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Non-adherence: A challenge of non-adherence for early rehabilitation after coronary artery bypass surgery; secondary results from the SheppHeartCABG trial

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Abstract

Background: Attending and maintaining cardiac rehabilitation programme is a challenge.

Aims: To explore associations between non-adherence to early Coronary Artery Bypass Graft (CABG) rehabilitation and sociodemographic and clinical baseline data.

Methods: CABG patients were randomized 1:1 to either 4 weeks of comprehensive early rehabilitation or usual care. Outcomes were assessed at three [time-points points in time]: baseline, discharge and 4 weeks post-CABG. Differences in sociodemographic and clinical baseline data in adherent versus non-adherent patients were tested using the Pearson χ^2 test for categorical variables. To test associations between non-adherence to exercise training and sociodemographic and clinical baseline data, multivariate logistic regression was used to estimate odds ratio (OR) for in-hospital training and post-discharge training adjusted for age, sex and Left Ventricular Ejection Fraction (LVEF).

Results: Non-adherence to in-hospital versus post-discharge exercise training was 31% (n=48) versus 53% (n=81). Female non-adherence was 20% versus 70%. Non-adherence to in-hospital versus post-discharge mindfulness was 87% versus 70%. Male non-adherence to mindfulness was 85% versus 70%. Non-adherence to psycho-educational consultations was 3%, most of whom were men. Patients with university level education were more adherent to in-hospital exercise training than patients with lower educational level (odds ratio=3.14 (95% confidence interval (CI); 1.16-8.51), $p=0.02$). Diabetic patients were more non-adherent to exercise training after discharge (3.74, (1.54-9.08), $p=0.004$) as were overweight patients (0.37(0.17—0.80), $p=0.01$).

Conclusions: This study demonstrated wide acceptance of psycho-educational consultations in post-CABG patients. Adherence to physical rehabilitation was low especially after discharge from hospital and the opportunity to attend a mindfulness programme was not used.

Keywords: Adherence, early rehabilitation, coronary artery bypass grafting, exercise psycho-education.

Trial registration: www.clinicaltrials.gov identifier; NCT02290262

INTRODUCTION

Open heart surgery represents both a physical and mental strain on the patients that might delay return to normal everyday life.¹⁻³ Phase two rehabilitation⁶ (outpatient rehabilitation) and, perhaps, phase one rehabilitation (during early admission), helps patients to return to their everyday life⁴ after CABG.^{5,6} In this article we regard both phases as early rehabilitation and part of the CABG treatment.

Poor adherence to treatment is common and has implications for cost and effectiveness. The World Health Organization (WHO)⁷ define adherence as “the extent to which a person’s behavior corresponds with agreed recommendations from a healthcare provider”. Physical training is safe, even during the early postoperative period,⁸ however adherence to physical training is a challenge during phase one rehabilitation.⁹ Previous research has focused on phase two rehabilitation adherence for post-CABG patients¹⁰ and has identified “belief in own capability” (self-efficacy) in relation to exercise training to increase adherence.¹¹ Furthermore, belief in the effectiveness of cardiac rehabilitation is a predictor of adherence.¹²

Results from the randomized clinical trial SheppHeartCABG (Shaping outcomes by Exercise Training and Psycho-education in Phase One for Heart Patients) showed no differences between the intervention group (exercise training and psycho-education) and the usual care group on the primary outcome, the Six Minute-Walk Test (6MWT) four weeks after surgery.¹² Poor adherence to the programme could, perhaps, explain the negative results. We made an ancillary analysis and detected an association between the two groups. For this reason, we wish to explore what predicts low adherence to cardiac rehabilitation in this population.

The objective of this paper was to explore the association of non-adherence to early rehabilitation after CABG and sociodemographic and clinical baseline data.

METHODS

A total of 326 patients referred for CABG (on-pump technique) were randomized to comprehensive early rehabilitation versus usual care in the SheppHeartCABG randomized controlled trial (Figure 1). Sixteen patients dropped out or refused consent to use their data during the intervention. Of the 310 remaining patients, 152 were allocated to the experimental group, 132 male and 20 female patients with a mean age of 65 years ($SD \pm 9.1$). Sociodemographic data were age, sex, habitation status, occupational status and educational level. Clinical baseline data were body mass index (BMI), New York Heart Association (NYHA) classification, Left Ventricular Ejection Fraction (LVEF), diabetes mellitus (DM) and smoking. Prescribed medication was retrieved from medical records at baseline after signed consent.

