BRIDGING THE GAP

Adapting transitional care to older cardiac patients' needs

Lotte Verweij

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General introduction

GENERAL INTRODUCTION

Cardiac disease is the leading cause of hospitalization and mortality in older persons. Within the next decades, the world's older (≥70 years) population will double to nearly 20% in 2050[1] and it is predicted that the global burden of cardiac diseases will increase proportionally.[2-4] Especially in the older population with cardiac disease, the readmission and mortality rates after hospitalization are high.[5-7] This is reflected in a readmission rate of approximately 20% of older patients with heart failure and acute myocardial infarction, and 8% deaths within 30 days of discharge.[7, 8] Multimorbidity and geriatric conditions, such as malnutrition, functional impairment and frailty are common in this population and increase the risk of readmissions and mortality.[2, 6, 9-11] In frail patients with cardiovascular disease, the risk of readmission and mortality is 2-3 times higher compared to patients without frailty.[2]

Risks and challenges in older cardiac patients

Comorbid diseases, such as diabetes mellitus or chronic obstructive pulmonary disease (COPD), are often present in patients with cardiovascular disease. Even five or more comorbidities may be seen which is associated with a high 30-day readmission risk after hospitalization.[2] When a geriatric condition is present, a state of frailty is usually determined.[12] The definition of frailty is subject to discussion,[13-15] however, an often applied definition according to Clegg *et al*. is, *'frailty is a long term condition characterized by lost of biological reserves across multiple systems and vulnerability to decompensation after a stressor event and is strongly related with adverse outcomes'*.[16] The prevalence of frailty in heart failure patients is around 45% and heart failure patients are six times more likely to be frail compared to the general population.[12] The clinical and pathophysiological aspects of heart failure are strongly associated with symptoms of frailty, such as decline in muscle mass and strength (sarcopenia), weakness and fatigue.[12] Also in older patients with acute myocardial infarction, mobility impairment was found to be a strong predictor of functional decline.[6] In summary, frailty has a negative impact on cardiac patient's prognosis and is associated with unplanned hospital readmission and mortality.[17, 18]

Nowadays, the treatment of older cardiac patients shifts from a 'comorbidity approach', -a focus on one central disease-, towards a 'multimorbidity approach', -focusing on the contributive, combined effects of chronic co-existing diagnoses and geriatric syndromes- (see Figure 1).[2] This multimorbidity approach involves treatment of several conditions simultaneously and incorporates a broad perspective on factors that influence treatment. Since many geriatric conditions such as malnutrition and functional impairment are preventable or reversible, it is necessary to identify patients at risk in an early stage. In this way, a personalized

plan on treating and preventing geriatric conditions alongside the medical treatment plan, can be developed, which is associated with improved outcome.[12]

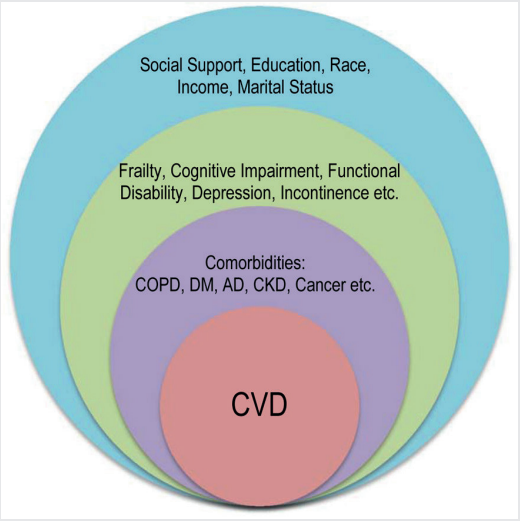

Figure 1. Adapted from Bell *et al*. 2016: Multimorbid conceptual framework demonstrating a patient-centric approach to managing cardiovascular disease in the context of multiple chronic conditions, geriatric syndromes, functional status and social determinants of health.[2]

Currently, all Dutch hospitals are required to screen patients ≥70 years with the Dutch Safety Management System (DSMS)-tool.[19] The tool was introduced to detect older patients at high risk of functional loss by screening on (the risk of) four geriatric conditions: delirium, falling, malnutrition and functional impairment. The tool's predictive performance on adverse outcomes such as healthcare demand and mortality, has been tested in various populations.[19] However, information on the performance in a cardiac population is lacking and it is unclear if older high-risk cardiac patients are currently adequately detected.

Integrating disease management, case management and rehabilitation, based on patients' needs

During hospitalization the focus is mainly on guideline-based disease management as opposed to case management.[9] Consequently, care is less focused on other conditions, such as multimorbidity and geriatric conditions, which could hinder treatment and the process of recovery.[2] For example, the interaction between the treatment of heart failure and a high fall risk due to orthostatic hypotension in patients, is often overlooked. In addition, the disease management approach focuses less on patients' personal needs, which could interfere with patients' own priorities and consequently leading to less treatment adherence and higher

disease burden.[20] This mismatch is related to the fact that healthcare providers are not always aware that patients prioritize other outcome measures such as independence and quality of life.[21]

A case management model focuses on a broader perspective and is based on patient's needs and goals, to support the patient across healthcare departments or settings.[22] Transitional care models often work from a case management perspective and are developed to support guidance for frail and chronically ill patients between care settings, with the goal to ensure continuity of care and improve outcome.[22] Especially patients who are transferred between care settings or discharged home are at high risk of adverse events.[22] Transitional care services have shown to reduce hospital readmissions and mortality in older chronically ill patients.[23-25] Studies on transitional care services in older cardiac patients, however, are mainly focused on heart failure patients and show inconclusive results on readmission and mortality.[26-29] It remains unclear how the older cardiac population may benefit from a case management-based transitional care model.

Cardiac rehabilitation programs in older cardiac patients aim to support recovery and prevent poor outcomes after hospitalization.[30, 31] However, the participation rates among frail cardiac patients are as low as 20 to 30%.[32] Currently, the trend is shifting from mainly center-based rehabilitation towards alternative settings, such as home-based. One of the main goals of these programs is to increase the participation rate. However, the evidence on these approaches is limited.[33-35] Home-based rehabilitation integrates the rehabilitation process into the patient's own environment and emphasizes on patient's own needs and goals and aims to remain functional abilities and to prevent for functional decline.[35]

Transitional care in cardiac patients

The transitional care concept refers to individual interventions and programs with multiple activities, designed to improve shifts or transitions from one setting to the next.[36] After discharge home, cardiac patients often experience difficulties, for example in medication management,[37] recognizing physical signs and symptoms of deterioration[38] and resuming physical activity.[39] Adequate continuity of care, including aftercare, is commonly lacking in the Dutch healthcare system in this population, resulting in an increased risk of readmission and mortality.

Given the high risk of readmission and mortality in hospitalized older (≥70 years) cardiac patients[7, 40] and given the potential reduction of these risks by adequate risk identification and interventions,[6, 9, 41] the need for optimization of care processes in this population is high. Therefore, the Cardiac Care Bridge (CCB) transitional care intervention was developed to contribute to the continuity of care from hospital to home in older (≥70 years) cardiac patients who are at high risk of readmission and mortality.[42] With this patient-centered approach, case management, disease management and cardiac rehabilitation were combined. The intervention was assessed in a randomized study and compared with usual

care. The CCB intervention is provided in three phases within the care continuum from hospital to home. In phase 1 (clinical phase), patients were screened for their risk of readmission and mortality and they received an assessment to identify geriatric conditions. In patients who were randomized into the intervention group, a geriatric assessment-based care plan was developed in collaboration with the patient. In phase 2 (discharge phase), an in hospital face-to-face handover was organized between the cardiac hospital nurse and a community nurse. In phase 3 (post-clinical phase), the community care nurse performed four to five home-visits in total, with the first visit within three days of hospital discharge. Here the focus was mainly on the geriatric assessment-based care plan, medication reconciliation and observation of early signs and symptoms of physical deterioration. Additionally, a physical therapist, specialized in cardiac rehabilitation, performed up to nine home visits for cardiac rehabilitation. By combining case management, disease management and home-based cardiac rehabilitation, the aim was to reduce readmission and mortality.[42]

Medical Research Council Framework

The UK Medical Research council theoretical framework guided the phases of development, piloting, implementation and evaluation of the CCB intervention (see Figure 2).[43, 44] This systematic approach improves the quality of intervention development and a structured evaluation.

AIM AND OUTLINE OF THIS THESIS

This thesis is focused on three topics to improve care for older cardiac patients:

1. Cardiovascular risk screening and screening of risk of readmission and mortality;
2. Integration of case management, disease management and cardiac rehabilitation in a transitional care program;
3. Evaluation of new approaches in cardiac rehabilitation.

PART 1. Risk screening in older cardiac patients

Early detection of patients at risk for cardiovascular mortality is necessary to start early and adequate risk factor control. Existing risk screening instruments are of limited validity to estimate the 10-year risk of cardiovascular mortality in the older population (≥70 years). Therefore, the Systematic Coronary Risk Evaluation – Older Persons (SCORE-OP) instrument for the estimation of 5 and 10 year cardiovascular mortality was developed by Cooney *et al*.[45] In **Chapter 2**, we evaluated the instruments' external validity in the EPIC-Norfolk cohort, including community dwelling older persons comparable to the Dutch population regarding levels of cardiovascular risk factors.

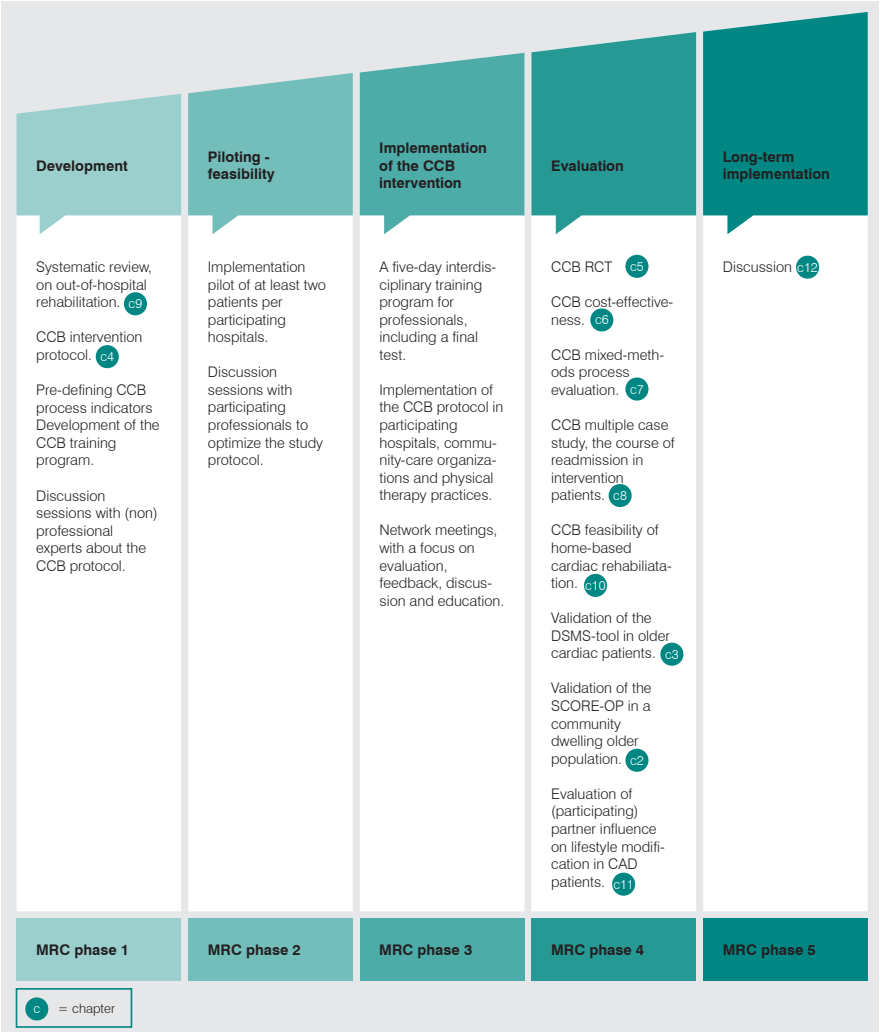

Figure 2. Phases of the Medical Research Council framework and application in this thesis. Abbreviations: CCB: Cardiac Care Bridge; RCT: Randomized Controlled Trial; DSMS: Dutch Safety Management System; SCORE-OP: Systematic Coronary Risk Evaluation – Older Persons; CAD: Coronary Artery Disease.

Screening of patients for the risk of serious complications is currently part of routine practice in all older patients (≥70 years) admitted to Dutch hospitals. By identifying patients at risk on four geriatric conditions; falling, delirium, malnutrition and functional impairment, deployement of early interventions may prevent adverse outcomes such as functional decline, hospital readmission and mortality.[19, 46] The DSMS-tool's performance has not been evaluated in the cardiac patient population, which could lead to an over- or underestimation of patients at risk, for instance caused by misinterpretation of unintentional weight loss in patients taking diuretics.[12] We performed a validation of the DSMS-tool in a cohort of 529 Dutch cardiac patients of ≥70 years in **Chapter 3**.

PART 2. Organization of transitional care in older cardiac patients: The Cardiac Care Bridge

Chapter 4 presents the protocol of the CCB randomized trial. In **Chapter 5**, the results of the CCB intervention are reported in terms of the main composite outcome of hospital readmission and mortality at six months after randomization and for the secondary outcomes at three and twelve months. The costs of care interventions need to be included in any evaluation on the overall feasibility. In addition to the main outcomes, results in terms of quality of life may be equally important in the equation both to patients and healthcare providers. Therefore, in **Chapter 6** we present an economic evaluation of the CCB intervention.

In addition to evaluation of effectiveness, the Medical Research Council promotes thorough evaluation of new complex interventions with multiple interacting components on the level of intervention delivery (or fidelity: in reality, was the intervention delivered as intended by the protocol) and to understand the mechanism of impact.[47, 48] In **Chapter 7**, a mixed methods process evaluation on intervention fidelity is reported, combined with an evaluation of the involved healthcare providers' perspective on the intervention to explain results on the intervention fidelity. In **Chapter 8**, we performed a multiple case study to evaluate the role of the CCB intervention in the prevention of readmissions. Five CCB intervention patients and the involved CCB formal and informal care networks were thoroughly studied to elaborate on the level of impact.

PART 3. New approaches in cardiac rehabilitation

In routine practice, a patient's medical diagnosis is often leading in determining the need for rehabilitation, as opposed to factors such as the level of frailty.[8] In the older population, a multifactorial approach is more appropriate to achieve adequate results.[49] Hospital-based inpatient rehabilitation in older patients has a positive effect on improvement on physical functioning and in the prevention of new disabilities.[30] However, the effectiveness of alternative approaches such as home-based rehabilitation remained unclear. In **Chapter 9**, we studied the effectiveness of alternative out-of-hospital multidisciplinary rehabilitation

approaches in older patients after acute hospitalization.

In frail older cardiac patients, several challenges are present to participate in center-based cardiac rehabilitation programs, that are part of the current usual care. The low participation rates (20-30%) are caused by a number of limitations including transportation difficulties, patients' own perception on the potential benefit of the program and the intensity of the programs.[32] Current rehabilitation guidelines for physical therapists do not provide clear recommendations on how to adapt cardiac rehabilitation programs to a frail population. Home-based cardiac rehabilitation is an alternative to the clinical setting and was associated with beneficial effect in non-frail populations.[34, 35] In **Chapter 10**, we studied the experiences of physical therapists with and their performance in adapted cardiac rehabilitation guidelines to a frail population in a home-based setting.

With a shifting trend towards home-based cardiac rehabilitation, the partner role may gain importance in achieving results. The RESPONSE-2 trial evaluated nurse-coordinated referral to community-based lifestyle interventions in patients with coronary artery disease on smoking cessation, weight reduction and physical activity.[50] Partners of patients referred to the lifestyle interventions were invited to join regardless of their own lifestyle-related risk factors. To evaluate the impact of partners on patient's lifestyle-related risk factor modification, we performed a secondary analysis of the RESPONSE-2 trial in **Chapter 11**.

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Part 1

Risk screening in older cardiac patients

Chapter 2

Validation of the Systematic COronary Risk Evaluation - Older Persons (SCORE-OP) in the EPIC-Norfolk prospective population study

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ABSTRACT

BACKGROUND: The Systematic COronary Risk Evaluation – Older Persons (SCORE-OP) algorithm is developed to assess 10-year risk of death due to cardiovascular disease (CVD) in individuals aged ≥65 years. We studied the performance of SCORE-OP in the European Prospective Investigation of Cancer Norfolk (EPIC-Norfolk) prospective population cohort.

METHODS: 10-year CVD mortality as predicted by SCORE-OP was compared with observed CVD mortality among individuals in the EPIC-Norfolk cohort. Persons aged 65-79 years without known CVD were included in the analysis. CVD mortality was defined as death due to ischemic heart disease, cardiac failure, cerebrovascular disease, peripheral-artery disease or aortic aneurysm. Predicted 10-year CVD mortality was calculated by the SCORE-OP algorithm, and compared to observed mortality rates. The area under the receiver operator characteristics curve (AUROC) was calculated to evaluate discriminative power. Calibration was evaluated by calculating ratios of predicted vs observed mortality and by Hosmer-Lemeshow tests.

RESULTS: A total of 6590 individuals (45.8% men), mean age 70.2 years (standard deviation 3.3) were included. The predicted mortality by SCORE-OP was 9.84% (95% confidence interval (CI) 9.76-9.92) and observed mortality was 10.2% (95% CI 9.52-11.04), ratio 0.96. AUROC was 0.63 (95% CI 0.60-0.65), and X^2 was 3.3 ($p = 0.92$).

CONCLUSION: SCORE-OP overall accurately estimates the rate of CVD mortality in a general population aged 65-79 years. However, while calibration is excellent, the discriminative power of the SCORE-OP is limited, and as such cannot be readily implemented in clinical practice for this population.

INTRODUCTION

In the next decades, the population of individuals aged 65 years and older will grow until 17% of the world's total population.[1] It is predicted that the global burden of cardiovascular diseases (CVD) will increase proportionally in this group.[2] While the effect of primary prevention is well documented in the younger population, there is increasing evidence that older individuals also benefit from primary prevention of CVD.[3]

The European guideline on CVD prevention recommends using SCORE (Systematic COronary Risk Evaluation) as a decision-making tool in primary prevention.[4] However, the original SCORE charts were only developed and validated in individuals up to 65 years of age and not validated for individuals older than 65 years. Recently, Cooney *et al*. derived and validated a risk assessment function, SCORE-OP (Older Persons) for individuals over 65 years of age.[5] This risk assessment function has only been externally evaluated in limited analysis in a small sample of individuals aged 65-69 years.[6] We therefore studied the performance of the SCORE-OP in the European Prospective Investigation of Cancer Norfolk (EPIC-Norfolk) prospective population study, a large population-based United Kingdom (UK) cohort with individuals aged up to 79 years.[7]

METHODS

Study population

For our current analysis, we used data from the EPIC-Norfolk prospective population study. This cohort consists of men and women aged 39-79 years residing in the county of Norfolk in the UK. Study details of this cohort have been described elsewhere.[7] In brief, 25,639 adults provided written informed consent for study participation. They attended a baseline health assessment and completed questionnaires about personal and family history of lifestyle including smoking status. Participants were asked whether they had any of the following conditions: diabetes mellitus, myocardial infarction or stroke (self-reported). Participants were followed-up for cause-specific mortality.

Study design

In accordance with the selection criteria of the SCORE-OP algorithm, we included all participants aged 65-79 years of the EPIC-Norfolk cohort. We excluded those with a history of CVD (myocardial infarction and stroke) at baseline, and participants with missing data on SCORE-OP variables. CVD mortality was defined as death where CVD was coded as the underlying or contributing cause. CVD was defined as ischaemic heart disease (ICD-10 codes I20-25), cardiac failure (ICD codes I11,

I13 and I50), cerebrovascular disease (ICD-10 codes I60-I69), peripheral artery disease (ICD-10 codes I70-I79) and aortic aneurysm (ICD-10 code I71).

Statistical methods

Baseline characteristics are summarized for men and women and excluded individuals separately by using numbers and percentages for categorical data, mean and standard deviations (SD) for continuous data with a normal distribution and median and interquartile range for continuous variables with a non-normal distribution. Our main parameter of interest was predicted 10-year CVD mortality as calculated with the SCORE-OP algorithm compared to observed 10-year CVD mortality.[5] Variables included in the SCORE-OP algorithm are age, sex, systolic blood pressure, smoking status, total cholesterol, HDL cholesterol and diabetes. Correspondingly, we limited the observed mortality rates in our cohort to the first 10 years with Kaplan-Meier (KM) estimates. We evaluated SCORE-OP by using ratios of predicted and observed CVD mortality. Discriminative power of SCORE-OP was evaluated by calculating the area under the receiver operator characteristic curve (AUROC). The Hosmer-Lemeshow goodness-of-fit test based on chi-square statistics was performed to assess calibration of the SCORE-OP algorithm. In accordance with the SCORE-OP charts we stratified by age and sex subgroups of 65-69, 70-74, 75-79 years. In addition, we stratified the study population by groups of 2% increments in SCORE-OP risk, and analyzed differences of the SCORE-OP performance in these risk groups by calculating ratios of predicted and observed 10-year CVD mortality. A sensitivity analysis of the SCORE-OP was performed on normotensive (systolic blood pressure $\leq$140mmHg) and hypertensive (systolic blood pressure $>$140mmHg) individuals.

SCORE-OP also provides coefficients for 5-year CVD mortality prediction.[5] We therefore compared the performance of 5-year SCORE-OP with observed 5-year CVD mortality (KM estimate), and evaluated with ratios of predicted and observed mortality, in addition to evaluating its discriminative power (AUROC) and calibration (Hosmer-Lemeshow).

We also compared the predicted 10-year CVD mortality as calculated using SCORE low-risk with SCORE-OP. Although the SCORE low-risk algorithm has not been developed and validated for individuals older than 65 years, we evaluated the performance in the same manner as SCORE-OP in the different age-sex groups (predicted/observed ratios, discrimination, and calibration) to compare the performance of both algorithms. Differences in discriminative power between SCORE low-risk and SCORE-OP were compared using the C-statistic.

To assess the clinical impact of SCORE-OP on the initiation of preventive therapies, we calculated the percentage of individuals above the 5% and 10% 10-year CVD mortality risk threshold for both the SCORE-OP and SCORE low-risk algorithms.[4,5]

RESULTS

The study population consisted of 8,145 participants aged 65-79 years. A total of 1,555 participants were excluded due to a history of CVD (n=665), missing data on baseline CVD (n=13) or missing data for the SCORE-OP variables (n=877), leaving 6,590 participants eligible for analysis (Figure 1). Mean age was 70.2 years (SD 3.3), 45.8% were men and 8.3% were current smokers. Mean body mass index was 26.5 kg/m^2 (SD 3.7), mean total cholesterol 6.4 mmol/l (SD 1.2), and mean LDL cholesterol was 4.2 mmol/l (SD 1.1). Excluded cases showed a 4.3% higher incidence of diabetes mellitus (Table 1).

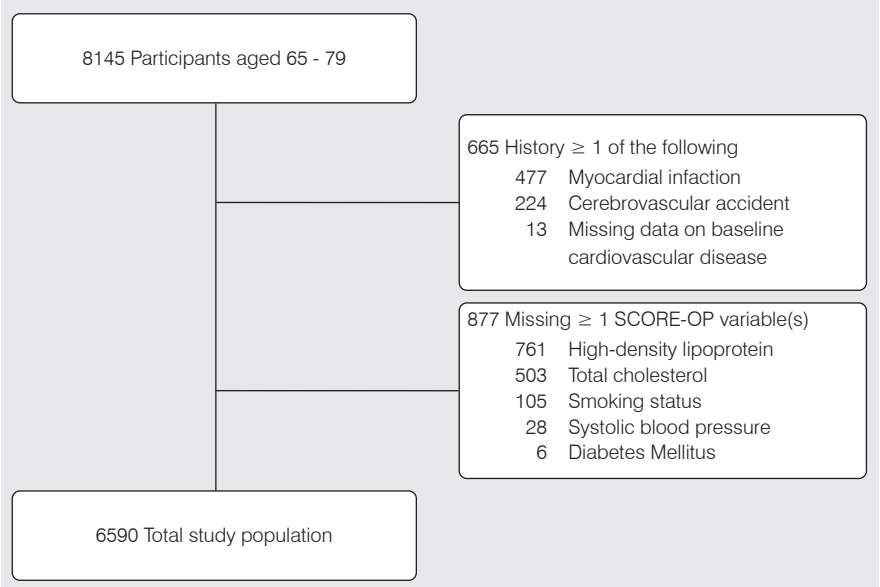


Figure 1. Flow chart, study population

Table 1. Population characteristics

	Total (*n* = 6590)	**Men (*n* = 3016)**	**Women (*n* = 3574)**
Age, years	70.2 ± 3.3	70.3 ± 3.3	70.2 ± 3.3
Weight, kg	72.3 ± 12.6	78.7 ± 11.0	66.8 ± 11.1
Body mass index, kg/m^2	26.5 ± 3.7	26.5 ± 3.2	26.5 ± 4.1
Current smokers	544 (8.3)	297 (9.3)	265 (7.4)
Systolic blood pressure, mmHg	143.8 ± 18.6	144.2 ± 18.7	143.5 ± 18.6
Diastolic blood pressure, mmHg	84.6 ± 11.5	85.3 ± 11.7	84.0 ± 11.3
Total cholesterol, mmol/l	6.4 ± 1.2	6.0 ± 1.1	6.7 ± 1.2
LDL cholesterol, mmol/l	4.2 ± 1.1	3.9 ± 1.0	4.4 ± 1.1
HDL cholesterol, mmol/l	1.4 ± 0.4	1.2 ± 0.3	1.6 ± 0.4
Triglycerides, mmol/l	1.6 [0.3-7.5]	1.7 [0.3-7.5]	1.6 [0.4-6.9]
Diabetes mellitus*	207 (3.1)	130 (4.3)	77 (2.2)

Abbreviations: Kg, kilogram; m^2, square meter; mmHg, millimeter mercury; mmol/l, millimole per liter; LDL, low-density lipoprotein; HDL, high-density lipoprotein. *Self-reported
Note: Data are presented as mean ± standard deviation, median and [IQR] or number (percentage)

Performance of SCORE-OP 10-year predicted cardiovascular mortality

Table 2 presents predicted 10-year CVD mortality according to the SCORE-OP algorithm and observed 10-year CVD mortality. In the total population the predicted CVD mortality was 9.84% (95% CI 9.76–9.92) whereas observed CVD mortality (KM estimate) was 10.2% (95% CI 9.52–11.04), yielding a ratio of 0.96. Goodness-of-fit for the SCORE-OP algorithm was excellent with a X^2 of 3.26, ($p = 0.92$). Discriminative performance was limited, with an AUROC of 0.63 (95% CI 0.60–0.65).

In men and women, the predicted 10-year CVD mortality versus observed CVD mortality ratio was 0.92 and 1.004, respectively. Goodness-of-fit for the SCORE-OP algorithm was excellent in both men and women with a X^2 of 13.27, ($p = 0.10$) and 10.03 ($p = 0.26$), respectively. Discriminative performance was limited in both groups with an AUROC of 0.60 (95% CI 0.57–0.63) in men and 0.58 (95% CI 0.54–0.62) in women.

When analyzed according to age-sex groups, SCORE-OP underestimated CVD mortality in all groups, with the exception of men and women aged 65-69 years (Figure 2). In men and women aged 65-69 years, predicted 10-year CVD mortality versus observed CVD mortality yielded a ratio of 1.29 and 1.46, respectively. Goodness-of-fit for the SCORE-OP algorithm in men and women aged 65-69 was excellent, however discriminative performance was severely limited with an AUROC of 0.54 (95% CI 0.49–0.60) in men and 0.49 (0.41–0.56) in

women (Table 2). In both men and women aged 70-74 and 75-79 years, SCORE-OP showed a similar magnitude of underestimation. In men and women aged 70-74 years, predicted 10-year CVD mortality versus observed CVD mortality yielded a ratio of 0.78 and 0.85, respectively. Goodness-of-fit for the algorithm showed excellent calibration with a X^2 of 7.93 (p = 0.44) in men and 6.52 (p = 0.59) in women. Discriminative performance in men and women of the same age was severely limited with an AUROC of 0.52 (95% CI 0.47–0.56) and 0.46 (0.41–0.52). In men and women aged 75-79 years, predicted 10-year CVD mortality versus CVD mortality yielded a ratio of 0.73 and 0.66, respectively. Goodness-of-fit for the algorithm remained excellent, with an X^2 of 2.66, (p = 0.95) in men and 6.28 (p = 0.62) in women while discriminative performance was severely limited with an AUROC of 0.47 (95% CI 0.39–0.55) in men 0.55 (95% CI 0.46–0.65) in women.

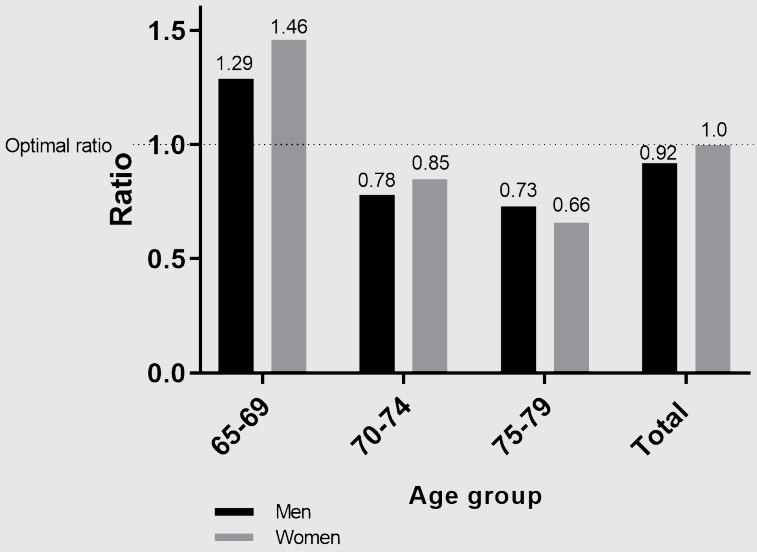


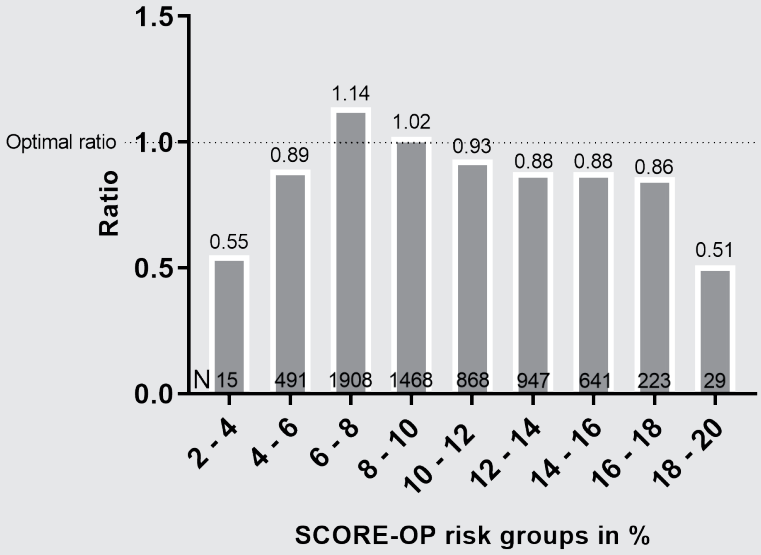
Figure 2. Ratios of predicted and observed 10-year CVD mortality
Note: Bars represent the ratio between predicted 10-year CVD mortality using SCORE-OP algorithm / observed 10-year CVD mortality by age and sex groups.

Table 2. Predicted by SCORE-OP and observed 10-year and 5-year CVD mortality, discrimination, and calibration

		% SCORE-OP		% Observed		AUROC		Hosmer Lemeshow test	
	N	CVD mortality	95% CI	CVD mortality	95% CI		95% CI	Chi square	p-value
10-year									
Overall	6590	9.84	9.76 – 9.92	10.20	9.52 – 11.04	0.63	0.60 – 0.65	3.26	0.92
Men	3016	12.70	12.62 – 12.79	13.80	12.57 – 15.15	0.60	0.57 – 0.63	13.27	0.10
Women	3574	7.43	7.39 – 7.47	7.40	6.53 – 8.29	0.58	0.54 – 0.62	10.03	0.26
Age-sex group									
Men 65-69	1508	11.26	11.17 – 11.35	8.70	7.39 – 10.33	0.54	0.49 – 0.60	5.24	0.73
Men 70-74	1196	13.78	13.68 – 13.88	17.60	15.59 – 20.19	0.52	0.47 – 0.56	7.93	0.44
Men 75-79	312	15.54	15.34 – 15.71	21.20	20.22 – 30.85	0.47	0.39 – 0.55	2.66	0.95
Women 65-69	1809	6.55	6.50 – 6.59	4.50	3.60 – 5.56	0.49	0.41 – 0.56	12.47	0.13
Women 70-74	1428	8.12	8.07 – 8.17	9.50	8.07 – 11.22	0.46	0.41 – 0.52	6.52	0.59
Women 75-79	337	9.24	9.16 – 9.32	14.00	10.61-18.37	0.55	0.46 – 0.65	6.28	0.62
5-year									
Overall	6590	3.55	3.31 - 3.39	3.70	3.25 – 4.18	0.64	0.60 – 0.68	4.49	0.81
Men	3016	4.77	4.74 – 4.81	5.30	4.59 – 6.22	0.61	0.56 – 0.65	11.68	0.17
Women	3574	2.15	2.14 – 2.16	2.30	1.86 – 2.85	0.51	0.44 – 0.57	7.48	0.17
Age-sex group									
Men 65-69	1508	4.23	4.19 – 4.26	3.70	2.81 – 4.74	0.57	0.49 – 0.65	7.72	0.46
Men 70-74	1196	5.18	5.14 – 5.22	6.60	5.34 – 8.22	0.55	0.49 – 0.62	16.29	0.04
Men 75-79	312	5.85	5.78 – 5.91	8.90	6.11 – 12.74	0.49	0.38 – 0.60	10.27	0.25
Women 65-69	1809	1.89	1.88 – 1.91	1.50	1.04 – 2.21	0.46	0.34 – 0.58	11.05	0.20
Women 70-74	1428	2.35	2.33 – 2.36	3.30	2.46 – 4.35	0.39	0.31 – 0.48	4.37	0.82
Women 75-79	337	2.67	2.65 – 2.70	2.40	1.21 – 4.75	0.57	0.37 – 0.77	2.03	0.98

Abbreviations: N, number; SCORE-OP, Systematic COronary Risk Evaluation Older Persons; CVD; cardiovascular disease; CI, confidence interval.

e-Figure 1 presents the ratios of predicted 10-year CVD mortality by SCORE-OP and observed CVD mortality in SCORE-OP risk groups of 2% increments. Prediction was most accurate in men and women with a risk score between 8 and 10%, yielding a ratio of 1.02. In the risk group of 6 to 8% SCORE-OP overestimated risk by 14%, whereas in the other risk groups it underestimated CVD mortality. In the risk groups of 2 to 4% and 18 to 20%, underestimation was nearly 50%. However, these groups consisted of a very limited number of individuals (2-4% n=15, 18-20% n=29).



e-Figure 1. Ratios of predicted and observed 10-year CVD mortality per SCORE-OP risk group
Note: Bars represent the ratio between risk groups per two percent according to SCORE-OP algorithm / observed 10-year CVD mortality.

In the blood pressure sensitivity analysis, normotensive individuals (systolic blood pressure ≤140 mmHg), had a ratio of predicted versus observed CVD mortality of 1.21 (AUROC 0.64 (95% CI 0.59-0.68), X^2 3.17 (p = 0.92)), and hypertensive individuals (systolic blood pressure >140 mmHg) had a ratio 0.83, (AUROC 0.61 (95% CI 0.58-0.64), X^2 13.58 (p = 0.09)).

Performance of SCORE-OP 5-year predicted cardiovascular mortality

In the population of 65-79 years, SCORE-OP 5-year risk of CVD mortality was 3.35% (95% CI 3.31-3.39) compared to observed CVD mortality of 3.70% (95% CI 3.20–4.20), yielding a ratio of 0.91. Goodness-of-fit for the SCORE-OP 5-year risk was excellent with a X^2 of 4.49 ($p = 0.81$). Discriminative performance remained limited with an AUROC of 0.64 (95% CI 0.60-0.68) (Table 2). In men and women, predicted 5-year CVD mortality versus observed CVD mortality yielded a ratio of 0.90 and 0.93, respectively.

Performance of the SCORE-OP versus SCORE low-risk in predicting 10-year cardiovascular mortality

When calculated for the total population aged 65-79 years, SCORE low-risk performed poorer than SCORE-OP. Predicted CVD mortality was 7.61% (95% CI 7.49–7.73) whereas observed CVD mortality was 10.20% (95% CI 9.52-11.04), yielding a ratio of 0.75 compared to a ratio of 0.96 with SCORE-OP. The AUROC was 0.66 (95% CI 0.64–0.69) vs 0.63 (95% CI 0.60–0.65) and the X^2 was 13.65 ($p = 0.09$) vs a X^2 of 3.26 ($p = 0.92$) in SCORE low-risk and SCORE-OP, respectively. There was a significant difference between the AUROC's of both algorithms (X^2 9.97) ($p = < 0.01$). SCORE low-risk also performed poorer compared to SCORE-OP in men and women separately with SCORE low-risk ratios of 0.67 and 0.83 and SCORE-OP ratios of 0.92 and 1.00, respectively. However, in the age subgroup of 65-69 years, SCORE low-risk performed better compared with SCORE-OP (ratio 0.90 vs 1.36, AUROC 0.66 (95% CI 0.60-0.73) vs 0.59 (95% CI 0.55–0.63), X^2 9.09 ($p = 0.34$) vs 7.98 ($p = 0.44$)). In individuals 70-79 years, SCORE-OP was superior to the SCORE low-risk algorithm with ratios of 0.82 vs 0.69 in men and women of 70-74 years and 0.65 vs 0.61 in men and women of 75-79 years.

Treatment thresholds

According to SCORE-OP, 98% (6468/6590) of all older (65-79 years) individuals had a 10-year mortality risk of ≥5%. According to SCORE low-risk a risk of ≥5% was observed in 67% (4391/6590). Above 70 years of age this percentage was 100% according to SCORE-OP whereas in SCORE low-risk the percentages for individuals of 70-74 years and 75-79 years were 83% (2172/2622) and 96% (625/649), respectively. With a cut-off point of ≥10% risk of 10-year mortality, 41% (2708/6590) of all older individuals were above this level according to SCORE-OP in contrast to 22% (1466/6590) according to SCORE low-risk.

DISCUSSION

In this validation study of the SCORE-OP algorithm in the EPIC-Norfolk cohort, we found that in a general population aged 65-79 years, SCORE-OP overall accurately estimates the rate of CVD mortality. While calibration was excellent, discriminative power was limited, both for the prediction of 5- and 10-year CVD mortality. When looking at sexes separately, point estimates of predicted and observed 10-year CVD mortality were accurate, the algorithm well-calibrated, but discriminative power markedly limited. Respectively, SCORE-OP over- and underestimated in the younger (65-69) and older (70-79) age-sex groups. These aspects should be addressed before widespread use of SCORE-OP in clinical practice is recommended.

SCORE-OP is developed for individual CVD risk prediction.[5] Therefore, the limited discrimination in our external validation study warrants attention. In the original paper by Cooney *et al.*, discriminative performance showed an AUROC of 0.74 in the overall population of 20,825 European individuals aged 65 years and over, and was comparable with their simulated external validation, which also reported an AUROC of 0.74.[5] This is in contrast to our findings showing an AUROC of 0.63 in the overall population aged 65-79 years. Several factors could have influenced our contrasting findings. First, when analyzing our data according to age-sex subgroups, we found a complex interplay between predicted and observed CVD mortality. In individuals aged 65-69 years, SCORE-OP overestimated 10-year CVD mortality, whereas in individuals aged 70-79 years a considerable underestimation was observed. Second, a well fitted model can have poor discrimination.[8] This is due to the influence of population disease prevalence on which the model is developed and the individual risk estimation which is leading in the discriminative performance. However, limited discrimination does not translate into low accuracy per se. Third, in our sensitivity analysis on systolic blood pressure, we found that SCORE-OP overestimates CVD mortality in normotensive individuals ($\leq$140 mmHg), and underestimates in hypertensive individuals ($>$140 mmHg), In addition, the discriminative performance was limited in both groups. This implies that also when taking an additional contributing risk factor into account, the model does not gain discriminative accuracy. This was also confirmed when SCORE-OP was analyzed according to separate risk groups. We found that a higher SCORE-OP risk score does not necessarily lead to more accurate estimation. However, the ratios of predicted and observed 10-year CVD mortality in the lower (2-4%) and higher risk groups (16-18% and 18-20%) could have been influenced by the low number of included individuals.

The current European CVD prevention guideline suggests preventive treatment in case of $\geq$5% risk of 10-year CVD mortality.[4] When calculated by the SCORE-OP algorithm, virtually all older individuals (98%) exceeded the 5% treatment threshold; above 70 years every individual had a risk $\geq$5%. Using an arbitrary

threshold of 10% risk, this number was reduced to 41% of the total population.[5] With such exceedingly high numbers of individuals at high risk, using a risk assessment tool to determine whether preventive therapies should be initiated is of limited added value in clinical practice, and potentially leads to a significant overtreatment of older adults.

The majority of studies referred to in the European CVD prevention guideline on preventive treatment were performed in adults up to 65 years.[4] The treatment recommendations are therefore not directly transferrable to individuals above 65 years. The guideline describes the potential benefits of cholesterol lowering therapy in primary prevention in the older population, but extensive evidence-based recommendations are lacking. Nevertheless, in secondary prevention treatment benefits of statins have shown to be similar in elderly (>65 years) as compared to middle aged individuals.[9,10] In addition, blood pressure treatment in the very old (>80 years) has been found to be beneficial in reducing the risk of CVD.[11] In a recent study of a nurse-led multicomponent primary CVD prevention program in older adults aged 70 to 78 years, positive results on systolic blood pressure (2.39 mmHg (95% CI 0.87-3.90) and cigarette smoking -1.85 (95% CI -3.36-0.35) were found in the intervention group.[12] Nevertheless, the intervention did not affect the SCORE-OP risk profile at six years follow-up. With the increasing possibilities to predict CVD risk in older adults, there is an increasing need for thorough evidence on CVD risk factor management to guide clinicians in clinical decision making.

In contrast to our findings, Brotons *et al*. found that in a Spanish population (N=974) aged 65-69 years, SCORE-OP estimated lower rates of 10-year CVD mortality as compared with SCORE low-risk.[6] Our findings show a higher risk estimation by SCORE-OP. The contrast in findings could be explained by the different statistical approaches, where Brotons *et al.* performed an analysis chiefly consisting of Kappa values between both algorithms, whereas we rigorously evaluated the overall population and relevant subgroups, calculating and comparing both calibration and discriminative performance.

Although CVD mortality is a hard and currently a leading outcome in risk estimation models, morbidity is at least as important due to the individual and societal impact.[4,13] In the current study we focused on the validation of the SCORE-OP tool for risk estimation of 10-year CVD mortality, and we did not asses CVD morbidity. We have previously demonstrated that a complex relationship exists between CVD mortality and morbidity when analyzed according to age and sex beyond the scope of the SCORE charts.[14] Ratios of morbidity to mortality are especially high in younger individuals and in women, but decrease with increasing age. Therefore, we also do not recommend applying the fixed multiplier (3x) as suggested by the European CVD prevention guideline in older individuals to calculate total CVD morbidity and mortality rates from calculated mortality rates alone.[4]

Strengths and limitations

There are several strengths to our study. First, we used the EPIC-Norfolk cohort as a representative cohort for low-risk countries according to the European Society of Cardiology.[15] Of this cohort, 6590 adults aged 65-79 years were eligible for our study and more than half of the included individuals were women. Second, we were able to compare the performance of the SCORE-OP with the current risk algorithm (SCORE low-risk), which has been previously validated in this population.[16] Finally, we were able provide insight into the nuanced differences in performance of the SCORE-OP algorithm in the overall population and in different subgroups, using a thorough statistical approach.

When interpreting the results of our study, some aspects should be taken into account. First, we excluded approximately 10% of cases from the dataset due to missing SCORE-OP variables. We compared demographics in the missing cases with the baseline demographics of included cases and except for 4.3% more cases with diabetes mellitus among excluded cases, we did not find significant differences. Second, the prevalence of diabetes mellitus was low in our overall study population (3.1%). This can be partly explained by the excluded cases with missing values on the SCORE-OP algorithm and the exclusion of individuals with a history of CVD. Nevertheless, compared to the prevalence of diabetes mellitus in the population of the original validation cohort (7%), our prevalence was lower, which could have influenced the CVD risk estimation by the SCORE-OP.[5] Third, the EPIC-Norfolk cohort is limited to individuals aged up to 79 years, and therefore we were not able to study the performance of the SCORE-OP in the very old population (≥80 years) as was performed in the internal validation study of Cooney *et al.*[5] Fourth, we did not compare our results with the performance of other well known risk algorithms, such as the Framingham and QRISK2 risk scores, algorithms that have incorporated interaction terms for age and other risk factors to adjust the risk scores for use in older adults.[13] This could provide further insight on alternative instruments with a more accurate performance in older individuals. Neither were we able to evaluate the effect of therapeutic strategies (initiation of lifestyle interventions and drug therapy) on cardiovascular mortality in our population due to a lack of data on these intervention after baseline data collection. Finally, although the ICD-10 codes of the outcomes in our study were mainly similar to the ICD-9 codes that were included in the original SCORE study, there are a few differences which could have contributed to a potential lower number of outcome events in our study.[16]

Conclusion

The SCORE-OP algorithm overall accurately estimates the rate of CVD mortality in a general population aged 65-79 years. However, while calibration was excellent, discriminative power was limited, both for the 5-year and the 10-year predictions. Therefore, SCORE-OP cannot readily be implemented in clinical practice in this

population. Further development and testing of the SCORE-OP to improve CVD risk stratification in older individuals is warranted.

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Chapter 3

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

Appendix 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, Appendices 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.

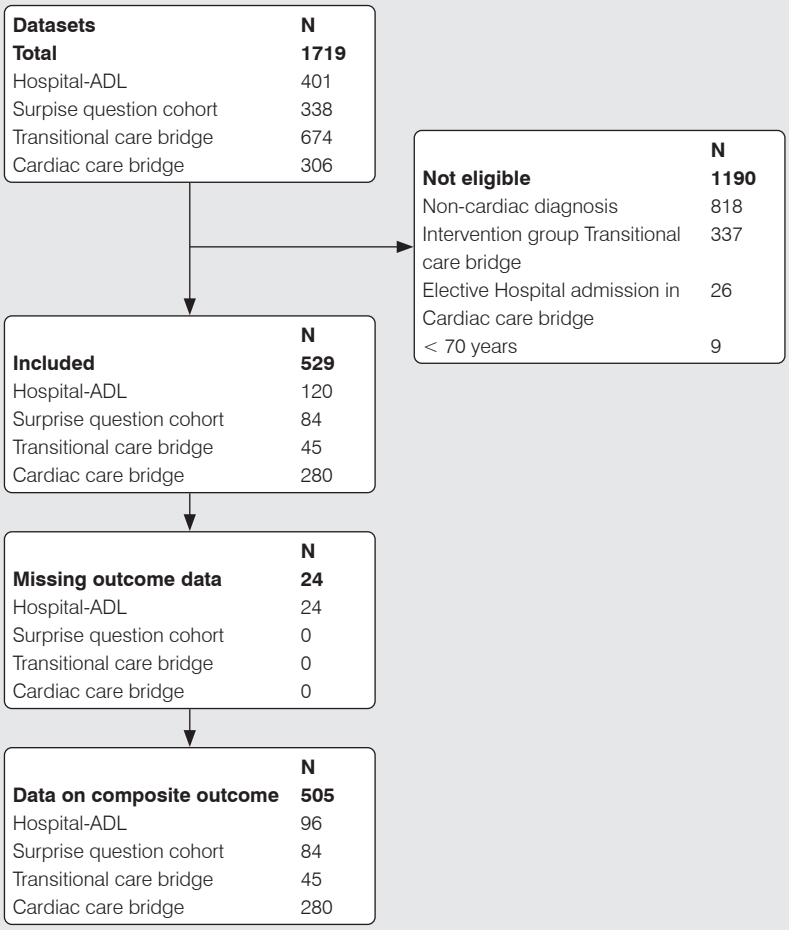

Figure 1. Flowchart

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 System[8]: 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) (Appendices 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 Appendix 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.

