Hospital-based comprehensive cardiac rehabilitation versus usual care among patients with congestive heart failure, ischemic heart disease, or high risk of ischemic heart disease: 12-Month results of a randomized clinical trial

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Background Current guidelines broadly recommend comprehensive cardiac rehabilitation (CCR), although evidence for this is still limited. We investigated the 12-month effect of hospital-based CCR versus usual care (UC) for a broadly defined group of cardiac patients within the modern therapeutic era of cardiology.

Methods We conducted a centrally randomized single-center clinical trial with blinded assessment of the primary outcome: registry-based composite of total mortality, myocardial infarction, or acute first-time readmission due to heart disease. Other outcomes were hospitalization, risk profile, and quality of life. The trial included 770 participants (20-94 years) with congestive heart failure (12%), ischemic heart disease (58%), or high risk of ischemic heart disease (30%). Comprehensive cardiac rehabilitation is composed of 6 weeks of intensive intervention and systematic follow-up for 10.5 months.

Results We randomized 380 patients to CCR versus 390 to UC. Randomization was well balanced. The primary outcome occurred in 31% of both groups (relative risk 0.96, 95% confidence interval 0.78-1.26). Compared with the UC group, CCR significantly reduced length of stay by 15% (95% confidence interval 1.1%-27.1%, $P = .04$), mean number of cardiac risk factors above target (4.5 vs 4.1, $P = .01$), patients with systolic blood pressure below target ($P = .003$), physically inactivity ($P = .01$), and unhealthy dietary habits ($P = .0003$). Short-Form-36 and Hospital Anxiety and Depression Scale did not differ significantly.

Conclusion At 12 months, the CCR and UC groups did not differ regarding the primary composite outcome. Comprehensive cardiac rehabilitation significantly reduced length of hospital stay and improved cardiac risk factors. (Am Heart J 2008;155:1106-13.)

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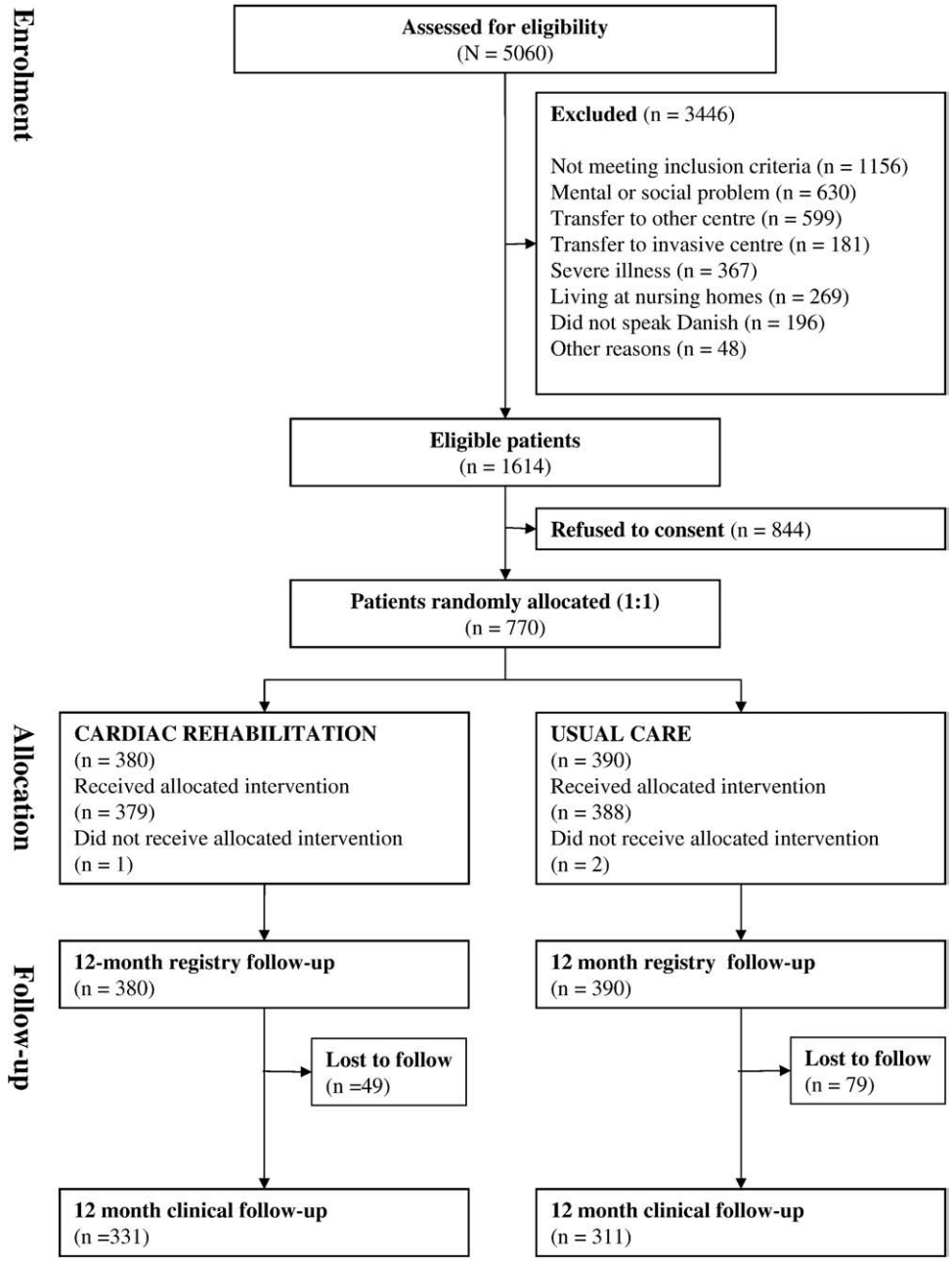
Cardiac rehabilitation may reduce mortality, morbidity, and risk factors among patients with myocardial infarction (MI).[1] Furthermore, cardiac rehabilitation may increase quality of life[2,3] and reduce readmission,[4,5] although this remains to be proven.[1]