Intervention

The comprehensive rehabilitation programme included both exercise training and a psycho-educational consultation. Four weeks of exercise training began at admission and lasted until four weeks after surgery. In-hospital and outpatient training were led by a physiotherapist providing pre-discharge instructions.

The in-hospital programme included: 1) respiratory therapy with four daily sessions of 7-10 deep breaths and breathing exercises consisted 3–5 min of breathing in the PEP-flute four times daily during postoperative days 1 through 4: 2) neck and shoulder exercises consisted shoulder lifts, shoulder rolls and head rolls with 10 sessions of each exercise twice daily from postoperative day 1 until hospital discharge: 3) walk exercises were performed in the hallway at the hospital ward on postoperative day 1 to 4 weeks post-surgery and began the first postoperative day with a 2×5 min walk with increased the intensity of walk and: 4) cycling conducted as two daily 10 minutes session with 5 min warm-up and 5 min cool-down on stationary bicycles from postoperative day 3 until hospital discharge.

The after-discharge programme consisted of daily resistance training and walking.

The psycho-educational programme began on the day of admission and included three in-hospital nurse consultations (one before surgery, one after admission to the ward after discharge from the intensive unit and the last before discharge) and one outpatient telephone nurse consultation three weeks after surgery. Psycho-education involved information and education on managing life after CABG, including both physical and emotional responses. The perspective was holistic to establish a joint approach to disease management and coping inspired by Parse's Human Becoming practice methodology.¹³ The consultations included a brief mindfulness intervention developed for the trial. Patients were introduced to mindfulness during the first consultation by a short exercise and instructed to use an audio mindfulness programme between consultations. The psycho-educational component was led by six nurses experienced in care of CABG patients.

All patients in the trial received usual care according to guidelines.^{14,15} Usual treatment involved preoperative and postoperative information provided by physicians, nurses and physiotherapists. Perioperative nursing included an introduction to post-operative pain and nausea medications, pain assessment, and post-operative activities. Early postoperative care focused on the observation of vital signs, while the remainder of the hospital admission focused on recovery and preparation for discharge. Usual care did not include either systematic exercise, mindfulness or systematic psycho-educational follow-up.

Outcomes measures

Adherence to the intervention was defined in the protocol as completing at least 75% of the exercises, mindfulness sessions and consultations.¹⁶ However, only one participant adhered to the programme at that level. Consequently, adherence was accepted if at least 50% of the exercise sessions and psycho-educational consultations were completed. The argument for changing adherence was pragmatic. Adherence to the exercise training intervention was assessed using the

patients' reported exercise diary and by the psycho-educational intervention recordings obtained at each consultation.

Statistical methods and strategy of analysis

Baseline sociodemographic and clinical data differences between adherent and non-adherent patients were tested using the Pearson χ^2 test for categorical variables.

The analysis for testing association between non-adherence to exercise training and sociodemographic and clinical data was multivariate logistic regression. This model was used to estimate odds ratio (OR) for training during hospitalization and training after discharge first non-adjusted and then adjusted for age, sex and LVEF which are known to influence physical capacity. The sociodemographic data age, occupational status and educational level, NYHA class, and LVEF were dichotomised. The rationale for dichotomizing was based on clinical application of the results and to increase the number of patients in each group and thereby increase power. It was clinically meaningful to know how a given variable divided into two groups influenced. The significance level was set at 0.05. Data was analysed using SPSS version 22 (IBM Corp., Armonk, NY, USA).

Ethical Considerations

Patients gave their informed written consent after receiving verbal and written information. All data was treated in confidence and patients were assured anonymity. The trial followed the recommendations of the latest Declaration of Helsinki and was approved by the regional Ethics Committee (no. H-4-2014-109) and the Danish Data Protection Agency (no. 30-1309). The trial was registered at ClinicalTrials.gov (ID NCT02290262).

RESULTS

Non-adherence related to sociodemographic and clinical baseline data see Table 1.