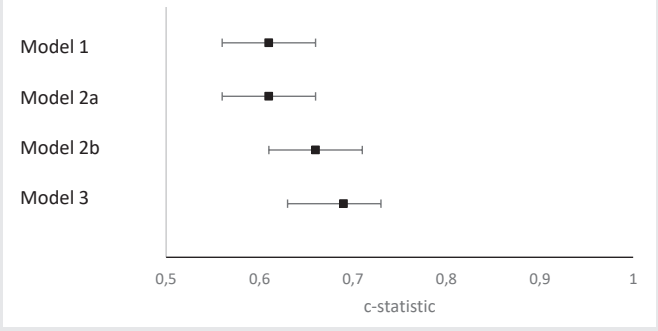

Figure 2. Areas under the curve and 95% confidence intervals for predictors of six-month readmission or mortality
Model 1: DSMS delirium, DSMS fall risk, DSMS functional impairment, DSMS malnutrition
Model 2a: sex, admission in the previous six months and cardiovascular diagnosis
Model 2b: sex, admission 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

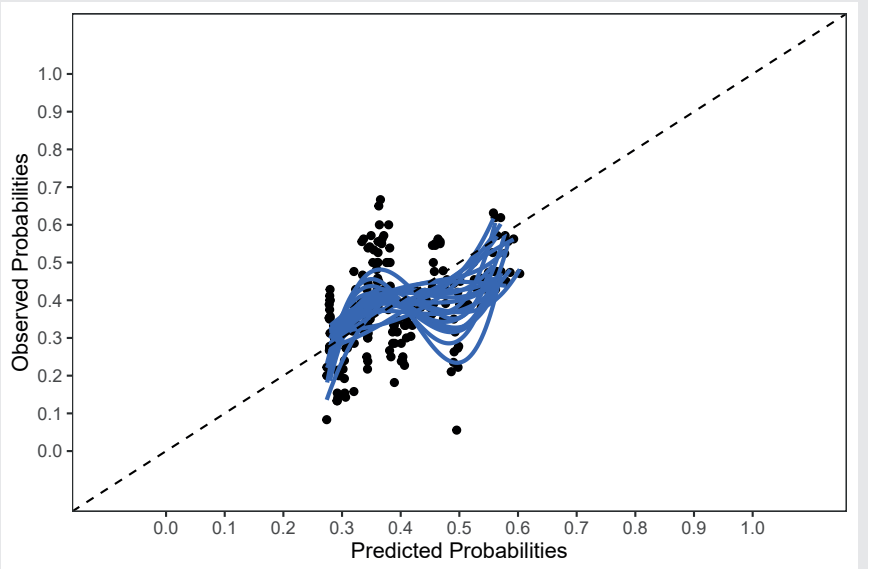

Figure 3. Calibration plot of readmission or mortality within six months (model 3) in the two observational cohorts

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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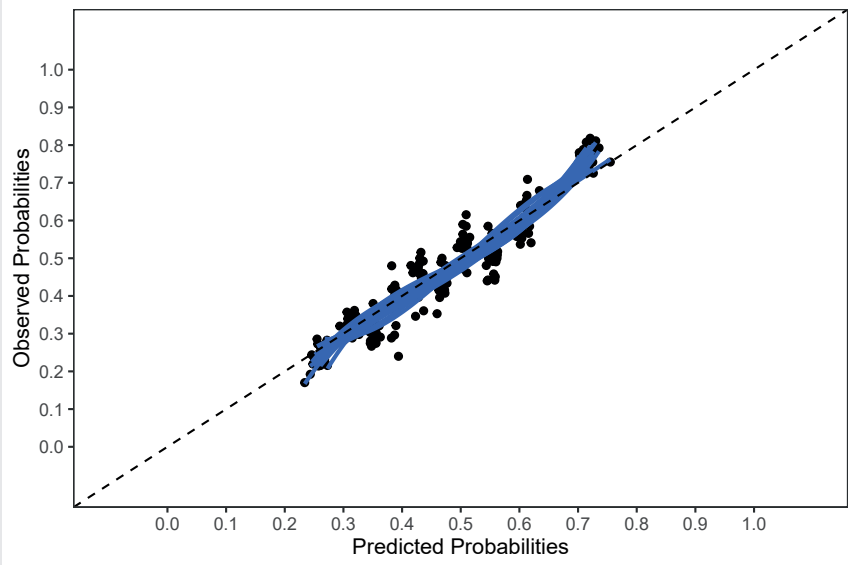
APPENDIX 1. FREQUENCY OF MISSING DATA PER VARIABLE IN THE FOUR COHORTS

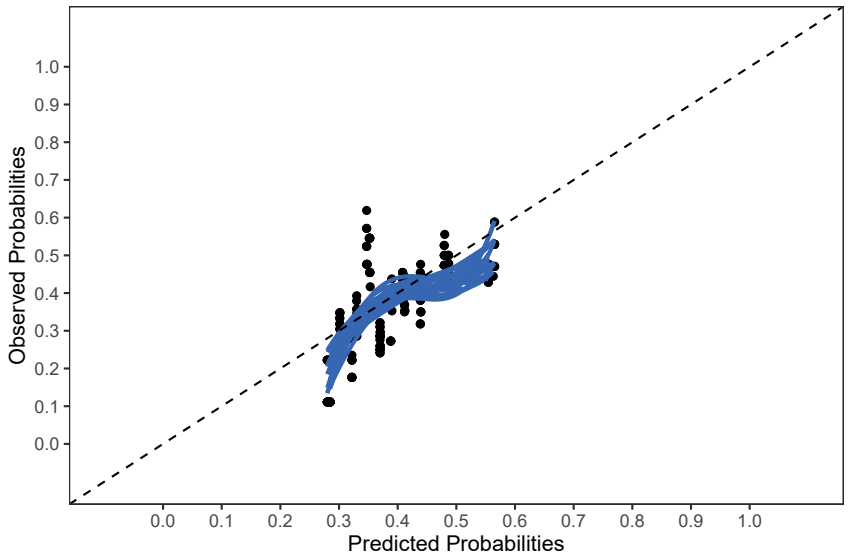
	Hospital-ADL (n=120)	Surprise question cohort (n=84)	Transitional care bridge study (n=45)	Cardiac care bridge study (n=280)
Sociodemographics				
Age	0	0	0	0
Gender	0	0	0	0
Educational level	0	84	0	1
Living arrangement	0	0	0	0
Hospital admission				
Diagnosis on admission	0	0	0	0
Length of stay	4	1	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

APPENDIX 2.



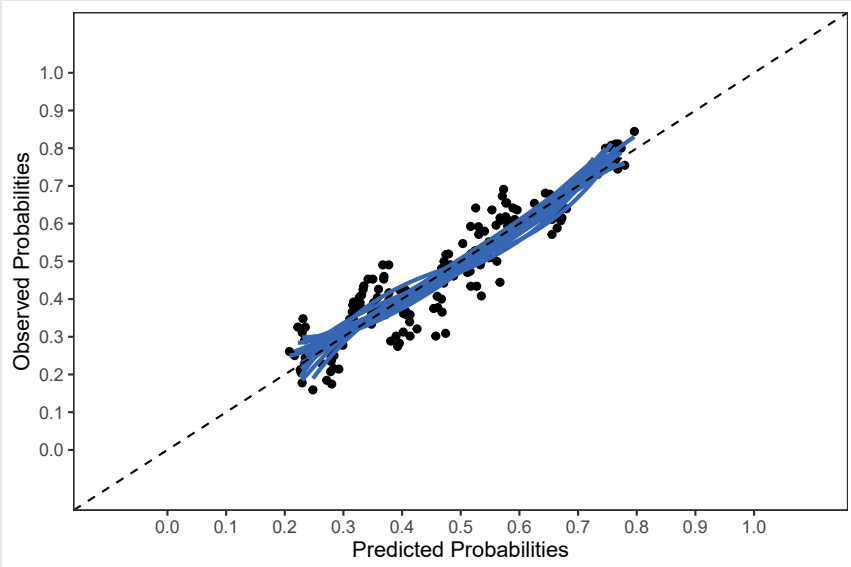
Supplemental figure 1. Calibration plot of readmission or mortality within six months (model 2b) in 250 bootstrapped samples.

APPENDIX 3.



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

APPENDIX 4.



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

Part 2

Organization of transitional care in older cardiac patients: The Cardiac Care Bridge program

Chapter 4

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.

TRIAL REGISTRATION: NTR6316. Date of registration: April 6, 2017.

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.

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.

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*

Time Frame	Intervention component	Baseline – outcome measures	Professionals involved	Intervention	Control
Week 3	Home visit 3. lifestyle promotion and self-management		CCRN[§]	X	
	Two home-based cardiac rehabilitation sessions		PT[¶]	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		CCRN[§]	X	
	Two home-based cardiac rehabilitation sessions		PT[¶]	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)

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 (appendix 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).

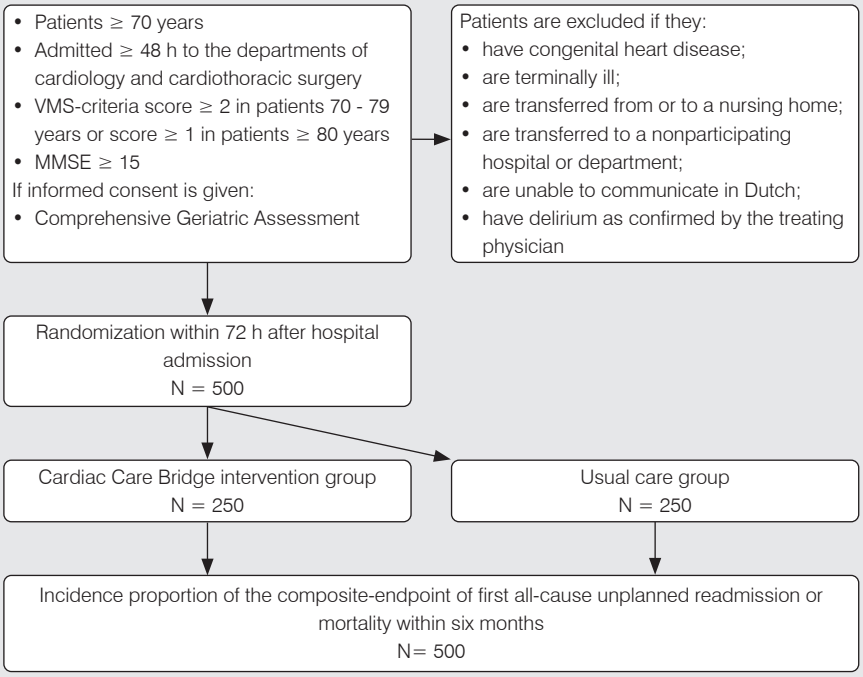

Figure 1. Flowchart of patient selection and randomization

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.

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

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	
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

Table 3. *Continued*

	CGA	Question or instrument	T0*	T0+[†]	T1[‡]	T2[§]	T3[‖]
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¶
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

Table 3. *(continued)*

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

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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APPENDIX 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 5

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

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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 $\geq$2 in patients aged 70-79 years or DSMS-score $\geq$1 in patients aged $\geq$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 $\leq$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 $\leq$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 $\geq$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).

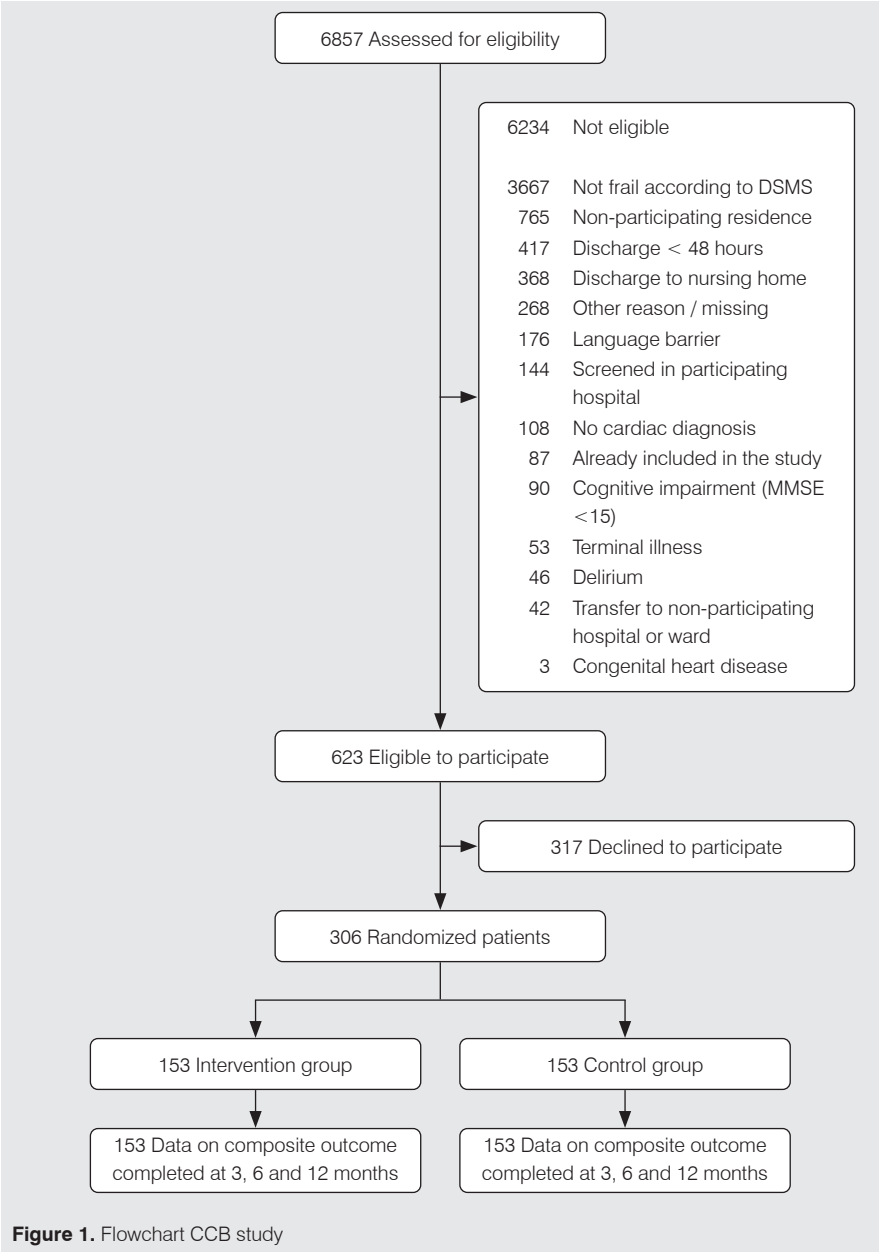

Figure 1. Flowchart CCB study

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%
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%

Table 1. *Continued*

		Intervention (n=153)		Control (n=153)	
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%
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)

Table 1. *Continued*

(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).

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.

Table 2. Primary and secondary outcomes in the CCB study

	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[a]							
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.

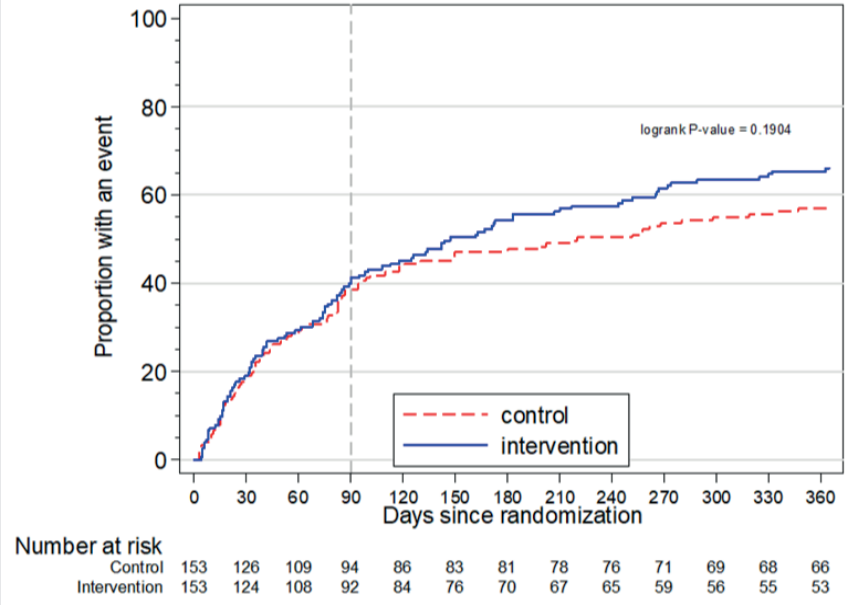

Figure 2. Kaplan-Meier curve of the composite outcome within 12 months
Legend: Dashed line at 90 days marks the end of the intervention period. The curves of the intervention and control group in the primary outcome diverged after the intervention was completed at 90 days follow-up.

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

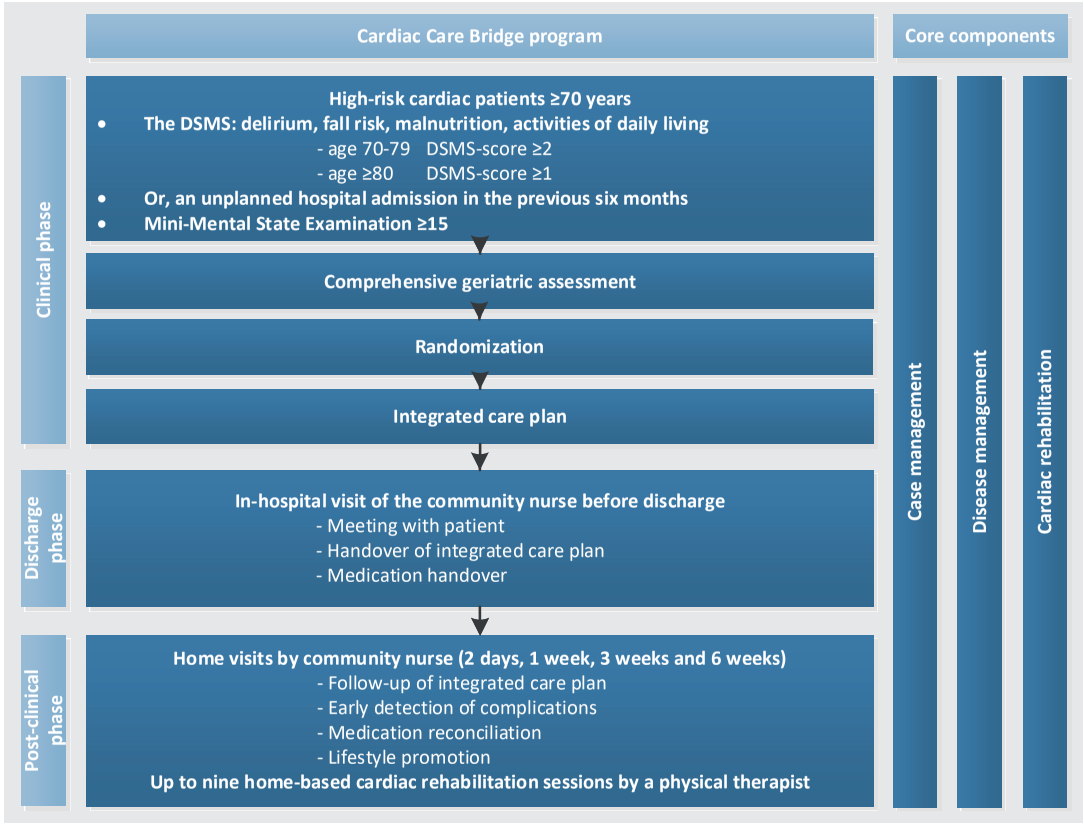
All Dutch citizens have an obligated health care insurance including coverage of primary care visits, hospital outpatient visits, hospital admissions, center-based cardiac rehabilitation (CR) and prescribed medication. In addition, Dutch citizens can purchase supplemental insurance for e.g. additional 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 RR[32] 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.

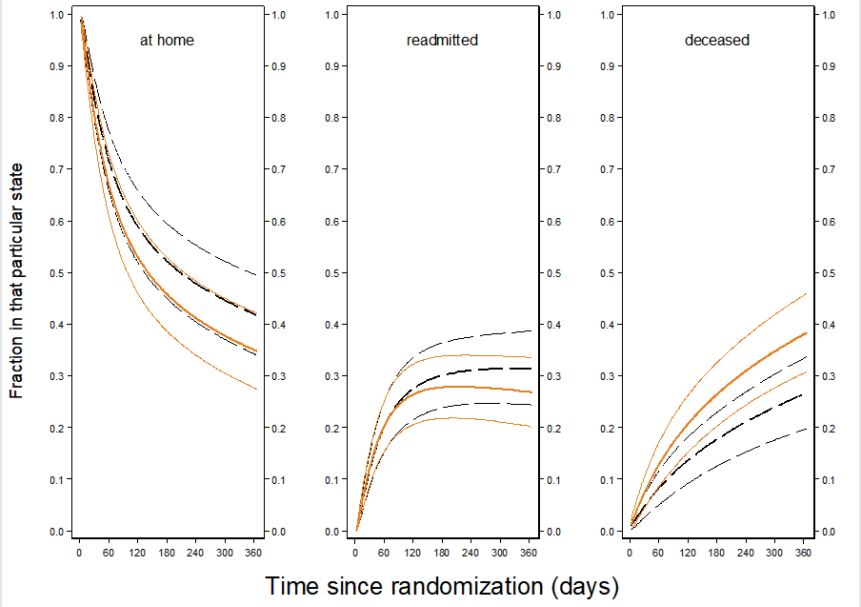


Figure A. Results of the unadjusted illness-deceased model up to 12 months follow-up

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.

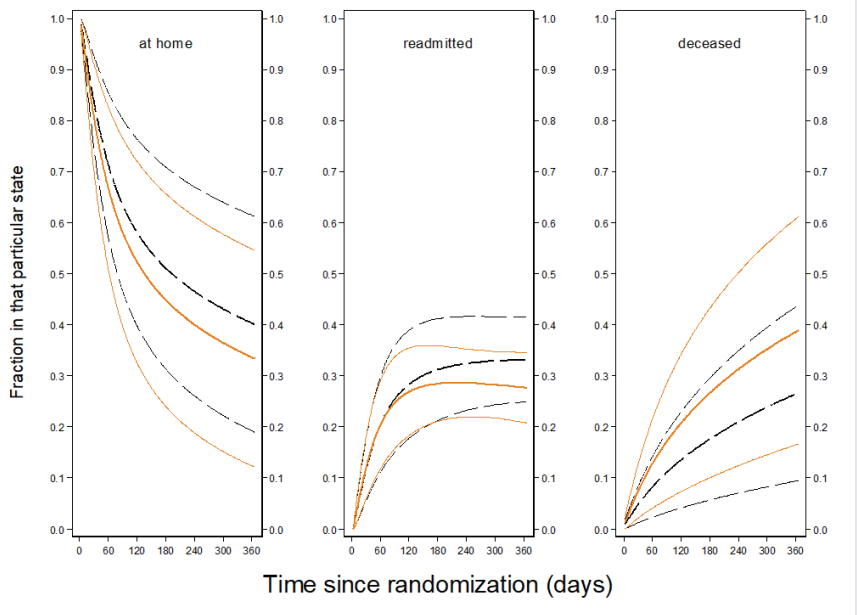


Figure B. Results of the adjusted illness-deceased model up to 12 months follow-up

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* (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†							
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).

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

† 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* (95% CI)	P-value	P-value interaction	Adjusted risk ratio* (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

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

Chapter 6

The Cardiac Care Bridge transitional care program for the management of older high-risk cardiac patients: an economic evaluation alongside a randomized controlled trial

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Submitted, Plos One

ABSTRACT

OBJECTIVE: To evaluate the cost-effectiveness of the Cardiac Care Bridge (CCB) nurse-led transitional care program in older (≥70 years) cardiac patients compared to usual care.

METHODS: The intervention group (n=153) received the CCB program consisting of case management, disease management and home-based cardiac rehabilitation in the transition from hospital to home on top of usual care and was compared with the usual care group (n=153). Outcomes included a composite measure of first all-cause unplanned hospital readmission or mortality, Quality Adjusted Life Years (QALYs) and societal costs within six months follow-up. Missing data were imputed using multiple imputation. Statistical uncertainty surrounding Incremental Cost-Effectiveness Ratios (ICERs) was estimated by using bootstrapped seemingly unrelated regression.

RESULTS: No significant between group differences in the composite outcome of readmission or mortality nor in societal costs were observed. QALYs were statistically significantly lower in the intervention group, mean difference -0.03 (95% CI: -0.07; -0.02). Cost-effectiveness acceptability curves showed that the maximum probability of the intervention being cost-effective was 0.31 at a Willingness To Pay (WTP) of €0,00 and 0.14 at a WTP of €50,000 per composite outcome prevented and 0.32 and 0.21, respectively per QALY gained.

CONCLUSION: The CCB program was on average more expensive and less effective compared to usual care, indicating that the CCB program is dominated by usual care. Therefore, the CCB program cannot be considered cost-effective compared to usual care.

INTRODUCTION

Cardiac disease is the leading cause of hospitalization and mortality in older individuals and leads to substantial healthcare costs.[1, 2] Approximately 14% of total US healthcare costs[1] and approximately 12% of the total healthcare expenditure in the Netherlands are caused by cardiac disease and the majority of costs is incurred in older individuals.[3] After hospitalization for cardiac disease, up to 25% of older cardiac patients are readmitted within the first six months.[4, 5] Geriatric conditions lead to physical and cognitive limitations, thereby complicating medical treatment and care during and after discharge. This increases the risk of adverse outcomes such as hospital readmission[6] and contribute to high healthcare costs.[7] There is increasing evidence that a large proportion of costly readmissions can be prevented.[8]

Transitional care interventions have the potential to reduce the risk of readmission and mortality.[9-11] However, in cardiac patients the evidence is not unequivocal.[9, 12-14] The Cardiac Care Bridge transitional care program (CCB program) was developed to reduce hospital readmission and mortality in older (≥70 years) cardiac patients at high risk of readmission and mortality.[15] This nurse-coordinated intervention combined case management, disease management and home-based rehabilitation in the transition of care. Although the analysis showed no significant between group differences in the primary outcome,[16] there may still be economic consequences of implementing the intervention. Therefore, the aim of this study is to assess the cost-effectiveness of the CCB program compared to usual care from a societal perspective, within six months after randomization among older (≥70 years) cardiac patients at high risk of readmission and mortality.

MATERIALS AND METHODS

Design

A cost-effectiveness analysis of the CCB program was performed alongside the CCB randomized controlled trial from a societal perspective. The study protocol was approved by the Medical Ethics Committee of the Amsterdam University Medical Centre (Protocol ID: MEC2016_024) and registered in the trial registration: NTR6316 (http://www.trialregister.nl). All participants provided written informed consent. This manuscript was designed according to the CHEERS criteria.[17]

Participants

The CCB multi-centre randomized trial was conducted between June 2017 and March 2019 in six hospitals in and surrounding Amsterdam, the Netherlands.[15,16] In total, 306 older (≥70 years) hospitalized cardiac patients at high risk of

readmission and mortality were included. Patients were eligible for inclusion if they were at high risk according to the Dutch Safety Management System (DSMS) screening on malnutrition, fall risk, delirium and functional impairment, or if patients had an unplanned hospital admission within six months prior to the index admission and were discharged home. The DSMS-score ranges between 0-4 and 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.

Randomization

Within 72 hours of hospitalization, eligible patients were asked to participate in the randomized trial by cardiac research nurses. After providing informed consent, a comprehensive geriatric assessment (CGA) was conducted with all participants. Subsequently, participants were randomized to the intervention or usual care group by a web-based program to ensure allocation concealment (Research Manager, https://my-researchmanager.com/en/). Participants were blinded to their group allocation according to a postponed informed consent procedure.[18]

Intervention

In brief, the CCB program included three phases (clinical, discharge and post-clinical phase) and consisted of three core components (case management, disease management and home-based cardiac rehabilitation).[15, 16] In the clinical phase, the cardiac research nurses developed an integrated care plan together with participants, based on cardiac and geriatric conditions as assessed by the CGA, and consulted other disciplines based on indication. In the discharge phase, community nurses visited participants in hospital prior to discharge to receive a face-to-face handover from the cardiac research nurse and to meet participants. The community-based physical therapist received a written handover and the discharge date to organize home-based cardiac rehabilitation. After discharge, the participants received four home visits from the community nurse which were focussed on medication reconciliation, evaluation of the health status and the integrated care plan, and topics related to lifestyle. The community nurse was in close contact with an affiliated pharmacist for medication reconciliation and with the community-based physical therapist who performed up to nine home-based cardiac rehabilitation sessions.

Usual Care

Standard primary care was provided in both the intervention and the usual care group. During hospitalization, participants received care as usual from their treating cardiologist. After discharge, participants received outpatient care from a cardiologist and cardiac nurse specialist according to the national cardiovascular guidelines.[19] The treating cardiologist referred participants to outpatient or centre-based cardiac rehabilitation programs on indication. For non-cardiovascular

problems, the general practitioner is the primary healthcare provider. In the Netherlands, basic healthcare insurance is obliged in all citizens. It includes coverage of primary care visits, hospital outpatient visits, hospitalizations, and prescribed medication. Supplementary insurance can be purchased and includes e.g., physical therapy and other paramedical services.

Outcomes

The primary outcome of the CCB study was the composite of first all-cause unplanned hospital readmission or mortality within six months follow-up. These outcomes were assessed by medical files of participating hospitals, the Dutch National Personal Records Database[20] and self-reported information during follow-up.

Health-related Quality of Life (HQoL) was evaluated at six months follow-up by using the 5-level EuroQol-5D questionnaire (EQ5D-5L).[21] Subsequently, the Dutch EQ-5D-5L tariff (based on the Dutch general society) was used to convert the EQ-5D-5L health states into utilities.[22] Finally, QALYs were calculated by multiplying the time subjects spent by the utilities of that health state. The changes in utilities between two measurement points were assumed linear.

Healthcare utilization and costs were measured from a societal perspective which means that all costs, including informal and healthcare costs, were included in the analyses (see Table 1).[23] Healthcare utilization at three and six months follow-up, was collected by use of an extended version of The Older Persons and Informal Caregivers Survey - Minimum Data Set (TOPIC-MDS) and included the length of hospital admissions, the number of emergency visits, the number of days in residential care, the number of days receiving day care, the number of general practitioner consultations, pharmacist consultations, hours of received personal care and home nursing, hours of received physical therapy and duration of outpatient rehabilitation or hospital-based rehabilitation.[24] These data were self-reported and supplemented with information from the hospital medical files. Informal care hours were self-reported by the informal caregiver. To convert healthcare utilization into healthcare costs, Dutch standard costs were multiplied by the volumes of utilization of these units.[25] All prices were converted into prices for the year 2018 using consumer price indices, see Table 1.[26]

To calculate the intervention costs, the intervention components were valued with Dutch standard costs according to the Dutch guidelines using a bottom-up micro-costing approach.[26] In addition, the time needed to perform a baseline assessment, to develop an integrated care plan and to arrange the home-based intervention, was based on an average time-investment estimation within the CCB study protocol and was valued using standardized salary costs, see Table 2.[15]

Table 1. Healthcare costs (€) used in the cost-effectiveness analysis

Healthcare utilization	Volume	Costs (€)*
Primary care		
General practitioner consultation	Visit	34.34
Community pharmacist medication reconciliation	Visit	49.33
Home care		
Community nursing	Hour	75.97
Personal care	Hour	52.04
Domestic care at home	Hour	23.53
Care hotel (in nursing home)	Day	174.83
Day-care	Day	139.45
Physical therapy	Visit	34.34
Physical therapy, home visit	Visit	45.77
Secondary care		
Emergency room	Visit	269.52
Hospital admission	Day	495.34
Hospital ICU admission	Day	2096.89
Outpatient clinic	Visit	94.70
Rehabilitation		
Institutional	Day	478.69
Outpatient cardiac rehabilitation	Hour	156.54
Residential and nursing home care	Day	174.83
Informal care		
Voluntary care, housekeeping, practical caregiver support	Hour	14.32

* Prices are obtained from the Dutch manual for cost-analysis in healthcare research.[25] Subsequently, prices per categories were indexed to the reference year 2018 by using a consumer price index.[26] The price of the pharmacist consultation is based on the Dutch guideline 'Generieke kosten medicatiebeoordeling' (General costs medication reconciliation).[27]

Missing data

Missing observations in cost and effect data were imputed using multiple imputation by chained equations (MICE) with predictive mean matching.[28, 29] The imputation model included variables that were related to missingness or the outcome, and all variables included in the analysis models (see Appendix 1). Based on the loss of efficiency (fraction of missing information/m$\leq$0.05), ten imputed datasets were needed.[29] These imputed datasets were analysed separately, after which the results were pooled using Rubin's rules.[30]

Table 2. CCB intervention costs (€)

	Minutes per participant	Costs (€) per hour*	Total CCB costs (€)
Secondary care			
Comprehensive geriatric assessment	100	19.29	32.15
Integrated care plan	30	19.29	9.64
Consultation geriatrician	15	117.59	29.39
Face-to-face handover cardiac nurse	30	19.29	9.64
Primary care			
Community nurse (home) visits, including in hospital face -to-face handover**	5-6 visits	NA	241.00
Pharmacist medication reconciliation***	20	147.48	49.33
Home-based cardiac rehabilitation (9 sessions)	285	45.77	411.93

* Prices are obtained from the Dutch manual for cost-analysis in healthcare research.[25] Subsequently, prices per categories were indexed to the reference year 2018 using a consumer price index.[26] ** Community nurse visits: 1-9 visits ≤ 3 months category frail / chronically ill, standard price. *** The price of the pharmacist consultation is based on the Dutch guideline 'Generieke kosten medicatiebeoordeling' (General costs medication reconciliation).[27]

Statistical analysis

All analyses were performed according to the intention-to-treat principle. Baseline characteristics were presented as mean with standard deviation (SD), median with interquartile range (IQR) or number with percentage. Seemingly unrelated regression (SUR) was performed to estimate cost and effect differences adjusted for confounders.[31] Variables were considered to be a confounder if their inclusion resulted in a ≥10% change in the beta-coefficient, and included sex, cardiovascular diagnosis and geriatric conditions: malnutrition, falling, delirium, functional impairment and cognitive status Mini-Mental State Examination-score.[15] Cost data generally have a highly skewed distribution due to many patients with low costs and few patients with (very) high costs, and no possibility of negative values. Therefore, statistical uncertainty was estimated by bootstrapping the SUR models using 5000 replications.

Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in total costs between the intervention group and the usual care group by the difference in the composite outcome (first readmission or mortality) for the cost-effectiveness analysis (CEA) and QALYs for the cost-utility analysis (CUA). Statistical uncertainty surrounding the ICERs was presented by showing the bootstrapped cost-effect pairs in cost-effectiveness planes. In a cost-effectiveness plane, the difference in effects between the intervention and usual care group is plotted on the x axis and the difference in costs on the y axis. Cost-effectiveness acceptability curves (CEAC) were estimated, showing the probability that the

intervention is cost-effective compared to control for all possible values of the willingness to pay (WTP) threshold. The WTP threshold represents the amount of money that society is willing to pay to obtain one unit of effect extra.[32]

Two sensitivity analyses were performed. First, the main analysis was repeated without adjustment for confounders. Second, analyses were performed from a healthcare perspective in which only healthcare costs were included.

IBM SPSS version 26.0 0 (SPSS Inc., Chicago, IL, USA) and Stata Statistical Software: Release 16 (College Station, TX: StataCorp LP) were used in the data analyses.

RESULTS

In total, 306 participants were included in the CCB study and were randomly allocated to the intervention (n=153) or the usual care group (n=153). Table 3 presents the baseline characteristics. The only baseline difference found was a higher risk of delirium in the intervention group compared to the usual care group, 61.4% and 50.3% (p=0.05) respectively.

Complete outcome data on the composite outcome were available for all participants, see Figure 1. Data on costs over six months follow-up were complete in 75 (24.5%) intervention participants and in none of the participants in the usual care group. In total, 227 participants (74.2%) had complete data on QALYs at six months follow-up, of whom 119/153 participants (77.8%) in the intervention group and 108/153 participants (70.6%) in the usual care group. Between group differences were tested in participants with and without missing data on costs and no significant differences were found.

Outcomes

Table 4 shows the unadjusted mean outcomes over six months follow-up. In the intervention group, the proportion of participants with the primary composite outcome of readmission or mortality was 54% compared to 48% in the usual care group (risk difference (RD), 6% (95% confidence interval (CI) -5%; 18%). The mean difference in QALYs between the intervention (mean 0.35, SD 0.14) and usual care group (mean 0.38, SD 0.14) was -0.03 (95% CI: -0.07; -0.02).

Costs

Table 4 shows the crude mean costs over six months follow-up after multiple imputation. There was no difference in total societal costs between groups. Informal care costs were significantly higher in the intervention versus the usual care group. Primary care costs were the largest cost driver in both groups.

Table 3. Baseline characteristics.[16]

	Intervention group, n=153	Usual care group, n=153
Socio-demographics		
Male	70 (45.8)	86 (56.2)
Age, years	82.5 ± 6.1	82.3 ± 6.5
Cohabitating	66 (43.1)	68 (44.4)
Disease related characteristics		
Hospital admission ≤ 6 months of index hospitalization	66 (43.1)	73 (47.7)
Cardiac diagnosis on admission		
- Heart failure	86 (56.2)	91 (59.5)
- Acute Coronary Syndrome	19 (12.4)	24 (15.7)
- Other	48 (31.4)	38 (24.8)
Charlson Comorbidity index	3 [1-4]	3 [1-4]
Geriatric conditions		
(Risk of) delirium*	94 (61.4)	77 (50.3)
Fall risk (fall ≤ 6 months)	67 (43.8)	78 (51.0)
Functional impairment (Katz-6, score ≥2)	65 (42.5)	54 (35.3)
(Risk of) malnutrition (SNAQ)	57 (37.3)	43 (28.1)
Cognitively impaired, MMSE 15-23	47 (30.7)	48 (31.4)

N (%), mean ± standard deviation, median [IQR]. * Assessment of 1. cognitive impairment; 2. help with self-care ≤ 24 hours; 3. a previously delirium (>1 point = at risk).
Abbreviations: MMSE mini-mental state examination, SNAQ short nutritional assessment questionnaire.

Cost-effectiveness

The results of the CEA are presented in Table 5, and Figures 2 and 3. Table 5 and Figure 2 show that the ICER and 64% of the cost-effect pairs are in the northwest quadrant of the CE-plane, indicating that the intervention is on average more expensive and less effective (higher incidence of the composite outcome of first readmissions and mortality) compared to usual care. The CEA curve in Figure 3 shows that the probability of the intervention being cost-effective compared to the usual care group was 31% when the WTP is €0 per prevented case of readmission or mortality. This probability decreases to 14% when the WTP is €50,000 per prevented case of readmission or mortality.

Cost-utility

The results of the CUA are shown in Table 5, Figure 4 and 5. Table 5 and Figure 4 show that the ICER and 65% of the cost-effect pairs are in the northwest quadrant of the CE-plane, indicating that the intervention was more expensive and less effective (less QALYs) compared to usual care. In Figure 5, the CEA curve shows

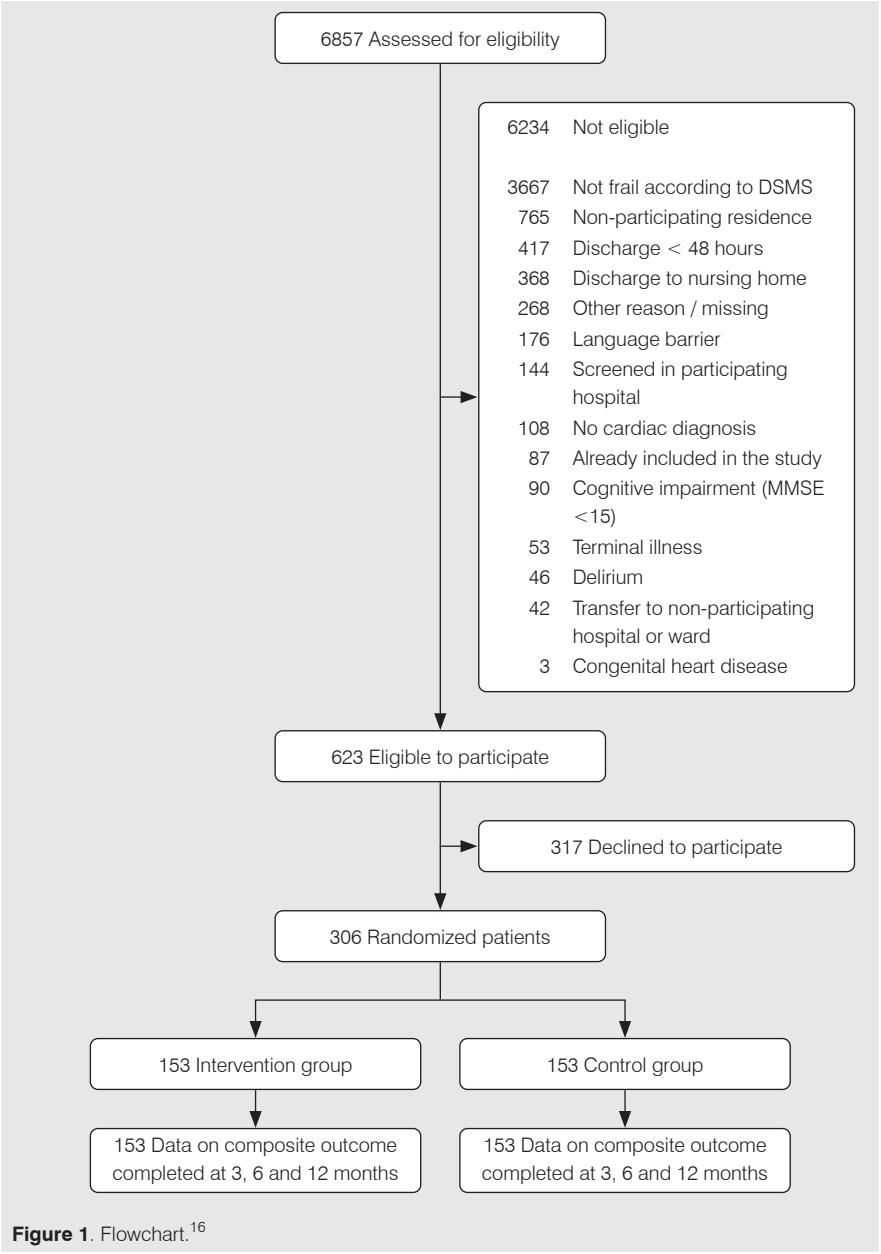

Figure 1. Flowchart.[16]

Table 4. Unadjusted mean costs (€) and effects over 6 months follow-up after multiple imputation

	Intervention group (N=153)	Usual care group (N=153)	Mean difference	95%CI
Outcomes				
Readmission or mortality	0.54 (0.50)	0.48 (0.50)	0.06	-0.04; 0.18
QALY	0.35 (0.14)	0.38 (0.14)	-0.03	-0.07; -0.02
Costs (€)				
Healthcare costs (primary care)	8348 (18030)	8501 (21338)	-153	-1534; 1228
Healthcare costs (secondary care)	5336 (8139)	5256 (7772)	-80	-468; 628
Informal care costs	2445 (9178)	962 (3407)	1483	1009; 1956
Total costs from a societal perspective (including all costs)	16126 (23288)	14833 (23438)	1294	-343; 2931
Total costs from a healthcare perspective (primary and secondary care costs)	13717 (19425)	13873 (22631)	-155	-1630; 1320

Mean, standard deviation (SD). CI: confidence interval. QALY: quality adjusted life years.

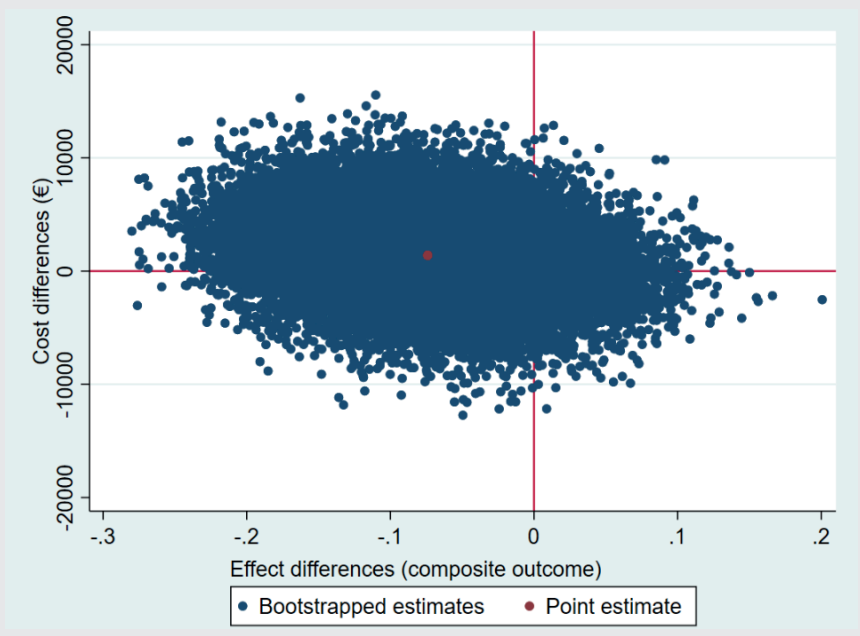

Figure 2. Cost-effectiveness plane for estimated readmission or mortality comparing the intervention group with the usual care group.

