54% (83/153) in de interventiegroep en 48% (73/153) in de controlegroep (Relatief Risico (RR) 1,14, 95% BI 0,91-1,42, p=0,253). Na 12 maanden werden vergelijkbare resultaten op deze uitkomst gevonden. Voor de uitkomsten heropname (op drie, zes en twaalf maanden) en overlijden (op drie en twaalf maanden) werden geen statistisch significante verschillen waargenomen tussen de interventie- en de controlegroep. Echter, binnen twaalf maanden overleed 39% van de patiënten in de interventiegroep en 27% van de patiënten in de controlegroep (RR 1,44, 95% BI 1,04-2,00, p=0,028). Deze resultaten laten zien dat de Cardiologische Zorgbrug studie niet in staat was om het hoge risico op heropname en overlijden bij

kwetsbare oudere hartpatiënten te verminderen. Mogelijk heeft de geselecteerde patiëntengroep geen baat meer bij hoog-intensieve preventieve interventies. Andere interventies, die meer gericht zijn op comfort en kwaliteit van leven, zouden beter kunnen aansluiten bij kwetsbare oudere hartpatiënten.

Hoofdstuk 9 onderzocht de ervaringen van patiënten die deelnamen aan de interventiegroep van de Cardiologische Zorgbrug studie. Drie thema's kwamen naar voren: 1) waardering voor de continuïteit van zorg; 2) wisselende ervaringen met herstel; en 3) de aanwezigheid van een bestaand zorgnetwerk. Deelnemers voelden zich in de Cardiologische Zorgbrug studie gesteund door de begeleiding van zorgverleners na ontslag wat bijdroeg aan de ervaren continuïteit van zorg. Patiënten hadden wisselende ervaringen met de bijdrage van de Cardiologische Zorgbrug studie aan het herstel. Sommige deelnemers ervaarden fysieke verbeteringen, terwijl anderen zich belemmerd voelden in hun herstel door bijkomende ziekten of door kwetsbaarheid. De huisbezoeken van de wijkverpleegkundige werden gewaardeerd, al zagen niet alle deelnemers de meerwaarde ervan in. Deelnemers met een bestaand professioneel zorgnetwerk benaderden bij voorkeur dit netwerk in plaats van de zorgverleners binnen de Cardiologische Zorgbrug. De conclusie van deze kwalitatieve studie was dat de intensiteit en inhoud van de Cardiologische Zorgbrug studie in de toekomst meer op maat zou kunnen worden aangeboden door de interventies nog meer af te stemmen op de zorgbehoeftes van oudere hartpatiënten. Hierbij kan nog meer rekening gehouden worden met hun kwetsbaarheid, zelfmanagementvaardigheden en het bestaande zorgverlenersnetwerk, zowel professioneel als informeel.

Dit proefschrift onderzocht de integratie van cardiologische en geriatrische zorg voor oudere hartpatiënten. **Hoofdstuk 10** beschrijft een discussie van de belangrijkste bevindingen van dit proefschrift voor onderzoek, praktijk en onderwijs. Onze bevindingen laten zien dat de ziektelast en de sterftekans bij oudere hartpatiënten zeer hoog zijn. De integratie van cardiologische en geriatrische zorg dienen de komende jaren een prioriteit te zijn, ook vanwege de toename van het aantal oudere hartpatiënten. Vanuit dit proefschrift kunnen een aantal aanbevelingen worden gedaan.

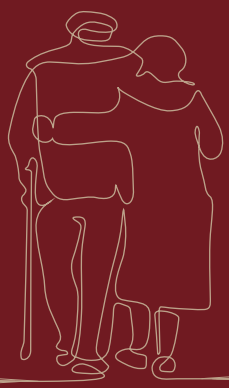
Ten eerste, de huidige modellen om risico te schatten ('predictiemodellen') zijn onvoldoende in staat om oudere hartpatiënten te identificeren die een hoog risico op ongewenste uitkomsten hebben. Toekomstig onderzoek is nodig om te onderzoeken of het beter is om voor deze doelgroep predictiemodellen te maken met een combinatie van ziekte-specifieke en geriatrische risicofactoren. Er kan momenteel geen goed onderscheid gemaakt worden tussen patiënten met een hoog risico en een zeer hoog risico op ongewenste uitkomsten. Zolang hiervoor nauwkeurige modellen ontbreken, wordt dit niet aanbevolen aan de praktijk.