In the experimental group 31% were non-adherent to the exercise training programme during hospitalization. A total of 53% patients did not participate in outpatient exercise training, with females showing a lower value than men - 20% females did not participate in hospital and 70% out of hospital. Non-adherence to mindfulness for all groups was 87% in-hospital and 70% after discharge. A total of 85% male patients did not used mindfulness in hospital and 70% after discharge. In contrast only 3% were non-adherence to the psycho-educational consultations of which 4 (80%) were men.

Baseline sociodemographic data and clinical characteristics of the experimental group tested for adherence/non-adherence differences are presented in Table 2. Non-adherence during hospitalization was associated with educational level and with diabetes. Use of beta-blockers during hospitalization and the occupational status were different among patients adherent and non-adherent to exercise training. After discharge differences in the use of anti-diabetic and analgesic medication were found, while there were no differences in age, sex, NYHA class and LVEF.

Those patients who had obtained a university degree were more adherent than others OR=3.14, (CI; 1.16-8.51) adjusted for age, sex and LVEF (Table 3) and diabetic patients were more non-adherent to exercise training after discharge than patients without diabetes (3.74 (1.54-9.08), $p=0.004$). Accordingly, the use of anti-diabetic medication was associated with non-adherence to exercise training after discharge OR=5.49, CI (1.78-16.97). Also, patients with prescribed beta-blocker medication were more non-adherent to exercise training during hospitalisation than patients not using such medication OR=0.40, CI (0.17-0.97). Patients with normal weight were more adherent to exercise training after discharge than overweight patients (0.37 (0.17-0.80), $p=0.01$).

DISCUSSION

This study represents the largest experimental sample from a randomized controlled trial on CABG patients participating in an early rehabilitation programme, however two thirds of the patients did not adhere to the programme. Although the efficacy of cardiac rehabilitation programmes is evident non-adherence to cardiac rehabilitation programmes is a well-known phenomenon.¹⁷ Several factors either isolated or interconnected have an influence on adherence to cardiac rehabilitation programmes. A recent review found that clinical factors, logical factors and health system factors are main factors for non-adherence in cardiac rehabilitation,¹⁸ Fortunately many of these factors are modifiable, however they need to be addressed.

Non-adherence to the exercise training programme was lower in-hospital than after discharge. Low practical and social support are identified as factors associated with non-adherence in cardiac rehabilitation¹⁹ and could explain the difference between in-hospital and out-patient results in this study. This is supported by the fact that presence of healthcare professional's influences positively on patients' participation in rehabilitation.¹⁷ Patients with a low social profile should receive specific reinforcement to improve adherence. In addition, adherence to the psycho-educational component was high, but mindfulness was poorly practiced between consultations which might perhaps indicate that patients need support to remain active participants in the programme. Neither male nor female patients adhered to the mindfulness component in-hospital, but male patients doubled their mindfulness activity after hospital discharge. Men and women benefits similarly from cardiac rehabilitation,²⁰ but women are less often referred to cardiac rehabilitation than men²¹ and have a particularly low rate for participating in cardiac rehabilitation.²⁰

Belief in the efficacy of rehabilitation is a predictor of adherence.^{11,13} Likewise, expectations can affect outcomes. Expectations are both positive and negative, depending on whether a patient believes that cardiac rehabilitation makes a difference.²³ Patients need to understand why rehabilitation is important and about $\geq 50\%$ of prescribed sessions are not attained by patient during cardiac rehabilitation¹¹, and the number might even be higher.²⁴

Previous studies have emerged an association between being overweight and adherence to cardiac rehabilitation ^{22,23} and being overweight could be the reason for being physically inactive. Being overweight have been found showed a predictor for not completing the phase two cardiac rehabilitation programme.²⁴ Furthermore, an association between diabetes and non-adherence to exercise training was identified which is similar to previous studies. ^{25–27} While in other studies patients with diabetes seem to be more adherent to a cardiac rehabilitation programme than patients with other co-morbid diseases, ^{28,29} it is plausible that patients with diabetes have more comorbidities or reduced physical function that might interact with their adherence to rehabilitation programmes. Non-adherence could also be explained by intake of beta-blockers, as beta-blockers can have negative influence on exercise tolerance.¹¹

The findings showed that patients with a high educational level were more adherent to exercise training than patients without a degree as is known for patient with myocardial infarction^{30,31} and indicates that special attention is needed to improve adherence to cardiac rehabilitation in those patients.