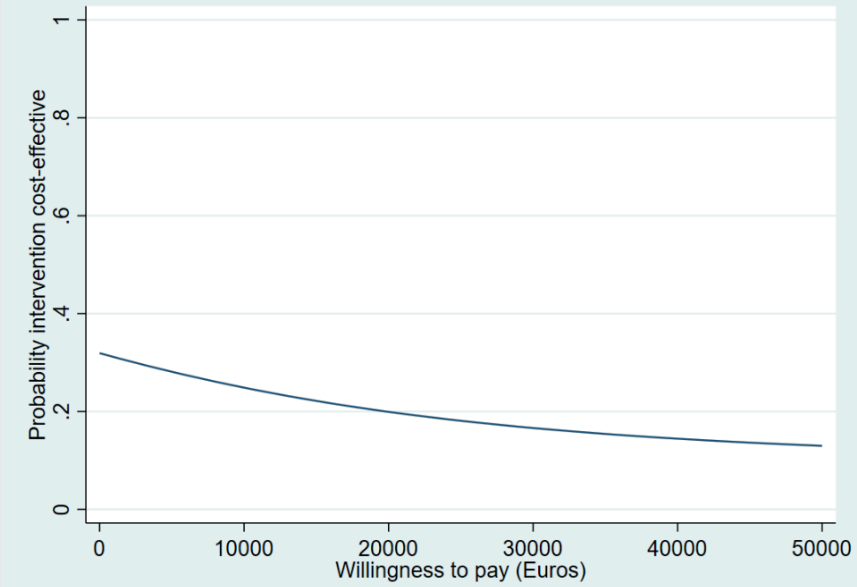

Figure 3. Cost-effectiveness acceptability curve for readmission or mortality, showing the probability that the intervention is cost-effective compared to usual care over a range of WTP values.

that the probability that the intervention is cost-effective compared to the usual care group was 32% when the WTP is €0 per QALY gained. This probability decreases to 21% when the WTP is €50,000 per QALY.

Sensitivity analyses

In Table 5, the results of the sensitivity analyses for the CEA and CUA are also presented. Results of the sensitivity analyses of the societal perspective as well as analyses from healthcare perspective, were in line with the results from the main analysis.

Table 5. Differences in readmission or mortality, QALYs and costs in €, ICERs, distribution of bootstrapped cost-effect pairs over the quadrants of the CE-plane, and the probability of cost-effectiveness at different ceiling ratios.

	Cost Δ (95% CI)	Effect Δ (95% CI)	ICER	CE-plane	CE-plane	CE-plane	CE-plane	Probability that CCB-intervention is CE at WTP		
				NE	SE	SW	NW	WTP= €0	WTP= €30,000	WTP= €50,000
Main outcome: societal perspective adjusted for confounding										
Composite outcome of readmission or mortality at 6 months	1404 (-4050;6648)	-0.074 (-0.184;0.036)	-22,903	5%	5%	26%	64%	31%	18%	14%
QALYs	1346 (-4104;6554)	-0.025 (-0.059;0.008)	-55,190	4%	3%	28%	65%	32%	24%	21%
Sensitivity analysis: societal perspective										
Composite outcome	1435 (-3860;6551)	-0.065 (-0.177;0.046)	-24,458	7%	6%	24%	63%	31%	19%	17%
QALYs	1435 (-3826;6512)	-0.025 (-0.059;0.009)	-56,344	4%	4%	26%	66%	31%	24%	20%
Sensitivity analyses: healthcare perspective										
Composite outcome	-156 (-5339;4191)	-0.074 (-0.184;0.036)	-195	3%	7%	45%	45%	52%	28%	21%
QALYs	-208 (-5397;4121)	-0.025 (-0.059;0.008)	1613	2%	5%	48%	45%	54%	42%	38%

Abbreviations and explanation: NE quadrant: more effective and more expensive, SE quadrant: more effective and less expensive, SW quadrant: less effective and less expensive, NW quadrant: less effective and more expensive. CCB: Cardiac Care Bridge, CE: cost-effective, WTP: willingness to pay, QALY: quality adjusted life years.

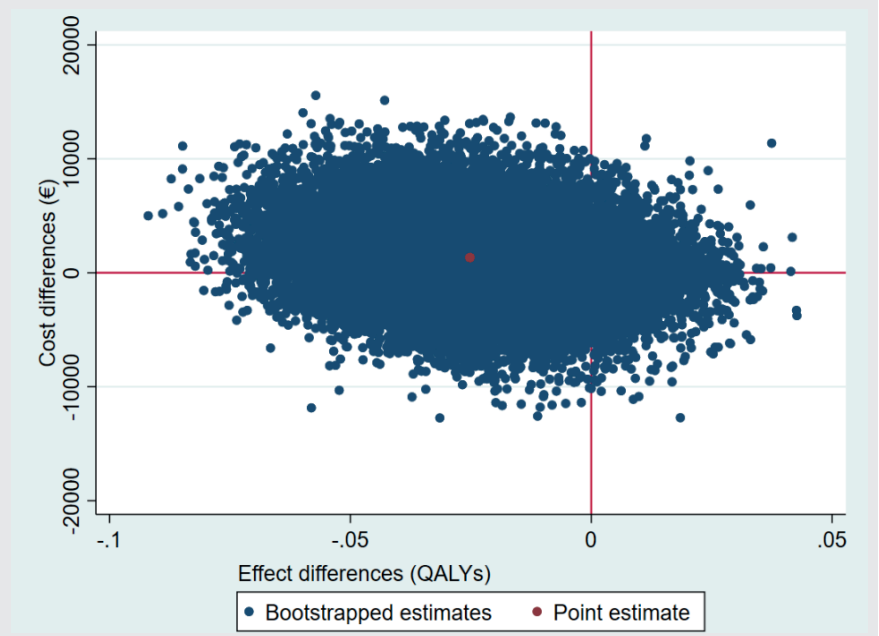

Figure 4. Cost-effectiveness plane for QALYs comparing the intervention group to the usual care group.

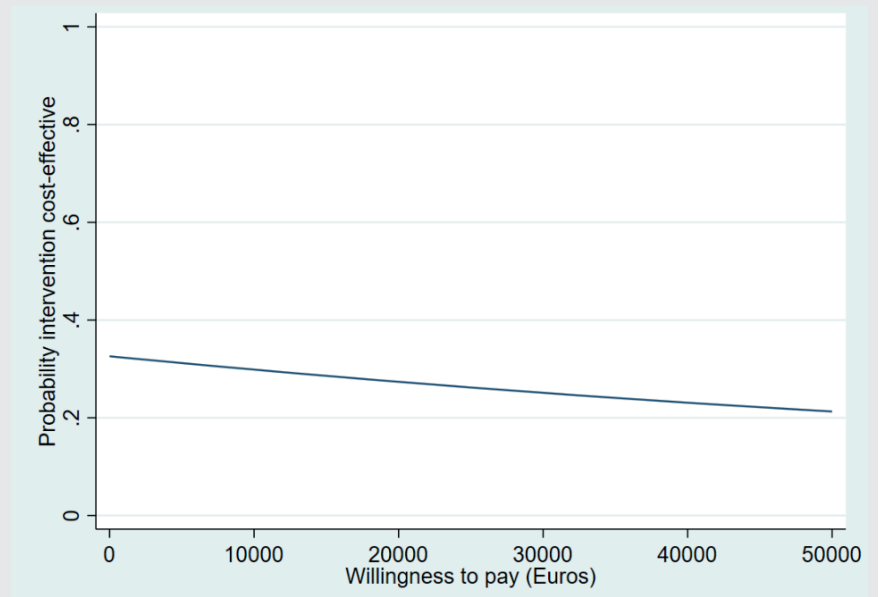

Figure 5. Cost-effectiveness acceptability curve for QALYs, showing the probability that the intervention is cost-effective compared to usual care over a range of WTP values.

DISCUSSION

In this study, no significant differences were found on the composite outcome of first unplanned readmission or mortality and total societal costs. In addition, the numbers of QALYs was significantly lower in the intervention group. Thus, the CCB program was on average more expensive and less effective than usual care, meaning that the CCB program was dominated by usual care.

Although our study is the first cost-effectiveness study of an intervention combining case management, disease management and home-based cardiac rehabilitation in the transition of care,[15, 16] there are some previous studies on cost-effectiveness of nurse-led transitional care interventions in heart failure patients. For example, the systematic review of Bryant *et al*.[33] showed that such interventions had a favourable effect on outcomes such as rehospitalization and reduced costs in patients with heart failure compared to usual care. Other studies on nurse-led transitional care services, showed similar favourable outcomes and reduced costs, but did not report QALYs.[14, 34] The most likely explanation for the contrasting results regarding both costs and effects found in our study is that our study population was older (mean age 82 years) and more frail than in the previously published studies.[16] Despite the lack of clinical effects, we considered it important to conduct a full economic evaluation, because there may still be a relevant impact on costs. Also, even when both cost and effect differences are not statistically significant, based on the joint uncertainty surrounding costs and effects there may be values of the ceiling ratio at which the intervention is considered cost-effective compared to usual care.

The CCB intervention was evaluated in a randomized controlled trial design and implemented on top of the usual care systems.[16] Although healthcare costs did not significantly differ between the intervention and usual care group, there was a statistically significant difference in informal care costs. It was part of the CCB protocol to involve informal caregivers in the process which may have resulted in higher overall informal caregiver support.[15]

Strengths and limitations

Several strengths are relevant to our study. First, data on readmissions and mortality were collected using both self-reported data and hospital and municipality records. This reduced the chance of recall bias and improved the validity of the data. Second, in order to estimate the costs of the CCB intervention, we used a bottom-up micro-costing approach which is a more precise method to estimate costs than a top-down costing approach.[25] Third, costs were measured from a societal perspective. This is the broadest approach possible and takes all costs into account regardless who pays for them.[25] This enables the identification of potential shifts in costs between budgets. For example, early discharge

may reduce healthcare costs but may increase informal care costs. Finally, we performed a sensitivity analysis from a healthcare perspective. This perspective is used for decision making in many countries, such as for example the United Kingdom. Thus, it also allows for comparison of the results with cost-effectiveness studies from these countries.[25]

Some aspects of our study warrant consideration. There was a high percentage of missing data on both costs and on HQoL. This missingness was probably caused by several factors, such as withdrawal from follow-up visits, recall problems and non-response from informal caregivers. Considering that people tend to underestimate their healthcare use[35] and the high age of the included participants, recall bias on healthcare use (i.e. other than hospital readmission) was probably present and may have led to an underestimation of costs in all participants. To reduce the chance of recall bias as much as possible, measurements were performed at both three and six months follow-up.[36] In this study, multiple imputation was used to impute missing data, since this is considered the most valid method to deal with missing data.[37] Baseline variables that were used as predictor variables for multiple imputation were carefully selected, based on their association with missingness or the outcome. Last, from the CCB process evaluation, it is known that the mean intervention fidelity rate was only 67%, which could have influenced the effect on the composite outcome and intervention costs.[38] However, we calculated the intervention costs from a standardized intervention cost price instead of a fidelity-based cost price based per individual which could have resulted in a slight overestimation of the actual intervention costs.

Implications

Based on the current study results, the CCB program cannot be considered cost-effective compared to usual care. Considering the resources needed to implement such an intervention, we recommend against implementation of the intervention in clinical practice in its current form. Further research is needed to find suitable interventions to meet frail cardiac patients' needs and to reduce adverse outcomes and costs, and increase HQoL.

Conclusion

The CCB program was on average more expensive from a societal perspective and less effective compared to usual care, indicating that the CCB program is dominated by usual care. Therefore, the CCB program cannot be considered cost-effective compared to usual care.

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APPENDIX 1. VARIABLES INCLUDED IN THE IMPUTATION MODEL

Outcome variables	Predictor variables*	Covariates included in the model
Healthcare costs (primary, secondary and informal care): baseline and 6 months follow-up	Nationality	Hospital of inclusion
Healthcare costs (primary and secondary care): 3 months follow-up	AUDIT-C alcohol use questionnaire, baseline	Dutch Safety Management System-score: baseline
HQoL, EQ5D-5L: baseline, 3 and 6 months follow-up	Index hospital admission acute	Diagnosis heart failure, acute coronary syndrome, other
Composite outcome readmission and mortality: 6 months follow-up		Charlson Comorbidity Index: baseline
		Age
		Sex
		Mini Mental State Examination: baseline
		Living arrangement
		Admission in six months prior to admission

* Predictor variables included variables that differed between the intervention group and the usual care group at baseline, variables that were related to missingness of data and variables that were associated with the outcomes.

Chapter 7

The Cardiac Care Bridge randomized trial in high-risk older cardiac patients: A mixed-methods process evaluation

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ABSTRACT

AIM: To evaluate healthcare professionals' performance and treatment fidelity within the Cardiac Care Bridge (CCB) nurse-coordinated transitional care intervention in older cardiac patients to understand and interpret the study results.

DESIGN: A mixed-methods process evaluation based on the Medical Research Council Process Evaluation framework.

METHODS: Quantitative data on intervention key-elements were collected from 153 logbooks of all intervention patients. Qualitative data were collected using semi-structured interviews with 19 CCB professionals (cardiac nurses, community nurses and primary care physical therapists), from June 2017 until October 2018. Qualitative data-analysis is based on thematic analysis and integrated with quantitative key-element outcomes. The analysis was blinded to trial outcomes. Fidelity was defined as the level of intervention adherence.

RESULTS: The overall intervention fidelity was 67%, ranging from severely low fidelity in the consultation of in-hospital geriatric teams (17%) to maximum fidelity in the comprehensive geriatric assessment (100%). Main themes of influence in the intervention performance that emerged from the interviews are interdisciplinary collaboration, organizational preconditions, confidence in the program, time management and patient characteristics. In addition to practical issues, the patient's frailty status and limited motivation were barriers to the intervention.

CONCLUSION: Although involved healthcare professionals expressed their confidence in the intervention, the fidelity rate was suboptimal. This could have influenced the non-significant effect of the CCB intervention on the primary composite outcome of readmission and mortality six months after randomization. Feasibility of intervention key elements should be reconsidered in relation to experienced barriers and the population.

IMPACT: In addition to insight in effectiveness, insight in intervention fidelity and performance is necessary to understand the mechanism of impact. This study demonstrates that the suboptimal fidelity was subject to a complex interplay of organizational, professionals' and patients' issues. The results support intervention redesign and informs future development of transitional care interventions in older cardiac patients.

INTRODUCTION

The 30-day rehospitalization and mortality rates of older patients with acute myocardial infarction or heart failure are high: 20% and 8% respectively.[1] The burden of hospitalization among older patients is considerable, and geriatric conditions are often overlooked while the focus mainly lies on the disease.[2] These factors increase the risk of adverse events such as readmissions.[3, 4] In the phase in which patients are discharged, the risk of adverse events increases again,[5] while medication regimes and treatment advices are often not well understood or mixed-up with previous advices,[6] and signs of physical deterioration are often detected too late.[7] Lastly, older cardiac patients are often not referred to traditional cardiac rehabilitation programs because they are too intensive, or, when patients are referred, they often do not participate due to the intensity, travel issues and hindering comorbidities.[8] The cardiac rehabilitation uptake is only 20-30% among older patients. However, the risks of recurring events and mortality of non-participators are increased.[9]

To reduce the previously mentioned risks and to overcome the shortcomings within the continuity of care, we developed the Cardiac Care Bridge (CCB) nurse-coordinated, interdisciplinary, transitional care program, and evaluated it in a multi-center randomized trial in 306 frail, older (≥70 years) hospitalized cardiac patients in the Netherlands.[10, 11] The intervention included case management, disease management and home-based cardiac rehabilitation, integrated in the process from hospital to home. The transitional care model focuses on continuity of care when patients transfer between healthcare settings[5, 12], and is mostly based on a case management approach with a broad focus on patients' needs.[5] A follow-up after six months did not show a statistically significant difference on the main composite outcome of readmission and mortality.[11]

Background

Complex care interventions with multiple interacting components such as the CCB intervention, are often studied within a traditional randomized trial design to explore its effectiveness. However, to interpret the results, it is important to investigate to what extent the intervention protocol is delivered as designed (treatment fidelity) and what factors may have influenced the intervention performance.[13-15] Studies on treatment fidelity are often integrated in process evaluations alongside effectiveness studies of complex interventions, and explore causal assumptions, implementation success and flaws, contextual factors and the mechanisms of impact of the intervention.[16, 17] In brief: the *why, who, what, where, how* and *how much* should be integrated in the evaluation of complex interventions.[14, 18] The 'why' is addressed in the introduction section and the items *who, what* and *where* are described in the CCB intervention protocol.[10] Exploration

of how and how much of the intervention was performed, supports interpretation of the study results and informs future intervention (re)design and implementation. Therefore, it is necessary to evaluate the CCB study results by assessing the level of treatment fidelity and the healthcare professionals' perspective on the CCB intervention performance.

THE STUDY

Aim

The aim of the study is to analyze the CCB study results by assessing the level of treatment fidelity and the healthcare professionals' perspective on the CCB intervention performance.

Design

A mixed-methods concurrent, primarily qualitative study was conducted alongside the CCB study. Data were collected and analyzed before the CCB study results on effectiveness were known, to avoid a potential bias in the interpretation of the data.[19] This process evaluation was based on the Medical Research Council Process Evaluation framework, which has operationalized implementation theories including RE-AIM.[17] The RE-AIM implementation theory formed the theoretical basis of the CCB intervention implementation.[20, 21] To induce change by the CCB intervention, we applied implementation strategies based on leading theories of change, such as motivational, educational and facilitating strategies.[22] Figure 1 provides the logic model of the CCB intervention that structured the process evaluation.[17]

The CCB intervention and patients

Patients were eligible for inclusion in the CCB study if they were admitted to the department of cardiology or thoracic surgery, were at high risk of adverse events according to the Dutch Safety and Management System criteria[32] or experienced a hospital readmission in the six months prior to the index admission, and if the Mini Mental State Examination was scored $\geq$ 15.

Eligible patients all received a comprehensive geriatric assessment at baseline and were randomized into either the CCB intervention or usual care. The CCB intervention consisted of three core components, case management, disease management and cardiac rehabilitation, provided in three phases, the clinical, discharge and post-clinical phase. The clinical phase included a geriatric assessment based integrated care plan and geriatric team consultation based on findings from the geriatric assessment. The discharge phase included an in-hospital face-to-face handover with the community-based registered nurse

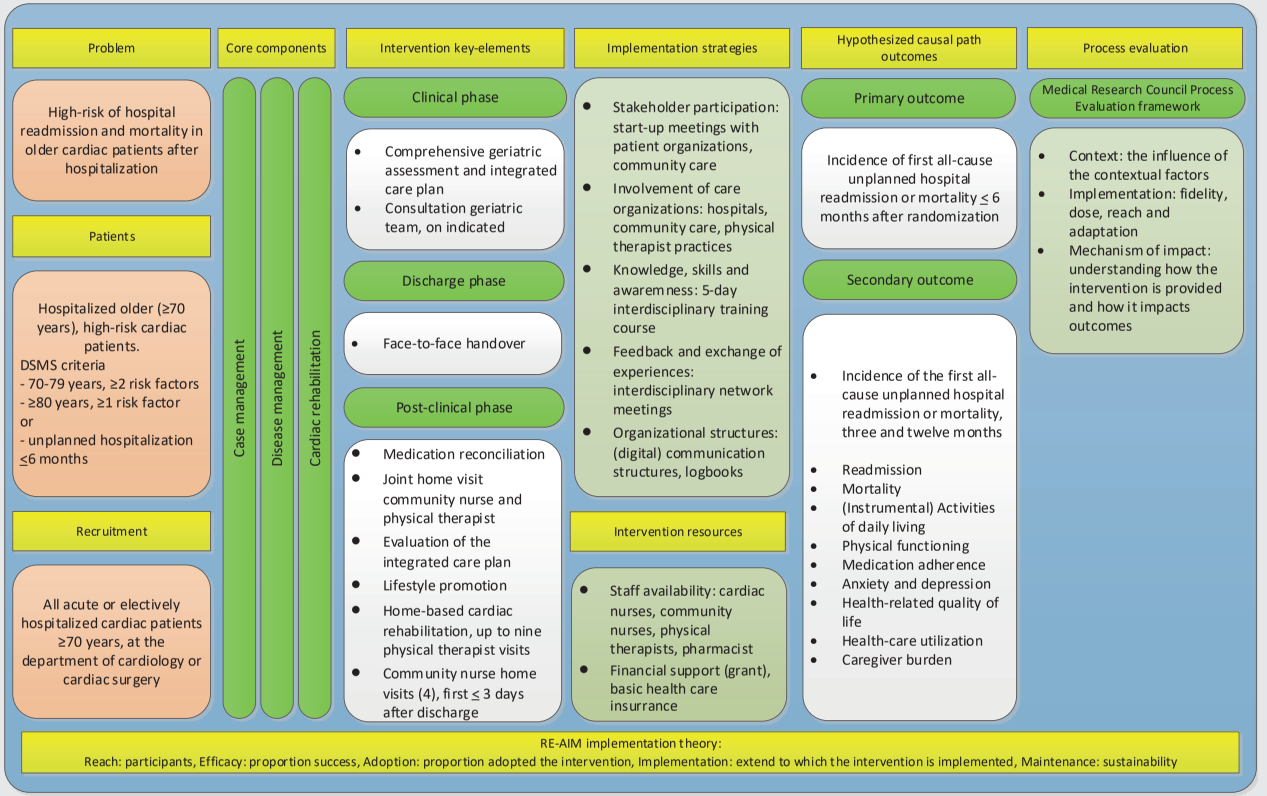

Figure 1. Logic model of the CCB intervention[5, 9, 12, 19-31]
Abbreviation: DSMS = Dutch Safety Management System

(community nurse). In the post-clinical phase, four home visits from the community nurse were performed, focused on medication reconciliation, lifestyle promotion, evaluation of the care plan and early detections of physical deterioration. A CCB-affiliated pharmacist assisted the community nurses with medication reconciliation. Physical therapists provided home-based cardiac rehabilitation, with a total of nine visits. Full study details are published elsewhere.[10]

To implement the CCB intervention, a five-day interdisciplinary training program on case management, disease management and home-based cardiac rehabilitation was organized for all participating healthcare professionals. Managers of involved healthcare organizations were asked to provide education time for the participating staff. Additional intervention costs on top of the usual care costs were reimbursed by the study.

In total, 306 patients were recruited in six hospitals in the Netherlands from June 2017 until March 2019, of whom 153 were randomized into the intervention group. The included patients had a mean age of 82 years (standard deviation 6); 51% was male and 58% was admitted for heart failure. Regarding their risk profile, 45% had an unplanned hospital readmission in the six months prior to the index hospitalization, 56% were at risk of delirium, 47% had fallen in the six months prior to the hospitalization, 39% had ADL-limitations and 33% were at risk of malnutrition. There were no significant differences in baseline characteristics.[11]

Sample/participants (CCB healthcare professional)

This process evaluation focused on the experiences and performance of CCB healthcare professionals, including cardiac nurses, community nurses and primary care physical therapists. Other collaborating disciplines were not included in this process evaluation, because they performed usual care and did not adjust work processes. CCB healthcare professionals were purposefully sampled to reach maximal variation in work regions, work experience and experience with the CCB intervention.[17, 19, 33] They were invited to participate if they treated at least one CCB patient. Invitations were sent by email and a telephone reminder was made after two weeks without response. All 19 invited healthcare professionals participated in the interviews.

Data collection on CCB care delivered

Data were collected on the three key functions of the Medical Research Council framework for Process Evaluation, defined as: (1) 'context' (*the influence of the contextual factors on providing CCB care*), (2) 'implementation' (*fidelity, dose, reach and adaptation*), and (3) 'mechanism of impact' (*understanding how the CCB intervention is provided and how the intervention impacts outcomes*). *Fidelity* has been defined as CCB care delivered as intended.[34, 35] Intervention dose has been defined as the number of delivered intervention key-elements per individual. The intervention *reach* has been defined as the number of patients who received

the CCB intervention and *adaptation* has been defined as the manner in which CCB healthcare professionals performed the intervention in relation to the study protocol.[35]

Quantitative data to assess key function (2) 'implementation' (*fidelity, dose and reach*) were prospectively collected alongside the CCB study, according to predefined quality indicators on the intervention key-elements see Table 1 (Appendix 1. CCB quality indicator example). Data sources were hospital chart files and self-reported logbooks from home visits of the community nurses and physical therapists.

Qualitative data on key functions (1) 'context', (2) 'implementation' (*adaptation*); and (3) 'mechanism of impact', were collected using semi-structured interviews. Interviews were held in a private room at a location of the healthcare professional's preference and were conducted during the CCB study period between June 2017 and October 2018, by three researchers (Ms. LV (MSc.), Mr. MT (MSc.) and Ms. DS (MSc.)). The topic list was based on the key functions and the CCB logic model (Figure 1) (Appendix 2, Topic list).[17, 19] During the interviews, notes were made, and at the end of the interviews, a verbal summary of the main topics was provided to the participants to verify the interpretation of the collected data.[36] The interviews lasted between 30 and 60 minutes each. The interviews were audio recorded and transcribed ad verbatim.

Ethical considerations

Ethical approval was provided by the Medical Ethics Committee of the Amsterdam UMC, University of Amsterdam (Protocol ID: MEC2016_024). Written informed consent was obtained from all interviewed CCB healthcare professionals.

Data analysis

Descriptive statistics were analyzed for key function (2) 'implementation'. The intervention fidelity was calculated per intervention patient. The denominator of the key-elements was set on the number of feasible key-elements for an individual. Intervention key-elements missed due to, for example, hospital readmission, mortality, or disabilities that withheld patients from participation in, for instance, the home-based cardiac rehabilitation, were not counted in the denominator. The mean fidelity rate was calculated per intervention key-element. In addition, we calculated an overall unweighted average of the patient-specific adherence percentage across all intervention patients. Outcomes were presented as number with a percentage, and as median with an interquartile range. Missing data from logbooks were interpreted as 'care not delivered'. Analysis were performed in IBM SPSS Statistics version 23 (Armork, New York, USA).

Qualitative data analysis followed the phases of thematic analysis, a six phase guidance to systematically analyze qualitative data.[36] Two members of the research team (LV, DS) independently analyzed the data. The first phase

comprised of the open coding of the collected data. After every two interviews, codes were compared, and differences were discussed to reach consensus. Main themes were formed from matching codes by LV and DS, to reflect the data. Interviews were stopped when theoretical saturation was reached and no new codes and themes were formed.[37, 38] MAX-QDA 12 Standard (Berlin, Germany) was used in the analysis.

After the collection of quantitative and qualitative data, the findings on the intervention performance were integrated with the information from the interviews. The quantitative data supported the interpretation of the qualitative data and vice versa. This manuscript was reported according to the COREQ-checklist for the reporting of qualitative research.[39]

RESULTS

Intervention fidelity, dose and reach

Data on performance regarding the key-elements of the intervention were collected for all intervention patients. Table 1 provides an overview of the intervention *fidelity, dose and reach* of the intervention key-elements in the clinical, discharge and post-clinical phase.

In the clinical phase, the geriatric assessment and integrated care plan were performed with all patients. Referral to the geriatric team, based on the geriatric assessment indication, was reported in only a few patients (17%). In the discharge phase, a face-to-face handover was performed in 37%. Alternatively, handovers by telephone (14%) or in writing (49%) were performed. In the post-clinical phase, 62% of the community nurses home visits were performed and in 57% within 3 days (interquartile range 2-4) after discharge. In 60% of the patients, home-based cardiac rehabilitation sessions were delivered as intended. The number of eligible patients for cardiac rehabilitation (n=116) was lower than the number of eligible patients for the community nurse home visits (n=133), mainly due to patients' physical or mental inabilities. The mean individual patient fidelity rate across all key-elements that patients were entitled to, was 67%.

Interviews with healthcare professionals

In total, 19 CCB healthcare professionals were interviewed, including 5 cardiac nurses, 6 community nurses and 7 physical therapists. Most of the participants were female (90%), and they had a median age of 37 years (interquartile range 27-54). Their median work experience was 20 years (interquartile range 6-30); see Table 2.

The themes derived from the interviews are framed and summarized within the key functions (1) 'context', (2) 'implementation' and (3) 'mechanism of impact', and integrated in the information on the intervention key-elements. The main

Table 1. Fidelity, dose and reach in the CCB intervention key-elements

Intervention key-elements	N	%
Clinical phase		
CGA and CGA-based integrated care plan	153/153	100
Geriatric consultation based on indication†	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‡	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 (28)	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§	70/116	60
Number of home-based rehabilitation sessions	Median 4	IQR 2-6
Mean patient-specific fidelity percentage	**153**	**67**

† Geriatric team consultation was indicated in case of ≥1 problem within the psychological domain or ≥5 geriatric problems in total. ‡ Four home visits according to the CCB protocol.
§ Max. nine home-based rehabilitation session, according to the CCB protocol. Abbreviations: CGA comprehensive geriatric assessment, IQR interquartile range

themes were: (1) interdisciplinary collaboration, (2) organizational preconditions, (3) confidence in the CCB intervention, (4) time management, and (5) influence of patient characteristics on the intervention.

Key function 1. Context

Contextual factors that could have affected the intervention performance were summarized in the themes 'interdisciplinary collaboration' and 'organizational preconditions'.

Theme 1. Interdisciplinary collaboration

Within the intervention period, the community nurse intensified the collaboration with nurse-specialists, general practitioners, a CCB-affiliated pharmacist and outpatient clinics. CCB healthcare professionals met each other during training sessions, meetings and face-to-face handovers. This reduced barriers

Table 2. Characteristics of interviewed CCB healthcare professionals

Respondent	Age	Gender	Profession	Education	Work experience, years	N CCB patients treated
R1	24	Female	Cardiac nurse	Bachelor	1	20
R2	27	Female	Cardiac nurse	Bachelor	7	15
R3	24	Female	Cardiac nurse	Master	4	10
R4	54	Female	Cardiac nurse	Bachelor	34	30
R5	37	Female	Cardiac nurse	Vocational	9	20
R6	37	Female	Community nurse	Vocational	22	5
R7	62	Female	Community nurse	Vocational	41	15
R8	44	Female	Community nurse	Bachelor	20	4
R9	45	Female	Community nurse	Bachelor	24	10
R10	49	Female	Community nurse	Bachelor	20	15
R11	52	Female	Community nurse	Vocational	20	10
R12	23	Female	Physical therapist	Master	2	1
R13	25	Female	Physical therapist	Bachelor	2	2
R14	34	Female	Physical therapist	Master	10	1
R15	58	Female	Physical therapist	Master	35	1
R16	57	Female	Physical therapist	Bachelor	30	1
R17	28	Male	Physical therapist	Bachelor	6	3
R18	36	Male	Physical therapist	Bachelor	8	4
R19	59	Female	Physical therapist	Bachelor	36	8

to interprofessional communication in case of questions, observed physical deterioration or other symptoms (quote 1).

> *Quote 1 "… the fact that you know each other, makes it easier to contact…" (Respondent 6 community nurse)*

The collaboration between physical therapists and community nurses was considered valuable to motivate patients when working on the same goals from different perspectives. Although the joint visits were performed only in 41% of the cases, which was mainly due to different work schedules, all interviewed healthcare professionals mentioned the value of the collaboration and integrated alternative communication routes such as contact by telephone (quote 2); see Table 1.

> *Quote 2 "I think we, the physical therapist and I, accomplished a lot. There was a woman, … She went for groceries with her walker the first day after discharge;*

and there she sat in the middle of the street. She simply overestimated her situation ... Together with the physical therapist we enabled her to do the groceries again; then, you feel satisfied…." (Respondent 8 community nurse)

Theme 2. Organizational preconditions

Cardiac nurses experienced the geriatric assessment as an important precondition of the intervention, although time-consuming. They mentioned time limitation and a lack of consistency in their work schedules as barriers to the performance. Furthermore, cardiac nurses did not always recognize the advantage of consulting a geriatric team regarding patient care, and thought they were able to address the observed geriatric problem themselves (quote 3).

Quote 3 "The protocol says to consult a geriatric team if indicated, but I think… it takes a lot of time, and what does the geriatric team actually additionally do?" (Respondent 1 cardiac nurse)

A high hospital turnover was mentioned as an additional reason for not consulting geriatric teams. These barriers resulted in the limited number of referrals (17%) of indicated patients to geriatric teams; see Table 1.

The CCB healthcare professionals mentioned the high in-hospital turnover and the registration burden as general barriers to perform the intervention key-elements. Cardiac nurses were, for example, responsible for the geriatric assessment as part of the intervention, as well as for the regular nursing assessment. In addition, healthcare professionals did not have enough time to plan the face-to-face handover (quote 4).

Quote 4 "As soon as they (patients) are a little recovered, they are discharged; we kind of throw them out. It sounds very worrisome, but … [silence] There is enormous pressure on the beds, because new patients are already queued at the front door…." (Respondent 4 cardiac nurse)

Physical therapists mentioned the high costs and limited reimbursement of the home-based rehabilitation as a barrier. The CCB study reimbursed the rehabilitation costs if this was not covered by the patient's insurance policy. Nevertheless, the physical therapists had to invest more time to obtain the reimbursement and expressed their concerns regarding the feasibility.

Key function 2. Implementation

Relevant themes that could have affected the implementation of the program were: 'belief in the effectiveness of the program', 'time management' and 'influence of patients characteristics'.

Theme 3. Confidence in the program

Cardiac nurses considered the assessment of geriatric problems in-hospital as a valuable intervention in this frail population to identify geriatric conditions and to develop the care plan. Nevertheless, they considered the time after discharge as the most important part of the CCB intervention. All community nurses believed they contributed to the prevention of adverse events, such as readmission due to the early recognition of signs of heart failure decompensation or other deteriorating conditions (quote 5).

> *Quote 5 "…people say that they know very well when they are decompensating (in heart failure), but when the early signs appear, most people don't respond adequately… People remain very passive and do not act, they do not realize that their situation is deteriorating again." (Respondent 10 community nurse)*

The physical therapists noticed improvement over time in the physical condition of treated patients. They mentioned the confidence of the patient in their ability to achieve results as an important factor of success, and they mentioned anxiety to exercise and to experience physical complaints as an important barrier to training success (quote 6).

> *Quote 6 "Yes, I think it is a good idea to guide patients after hospitalization… They can train with me until a level that they have enough energy and power. And so, they are not afraid to exercise anymore. Yes, anxiety is very important." (Respondent 12 physical therapist)*

Theme 4. Time management

The geriatric assessment and included physical tests were time-consuming, and often went at the expense of activities such as the geriatric team consultation. Cardiac nurses also mentioned logistic barriers: for example, patients had to leave for diagnostic tests or relatives were visiting.

The community nurses highly valued collaboration with the cardiac nurses, and vice versa. Belief in the added value of the face-to-face handover was a common statement. The healthcare professionals experienced it as a valuable method to communicate about the patients' condition (quote 7).

> *Quote 7 "…you have the opportunity to ask questions, which make uncertainties about the treatment clear. So yes, so during the first home visit you can immediately start. Thereby, meeting the patient was also very important, so they already knew who was coming after discharge." (Respondent 8 community nurse)*

Nevertheless, the handover was only done face-to-face in 37% of the cases. Travel distances to the hospital of up to 30 minutes led to a low performance rate. These situations forced alternative work strategies, such as handover by telephone, which was performed 14% of the time, and written handovers, in 49% of the cases.

The median time period until the first home visit was 3 days (interquartile range 2-4); see Table 1. Some community nurses decided on alternatives, such as calling patients at the day of discharge, or the day after discharge in case they were not able to perform a home visit within two days.

The community nurses mentioned that with every patient they visited, something failed in the medication process. They were proactive and contacted the hospital, the general practitioner or the CCB pharmacist. The process of medication verification and problem solving was time-consuming but highly valued by nurses, and performed with 89%; see Table 1. The community nurses also valued the collaboration with the CCB pharmacist because of the quick access and problem solving in case of medication problems.

Key function 3. Mechanism of impact

Patient characteristics such as the high level of frailty and comorbidities were mentioned as important contributors to the intervention's impact.

Theme 5. Influence of patient's characteristics

The physical therapists noticed that once patients had set a goal, they were motivated to exercise and practice. However, motivating patients was a struggle sometimes, according to the therapists. Some patients declined participation in home-based cardiac rehabilitation (quote 9). In total, 60% of eligible patients participated in the home-based rehabilitation session, with a median number of training sessions of 4 (interquartile range 2-6); see Table 1.

> *Quote 9 "There was a woman who didn't want me to come over. So, I contacted the community nurse and we had a joint visit... Then everything seemed to be good. Afterwards when I stood there in front of her door, she wouldn't let me in." (Respondent 13 physical therapist)*

Goal setting was mentioned as an important contributor to convince patients of the added value of physical therapy (quote 10). However, many patients found it difficult to formulate goals.

> *Quote 10 "…He (patient) thought it all took too much time. But when we finally found out that sportfishing was very important for him, we (community nurse, physical therapist) focused on that goal." (Respondent 8 community nurse)*

Physical therapists mentioned that the intensity of two training sessions per week was not feasible for every patient due to their condition, such as tiredness or poor health. The high level of frailty of the population was of large influence on the execution of the intervention. Physical therapists observed that patients often had comorbidities that limited them in their level of activity and therefore made patient-tailored adjustments to the CCB protocol.

DISCUSSION

This process evaluation explored the delivered CCB intervention key-elements and the considerations regarding the intervention fidelity from CCB healthcare professionals' perspectives. We found that the overall proportion of intervention fidelity was suboptimal and intervention key-elements were often not performed as intended. CCB healthcare professionals mentioned various causes, such as time limitation, logistical barriers and patient characteristics. With the incorporation of alternative work processes such as alternative handovers and adjusted rehabilitation programs, they adjusted the CCB intervention to the circumstances and individual case of the patients. The CCB healthcare professionals expressed their confidence in the intervention's contribution to patients' wellbeing and the ability to prevent hospital readmissions and mortality. However, they also expressed doubts on the feasibility of individual intervention components regarding, for example, the intensity of the home-based rehabilitation program in relation to the study population, the planning of joint home visits and interdisciplinary collaboration.

The CCB study showed a non-significant effect on the primary composite outcome of readmission and mortality at six months follow-up (Jepma *et al*., submitted). Although CCB healthcare professionals expressed their confidence and believe in the intervention, this was not reflected in the results on effectiveness. The current process evaluation unraveled at least a part of the black box regarding the non-significant results. The suboptimal intervention fidelity could have influenced the lack of intervention effect. However, in a previous study on a transitional care intervention in heart failure patients with a fairly good intervention fidelity, no intervention effect was found either.[40] In contrast, recent systematic reviews on the topic showed positive effects on readmission and mortality rates.[26, 41] Besides intervention fidelity, the conflicting results could also be caused by an older and frail patient population in the CCB study.

Regarding the performance on intervention key-elements, the cardiac nurses expressed the additional value of the geriatric assessment, although they had to overcome logistical barriers and timing issues while the geriatric assessment was performed on top of the regular nursing assessment. It was remarkable that the cardiac nurses expressed low priority regarding the consultation of geriatric

teams. Although education on the additional value of in-hospital geriatric team consultation was part of the CCB training program, a skeptical view on the actual contribution was mentioned, and cardiac nurses mentioned that they thought they were able to act on observed geriatric problems. Apparently, the current procedure within the CCB intervention, with protocolized geriatric team consultation, did not provide enough impulse for close collaboration.[10] An alternative approach in which geriatric teams work proactively on hospital wards, may overcome with these barriers. For example, in-hospital geriatric co-management with a proactive approach showed promising results.[42] This approach prevents that the collaboration is dependent on levels of priority among hospital staff in consulting geriatric teams, and the approach enables focusing on preventive instead of reactive strategies.

The community nurses mentioned early detection of physical deterioration and medication reconciliation as the most important study components. The risk of readmission is especially high within the first 30 days after discharge,[43] and can potentially be reduced by high-intensity transitional care interventions, including a home visit within three days after discharge.[31] Therefore, an early [≤3 days] community nurses' home visit was included in the CCB intervention. During the study period, community nurses were in close contact with the CCB-affiliated pharmacist and experienced quick access, effective problem solving and efficient referral to other disciplines regarding medication problems. The contributing value of intensive medication guidance in the transition of care is reported in the study of Daliri *et al*.[44] They found that better information transfer to primary care providers and the involvement of the community-based pharmacist after discharge, led to significantly less medication-related problems. Currently, community-based pharmacists do not have a structural role in community care in the Netherlands. Since up to 49% of the older patients experience medication-related problems after discharge, and community nurses are often involved in the post-discharge phase, it is a promising collaboration to further explore.[45] Many medication-related problems are caused by inadequate patient information.[46, 47] or a lack of a proper handover to primary caregivers[48, 49] The potential of these interventions is high in the prevention of 30-day readmission rates.[50] However, within the CCB intervention, no additional effect was found.

Although the beneficial effects of cardiac rehabilitation in older patients have been documented, the participation rate is still very low (14% in Medicare beneficiaries), which is caused by factors such as comorbidities and functional limitations.[9] Therefore, a home-based cardiac rehabilitation program was integrated in the CCB program.[10] In total, 60% of the CCB intervention patients participated in the cardiac rehabilitation program. Physical therapists mentioned it was challenging to motivate patients to participate, but found that patients' personal goal setting was an important motivating factor. This was also reported by Tinetti *et al*., who emphasized the importance of 'patient goal directed care'

to achieve results.[51] However, patients' health status, tiredness and anxiety were mentioned as hindering. These factors could be part of a 'post-hospital syndrome' that was possibly manifested in the frail older cardiac population within the CCB study.[52] Especially older cardiac patients are at high risk of developing this complex mechanism,[52] which, among others, is triggered by the underlying disease in combination with different kind of stressors during hospital stay.[53] As a result, patients become deconditioned and cognitive functions may decrease. This potentially influenced the decreased motivation for the home-based cardiac rehabilitation program.

From a healthcare professional's perspective, the fairly low fidelity rate to the CCB key-elements (total mean fidelity rate of 67%) could be explained by several factors, such as time limitations and other logistical barriers. However, they expressed their beliefs in the intervention and started implementing CCB intervention aspects in daily work routines. Several initiatives grew towards structural implementation, such as standard community nurses home visits of heart failure patients in collaboration with CCB participating hospitals. This eventually led to the early termination of the CCB study.[11] Another point of concern is the influence of the CCB population characteristics such as the high age, the high level of comorbid diseases and the level of frailty, on the intervention fidelity, which should not be underestimated.[11] The included population, those who were in an advanced stage of disease and beyond the point of no return, might have benefitted more from advance care planning and end-of-life transitional care interventions.[54, 55] The feasibility of the intervention components needs to be reconsidered from this perspective as well.

Limitations

By using a mixed-methods design, we were able to form an integrated conclusion on the intervention outcome.[17, 33] However, the quantitative data from the logbooks were subject to a limitation of the study. The data were reported by the CCB healthcare professionals, who could have failed registration or could have registered without actually having performed the key-element.[33] Missing data were interpreted as 'care not delivered', which potentially led to under-registration of the key-elements. This could affect the conclusion on the influence of the limited fidelity rates on the CCB main outcome of no effect. However, in the interviews, healthcare professionals mentioned various barriers in the performance of various key-elements which makes the lower fidelity rates reliable. Furthermore, the data of the in-hospital intervention performance was collected from the hospital chart file, which was a reliable source. We therefore believe that the reported key-element reflects the reality of the CCB intervention fidelity. Another point of concern is related to the logistical barriers to perform face-to-face handovers and joint home visits, as expressed by the healthcare professionals. Although the involved staff was equipped with tablets and could have chosen to use modern communication

routes, they rather called each other to discuss the case or waited for the written handover. Optimization of the use of modern communication routes could have overcome the fairly low fidelity rates in the communication between healthcare professionals.

Despite these limitations, the current findings enable adjustments to the CCB intervention, such as proactive geriatric team consultation, alternatives for the face-to-face handover and a patient-tailored cardiac rehabilitation program to overcome the barriers and adjust the intervention to the needs of the CCB patient population, or otherwise to reconsider the target population carefully.

Conclusion

CCB healthcare professionals expressed their confidence in the CCB intervention and its contribution to prevent hospital readmissions and mortality. However, the intervention fidelity was suboptimal and intervention key-elements were often not performed as intended. The low fidelity rate could have influenced the non-significant effect of the CCB intervention on the primary composite outcome of readmission and mortality six months after randomization. However, besides the intervention fidelity, the patient's frail health status and the motivation to participate in the intervention might have influenced the outcome. For future purposes, the feasibility of intervention key-elements as well as the target population need to be reconsidered.

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APPENDIX 1. CCB QUALITY INDICATOR EXAMPLE†

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

† Other quality indicators are available upon request.

APPENDIX 2. TOPIC LIST INTERVIEWS

Cardiac nurses	Community nurses	Physical therapists
CCB experience	CCB experience	CCB experience
Patient selection	Patient selection	Patient selection
Comprehensive geriatric assessment	Comprehensive geriatric assessment	Comprehensive geriatric assessment
Interdisciplinary collaboration in hospital, geriatric team	Face-to-face handover and alternatives	Handover (written)
Integrated care plan development	Home visits, timing and content	Integrated care plan
Discharge planning	Medication reconciliation and collaboration with the CCB affiliated pharmacist	Home visits, functional and exercise training
Face-to-face handover and alternatives	Home-based cardiac rehabilitation and collaboration with the physical therapist	Joint home visit with the community nurse
Registration and administration time	Joint home visit with the physical therapist	Interdisciplinary collaboration
Planning	Lifestyle promotion	Detection of early signs and symptoms
CCB education / course program	Evaluation of the integrated care plan	Readmissions and preventability
Feasibility	Detection of early signs and symptoms	Registration and administration time
	Readmissions and preventability	Travel time and planning
	Registration and administration time	CCB education / course program
	Travel time and planning	Feasibility
	CCB education / course program	
	Feasibility	

Chapter 8

The course of readmission in frail older cardiac patients: A qualitative multiple case study on factors contributing to unplanned hospital readmission

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ABSTRACT

AIM: The aim of this study is to explore patients' and (in)formal caregivers' perspectives on their role(s) and contributing factors in the course of unplanned hospital readmission of older cardiac patients in the Cardiac Care Bridge program.

DESIGN: This study is a qualitative multiple case study alongside the CCB randomized trial, based on grounded theory principles.

METHODS: Five cases within the intervention group, with an unplanned hospital readmission within six months after randomization, were selected. In each case, semi-structured interviews were held with patients (n=4), informal caregivers (n=5), physical therapists (n=4), and community nurses (n=5) between April and June 2019. Patients' medical records were collected to reconstruct care processes before the readmission. Thematic analysis and the six-step analysis of Strauss & Corbin have been used.

RESULTS: Three main themes emerged. Patients experienced acute episodes of physical deterioration before unplanned hospital readmission. The involvement of (in)formal caregivers in adequate observation of patients' health status is vital to prevent rehospitalization (theme 1). Patients and (in)formal caregivers' perception of care needs did not always match, which resulted in hampering care support (theme 2). CCB caregivers experienced difficulties in providing care in some cases, resulting in limited care provision in addition to the existing care services (theme 3).

CONCLUSION: Early detection of deteriorating health status that leads to readmission was often lacking, due to the acuteness of the deterioration. Empowerment of patients and their informal caregivers in the recognition of early signs of deterioration and adequate collaboration between caregivers could support early detection. Patients' care needs and expectations should be prioritized to stimulate participation.

IMPACT: (In)formal caregivers may be able to prevent unplanned hospital readmission of older cardiac patients by ensuring: (1) early detection of health deterioration, (2) empowerment of patient and informal caregivers, and (3) clear understanding of patients' care needs and expectations.

INTRODUCTION

In the older population, approximately 27% of early hospital readmissions are preventable.[1] Hospital readmissions of older cardiac patients are common and occur up to 25% of all cases.[2–4] The risks of (re)hospitalization and the burden of the disease are high in this population.[5] Geriatric conditions, such as functional decline, malnutrition, fall risk, and cognitive impairment, contribute to this risk of readmission and the burden of the disease.[6–8] However, these conditions often remain unrecognized or are insufficiently treated.[6]

To prevent adverse outcomes such as rehospitalization with frail older cardiac patients, the Cardiac Care Bridge (CCB) transitional care program was developed, based on case management, disease management, and home-based cardiac rehabilitation.[9] The intervention was provided by an interdisciplinary team of cardiac hospital nurses, community nurses, and community physical therapists during hospitalization and up until 12 weeks after discharge.[9] Despite the intensive CCB program, hospital readmissions were not prevented in the studied population in comparison with usual care.[10] In the CCB process evaluation on intervention fidelity and experiences of involved caregivers and patients within the intervention, the CCB intervention was evaluated.[11,12] However, in-depth information on how the care system functioned in the course of unplanned hospital readmission and how the mechanism of the CCB program impacted individuals remained unclear and is studied in this multiple case study.