Ten tweede, een hogere leeftijd zou geen reden moeten zijn om oudere patiënten uit te sluiten van leefstijlgerelateerde interventies ter secundaire preventie van cardiovasculaire complicaties. Bij het bespreken van leefstijlveranderingen dient rekening gehouden te worden met de behandelvoorkeuren van oudere hartpatiënten en met uitkomsten die voor hen belangrijk zijn, zoals kwaliteit van leven en functionele onafhankelijkheid.

Ten derde was de intensieve transmurale interventie van de Cardiologische Zorgbrug niet in staat om het zeer hoge risico op heropname of overlijden te verlagen. Andere, effectieve interventies zouden kunnen worden ontwikkeld. Alternatief kunnen de bevindingen leiden tot de conclusie dat deze groep patiënten meer baat kan hebben bij interventies die zich richten op kwaliteit van leven en naar comfort door het verzachten van klachten ('palliatieve' interventies). Er is meer onderzoek nodig om dat onderscheid te kunnen maken, tussen individuele patiënten die baat hebben bij intensieve preventieve interventies en patiënten die meer baat hebben bij palliatief beleid.

Addendum

Author contribution
PhD Portfolio
Publication list
Dankwoord
Curriculum Vitae



Author contribution

Chapter 1

General introduction

Concept and design	Patricia Jepma
Data collection	Not applicable
Statistical analysis	Not applicable
Interpretation of data	Not applicable
Drafting the manuscript	Patricia Jepma
Critical revision of the manuscript	Wilma JM Scholte op Reimer, Ron JG Peters, Bianca M Buurman, Corine HM Latour

Chapter 2

P. Jepma, G. ter Riet, M. van Rijn, C.H.M. Latour, R.J.G. Peters, W.J.M. Scholte op Reimer, B.M. Buurman. Readmission and mortality in patients ≥ 70 years with acute myocardial infarction or heart failure in the Netherlands: a retrospective cohort study of incidences' and changes in risk factors over time. Netherlands Heart Journal 2019;27:134-141

Concept and design	Patricia Jepma, Gerben ter Riet, Ron JG Peters, Wilma JM Scholte op Reimer, Bianca M Buurman
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Chapter 3

P. Jepma*, B. van Grootven*, C. Rijpkema, L. Verweij, M.M.G. Leeflang, J.G. Daams, M. Deschodt, K. Milisen, J. Flamaing, B.M. Buurman. Prediction models for hospital readmissions in patients with heart disease: a systematic review and meta-analysis. Submitted

Concept and design	Patricia Jepma, Bastiaan van Grootven, Corinne Rijpkema, Lotte Verweij, Mariska MG Leeflang, Joost G Daams, Mieke Deschodt, Koen Milisen, Johan Flamaing, Bianca M Buurman

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Chapter 4

P. Jepma, L. Verweij, A. Tijssen, M.W. Heymans, I. Flierman, C.H.M. Latour, R.J.G. Peters, W.J.M. Scholte op Reimer, B.M. Buurman, G. ter Riet. The performance of the Dutch Safety Management System frailty tool to predict the risk of readmission or mortality in older hospitalised cardiac patients. Accepted. BMC Geriatrics, April 2021

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Chapter 5

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Interpretation of data	Patricia Jepma, Harold T Jørstad, Marjolein Snaterse, Gerben ter Riet, Ron JG Peters, Wilma JM Scholte op Reimer
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Chapter 6

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Chapter 7

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Chapter 8

P. Jepma*, L. Verweij*, B.M. Buurman, M.S. Terbraak, S. Daliri, C.H.M. Latour, G. ter Riet, F. Karapinar - Çarkit, J. Dekker, J.L. Klunder, S. Liem, A.H.M. Moons, R.J.G. Peters, W.J.M. Scholte op Reimer. The Nurse-Coordinated Cardiac Care Bridge Transitional Care Programme: A Randomised Clinical Trial. Submitted

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Interpretation of data	Patricia Jepma, Lotte Verweij, Bianca M Buurman, Michel S Terbraak, Sara Daliri, Corine HM Latour, Gerben ter Riet, Fatma Karapinar-Çarkit, Ron JG Peters, Wilma JM Scholte op Reimer
Drafting the manuscript	Patricia Jepma, Lotte Verweij
Critical revision of the manuscript	Bianca M Buurman, Michel S Terbraak, Sara Daliri, Corine HM Latour, Gerben ter Riet, Fatma Karapinar-Çarkit, Jill Dekker, José L Klunder, Su-san Liem, Arno HM Moons, Ron JG Peters, Wilma JM Scholte op Reimer