Causes of lack of rehabilitation after open heart surgery are multifactual.²⁴ It is evident that patients experience memory loss and other cognitive effects related to the open-heart surgery technique after discharge³² independent of on-pump or off-pump technique. This could obviously have an influence on the level of adherence to the rehabilitation program. In addition, previous studies have shown that the surgical procedure could impact the patient physiologically which can influence the patient's physical and mental capacity post-operatively and involve no surplus energy for physical and mental training.^{33–35} Even though, this study shows that sociodemographic and medical variables impact adherence to rehabilitation programmes at different moments during hospitalization and after discharge, further research ought to focus on these factors to increase accomplishment of rehabilitation programmes.

Study strengths and limitations

The trial had a relatively high inclusion rates, however the sample reflects the sex ratio in the CABG population with fewer females which affects statistical power to address sex issues. Patients were included consecutively in an unselected CABG population with a reasonable number of exclusion and inclusion criteria securing external validity. The trial applied central stratified randomisation securing against selection bias and blinded assessment statistical analysis, reducing detection and interpretation bias. Patients participating in a clinical trial might be affected, because there is a risk of performance bias for the usual care group (control). Participants in rehabilitation trials are highly selected with regards to comorbidity and personal competences. Further, being more physically active in the usual care group is well-known in exercise-based trials. in terms of their physical and mental health by contact with health professionals which could cause bias. Finally, we conducted many subgroup analyses, which introduces risk of random findings due to multiple comparisons, which should be acknowledged in the interpretation of the results.

IMPLICATIONS FOR PRACTICE

There is a need for examining ways to increase adherence to early rehabilitation after CABG. The level of non-adherence to the exercise training programme was lowest during hospitalisation. The consultation part of the psycho-educational approach made sense for the patients based on data. An explanation could be the holistic approach in which the patients were involved in deciding topics/items for the consultation and making decisions. In contrast, non-adherence to the mindfulness component was high both in hospital and after discharge. Low adherence level might indicate importance of detailed instructions and follow-up. The findings regarding educational level, being overweight and diabetes should receive attention combined with the use of psycho-educational consultation when designing interventions to increase adherence in early rehabilitation after CABG surgery.

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IEH drafted the manuscript in collaboration with SKB. IEH and LCT designed the analysis plan and IEH performed the statistical analyses. IEH, LCT, IE, PM, PSO and SKB all revised the manuscript critically.

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DECLARATION OF CONFLICTING INTERESTS

The authors declare that there is no conflict of interest.

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Figure 1. Consolidated Standard of Reporting Trials (CONSORT) flow diagram. Flow of patients in the SheppHeartCABG trial.

*Dropout: dropped out and wanted to extract their data from the trial

**Dropout: dropped out from the trial with acceptance to use data.

Table 1. Sociodemographic and clinical baseline characteristics of the experimental group for those are adherent and those are non-adherent to the programme

	Experimental adherent (n= 51)	Experimental non-adherent (n= 101)
Age in years, mean ($\pm$SD)	65 (7.7)	65 (9,7)
Male, n (%)	46 (90)	86 (85)
Female, n (%)	5(10)	15 (15)
Cohabitation status,		
Single/divorced/widowed	7 (14)	25 (25)
Married/domestic partner	44 (86)	76 (75)
Occupational status, n (%)		
Active employment	25(49)	36 (37)
Pensioner	25 (49)	61 (60)
Early retirement	1 (2)	3 (3)
Person on job release scheme	0 (0)	1 (1)
Educational level, n (%)		
Vocational level	22 (43)	47 (47)
College	11 (22)	25 (25)
University	15 (30)	19 (19)
None	1 (2)	1 (1)
Undisclosed	2 (4)	9 (9)
Body mass index¹, n (%)		
< 18.5 (kg/m ²)	0 (0)	1 (1)
$\geq$ 18.5 < 25 (kg/m ²)	22 (43)	17 (17)
$\geq$ 25 < 30 (kg/m ²)	19 (37)	45 (45)
>30 (kg/m ²)	10 (20)	37 (37)
Undisclosed	0 (0)	1(1)
Type of heart disease, n (%)		
Ischemic heart disease,	31(61)	72 (71)
Others	1 (2)	2 (2)
Undisclosed	19(37)	27 (27)
NYHA-class², n (%)		
NYHA-class I	24 (47)	20 (20)
NYHA-class II,	14 (27)	39 (39)
NYHA-class III	7 (14)	24 (24)
NYHA-class IV	0 (0)	2 (2)