BACKGROUND

Various system- and patient-related factors increase the risk of hospital readmission of frail older cardiac patients.[13–18] A conceptual framework was developed, based on these system- and patient-related factors to explore CCB patients' and (in) formal caregivers' perspectives on their role(s) and contributing factors in the course of unplanned hospital readmission, see Figure 1 and Appendix 1. We classified all factors in three main themes. First, the system-related factors, consisting of 'organizational structure' and 'transitional care services'. Second, the factors overlapping both system- and patient-related factors, consisting of 'care-team interactions', 'support of formal caregivers', and 'observation of the health status'. Third, the patient-related factors, consisting of 'goal setting', 'health status', 'care needs', 'patients' health behavior', and 'support of informal caregiver'. This conceptual framework was used to study the functioning of the informal and CCB formal care system and the contributing factors within the course of readmission, from CCB caregivers', informal caregivers', and patients' perspectives.

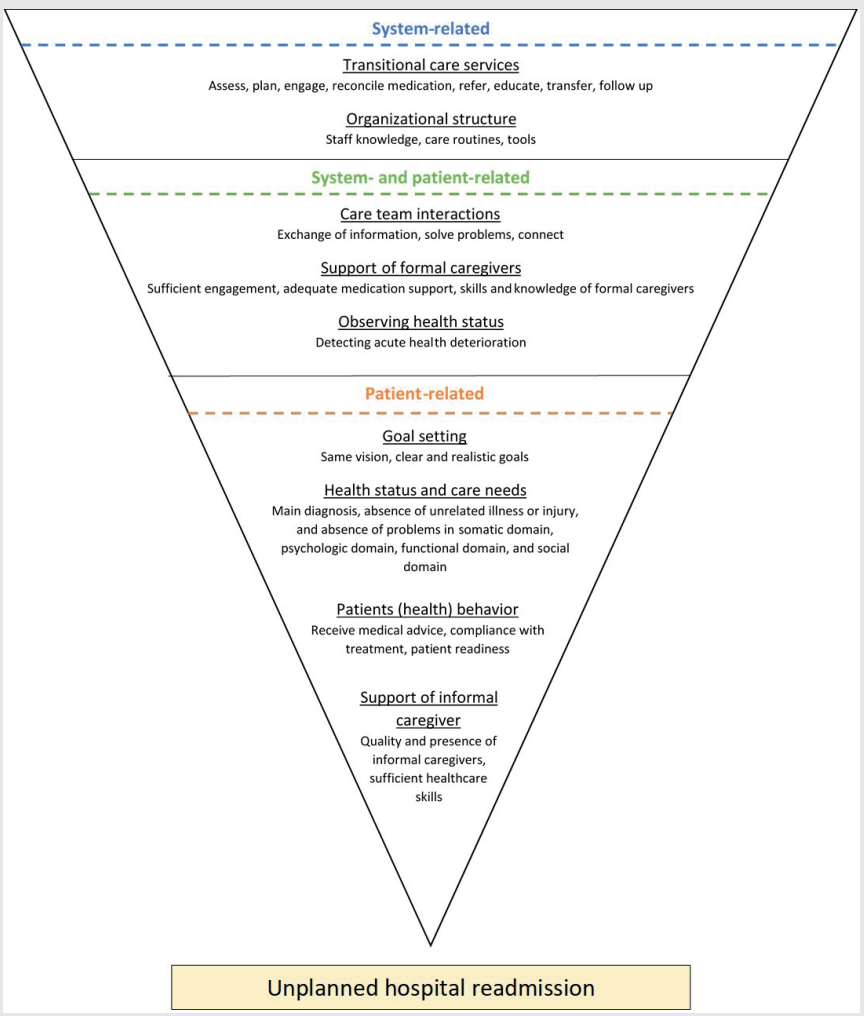

Figure 1. Conceptual framework of factors contributing to unplanned hospital readmission

THE STUDY

Aims

This study aimed to explore patients' and (in)formal caregivers' perspectives on their role(s) and the contributing factors in the course of unplanned hospital readmission of older cardiac patients in the CCB program.

Design

We performed a qualitative multiple case study based on grounded theory principles.[19,20] This design is a valuable qualitative method for the evaluation of processes within complex interventions because evaluation takes place within a real context and with multiple sources of evidence to replicate similarities and differences across cases.[21] Cases were analyzed using multiple perspectives of (in)formal caregivers and patients through interviews and also included patients' medical records, maintained by CCB caregivers with notes on vital signs and reported events during the CCB intervention until hospital readmission.

CCB intervention

The CCB study was a multi-center randomized controlled trial on nurse-coordinated, interdisciplinary transitional care of frail, older (≥70 years) hospitalized cardiac patients. In total, 306 patients were included in six hospitals in the Netherlands.[9,10] The composite primary outcome was all-cause unplanned hospital readmission and mortality within 6 months, after randomization. A detailed description of the intervention is published elsewhere.[10] In brief, the CCB program included three phases (clinical, discharge, and post-clinical phase) and consisted of three core components, see Figure 2. The clinical phase included a comprehensive geriatric assessment (CGA), conducted by a registered cardiac hospital nurse, and an integrated care plan. In the discharge phase, an in-hospital face-to-face handover with the community-based registered nurse was performed, including the integrated care plan, medication list, and the medical record. In the post-clinical phase, four home visits by the community nurse were performed, focusing on medication reconciliation, a healthy lifestyle, evaluation of the care plan, and early detection of physical deterioration. A pharmacist from the study group assisted the community nurses with medication reconciliation. Physical therapists provided home-based cardiac rehabilitation twice a week, with a total of up to nine visits. Full study details are published elsewhere.[10]

Participants

For this multiple case study, five cases within the CCB intervention group were purposefully selected based on saturation within the study,[19,22] using the following criteria: (1) CCB intervention patients that received the CCB intervention in the post-clinical phase and were physically and mentally able to be interviewed, (2) patients had unplanned hospital readmission(s) of at least two days within six months after randomization in the CCB study, (3) only CCB patients included between July 2018 and April 2019 (maximum of six months before the interviews) were selected, to prevent recall bias. A representative selection for the CCB patient population with unplanned hospital readmission was approached, as most patients were diagnosed with heart failure, spread in level of frailty (DSMS) and various hospitals of inclusion and caregivers working within those regions,

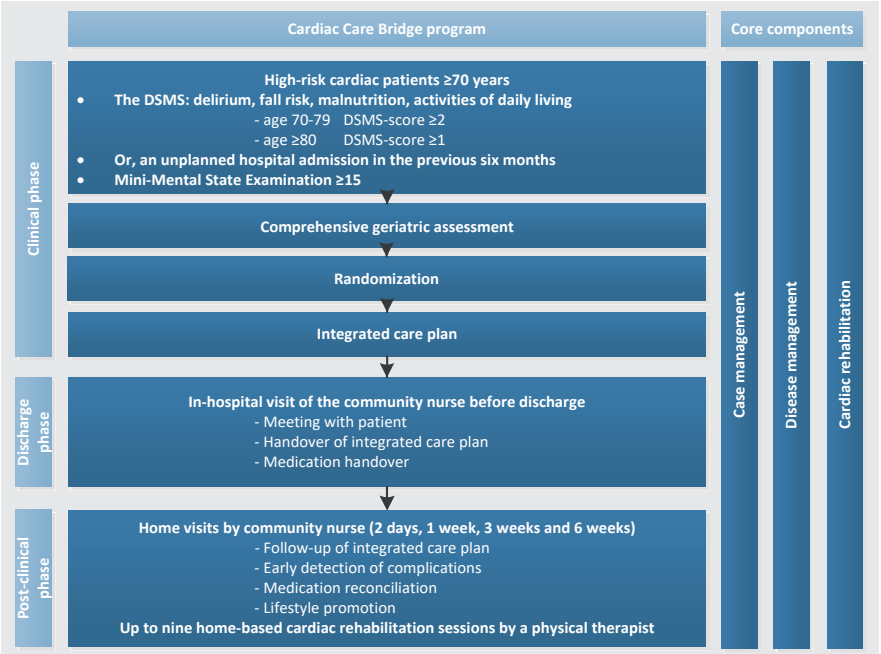

Figure 2. CCB transitional care program.[9,10]

see Table 1.[10] Within each case, data collection focused on the perspectives of the patient, informal caregiver(s), and CCB formal caregivers in the post-clinical phase, and on patients' medical records. Patients and their informal caregivers were contacted and invited to participate by telephone. The CCB formal caregivers were invited by e-mail and reminded by telephone if necessary.

Data collection

Data of each case were collected by two or three interviews, one with the patient and their informal caregiver, one with their CCB physical therapist, and one with their CCB community nurse. Between April and June 2019, a total of fourteen interviews were conducted by researcher CR. Four of the five interviews were held with the patient and informal caregiver simultaneously. One patient was unable to participate in the interview because of her poor health and hospice admission.

Semi-structured interviews were conducted using an interview guide that consisted of open questions.[22,23] Two interview guides were established, one for the patient and their informal caregiver(s) and one for the CCB formal caregivers. The interview guide was based on the conceptual framework (Figure 1) and on information from patients' medical records, which was used by CCB caregivers for registration of intervention components during the intervention in the post-

clinical phase (Figure 2). The medical record reviews provided information on clinical signs of deterioration of the patient's condition and reported interventions by CCB caregivers. Based on this information, a timeline was developed, which was used during the interviews to recall the received/provided care before the unplanned readmission. Additional data on patients' baseline characteristics regarding admission, diagnosis, comorbidities, frailty measures, and the reason for the first readmission, were collected from the medical records.

The interview questions were asked conversationally, with clear questions and in direct, comforting, and simple wording. Participants were free to add important aspects to the discussion.[23] Interviews lasted approximately 45 minutes and took place at the patients' homes or at the physical therapists' or community nurses' workplace, without the presence of third parties. The interviews were audio-recorded and (field) notes were made.

Ethical considerations

This study has been approved by the Medical Ethics Committee of the CCB University Medical Center in CCB (Protocol ID: MEC2016_024). Informed consent was signed by the participants before the interviews.[23] Participants were informed about the purpose of this study both orally and in written. Participants could stop at any time and they were allowed to ask for data deletion.

Data analysis

In this study, thematic analysis was applied.[22,24] Themes were derived from the interviews by CR and LV. Data analysis started directly after the first interview to enable adjustment of the interview guide(s) during the phase of data collection. The anonymity of the participants was guaranteed by transcribing the interviews anonymously. Six steps of data analysis were followed: 1) transcribing the audio records, 2) familiarization with the data, in which collecting and coding were alternated, 3) reading and re-reading; open coding was applied to identify concepts and dimensions in, 4) axial coding, relating categories to their subcategories, 5) modifying codes, removing duplications, ordering codes hierarchically, and integrating theory; selective coding was performed, in which core categories were integrated into theories, and 6) looking for patterns in the data.[23,25] The coding process was performed in MAXQDA version 2018.[26] The manuscript was reported according to the COREQ checklist for reporting qualitative research.[27]

Rigor

In this study, dependability was enhanced by using an interview guide, which ensured that interviews were conducted likewise.[22] Moreover, there were multiple data analysts during the coding process.[22] To provide credibility, a member check was performed during the interviews by summarizing and confirming information by participants, ensuring accuracy of the interpretation.[23] Additionally, with all five

cases, the entire spectrum of each case was evaluated from two to three various perspectives (i.e. patients' and (in)formal caregivers'). After the evaluation of the fifth case, no new information emerged from the interviews.[22]

FINDINGS

In total, five cases were studied, including interviews with patients (n=4), informal caregivers (n=5), and CCB formal caregivers (physical therapists n=4, community nurses n=5). Of these, four interviews were performed with the patient and informal caregiver collectively, leading to a total of 14 interviews. A description of all cases and participants is presented in Table 1.

Three main themes were derived from the data:
1. (in)formal caregivers' involvement in adequate observation of patients' health status to prevent rehospitalization;
2. patients' care support from (in)formal caregivers;
3. the (functioning of the) CCB transitional care program within the existing (in) formal caregivers system.

Theme 1. (In)formal caregivers' involvement in adequate observation of patients' health status to prevent rehospitalization

Within this theme, a few important issues were reported. First, regarding the response to health deterioration, and second, about the (un)avoidability of readmissions.

Response on health deterioration

In cases 3 and 4, the patient's health status was poor and complex due to comorbid diseases and an advanced state of their cardiac disease (Table 1). In these cases, both CCB caregivers mentioned that they observed clinical deteriorations during home visits.

> *"It is always the same type of problem, (...) or it is because of the kidneys that do not work well. Then (...) she is unable to take diuretics properly, which means she decompensates again. Then she has atrium fibrillation, which is not under control (...) and then it's the hypoglycemia again".* (CCB community nurse case 4)

In some cases, home visits by CCB caregivers enabled timely observation of and adequate response to the deteriorating health signs. In case 4, the CCB community nurse noticed hyperglycemia and urinary incontinence during a home visit and brought a urine sample to the general practitioner. Renal failure

Table 1. Characteristics of cases and (in)formal caregivers

		Case 1	Case 2	Case 3	Case 4	Case 5
Patient	*Gender*	Female	Male	Female	Female	Female
	Age (years)	89	91	81	81	88
	Cardiac disease	Arrhythmias and conduction disorders	Heart failure decompensation	Heart failure decompensation	Valve deficit	Palpitations
	Comorbidity	Heart failure	COPD, diabetes mellitus	COPD, kidney failure	Heart failure, peripheral vascular disease, diabetes mellitus, hemiplegia	Heart failure, kidney failure
	Perceived health status by formal caregivers after hospital discharge	Frail, slightly confused, excessive fatigue, limited exercise capacity	Malnutrition, weight loss, excessive fatigue, limited physical condition	Shortness of breath, nausea, limited physical condition, sudden exposing excessive fatigue	Complex health status, in the final stage of life	Severe shortness of breath, excessive fatigue, deteriorating physical condition, limited exercise capacity
	High-risk patients DSMS-score[†]	3	0	3	2	3
	Acute hospitalization within six months prior to index admission[‡]	No	Yes	Yes	Yes	Yes
	Readmission after index admission	Within 3 and 4 months	Within 5 months	Within 1, 2, 4 and 5 months	Within 1, 3, 5 and 6 months	Within 5 days
	Reason of first readmission	Collapse	Unknown	Acute heart failure and dyspnea with COPD exacerbation	Wound infection after thromboend-atherectomy	Cardiac asthma

Table 1. *Continued*

		Case 1	Case 2	Case 3	Case 4	Case 5
Informal caregiver	*Sex*	Female	Female	Female	Male	Male
	Relationship with patient	Daughter	Wife	Daughter	Husband	Son
	Age (years)	61	86	58	86	60
	Number of informal care hours (per week)	15	Daily	20	Daily, on indication	6
CCB community nurse	*Sex*	Female	Female	Female	Female	Female
	Age (years)	64	41	50	50	54
	Work experience (years)	42	17	25	25	30
CCB physical therapist	*Sex*	Female	Female	Female	NA	Male
	Age (years)	54	51	60	NA	59
	Work experience (years)	31	25	40	NA	15
Existing care system[§]		Specialized cardiac nurse of the out-patient clinic	Regular home care, pharmacist	Regular home care, specialized cardiac nurse of the out-patient clinic	Regular home care, specialized cardiac nurse of the out-patient clinic	Regular home care

Abbreviations: COPD Chronic Obstructive Pulmonary Disease, DSMS Dutch Safety and Management System (VMS veiligheidsprogramma, 2009), [†] Maximum score: 4 and patients at high risk of functional decline: ≥80 years DSMS-score ≥1 (VMS veiligheidsprogramma, 2009), [‡] Increases the risk of hospital readmission, [§] all patients received care from the general practitioner and cardiologist.

was diagnosed, as well as decompensation of heart failure, which resulted in hospital readmission. In case 3, the CCB community nurse observed that the patient experienced shortness of breath and the patient felt that she 'walked on cotton'. Due to these observations, outpatient intravenous diuretic therapy was arranged, and hospital readmission was prevented. Later in this case, the patient experienced a high heart rate during a home visit and the CCB physical therapist alarmed the physicians. This resulted in readmission for atrial fibrillation.

In the other three cases (1, 2, and 5), the CCB caregivers indicated they did not observe health deteriorations during the home visits, except for the occasional 'off day'. During these days, patients felt tired, were short of breath, or had flu-like symptoms. CCB caregivers interpreted this as fluctuations reflecting patients' vulnerability.

> *"You saw progress again, except for a single off day. That is what everyone can have of course".* (CCB physical therapist case 1)

The CCB caregivers were not involved in observing the health deteriorations that led to readmission(s), but the informal caregiver, general practitioner, or regular homecare nurses were involved instead.

Timely observation of health deterioration was complicated according to CCB caregivers because of their acute occurrence and since they were not involved on a daily basis. The low frequency of home visits limited continuity of care and, therefore, early detection of health deterioration lacked in some cases.

> *''…that is difficult, health deterioration or problems in medication adherence would be better observed when you would come every day''.* (CCB community nurse case 2)

In case 1, the CCB community nurse reported that she noted an increase in blood pressure in the week before readmission. Figure 3 shows a rising systolic blood pressure in the days before readmission. However, the CCB community nurse reported that she observed an improved clinical condition and did not feel the urge to act. The vital signs and weight curves during home visits in the other cases are displayed in Appendix 2.

Health observations and vital signs were not consistently reported in the CCB medical record during home visits. Therefore, the course of the patients' health might not always be properly observed and interpreted. This may have influenced the observation of early signs and symptoms of deterioration and this lack of continuity of care could have contributed to unplanned hospital readmission. A reason mentioned by the CCB caregivers is the administrative burden of double registration.

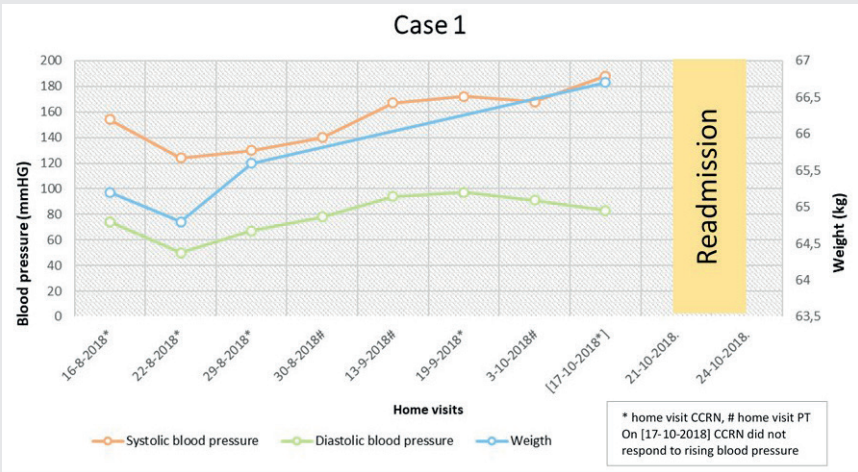

Figure 3. Blood pressure (left) and weight (right) of case 1, as measured by the CCB community nurse (*) or CCB physical therapist (#) during home visits

(Un)avoidability of the readmissions

Despite the above-mentioned factors of influence, patients, informal caregivers, and CCB formal caregivers in cases 1, 2, 4, and 5 mentioned they were convinced that the readmissions were unavoidable due to the frail patient's situation, the level of the disease, and present comorbidities. Patients' health status deteriorated suddenly and the CCB caregivers could not always observe this process in time.

> *"You cannot always prevent that. Uhm... that's just how it is. Sometimes you cannot really see it coming, especially if they become short of breath".* (CCB community nurse case 5)

In all five cases, the informal and formal caregivers reported that they expected a future readmission. The patient and informal caregiver in case 2 mentioned that it was patient's frailty status ensuring the readmission was unavoidable. In case 4, the readmission was experienced as unavoidable because of the patient's advanced stage of heart failure. After the readmission, a palliative care process was started. In case 5, the patient stated that she thought she was discharged too early, and was readmitted five days after discharge.

> *Patient: "No, the readmission could not have been prevented". Informal caregiver: "No, you strictly adhere to the nutrition and fluid restrictions, it's just your vulnerability''.* (Case 2)

Theme 2. Patient care support from (in)formal caregivers

Within this theme, the support of the CCB formal caregivers and informal caregivers are discussed in relation to the course of readmission. In some cases, the collaboration between CCB caregivers, informal caregivers, and patients went well; in other cases, discrepancies in care expectations occurred.

Support of the CCB community nurse

In case 3, the CCB formal caregivers focused on the patients' confidence and trust regarding their health status. The CCB community nurse reported that patients gained trust when clinical parameters like the blood pressure were measured. Additionally, she motivated the patient on energy management and early symptom recognition in daily circumstances. In case 4, the CCB community nurse specified that she performed additional home visits because of the patient's deteriorated health status. The medication prescription changed frequently, which needed close monitoring due to the influence on e.g. the blood pressure. In these cases, the CCB community nurse and patient had a good care-related relationship and adequate care support was provided. In the other cases (1, 2, and 5), the CCB community nurses experienced that they could not contribute to the patients' care needs on top of the actively involved informal caregivers and well-functioning regular home care. It was difficult for them to apply motivational techniques, for example, the CCB community nurse of case 1 hoped to contribute by providing information and motivating the patient and informal caregivers, she could not find the opportunity.

> *''There was no regular homecare involved (…) I tried to arrange this (…). I tried to do it, but the family did not want regular homecare''.* (CCB community nurse case 1)

In case 2, the CCB community nurse reported that the patient and informal caregiver were very independent and therefore, her care tasks were less necessary. Except for the recommendation to consult a dietitian because of malnutrition, the CCB community nurse did not feel further support was necessary. Patients' and informal caregivers' needs were focused on empowerment and advice instead of 'hands-on acting'.

Support of physical therapist

In case 1, the role of the CCB physical therapist was to support the patient in achieving their goals to extent the functional capacity by exercising, and she instructed the informal caregivers on how to support the patient with exercises. In case 2, the physical condition was limited and the motivation to exercise lacked. The CCB physical therapist mentioned that she regularly walked outside with the patient, encouraged the neighbors to go for a weekly walk, and stimulated home-

trainer exercising.

> *''I have regularly went outside with him. (…) I asked the neighbors to go for a walk with him. (…) I tried to stimulate home-trainer exercises to see if I can find some intrinsic motivation, without imposing on him''.* (CCB physical therapist case 2)

In cases 3 and 5, patients felt they had different expectations of the home-based rehabilitation program than the CCB physical therapist. These CCB formal caregivers adhered firmly to the CCB protocol by providing the physical exercises that were suggested and patients did not sufficiently emphasize their goals. However, this situation affected the mutual relationship and resulted in the refusal of the rehabilitation program.

> *"The PT can come by (…) but I won't do any exercise (...) let me sit comfortably and I walk to the toilet and walk to the bedroom (...) and it all works out".* (Patient case 5)

Support of informal caregivers

In most cases (1, 2, 3, and 4), the informal caregivers lived nearby and were involved in noticing health deteriorations.

> *"I am the one who can quickly notice health deteriorations and if I am aware of the criteria, then it is okay".* (Informal caregiver case 2)

In these cases, the informal caregivers were involved on a daily basis. The informal caregivers in case 1 had a medical background, provided support by monitoring the patients' blood pressure, and stimulated physical activity by walking outside together. However, the informal caregivers experienced informal care as stressful and burdensome. In case 2, the formal CCB caregivers mentioned that the informal caregiver was proactive, observed the patients' health status, and arranged healthcare needs. However, her own health often came second. In cases 3 and 4, the informal caregivers experienced physical limitations that impeded their ability to provide care support.

Theme 3. The (functioning of the) CCB transitional care program within the existing (in)formal caregivers system

Within this theme, the collaboration between CCB caregivers and the existing caregivers' network is discussed to explore the CCB caregivers' role within the course of readmission. An important finding within this theme is that during the transitional care intervention, the CCB caregivers were not contacted by patients, informal caregivers, or other involved formal caregivers in case of

health deterioration. Patients and informal caregivers preferred to contact formal caregivers in the existing network.

Collaboration between CCB caregivers and the existing caregivers' network

CCB caregivers expressed that they sometimes experienced difficulties in recognizing their contribution to the existing care system, which resulted in their withdrawal from some cases. In cases 2, 3, and 4, the CCB community nurses did experience the value of their contribution, which positively influenced the continuity of care. They had contact with other involved healthcare providers (e.g. regular homecare services, general practitioner, specialized cardiac nurse) in case of health deterioration and new medication regimes, and discussed adjustments in the care plans. In case of health deterioration, communication went via the existing network and the CCB community nurses were not informed by this network. According to the CCB community nurse, this was a logical route and ensured a good distribution of roles and clear expectations

> *"In those days you are not there and (...) at once the health status declines and (…) if you are just not visible at that time then (...) she will not call me, she did not''.* (CCB community nurse case 3)

In the other two cases (1 and 5), the CCB caregivers mentioned they did not have care-related contact with other formal caregivers due to an already good functioning existing caregivers network. This resulted in a feeling of redundancy of the CCB formal caregivers and reluctance to provide CCB care. In all four cases with both CCB caregivers involved, there was limited communication and interaction between the CCB community nurse and CCB physical therapist about the case. They reported that communication was not always necessary, and they were usually (i.e., outside CCB intervention) not used to these interactions. However, this lack of (interdisciplinary) collaboration and communication influenced the continuity of care.

> *''I think the communication with other caregivers could be uh .. better. There is no extensive reporting in patients' logbooks of things that have been done or should be monitored''.* (CCB community nurse case 2)

DISCUSSION

This multiple case study explored patients' and (in)formal caregivers' perspectives on their role(s) and contributing factors in the course of unplanned hospital readmission of older cardiac patients in the CCB program. Three main themes emerged from our analysis, (1) (in)formal caregivers' involvement in adequate

observation of patients' health status to prevent rehospitalization, (2) patients' care support from (in)formal caregivers, and (3) the (functioning of the) CCB transitional care program within the existing (in)formal caregivers' system. The outcomes of this study can contribute to the optimization of care processes for older cardiac patients.

Although involved CCB caregivers mentioned that some unplanned readmissions were unavoidable in the cases reported, they also mentioned that their early observations in other cases prevented unplanned readmissions. The findings within the first theme suggest that early observation of health deterioration could lead to adequate response from (in)formal caregivers, which potentially prevents unplanned hospital readmission or further deterioration.[28] Pattern recognition of the clinical course by vital sign measurements and the intuition of (in)formal caregiver(s) are important contributors to the prevention of unplanned readmission.[29] For example, weight gain is a strong predictor for health deterioration and hospital readmission of patients with heart failure.[30,31] However, CCB caregivers reported they were not always able to adequately observe health deterioration due to the low frequency of home visits and inadequate reporting of vital signs due to the administrative burden. In patients with a risk of health deterioration, the continuity of care can be improved by continuously observing the clinical course with the use of home-based telemonitoring.[28,32] This method could provide formal caregivers with the daily real-time vital signs data that are needed to outline the clinical course and adequately respond.[32–35] However, this requires the involvement of patients and informal caregivers, particularly when it comes to measuring weight. Additionally, formal caregivers need to be able to quickly respond to changes in vital signs. Telephone follow up might also be a solution, since that has proven to be effective in reducing unplanned readmissions when added to standard care.[36]

Support of (in)formal caregivers is of great importance to avoid unplanned hospital readmission of cardiac patients.[14,17] The main findings within the second theme, 'patients' care support from (in)formal caregivers', showed that informal caregivers often have the opportunity to observe health deterioration at an earlier stage than formal caregivers. However, due to their own physical or mental limitations and a lack of medical knowledge, informal caregiver support was also experienced as complicated. Although patient and informal caregiver empowerment is an important professional skill, CCB caregivers were not always able to adequately apply this in the studied cases. A possible explanation could be the limited integration of patient and informal caregiver empowerment within the CCB training program, which showed to be effective regarding readmission of heart failure patients.[37] Furthermore, some CCB formal caregivers adhered firmly to the CCB protocol, i.e., by conducting home visits strictly according to the protocol and providing the physical exercises that were suggested. In some cases, this led to differences in expectations between CCB caregivers, informal

caregivers, and patients. Some patients were not always willing to fully participate in the CCB program as they e.g. refused to participate in the home-based rehabilitation and did not always clearly emphasize their goals.[11,12] To align with the patients' goals, motivational interviewing techniques were integrated into the CCB training program. Motivational interviewing focuses on patients' willingness and confidence to change behavior, enables formal caregivers to empower patients, and contributes to the prevention of unplanned hospital readmission.[38–40] Although CCB caregivers were trained in motivational techniques, it remained difficult to support patients in formulating their goals.

The main findings within the third theme, '(functioning of the) CCB transitional care program within the existing (in)formal caregivers system', suggest that the limited integration of the CCB transitional care service within the existing (in)formal caregivers system could have hampered the continuity of care. In some cases, adequate interdisciplinary collaboration and communication were observed and resulted in a perceived optimal continuity of care and clear communication routes. However, some CCB caregivers felt they could not optimally provide CCB care because of experienced resistance of other (in)formal caregivers. Instead of adding up to the existing care system, the CCB caregivers sometimes withdrew from the case because they felt redundant. It is important to focus on the optimal integration of CCB care within the existing care systems, based on patients' needs and in adequate collaboration with other (in)formal caregivers to optimize continuity of care and prevent unplanned hospital readmission.

Although CCB caregivers mentioned that some of the unplanned hospital readmissions were unavoidable due to an advanced stage of the disease, the burden of hospitalization is high due to the risk of adverse events.[41] Alternative care programs such as 'hospital care at home' can be an alternative to avoid adverse events associated with hospital readmission.[42] Additionally, some of the studied cases might benefit from interventions that merely focus on improving the quality of life rather than improving physical health, which might still reduce unplanned hospital readmission.[10] Palliative care principles can improve the quality of life of heart failure patients.[43,44] In addition to contemporary heart failure management, a palliative care nurse can be involved to combine palliative care goals with the goal of improving heart failure symptoms.[43]

Limitations

Some issues should be considered for the interpretation of the current study results. First, due to the thoroughness of the multiple case study design, only five CCB intervention cases with unplanned readmission have been included. However, these cases are considered representative for the population of CCB patients with unplanned hospital readmission, as they were selected to represent the diversity of living environments, socioeconomic status, and formal caregivers among patients. Second, the interviewed patients and their (in)formal caregiver

network sometimes experienced difficulties in remembering details regarding their care process. Multiple caregivers were often involved, which made it difficult for patients to remember specific situations. Additionally, not all CCB caregivers reported their care activities comprehensively in the medical record, which complicated the reconstruction of particular situations. To avoid recall bias by patients and (in)formal caregivers as much as possible, we included cases with a maximum of six months after randomization in the CCB study. Furthermore, for each case, a personal timeline of events was made to help the participants recall the situation. Finally, no formal caregivers from the existing care systems have been interviewed, which could have contributed to an even broader perspective. However, by performing two to three interviews from different perspectives per case, we triangulated the case-specific information, and the accumulated information contributed to a broad perspective.

Conclusion

In this multiple case study on the perspectives of patients and (in)formal caregivers on their role(s) and contributing factors in the course of unplanned hospital readmission of older cardiac patients in the Cardiac Care Bridge (CCB) program, we found that early detection of a deteriorating health situation is often lacking, while formal caregivers are not always present at the right time. The focus of care should merely be on the empowerment of patients and informal caregivers, since they have the potential to fill the gap between home visits. Moreover, collaboration and communication between caregivers must be optimized to enable continuity of care. Additionally, CCB caregivers experienced difficulties in providing care within the existing caregivers' system. Within the CCB program, patients were not always easily motivated to participate in the home-based program, often due to contrasting care expectations and the lack of patient's goals. In some cases, the advanced stage of disease could have influenced the lack of goal setting and the feeling that some of the unplanned hospital readmissions were unavoidable. From this perspective, the CCB program should be reconsidered for individual patients. Our findings provide considerations for future intervention (re)design and the target population.

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APPENDIX 1. BACKGROUND THEORETICAL FRAMEWORK

In order to understand patients' and (in)formal caregivers' perspectives on their role(s) and contributing factors in the course of unplanned hospital readmission of CCB intervention patients, the system-related, system- and patient-related, and patient-related factors should be investigated.

System-related factors

The organizational structure is a system-related factor that should be of good quality in order to avoid unplanned hospital readmission. Generally, the organizational structure provides support for providing care. The quality and the interaction among different formal caregivers facilitate the care to be planned and implemented.[16] A good organizational structure consists of good staff knowledge of transitional care, in which formal caregivers are skilled in delivering transitional care.[16] Additionally, the care routines need to be clear and schedules must be used by caregivers to deliver transitional care. The care must be focused on the patients' needs and monitor the outcomes.[16] The integrated care plan of the CCB patients' needs to be focused on the patients' needs.

There are eight evidence-based care processes that promote the coordination of transitional care and need to be sufficient in order to reduce hospital readmission.[15,16] First, assessing the patients' preferences, needs, and strengths.[16] Second, setting interdisciplinary goals and deliver the care based on the preferences, needs, and strengths of the patient.[16] Third, engage the patient in implementing the care plan, by making the care plan congruent with their preferences and needs.[16] Fourth, reconcile of medication is important and can be ensured by correcting the inaccuracies and errors of medication and provide a correct integrated medication list.[16] Fifth, it is important to refer to ''schedules and confirm the feasibility of services planned for home-based care''.[16] Sixth, the patient and informal caregiver must be educated, they need to have a clear understanding of the care plan, the medication and how to respond to changes in health or medical conditions.[16] Seventh, it is important to transfer summaries of care plans to other caregivers.[16] Finally, there must be a follow-up of phone calls and home visits to stimulate the patient and informal caregiver to implement the care plans at home.[16] The informal and formal CCB care system has to meet these evidence-based transitional care processes to promote the coordination of transitional care.

System- and patient-related factors

The care team interactions should consist of good interdisciplinary communication and coordination between caregivers to avoid readmission.[14,17] The CCB

caregivers should make a connection with the patient and informal caregiver, by building a care-related relationship.[16] Additionally, connection with other caregivers is important ''to recognize each other as a team member''.[16] The exchange of information is important for good communication, coordination and continuity of care.[16] Poor care team interactions can contribute to readmission of elderly cardiac patients. The CCB caregivers have to work in interdisciplinary collaboration and therefore, should have a good connection and communication with other caregivers in order to prevent unplanned hospital readmission.

Support of formal caregivers after hospital discharge is important to avoid hospital readmission. Insufficient engagement with patients and their informal caregivers can lead to hospital readmission of the patients.[17] Inadequate medication support can lead to drug treatment-related problems that negatively affect the recovery of the patients.[14] The medication support needs to be adequate in explanation, there should be few changes in treatment, there should be good communication between pharmacy and caregivers, and there should be no delay in receiving new medication.[14] Additionally, formal caregivers should support patients with coordinating care, motivational techniques and empowerment of the patient and informal caregiver in order to prevent disorders that may lead to hospital readmission.

Observing health status is both a system- and patient-related factor because both the system and patient should monitor and manage symptoms related to patients' deteriorating health status to prevent for adverse events, such as unplanned hospital readmission.[18] The caregivers in the system can provide disease management, by educating patients to manage their health status in order to stimulate patients' self-care and observing deteriorations in health.[18] It is important for CCB caregivers to promote health management and patients should adhere to this by monitoring their health status.

Patient-related factors

Goal setting is important for caregivers, patients, and informal caregivers to have the same vision and goals.[14,16] The recovery goal should be realistic and clear to obtain an optimal recovery process.[14] In addition, the goal for the patients should not lead to 'pushing themselves too far'.[14] This will have a negative influence on the recovery process and can lead to hospital readmission of the patient.[14] Therefore, during every home visit, the recovery goals should be evaluated and adjusted. The formal caregivers should have an interdisciplinary goal to achieve valuable collaboration. The recovery goal of the CCB study patients should be realistic and clear to obtain an optimal recovery process, otherwise an unplanned hospital readmission may follow.

The health status and healthcare of the patient can be the cause of unplanned hospital readmission.[13,14] First of all, the main diagnosis can lead to another hospital admission.[13] But also unrelated illnesses or injuries can lead to hospital

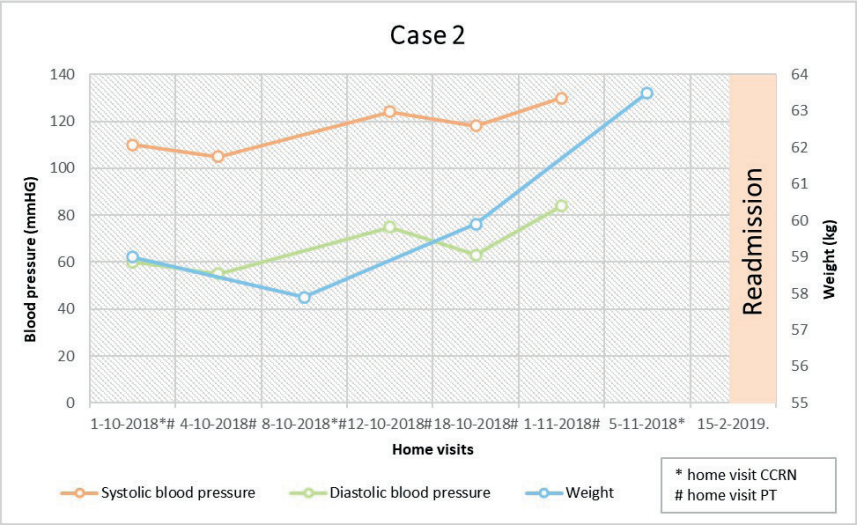
readmission, for example, a medication adverse reaction or post-procedure complications.[15] Additionally, geriatric problems can lead to acute hospitalization of elderly patients.[8] In the somatic domain, malnutrition, obesity, pain, fall risk, incontinence, and constipation can have an influence on hospital readmission.[8] Furthermore, the comorbidity and polypharmacy of frail elderly cardiac patients are often directly linked to the hospital readmission.[14] Patients with comorbidity can have struggles to manage chronic illnesses after hospital discharge.[14] Polypharmacy, often associated with comorbidity, can lead to medication problems which can contribute to hospital readmission.[14] In the psychological domain, problems occur such as depressive symptoms, prevalent delirium, and cognitive impairment.[8] These psychological problems can lead to unplanned hospital readmission. [14] This is due ''near-death experiences, adapting to major lifestyle changes, relationship difficulties and feeling socially isolated''.[14] In the functional domain, impairment of activities of daily living may play a role in the readmission of patients.[8] Finally, the social domain of the patient may have an impact on hospital readmission of elderly patients due to high perceived informal caregiver burden.[8] Formal caregivers should help frail elderly cardiac patients with these health-related problems to avoid hospital readmission. The healthcare and health status of the CCB patient needs to be investigated, in order to understand how the system of caregivers react to the patients' needs.

The health behavior of the patient can contribute to hospital readmission.[13,17] This patient-related factor can avoid hospital readmission by adjusting the health behavior of the patient himself. Some patients may have discharge against medical advice and this behavior may lead to hospital readmission.[45] In addition, non-compliance with treatment is another behavior that may lead to hospital readmission.[13] Sometimes the patients' readiness is lacking.[15] For example, if patients have a lack of knowledge and adherence to a healthy diet, or a lack of knowledge and adherence to medication, or poor lifestyle choices, or do not follow the discharge plan.[15] All these aspects can contribute to unplanned hospital readmission and therefore caregivers should help the patient to change their health behavior.[15] The patients' health behavior needs to be investigated because the CCB patients might have non-compliance with their treatment, poor lifestyle choice or adherence to medication. This requires good anticipation of the care system of the patient to avoid hospital readmission.

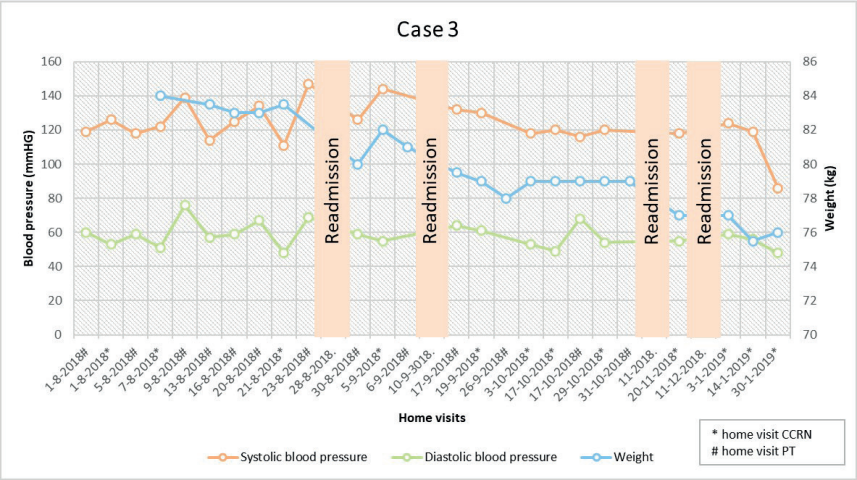
Social support of an informal caregiver, such as support with activities of daily living, is important for patients to avoid readmissions.[14,15] Patients can be heavily reliant on an informal caregiver for (social) support. This can lead to ''high levels of strain'' for informal caregivers.[14] This reliance on an informal caregiver is as a major risk for the patient to manage at home, particularly in combination with poor mobility, social isolation and/or psychological problems.[14] Additionally, the removal of informal caregivers can be a contributing factor to hospital readmissions.[14] Some informal caregivers have insufficient healthcare skills, consisting of lack of

disease knowledge and unable to handle tasks complexity.[46] Issues for informal caregivers are being isolated from social contacts, suffering from anxiety due to the responsibility of the patient, and inadequate professional support.[47] Many informal caregivers have serious health problems themselves and still need to take care of the patient.[47] Informal caregivers can have insufficient healthcare skills, which can lead to poor support. This poor support can lead to hospital readmission of the CCB patient.

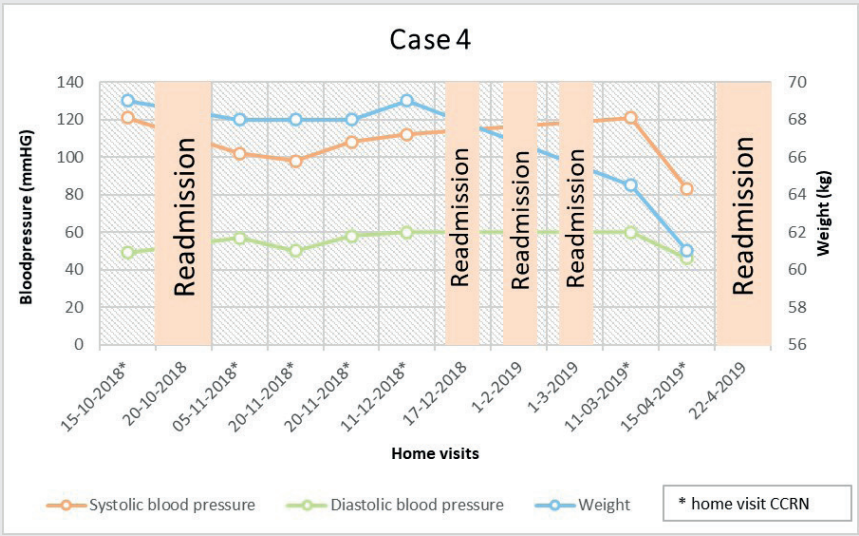
APPENDIX 2. FIGURES



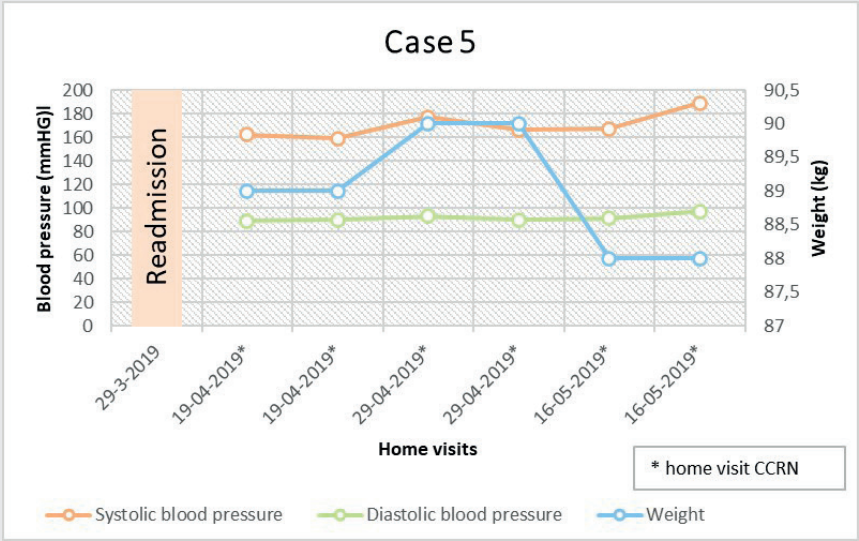
Blood pressure (left) and weight (right) of case 2 measured by community nurse (*) or physical therapist(#) during home visits



Blood pressure (left) and weight (right) of case 3 measured by community nurse (*) or physical therapist(#) during home visits



Blood pressure (left) and weight (right) of case 4 measured by community nurse (*) or physical therapist(#) during home visits



Blood pressure (left) and weight (right) of case 5 measured by community nurse (*) or physical therapist(#) during home visits

Part 3

New approaches in cardiac rehabilitation

Chapter 9

Effects of postacute multidisciplinary rehabilitation including exercise in out-of-hospital settings in the aged: systematic review and meta-analysis

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ABSTRACT

OBJECTIVE: Many older individuals receive rehabilitation in an out-of-hospital setting (OOHS) after acute hospitalization; however, its effect on mobility and unplanned hospital readmission is unclear. Therefore a systematic review and meta-analysis were conducted on this topic.

DATA SOURCES: Medline OVID, Embase OVID, and CINAHL were searched from their inception until February 22, 2018.

STUDY SELECTION: OOHS (ie, skilled nursing facilities, outpatient clinics, or community-based at home) randomized trials studying the effect of multidisciplinary rehabilitation were selected, including those assessing exercise in older patients (mean age ≥ 65 years) after discharge from hospital after an acute illness.

DATA EXTRACTION: Two reviewers independently selected the studies, performed independent data extraction, and assessed the risk of bias. Outcomes were pooled using fixed- or random-effect models as appropriate. The main outcomes were mobility at and unplanned hospital readmission within 3 months of discharge.

DATA SYNTHESIS: A total of 15 studies (1255 patients) were included in the systematic review and 12 were included in the meta-analysis (7 assessing mobility using the 6-minute walk distance (6MWD) test and 7 assessing unplanned hospital readmission). Based on the 6MWD, patients receiving rehabilitation walked an average of 23 meter more than controls (95% confidence interval (CI): −1.34 to 48.32; I^2: 51%). Rehabilitation did not lower the 3-month risk of unplanned hospital readmission (risk ratio: 0.93; 95% CI: 0.73-1.19; I^2: 34%). The risk of bias was present, mainly due to the nonblinded outcome assessment in 3 studies, and 7 studies scored this unclearly.