Chapter 9

P. Jepma, C.H.M. Latour, I.H.J. ten Barge, L. Verweij, R.J.G. Peters, W.J.M. Scholte op Reimer, B.M. Buurman. Experiences of frail older cardiac patients with a nurse-coordinated transitional care intervention - a qualitative study. Submitted

Concept and design	Patricia Jepma, Iris HJ ten Barge, Lotte Verweij, Bianca M Buurman
Data collection	Patricia Jepma, Iris HJ ten Barge
Statistical analysis	Patricia Jepma, Iris HJ ten Barge
Interpretation of data	Patricia Jepma, Corine HM Latour, Iris HJ ten Barge, Lotte Verweij, Bianca M Buurman
Drafting the manuscript	Patricia Jepma, Corine HM Latour, Bianca M Buurman

Critical revision of the manuscript	Iris HJ ten Barge, Lotte Verweij, Ron JG Peters, Wilma JM Scholte op Reimer

Chapter 10

General discussion

Concept and design	Patricia Jepma
Data collection	Not applicable
Statistical analysis	Not applicable
Interpretation of data	Not applicable
Drafting the manuscript	Patricia Jepma
Critical revision of the manuscript	Wilma JM Scholte op Reimer, Ron JG Peters, Bianca M Buurman, Corine HM Latour

*Both authors equally contributed to this manuscript.

PhD Portfolio

Name PhD student:	Patricia Jepma
PhD period:	2015-2021
Name PhD supervisors:	Prof. dr. W.J.M. Scholte op Reimer Prof. dr. R.J.G. Peters
PhD co-supervisors:	Prof. dr. B.M. Buurman-van Es Dr. C.H.M. Latour

1. PhD training

	Year	Workload (ECTS)
General courses		
- The AMC World of Science	2015	0.7
- Expert Management of Medical Literature: Pubmed	2015	0.1
- Expert Management of Medical Literature: citation analysis and impact factors	2015	0.1
- Basiskwalificatie Didactische Bevoegdheid	2015	10
- Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers (BROK)	2015, 2019	1.0
- Research Data management	2016	0.9
- Oral presentation in English	2016	0.8
- Clinical epidemiology: Randomized Clinical trial	2016	0.6
- Practical Biostatistics	2016	1.1
- Projectmanagement	2016	0.6
Specific courses		
- Missing data: consequences and solutions, Amsterdam Public Health	2019	0.2
- Ted-talk training, debat.nl	2019	0.3
Seminars, workshops and masterclasses		
- Workshop Onderzoek in de praktijk, HBO-V van de toekomst, Hogeschool van Amsterdam.	2017	0.2
- Masterclass Transitional care by Prof. dr. Mary Naylor, Amsterdam UMC	2018	0.2

- Masterclass Intermediate care interventions by Prof. dr. Inzitari, Amsterdam UMC	2018	0.2

Oral presentations

- Heropname en overlijden bij oudere hartpatiënten, Geriatriedagen, Den Bosch	2017	0.5
- De Cardiologische Zorgbrug studie, Carvasz, Ede	2017	0.5
- Transmurale zorg voor kwetsbare oudere hartpatiënten, Amsterdam UMC, Symposium Research for all, Amsterdam	2018	0.2
- De Cardiologische Zorgbrug studie, symposium Implementatie van geriatrisch comanagement en innovatieve zorgmodellen, Leuven	2019	0.5
- Validatie van het VMS-screeningsinstrument voor kwetsbare ouderen in een cardiologische populatie, Geriatriedagen, Den Bosch	2020	0.5
- Symposium Cardiologische Zorgbrug studie, Geriatriedagen, Den Bosch	2020	0.5
- Effect of Nurse-Coordinated Transitional Care in High Risk Older Cardiac Patients: The Cardiac Care Bridge Randomized Clinical Trial, EUGMS, online	2020	0.5
- De Cardiologische Zorgbrug: de brug van ziekenhuis naar huis voor kwetsbare oudere hartpatiënten, NVVC, Arnhem	2020	0.5