Undisclosed	6(14)	16 (16)
LVEF ³, n (%)		
Normal (50-70)	40 (78)	72 (71)
Under normal (36-49)	9(18)	21 (21)
Low (<35)	2 (4)	7 (7)
Undisclosed	0(0)	1 (1)
Smoker, n (%)		
Current smoker	5 (10)	15 (15)
Previous smoker	27 (53)	51 (50)
Non-smoker	19(36)	35 (33)
Diabetes Mellitus, n (%)		
Type I	1(2)	5 (5)
Type II	4 (8)	25 (25)
Undisclosed	0(0)	1 (1)
Prescribed medication, n (%)		
Blood pressure-lowering drugs	30 (59)	59 (58)
ACE inhibitor	8 (16)	19 (19)
Beta-blocker	16 (31)	27 (27)
Calcium antagonist	11 (22)	22 (22)
Antiarrhythmic drugs	2 (4)	1 (1)
Antiplatelet drugs	44 (83)	83 (82)
Diuretic	5 (10)	22 (22)
Anti-diabetic	2(4)	22 (22)
Statin	45 (88)	81 (80)
Antidepressant	2 (4)	7 (7)
Pain reliever	2(4)	14 (14)
Sleeping medicine	1(2)	3 (3)

¹BMI; Body Mass Index; ²LVEF Left Ventricular Ejection Fraction ³NYHA; New York Heart Association Functional Classification

Table 2. Sociodemographic and clinical baseline data related to differences in adherence and non-adherence to the separate intervention components.

Experimental group	< 50% Exercise training during hospita- lisation <i>n</i> =47 (31%)	P- value	< 50% Exercise training after discharge <i>n</i> = 81 (53%)	P- value	< 50% Mindfulness during hospita- lisation <i>n</i> =132 (87%)	P- value	< 50% Mindfulness after discharge <i>n</i> =106 (70%)	p- value	< 50% Psycho- educational consultations <i>n</i> =5 (3%)	P- value
Age in years,										
> 65 years	19 (40)	0.95	51 (63)	0.31	51 (39)	0.16	43 (41)	0.93	1 (20)	0.34
<65 years	28 (60)		30 (37)		81 (61)		63 (59)		4(80)	
Sex, <i>n</i> (%)										
Male	43 (91)	0.26	67 (83)	0.11	112 (85)	0.06	92 (87)	0.98	4 (20)	0.64
Female	4 (9)		14(17)		20 (115)		14 (13)		1(80)	
Cohabitation status, <i>n</i> (%)										
Single/divorced/Widowed	11 (23)	0.70	23 (28)	0.15	28 (21)	0.90	20 (19)	0.32	2 (40)	0.29
Married/domestic partner	36 (77)		58 (72)		104 (79)		86 (81)		3 (60)	
Occupational status, <i>n</i> (%)										
Active employment	20 (43)	0.04	29 (36)	0.05	55 (42)	0.57	44 (41)	0.78	0 (0)	0.06
Retired	27 (57)		52 (64)		77 (58)		62 (59)		5 (100)	
Educational level, <i>n</i> (%)										
Vocational level/college	41 (87)	0.04	63(78)	0.52	100 (76)	0.36	83 (78)	0.56	4 (80)	0.87
University	6 (13)		18 (22)		32 (24)		23 (22)		1(20)	
NYHA class¹, <i>n</i> (%)										
Unknown	9 (19)	0.15	11 (14)	0.64	16 (12)	0.27	17 (16)	0.23	2 (40)	0.21
NYHA class I +II	25 (53)		51 (63)		87 (66)		70 (66)		2 (40)	
NYHA class III+IV	13 (28)		19 (23)		29 (22)		19 (18)		1 (20)	
LVEF², <i>n</i> (%)										
Normal	38 (81)	0.73	67 (83)	0.23	116 (88)	0.78	93 (88)	0.81	4 (80)	0.57
Low	9 (19)		14 (17)		16 (12)		13 (72)		1(20)	
BMI³, <i>n</i> (%)										
Normal	12 (26)	0.71	15 (18)	0.01	36 (27)	0.83	28 (26)	0.81	2 (40)	0.84
Overweight	35 (74)		66 (82)		96 (73)		78 (74)		3 (60)	
Diabetes Mellitus, <i>n</i> (%)										
Yes	10 (21)	0.83	26 (32)	0.02	29 (22)	0.76	23 (22)	0.76	1 (20)	0.90
No	37 (79)		55 (68)		103 (78)		83 (78)		4 (80)	