CONCLUSION: OOHS-based multidisciplinary rehabilitation leads to improved mobility in older patients 3 months after they are discharged from hospital following an acute illness and is not associated with a lower risk of unplanned hospital readmission within 3 months of discharge. However, the wide 95% CIs indicate that the evidence is not robust.

INTRODUCTION

Every year, approximately 10% of the population aged ≥65 years is acutely admitted to hospital because of a variety of diseases, such as cardiovascular, pulmonary, and infectious diseases.[1] Many of these patients suffer from disabilities and limitations in activities of daily living that are associated with adverse health outcomes after hospitalization.[1,2] More than 20% of older patients die within 3 months[1] and over 30% die 1 year after hospital discharge.[2] Of those alive at 3 months, many develop new limitations in activities of daily living when compared to their abilities 2 weeks before hospitalization.[1,3] These patients are at risk of ending up in a vicious circle because these increased disabilities are in turn associated with increased all-cause 30-day hospital readmission.[4]

Longitudinal studies in community-dwelling older patients showed that many were able to recover from limitations in activities of daily living and frailty and that it is not an inherently irreversible process.[5-8] A recent systematic review and meta-analysis of hospital-based inpatient geriatric rehabilitation, including exercise training, demonstrated that rehabilitation strategies cannot only restore functioning but also prevent disabilities.[9]

Many studies focus on a diagnosis-based population despite other factors (ie, level of frailty) playing an important role in determining rehabilitation needs.[8] The medical diagnosis often insufficiently correlates with disease-related functional consequences. To restore or prevent disabilities in older individuals, rehabilitation programs need to apply a broader multifactorial approach rather than focusing only on body function.[10-12] This is often implemented using a comprehensive geriatric assessment to assess a patient's health status, geriatric condition, body function, and personal goals and results in a multidisciplinary care and rehabilitation plan.[13,14]

There is currently no aggregated evidence available regarding multidisciplinary rehabilitation treatment in an out-of-hospital setting (OOHS) (ie, skilled nursing facilities, outpatient clinics, or community-based at home) for older adults after hospital discharge following an acute illness. Current evidence on this type of rehabilitation has mainly focused on patients' poststroke[15,16] or hip fracture[17,18] and on older patients who reside in a nursing home and require long-term care.[19]

Therefore this systematic review and meta-analysis analyzed the effectiveness of multidisciplinary rehabilitation (including exercise compared to usual care or other forms of rehabilitation) on mobility (as a measure of body function) and unplanned hospital readmission in older patients (mean age ≥65) 3 months after hospital discharge following an acute illness.

METHODS

This systematic review is registered in the Prospero register of systematic reviews (registration number: CRD42017058592). It has been reported according to the PRISMA guidelines.[20]

Study selection

Inclusion criteria for studies were as follows: design: randomized controlled trials published in peer-reviewed journals. Population: mean age ≥ 65 years; discharged from hospital following an acute illness (ie, myocardial infarction, exacerbation of chronic obstructive pulmonary disease, or dysregulated diabetes mellitus). Intervention: rehabilitation in an OOHS (ie, a skilled nursing facility, outpatient clinic, or community-based at home); rehabilitation programs starting in hospital and continuing in an OOHS; rehabilitation containing at least exercise therapy, because this is an important contributing intervention to recover from or prevent a decline in body function,[21,22] and including treatment from at least 2 disciplines; intervention compared to care-as-usual or other forms of rehabilitation. Outcome: primary: mobility (as a measure of body function) and unplanned hospital readmission within 3 months of the initial hospitalization; secondary: mobility (as a measure of body function) and unplanned hospital readmission within 6 and 12 months of the initial hospitalization.

The focus of the primary and secondary outcome measures at 3 and 6 months after discharge was based on the rationale that older patients are at increased risk of adverse events and declining body function in the first 6 months after hospital discharge.[1,2,23] The effect of rehabilitation at 12 months was included to present the long-term effects of the interventions.

Studies were excluded if the intervention was offered after planned hospitalization, was situated within an emergency department, or focused on institutionalized long-term care. Studies on patients with neurological and traumatic injuries (eg, hip fractures) were excluded as there is sufficient evidence that rehabilitation programs are effective in these populations.[15-18] Studies were also excluded if the focus was on patients with a severe psychological or psychiatric comorbidity or cognitive impairments.

Definition of the mobility outcome as a measure of body function

Although daily functioning is widely used as an important patient-reported outcome measure, many variations exist on the use of the term *functioning*.[24] According to the International Classification of Functioning, *functioning* consists of 3 main functions: *body functions*, *activities*, and *involvement in life situations*.[24] This systematic review focuses on mobility (eg, a 6-minute walk distance (6MWD) test) as a measure of body function.

The 6MWD test reflects the functional capacity level and is an indicator of activities of daily living as part of body function according to the International Classification of Functioning.[25] The 6MWD test is a predictor of morbidity and mortality in older patients.[25]

Information sources

A clinical librarian (J.G.D) conducted a systematic literature search in Medline OVID, Embase OVID, and CINAHL selecting articles that were published between their inception and February 22, 2018. A scoping search was initially performed to identify relevant references in Medline OVID. Reference lists of eligible studies were searched by hand to identify studies potentially missed in the database searches. Appendix 1 shows the full search strategy.

Study selection

The studies identified in the scoping search were managed in EndNote[26] and subsequently exported to Covidence[27] and Review Manager (version 5.3),[28] which were used for the screening process, data collection, and analysis. Two authors (L.V. and E.V.D.K.) independently screened the titles, abstracts of the identified studies, and full texts after the first screening. After selection, they subsequently extracted data from these studies. In case of a discrepancy, a consensus was reached through discussion with a third reviewer (B.M.B).

Data collection

Based on the Cochrane data collection form[29] and the TIDieR guideline for the description of interventions,[30] data were extracted on: (1) study characteristics (eg, authors, publication year, journal, country, study setting, study population, sample size, and follow-up); (2) patient characteristics (eg, mean age and gender distribution); (3) description of the intervention based on TIDieR guidelines (eg, what [intervention components either exercise, diet, or education], who [multidisciplinary], how, where, and how much)[30]; (4) intensity (eg, aerobic or anaerobic training, muscle strengthening, balance and stretching exercises, functional exercise, and frequency); (5) statistics (eg, absolute numbers, effect size, and 95% confidence intervals [CIs]).

In the case of missing data, the authors were contacted by e-mail and asked for the additional information. One reminder e-mail was sent after 4 weeks.

Assessment of risk of bias

The Cochrane Collaboration's risk of bias tool was used to evaluate the quality of the included studies.[31] Two reviewers (L.V. and E.V.D.K.) independently assessed each study based on the sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data,

selective outcome reporting, and other sources of bias.

In the evaluation, a distinction was made between the mobility and unplanned hospital readmission outcomes considering the effect of blinding the outcome assessors. Not blinding the outcome assessors to the rehabilitation intervention was unlikely to have influenced the unplanned hospital readmission rates but could have influenced the measurement of mobility.

Publication bias

A plan was made to assess small study bias using the Egger regression asymmetry test if at least 10 studies were included in the meta-analysis.[29]

Data synthesis

Review manager software[28] was used to pool study data regarding mobility and unplanned hospital readmissions. The mean difference (MD) and 95% CI was calculated for the continuous mobility outcome from the 6MWD data, which were reported in most studies included on the topic. The pooled risk ratio (RR) and its 95% CI were calculated for the unplanned hospital readmission outcome. Heterogeneity across studies was evaluated using the I^2 statistic.[29] A fixed-effects model was used for I^2 values $\leq$ 40%, and a random-effects model (according to the DerSimonian and Laird method to account for substantial statistical heterogeneity) was used for I^2 values $>$ 40%.[29] A sensitivity analysis of the meta-analysis was also performed to assess the influence of sequentially omitting individual studies on pooled estimates.

RESULTS

Online database searches in Medline OVID, Embase OVID, and CINAHL identified 6187 references. The review process is summarized in figure 1. After removing duplicates, the titles and abstracts of 4355 studies were screened. A total of 143 studies were considered for a full-text review, whereas 128 studies were excluded due to inadmissible patient populations (n=68); nonrandomization of the trial (n=19); no rehabilitation intervention, lack of exercise components, or no multidisciplinary approach (n=14); no acute hospitalization (n=12); the study protocol description (n=8); other outcomes (n=5); or excluded settings (n=2). Ultimately, 15 studies were eligible for inclusion in the systematic review, 7 were eligible for inclusion in the 6MWD meta-analysis and 7 were eligible for the meta-analysis on unplanned hospital readmission.

Study characteristics

The number of participants in the included studies collectively totaled 1255 (624 in the intervention group and 631 in the control group). The mean participant

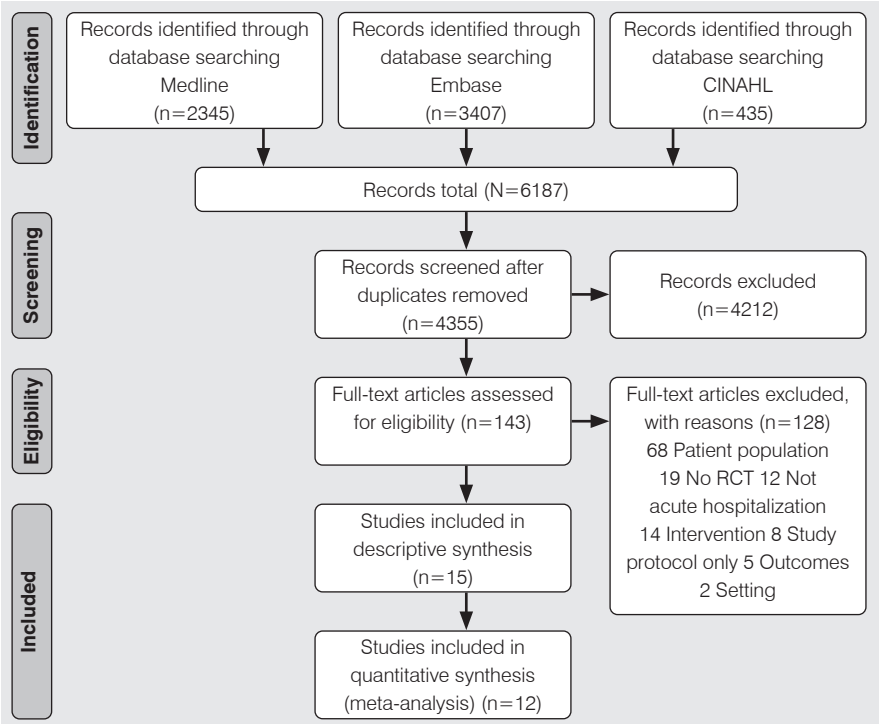

Figure 1. Flow chart

age was 74 years (range: 65–85). Four studies reported on a general patient population,[32-35] 5 reported on pulmonary patients,[36-40] and 6 reported on cardiac patients (table 1).[41-46]

Of the 15 included studies, 11 involved transitional rehabilitation interventions that started rehabilitation during hospitalization[32-37,40,42,43] or in an outpatient rehabilitation center.[38,41] The interventions continued with rehabilitation that was home-based,[32-36,38,40,41,43] in an outpatient setting,[37] or in a skilled nursing facility.[42] Of the remaining 4 studies, 2 only provided rehabilitation at home[44,45] and 2 provided rehabilitation in an outpatient setting.[39, 46]

The exercise component of the included studies consisted of intensity training (ie, walking and endurance exercises), strengthening exercises, and balance and stretching exercises and was mainly performed by physical therapists, occupational therapists, or a multidisciplinary team that was not further specified (table 2). In general, each study included an educational component in the intervention (ie, written or verbal exercise instructions) and counseling and teaching strategies for coping with dyspnea and stress, which were provided by those with expertise on the topic (see table 2). Dieticians were mainly involved in studies on cardiac patients in the context of dietary counseling,[41,44,45] and in 1 study they were used to

Table 1. Characteristics of included studies

First author, year of publication	Country	N I/C	Mean age (SD) I/C	Setting*	Outcome (Instrument)†	OA (mo)	Outcome (I) ‡	Outcome (C) ‡
General illness								
Courtney, 2009[33]	Australia	64/64	78 (6.3)/79.4 (7.3)	Inpatient, hospital	Readmission	3	11/58	16/64
				Community, home		6	13/49	27/58
Courtney, 2012[34]	Australia	64/64	78 (6.3)/79.4 (7.3)	Inpatient, hospital	Mobility (WIQ-distance)	3	54.83 (27.79)	21.59 (26.17)
				Community, home		6	62.89 (28.17)	19.93 (24.93)
Buhl, 2016[32]	Denmark	14/12	73.3 (6.29)/72.4 (7.43)	Inpatient, hospital	Mobility (DEMMI)	3	NR	NR
				Community, home	Readmission	3	2/14	1/12
Sahota, 2017[35]	United Kingdom	125/125	83.6 (6.6)/84.5 (5.9)	Inpatient, hospital	Readmission	3	45/125	39/125
				Community, home				
Pulmonary illness								
Behnke, 2000[36]	Germany	15/15	65 (1.9)/68 (2.2)	Inpatient, hospital	Mobility (6MWD)	3	NR	NR
				Community, home		6	NR	NR
Eaton, 2009[37]	New Zealand	47/50	70.1 (10.3)/69.7 (9.4)	Inpatient, hospital	Mobility (6MWD)	3	362 (119)	313 (126)
				Outpatient, rehab clinic	Readmission	3	11/47	16/50
Ko, 2011[38]	China	30/30	73.5 (7.7)/73.8 (6.4)	Outpatient, rehab clinic	Mobility (6MWD)	3	328.77 (85.22)	313.23 (76.79)
				Community, home		6	333.30 (84.86)	316.73 (72.72)

						12	330.62 (86.11)	294.66 (113.31)
					Readmission	3	6/30	8/30
						6	11/30	11/30
						12	16/30	13/30
Seymour, 2010[39]	United Kingdom	30/30	67 (10)/65 (10)	Outpatient, rehab clinic	Mobility (ISWT)	3	216 (126)	183 (98)
					Readmission	3	2/30	10/30
Song, 2014[40]	South Korea	20/20	66.6 (7.1)/68.1 (6.5)	Inpatient, hospital	Mobility (6MWD)	3	333.5 (79.2)	312.7 (72.1)
				Community, home				
Cardiac illness								
Davidson, 2010[41]	Australia	53/52	71.6/73.9	Outpatient, clinic	Mobility (6MWD)	3	361.2 (132.34)	274.98 (106.6)
				Community, home		12	386.6 (129.97)	247.27 (122.96)
					Readmission	12	22/49	27/39
Dolansky, 2011[42]	United States	17/21	77.6 (6.9)/76.5 (6.9)	Inpatient, hospital	Mobility (N steps walked)	3	1307 (652)	782 (544)
				Inpatient, SNF*				
				Community, home				
Li, 2015[43]	China	37/40	80.3 (3.8)/81.1 (4.5)	Inpatient, hospital	Mobility (6MWD)	3	347.6 (63.71)	338.3 (76.25)
				Community, home				
Oerkild, 2011[45]	Denmark	39/36	74.7 (5.9)/74.4 (5.8)	Community, home	Mobility (6MWD)	3	Δ17.4 (82.04)	Δ36.1 (83.95)
Oerkild, 2012[44]	Denmark	19/21	77.3 (6.0)/76.5 (7.7)	Community, home	Mobility (6MWD)	3	Δ36.3 (82.84)	Δ10.1 (78.91)

Table 1. *Continued*

First author, year of publication	Country	N I/C	Mean age (SD) I/C	Setting*	Outcome (Instrument)†	OA (mo)	Outcome (I) ‡	Outcome (C) ‡
Sandström, 2005[46]	Sweden	50/51	71 (64-84)/71 (65-83)	Outpatient, rehab clinic	Readmission	3	10/50	6/51
						12	11/50	11/51

NOTE. Δ delta: difference between baseline measures and follow-up measures.
Abbreviations: C, control; I, intervention; ISWT, Incremental Shuttle Walk Test; NR, not reported; OA, outcome assessment; SNF, Skilled Nursing Facility; WIQ: Walking Impairment Questionnaire; DEMMI: de Morton Mobility Index.
* Setting: SNF.
† Instruments: WIQ/DEMMI/6MWD in meters/ISWT.
‡ Data on mobility are presented as mean, standard deviation (SD), unplanned hospital readmission in absolute numbers.

prescribe a high-protein diet to a general patient population.[32] Each study included a multidisciplinary team made up of, for example, registered nurses, physical therapists, occupational therapists, and dieticians (see table 2). Three studies performed a comprehensive baseline geriatric assessment[33-35]; however, the duration and intensity of rehabilitation sessions differed substantially in these studies, ranging from 15 minutes[36] to 120 minutes[38,39] per session. The frequency of sessions in the rehabilitation programs ranged from 1 in-hospital session and 1 outpatient session in total[40] to 6 sessions per week over 12 months.[45]

All studies defined usual care as providing information and advice on lifestyle and exercise and providing follow-up visits or telephone calls by a physician or nurse (specialist). In addition to this usual care, 2 studies described rehabilitation advice as usual care but did not elaborate on the details of this advice.[33,34] One study described standard rehabilitation as usual care that involved group-based exercise training twice a week, education, and dietary counseling.[45] Another study described standard rehabilitation as an in-hospital multidisciplinary approach by physical therapists and occupational therapists during weekdays with a training schedule based on an individual assessment.[35]

Risk of bias

Figure 2 summarizes the risk of bias assessment in the included studies. Sequence generation was clearly described in all studies with the exception of the studies by Oerkild *et al*.[44] and Sahota *et al*.[35] Oerkild introduced selection bias by

Table 2. Description of interventions

First author, year of publication	Intensity and dose	What is delivered? Exercise				What is delivered? Education - instruction about				What is delivered? Dietary	Who delivered? Disciplines
General illness		Intensity	Strength	Balance / stretching	Exercise	Lifestyle	Coping	Medication	Not specified / other		
Courtney, 2009[33]	24 wks	x	x	x	x	x	NT	NT	NA	NT	RN, PT
Courtney, 2012[34]	24 wks	x	x	x	x	x	NT	NT	NA	NT	RN, PT
Buhl, 2016[32]	13 wks	NT	x	NT	x	NT	NT	NT	NA	x	Dt, PT
Sahota, 2017[35]	In hospital 7/w, transition, home visits based on needs	Personalized rehabilitation plan						NT	NA	NT	OT, PT, SSP
Pulmonary illness											
Behnke, 2000[36]	6 months 15 min 3/d	x	NT	NT	x	NT	NT	NT	NA	NT	PT, MS, RPh
Eaton, 2009[37]	8 wks, 1h 2/w	x	x	NT	NT	NT	x	x	NA	NT	MT, APN, MDT
Ko, 2011[38]	8 wks, 120 min 3/w	x	x	NT	x	NT	x	NT	NA	NT	PT, APN
Seymour, 2010[39]	8 wks, 120 min 2/w	x	x	NT	NT	NT	NT	NT	x	NT	PT, MT

Table 2. *Continued*

First author, year of publication	Intensity and dose	What is delivered? Exercise				What is delivered? Education - instruction about				What is delivered? Dietary	Who delivered? Disciplines
General illness		Intensity	Strength	Balance / stretching	Exercise	Lifestyle	Coping	Medica-tion	Not specified / other		
Song, 2014[40]	8 wks	x	NT	x	x	NT	x	x	NA	NT	MT, APN
Cardiac illness											
Davidson, 2010[41]	12 wks	x	x	NT	NT	NT	NT	NT	x	x	RN, PT, RPh, OT, Dt
Dolansky, 2011[42]	2 wks	x	NT	NT	x	NT	NT	NT	x	NT	RN, PT, OT
Li, 2015[43]	12 wks, 5/wk	x	NT	NT	x	NT	NT	NT	NA	NT	MT, PT, APN
Oerkild, 2011[45]	12 months, 30 min 6/wk	x	NT	NT	NT	x	NT	NT	NA	x	PT, Dt
Oerkild, 2012[44]	12 months, 30 min 6/wk	x	NT	NT	x	x	NT	NT	NA	x	PT, MS, Dt
Sandström, 2005[46]	3 months, 50 min 3/wk	x	NT	NT	x	NT	NT	NT	x	NT	MDT

RN: Registered Nurse; PT: Physical Therapist; Dt: Dietician; RPh: Registered Pharmacist; MS: Medical Specialist; MT: Medical Team; APN: Advanced Practice Nurse; MDT: Multidisciplinary Team; OT: Occupational Therapist; SSP: Social Service Practitioner; NT: Not Tested; NA; Not Applicable

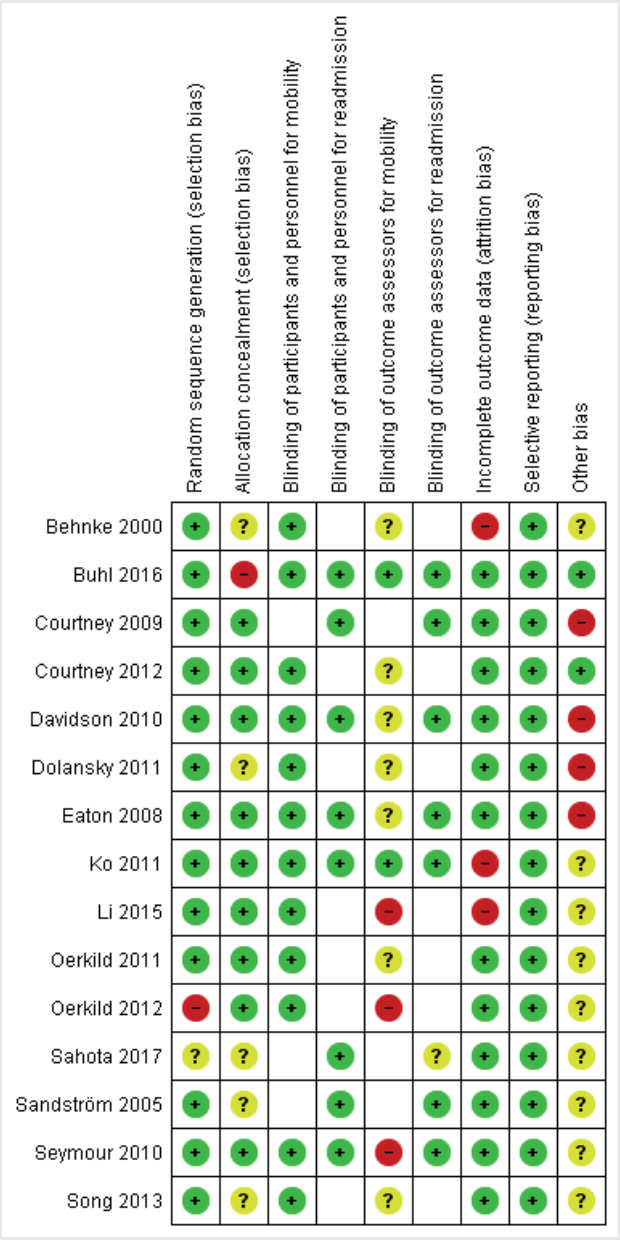

Figure 2. Risk of bias table
Legend: green: low risk of bias. yellow: unclear risk of bias. red: high risk of bias. white: outcome is not reported.

inviting patients to participate in another program, and those who declined were invited to participate in the study program. Sahota did not describe the process of sequence generation. Five studies did not report the allocation concealment process,[35,36,40,42,46] and 1 study reported a partially-influenced allocation process.[32] Buhl *et al*.[32] reported that patients living too far from the municipality were included in the control group. Blinding of the outcome assessors to the mobility outcome was poorly described or, in the case of 3 studies, poorly performed.[39,43,44] To assess the risk of bias due to incomplete outcome data, studies were evaluated on the registration or publication of the study protocol and attrition rates with a cutoff point of 20%. Three studies reported a high attrition rate.[36,38,43] All studies reported on predefined outcomes, therefore reporting bias was scored as a low risk. Other possible introduced biases were caused by financial incentives to participants,[42] underpowering due to low consensus rates,[37] a high rate of noncompliance to the intervention,[33] and early termination of the study due to health policy changes.[41]

Publication bias

The limited number of studies in the meta-analyses (7 6MWD studies and seven unplanned hospital readmission studies) meant that the minimal requirement of 10 studies for testing publication bias was not met.

Mobility

Twelve studies assessed the mobility outcome: 2 included a general population,[32,34] 5 included patients with pulmonary disease,[36-40] and 5 included patients with cardiac disease.[41-45] The effect of rehabilitation on the 6MWD test was assessed in 8 of the studies.[36-38,40,41,43-45] Other measurement scales used to assess mobility included the Incremental Shuttle Walk Test (ISWT),[39] the de Morton Mobility Index,[32] and the Walking Impairment Questionnaire (WIQ, self-reported).[34] Data from the WIQ suggested that the intervention group showed greater mobility at 3 and 6 months after discharge.[34] Data from the ISWT also reported that the intervention group showed greater mobility at 3 months after discharge.[39] Dolansky *et al*.[42] counted the number of steps walked using a pedometer and reported a positive trend (see table 1) in the intervention group compared to the control group.[42]

Seven studies provided sufficient data for a meta-analysis of the 6MWD (figure 3A). The overall MD was 23 m at 3 months (95% CI: −1.34 to 48.32; I^2: 51%); however, the I^2 test result suggests substantial heterogeneity between studies. The study by Oerkild *et al.*[45] appeared to be an influential trial because its omission led to a larger pooled effect in favor of OOHS rehabilitation (MD: 31.3; 95% CI: 8.06–54.68), whereas omission of the Davidson *et al.*[41] study led to a smaller pooled effect (MD: 10.76; 95% CI: −7.29 to 28.81) (table 3).

Data on mobility measured by the 6MWD at 6 months after hospital discharge were reported in 2 studies. The study of Ko *et al*.[38] showed a favorable effect of the rehabilitation program on the 6MWD in the intervention group (330 m) than

Table 3. Sensitivity analysis mobility (6MWD) in meters at 3 months after discharge

	Total included studies	Sample size of included studies combined	Random Effects model Mean Difference (95% confidence interval)
Complete meta-analysis	N = 7	n = 421	23.49 (-1.34 - 48.32)
Without Oerkild 2011[45]	N = 6	n = 346	31.37 (8.06 - 54.68)
Without Oerkild 2012[44]	N = 6	n = 383	23.65 (-5.12 - 52.41)
Without Davidson 2010[41]	N = 6	n = 329	10.76 (-7.29 - 28.81)
Without Eaton 2008[37]	N = 6	n = 357	20.93 (-6.07 - 47.93)
Without Ko 2011[38]	N = 6	n = 370	25.55 (-3.98 - 55.07)
Without Li 2015[43]	N = 6	n = 360	27.22 (-3.07 - 57.51)
Without Song 2013[40]	N = 6	n = 381	24.49 (-4.82 - 53.80)

in the control group (316 m), and Behnke *et al*.[36] also reported a favorable effect at 6 months ($P < 001$) in the intervention group but did not provide any detailed information.[36] Two studies reported the effect of rehabilitation on mobility at 12 months after hospital discharge measured by the 6MWD.[38, 41] Ko reported a favorable effect in the intervention group (331 m) than in the control group (295).[38]

Unplanned hospital readmission

Eight studies assessed the effect of rehabilitation on unplanned hospital readmissions: 7 reported on readmissions within 3 months,[32,33,35,37-39,46] 2 reported on readmissions within 6 months,[33,38] and 2 reported on readmissions within 12 months.[41,46]

Seven studies provided sufficient data for a meta-analysis of unplanned hospital readmissions within 3 months, which was the primary endpoint.[32,33,35,37-39,46] The pooled RR based on a fixed-effects model was 0.93 (95% CI: 0.73–1.19) (figure 3B). Within 6 months of hospitalization, only 1 study reported significantly fewer hospital readmissions in the intervention group than the control group,[33] and data requested from Ko showed comparable unplanned hospital readmission rates (intervention group and control group: 37%).[38] Within 12 months of hospital discharge, Davidson reported lower hospital readmission rates in the intervention group (odds ratio: 0.20; 95% CI: 0.07–0.58; relative risk: 0.63).[41]

In the sensitivity analysis of the unplanned hospital readmissions within 3 months, the studies of Sahota *et al*.[35] and Seymour *et al*.[39] substantially influenced the pooled effect size. When the study of Sahota was excluded from the meta-analysis, the pooled RR changed to 0.77 (95% CI: 0.54–1.10), and omission of the study of Seymour changed the pooled RR to 1.02 (95% CI: 0.79–1.31) (table 4).

Table 4. Sensitivity analysis unplanned hospital readmission within 3 months after discharge

	Total included studies	Sample size of included studies combined	Fixed Effect model Risk Ratio (95% confidence interval)
Complete meta-analysis	N = 7	n = 719	0.93 (0.73 – 1.19)
Without Seymour 2010[39]	N = 6	n = 659	1.02 (0.79 – 1.31)
Without Eaton 2008[37]	N = 6	n = 622	0.97 (0.74 – 1.27)
Without Ko 2011[38]	N = 6	n = 659	0.95 (0.73 – 1.23)
Without Courtney 2009[33]	N = 6	n = 597	0.96 (0.74 – 1.26)
Without Sahota 2017[35]	N = 6	n = 469	0.77 (0.54 – 1.10)
Without Sandström 2005[46]	N = 6	n = 618	0.88 (0.68 – 1.14)
Without Buhl 2016[32]	N = 6	n = 690	0.92 (0.71 – 1.18)

DISCUSSION

The randomized trials used in this systematic review support the idea that rehabilitation of older patients in an OOHS improves mobility, which was reflected in an average increase of 23 m on the 6MWD test at 3 months after discharge from hospital following an acute illness. The review also indicates that rehabilitation of older patients in an OOHS after discharge from hospital following an acute illness does not lower the risk of unplanned hospital readmission after 3 months. However, the wide 95% CI and the instability of the pooled effect on mobility indicate that this evidence is not robust.

In the United States, rehabilitation programs after hospitalization have gained importance due to the recent introduction of payment penalties for hospitals with higher than average 30-day readmission rates.[47] The posthospital syndrome described by Krumholz *et al*.[48] is a multifactorial phenomenon that occurs after acute hospitalization and increases the risk of rehospitalization. The association of functional impairment and readmission rates after hospitalization has increased awareness of the importance of rehabilitation.[4] However, in this systematic review and meta-analysis, a positive trend was observed for mobility when treated by a multidisciplinary rehabilitation program but not for unplanned hospital readmission. Although most of the studies continued rehabilitation programs from 1 care setting to another, it was often not as coordinated as in a transitional care system. Transitional care is effective at reducing hospital readmission rates when the care continues between healthcare settings and contains elements of care coordination, communication between primary care and hospitals, and includes intensive follow-up after hospital discharge.[49,50] Only 4 of the included studies described a transitional care system including the effective elements, of which only 2 reported the hospital readmission outcome.[33,35] This could explain

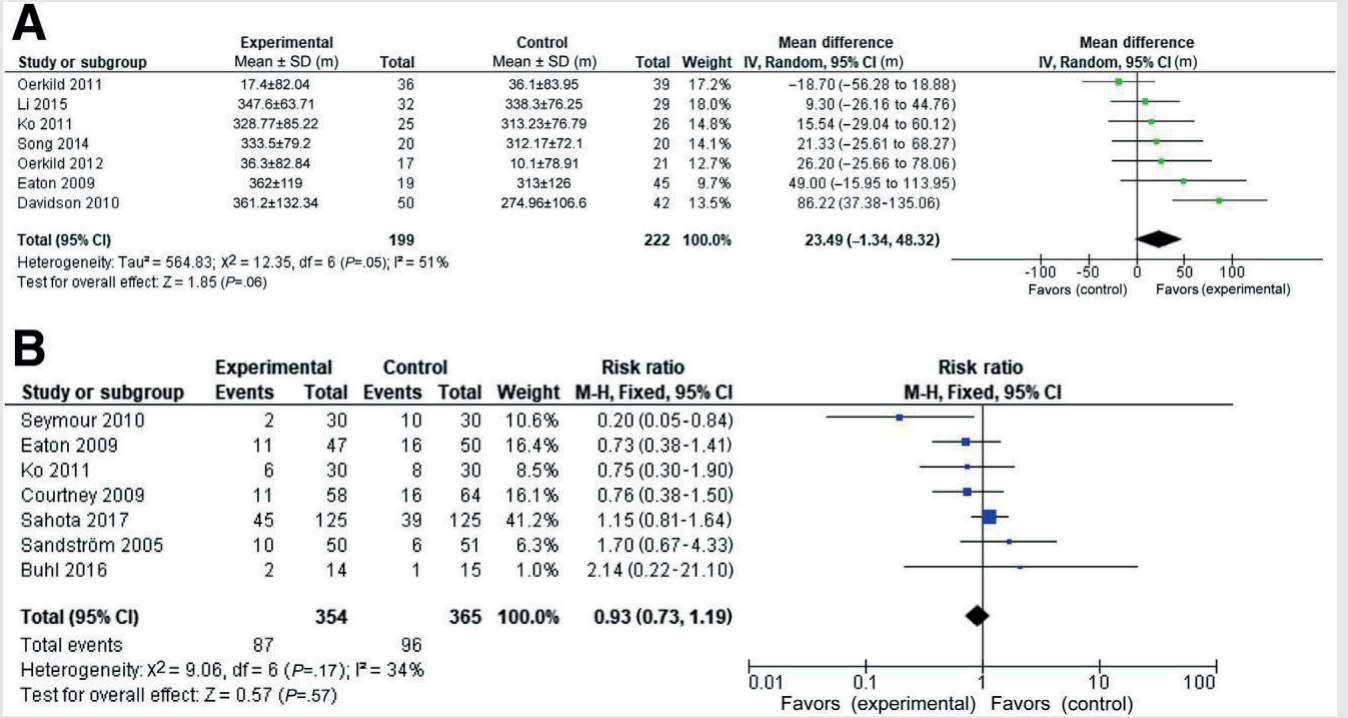

Figure 3. (A) Meta-analysis mobility (6MWD in meters) at 3 months after hospital discharge. (B) Meta-analysis unplanned hospital readmission within 3 months after hospital discharge.

the positive trend for mobility in this meta-analysis but not for unplanned hospital readmission rates.

A difference of 23 m in the 6MWD test was considered to be clinically relevant according to Bohannon *et al*,[51] who defined clinical relevance as a change of 14–30.5 m against a background of 295–551 m on the 6MWD test. In the sensitivity analysis, omitting the study of Oerkild *et al*.[45] increased the pooled effect on the 6MWD test from 23 to 31 m. Their intervention was compared with usual care, which was outpatient cardiac rehabilitation. This could partly explain the favorable effect in the control group in contrast to the results obtained by other studies in the meta-analysis and thus the improved effect in the meta-analysis upon omission. Omitting the study of Davidson *et al.*[41] resulted in a smaller pooled effect (MD: 10.76), which could be because the study was stopped prematurely and could have led to the wrong conclusions being drawn because of the smaller sample size.[41]

Omitting the study of Sahota[35] in the meta-analysis on unplanned hospital readmission caused the RR to change from 0.93 to 0.77, whereas omitting the study by Seymour[39] changed the preventive effect from 7% to a 2% increased risk. Sahota included an older and frailer patient population with a higher risk of adverse events, which could have influenced the effect.[35] Another contributing factor could be their large sample size when compared to other included studies, which may have led to this study having a greater influence in the meta-analysis. The small sample size of the Seymour study (intervention group: 30; control group: 30) could have led to an overestimation of the effect.[46]

Most of the included studies focused on specific patient populations, such as patients with cardiac and pulmonary diseases[36-46]; however, 4 studies were performed in general patient populations.[32-35] The content of the rehabilitation programs provided in the studies did not differ much between these populations. All interventions consisted of multiple rehabilitation components, such as exercise and education. Nevertheless, the execution of the rehabilitation components varied between the studies or a thorough description of the content was missing in the manuscript; for example, 1 study failed to use the frequency, intensity, time, and therapy criteria to report items in the description of an exercise intervention.[52] Another study did not report the provided intervention according to the TIDieR guidelines for the reporting of interventions.[30] Using the TIDieR guidelines would make the aggregation and comparison of interventions possible on a level of what was provided by whom, how, where, and when. Therefore it was not feasible to analyze the effectiveness of the different components of the intervention, neither was it possible to perform subanalysis on the dose of the intervention.

Nutritional status is an important factor for optimal physical training results and physical recovery (eg, intake of proteins). It is also relevant in acutely hospitalized patients where 52% experience malnutrition[1]; however, dieticians were only involved in 4 of the included studies.[32,41,44,45] Gill *et al*.[12] stated that

exercise programs should comprise balance exercises, muscle strengthening, transfer exercises, and functional exercises to be beneficial in frail older patients. The studies utilized in this manuscript mainly focused on intensity training and 4 of these were combined with strengthening exercises.[37-39,41] Only 2 studies[33,34] combined all the components of exercise training as suggested by Gill and 1 study[35] described an individual approach. This could have influenced the effect in the meta-analysis.

The location of the intervention in the included studies varied between an outpatient setting, a community-based at home setting, and a temporary inpatient setting (eg, a skilled nursing facility). The influence of the rehabilitation location and environment on the outcome was studied previously and showed no significant effects in traditional center-based inpatient approaches and alternative models such as telehealth and home-based rehabilitation.[53-55]

Strengths and limitations

To the best of the author's knowledge, this is the first systematic review to examine the effectiveness of multidisciplinary rehabilitation in an OOHS in older patients after they are discharged from hospital following an acute illness. Three large international databases (Medline OVID, Embase OVID, and CINAHL) were screened. No publication was excluded based on language due to the availability of English abstracts in these databases. Although most of the international publications were covered in these databases, some specific language publications may possibly have been omitted due to their only being available in databases such as Bireme (a Latin American database). The included studies were all randomized trials. The blinding issues in patients and personnel in the included studies were caused by the nature of the intervention; however, the quality of the included studies was limited due to a lack of blinding of the outcome assessors. This could have introduced bias and could have led to an overestimation of the effects. Different studies used different types of outcome measures to report mobility. Therefore, it was not possible to include all studies in the meta-analysis. The sensitivity analysis in both meta-analyses provided an insight into the contribution of each study, in the estimate of the true value of unplanned hospital readmissions (fixed effect) or the mean of all possible values for the 6MWD (random effect).

Implications for further research

Many studies focus on a diagnosis-based population despite other factors (ie, level of frailty) playing an important role in determining rehabilitation needs.[8] The medical diagnosis often correlates badly with the disease-related functional consequences. These needs may be better determined through a comprehensive geriatric assessment that focuses on a patient's disease, geriatric condition, functional status, and the patient's own preferences rather than being determined

solely from a disease perspective. This would create a more homogeneous patient population and enable tailored rehabilitation interventions to be tested. In addition, patients also transfer back and forth between healthcare settings. Therefore, transitional care rehabilitation interventions should be considered to ensure continuity of care and reduce adverse outcomes such as hospital readmissions.[49,50]

Furthermore, a clear definition of functional capacity is often lacking in rehabilitation intervention manuscripts and should be integrated according to the definition of the International Classification of Functioning. Functional capacity is often described when only physical performance is reported instead of the 3 domains of *functioning: body function, activities*, and *involvement in life situations*.[24] A clear definition and a detailed description of the intervention according to the frequency, intensity, time and therapy criteria and TIDieR guidelines would help to improve comparability and determine the effectiveness of each component of the intervention.

Conclusion

This review shows that OOHS-based multidisciplinary rehabilitation leads to improved mobility in older patients (aged ≥ 65) 3 months after discharge from hospital following an acute illness. However, this type of rehabilitation is not associated with a lower risk of unplanned hospital readmission within 3 months of hospital discharge. Nevertheless, the wide 95% CI and the instability of the pooled effect on mobility illustrated by the sensitivity analysis indicate that the evidence is not robust.

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APPENDIX 1. SEARCH STRATEGY

	Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present> Search date: 22 February 2018
#	**Searches**
1	exp aging/ or exp aged/ or exp nursing homes/ or homes for the aged/ or frail elderly/
2	(older person? or older patient? or seniors or senior citiz* or elder or elders or elderly or geriatric* or frailty or postmenopausal women or community-dwelling or nursing home? or resident* or old* people or old* person? or old* patient? or old* client?).ab,kf,ti.
3	(geriatr* or age or aging or elderl*).jw.
4	or/1-3 [geriatric]
5	rehabilitation/ or "activities of daily living"/ or exp exercise therapy/ or telerehabilitation/ or rehabilitation centers/ or geriatric assessment/
6	(rehabilitation or exercise? oradl or iadl or (daily adj2 (activit* or living or function*)) or barthel index or katz index or alds or amsterdam linear or living indepently or living alone or (function* adj3 (status or capacit* or physical or decline or disabil*)) or geriatric assessment).ab,kf,ti.
7	or/5-6 [rehabilitation]
8	4 and 7 [geriatric rehabilitation]
9	home care services/ or outpatients/ or patient compliance/
10	(nursing facilit* or home based or patient home or (home adj2 care) or outpatient or transitional care or home visit or (intervention adj3 home?) or (patient? adj3 complian*)). ab,kf,ti.
11	or/9-10 [outpatient care]
12	hospitalization/ or patient admission/ or patient readmission/
13	(hospital* or admission or readmission or discharge or centre based or center based). ab,kf,ti.
14	12 or 13 [hospitalization]
15	(acute* or rehabilitation).ab,kf,ti.
16	rehabilitation.fs.
17	15 or 16 [acute]
18	pulmonary disease, chronic obstructive/ or exp myocardial infarction/ or exp chest pain/ or heart aneursym/ or exp endocarditis/ or exp heart failure/
19	(copd or chronic obstructive or pulmonary rehabilitation or myocardial infarction or cardiac rehabilitation or (pain adj3 chest) or angina pectoris or heart aneurysm? or cardiac aneurysm? or endocarditis or heart failure or myocardial failure or cardiac failure).ab,kf,ti.
20	18 or 19 [acute specific disorders]
21	14 and 17
22	14 and 20
23	acute hospital*.ab,kf,ti.

24	((acute* adj2 ill*) or (acute adj2 disease?) or (acute adj2 assessment units) or (acute* adj2 admi*) or (acute* adj2 readmi*) or (acute adj2 care) or (stabiliz* adj4 condition) or (stabiliz* adj2 patient?)).ab,kf,ti.
25	or/21-24 [acute hospitalization]
26	and/8,11,25
27	animals/ not humans/
28	26 not 27
29	(trial? or stud* or blind* or random* or experimental or control or placebo?).ab,kf,ti.
30	comparative study/
31	(clinical study or clinical trial or controlled clinical trial or randomized controlled trial).pt.
32	exp clinical trials as topic/
33	or/29-32 [RCT's]
34	28 and 33
35	remove duplicates from 34

	Ovid Embase Classic+Embase <1947 to 2018 February 22> Search date: 22 February 2018
#	**Searches**
1	exp aging/ or exp aged/ or nursing home/ or exp elderly care/
2	(older person? or older patient? or seniors or senior citiz* or elder or elders or elderly or geriatric* or frailty or postmenopausal women or community-dwelling or nursing home? or resident* or old* people or old* person? or old* patient? or old* client?).ab,kw,ti.
3	(geriatr* or age or aging or elderl*).jx.
4	or/1-3 [geriatric]
5	rehabilitation/ or exp exercise/ or daily life activity/ or exp kinesiotherapy/ or rehabilitation center/ or geriatric assessment/
6	(rehabilitation or exercise? oradl or iadl or (daily adj2 (activit* or living or function*)) or barthel index or katz index or alds or amsterdam linear or living indepently or living alone or (function* adj3 (status or capacit* or physical or decline or disabil*)) or geriatric assessment).ab,kw,ti.
7	or/5-6 [rehabilitation]
8	4 and 7 [geriatric rehabilitation]
9	home care/ or outpatient/ or outpatient care/ or outpatient department/ or patient compliance/
10	(nursing facilit* or home based or patient home or (home adj2 care) or outpatient or transitional care or home visit or (intervention adj3 home?) or (patient? adj3 complian*)). ab,kw,ti.
11	or/9-10 [outpatient care]
12	hospitalization/ or hospital admission/ or hospital discharge/ or hospital readmission/
13	(hospital* or admission or readmission or discharge or centre based or center based). ab,kw,ti.

14	12 or 13 [hospitalization]
15	(acute* or rehabilitation).ab,kw,ti.
16	rh.fs.
17	15 or 16 [acute]
18	chronic obstructive lung disease/ or exp heart infarction/ or thorax pain/ or heart aneursym/ or exp endocarditis/ or exp heart failure/
19	(copd or chronic obstructive or pulmonary rehabilitation or myocardial infarction or cardiac rehabilitation or (pain adj3 chest) or angina pectoris or heart aneurysm? or cardiac aneurysm? or endocarditis or heart failure or myocardial failure or cardiac failure).ab,kw,ti.
20	18 or 19 [acute specific disorders]
21	14 and 17
22	14 and 20
23	acute hospital*.ab,kw,ti.
24	((acute* adj2 ill*) or (acute adj2 disease?) or (acute adj2 assessment units) or (acute* adj2 admi*) or (acute* adj2 readmi*) or (acute adj2 care) or (stabiliz* adj4 condition) or (stabiliz* adj2 patient?)).ab,kw,ti.
25	or/21-24 [acute hospitalization]
26	and/8,11,25
27	(animal/ or animal experiment/ or animal model/ or nonhuman/ or rat/ or mouse/ or (rat or rats or mouse or mice).ti.) not human/
28	26 not 27
29	(trial? or stud* or blind* or random* or experimental or control or placebo?).ab,kw,ti.
30	exp controlled clinical trial/ or clinical study/ or "clinical trial (topic)"/ or comparative study/
31	or/29-30 [RCT's]
32	28 and 31
33	remove duplicates from 32

	CINAHL Plus with Full Text **Search date: 22 February 2018**
#	**Query**
S23	s7 and s10 and s21
S22	7 AND S10 AND S21
S21	S15 OR S19 OR S20
S20	AB (acute hospital* OR (acute* NEAR/2 ill*) or (acute NEAR/2 disease?) or (acute NEAR/2 assessment units) or (acute* NEAR/2 admi*) or (acute* NEAR/2 readmi*) or (acute NEAR/2 care) or (stabiliz* adj4 condition) or (stabiliz* NEAR/2 patient?)) OR TI (acute hospital* OR (acute* NEAR/2 ill*) or (acute NEAR/2 disease?) or (acute NEAR/2 assessment units) or (acute* NEAR/2 admi*) or (acute* NEAR/2 readmi*) or (acute NEAR/2 care) or (stabiliz* adj4 condition) or (stabiliz* NEAR/2 patient?)) OR SU (acute hospital* OR (acute* NEAR/2 ill*) or (acute NEAR/2 disease?) or (acute NEAR/2 assessment units) or (acute* NEAR/2 admi*) or (acute* NEAR/2 readmi*) or (acute NEAR/2 care) or (stabiliz* adj4 condition) or (stabiliz* NEAR/2 patient?))