Poster presentations

- Study protocol of the Cardiac Care Bridge Study, European Council of Nursing Congress, Rotterdam	2016	0.5
- Studieprotocol Cardiologische Zorgbrug studie, Ageing & Later Life, Amsterdam.	2016	0.5
- Onderzoeksprogramma Complex Care, Netwerkbijeenkomst Tussen Weten en Doen II, Utrecht	2016	0.5

- Successful lifestyle modification in older patients with coronary artery disease: results from the RESPONSE-2 trial, Europrevent, Lisboa	2018	0.5
- Successful lifestyle modification in older patients with coronary artery disease: results from the RESPONSE-2 trial, EUGMS, Krakau	2018	0.5
- A qualitative study of older patients' perspectives towards lifestyle modification after a cardiac hospital admission, EUGMS, Krakau	2019	0.5
- Successful lifestyle modification in older patients with coronary artery disease: results from the RESPONSE-2 trial, ESC, online	2020	0.5

(Inter)national conferences

- Het ouder wordende hart, Geriatriedagen, Den Bosch	2018	0.25

Other

- Journal club, Bachelor of Nursing, Amsterdam University	2015 - present	2.0
- Transitional care research meetings	2015 - 2018	1.5

2. Teaching

	Year	**Workload (ECTS)**
Lecturing		4.0
Amsterdam School of Health Professions - Bachelor of Nursing		
- Clinical reasoning in older patients	2018 - present	
- Evidence Based Practice 1	2017 - present	
- Transitional care bridge	2017 - present	

- Evidence Based Practice 2	2019	
- Minor Health Sciences	2021 - present	
Amsterdam School of Health Professions – Post-bachelor course		
- Transitional Care Bridge	2016-2018	
- Cardiac Care Bridge	2016-2018	

Tutoring, Mentoring		4.0
- Mentoring 2th, 3th and 4th -year bachelor nursing students	2015 - present	
- Examine graduation	2016 - present	
- Project E-health	2016	
- Project Urban Vitality	2016	
- Project vulnerable older patients	2016 - 2018	
- Project transitional care	2019	
- Supervise graduation	2019 - present	

Supervising		
- Iris ten Barge, master thesis	2018	1.0
- Simone Du Puy, master thesis	2019	1.0
- Corinne Rijpkema, master thesis	2020	1.0

Other		4.0
- Development Post-bachelor course Transitional Care Bridge	2016	
- Development Post-bachelor course Cardiac Care Bridge	2016	

- Course coordinator ‘community care week year 2’	2017-2018
- Development transitional care course	2017
- Graduation coordinator	2019 - present
- Development minor Health Sciences	2019 - 2020

3. Parameters of Esteem

Year

Grants

- Implementatie en borging van de Cardiologische Zorgbrug, ZonMw	2016
- Promotiebeurs voor leraren , Nederlandse organisatie voor wetenschappelijk onderzoek (NWO)	2017

Publication list

Scientific publications

1. **Jepma P**, Verweij L, Tijssen A, Heymans MW, Flierman I, Latour CHM, Peters RJG, Scholte op Reimer WJM, Buurman BM, ter Riet G. The performance of the Dutch Safety Management System frailty tool to predict the risk of readmission or mortality in older hospitalised cardiac patients. Accepted. BMC Geriatrics, April 2021.

2. **Jepma P**, Snaterse S, Du Puy S, Peters R.J.G., Scholte op Reimer W.J.M. Older patients' perspectives toward lifestyle-related secondary cardiovascular prevention after a hospital admission – A qualitative study. Age Ageing. 2021;afaa283. DOI: 10.1093/ageing/afaa283.

3. **Jepma P***, Verweij L*, Buurman BM, Terbraak MS, Daliri S, Latour CHM, ter Riet G, Karapinar-Çarkit F, Dekker J, Klunder JL, Liem S, Moons AHM, Peters RJG, Scholte op Reimer WJM. The nurse-coordinated Cardiac Care Bridge transitional care programme: a randomised clinical trial. Submitted 2021.

4. **Jepma P***, van Grootven B*, Rijpkema C, Verweij L, Leeflang MMG, Daams JG, Deschodt M, Milisen K, Flamaing J, Buurman BM. Prediction models for hospital readmissions in patients with heart disease: a systematic review and meta-analysis. Submitted 2021.