Smoker, n (%)										
Smoker	7 (15)	0.38	17 (21)	0.52	26 (20)	0.62	21 (20)	0.72	0 (0)	0.27
Non-smoker	40 (85)		64 (79)		106 (80)		85 (80)		5 (100)	
Medication⁴, n (%)										
Blood pressure-lowering drugs,	27 (57)	0.85	45 (56)	0.42	79 (60)	0.40	66 (62)	0.16	4 (80)	0.32
ACE inhibitor	8 (17)	0.87	17 (21)	0.27	24 (18)	0.73	16 (15)	0.19	0 (0)	0.29
Beta-blocker	8 (17)	0.04	24 (30)	0.69	36 (27)	0.47	29 (27)	0.70	0 (0)	0.15
Calcium antagonist	7 (15)	0.18	18 (23)	0.81	27 (21)	0.35	14 (18)	0.10	0 (0)	0.23
Antiarrhythmic drugs	1 (2)	0.83	1 (1)	0.48	3 (3)	0.51	1 (6)	0.19	0 (0)	0.72
Antiplatelet drugs	39 (83)	0.90	66 (81)	0.46	109 (83)	0.40	89 (84)	0.84	5 (80)	0.31
Diuretic	12 (26)	0.09	19 (23)	0.05	24 (18)	0.73	20 (19)	0.59	2 (40)	0.19
Anti-diabetic	11 (23)	0.08	20 (83)	0.00	21 (16)	0.92	19 (18)	0.27	0 (0)	0.33
Statin	36 (76)	0.17	67 (83)	0.95	109 (83)	0.79	88 (83)	0.95	2 (40)	0.01
Antidepressant	2 (4)	0.60	6 (7)	0.41	9 (7)	0.23	6 (6)	0.84	0 (0)	0.57
Pain reliever	8 (17)	0.44	10 (12)	0.57	17 (13)	0.39	14 (13)	0.74	3 (60)	0.00
Sleeping medicine	2 (4)	0.65	2 (2)	0.54	5 (4)	0.38	4 (4)	0.61	0 (0)	0.68

¹NYHA; New York Heart Association, ²LVEF; Left Ventricular Ejection Fraction, ³BMI; Body Mass Index, ⁴Tested for differences in non-adherence/adherence to medication to the separate intervention components.

Table 3. Sociodemographic and clinical baseline characteristics associated with training during hospitalization and training after discharge in CABG-patients participating in a four weeks comprehensive rehabilitation programme. Univariate and multivariate factors associated with training during hospitalization and training after discharge.