S19	S13 AND S18
S18	S16 OR S17
S17	AB (copd or chronic obstructive or pulmonary rehabilitation or myocardial infarction or cardiac rehabilitation or (pain NEAR/2 chest) or angina pectoris or heart aneurysm? or cardiac aneurysm? or endocarditis or heart failure or myocardial failure or cardiac failure) OR TI (copd or chronic obstructive or pulmonary rehabilitation or myocardial infarction or cardiac rehabilitation or (pain NEAR/2 chest) or angina pectoris or heart aneurysm? or cardiac aneurysm? or endocarditis or heart failure or myocardial failure or cardiac failure) OR SU (copd or chronic obstructive or pulmonary rehabilitation or myocardial infarction or cardiac rehabilitation or (pain NEAR/2 chest) or angina pectoris or heart aneurysm? or cardiac aneurysm? or endocarditis or heart failure or myocardial failure or cardiac failure)
S16	(MH "Pulmonary Disease, Chronic Obstructive+") or (MH "Myocardial Infarction+") or (MH "Chest Pain+") or (MH "Coronary Aneurysm") or (MH "Endocarditis+") or (MH "Heart Failure+")
S15	S13 AND S14
S14	SU (acute* or rehabilitation)
S13	S11 OR S12
S12	AB (hospital* or admission or readmission or discharge or centre based or center based) OR TI (hospital* or admission or readmission or discharge or centre based or center based) OR SU (hospital* or admission or readmission or discharge or centre based or center based)
S11	(MH "Hospitalization+") OR (MH "Patient Admission") OR (MH "Readmission")
S10	S8 OR S9
S9	AB (nursing facilit* or home based or patient home or (home NEAR/1 care) or outpatient or transitional care or home visit or (intervention NEAR/2 home?) or (patient? NEAR/2 complian*)) OR TI (nursing facilit* or home based or patient home or (home NEAR/1 care) or outpatient or transitional care or home visit or (intervention NEAR/2 home?) or (patient? NEAR/2 complian*)) OR SU (nursing facilit* or home based or patient home or (home NEAR/1 care) or outpatient or transitional care or home visit or (intervention NEAR/2 home?) or (patient? NEAR/2 complian*))
S8	(MH "Home Nursing") OR (MH "Home Rehabilitation+") OR (MH "Home Health Care+") OR (MH "Outpatients") OR (MH "Outpatient Service")
S7	S3 AND S6
S6	S4 OR S5
S5	AB (rehabilitation or exercise? oradl or iadl or (daily NEAR/1 (activit* or living or function*)) or barthel index or katz index or alds or amsterdam linear or living indepently or living alone or (function* NEAR/2 (status or capacit* or physical or decline or disabil*)) or geriatric assessment) OR TI (rehabilitation or exercise? oradl or iadl or (daily NEAR/1 (activit* or living or function*)) or barthel index or katz index or alds or amsterdam linear or living indepently or living alone or (function* NEAR/2 (status or capacit* or physical or decline or disabil*)) or geriatric assessment) OR SU (rehabilitation or exercise? oradl or iadl or (daily NEAR/1 (activit* or living or function*)) or barthel index or katz index or alds or amsterdam linear or living indepently or living alone or (function* NEAR/2 (status or capacit* or physical or decline or disabil*)) or geriatric assessment)

S4	(MH "Physical Therapy+") OR (MH "Rehabilitation") OR (MH "Recreational Therapy") OR (MH "Telerehabilitation") OR (MH "Activities of Daily Living+") OR (MH "Therapeutic Exercise+") OR (MH "Rehabilitation Centers+") OR (MH "Geriatric Assessment+")
S3	S1 OR S2
S2	AB (older person? or older patient? or seniors or senior citiz* or elder or elders or elderly or geriatric* or frailty or postmenopausal women or community-dwelling or nursing home? or resident* or old* people or old* person? or old* patient? or old* client?) OR TI(older person? or older patient? or seniors or senior citiz* or elder or elders or elderly or geriatric* or frailty or postmenopausal women or community-dwelling or nursing home? or resident* or old* people or old* person? or old* patient? or old* client?) OR SU (older person? or older patient? or seniors or senior citiz* or elder or elders or elderly or geriatric* or frailty or postmenopausal women or community-dwelling or nursing home? or resident* or old* people or old* person? or old* patient? or old* client?)
S1	(MH "Aged+")

Chapter 10

Feasibility of home-based cardiac rehabilitation in frail older patients: a clinical perspective

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ABSTRACT

BACKGROUND: Home-based cardiac rehabilitation (CR) is an attractive alternative for frail older patients who are unable to participate in hospital-based CR. Yet, the feasibility of home-based CR provided by primary care physiotherapists (PTs) to these patients remains uncertain.

OBJECTIVE: To investigate physiotherapists' (PTs) clinical experience with a guideline-centered, home-based CR protocol for frail older patients.

METHODS: A qualitative study examined the home-based CR protocol of a randomized controlled trial. Observations and interviews of the CR-trained primary care PTs providing home-based CR were conducted until data saturation. Two researchers separately coded the findings according to the theoretical framework of Gurses.

RESULTS: The enrolled PTs (n=8) had a median age of 45 years (IQR 27-57), and a median work experience of 20 years (IQR 5-33). Three principal themes were identified that influence protocol-adherence by PTs and the feasibility of protocol-implementation: 1. feasibility of exercise testing and the exercise program; 2. patients' motivation and PTs' motivational techniques; 3. interdisciplinary collaboration with other healthcare providers in monitoring patients' risks.

CONCLUSION: Home-based CR for frail patients seems feasible for PTs. Recommendations on the optimal intensity, use of home-based exercise tests and measurement tools, and interventions to optimize self-regulation are needed to facilitate home-based CR.

INTRODUCTION

Comprehensive cardiac rehabilitation (CR) is recommended in elderly patients who experienced a hospital-admission for cardiovascular diseases (CVD).[1, 2] Likewise, the benefits of CR in frail older populations have been extensively researched and documented.[3-6] Frailty may be defined as a syndrome of physiological decline characterized by marked vulnerability to adverse health outcomes such as hospital readmission and mortality.[7, 8] Consequently, performing CR in the frail elderly patient with CVD is met with distinctive challenges,[5, 6] like low participation rates (i.e., 20-30%) in hospital-based CR because of a lack of transportation facilities, the patient's perception about the worth of the rehabilitation program, and their apprehensions regarding the risks of exercising.[9]

To mitigate these reservations, home-based CR is gradually becoming a good alternative to hospital-based CR to effectively improve the physical functioning of low-to-moderate risk (non-frail) patients.[3, 10] Yet, the feasibility of a home-based CR program for frail older patients from a primary care physiotherapist's perspective is uncertain. The current CR guidelines for physiotherapists (PTs) are largely based on researches involving non-frail patients and not according to the home situation, besides a lack of specific recommendations for modifying CR in the presence of frailty and comorbidities.[1, 2, 11-14] Therefore, the current study aimed to investigate physiotherapists' (PTs) clinical experiences in light of the present guidelines and the home-based CR protocols followed for frail older patients.

METHODS

Study design

The conduct of this qualitative study involved observing primary care PTs who performed home-based CR in frail older patients, followed by semi-structured personal face-to-face interviews. The home-based CR component was a part of a larger randomized trial, the 'Cardiac Care Bridge (CCB)' in collaboration with a teaching and five other regional hospitals in and around Amsterdam.[15, 16]

The Medical Ethical Review Board of the Amsterdam University Medical Centre approved the study protocol for the CCB (MEC2016_024). All participants provided written informed consent before participating. This manuscript is reported according to the COREQ checklist for reporting qualitative research.[4]

Home-based CR in the CCB intervention

The CCB trial, conducted from June 2017 to March 2020, evaluates the effects of a transitional care program to prevent hospital readmission and mortality in frail, elderly patients with CVD (see Figure 1). The detailed study design and outcomes

of the CCB study have been described in a previously published report.[15, 16] Briefly, the CCB program is an integrated transitional-care program from the hospital to the patients' home and is composed of three components: 1) case management, 2) disease management, and 3) home-based PT-led CR. Component 1 consisted of an in-patient comprehensive geriatric assessment-based integrated care plan implemented during the hospital stay and followed-up at home. In component 2, cardiac and community nurses coordinated with an affiliated pharmacist to carry out medication-checks, monitor medical parameters, and administer lifestyle coaching. In the last component, the PTs focused on facilitating participation in activities of daily living, performing regular exercises, monitoring weight, heart rate, and blood pressure, besides educating the patient striving for an active lifestyle.

The CCB-integrated-home-based-CR protocol was based on the Dutch cardiac rehabilitation guidelines for PTs,[1, 2] and was adapted for the CCB by two skilled PTs (MT, FdH) with more than 5 years of experience in the field of cardiopulmonary rehabilitation. The principal modifications done to the CR-guidelines include - a substitution of regular exercise field tests, namely the six-minute walk test and the 6-10 repetition maximum strength test, with a home-executable version as a two-minute step test and the 30-second chair-stand test,[17] respectively; elaborate directions for increasing exercise intensity and physical activity in old patients with CVD; specific instructions on when and how to communicate and collaborate with the community nurse; and how to act in the case of an emergency in the home setup. The CCB-CR protocol also consisted of recommendations for goal setting, exercise intensity, and exercise forms tailored for these patients (see Figure 1). Following discharge from the hospital, the first 3 weeks of home-based CR had 2 sessions/week which focused on familiarization with exercise at Borg RPE (Borg Rating of Perceived Exertion) of 10-11 points,[18] and gain in muscle strength and increasing participation in activities of daily living (ADL) as indicated by an increase from 250 metabolic equivalents (METs) in the first week to 350 METs by week-3. In the following weeks, week 4-6, the prescribed sessions were once-a-week, ADL performance was further increased by 50 METs/week to achieve 500 METs by week-6, and exercise intensity was raised to Borg-RPE 12-13 indicating improved functional capacity, and if possible, the aerobic capacity.

Patient population

Patients aging $\geq$70 years falling in the high-risk category of functional loss (measured by the Dutch Safety Management System (DSMS) screening instrument) and admitted for more than 48 hours to the cardiology or cardiac surgery departments of the participating hospitals, were eligible for participation in the CCB study. The DSMS screens for four geriatric conditions - limitation in Activities of Daily Living (ADL), falls, malnutrition, and the risk of delirium. Patients are considered at high risk of functional decline if they are 70-79 years old with

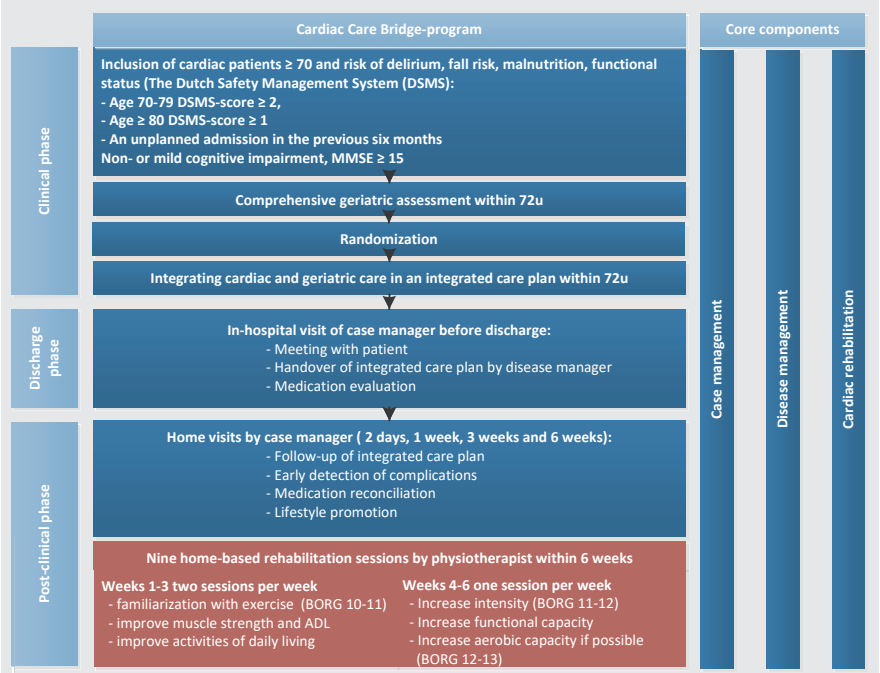

Figure 1. Overview of the CCB program including home-based cardiac rehabilitation
Legend: Blue depicts the nurse coordinated care, red describes the exercise components of home-based cardiac rehabilitation by physiotherapists. In addition, PT coached on active lifestyle and monitored complications.
Abbreviations: DSMS = Dutch Safety Management System, BORG = Borg scale of perceived exertion

> 2 geriatric conditions, or aged > 80 years with > 1 geriatric condition. The exclusion criteria followed were - failure to provide informed consent and follow instructions owing to severe cognitive impairment (Mini-Mental State Examination, MMSE < 15), known case of congenital heart disease, a life expectancy of ≤ 3 months, those transferring to another hospital or nursing home, and unable to communicate in the Dutch language. The CCB-research nurses collected baseline data for patients during their hospital admission.[15]

Physiotherapists

PTs enrolled in the CCB study were either members of a local PT network 'Lung Rehabilitation Network, Amsterdam (LoRNA)', affiliated with homecare organizations or were experienced in the field of rehabilitation for CVDs along with the relevant educational qualification necessary to work with CR. Additionally, they had some experience with home-based care and treatment for older patients with comorbidities. These PTs received five additional training sessions on

cardiac disease and frailty, and on the CR protocol followed in the CCB study. The training sessions covered the following items - pathology of congestive heart failure, adaptations of exercise frequency, intensity, type, and timing (FITT-factors) according to comorbidity and frailty, polypharmacy, motivational interviewing, when and how to collaborate with CCB community nurses, and practical application of the study protocol.[15] The PTs in the CCB study were then approached for the current qualitative study after they had completed home-based CR in at least one patient.

Data collection and measurements

The process of data collection consisted of observations and interviews performed by MT, a PT researcher with experience in CR and trained in performing qualitative research. The observations and interviews were structured according to the Gurses' framework (see Appendix 1) on compliance to evidence-based guidelines.[19]

The observations regarding PTs' adherence/non-adherence to the CCB-CR protocol and identifying the potential barriers and facilitators were executed in weeks 2-5 of the treatment period. MT recorded patient's characteristics (e.g. present comorbidity, motivation), provider's characteristics (e.g. displayed habits), and the system characteristics (e.g. serviceability of the patient registry, used exercise materials, and measurement instruments) on the observation form (see Appendix 2).

Following an observation, MT interviewed the PT about their experiences regarding the feasibility of the home-based CCB-CR protocol and perceived barriers and facilitators. Similar to the observation-phase, demographic characteristics (age, gender, work experience, and education) for all PTs were recorded The interview topics (Appendix 3) based on Gurses' framework were - *provider characteristics* (e.g. knowledge of the content of the CCB-CR protocol), *guideline characteristics* (e.g. compatibility of the CCB-CR protocol with daily practice, experienced complexity of the protocol), *system characteristics* (e.g. experienced workload, work environment), and *implementation characteristics* (e.g. involvement of their organization's management).[19] Each interview lasted approximately 45 minutes and all proceedings were audio-recorded and transcribed ad verbum. Data were collected until data saturation (when the same information is repeated) was reached.[20]

Data analysis

First, two researchers (MT and LV) independently coded (coding category based on Gurses' framework, see Appendix 1) the extended field notes of the observations and 'ad verbatim' transcriptions of the interviews in Max-QDA 12.[19] Subsequently, axial and selective coding was used to compare categories and identify the central themes related to the feasibility of the CCB-CR protocol.21

The examiners added newly-identified categories to the observation and interview forms after each analysis, wherever applicable. Disagreements between the two researchers regarding the coding categories were settled by discussion. Descriptive statistics (mean and standard deviation SD, median and interquartile range IQR or percentages and range) for the baseline participant and patient characteristics were computed and tabulated.

RESULTS

Study population

Data saturation was reached after the sixth and confirmed in the seventh and eighth observation and interview. The eight observed and interviewed PTs (median age 45 years, IQR 27-57) had a median work experience of 20 years (IQR 5-33) (Table 1). Four PTs were skilled in CR and seven had practiced geriatric care. All eight PTs had more than one year of experience in home-based treatment, and seven had previously worked in multidisciplinary teams. All PTs had treated at least one patient in the CCB before observations and interviews took place. The cumulative number of patients treated by the PTs at the time of observations was 21.

The average age of patients in the observed treatment sessions was 81 ± 8.2 years, of which five were males (Table 2). The majority of the patients had at least two geriatric conditions (out of limitations in Activities of Daily Living (ADL), falls, malnutrition, and risk of delirium) according to the DSMS screening. All patients were diagnosed with chronic heart failure and the cause for hospital admissions were decompensated congestive heart failure (n=5), endocarditis (n=1), angina pectoris (n=1), and pacemaker implantation (n=1). The following comorbidities were reported - diabetes mellitus (n=4), peripheral arterial disease (n=2), chronic obstructive pulmonary disease (n=1), knee osteoarthritis (n=1), stroke (n=1), and renal failure (n=2).

Table 1. Characteristics physiotherapists

Therapist (n=8)	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**Total (Median)**
Age (years)	23	64	25	56	54	58	57	28	45 (IQR 27-57)
Gender (m/f)	f	m	f	f	f	f	f	m	Male: 25%
Work experience (years)	2	38	2	32	10	35	29	6	20 (IQR 5-33)
Specific work experience (More than one year)									
Cardiac Rehabilitation (CR)	-	-	-	-	+	+	+	+	n=4 (50%)
Geriatrics	+	+	-	+	+	+	+	+	n=7 (87.5%)
Home-based treatment	+	+	+	+	+	+	+	+	n=8 (100%)
Working in multidisciplinary team	+	+	-	+	+	+	+	+	n=7 (87.5%)
Education on CR	-	-	-	-	+	MSc	+	-	n=3 (37.5%)
Education Geriatrics	-	+	-	-	MSc	MSc	-	-	n=3 (37.5%)
Other relevant education	COPD	Home care	-	Home care	-	COPDPAD MI	COPD	-	

Abbreviations: CR = cardiac rehabilitation; COPD = chronic obstructive pulmonary disease; PAD = peripheral artery disease; MI = motivational interviewing; MSc = Master of Science level; IQR = Interquartile range; n=number; - = no; + = yes

Table 2. Baseline characteristics of the patients (n=8) in the observed treatment sessions

Characteristic	Mean (SD) or n (%)
Age	82.8 (SD 7.8)
Gender (male)	5 (62.5%)
Nationality	
Dutch	6 (75%)
Suriname	1 (12.5%)
German	1 (12.5%)
Highest Education	
Primary school	1 (12.5%)
Secondary school	2 (25%)
Lower professional education	3 (37.5%)
Higher professional education or university	2 (25%)
Screening instrument for frail older adults of the Dutch Safety Management System (DSMS)	
Score 1	1 (12.5%)
Score 2	5 (62.5%)
Score 3-4	2 (25%)
Mini-Mental State Examination (MMSE)	25.1 (SD 2.9)
Reason hospital admission	
Heart failure	5 (62.5%)
Atrial Fibrillation	1 (12.5%)
Endocarditis	1 (12.5%)
Unstable angina	1 (12.5%)
Number of medicines	10.3 (SD 1.5)
Charlson comorbidity index	
0 comorbidities	2 (25%)
1-2 comorbidity	3 (37.5%)
3-4 comorbidities	3 (37.5%)

SD, standard deviation; n, number
DSMS: 1 point is scored for each present geriatric condition (max 4): limitations in Activities of Daily Living (ADL), falls, malnutrition and risk of delirium.
MMSE: score < 24 indicates cognitive impairment

Adherence and feasibility themes

Table 3 summarizes the reasons reported by PTs for adherence or non-adherence to the CCB-CR protocol.[19] Mean intercoder agreement in the analyses of the combined observations and interviews was 94.5% (range 90-100%). Our analyses revealed three sets of themes that influenced the practicability of the protocol. The subsequent paragraphs elaborate on each theme structured according to the system, provider, guideline, implementation, and patient characteristics.[19] Briefly, the first theme encompasses the feasibility of exercise testing and the exercise program. The second theme covers the motivational aspects of home-based CR, consisting of both patient motivation or self-regulation and the use of motivational techniques by the PT. The third theme elucidates on the interdisciplinary-collaboration and task-division between the community nurse and other healthcare providers in monitoring the patients' health status and risks of hospital readmission.

Theme 1. Feasibility of exercise testing and the exercise program according the CCB-CR protocol

System characteristics

Most PTs reported the commonest barrier to be the administration of exercise tests and the time consumed in repeated blood pressure measurements. It was further observed that sufficient availability of time facilitated the application of the Borg-RPE scale and METs table, supplemented with the availability of practical tools (like dumbbells, mobile sitting bicycle) and the PT's experience in using the equipment, encouraged the PT to prescribe higher intensity exercises. As a facilitator to adhere to the CCB-CR protocol, some PTs reported a positive culture for change in the organization, (quote 1 (Q1)).

> *(Q1) "Their (the management's) opinion is that you should improve yourself every time by following education or by any way possible. So, they create space to do this (e.g. for participation in the CCB intervention)." (PT C)*

Provider characteristics

As facilitators to adhere to the CCB-CR protocol, most PTs reported an increase in the patients' physical activity levels (Q2) resulted in a positive attitude and expectations of better outcomes from the home-based CR. All PTs reported a positive attitude to participate in research and displayed sufficient knowledge of the CCB-CR protocol during the observations.

> *(Q2)"Nine out of ten patients sit too much and that won't help them. So, I am convinced that the intervention can prevent hospital readmissions." (PT C)*

Table 3. Reasons for physiotherapists' adherence or non-adherence to the CCB Cardiac Rehabilitation protocol

Characteristics Gurses	Adherence	Non-adherence
System characteristics	- Positive culture for change - Pre-existing network for organized teamwork (e.g. community care organization) - Availability of measurement instruments (e.g. for blood pressure, oxygen saturation)	- Task: high workload, time restrictions - Tools: Manageability of paper care file - No functioning communication transfer system from hospital to physiotherapist (e.g. secure email system)
Provider characteristics	- Positive attitude and outcome expectancies intervention - Motivation to participate in research - Normative beliefs that measurements should be performed properly - Familiarity with tools (BORG, METs) - Knowledge of content CCB exercise protocol	- Usual habits of practice with frail elderly - Pre-existent high level of expertise with frail elderly - Low outcome expectancies of parts of the program (e.g., application of METs or aerobic exercise)
Guideline characteristics (provided exercise program)	- Low complexity of exercise program - Observability of patient improvements	- Limited compatibility with patients - Limited time for try-out (only nine sessions of 30 minutes)
Implementation characteristics	- Intervention supported by direct leadership - Financial support for the intervention	- Limited financial support for long term implementation - More time needed for treatment and traveling than was financed
Patient characteristics	- High level of motivation to be independent - Higher activity level before hospital admission	- Comorbidities: diabetes, wounds, gout, COPD, anemia, knee osteoarthritis, kidney failure, stroke, psychiatric condition - Low level of motivation - Sedentary lifestyle before hospital admission

Abbreviations: BORG = Borg scale of perceived exertion ranging from 6-20, MET = Metabolic Equivalents Table, COPD = Chronic Obstructive Pulmonary Disease

All PTs adhered to the suggested exercise tests (two-minute step test and 30-second chair stand test) and described them as feasible for evaluating patients' strength and endurance.[17, 22] Most PTs did not use the table with metabolic equivalents of tasks (METs), which was intended to provide insight into patients' daily activities energy expenditure, frequently.[23] Additionally, most PTs reported a lack of knowledge on how to calculate METs and their non-applicability

to frail patients and preferred the 'patient-specific functioning scale' or the activity log.[24] Likewise, most PTs reported difficulty in applying the Borg-RPE scale of perceived exertion to estimate exercise intensity due to the patients' limited ability to discriminate between the scale's levels (Q3).[18]

> *(Q3)"With this lady, I didn't even try to explain the BORG properly, because it just costs too much time and energy in contrast to what it yields. That is something you judge within two times when they indicate the same score." (PT E)*

It was observed that all PTs prescribed functional exercises (e.g. walking stairs) as recommended in the CCB-CR protocol. All PTs reported that their objective of home-based CR was not an improvement in cardiovascular fitness alone, but encouraging the patients to improve their physical functioning and self-management.

Guideline characteristics

All PTs reported that adherence to the CCB-CR protocol was facilitated by the simplicity of the protocol (Q4), except for the description of the METs. Some PTs also reported a need for more examples of home exercises.

> *(Q4) "Well, I think the protocol, which can be found in the CCB file online, is really quite clear. I mean considering its complexity. I don't think it is very complex." (PT D)*

Patient characteristics

A reported barrier for exercise therapy was the presence of a psychiatric condition. To adapt the exercise therapy to the patient's characteristics, most PTs indicated that they adjusted the following FITT-factors - training intensity because chronic heart failure limited the patient's exercise capacity; exercise type and intensity if comorbidities limited the exercise possibilities (e.g. gout); and timing, i.e., postponing exercise in kidney failure. Some PTs were able to prescribe aerobic training (e.g. walking or cycling > 5 minutes) to some of their patients in the last two weeks of the treatment period. Exercise intensity could vary between training sessions and no PTs reported any adverse events in patients during or after the exercise sessions.

The researcher did not observe and neither did any PT reported any *implementation characteristics* related to this theme.

Theme 2. Motivational aspects

Provider characteristics

All PTs spent time on motivating patients to increase daily activities and the patients' self-regulation, as instructed in the CCB-CR protocol. PTs used goal setting to match the exercise needs of the patients, like exercising to walk independently to the mailbox. However, some PTs found it difficult to motivate sedentary patients, while it was easier if the patient was self-motivated to be independent in daily activities (Q5). All PTs had to balance the time spent on motivational interviewing and exercise. One PT prioritized patient-coaching over exercise therapy, while some PTs indicated a need for further training in motivational techniques that may be used in older patients with CVD.

> *(Q5) "No, because he is committed, because he really wants to. That is to say: his youngest son is handicapped. And he really wants to be able to independently take a cab to go to his son, and then be able to walk with his walking aid together with his son and go to a restaurant for a cup of coffee. And that is just not possible at this moment." (PT D)*

Further, PTs inspired self-management in patients by spreading CR-sessions over a longer period than the suggested six weeks, asking open-ended questions, and letting the patient formulate their own goals and concrete actions, such as restrictions of fluid intake in congestive heart failure (Q6).

> *(Q6) "How should we approach this? Do you want to do it yourself? Or with a dietician? Or do you want to use a fluid diary?" (PT F)*

Patient characteristics

Some PTs indicated that it was harder to motivate patients for exercise or physical activity if the patient had a sedentary lifestyle or anxiety (Q7). They also reported that two patients had dropped out from physiotherapy because they found the number of care workers visiting them overwhelming.

> *(Q7) "No. I already did it this morning. I'm finished. I'm afraid to end up horizontally."*

No relevant system, guideline, or implementation characteristics for this theme were observed or reported during the PT interviews.

Theme 3. Interdisciplinary collaboration in monitoring health status and risks of readmission

System characteristics

All therapists monitored blood pressure, heart rate, and weight. Some PTs reported that occasionally, the home-care nurses measured and reported the patients' weight, allowing the PT or CCB-community nurse to focus on the interpretation of the measurement outcomes.

All PTs indicated that communication with other caregivers was facilitated through personal interactions (like from the training sessions or joint intake), and having collaboration-agreements with home care organizations. An often reported barrier for inter-professional communication was the absence of an institutional, secured communication system. All PTs preferred to communicate by telephone or email if a situation was urgent, or through the documented patient-log, if less urgent.

Provider characteristics

All PTs said they were more aware of their responsibility in the interdisciplinary team to monitor patients' health status by measuring blood pressure, heart rate, and weight, and reported three potential risk situations for hospital readmission, namely hypertension after medication changes, weight loss (risk of sarcopenia), and weight gain (potential decompensated heart failure) (Q8). Most PTs said they were satisfied with their collaboration with the community and hospital nurses (Q9).

> *(Q8) "I had measured the blood pressure, which was quite low. And then it turned out that she had stopped with a medicine. She didn't really know which one. Luckily, someone from homecare came along and found out which medicine it was." (PT C)*

> *(Q9) "Yes, I really appreciate that (meaning close collaboration with the nurse from the hospital). Because last week I called, because he had a low blood pressure, around 100 (systolic), so that is fine, but he was worried about it. I said: "Well, if it worries you. We discussed dizziness and other signs to monitor and how to respond when this happens…." "Yes, but I do worry about it". ... I said: "Well, let's call." So, I called the hospital. I got her on the phone right away (meaning the cardiac nurse). She said the same as I did. And that, yes, that. He felt understood. And that was really satisfying." (PT F)*

Neither did the researcher observe, or did the PTs report any guideline, implementation, or patient characteristics relevant to this theme 3.

DISCUSSION

The present study efficiently demonstrates that PTs find home-based cardiac rehabilitation (CR) to be feasible in frail older patients with CVD. Accordingly, no adverse events were reported. We identified three main issues that may be targeted for further improvements in home-based CR in these patients - 1) room for personalization of exercise testing and exercise intensity according to patients' capabilities; 2) accounting for patients' motivation and level of self-regulation when formulating activity goals; 3) facilitating interdisciplinary communication in primary care. Through well-executed interviews, PTs reported experienced leadership as a facilitator and timing issues as an important barrier for the implementation of home-based CR. Our study is a first step toward offering frail older patients with CVD an alternative to traditional hospital-based CR, and the results may aid in developing a personalized, home-based CR program for this population.

We observed sufficient PT-reported CR-content acceptance and satisfactory levels of PT protocol adherence, ascertaining the feasibility of our home-based CR program. Based on our results and supported by the current literature, the guidelines for exercise prescription should, ideally, provide sufficient room for customization of exercise intensity according to patients' performance capabilities.[25] This recommendation translates into CR-exercise protocols that suggest a range of exercises from low to high intensity, beginning with improving the patients' muscle strength through functional training and practicing ADLs in the first three weeks of CR, e.g. chair rising for one frail patient and stair climbing for another.[25-27] For patients who can perform more than 5 minutes of exercise at $>$ 3 METs, CR-exercise protocols can incorporate endurance-building exercises according to the patient's activity goals. To evaluate physical capacity within the patient's home setup, the 2-minute step test, and the 30-second chair stand test were practical alternatives for the regular hospital-based cardiac exercise testing protocol (e.g. 6-minute walk test). Also, the present study's findings suggest that a physical-activity log or METs table was less feasible in older patients with CVD. A more attractive alternative for the home situation can be the use of an activity tracker, which provides the patient an insight into their recovery process while encouraging them to become more active and engaged.[28-30]

Our findings reaffirm the concept that the individual's level of motivation for physical activity and self-regulation in undertaking and sustaining such activities should be considered when formulating activity goals for frail older patients.[31] Additional recommendations to communicate these goals to the target geriatric population, such as tailored information about the risks and benefits of physical activity in this population,[32] motivational interviewing techniques,[33] and tools that support shared-decision-making,[34] can potentially help in personalizing CR-protocols for frail older patients.

Finally, secured transmural interdisciplinary communication systems may aid

primary care PTs in monitoring and exchanging health and risk information. Current communication systems and electronic patient records vary with organizations, forcing health professionals to fall back to less secure communication channels such as writing, faxing, email, or telephone.

Our results are corroborated by systematic reviews and the American Heart Association's guidelines, in which they reported that home-based CR was as effective and safe as center-based CR in patients with low-to-moderate risk.[3, 5, 10] O'Neill *et al*. also reaffirmed the safety and effectiveness of CR in older patients.[25] The results of our study ascertain that home-based CR is also feasible in very old (above 80 years) and frail populations and it is possible to organize home-based CR in primary-care PT practices in the Netherlands. Future studies should investigate the safety and effectiveness of this intervention in this population. Patients' adherence and satisfaction to the CCB-intervention have been evaluated and published separately.[35, 36]

Strengths and limitations

There are several strengths of the study. We used a qualitative design that combined observations with consecutive interviews, thereby obtaining a unique in-depth insight into how contextual variables and characteristics of frail older patients influence a PT's professional practice.[37] This way we were able to evaluate the observed-adherence of PTs to the suggested CCB-CR protocol and identify points of improvement for improving the feasibility of home-based CR in frail older patients. Second, by separately coding all transcripts we reduced the risk of confirmation bias. The different professional backgrounds of the coders (nurse and PT) resulted in an inter-professional assessment of the relevant themes that influenced feasibility. After a consultation, the researchers attained an excellent intercoder agreement which supports the robustness of our study outcomes. Finally, the PT-sample varied in age, experience, and education, giving a realistic representation of Dutch primary care PTs. The review of Taylor *et al*. shows that PTs in other countries like Australia, Canada, and the United Kingdom were able to perform home-based CR in non-frail patients.[3] Our findings add to the body of knowledge by suggesting that trained primary care PTs can also utilize home-based CR in frail older patients.

Some aspects of our study warrant consideration. First, the sample size in our study was small, potentially limiting the scope of our findings. However, our observations and interviews with the last two PTs did not reveal new codes or themes. Combining data from observations and interviews may have accelerated saturation. Second, not all included patients in the CCB-study were willing to participate in home-based CR. Also, PTs reported that two patients had dropped out of the home-based CR component of the CCB-study because they found the many healthcare professionals visited them to be overwhelming. Our result may therefore not apply to highly unmotivated frail patients. Finally, our study

was conducted in the Netherlands. Studies in other countries with their specific healthcare systems may provide additional insights on the local challenges for implementation.

Recommendations for further research and implementation

Findings in our pilot study indicate that home-based CR is feasible, but with adjustments to meet the needs of frail older patients, such as 1) replacing the usual exercise tests (like the 6-minute walk test) with more functional (30-second chair stand test) and feasible tests (e.g. 2-minute step test);[38] 2) using different tools for measuring activity levels (e.g. activity tracker instead of METs);[39] and 3) adapting exercise type and intensity according to the patient's comorbidities and capability.[40] Further research is needed to confirm the applicability of exercise tests and select the best tool for measuring daily activity levels. It is unclear which exercise components lead to the best results regarding physical functioning, hospital readmission, and mortality. To objectively assess the effects of physical therapy in frail older patients, activity levels (e.g. activity monitor) are more practical than the VO_2-max measures.[41, 42] Considering the heterogeneity of frail older patients with CVD, more research analyzing subgroups within this population is needed to identify groups for whom home-based CR is feasible, safe and effective.[43]

Conclusion

This study suggests that primary care PTs found the CCB-home-based CR protocol to be feasible when administered to a sample of frail older patients. Important challenges to further improve home-based CR are the identification of an optimal level of CR intensity, selection and identification of exercise tests and measures that are suited for home-based CR, and the integration of interventions to optimize the patients' self-regulation.

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APPENDIX 1. THEORETICAL FRAMEWORK OF GURSES

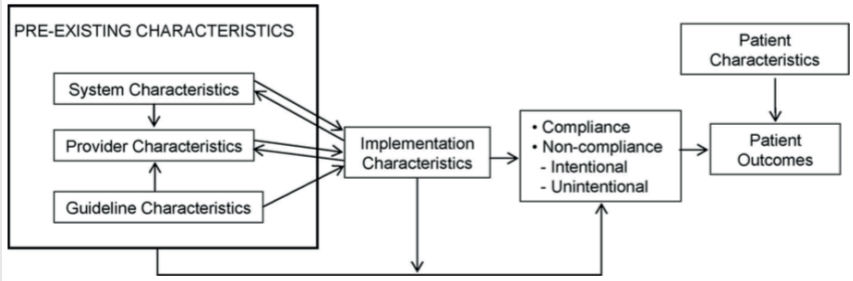

Figure 1. Conceptual interdisciplinary framework of clinicians' compliance with evidence-based guidelines, by Gurses 2010

The framework of Gurses (figure 1) shows the expected interrelationships among four major categories of factors (System-, Provider-, Guideline-, and Implementation characteristics) that influence guideline compliance. System- (e.g. a checklist or communication system) and guideline characteristics (e.g. relative advantage, complexity, compatibility) can positively and negatively influence provider characteristics (e.g. awareness, agreement with the guidelines, self-efficacy). Pre-existing characteristics influence compliance with the guideline through their impact on implementation characteristics. These implementation characteristics (e.g. tension for change) function as mediators and moderators of the pre-existing characteristics towards the behavior of clinicians' compliance or non-compliance to guidelines. For example, low self-efficacy (provider characteristic) may diminish implementation quality and thus lead to low compliance (mediation). Or, as a moderator, adequate implementation can diminish the impact of low self-efficacy. Clinicians' compliance to guidelines influence patient outcomes, but patient outcomes are also influenced by patient characteristics. For example, present comorbidity may influence guideline adherence, e.g. PTs may prescribe too low exercise intensity because they don't understand complex interactions between diseases and as a consequence decide to underload the patient just to be safe. Finally, next to unintentional errors (e.g. forgetting to check glucose levels before and after exercise), careful and deliberate clinical decision-making may lead PTs to intentionally deviate from the guidelines, e.g. postponing aerobic exercise due to a COPD exacerbation.

APPENDIX 2. OBSERVATION FORM ADHERENCE / NON-ADHERENCE TO STUDY PROTOCOL PROVIDED IN CCB TRAINING

Factors	Barriers	Possible actions
Caregiver		
Knowledge about the protocol/guideline - Does the caregiver know how to follow the protocol/ guideline?		
Attitude towards the protocol/guideline - Does the caregiver believe that following the protocol/ guideline is of value?		
Usual habits in daily practice - What does the caregiver normally do in comparable situations?		
Work environment		
Task - Who is responsible for following the protocol/ guideline?		
Means and technical tools - Which materials are available and are being used? (e.g. training material: e.g. dumbbells)		
Decision support - How often are tools available and how often are they in use?		
Physical environment - In what way does the environment influence adherence or non-adherence to the protocol/ guideline?		
Organizational structure - In what way does the organizational structure influence adherence or non-adherence of the protocol/ guideline?		
Administrative support - In what way does administrative support structure influence adherence or non-adherence of the protocol/ guideline?		
Monitoring/feedback of performance? - How does the caregiver know that they adhere to the protocol/guideline?		
Culture in the organization - In what way does the culture in the organization influence adherence or non-adherence of the protocol/ guideline?		

Factors	Barriers	Possible actions
The CR protocol/guideline		
Applicability to patients in the CCB study		
Difficulty/Ease of following the protocol/guideline - In what way does the protocol/guideline influence the workload of the caregiver?		

APPENDIX 3. INTERVIEW FORM ADHERENCE / NON-ADHERENCE TO STUDY PROTOCOL PROVIDED IN CCB TRAINING

Factors	**Exemplary questions**
Caregiver	
Knowledge of the protocol/guideline - Does the caregiver know how to follow the protocol/guideline?	Can you explain in what way you apply the protocol/ guideline in daily practice? Can you provide an example? - How new is the information in the protocol for you? - How do you experience the extensiveness of the protocol? - How do you experience the complexity of the protocol? - What is your opinion about the applicability of the BORG-scale, MET-scale? - What is your opinion about monitoring vital parameters such as: weight, medication, blood pressure?
Attitude towards the protocol/ guideline - Does the caregiver believe that following the protocol/guideline is of value?	Can you explain how important it is for you to adhere to the protocol? Can you give an example of what will or will not happen if you do not follow the protocol? - Which parts of the protocol do you disagree with? - To what extent do you feel capable of following the protocol? - How hard is it for you to follow the protocol? - What is your opinion about the prescribed intensity in the protocol? - To what extent did you experience a need to implement this protocol in daily practice? - What is your experience with interprofessional collaboration within this study? Did you have contact with another caregiver? In what way? What was your contact about? - What went well / wrong in interprofessional collaboration? - What is your opinion about performing measurements in this study? (BORG/MET/Exercise tests: two-minute step test)
Usual habits in daily practice - What does the caregiver normally do in comparable situations?	Can you explain the usual procedure prior to this protocol? How satisfied are you with the usual procedure? To what extent is it possible to change 'old' habits in accordance with the study protocol?
Self-experienced compliance with the study protocol - How often does the care provider do everything according to the study protocol?	Can you tell me to what extent you are currently following the study protocol? E.g. 80%/90%. What do you encounter when you do or do not follow the protocol? To what extent does the therapist need advice in the protocol regarding abnormalities, e.g. due to comorbidity?

Factors	Exemplary questions
Work environment	
Task - Who is responsible for following the study protocol?	Can you tell who in your institution is/are responsible for following the study protocol? - What is the general workload? How often do you have a lot to do? - How much time do you have to carry out the study protocol? - How tired were you last week? - How tense did you feel last week? - How satisfied are you with the quality of your care? - How satisfied are you with your work? **Social norms** - To what extent did you feel pressure to follow the study protocol? - To what extent were you rewarded for following the study protocol?
Means and technique - What stocks and materials are available or in use?	What materials are currently available to carry out the care according to the protocol? - Think of checklist, training schedule, logbook, workbook, point software, digital map. - How up to date is this material? Also think about blood pressure meter/saturation meter etc. - What materials are actually used?
Decide support - How often are tools available and used?	What tools are available to follow the study protocol? (e.g. overview map, workbook)
Physical environment - In what way does the environment influence whether or not the study protocol is followed?	Can you tell how the environment influences whether you can follow the study protocol? For example, how busy or noisy is the environment?
Organizational structure - In what way does the organizational structure (e.g. staffing) influence whether or not the study protocol is followed?	Can you tell me how the organizational structure affects whether or not you can follow the study protocol? How do you normally experience the effectiveness of your organization? To what extent do you experience support from your organization for following the study protocol?
Administrative support - In what way does the current administrative support influence whether the study protocol is followed?	Can you tell me how the administrative support affects whether or not you can follow the study protocol? Is information available on time?

Factors	Exemplary questions
Monitoring/feedback on performance - How does the care provider know that they are/are not following the study protocol?	Can you tell me how you get feedback on following the study protocol? If applicable: Do you need that feedback? Can you tell how this is monitored? How do you experience the financial support for the implementation according to the study protocol?
Culture - How does (working) culture influence whether you follow the study protocol?	Can you tell me in what way the (working) culture influences whether or not you are able to follow the study protocol? How is the culture (e.g. open, about deviations from prescribed actions may be communicated)?
The study protocol	
Applicability to patients in the CCB Is the study protocol applicable to the specific patients in the cardiological care bridge? Think of: age, type and severity of comorbidity, patient motivation, degree of independence.	Can you tell me to what extent the study protocol is applicable to the patients you have seen within the cardiological care bridge? To what extent do you feel that you have been able to give cardiac rehabilitation instead of geriatric rehabilitation? To what extent does comorbidity influence the following of the protocol? To what extent do you have knowledge about the comorbidity the patient had? In what way does the motivation of the patient(s) influence following of the protocol? Do you lack knowledge in motivating the patient? To what extent did the patient's fear influence the following of the protocol?
Ease of following the study protocol How does the study protocol influence the workload of the care provider?	Can you tell how following the study protocol affects your workload? What makes the time pressure higher when performing cardiac rehabilitation in this specific patient group? What is the benefit or additional benefit of the study protocol? To what extent do you experience room to try out the study protocol through trial and error? What do you think of the level of evidence that supports the study protocol?

Chapter 11

The influence of partners on successful lifestyle modification in patients with coronary artery disease

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ABSTRACT

BACKGROUND: Marital status is associated with prognosis in patients with cardiovascular disease (CVD). However, the influence of partners on successful modification of lifestyle-related risk factors (LRFs) in secondary CVD prevention is unclear. Therefore, we studied the association between the presence of a partner, partner participation in lifestyle interventions and LRF modification in patients with coronary artery disease (CAD).

METHODS: In a secondary analysis of the RESPONSE-2 trial (n=711), which compared nurse-coordinated referral to community-based lifestyle programs (smoking cessation, weight reduction and/or physical activity) to usual care in patients with CAD, we investigated the association between the presence of a partner and the level of partner participation on improvement in >1 LRF (urinary cotinine <200ng/l, ≥5% weight reduction, ≥10% increased 6-minute walking distance) without deterioration in other LRFs at 12 months follow-up.

RESULTS: The proportion of patients with a partner was 80% (571/711); 19% women (108/571). In the intervention group, 48% (141/293) had a participating partner in ≥1 lifestyle program. Overall, the presence of a partner was associated with patients' successful LRF modification (adjusted risk ratio (aRR) 1.93, 95% confidence interval (CI) 1.40 – 2.51). A participating partner was associated with successful weight reduction (aRR 1.73, 95% CI 1.15 – 2.35).

CONCLUSION: The presence of a partner is associated with LRF improvement in patients with CAD. Moreover, patients with partners participating in lifestyle programs are more successful in reducing weight. Involving partners of CAD patients in weight reduction interventions should be considered in routine practice.

INTRODUCTION

Compared with married couples, being unmarried, divorced or widowed is associated with a higher risk of developing cardiovascular disease (CVD), and with worse prognosis in individuals with established CVD.[1-3] In patients with coronary artery disease (CAD), lifestyle modification and aggressive risk factor management, including cardiac rehabilitation, is recommended by all major guidelines.[4-6] In these patients, the presence of a partner and partner participation may also prevent a proportion of subsequent CAD-related events. However, the guidelines are unclear on how partners should be involved and little is known about the effects of partner participation.[6]

Involving partners in smoking cessation, weight reduction and physical activity increase seems pivotal, as household partners often share lifestyle habits and health risks.[2, 7-9] Furthermore, it has been demonstrated that when one individual initiates a lifestyle change, for example stops smoking, the partner is likely to follow suit.[10] The EUROACTION trial showed positive effects of a family-based approach on lifestyles and improvement in lifestyle related risk factors (LRFs) in patients at high risk of CAD and in those with CAD and their partners.[11] Interventions targeting couples instead of individuals could lead to greater success in improving LRF profiles.[12]

Few studies exist on the role of partners in secondary prevention of CVD. In the RESPONSE-2 trial, we found a positive association between partner participation and successful LRF modification in CAD patients referred to community-based lifestyle programs.[13] The aim of our current study was to investigate the association between the presence of partners, partner participation in lifestyle interventions and LRF modification in patients with CAD.

METHODS

Study design

We performed our analysis in the RESPONSE-2 study, a randomized clinical trial conducted in 15 medical centres in the Netherlands.[13] The study was designed to evaluate the effect of nurse-coordinated referral of patients with CAD and their partners to a comprehensive set of up to three community-based lifestyle programs aiming to improve LRFs. The three lifestyle programs targeted smoking cessation, weight reduction, and physical activity increase. Details of the protocol and the main study results have been published elsewhere.[13, 14] Briefly, we analysed data of all patients with completed outcome data at 12 months follow-up (N=711). Review boards of all participating hospitals approved the RESPOSNE-2 protocol, which is in line with the 1975 Declaration of Helsinki.[13] All

included patients provided written informed consent.

Study population

Patients were eligible to participate in the RESPONSE-2 trial if they were within eight weeks after hospitalization for an acute coronary syndrome (ACS) and/or coronary revascularization, and if they had one of the following LRFs: 1) self-reported current smoking or stopped within 6 months before hospital admission; 2) body mass index (BMI) $\geq$ 27 kg/m^2; 3) self-reported physical inactivity ($<$ 30 minutes activity of moderate intensity 5 times per week), and if they were motivated to attend $\geq$ 1 lifestyle program.[13, 14] Patients were excluded if they had a planned revascularization after discharge, a life expectancy $\leq$ 2 years, congestive heart failure New York Heart Association functional class III or IV, were unable to visit the outpatient clinic and/or lifestyle program; had no internet access, or a Hospital Anxiety and Depression Scale $>$ 14. Patients were randomized either to the intervention (on top of usual care) or usual care alone group. Usual care, offered to all patients irrespective of randomization, consisted of visits to the cardiologist and cardiac rehabilitation according to national and international guidelines.[4, 15] Furthermore, usual care included up to four visits to a nurse-coordinated secondary prevention program, consisting of risk factor counselling and medication control / titration.[14]

Intervention

Patients in the intervention group were referred by nurses with experience in cardiovascular care to up to three existing community-based lifestyle programs. The number and sequence of the lifestyle programs were determined by the patient's risk profile and preference.[13, 14]

Nurses were trained in a systematic referral approach, consisting of risk status assessment, discussing the current risk status with patients, and assessing the level of motivation to change. Depending on motivation, participation in lifestyle program(s) was advised, followed by referral to the lifestyle program after patient consent. Partners were invited to participate in the lifestyle programs irrespective of their own lifestyle or risk factors, and free of charge. At 12 month follow-up, patients were considered as having a partner if they confirmed having a partner based on the question "do you have a partner?", regardless of their cohabiting status. Partners were considered 'participating' if they attended $>$ 1 lifestyle program(s) during at least one session. Patients and partners could follow multiple programs simultaneously.