5. **Jepma P**, Latour CHM, ten Barge IHJ, Verweij L, Peters RJG, Scholte op Reimer WJM, Buurman BM. Experiences of frail older cardiac patients with a nurse-coordinated transitional care intervention – a qualitative study. Submitted 2021.

6. Verweij L*, Petri ACM*, Vroomen MacNeil JL, **Jepma P**, Latour CHM, Peters RJG, Scholte op Reimer WJM, Buurman BM, Bosmans JE. The Cardiac Care Bridge transitional care program for the management of older high-risk cardiac patients: an economic evaluation alongside a randomized controlled trial. Submitted 2021.

7. Terbraak MS, Verweij L, **Jepma P**, Buurman BM, Jørstad HT, Scholte op Reimer WJM, van der Schaaf M. Feasibility of home-based cardiac rehabilitation in frail older patients: a clinical perspective. Submitted 2021.

8. Rijpkema C, Verweij L, **Jepma P**, Latour CHM, Peters RJG, Scholte op Reimer WJM, Buurman BM. The course of readmission in frail older cardiac

patients. J Adv Nurs. 2021. DOI: 10.1111/jan.14828.

9. Verweij L, Spoon DF, Terbraak MS, **Jepma P**, Peters RJG, Scholte op Reimer WJM, Latour CHM, Buurman BM. The Cardiac Care Bridge randomized trial in high-risk older cardiac patients: A mixed-methods process evaluation. J Adv Nurs. 2021;77(5):2498-2510. DOI: 10.1111/jan.14786.

10. Daliri S, Kooij MJ, Scholte op Reimer WJM, ter Riet G, **Jepma P**, Verweij L, Peters RJG, Buurman BM, Karapinar-Çarkit F. Effects of a transitional care program on medication adherence in an older cardiac population: a randomized trial. Submitted 2021.

11. **Jepma P**, Jørstad HT, Snaterse M, Ter Riet G, Kragten JA, Lachman S, Minneboo M, Boekholdt SM, Peters RJG, Scholte op Reimer WJM. Lifestyle modification in older versus younger patients with coronary artery disease. Heart. 2020;106:1066-1072. DOI: 10.1136/heartjnl-2019-316056

12. Habes EV, **Jepma P**, Parlevliet JL, Bakker A, Buurman BM. Video-based tools to enhance nurses' geriatric knowledge: A development and pilot study. Nurse Educ Today. 2020;90:104425. DOI: 10.1016/j.nedt.2020.104425

13. **Jepma P**, ter Riet G, van Rijn M, Latour CHM, Peters RJG, Scholte op Reimer WJ, Buurman BM. Readmission and mortality in patients ≥70 years with acute myocardial infarction or heart failure in the Netherlands: a retrospective cohort study of incidences and changes in risk factors over time. Neth Heart J. 2019;27(3):134-141. DOI: 10.1007/s12471-019-1227-4.

14. Verhaegh KJ, **Jepma P**, Geerlings SE, de Rooij SE, Buurman BM. Not feeling ready to go home: a qualitative analysis of chronically ill patients' perceptions on care transitions. Int J Qual Health Care. 2019;31(2):125-132. DOI: 10.1093/intqhc/mzy139.

15. **Jepma P***, L. Verweij*, Buurman BM, Latour CHM, Engelbert RHH, ter Riet G, Karapinar-Çarkit F, Daliri S, Peters RJG, Scholte op Reimer WJM. The cardiac care bridge program: design of a randomized trial of nurse-coordinated transitional care in older hospitalized cardiac patients at high risk of readmission and mortality. BMC Health Services Research. 2018;18:508. DOI: 10.1186/s12913-018-3301-9.

16. Snaterse M, Dobber J, **Jepma P**, Peters RJG, ter Riet G, Boekholdt SM, Buurman BM, Scholte op Reimer WJM. Effective components of nurse-coordinated care to prevent recurrent coronary events: a systematic

review and meta-analysis. Heart. 2016;102(1):50-56. DOI: 10.1136/heartjnl-2015-308050.

Practice publications

1. **Jepma P**, Snaterse M. Leefstijlgerelateerde secundaire preventie bij oudere patiënten. Nurse Academy. 2021(1):21-26.