	Exercise training during hospitalization				Exercise training after discharge			
	Unadjusted		Adjusted ¹		Unadjusted		Adjusted ¹	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Age								
< 65 years	0.98 (0.49-1.97)	0.95	0.91 (0.44-1.86)	0.08	0.71 (0.37-1.37)	0.31	0.72 (0.37-1.40)	0.34
>65 years	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Sex								
Male	1.93 (0.61-6.13)	0.26	1.82 (0.56-5.80)	0.31	0.44 (0.16-1.22)	0.11	0.43 (0.15-1.20)	0.11
Female	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Cohabitation status								
Single/divorced/widowed	1.18 (0.51-2.68)	0.70	1.58 (0.65-3.84)	0.31	1.91 (0.85-4.30)	0.12	1.83 (0.78-4.31)	0.16
Married/domestic partner	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Occupational status								
Active employment	1.22 (0.53-2.80)	0.63	1.13 (0.48-2.68)	0.78	0.51 (0.27-0.99)	0.05	0.54(0.24-1.20)	0.13
Retired (1)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Educational level								
Vocational level/college	2.60 (1.01-6.79)	0.05	3.14 (1.16-8.51)	0.02	1.28 (0.60-2.724)	2.71	1.23 (0.57-2.68)	0.60
University (1)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Diabetes Mellitus								
Yes	1.10 (0.48-2.52)	0.83	0.96 (0.41-2.26)	0.93	0.27 (0.112-0.64)	0.003	3.74(1.54-9.08)	0.004
No (1)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
NYHA class²								
NYHA class I+II	1.10 (0.35-3.34)	0.87	1.24(0.38-4.00)	0.72	0.91 (0.30-2.78)	0.87	1.27 (0.39-4.07)	0.69
NYHA class III+IV	0.49 (0.21-1.14)	0.10	0.50 (0.21-1.21)	0.13	0.70 (0.31-1.57)	0.83	0.81 (0.35-1.88)	0.62
Unknown	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
LVEF³								
Normal	0.39 (0.15-1.07)	0.07	0.41 (0.15-1.12)	0.08	0.53 (0.19-1.50)	0.23	0.48 (0.167-1.36)	0.17
Low	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
BMI⁴								
Normal	0.90 (0.41-1.97)	0.78	1.04 (0.46-2.32)	0.92	0.39 (0.19-0.82)	0.01	0.37 (0.17-0.80)	0.01

Overweight	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Smoker								
Smoker	0.66 (0.26-1.67)	0.80	1.36 (0.52- 3.56)	0.53	0.77 (0.34-1.74)	0.77	1.39 (0.59-3.28)	0.45
Non-smoker	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Medication								
Blood pressure-lowering drugs	0.94 (0.46-1.88)	0.85	0.87 (0.43-1.78)	0.83	0.76 (0.40-1.47)	0.42	0.76 (0.39-1.48)	0.43
ACE inhibitor,	0.92 (0.37-2.30)	0.87	0.81 (0.31-1.10)	0.65	1.62 (0.69-3.81)	0.27	1.81 (0.75-4.36)	0.19
Beta-blocker,	0.41 (0.17-0.97)	0.043	0.40 (0.17-0.97)	0.04	1.15 (0.58-2.34)	0.69	1.27 (0.61-2.62)	0.53
Calcium antagonist,	0.39 (0.17-0.93)	0.39	0.42 (0.22-1.41)	0.22	1.10 (0.51-2.39)	0.81	1.13 (0.51-2.49)	0.76
Antiarrhythmic,	0.79 (0.70-9.0)	0.85	0.56(0.08-10.87)	0.94	0.43 (0.38-4.87)	0.50	0.27 (0.20-3.76)	0.33
Antiplatelet drugs,	0.94 (0.37-2.37)	0.89	0.90 (0.34-2.32)	0.82	0.72 (0.30-1.73)	0.46	0.76 (0.31-1.85)	0.54
Diuretic,	0.49 (0.20-1.14)	0.10	1.76 (0.68-4.54)	0.25	2.41 (0.98-5.92)	0.054	1.96 (0.74-5.19)	0.17
Anti-diabetic,	2.16 (0.89-5.27)	0.10	2.10 (0.84-.5.16)	0.11	5.49 (1.77-16.97)	0.003	5.49 (1.78-16.97)	0.003
Statin	0.54 (0.23-1.30)	0.17	0.49 (0.20-1.19)	0.13	1.03 (0.44-2.40)	0.95	0.97 (0.42-2.27)	0.95
Antidepressant	1.60 (0.32-8.04)	0.57	0.64 (0.12-3.47)	0.61	0.55 (0.13-2.29)	0.41	1.81 (0.44-7.53)	0.41
Pain reliever	1.45 (0.56-3.78)	0.44	1.81 (0.66-5.00)	0.25	1.30 (0.51-3.27)	0.57	0.76 (0.30-1.93)	0.58
Sleeping medicine	0.66 (0.11-4.10)	0.66	1.80(0.28-11.33)	0.53	1.74 (0.28-10.74)	0.55	0.58 (0.09-3.72)	0.56

¹ Adjusted for age, sex and Left Ventricular Ejection Fraction (LVEF), ²NYHA; New York Heart Association ³LVEF Left Ventricular Ejection Fraction ⁴BMI; Body Mass Index