Three lifestyle programs, Luchtsignaal®, Weight Watchers®, and Philips Direct Life®, were used in their existing format, uniformly, in all participants and their partners. The lifestyle programs have been described in detail elsewhere.[13,14] In brief, Luchtsignaal® is a telephone-based smoking cessation program based on motivational interviewing by trained professionals. Pharmacological therapy

for smoking cessation was prescribed on indication. Weight Watchers® aims at weight reduction through a healthy diet, changing unhealthy behaviours, and physical activity. A Weight Watchers' coach provided weekly group-based sessions. Philips Direct Life® aims to improve physical activity, and includes the use of an accelerometer to measure the participant's level of activity combined with an online coach, who provides personalized feedback. Participating partners also received an accelerometer to evaluate their activity level.

Data collection and measurements

Data were collected by a nurse at baseline (first visit ≤ 8 weeks after discharge) and at 12 months follow-up, and included cardiovascular risk factors, cardiovascular history, partner status, physical activity, smoking status, medication use and partner's cardiovascular risks (self-reported). Smoking status was evaluated by a urinary cotinine test with a detection limit of 200 ng/ml (UltiMed one step, Dutch Diagnostic, Zutphen, the Netherlands), body mass index (BMI) was calculated by weight and height, waist circumference was measured, and physical activity was evaluated by the 6-minute walking distance (6MWD). At follow-up, in addition to partner status, we evaluated partner participation in the lifestyle programs.

Outcomes

The primary outcome of the current analysis was 'overall success' in achieving LRFs to target and improvements in LRFs separately, according to partner status (dichotomous). Overall success was defined as improvement of ≥ 1 LRF, without deterioration in the remaining LRFs. Improvement per LRF was defined as: 1) urinary cotinine level < 200 ng/ml; 2) weight loss of ≥ 5%; and 3) ≥ 10% increase on the 6MWD. Deterioration was defined as: 1) a positive cotinine test (> 200 ng/ml) in non-smokers at baseline; 2) any weight gain in combination with a BMI > 25 kg/m^2; and 3) any decrease in 6MWD compared to baseline. In addition, we analysed the association of having a partner on the improvement of ≥ 2 LRFs. Sex differences were analysed by a stratified analysis.

In a secondary analysis in the intervention group only, we analysed the proportion of patients with a partner who participated in the lifestyle programs (participating partner) compared with patients with a partner not participating in the lifestyle programs (non-participating partner), on overall success (improvement of ≥ 1 LRF), on improvement of ≥ 2 LRFs (super responders) and for each LRF separately. Analyses were stratified by sex.

Statistical methods

Categorical data are presented as frequencies and percentages. Continuous data are presented as means and standard deviations (SD) for normally distributed data, and as medians with interquartile ranges (IQR) for non-normally distributed data.

In the primary outcome analysis, the association of the presence of a partner on patients' LRF modification was evaluated using logistic regression analysis. Independent variables were 'having a partner' (yes/no), allocation (intervention/usual care), and an interaction term for these two variables. The interaction term allowed us to evaluate the extent to which the presence of a partner modifies the intervention effect.[16] Interaction was deemed present if the p-value of the interaction term was <0.10. If the interaction p-value was ≥ 0.10, the interaction term was deleted from the model. Potential confounders were one by one tested and considered at a cut-off point of a minimum of 10% change in the beta-coefficient in the partner variable.[16] The identified confounders included age, sex, level of education, history of cardiovascular disease, and baseline BMI, 6MWD and smoking status. These variables were included in the logistic regression model and compared with the unadjusted results. Both adjusted and unadjusted odds ratios (OR) with 95% confidence intervals (CI) were converted into relative risks (RR) with 95% CI.[17]

In the secondary analyses, the association between partner participation (participating partner vs. non-participating partner) and LRF modification was tested in an unadjusted and adjusted logistic regression analysis, using the same set of confounders as in the primary analysis. The secondary analysis was performed in the intervention group only. Comparisons in the secondary analysis were made between patients with participating partners vs. patients with non-participating partners. Resulting (adjusted) ORs were converted into RRs with 95% CI.[17]

IBM SPSS statistics version 24.0 (IBM Corp., Armonk, New York, USA) was used for the analyses and a p-value <0.05 was considered significant, unless otherwise specified.

RESULTS

Population characteristics

In total, 711 patients included in the RESPONSE-2 trial completed the 12 months follow-up and were available for the outcome analysis. Population characteristics are presented in Table 1. 80% of the patients had a partner (571/711), of whom 19% (108/571) were women. Overall, patients with a partner were less likely to be smokers (43% vs. 66%), and reported lower levels of physical activity at baseline (64% vs. 55%). In partners, the most frequently self-reported LRF was overweight (44%), followed by inactivity (40%) and smoking (26%).

Of the patients with a partner, 51% (293/571) were in the intervention group. In total, 41 of these patients participated in the smoking cessation program Luchtsignaal®, 164 in the weight reduction program Weight Watchers®, and 141 in the physical activity program Direct Life®. Of those with a partner, 48%

Table 1. Population characteristics

	Total group N=711			Intervention group with partner n=293		
	No partner	Partner		Participating partner	Non-participating partner	
	n=140	n=571	p-value	n=141	n=152	p-value
Demographics						
Age, years	58 ±9	59 ±9	0.32	59 ±8	58 ±10	0.32
Female	41 (29)	108 (19)	0.007	21 (15)	38 (25)	0.03
Cohabiting	NA	542 (95)	NA	132 (94)	141 (93)	0.93
Lower education (≤13 years)	92 (66)	338 (59)	0.15	77 (55)	83 (55)	0.99
Patient risk profiles						
Smoking† or quit ≤6 month of baseline	93 (66)	246 (43)	<0.001	55 (39)	76 (50)	0.06
BMI, kg/m^2	29 ±5	30 ±4	0.48	30 ±4	29 ±4	0.06
Overweight (BMI >27 kg/m2)	94 (67)	428 (75)	0.07	116 (82)	105 (69)	0.009
Physical inactivity (<30 min per day)	77 (55)	366 (64)	0.05	98 (70)	91 (60)	0.09
6MWD, m	474 ±118	490 ±107	0.15	449 ±100	506 ±117	0.22
History of CVD	43 (31)	202 (35)	0.30	45 (32)	46 (30)	0.76
Number of lifestyle related risk factors, patients						
1						
Smoking only	25 (18)	40 (7)	<0.001	3 (2)	15 (10)	0.006
Overweight (BMI >27 kg/m2) only	20 (14)	107 (19)	0.22	24 (17)	28 (18)	0.75
Physical inactivity only	4 (3)	61 (11)	0.004	14 (10)	16 (11)	0.87
2						

Table 1. *Continued*

	Total group N=711			Intervention group with partner n=293		
	No partner	Partner		Participating partner	Non-participating partner	
	n=140	n=571	p-value	n=141	n=152	p-value
Smoking and overweight	18 (13)	59 (10)	0.39	16 (11)	18 (12)	0.90
Smoking and physical inactivity	17 (12)	43 (8)	0.08	8 (6)	16 (11)	0.13
Overweight and physical inactivity	23 (16)	158 (28)	0.006	48 (34)	32 (21)	0.01
3						
Smoking and overweight and physical inactivity	33 (24)	104 (18)	0.15	28 (20)	27 (18)	0.65
Partner risk profiles						
Smoking partner (self-reported)	NA	147 (26)	NA	30 (21)	50 (33)	0.03
Overweight partner (self-reported)	NA	249 (44)	NA	71 (50)	47 (31)	0.001
Physical inactivity partner (self-reported)	NA	231 (40)	NA	61 (43)	55 (36)	0.17
Referred to a lifestyle program						
Luchtsignaal®, smoking cessation, N=76	NA	NA	NA	16 (21)	25 (33)	0.64
Weight Watchers®, weight reduction, N=222	NA	NA	NA	90 (41)	74 (33)	0.23
Direct Life®, physical activity, N=177	NA	NA	NA	81 (46)	60 (34)	0.008

Abbreviations: BMI, body mass index; 6MWD, six minute walk distance; kg, kilogram; m^2, square meters; m, meter. Data is presented as N, number (%), mean ± SD, standard deviation. †Urinary cotinine level ≥200 ng/ml

(141/293) had a participating partner (participation in ≥ 1 lifestyle program). Compared with men, women less frequently had a participating partner (51% vs. 36%) (Table 1).

Of the partners in the intervention group, 80 reported smoking, 118 reported overweight and 116 reported a low activity level. In total, 11% (16/141) of the participating partners participated in the smoking cessation program, 64% (90/141) in the weight loss program and 57% (81/141) in the physical activity program (Table 1).

Influence of the presence of a partner on patient's lifestyle modification

Figure 1 presents the percentages of patients with overall success on lifestyle modification and individual LRFs, stratified by the presence of a partner and level of partner participation (intervention group only). Patients with a partner were more successful in improving ≥ 1 LRF than patients without a partner (35% vs. 21%, p-value <0.001). After controlling for potential confounders, patients with a partner were almost twice as likely to achieve overall success in lifestyle modification than those without a partner (aRR 1.93, 95% CI 1.40 – 2.51) (Table 2). We found no indication of important effect modification according to sex (interaction term for sex and the presence of a partner, p-value 0.44). Patients with a partner were also more likely to improve on ≥ 2 LRFs [10% vs. 6%, (aRR 2.11, 95% CI 1.03 – 4.03)].

For individual LRFs, more patients with a partner stopped smoking than patients without a partner [50% vs. 41%, p-value 0.12, (aRR 1.22, 95% CI 0.93 – 1.51)] although this difference was not statistically significant. The presence of a partner was not associated with attaining ≥ 5% weight reduction (aRR 1.06, 95% CI 0.67 - 1.60), or improvement of physical activity as measured by the 6MWD (aRR 1.12, 95% CI 0.82 - 1.47) (Table 2).

Influence of partner participation on the probability of successful lifestyle modification by patients

In the intervention group, patients with a participating partner (i.e. partners who attended ≥ 1 lifestyle program), more frequently achieved ≥ 1 LRF on target than patients with a non-participating partner (45% vs. 34%, p-value 0.05) (Figure 1), although this difference ceased to be statistically significant after adjustment for confounders (aRR 1.25, 95% CI 0.92 – 1.62) (Table 2).
The interaction term between sex and partner participation was not statistically significant (p-value 0.35). A positive, yet non-significant association was found between participating partners and improvement of ≥ 2 LRF (aRR 1.81, 95% CI 0.98 – 3.12) (Table 2).
For individual LRFs, patients with a participating partner were more successful in attaining ≥ 5% weight loss (42% vs. 26% p-value 0.01, aRR 1.73, 95%

Table 2. Primary and secondary outcomes of partner influence on successful lifestyle modification.

Total group analysis N=711	**Explanatory variable**	**RR**	**95% CI**	**aRR†**	**95% CI**	**Interaction p-value***
Primary outcome						Partner by treatment
Overall success‡	Partner	1.94	1.43 - 2.49	1.93	1.40 - 2.51	0.18
						Partner by sex
Men overall success‡	Partner	1.83	1.26 - 2.51	1.85	1.24 - 2.57	0.44
Women overall success‡	Partner	2.74	1.25 - 4.80	2.96	1.32 - 5.13	
						Partner by treatment
Success ≥ 2 LRF∞	Partner	1.80	0.90 - 3.44	2.11	1.03 - 4.03	0.68
Smoking cessation						
Urinary cotinine <200ng/ml	Partner	1.23	0.94 - 1.52	1.22	0.93 - 1.51	0.30
Weight reduction						
≥ 5% weight reduction	Partner	1.10	0.71 - 1.60	1.06	0.67 - 1.60	0.13
Physical activity						
≥ 10% increase in 6MWD	Partner	1.08	0.79 - 1.37	1.12	0.82 - 1.47	0.11
Intervention group analysis N=293						
Secondary outcome						
Overall success‡	Participating partner	1.33	1.00 - 1.67	1.25	0.92 - 1.62	NA
						Participating partner by sex

Men overall success‡	Participating partner	1.45	1.05 - 1.86	1.35	0.94 - 1.78	0.35
Women overall success‡	Participating partner	1.02	0.48 - 1.64	0.95	0.41 - 1.62	
Success ≥ 2 LRF∞	Participating partner	1.87	1.04 - 3.12	1.81	0.98 - 3.12	NA
Smoking cessation						
Urinary cotinine <200ng/ml	Participating partner	1.15	0.79 - 1.50	1.07	0.70 - 1.44	NA
Weight reduction						
≥ 5% weight reduction	Participating partner	1.64	1.13 - 2.18	1.73	1.15 - 2.35	NA
Physical activity						
≥ 10% increase in 6MWD	Participating partner	1.07	0.76 - 1.39	1.10	0.77 - 1.44	NA

Abbreviations: (a)RR, (adjusted) risk ratio; CI, confidence interval, LRF, lifestyle related risk factor. * Interaction was not present and interaction terms were not included. † Analyses are adjusted for age (continues), gender, level of education (≤13 years), history of cardiovascular disease, body mass index, six minute walking distance, pre-event (<6 months before hospital admission) or current smoker (except for smoking cessation analysis). ‡ Improvement in overall success is defined as improvement on ≥1 LRF without deterioration of the other two. ∞Defined as improvement of ≥2 LRF without deterioration of another.

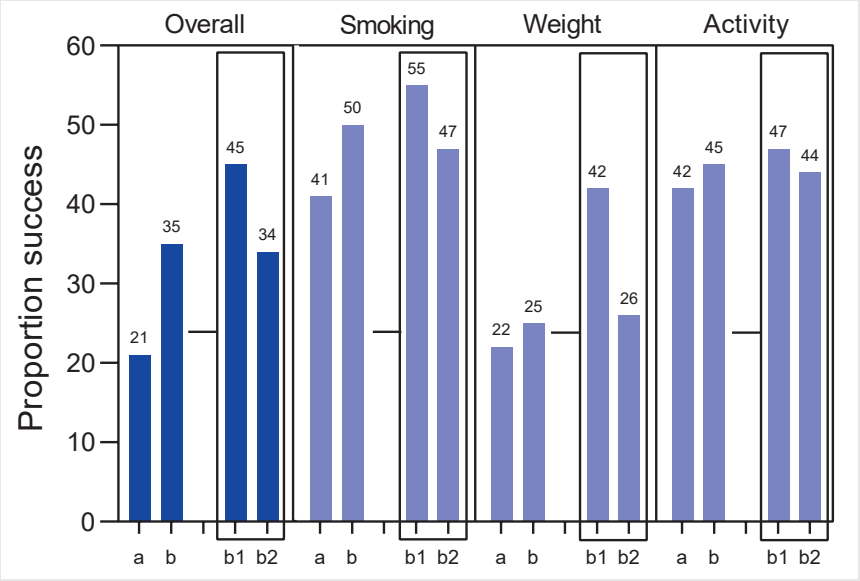

Figure 1.

a	Total group, patients without a partner	n=140	b1	Intervention group, with a participating partner	n=141
b	Total group, patients with a partner	n=571	b2	Intervention group, with a non-participating partner	n=152

Proportion of patients with overall success on lifestyle related risk factor (LRF) modification (defined as improvement on one LRF without deterioration of the other two) and proportion success on modification of LRF separately, smoking cessation (cotinine <200 ng/ml), weight reduction (≥5%) and improvement of physical activity (≥10% 6MWD)

CI 1.15 – 2.35). The association for smoking cessation was weak and not statistically significant (aRR 1.07, 95% CI 0.70 – 1.44) which was also the case for improvement in physical activity (aRR 1.10, 95% CI 0.77 – 1.44) (Figure 1 and Table 2).

DISCUSSION

In our study the presence of a partner was associated with a higher rate of successful lifestyle modification. In addition, partner participation in the lifestyle programs was associated with a higher success rate for weight reduction. Although our patient population was predominantly male, the improvements

on LRFs associated with having a partner and partner participation was in our analysis not sex dependent. Our findings suggest that partners have an important role in secondary prevention of CAD, and should be included when referring patients to lifestyle programs aiming at weight reduction.

Guidelines on secondary prevention currently advocate the involvement and support of partners in secondary prevention programs, but remain unclear about the practical implications.[5, 6] The ESC guideline indicates 'partner support' as an important contributor to smoking cessation, and in the Dutch national guideline 'partner involvement' is defined as partners attending the information sessions in the cardiac rehabilitation program.[5, 6] Our findings constitute several steps towards formulating evidence-based recommendations for integrated partner participation in lifestyle programs focussing on weight reduction, and should be considered for future guidelines on secondary prevention aiming to stimulate successful lifestyle modification in patients with CAD.

The positive association of participating partners on weight reduction was not found for smoking cessation and physical activity, either separately or combined. Based on our data, we can only speculate as to mechanisms explaining these findings. In smoking cessation, the impact of Luchtsignaal® on patients' smoking cessation was limited and therefore, the participating partner influence may have been limited as well.[18, 19] In addition, non-smoking partners could have less easily participated in the smoking cessation program Luchtsignaal® due to the telephone approach, focussing on individual's smoking behaviour. However, of the smoking partners in the intervention group, the majority did not participate in the smoking cessation program (see Table 1). This seems a missed opportunity, while the social support at home and at work is reported to be of critical importance to change smoking habits.[18] The exposure to environmental tobacco smoke, reduces the likelihood of smoking cessation up to 70%.[20] Smoking partners are important contributors to environmental tobacco smoke at home and therefore, their role is critical to achieve sustainable change in patient's smoking bevaviour.[11, 21] However, further exploration on how partners can be motivated to participate in smoking cessation programs is needed.

From our data, we were unable to find an association between the presence of (participating) partners and the improvement of patient's physical activity. This is in contrast to results of studies focussing on other populations or other types of lifestyle interventions. For example, just the presence of a partner was already positively associated with physical activity in the study of Green *et al*.[22] They found a 20% lower activity level ($p=0.008$) in patients without a partner compared to those with a partner, at one month after an acute coronary syndrome. Other intervention programs targeting LRFs in CAD patients focussing on a family-based lifestyle intervention[11] and a couple-based approach,[23] showed positive effects on the level of physical activity. The interventions targeting physical activity within both programs, worked from a centre-based approach where

patients and partners were guided by a physical therapist.[11, 23] It may be possible that our outcome definition, where a successful improvement was defined as >10% increase in 6MWD between baseline and 12 months,[13] might not have been sensitive enough to detect smaller increases in levels of physical fitness. Furthermore, the 6MWD does not measure overall increases in non-sedentary behaviour, which might positively impact weight management, but not per se lead to large improvements in 6MWD. Finally, the way that the individual lifestyle programs were offered could impact partner participation in different ways. For instance, Weight Watchers® included real-life coaching sessions for patients and partners, whereas DirectLife® included digital feedback on the results from the activity tracker for each individual. The participating partner role may have been stimulated more in the Weight Watchers program and could explain the contrast in participating partner effect between weight reduction and physical activity.

Environmental influences on lifestyle modification are complex and changing social environments is challenging.[24] For sustained modification of lifestyle habits, integration of modified lifestyles in daily routines and social systems has been shown to be necessary.[25, 26] The partner role can be highly influential, but this influence can however both work positively and negatively on the process of behavioural change and prognosis in patients with CVD.[27] For instance, household partners are often concordant in lifestyle and cardiovascular risk factors.[7, 9] In a somewhat older general population with unhealthy lifestyles (smoking, overweight and inactivity) an individual's lifestyle modification was shown to be associated with lifestyle modification of the partner.[28] The interplay between individual risk factor improvement and partner participation is however complex. Significant interaction was found between relationship satisfaction and patient's LRF improvement.[23] Patients who were satisfied in their relationship had a significantly higher long-term survival rate after coronary artery bypass graft compared to those not satisfied with their relationship.[29] Dalteg *et al*. described the high impact of cardiac disease on multiple levels within the relationship, affecting partner role, communication and overprotectiveness.[30] The importance of not only involving couples in lifestyle interventions targeting patients with cardiac disease, but also considering the relationship itself within the intervention to achieve sustainable results has been emphasized.[27, 31] This might be an important factor which could have affected our current study results.

Strengths and limitations

Several strengths are relevant to our study. First, we are the first to study the association of the presence of a partner and partner participation in a large randomized trial including community-based lifestyle programs on LRF modification in a representative population of CAD patients. The study included a variety of patients with and without partners, and systematically registered participating partners in the lifestyle programs. Second, we did not limit the

partner analysis to married couples, thereby increasing generalisability. Finally, the presence of a partner and partner participation was registered at baseline and was verified at 12 months follow-up to ascertain the role of the partner during the intervention and follow-up periods.

Some aspects of our study warrant consideration. First, while this study represents a secondary analysis of the RESPONSE-2 trial data, the study was not primarily powered for the comparison of partner influence on lifestyle modification. However, this has limited consequences for the calculated effect sizes, whose accompanying confidence intervals narrow. Second, participating partners in the lifestyle programs were (by definition) only present in the intervention group. Therefore, a comparison to investigate the participating partner effect could only be made with non-participating partners under the same treatment condition in the intervention group. Third, besides data on the partners' LRFs and lifestyle program participation, we did not collect data on partner characteristics such as the level of education, health literacy and perception on the disease and the importance of lifestyle modification. These partner characteristics could potentially have affected the effects of partner participation. Fourth, we defined participating partners as those who joined patients in the RESPONSE-2 lifestyle programs. Although, information on the number of partners that participated in the lifestyle programs was registered (see Table 1), information on the number of sessions the partners attended, was not available. Analysis of 'dose response relation' between the number of sessions a partner attended and the likelihood of patient LRF modification, was therefore impossible. In addition, partners in the control group could have joined patients in the usual care treatments, e.g. nurse specialists' consultations, and could be considered as participating partners as well. The findings in the intervention group are in anyway not affected by this. Finally, while we found an association between the presence of a partner and partner participation on successful lifestyle modification, the results do not elucidate the psychological mechanisms which explain the positive association on weight reduction and not on smoking cessation and physical activity. Identifying these mechanisms could inform and further help improve community-based lifestyle programs for patients and partners.

Conclusion

The presence of a partner was associated with successful improvement on lifestyle related risk factors in patients with coronary artery disease. Moreover, patients with partners who participated in the lifestyle programs, were more successful in achieving clinically important weight loss compared to those with a non-participating partner. Involvement of partners in weight loss interventions should be considered in routine clinical practice.

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Chapter 12

General discussion

GENERAL DISCUSSION

This thesis focused on three topics to improve care for older cardiac patients:
1. Cardiovascular risk screening and screening of risk of readmission and mortality;
2. Integration of case management, disease management and cardiac rehabilitation in a transitional care program;
3. Evaluation of new approaches in cardiac rehabilitation.

PART 1

In part 1 of this thesis we evaluated the performance of two screening tools to evaluate cardiovascular risk in community dwelling older adults and risk of readmission and mortality in hospitalized older cardiac patients. Although both screening tools are currently used in clinical practice, these instruments have not been validated in the population where they are applied to. First, we investigated if the Systematic COronary Risk Evaluation – Older Persons (SCORE-OP) algorithm accurately estimates the rate of cardiovascular mortality in a population of age 65 to79 years.[1] The SCORE-OP algorithm was recently developed and tested on its internal validity.[2] We performed an external validation using the EPIC-Norfolk cohort, and found that the discriminative power was limited for both the 5-year and the 10-year estimation of cardiovascular mortality in older adults. In the external validation, we found an area under the curve (AUC) of 5- and 10-year cardiovascular mortality of 0.64 and 0.63, respectively, compared to an area under the curve of 0.74 in the original study.[1,2] Although calibration of the algorithm was excellent, the SCORE-OP overestimated 10-year CVD mortality in individuals aged 65-69 years, whereas in individuals aged 70-79 years a considerable underestimation was observed. The contrasting prevalence of diabetes mellitus of 3.1% compared to 7% in the original validation cohort could have been a factor explaining the differences in estimates. In addition, the SCORE-OP algorithm does not include determinants, such as geriatric syndromes and psychosocial factors, that worsen the prognosis in older adults.[3]

Preventive care at an early phase is highly important in older cardiac patients at high risk for readmission and mortality at hospital admission, so it is meaningful to trace those patients.[4] In the Netherlands, all patients of 70 years and older who are admitted to the hospital are screened for risk of adverse events by the Dutch Safety Management System (DSMS) tool since 2012.[5] This tool screens (the risk of) four geriatric conditions, including falling, delirium, malnutrition and functional impairment. Based on the number of geriatric conditions, the DSMS-score ranges between 0-4. Patients aged between 70-79 years are considered at high-risk if they score ≥3 and patients of ≥80 years are considered at high-risk if they score ≥1 point. Based on the individual risk profile, the need for a comprehensive geriatric

assessment and interventions is evaluated by a geriatric team. The DSMS-tool was validated in several populations, however not in an older cardiac patient population.[6] Our results showed that the DSMS-tool has at its best a moderate discriminative performance with an AUC of 0.61 in older cardiac patients and fails to adequately identify patients at high risk of readmission or mortality within six months after hospitalization.[7] The geriatric conditions screened by this tool do not relate strongly enough to readmissions and mortality in the older cardiac patient population. In extended models, we tested variables of various domains such as the psychological, social, functional domain on their contribution to the model's predictive performance. By adding disease-related variables to the model (i.e. admission diagnosis and the Charlson Comorbidity Index), the discriminative performance increased to an AUC of 0.69.

In conclusion, the validation of two screening tools (SCORE-OP and DSMS) that are currently used in clinical practice, showed that they cannot provide a reliable prognosis in the populations they are applied to. While our results indicate that the risk estimation improved when geriatric and disease-related were combined in the DSMS analysis, future research should focus on the identification of risk factors from both geriatric and disease-related perspectives and combine them in risk estimation models.

Implication for research

External validation is essential before implementing screening tools in clinical practice. Though the performance of both the SCORE-OP and DSMS-tool is not optimal to provide a reliable prognosis on cardiovascular risk in community dwelling adults and risk of readmission and mortality in the older cardiac population, respectively, they are still the best currently available. Further development and testing of both instruments is needed.

Recent studies on risk factors for cardiovascular mortality in community dwelling older adults found that the traditional risk factors, such as systolic blood pressure and plasma cholesterol levels, were of limited value.[8, 9] In addition, these studies did find factors, such as polypharmacy and apathy, as new determinants of cardiovascular risk.[9] Further studies identifying older adults at high risk of cardiovascular mortality should focus on risk factors beyond the traditional cardiovascular risk factors. Factors as comorbidities, geriatric conditions and even factors such as patient-reported health status should be considered.[10]

Although we searched for an improved discriminative performance of the DSMS-tool by the extended models, the results remained moderately discriminative at best. We tested a wide variety of variables with many potential mechanisms of impact. However, we were not able to explore the contribution of variables that are related to the severity of the disease, such as the New York Heart Association (NYHA) class in case of heart failure. In a systematic review on risk assessment models for readmission in cardiac patients, disease-related factors

such as the presence of heart failure and comorbidities, e.g., chronic obstructive pulmonary disease and renal failure, were found to be strong indicators for risk of readmission.[11]

Future research on the estimation of both cardiovascular risk in community dwelling adults and the risk of readmission and mortality in older cardiac patients should focus on combining risk factors such as disease-related factors and geriatric conditions. Furthermore, external validation processes should be enhanced as it is necessary to determine the generalizability of screening tools and prediction models before implementation in clinical practice with clinical implications.

Implication for practice

The low discriminative performance of the SCORE-OP indicates that the tool is not able to adequately identify older adults at risk of 5- and 10-year cardiovascular mortality, which results in potential over- or undertreatment.[1] We found that adults between 65 and 69 years at risk were more accurately identified by the original SCORE low-risk, compared to SCORE-OP, with an AUC of 0.66 and 0.59, respectively. As such, if the SCORE instruments is applied, we suggest to use the SCORE low-risk instrument in adults between 65-69 years and the SCORE-OP in adults ≥70 years.[1] Furthermore, we found that 98% of the individuals included in our dataset exceeded the treatment threshold of 5% risk of 10-year cardiovascular mortality, as suggested by the European cardiovascular disease prevention guideline.[1, 12] By increasing the threshold to 10%, the individuals exceeding this threshold reduced to 41%. Clinicians are encouraged to weigh the benefits of preventive treatment in relation to possible harm of no treatment or adverse medication effects in a shared decision setting with the person of concern.

Our findings indicate that the DSMS-tool is not able to adequately identify cardiac patients at high risk for readmission or mortality. In the extended models, we found that the admission diagnosis and the Charlson Comorbidity Index increased the discriminative performance. Still, the performance is at its best moderate with an AUC of 0.69.[7] Until better alternatives to identify high-risk cardiac patients are available, clinicians should indicate high-risk patients on the DSMS-tool and on additional risk factors such as (the stage of) the disease and the presence of comorbidity. Currently in the Netherlands, a high-risk score on the DSMS generates an automatic geriatric team consultation. The geriatric team indicates if a further comprehensive geriatric assessment and consequent treatment is indicated.[13] While the performance of the DSMS-tool is not optimal, clinicians should be aware of actively consulting the geriatric team in case they observe risk factors that not directly lead to an automatically generated geriatric team consultation. Alternatively, geriatric co-management with a pro-active instead of a reactive approach, could be considered in order to early identify patients at risk. In this model, geriatrics teams are structurally involved in the

treatment and showed positive trends on length of stay and mortality rates[14] and is currently studied in cardiac patients.[15]

PART 2

Supported by the positive findings of the Transitional Care Bridge intervention in a frail older general medical population[16] and the positive findings of transitional care interventions in non-frail heart failure patients,[17, 18] we developed and evaluated a multidisciplinary transitional care model, combining case management, disease management and home-based cardiac rehabilitation in frail older (≥70 years) cardiac patients. This Cardiac Care Bridge (CCB) transitional care program was evaluated in a multi-center randomized trial and aimed to reduce unplanned readmission and mortality in the first six months after randomization.[19] Our hypothesis, that the integration of the three combined intervention components in the transition of care could bridge the gap between the components and between care settings, was unfortunately not confirmed in our study population.[20] The CCB program did not reduce the primary outcome of (time-to-event) rates of hospital readmission or mortality compared to usual care. Twelve months after randomization (nine months after the intervention period), we found a statistically significant difference on the secondary outcome of mortality in favor of the control group. The outcome of unplanned hospital readmission did not show a difference at that time point. The lack of improvement in de CCB population may be a consequence of the selected population, with a high mean age of 82 years and a high prevalence of geriatric conditions (e.g. risk of falling , malnutrition and functional impairment) and multimorbidity.[20] We may have targeted a population that was insufficiently susceptible to the intervention, possibly explained by selecting participants using the DSMS-tool.[5] The population mean age in previous studies was 70 to 74 years and the included populations were not selected by frailty measures.[17, 18] Furthermore, the results of our study may be influenced by the suboptimal mean fidelity rate of 67% of the key-elements in the CCB program.[21] The limited abilities and motivation in the CCB population resulted in reluctance in intervention components, such as the home-based rehabilitation.

In the CCB process evaluation, the intervention fidelity and involved healthcare professionals' perspective on the CCB program were evaluated.[21] The interviewed CCB professionals expressed their confidence in the contribution of the program. However, doubts were expressed on the feasibility of some intervention components, for which lack of time was indicated as critical. Concerns were also expressed regarding the intensity and the need for adaptation of the home-based rehabilitation program in relation to the frail population in the study, which is further evaluated in Part 3. Patients did not always want to participate or experienced exercises as too intensive resulting in reduction of the intensity of the rehabilitation program by the physical therapists to better meet patients' needs. Furthermore, a very low fidelity rate was reported for the consultation of the in-hospital geriatric

team. The high hospital turnover was indicated as a cause, but CCB cardiac nurses also indicated that they were not convinced about the contributive value of the involvement of the geriatric team. The latter was unexpected since during the 5-day training course prior to participation in the study, geriatric team members informed about the possibilities to provide support at the hospital wards and referred to the benefits of comprehensive geriatric assessment-based treatment.[13] In reflecting on explanations for failure of the intervention in the randomized trial, the influence of the suboptimal fidelity rate should be considered. A higher fidelity rate could have had a positive influence on the primary composite outcome. On the other hand, a higher fidelity rate could also have had a negative influence on the outcome, considering the higher mortality rate in the intervention group at twelve months follow-up.

In addition to the process evaluation, we studied five cases of the CCB intervention group to gain in-depth insight into the occurrence of unplanned hospital readmissions.[22] We evaluated patients' and (in)formal caregivers' perspectives on their roles within the course of readmission. Included patients frequently experienced acute episodes of health deterioration causing hospital readmissions, and CCB professionals were not always present at the right time to intervene. These results show that early detection of deteriorating health situations at home is challenging. A focus on empowerment of patients and informal caregivers to adequately monitor and respond in these situations, may help to bridge the gap between professionals' home visits. In addition, communication routes should be very clear to patients and informal caregivers, including instruction on how and whom to contact in changing health situations. The use of mobile communication and remote monitoring can be considered to bridge the gap between professionals' home visits.[23, 24] Flexibility in planning home visits or mobile follow-up contacts based on professionals' indication, instead of fixed visits in the CCB project, was found to better meet patients' needs. Within the CCB intervention, patients were not always motivated to participate in the intervention.[22] Reasons for this were contrasting care expectations and the lack of patients' goals. The advanced stage of disease in some cases, could have influenced the lack of goal setting and made some of the unplanned hospital readmissions unavoidable according to informal caregivers and involved professionals. Another point of concern pointed out in the multiple case study are the difficulties experienced by the CCB professionals in providing CCB care within existing care systems. They felt redundant in some cases and were not able to empower the existing (in)formal care team in the comprehensive geriatric assessment and treatment plan-based care needs.

Implication for research

Studying complex intervention in healthcare is challenging. The Medical Research Council developed a framework for the evaluation of complex interventions,

including phases from intervention development, testing, evaluation to implementation.[25] Many study designs can be considered for the evaluation of the complex intervention, depending on the type of intervention, requirements regarding the phase of evaluation and the underlying research question. In the process of developing, testing and evaluation of the CCB intervention, we have chosen a mixture of qualitative and quantitative study designs for optimal evaluation from several perspectives. To evaluate the CCB intervention effect, we used a traditional randomized controlled trial design (RCT) to achieve an optimal unbiased evaluation of the intervention. However, this study design has limitations in the evaluation of complex interventions.[26, 27] For instance, by choosing a RCT design, we were not able to fully implement the CCB intervention at the hospital wards because of contamination of patients in the control group, and we were not able to prevent community nurses from integrating CCB intervention components within the regular community care system because of their personal positive experiences with the CCB intervention. The latter forced us to terminate the CCB study early, because the risk of losing a contrasting difference between the intervention and control group.[20] Although the traditional randomized trial design is considered as the most robust design in the evaluation of intervention effects, designs such as a 'stepped wedge' design should be considered for the study of complex intervention such as the CCB.[26, 27] A stepped wedge design allows for implementation of the intervention on clusters level (wards in case of the CCB) and uses clusters where the intervention is not (yet) implemented as a comparison. However, this design also has limitations regarding the risk of contrasting populations and intervention performance between clusters, and it requires a larger study population to study effectiveness. Although the CCB study was prematurely terminated, it had enough power to calculate effect sizes because of the high incidence rate of readmission and mortality in both study groups.[20] Also, an implementation pilot study prior to the trial start, to test the intervention logistics in all involved hospitals and collaborating community care organizations, was performed. However, a thorough feasibility study could have early identified some of the experienced barriers within the CCB study and would have enabled us to adjust selection criteria and intervention components where needed.[26, 27]

The high incidence rate of readmission and mortality in the CCB population was likely a result of the very old and frail patient population with a high number of comorbidities.[20] The population included in the study already had many healthcare professionals involved and the CCB intervention did not contribute to the prevention of readmission and mortality. This suggests that the included population was not responsive to high intensity interventions and was beyond the reach of preventive interventions. Advance care interventions may have been more suitable in this population as they concentrate on patient-centered preferences to increase comfort, quality of life and also reduce readmission.[28-30] Future research

should focus on the identification of patients who may benefit from preventive interventions and test if the CCB intervention is effective in a potentially more responsive population with a potential to rehabilitate.

Implication for practice

Because participating CCB healthcare professionals experienced beneficial effects of the CCB intervention, some of them started implementation of intervention components in daily practice. Nevertheless, based on our findings it is not recommended to implement the CCB intervention in patient populations comparable to the population in our study.[20] The study population was considered very old and at high-risk of readmission and mortality. This was confirmed by the high incidence of events of approximately 50% in both treatment groups. CCB healthcare professionals and (in)formal caregivers expressed that adverse events, such as hospital readmission, were often not preventable in this population.[21] They also indicated that further deterioration could be prevented by enforcing a hospital admission already in an early stage. While healthcare professionals are not 24h available to observe health status, the empowerment of patients and informal caregivers to adequately monitor and respond to health deterioration at home is of great importance. Also, professionals within the existing care systems, such as the regular home care services and physical therapists, should be involved in the observation of health deterioration. Instead of implementing additional care services, the empowerment and better coordination of the existing (in)formal care system may be an alternative to avoid the burden of additional care services and health care costs. Furthermore, lessons can be learned from the 'hospital at home' principle, which focusses on home treatment as an alternative to hospital-based treatment. This approach showed positive effects on e.g. mortality and institutionalization in older chronically ill population.[31] Especially in frail heart failure patients, home-based treatment of decompensation of heart failure, 'hospital at home' could be an attractive alternative to prevent hospital readmissions and consequent risks of adverse events. However, although the 'hospital at home' principle has shown positive results, the intervention should be studied within the specific setting of heart failure patients and within the environment where it is implemented in before finally adapting it in usual care.

Healthcare professionals experienced difficulties in motivating patients to formulate their own goals as a starting point of the rehabilitation program.[21, 22] This could be explained by the advanced stage of disease of many included patients. However, it also requires specific skills to support patients in formulating their needs and goals. Although, we integrated the topic in the CCB training course, techniques are complex and may require more specific training.[32]

The CCB intervention is not recommended for clinical practice in its current form.[20] Refinement of the intervention requires reconsideration of the eligibility of patients for the CCB intervention and reconsideration of the intervention in relation

to the needs and preferences of the target population.

PART 3

In part 3 of this thesis, new approaches in cardiac rehabilitation were evaluated. A systematic review and meta-analysis was performed on the effectiveness of multidisciplinary rehabilitation strategies in an 'out-of-hospital-setting' among acute hospitalized older (≥65 years) patients.[33] The included rehabilitation strategies did not show a pooled effect on the 6-minute walking distance (6MWD) or on unplanned hospital readmission. However, the statistically non-significant improvement of 23 meters in 6MWD may be considered clinically relevant in older patients.[34] To our opinion, the 6MWD may not be the appropriate outcome measure in this population. Independency in daily activities, reduced risk of falling or quality of life may be relevant outcomes for future studies.[35] Studies on rehabilitation strategies often focus on a diagnosis-based population, instead of individual-based characteristics such as the level of frailty, that may play an important role in determining rehabilitation needs.[35] Exercise-based rehabilitation in patients with multimorbidity should be based on a rigorous health status assessment, include adapted exercises, integrate behavioral change techniques and adequate clinical reasoning techniques by healthcare professionals to adequately apply the rehabilitation programs and adapt it to patients' needs and preferences.[36] In addition, hospital-based rehabilitation programs are often too intensive for frail older patients after hospitalization, or patients are not able to transfer between home and rehabilitation centers.[37] Home-based rehabilitation programs have the potential to overcome these barriers and were shown to have equal effectiveness compared to hospital-based cardiac rehabilitation.[38, 39]

A CCB home-based cardiac rehabilitation program in frail patients after hospitalization was evaluated on its feasibility from community care physical therapists' perspectives.[40] Physical therapists assessed the CCB home-based cardiac rehabilitation program to be feasible in frail patients. Facilitating factors for home-based cardiac rehabilitation identified by the physical therapists were flexibility in tailoring exercises, for instance by lowering the training intensity, stimulating patients' motivation and self-regulation and monitoring the risk of readmission. For the purpose of implementation, factors such as a high workload and limited financial compensation were reported as barriers. These findings on barriers and facilitators, contribute to the development of tailored cardiac rehabilitation programs, based on the needs and preferences of frail patients in a home-based setting.

Furthermore, based on the RESPONSE-2 study in patients with coronary artery disease, we found that having a partner had a favorable influence on patients' lifestyle related risk factor modification (weight, smoking and physical activity).[41] In addition, partners who participated in the RESPONSE-2 community-based lifestyle interventions, had an additional favorable influence on patients'

weight reduction. These findings suggest that partners may play an important role in secondary prevention of patients with coronary artery disease, and it should be considered to include partners when referring patients to lifestyle programs focusing on weight reduction.

Implication for research

The study of the home-based cardiac rehabilitation program in frail older patients, showed that it was a feasible intervention by personalized adjustments to the leading rehabilitation guidelines and that this approach did not lead to intervention related adverse events.[40] Nevertheless, the intervention as part of the CCB program was not able to improve readmission and mortality rates in six months follow-up.[20] This home-based approach addresses the logistical barriers to participate in cardiac rehabilitation and it enabled a patient centered approach, based on patients' needs and preferences.[40] For future purpose, one should consider performing a well powered intervention study with a suitable design, to evaluate the impact of home-based cardiac rehabilitation by community physical therapists on patient centered outcomes such as independence in daily activities.

We found that participating partners of patients with coronary artery disease in the RESPONSE-2 trial, significantly contributed to weight loss but not to smoking cessation or improved physical activity.[41] The partner role in secondary prevention has potential but needs to be further explored on what specific factors contribute to the beneficial effects of partners participation.[42-44]

Implication for practice

We found that earlier studies on interventions addressing multidisciplinary rehabilitation in an out-of-hospital-setting, neither lead to a significantly improved 6-minute walking distance, nor to reduced readmission rates.[33] Based on these findings, we cannot make a recommendation regarding home-based rehabilitation. The body of evidence on the topic is still limited and the intervention description in the included studies did not always meet the FITT-criteria (frequency, intensity and time and therapy).[45] This made it difficult to replicate and compare the included interventions. Only a few included studies in the systematic review focused on home-based cardiac rehabilitation and none included frail cardiac patients.[46, 47] Although the literature is currently not conclusive regarding the efficacy of home-based rehabilitation in older cardiac patients, CCB physical therapists do consider it safe and feasible.[21, 40] The physical therapists involved in the evaluation pointed to the great importance to adjust the recommendations on training exercises in leading guidelines to individual needs and preferences and found alternatives to treat patients. Identifying the needs and the preferences was, however, challenging and motivating patients was experienced as complex. The population studied was at high age, frail and had considerable comorbidity, which were experienced by physiotherapists as factors that seriously limited

motivation. Since finding intrinsic motivation is considered to be a conditional factor in achieving goals in rehabilitation,[48] future research on improving cardiac rehabilitation in frail older patients should include motivation strategies more explicitly.

Based on the findings in the secondary analysis of the RESPONSE-2 trial, it is advised to structurally involve and refer partners to weight reduction programs in patients who require lifestyle related risk factor modification.[41] Including partners seems to support a structural change in risk factor behavior.

Bridging the gap - implication for education

This thesis shows that integrating case management, disease management and cardiac rehabilitation in a patient population at high risk of readmission and mortality, was highly challenging. One considerable challenge in interdisciplinary collaboration across healthcare settings is communication. Communication between disciplines is often based on written reports and is rarely based on shared patient goals and care plans with an integrated approach. Involved healthcare professionals reported they did not have enough knowledge on each other's professional skills and possibilities. In addition, in-hospital care is currently mainly focused on guideline-based disease management and a focus on patients' own needs and preferences from a case management perspective is often lacking.[49] However, after hospital discharge, there is a lack of adequate integrated disease management within the current system of community care which results in a lack of adequate recognition of deteriorating health in cardiac patients.[21] The CCB training course, which was a condition for working with the CCB intervention, focused not only on the integration of case management, disease management and cardiac rehabilitation across healthcare settings but also on interdisciplinary collaboration, based on a personalized integrated care plan. The CCB training, and the in-person contacts that were involved, contributed to the intensified collaboration between healthcare professionals across settings. To encourage the interdisciplinary collaboration during the CCB training, a case-based approach was used. Healthcare professionals were invited to work together on the case-based assignments to promote the collaboration between them. By providing interdisciplinary case-based education, starting already at the level of Bachelor of Science, we may be able to change and improve future interdisciplinary collaboration across healthcare settings to patients' benefit.[50, 51]

We found that supporting patients in formulating their own goals and to motivate them in rehabilitation interventions, was experienced as challenging and requires specific professional skills. Also, the empowerment of the existing (in) formal care team, to support patients in their needs after hospitalization for a cardiac disease was experienced as difficult. Future education could focus on these challenging and complex factors by integration of, for example, motivational interviewing techniques in educational programs and techniques to empower

patients and the (in)formal caregivers.

Conclusion

This thesis focused on adapting transitional care to older cardiac patients' needs. Bridging the gap between hospital and home by combining disease management, case management and home-based cardiac rehabilitation did not lead to the desired improvement of readmission and mortality in frail, older cardiac patients. The CCB intervention is not recommended for clinical practice in its current form, although healthcare professionals have already adapted parts of the CCB protocol in their daily practice. Potentially, it may be applied more successfully with adequate risk assessment to accurately identify eligible patients and reconsideration of the intervention in relation to the target population. Interventions should be integrated within existing care systems as much as possible. To achieve goals, patients' own needs and preferences should be leading in future intervention development. Educational strategies focusing on interdisciplinary collaboration, system empowerment and identifying patients' own drivers could improve the intervention quality. By taking all these elements into accounts, we may be able to bridge the gap between hospital and home in frail older cardiac patients.

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Chapter 13

Summary
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Author contribution
PhD Portfolio
List of publications
Dankwoord
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SUMMARY

BRIDGING THE GAP

Adapting transitional care to older cardiac patients' needs

This thesis focuses on bridging the gap between current practice and older cardiac patients' needs in the transition of care. In **chapter 1** the context in which the research in this thesis was conducted, is presented. The hospital readmission and mortality rates of older cardiac patients are high, 20% and 8%, respectively. Multimorbidity and geriatric conditions such as malnutrition, fall risk and frailty, are common in this population and increase this risk. In frail patients with cardiovascular disease, the risk of readmission and mortality is 2-3 times higher compared to patients without frailty. The identification of patients at risk is important to enable adequate treatment, based on patients' individual risk factors and needs. Especially patients who are transferred between care settings or discharged from hospital to home, are at high risk of adverse events. The aims of this thesis were 1) to evaluate strategies to identify patients at high risk of readmission and mortality, 2) to evaluate a transitional care intervention in frail older cardiac patients and 3) to evaluate new approaches in cardiac rehabilitation.

PART 1. Risk screening in older cardiac patients

In **chapter 2**, the performance of the Systematic COronary Risk Evaluation – Older Persons (SCORE-OP) in the European Prospective Investigation of Cancer Norfolk (EPIC-Norfolk) population cohort was studied, to assess 10-year risk of death due to cardiovascular disease (CVD). The use of the instrument is recommended by the European guideline on CVD prevention as a decision-making tool in primary prevention, however, it was not yet tested in an external cohort. In persons aged 65-79 years without known CVD, the predicted 10-year CVD mortality was calculated by the SCORE-OP algorithm and compared to observed mortality rates. A total of 6,590 individuals (45.8% men) with a mean age of 70 years were included in the analysis. Results showed that the ratio of the SCORE-OP predicted and the observed 10-year CVD mortality was nearly optimal (0.96). However, the discriminative performance of the instrument was moderate with an area under the curve (AUC) of 0.63. Based on the findings we conclude that due to the limited discriminative power, SCORE-OP cannot be readily implemented in clinical practice.