2. Verweij L, **Jepma P**. Complexe interventies onderzoeken met het MRC framework. In: Eskes AM, van Oostveen CJ. Onderzoek langs de meetlat: Onderzoeksdesigns voor verpleegkundigen. Houten: Bohn Stafleu van Loghum; 2021. P.125-130.

3. Verweij L, **Jepma P**. De Cardiologische Zorgbrug. Nurse Academy O&T. 2020(1):25-30.

4. Verweij L, **Jepma P**. De Cardiologische Zorgbrug. Nurse Academy. 2019(4):25-29.

5. Verweij L, **Jepma P**. Complexe interventies: het wat, hoe en waarom. TVZ - Verpleegkunde in praktijk en wetenschap. 2019;129(5):56-57.

6. **Jepma P**, Verweij L. Onderzoek naar transmurale zorg voor kwetsbare oudere hartpatiënten Cardiologische Zorgbrug van start. Cordiaal. 2017;4:134-138.

*Both authors equally contributed to this manuscript.

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De overige leden van de promotiecommissie: prof. dr. R.H.H. Engelbert, prof. dr. T. Jaarsma, prof. dr. M. Muller, prof. dr. S.M.G. Zwakhalen, dr. E.P. Moll van Charante en dr. W.E.M. Kok. Dank voor het beoordelen van mijn proefschrift en

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De overige onderzoekers van Complex Care, Margriet en Ruth. Margriet, eerst betrokken bij mijn afstuderen op de HBO-V en nu collega's in onderzoek en onderwijs. Bedankt voor de fijne lunchgesprekken. Ruth, fijn om alvast bij jouw promotie te mogen afkijken, wat heb je dat goed gedaan. Ik wens jullie beiden veel succes in jullie verdere carrière.

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Collega's en studenten van de opleiding Verpleegkundige aan de Hogeschool van Amsterdam. Toen ik vroeger slapeloze nachten had voor mijn spreekbeurten, had ik nooit gedacht docent te worden. Mede dankzij jullie heb ik me hier toch in kunnen ontwikkelen! Ik hoop dat ik veel studenten heb weten te enthousiasmeren binnen ons mooie vak. Dank voor jullie interesse in mijn proefschrift.

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Lieve ik. You did it, time to write a new chapter!

Curriculum Vitae

Patricia Jepma werd op 3 juli 1990 geboren in Haarlem. Ze behaalde haar vwo-diploma's Cultuur & Maatschappij (2008) en Natuur & Gezondheid (2009) aan respectievelijk het Kaj Munk College en het Nova College in Hoofddorp. Van 2009-2013 studeerde Patricia HBO-Verpleegkunde aan de Hogeschool van Amsterdam. Hier werd haar passie voor ouderenzorg en onderzoek gewekt. In 2012 won ze de Anna Reynvaan studentenlezing met een literatuurstudie over barrières in pijnmanagement bij ouderen. In 2013 schreef Patricia een case study over een oudere patiënt voor het vak Klinisch Redeneren 4. De docent was onder de indruk van de kwaliteit en bracht Patricia in contact met haar copromotor prof. dr. Bianca Buurman-van Es bij de afdeling Ouderengeneeskunde van het Amsterdam UMC. Hier kreeg Patricia de kans om als onderzoeksassistent ervaring op te doen. Van 2013-2015 heeft Patricia de (pre)master Health Sciences met specialisatie Prevention & Public Health gevolgd aan de Vrije Universiteit in Amsterdam. Zij combineerde dit met werkzaamheden als onderzoeksassistent op Polifysiek en met onderwijstaken bij de HBO-Verpleegkunde, beiden bij de Hogeschool van Amsterdam. Patricia is in deze periode ook gestart als onderzoeksassistent op het Complex Care project, een samenwerking tussen de Hogeschool van Amsterdam en de afdelingen Ouderengeneeskunde en Cardiologie van het Amsterdam UMC. Binnen dit project heef zij haar masterthesis kunnen schrijven (hoofdstuk 2 van dit proefschrift). Per augustus 2015 resulteerde deze samenwerking in een promotietraject binnen Complex Care in combinatie met de functie van docentonderzoeker bij de opleiding HBO-Verpleegkunde. In 2017 ontving Patricia de promotiebeurs voor leraren van de Nederlandse organisatie voor Wetenschappelijk Onderzoek (NWO). Patricia kijkt met nieuwsgierigheid uit naar alle avonturen en uitdagingen die er in de toekomst op haar pad komen.