Chapter 3 describes the discriminative performance of the Dutch Safety Management System (DSMS)-tool to identify older (≥70 years) patients at high risk of readmission and mortality. This frailty tool is currently used in all patients admitted to the Dutch hospitals. However, the performance has not been studied in cardiac patients. A validation study was performed in a cohort of 529 acutely

hospitalized older (≥70 years) cardiac patients. DSMS-tool was positive in 45% for delirium, 41% for falling, 37% for functional impairments and 29% for malnutrition. We found that the DSMS-tool discriminated limited in older cardiac patients with an AUC of 0.61. Additional risk factors, i.e. admission diagnosis and the Charlson Comorbidity Index increased the discriminative performance to 0.69. 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.

PART 2. Organization of transitional care in older cardiac patients: The Cardiac Care Bridge program

Chapter 4 describes the rationale and study design of the Cardiac Care Bridge (CCB) randomized trial. The CCB trial was designed to evaluate the integration of case management, disease management and home-based cardiac rehabilitation in the transition from hospital to home, in frail older (≥70 years) cardiac patients and aimed at the reduction of the composite outcome of all-cause hospital readmission or mortality. The level of frailty was based on the DSMS-tool as described in chapter 3. On top of usual care, in the clinical phase, the intervention group received a comprehensive geriatric assessment-based integrated care plan and geriatric team consultation on indication. In the discharge phase, the community nurse received an in hospital face-to-face handover from the cardiac nurse and met with the patient. In the post-clinical phase, the community nurse performed four home visits after discharge home and worked in close collaboration with an affiliated pharmacist in medication reconciliation and community physical therapists who performed up to nine home visits focussing on cardiac rehabilitation. This was the first trial to combine case management, disease management and home-based cardiac rehabilitation in the transition of care.

Chapter 5 presents the main outcomes of the CCB trial. In total, 306 participants were included in six hospitals in the region of Amsterdam. The mean age of the population was 82 years, 90% was acutely hospitalized and in 58% the admission was caused by heart failure. On the DSMS-tool items, 56% of the participants were at risk of delirium, 47% was at risk of falling, 39% was functionally impaired, and in 33% an indication for malnutrition was present. The results showed that in frail older (≥70 years) cardiac patients, the CCB intervention on top of usual care did not improve the primary composite outcome of first all-cause hospital readmission or mortality at six months after randomization (relative risk (RR) 1.14, 95% CI 0.91-1.42). The incidence proportion of the primary outcome was high, with 54.2% (83/153) in the intervention group and 47.7% (73/153) in the

control group. We hypothesized that the selected patient population may not be responsive to high-intensity preventive strategies.

In **chapter 6**, the cost-effectiveness of the CCB intervention was evaluated. Outcomes included a composite measure of first all-cause unplanned hospital readmission or mortality, Quality Adjusted Life Years (QALYs) and societal costs within six months follow-up. No differences in the composite outcome nor in societal costs were observed. QALYs were statistically significantly lower in the intervention group, mean difference -0.03 (95% CI: -0.07; -0.02). The CCB intervention was on average more expensive and less effective compared to usual care. Therefore, the CCB program cannot be considered cost-effective compared to usual care.

In **chapter 7**, a process evaluation of the CCB intervention was performed to evaluate the involved healthcare professionals' performance and treatment fidelity within the intervention. Quantitative data on intervention key-elements were collected from logbooks of all intervention patients and qualitative data were collected by semi-structured interviews with involved healthcare professionals (cardiac nurses, community nurses and community physical therapists). The overall fidelity based on the intervention key-elements was 67%, ranging from severely low (17%) in consultation of the in-hospital geriatric team, to maximum fidelity in the comprehensive geriatric assessment (100%). Main themes influencing the intervention performance that emerged from the interviews were interdisciplinary collaboration, organizational preconditions, confidence in the program, time management and patient characteristics. For instance, the patient's frailty status and limited motivation were mentioned as barriers in the intervention performance and was the interdisciplinary collaboration highly valued, however, difficult to organize. For future purposes, the feasibility of intervention key-elements should be reconsidered in relation to experienced barriers and the population to better meet older cardiac patients' needs.

Chapter 8 presents a multiple case study of CCB intervention patients with an unplanned hospital readmission. The aim of this study was to explore patients' and (in)formal caregivers' perspectives on their role(s) and contributing factors in the course of unplanned hospital readmission. In each of the five selected cases, we performed semi-structured interviews with patients, informal caregivers, CCB physical therapists, and CCB community nurses. To reconstruct the care processes and trends in vital signs prior to the unplanned readmission, patients' medical records were studied. Patients experienced acute episodes of physical deterioration before unplanned hospital readmission. Results from the interviews could be grouped into three themes: 1) the involvement of (in)formal caregivers in adequate observation of patients' health status is vital to prevent rehospitalization; 2) patients and (in)formal caregivers' perception of care needs did not always match, which resulted in hampered care support; 3) CCB caregivers experienced difficulties in providing care in some cases, resulting in limited care provision

in addition to the existing care services. It often lacked early detection of a deteriorating health status that led to the readmissions due to the acuteness of the deterioration. Empowerment of patients and their informal caregivers in the recognition of early signs of deterioration and adequate collaboration between caregivers could support early detection.

PART 3. New approaches in cardiac rehabilitation

In **chapter 9** a systematic review was performed on multidisciplinary rehabilitation in out-of-hospital settings in older (mean age ≥65 years) patients after hospital discharge for an acute illness. We studied the effect of multidisciplinary rehabilitation programs in out-patient settings, skilled nursing facilities or at home, on the level of mobility according to the 6-minute walking distance (6MWD) and on hospital readmission rates at three months follow-up. A total of 15 studies met the inclusion criteria. Of those, 12 studies were included in the meta-analysis. Based on the meta-analysis we found that patients receiving rehabilitation walked an average of 23 meter (95% CI -1.34-48.32) more than controls which was, however, not significant. The included rehabilitation programs did not lower the 3-month risk of unplanned hospital readmission (RR 0.93; 95% CI 0.73-1.19). Based on the findings, we conclude that multidisciplinary rehabilitation in an out-of-hospital setting leads to positive, however not significant trend in mobility. The included rehabilitation programs were not associated with a lower risk of unplanned hospital readmission.

In **chapter 10**, we evaluated the feasibility of home-based cardiac rehabilitation as part of the CCB intervention. The experiences of physical therapists regarding the applicability of cardiac rehabilitation guidelines and what adaptations were needed in frail older patients in a home-based setting, were evaluated. The interviewed physical therapists considered home-based rehabilitation in the frail cardiac patient population as feasible. Three main themes emerged from the data that support protocol adherence by physical therapists in cardiac rehabilitation in frail older cardiac patients: 1) feasibility of the exercise program and exercise testing, 2) patients' motivation and physical therapists' motivational techniques, and 3) interdisciplinary collaboration with other healthcare providers in monitoring patients' risks. Physical therapists described facilitators, such as organized inter-professional collaboration, and barriers, for instance high workload and limited financial compensation, for long-term implementation. Further research on the topic should focus on the identification of the optimal level of exercise intensity, match exercise tests and tools, and should integrate effective motivational interventions to optimize motivation in frail older cardiac patients.

In **chapter 11**, we present the results of a secondary analysis of the RESPONSE-2 trial data, in which we studied the influence of partners on successful modification of lifestyle-related risk factors (LRFs) in patients with coronary artery disease (CAD). The intervention consisted of nurse-coordinated referral to

community-based lifestyle programs (smoking cessation, weight reduction and/or physical activity) and was compared to usual care. The association between the presence of a partner and the level of partner participation on improvement in >1 LRF (urinary cotinine <200ng/l, ≥5% weight reduction, ≥10% increased 6-minute walking distance) without deterioration in other LRFs at 12 months follow-up, was studied. In total, 711 participants were included in the analysis. In conclusion, the presence of a partner was associated with patients' successful overall LRF modification (RR 1.93, 95% CI 1.40-2.51). A participating partner in the lifestyle programs was associated with successful weight reduction (RR 1.73, 95% CI 1.15-2.35). Involving partners of CAD patients in weight reduction interventions should be considered in routine practice.

A reflection on the main findings in this thesis is presented in the general discussion in **chapter 12**. Bridging the gap between hospital and home by combining disease management, case management and home-based cardiac rehabilitation did not lead to the desired reduction of readmission and mortality in frail cardiac patients. The CCB intervention is not recommended for implementation in clinical practice in its current form. If, with future adequate risk assessment high-risk patients eligible for high-intensity preventive interventions can be identified, the CCB intervention may be reconsidered. Interventions should as much as possible be integrated within existing care systems. To achieve goals, patients' own needs and preferences should be leading in future intervention development. Educational strategies focusing on interdisciplinary collaboration, system empowerment and identifying patients' own drivers could improve the intervention quality. By taking all these elements into account, we might be able to bridge the gap between current practice and frail cardiac patients' needs in the transition from hospital to home.

SAMENVATTING

OVERBRUGGEN VAN DE KLOOF

Aanpassing van de transitie van zorg aan de noden van oudere hartpatiënten

Dit proefschrift richt zich op het overbruggen van de kloof ("bridging the gap") tussen de huidige praktijk en de behoeften van oudere hartpatiënten in transities van zorg. In **hoofdstuk 1** geven we de context waarin het onderzoek in dit proefschrift is uitgevoerd. Na een ziekenhuisopname zijn de percentages ziekenhuisheropname en overlijden van oudere hartpatiënten hoog, respectievelijk 20% en 8%. Bij deze oudere patiënten zijn vaak meerdere ziekten en aandoeningen aanwezig (multimorbiditeit), en ook geriatrische problemen zoals ondervoeding en vallen spelen een rol. Dat maakt deze groep kwetsbaar, en deze kwetsbaarheid verhoogt het risico op heropnamen en overlijden nog meer. Bij kwetsbare patiënten met hart- en vaatziekten is het risico van heropname en mortaliteit 2 tot 3 maal hoger dan bij patiënten zonder kwetsbaarheid. De identificatie van 'risicopatiënten' is dus heel belangrijk omdat ze zo'n groot risico lopen. Identificatie zorgt er ook voor dat we adequate behandeling kunnen inzetten, gebaseerd op de individuele risicofactoren en behoeften van patiënten. Vooral patiënten die van de ene zorginstelling naar de andere worden overgeplaatst, of van het ziekenhuis naar huis worden ontslagen, lopen een verhoogd risico op heropname en overlijden. De doelen van dit proefschrift waren 1) om strategieën te evalueren om oudere hartpatiënten met een hoog risico op heropname en sterfte te herkennen, 2) een interventie te evalueren voor oudere hartpatiënten die van het ziekenhuis naar huis worden ontslagen 3) nieuwe benaderingen in hartrevalidatie te evalueren.

DEEL 1. Risicoscreening bij oudere hartpatiënten

In **hoofdstuk 2** werd het vermogen van de Systematic COronary Risk Evaluation - Older Persons (SCORE-OP) -instrument bestudeerd, om het 10-jaars risico op overlijden door hart- en vaatziekten te beoordelen. Dit is in een populatie van het European Prospective Investigation of Cancer Norfolk (EPIC-Norfolk) bevolkingscohort gedaan, welke vergelijkbaar is met de Nederlandse bevolking als het gaat om het risico op hart- en vaatziekten. Het gebruik van het instrument wordt aanbevolen door de Europese richtlijn voor de preventie van hart- en vaatziekten om te gebruiken bij de besluitvorming voor het behandelen van patiënten met risicofactoren. Bij personen tussen de 65-79 jaar zonder aanwezige hart- en vaatziekten, werd het voorspelde risico op overlijden door hart- en vaatziekten binnen 10 jaar berekend met het SCORE-OP-instrument, en vergeleken met de waargenomen sterftecijfers in het cohort. In totaal werden 6,590 personen (45.8% mannen en een gemiddelde leeftijd van 70 jaar) in de analyse opgenomen.

Op basis van onze bevindingen concluderen wij dat de SCORE-OP beperkt in staat is om mensen met een verhoogd risico te onderscheiden van mensen zonder verhoogd risico ('area under the curve' (AUC) 0.63). De SCORE-OP kan daarom niet zonder meer in de klinische praktijk worden toegepast. Toekomstig onderzoek zal moeten uitwijzen of het onderscheidende vermogen kan worden geoptimaliseerd.

Hoofdstuk 3 presenteert een onderzoek waarbij is geëvalueerd of het VeiligheidsManagement Systeem (VMS)-instrument geschikt is om patiënten met een hoog risico op heropname en overlijden te onderscheiden van mensen die geen verhoogd risico hebben. Het VMS- instrument wordt momenteel gebruikt bij alle patiënten van 70 jaar en ouder die in Nederlandse ziekenhuizen worden opgenomen. Het vermogen van het VMS-instrument om risico's bij specifiek oudere hartpatiënten in te schatten, is echter niet onderzocht. Het VMS-instrument is in een groep van 529 acuut opgenomen oudere (≥70 jaar) hartpatiënten onderzocht. Met betrekking tot de VMS-items die werden uitgevraagd, had 45% van de populatie een verhoogd risico op een delier, 41% een verhoogd valrisico, 37% had problemen in het dagelijkse functioneren en 29% was ondervoed. Het VMS-instrument was slechts matig in staat om oudere hartpatiënten met een verhoogd risico op heropname en overlijden te onderscheiden van patiënten zonder verhoogd risico met een AUC van 0.61. Door andere risicofactoren zoals de opnamediagnose en een index voor comorbiditeit (Charlson Comorbidity Index) toe te voegen in de analyse, was het instrument iets beter in staat om het risico in te schatten met een AUC van 0.69. In conclusie, het VMS-instrument is niet in staat om het risico op heropname en overlijden van oudere hartpatiënten bij opname in het ziekenhuis accuraat in te schatten. Verder onderzoek naar risicofactoren die heropname en overlijden in kunnen schatten is nodig om de risicoschatting te verbeteren.

DEEL 2. Organisatie van transitie van zorg bij oudere hartpatiënten: De Cardiologische Zorgbrug

Hoofdstuk 4 beschrijft de achtergrond en de studieopzet van de Cardiologische Zorgbrug (CZB) studie. De CZB-studie is ontwikkeld om heropname en overlijden bij kwetsbare oudere (≥70 jaar) hartpatiënten na een ziekenhuisopname te reduceren. In de groep die de CZB-interventie kreeg, zijn de principes van casemanagement, diseasemanagement en hartrevalidatie aan huis geïntegreerd in het proces in het ziekenhuis en thuis. Bij casemanagement staat een brede benadering van de eigen behoeften en doelstellingen van patiënten voorop die ondersteunend is tijdens transities van zorg. Bij diseasemanagement staat de begeleiding in het ziekteproces voorop. Bovenop de gebruikelijke zorg in de ziekenhuisfase, ontving de interventiegroep een uitgebreid geriatrisch onderzoek waarop een zorgplan in samenspraak met de patiënt werd ontwikkeld. Ook werd het geriatrisch team geconsulteerd als dit nodig was. In de ontslagfase

bezocht een wijkverpleegkundige het ziekenhuis voor een 'warme' overdracht van de cardiologieverpleegkundige en voor een ontmoeting met de patiënt. In de fase na ontslag uit het ziekenhuis, voerde de wijkverpleegkundige vier tot vijf huisbezoeken uit en werkte nauw samen met een apotheker om het medicatiegebruik te evalueren, en met fysiotherapeuten die tot negen huisbezoeken gericht op hartrevalidatie uitvoerden. De CZB-studie was de eerste studie waarin casemanagement, diseasemanagement en hartrevalidatie werden gecombineerd in de transitie van zorg voor kwetsbare oudere hartpatiënten.

In **hoofdstuk 5** presenteren wij de belangrijkste uitkomsten van de CZB-studie. In totaal werden 306 mensen geïncludeerd in zes ziekenhuizen in de regio van Amsterdam. De gemiddelde leeftijd van de mensen in de studie was 82 jaar, in totaal was 90% was acuut opgenomen in het ziekenhuis en bij 58% werd de opname veroorzaakt door hartfalen. Op de items van het VMS-instrument had 56% van de populatie een verhoogd risico op een delier, 47% had een risico op vallen, 39% was beperkt in het dagelijks functioneren, en in 33% was sprake van ondervoeding. De resultaten toonden aan dat bij kwetsbare oudere ($\geq$70 jaar) hartpatiënten de CZB-interventie bovenop de gebruikelijke zorg, heropname en overlijden binnen zes maanden na opname niet verbeterde (relatief risico (RR) 1.14, 95% CI 0.91-1.42). Het aantal heropnames of overlijdensgevallen was in allebei de groepen hoog, met 54% (83/153) in de CZB-interventiegroep en 48% (73/153) in de groep die de normale zorg ontving. Op basis van de bevindingen waarbij er geen betekenisvol verschil tussen de groepen is aangetoond en de implementatie van de interventie veel inzet vraagt, kan de CZB niet worden aanbevolen voor toepassing in de dagelijkse praktijk.

In **hoofdstuk 6** is de economische evaluatie van de CZB-interventie beschreven. In de analyse zijn zowel de zorgkosten als ook de maatschappelijke kosten vergeleken tussen de interventie- en de 'normale' zorggroep en in relatie gezet tot de CZB-uitkomst heropname of mortaliteit binnen zes maanden en voor kwaliteit van leven gecorrigeerde tijd die patiënten in een bepaalde gezondheidsstatus doorbrachten ("Quality Adjusted Life Years": QALYs). Naast een niet-significant verschil op heropname of overlijden binnen zes maanden, waren de kosten vanuit maatschappelijk perspectief ook niet significant verschillend tussen de groepen. De QALYs waren wel significant lager in de interventiegroep, verschil in gemiddelden -0.03 (95% CI: -0.07; -0.02). Op basis van deze analyse kan worden geconcludeerd dat de CZB-interventie niet is aan te bevelen voor implementatie in de dagelijkse praktijk.

In **hoofdstuk 7** werd een procesevaluatie van de CZB-interventie uitgevoerd om de uitvoering en ervaring van de betrokken zorgprofessionals binnen de interventie te evalueren. Informatie over de mate waarin de belangrijkste interventie elementen zijn uitgevoerd werd verzameld in de logboeken van alle interventiepatiënten. Verder zijn er interviews gehouden met betrokken zorgverleners (cardiologieverpleegkundigen, wijkverpleegkundigen en eerstelijns

fysiotherapeuten). In totaal werd in 67% de belangrijkste kernelementen van de CZB-interventie uitgevoerd. Dit varieerde van zeer laag, waarbij slechts in 17% van de indicaties het geriatrische team in consult werd gevraagd, tot maximaal in de uitvoering van het geriatrische onderzoek (100%). Uit de interviews kwamen een paar hoofdpunten naar voren die de interventie-uitvoering beïnvloedden, 1) interdisciplinaire samenwerking, 2) organisatorische voorwaarden, 3) vertrouwen in de interventie, 4) tijdsmanagement en 5) patiëntkenmerken. Zo werden de kwetsbaarheid van de patiënt en de beperkte motivatie als barrières genoemd in de uitvoering van de interventie en werd de interdisciplinaire samenwerking als zeer waardevol, maar lastig te organiseren ervaren. Om beter aan de behoeften van oudere hartpatiënten tegemoet te komen en om de aansluiting bij de praktijk te optimaliseren, zouden de CZB-kernelementen opnieuw geëvalueerd moeten worden.

Hoofdstuk 8 presenteert een 'multiple case study' van CZB-interventiepatiënten met een ongeplande heropname in het ziekenhuis. Het doel van deze studie was om de perspectieven van patiënten, zorgverleners en mantelzorgers op hun rol(len) en beïnvloedende factoren op het beloop van ongeplande ziekenhuisopname, te onderzoeken. In elk van de vijf geselecteerde casussen voerden we interviews uit met patiënten, mantelzorgers, CZB-fysiotherapeuten, en CZB-wijkverpleegkundigen. Om goed in kaart te brengen wat er zich in de periode voorafgaand aan een ongeplande ziekenhuisopname heeft afgespeeld, zijn de gerapporteerde waardes van bloeddruk, hartslag en gewicht onderzocht. De informatie uit de interviews kon in drie thema's worden samengevat, 1) de betrokkenheid van mantelzorgers en zorgverleners buiten de CZB interventie bij de observatie van de gezondheidstoestand van patiënten is van vitaal belang om heropname te voorkomen; 2) de mening over de zorgbehoeften van de patiënten, mantelzorgers en zorgverleners kwamen niet altijd overeen waardoor de zorgverlening in gevallen negatief beïnvloed werd; 3) CZB-zorgverleners ervoeren in sommige gevallen belemmeringen in de zorgverlening door de aanwezigheid van andere zorgverleners of mantelzorgers en voelden zich soms overbodig. Het ontbrak vaak aan vroegtijdige herkenning van een verslechterende gezondheidstoestand die tot de heropnames leidde vanwege de acute mate van de verslechtering. Het versterken van het herkennen van vroege tekenen van verslechtering door patiënten en hun mantelzorgers en het stimuleren van een laagdrempelige samenwerking tussen zorgverleners kan het proces ondersteunen.

DEEL 3. Nieuwe benaderingen in hartrevalidatie

In **hoofdstuk 9** wordt een systematische samenvatting beschreven over multidisciplinaire revalidatie bij oudere (gemiddelde leeftijd ≥65 jaar) patiënten na een acute ziekenhuisopname. We onderzochten het effect van revalidatieprogramma's in een poliklinische setting, een wijkziekenboeg of thuis

op de mate van mobiliteit met de 6-minuten wandeltest en op heropnames in het ziekenhuis, drie maanden na ontslag. In totaal voldeden 15 studies aan de inclusiecriteria en konden er 12 studies worden samengevat in een meta-analyse. Op basis van de meta-analyses vonden we dat patiënten die revalidatie kregen, gemiddeld 23 meter (95% CI -1.34-48.32) meer liepen dan de controlegroep, dit was echter niet significant en kan op toeval berusten. De revalidatieprogramma's in de studies verlaagden het risico op een ongeplande heropname op 3 maanden eveneens niet significant (RR 0.93; 95% CI 0.73-1.19). We concludeerden dat multidisciplinaire revalidatie in de onderzochte settingen leidt tot een positieve maar niet significante trend in mobiliteit en niet tot de gewenste reductie van heropnames.

In **hoofdstuk 10** is de haalbaarheid van hartrevalidatie aan huis binnen de CZB-interventie geëvalueerd. Het onderzoek richtte zich op ervaringen van fysiotherapeuten met betrekking tot de toepasbaarheid van hartrevalidatierichtlijnen en welke aanpassingen nodig zijn bij kwetsbare oudere (≥70 jaar) patiënten in de thuissituatie. De geïnterviewde fysiotherapeuten beschouwden thuisrevalidatie bij kwetsbare hartpatiënten als haalbaar en drie belangrijke thema's kwamen naar voren die van invloed zijn op de haalbaarheid van het programma: 1) het op maat aanpassen van oefeningen (bijv. lagere intensiteit, verschillende inspanningstesten en -instrumenten); 2) het stimuleren van de motivatie van patiënten; 3) het samen met andere disciplines monitoren van het heropnamerisico. Fysiotherapeuten gaven aan dat bijvoorbeeld de interprofessionele samenwerking stimulerend was en dat bijvoorbeeld de hoge werkdruk en beperkte financiële compensatie voor implementatie op lange termijn barrières kunnen zijn. Het is belangrijk om in verder onderzoek de nadruk te leggen op het inspanningsniveau waarop patiënten het beste kunnen trainen, passende keuze voor inspanningstesten en instrumenten en effectieve motiverende interventies om de motivatie van kwetsbare oudere hartpatiënten te optimaliseren.

In **hoofdstuk 11** werd de invloed van partners op succesvolle verandering van leefstijl gerelateerde risicofactoren bij 711 patiënten met coronaire hartziekten onderzocht in de onderzoeksgegevens van de RESPONSE-2 studie. De RESPONSE-2 interventie bestond uit een verpleegkundig gecoördineerde verwijzing naar drie leefstijlprogramma's gericht op stoppen met roken, gewichtsverlies en/of lichaamsbeweging. Dit werd vergeleken met de gebruikelijke zorg. De invloed van de aanwezigheid van een partner en partnerdeelname aan de leefstijlprogramma's op de verbetering van ≥1 risicofactor (urine cotinine <200ng/l, ≥5% gewichtsverlies, ≥10% toename in de 6-minuten wandeltest), werd onderzocht. Na 12 maanden bleek het hebben van een partner geassocieerd te zijn met de verbetering van ≥1 risicofactor bij patiënten (RR 1.93, 95% CI 1.40-2.51). Actieve deelname van een partner aan de leefstijlprogramma's was geassocieerd met succesvolle gewichtsafname bij patiënten (RR 1.73, 95% CI

1.15-2.35). Het betrekken van partners van patiënten met coronaire hartziekten bij programma's die gericht zijn op gewichtsreductie is op basis van de bevindingen aan te bevelen.

Een reflectie op de belangrijkste bevindingen wordt gepresenteerd in de algemene discussie in **hoofdstuk 12**. Dit proefschrift laat zien dat het overbruggen van de kloof ("bridging the gap") tussen de huidige praktijk en de aansluiting bij de behoeften van oudere hartpatiënten in de transitie van zorg door middel van de CZB-interventie niet leidt tot de gewenste daling in heropname of overlijden. De CZB-interventie wordt in de huidige vorm niet aanbevolen voor implementatie in de klinische praktijk, zowel vanuit effectiviteits- als kostenperspectief. Als in de toekomst de hoog risicopatiënten adequater kunnen worden geïdentificeerd en beter in kaart kan worden gebracht welke doelpopulatie in aanmerking komt voor intensieve preventieve interventies, dan kan de CZB-interventie heroverwogen worden. Het is van belang dat 'nieuwe' interventies zoveel mogelijk worden geïntegreerd binnen bestaande zorgsystemen om integratie te bevorderen. Om doelstellingen te bereiken, zouden de individuele behoeften en voorkeuren van patiënten zelf nog meer leidend moeten zijn bij de toekomstige interventieontwikkeling. Educatieve strategieën die gericht zijn op interdisciplinaire samenwerking, zelfredzaamheid van patiënten, mantelzorgers en reeds betrokken zorgverleners en het identificeren van de eigen drijfveren van patiënten, kunnen de kwaliteit van de interventie verbeteren. Door met al deze elementen rekening te houden, kan de kloof tussen de huidige praktijk en de behoeften van kwetsbare oudere hartpatienten en tussen ziekenhuisopname en huis, in de toekomst mogelijk alsnog worden overbrugd.

AUTHOR CONTRIBUTION

Chapter 1

General introduction

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

Chapter 2

Lotte Verweij, Ron JG Peters, Wilma JM Scholte op Reimer, S Matthijs Boekholdt, Robert M Luben, Nicholas J Wareham, Kay-Tee Khaw, Corine HM Latour, Harald T Jørstad. Validation of the Systematic COronary Risk Evaluation - Older Persons (SCORE-OP) in the EPIC-Norfolk prospective population study. Int J Cardiol. 2019 Oct 15;293:226-230.

Concept and design	Lotte Verweij, Ron JG Peters, Wilma JM Scholte op Reimer, S Matthijs Boekholdt, Harald T Jorstad
Data collection	Robert M Luben, Nicholas J Wareham, Kay-Tee Khaw
Statistical analysis	Lotte Verweij, Harald T Jorstad
Interpretation of data	Lotte Verweij, Ron JG Peters, Wilma JM Scholte op Reimer, S Matthijs Boekholdt, Harald T Jorstad
Drafting the manuscript	Lotte Verweij, Harald T Jorstad
Critical revision of the manuscript	Ron JG Peters, Wilma JM Scholte op Reimer, S Matthijs Boekholdt, Corine HM Latour

Chapter 3

Patricia Jepma, Lotte Verweij, Arno Tijssen, Martijn W Heymans, Isabelle Flierman, Corine HM Latour, Ron JG Peters, Wilma JM Scholte op Reimer, Bianca M Buurman, Gerben 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. BMC Geriatr. 2021 May 8;21(1):299. doi: 10.1186/s12877-021-02243-5

Concept and design	Patricia Jepma, Lotte Verweij, Arno Tijssen, Martijn W Heymans, Isabelle Flierman, Corine HM Latour, Ron JG Peters, Wilma JM Scholte op Reimer, Bianca M Buurman, Gerben ter Riet
Data collection	Patricia Jepma, Lotte Verweij, Isabelle Flierman, Bianca M Buurman

Statistical analysis	Arno Tijssen, Martijn W Heymans, Gerben ter Riet
Interpretation of data	Patricia Jepma, Lotte Verweij, Arno Tijssen, Gerben ter Riet
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Critical revision of the manuscript	Arno Tijssen, Martijn W Heymans, Isabelle Flierman, Corine HM Latour, Ron JG Peters, Wilma JM Scholte op Reimer, Bianca M Buurman

Chapter 4

Lotte Verweij*, Patricia Jepma*, Bianca M Buurman, Corine HM Latour, Raoul HH Engelbert, Gerben ter Riet, Fatma Karapinar - Çarkit, Sara Daliri, Ron JG Peters, Wilma JM Scholte op Reimer. 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 Serv Res. 2018 Jun 28;18(1):508. doi:10.1186/s12913-018-3301-9

Concept and design	Patricia Jepma, Lotte Verweij, Bianca M Buurman, Corine HM Latour, Raoul HH Engelbert, Gerben ter Riet, Fatma Karapinar-Çarkit, Sara Daliri, Ron JG Peters, Wilma JM Scholte op Reimer
Data collection	Not applicable
Statistical analysis	Patricia Jepma, Lotte Verweij, Gerben ter Riet
Interpretation of data	Patricia Jepma, Lotte Verweij, Gerben ter Riet
Drafting the manuscript	Patricia Jepma, Lotte Verweij
Critical revision of the manuscript	Bianca M Buurman, Corine HM Latour, Raoul HH Engelbert, Gerben ter Riet, Fatma Karapinar- Çarkit, Sara Daliri, Ron JG Peters, Wilma JM Scholte op Reimer

Chapter 5

Lotte Verweij*, Patricia Jepma*, Bianca M Buurman, Michel S Terbraak, Sara Daliri, Corine HM Latour, Gerben ter Riet, Fatma Karapinar - Çarkit, Jill Dekker, Jose L Klunder, Su-San Liem, Arno HM Moons, Ron JG Peters, Wilma JM Scholte op Reimer. The Nurse-Coordinated Cardiac Care Bridge Transitional Care Programme: A Randomised Clinical Trial. Submitted

Concept and design	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
Data collection	Patricia Jepma, Lotte Verweij, Michel S Terbraak, Sara Daliri
Statistical analysis	Patricia Jepma, Lotte Verweij, Gerben ter Riet
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 6

Lotte Verweij*, Adrianne CM Petri*, Janet L Vroomen MacNeil, Patricia Jepma Corine HM Latour, Ron JG Peters, Wilma JM Scholte op Reimer, Bianca M Buurman, Judith E Bosmans. 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

Concept and design	Lotte Verweij, Janet L Vroomen MacNeil, Judith E Bosmans
Data collection	Lotte Verweij, Patricia Jepma
Statistical analysis	Lotte Verweij, Adrianne CM Petri, Judith E Bosmans
Interpretation of data	Lotte Verweij, Adrianne CM Petri, Janet L Vroomen MacNeil, Patricia Jepma, Corine HM Latour, Ron JG Peters, Wilma JM Scholte op Reimer, Bianca M Buurman, Judith E Bosmans
Drafting the manuscript	Lotte Verweij, Adrianne CM Petri, Judith E Bosmans
Critical revision of the manuscript	Janet L Vroomen MacNeil, Patricia Jepma, Corine HM Latour, Ron JG Peters, Wilma JM Scholte op Reimer, Bianca M Buurman, Judith E Bosmans

Chapter 7

Lotte Verweij, Denise F Spoon, Michel S Terbraak, Patricia Jepma, Ron JG Peters, Wilma JM Scholte op Reimer, Corine HM Latour, Bianca M Buurman. The Cardiac Care Bridge randomized trial in highrisk older cardiac patients: A mixed-methods process evaluation. J Adv Nurs. 2021 May;77(5):2498-2510. doi: 10.1111/jan.14786

Concept and design	Lotte Verweij, Denise F Spoon, Michel S Terbraak, Patricia Jepma, Ron JG Peters, Wilma JM Scholte op Reimer, Corine HM Latour, Bianca M Buurman
Data collection	Lotte Verweij, Denise F Spoon, Michel S Terbraak, Patricia Jepma
Statistical analysis	Lotte Verweij, Denise F Spoon, Michel S Terbraak, Patricia Jepma
Interpretation of data	Lotte Verweij, Denise F Spoon, Michel S Terbraak, Patricia Jepma, Ron JG Peters, Wilma JM Scholte op Reimer, Corine HM Latour, Bianca M Buurman
Drafting the manuscript	Lotte Verweij, Denise F Spoon, Michel S Terbraak, Patricia Jepma
Critical revision of the manuscript	Ron JG Peters, Wilma JM Scholte op Reimer, Corine HM Latour, Bianca M Buurman

Chapter 8

Corinne J Rijpkema, Lotte Verweij, Patricia Jepma, Corine HM Latour, Ron JG Peters, Wilma JM Scholte op Reimer, Bianca M Buurman. The course of readmission in frail older cardiac patients: A qualitative multiple case study on factors contributing to unplanned hospital readmission. J Adv Nurs. 2021 Jun;77(6):2807-2818. doi: 10.1111/jan.14828

Concept and design	Corinne J Rijpkema, Lotte Verweij, Bianca M Buurman
Data collection	Corinne J Rijpkema, Lotte Verweij, Patricia Jepma
Statistical analysis	Corinne J Rijpkema, Lotte Verweij
Interpretation of data	Corinne J Rijpkema, Lotte Verweij, Patricia Jepma, Corine HM Latour, Ron JG Peters, Wilma JM Scholte op Reimer, Bianca M Buurman
Drafting the manuscript	Corinne J Rijpkema, Lotte Verweij
Critical revision of the manuscript	Patricia Jepma, Corine HM Latour, Ron JG Peters, Wilma JM Scholte op Reimer, Bianca M Buurman

Chapter 9

Lotte Verweij, Eva van de Korput, Joost G Daams, Gerben ter Riet, Ron JG Peters, Raoul HH Engelbert, Wilma JM Scholte op Reimer, Bianca M Buurman. Effects of Postacute Multidisciplinary Rehabilitation Including Exercise in Outof-Hospital Settings in the Aged: Systematic Review and Meta-analysis. Arch Phys Med Rehabil. 2019 Mar;100(3):530-550

Concept and design	Lotte Verweij, Eva van de Korput, Raoul HH Engelbert, Wilma JM Scholte op Reimer, Bianca M Buurman
Data collection	Lotte Verweij, Eva van de Korput, Joost G Daams
Statistical analysis	Lotte Verweij, Eva van de Korput, Gerben ter Riet
Interpretation of data	Lotte Verweij, Eva van de Korput, Joost G Daams, Gerben ter Riet, Ron JG Peters, Raoul HH Engelbert, Wilma JM Scholte op Reimer, Bianca M Buurman
Drafting the manuscript	Lotte Verweij, Eva van de Korput
Critical revision of the manuscript	Joost G Daams, Gerben ter Riet, Ron JG Peters, Raoul HH Engelbert, Wilma JM Scholte op Reimer, Bianca M Buurman

Chapter 10

Michel S Terbraak, Lotte Verweij, Patricia Jepma, Bianca M Buurman, Harald T Jørstad, Wilma JM Scholte op Reimer, Marike van der Schaaf. Feasibility of home-based cardiac rehabilitation in frail older patients: a clinical perspective. Submitted

Concept and design	Michel S Terbraak, Lotte Verweij, Patricia Jepma, Bianca M Buurman, Wilma JM Scholte op Reimer

Data collection	Michel S Terbraak
Statistical analysis	Michel S Terbraak, Lotte Verweij
Interpretation of data	Michel S Terbraak, Lotte Verweij, Patricia Jepma, Bianca M Buurman, Harald T Jørstad, Wilma JM Scholte op Reimer, Marike van der Schaaf
Drafting the manuscript	Michel S Terbraak, Lotte Verweij
Critical revision of the manuscript	Patricia Jepma, Bianca M Buurman, Harald T Jørstad, Wilma JM Scholte op Reimer, Marike van der Schaaf

Chapter 11

Lotte Verweij, Harald T Jørstad, Madelon Minneboo, Gerben ter Riet, Ron JG Peters, Wilma JM Scholte op Reimer, Marjolein Snaterse on behalf of the RESPONSE-2 Study Group. The influence of partners on successful lifestyle modification in patients with coronary artery disease. Int J Cardiol. 2021 Jun 1;332:195-201. doi: 10.1016/j.ijcard.2021.04.007

Concept and design	Lotte Verweij, Harald T Jørstad, Marjolein Snaterse
Data collection	Harald T Jørstad, Madelon Minneboo, Marjolein Snaterse
Statistical analysis	Lotte Verweij, Gerben ter Riet
Interpretation of data	Lotte Verweij, Harald T Jørstad, Gerben ter Riet, Ron JG Peters, Wilma JM Scholte op Reimer, Marjolein Snaterse
Drafting the manuscript	Lotte Verweij, Harald T Jørstad, Marjolein Snaterse
Critical revision of the manuscript	Madelon Minneboo, Gerben ter Riet, Ron JG Peters, Wilma JM Scholte op Reimer, Marjolein Snaterse

Chapter 12

General discussion

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

*Authors equally contributed to the manuscript

PHD PORTFOLIO

Name PhD student:	Lotte Verweij
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
Courses		
European Academy of Nursing Science, Summer School for Doctoral Studies	2015 - 2017	7.5
Basiskwalificatie Didactische Bevoegdheid	2015	10
Clinical data management	2015	0.9
Medical Literature: Endnote	2015	0.1
Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers (BROK)	2015, 2019	1.0
Clinical epidemiology: Randomized Clinical trial	2016	0.6
Clinical epidemiology: Systematic Review	2016	0.7
Qualitative health research	2016	1.9
Scientific writing in English for publication	2017	1.5
Practical Biostatistics	2017	1.1
Kennis van zorgkosten - E-infusie	2018	0.3
Doelmatigheidsonderzoek: methoden en principes (K72), EpidM VUMC	2018	0.6
Ted-talk training, debat.nl	2019	0.3
Seminars, workshops and masterclasses		
Masterclass Transitional Care by Prof. dr. Mary Naylor	2017	0.2
Masterclass Hartcentrum Amsterdam UMC, de kwetsbare cardiologische patiënt en transitie zorg	2017	0.2
Weekly Research meeting Complex Care, University of Applied Sciences and Amsterdam UMC	2015 - 2021	2.0

Oral presentations

Cardiac Care Bridge, ECN, Rotterdam	2016	0.5
De Cardiologische Zorgbrug studie, CarVasz, Ede	2017	0.5
Validation of the Systematic COronary Risk Evaluation - Older Persons (SCORE-OP), EuroPrevent, Lisboa	2019	0.5
De Cardiologische Zorgbrug studie, symposium Implementatie van geriatrisch comanagement en innovatieve zorgmodellen, KU Leuven	2019	0.5
Validation of the Systematic COronary Risk Evaluation - Older Persons (SCORE-OP), EuGMS, Krakau	2019	0.5
Symposium Cardiologische Zorgbrug studie, Geriatriedagen, Den Bosch	2020	0.5
Bridging hospital to home: which are the options? ESC online conference	2020	0.5

Poster presentations

Cardiac Care Bridge study protocol, ECN, Rotterdam	2016	0.5
Geriatric rehabilitation in non-hospital setting, Geriatriedagen, Den Bosch	2017	0.5
Cardiac Care Bridge study protocol, EANS, Malmö	2017	0.5
Cardiac Care Bridge process evaluation, EuGMS, Krakau	2019	0.5
Influence of partners on lifestyle modification, including press release, ESC online conference	2020	0.5

2. Teaching

Lecturing

Lecturer, Amsterdam University of Applied Sciences, School of Nursing, 0,2 fte	2014 - present	4.0
Development of the post-bachelor courses Cardiac Care Bridge and Transitional Care Bridge	2016	2.0
Lecturer, Amsterdam University of Applied Sciences, School of Nursing – Post-bachelor courses Cardiac Care Bridge and Transitional Care Bridge	2016 - 2018	2.0

Supervising

Eva van de Korput, master thesis	2016	1.0
Denise Spoon, master thesis	2018	1.0
Corinne Rijpkema, master thesis	2019	1.0
Janne Petri, master thesis	2020	1.0

3. Parameters of esteem

Grants

Promotiebeurs voor leraren, Nederlandse organisatie voor wetenschappelijk onderzoek (NWO)	2016
Invoering en structurele borging van innovaties in het zorg- en welzijnsstelsel voor ouderen, ZonMw	2016

Award

Best of Journal of Nursing Scholarship Award - Health Policies and Systems, The Honor Society of Nursing, Sigma Theta Tau	2016

LIST OF PUBLICATIONS

Scientific publications

1. **Verweij L***, Jepma P*, Buurman BM, Terbraak MS, Daliri S, Latour CHM, ter Riet G, Karapinar-Çarkit F, Dekker J, de Jong JSSG, Liem S, Moons AHM, Peters RJG, Scholte op Reimer WJM. Effect of The Nurse-Coordinated Cardiac Care Bridge Transitional Care Program in High-Risk Older Cardiac Patients: A Randomized Clinical Trial. *Submitted*

2. **Verweij L***, Petri ACM*, MacNeil Vroomen JL, Jepma P, Latour CHM, Peters RJG, Scholte op Reimer WJM, Buurman BM, Bosmans J. 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*

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

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

5. Jepma P, Latour CHM, ten Barge IHJ, **Verweij L**, Peters RJG, Scholte op Reimer WJM, Buurman BM. Experiences with the Cardiac Care Bridge transitional care program: a qualitative study in frail older cardiac patients. *Submitted*

6. 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*

7. 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. BMC Geriatr. 2021 May 8;21(1):299. doi: 10.1186/s12877-021-02243-5

8. **Verweij L**, Jørstad HT, Minneboo M, ter Riet G, Peters RJG, Scholte op

Reimer WJM, Snaterse M, on behalf of the RESPONSE-2 Study Group. The influence of partners on successful lifestyle modification in patients with coronary artery disease. Int J Cardiol. 2021 Jun 1;332:195-201. doi: 10.1016/j.ijcard.2021.04.007

9. Rijpkema C, **Verweij L**, Jepma P, Latour CHM, Peters RJG, Scholte op Reimer WJM, Buurman BM. The course of readmissions in frail older cardiac patients: A multiple case study. J Adv Nurs. 2021 Jun;77(6):2807-2818. doi: 10.1111/jan.14828

10. **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 May;77(5):2498-2510. doi: 10.1111/jan.14786

11. **Verweij L**, Peters RJG, Scholte op Reimer WJM, Boekholdt SM, Luben RM, Wareham NJ, Khaw KT, Latour CHM, Jørstad HT. Validation of the Systematic COronary Risk Evaluation - Older Persons (SCORE-OP) in the EPIC-Norfolk prospective population study. Int J Cardiol. 2019;15;293:226-230. doi: 10.1016/j.ijcard.2019.07.020

12. **Verweij L**, Jepma P, 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 Serv Res. 2018 Jun 28;18(1):508. doi:10.1186/s12913-018-3301-9

13. **Verweij L**, van de Korput E, Daams JG, ter Riet G, Peters RJG, Engelbert RHH, Scholte op Reimer WJM, Buurman BM. Effects of post-acute multidisciplinary rehabilitation in out-of-hospital settings in the aged: Systematic review and meta-analysis. Arch Phys Med Rehabil. 2019;100(3):530-550. doi: 10.1016/j.apmr.2018.05.010

14. Vink P, **Verweij L**, van Erp WS, Lucas C, Vermeulen H. How is pain assessed in patients with disorders of consciousness? A survey of national policies in Dutch hospitals and nursing homes. British Journal of Neuroscience Nurses. 2015;11(1):34-40

15. Smeulers M, **Verweij L**, Maaskant JM, de Boer M, Krediet CTP, Nieveen van Dijkum EJM, Vermeulen H. Quality indicators for safe medication preparation and administration: a systematic review. PLoS One. 2015;17;10(4):e0122695.

doi: 10.1371/journal.pone.0122695

16. **Verweij L**, Smeulers M, Maaskant JM, Vermeulen H. Quiet please! Drug round tabards, are they effective and accepted? A mixed method study. J Nurs Scholarsh. 2014;46(5):340-8. doi: 10.1111/jnu.12092

17. Storm-Versloot MN, **Verweij L**, Lucas C, Ludikhuize J, Goslings JC, Legemate DA, Vermeulen H. Clinical relevance of routinely measured vital signs in hospitalized patients, a systematic review. J Nurs Scholarsh. 2014;46(1):39-49. doi: 10.1111/jnu.12048

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Other publications

1. **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

2. **Verweij L**, Jepma P. De Cardiologische Zorgbrug. Nurse Academy O&T. 2020(1):25-30

3. **Verweij L**, Jepma P. De Cardiologische Zorgbrug. Nurse Academy. 2019(4):25-29

4. **Verweij L**, Jepma P. Complexe interventies: het wat, hoe en waarom. TVZ - Verpleegkunde in praktijk en wetenschap. 2019;129(5):56-57

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DANKWOORD

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CURRICULUM VITAE

Lotte Verweij was born in Nijmegen, the Netherlands on March 13th 1983 and grew up with her parents Jacques Verweij and Lilian Verweij- van Herk and her younger sister Merel. After finishing secondary school in Almere, she started her vocational nursing education in Utrecht and graduated nursing school in 2006 at the Amsterdam University of Applied Sciences, faculty of Nursing. She started her career at the department of Neurosurgery and Neuro-Medium Care at the Academic Medical Center, Amsterdam, where she performed her last internship. Lotte became a Medium Care nurse in 2007, and in 2008 she was promoted to 'senior nurse' with a team leading position and a specific focus on quality improvement and innovation at the same department.

Alongside her clinical career, Lotte started a Master in Clinical Epidemiology 'Evidence-Based Practice' at the University of Amsterdam in 2009 and graduated in 2011. Her master thesis on 'the clinical relevance of routinely measured vital signs in hospitalized patients' was internationally published and awarded by The Honor Society of Nursing, Sigma Theta Tau. After graduation, in 2011, Lotte joined a research project on medication safety next to her clinical career, at the Department of Quality and Safety at the Academic Medical Center.

After living for one year in Toronto, Canada, Lotte started as a lecturer in Nursing at the Amsterdam University of Applied Sciences in 2014. In the same year she parallel started her doctorate with a focus on transitional care in older cardiac patients, under supervision of prof. dr. W.J.M. Scholte op Reimer and prof. dr. R.J.G. Peters.

In 2017 Lotte moved to Zürich, Switzerland and continued her work in Amsterdam until the end of her doctorate. In 2020 she started collaboration in a project focusing on 'hospital at home' of the Zollikerberg hospital. After graduating her doctorate, Lotte will start as a postdoctoral researcher at the University (Hospital) of Zürich, Institute for Implementation Science in Nursing. Lotte is very grateful for the enormous support from her supervisors in Amsterdam to finish her doctorate, and is now looking forward to focus on her life and career in Zürich.

Lotte is married to Menno Germans and is mother of two daughters, Fenne Lianne (2014) and Mara Sophia (2018).