According to guidelines,[6-8] comprehensive cardiac rehabilitation (CCR), including exercise training, patient education, psychological support, risk factor management, and clinical assessment, is indicated for patients with ischemic heart disease (IHD). Patients with congestive heart failure (CHF) and patients with a high risk (HR) of developing IHD also comprise a target group for CCR.[6,9] Nevertheless, cardiac rehabilitation trials have mostly included men with MI younger than 65 years.[10] Only a few trials have examined women[11] and patients older than 75 years.[12,13] The benefits and harms among broadly defined patients need further assesment.[10]

Figure 1



Flow of participants in the DANREHAB Trial.

A Cochran review[10] assessed the quality of cardiac rehabilitation trials: 82% had unclear randomization, and only 8% blinded outcome evaluation. This may exaggerate the estimates of intervention benefits.[10,14] Many randomized clinical trials describe interventions poorly,[9,10] and detailed descriptions of evidence-based cardiac rehabilitation interventions have been requested.[9,10,15] Most trials were carried out before 1995, their effects may be outstripped by new and highly effective treatments (eg, thrombolysis, statins). A 2004 review[1] indicated that the effect of cardiac rehabilitation is still valid in trials conducted after 1994, but this subgroup analysis had limited power.

We undertook a randomized clinical superiority trial—the DANREHAB Trial—to evaluate the effect of hospital-based CCR on mortality, reinfarction, and acute first-time

readmission due to heart disease compared with usual care (UC) among a broad group of patients. This article presents results after 12 months.

Methods

The methods of this pragmatic, open, single-center, centrally randomized, parallel group trial have been presented in detail elsewhere.[16] Our hypothesis was that CCR was significantly more beneficial than UC regarding primary and secondary outcome measures (see below). We briefly describe the method here.

Participants

We included patients with CHF, IHD, or HR who were admitted to the Department of Cardiology of Bispebjerg Hospital. Patients were identified on a daily basis from the hospital's administrative system. Patients were recruited at the end of their inpatient stay or at an outpatient visit arranged as part of their routine follow-up. The median duration between index event (date of inpatient admission) and recruitment was 11 days. The patients were diagnosed as having CHF in accordance with European guidelines.[16] Patients not fulfilling the criteria for CHF were diagnosed as having IHD if they had MI or angina pectoris in accordance with European guidelines,[16] percutaneous coronary intervention, or coronary artery bypass grafting. Patients with 3 or more classic risk factors (systolic blood pressure >140 mm Hg, total serum cholesterol >4.5 mmol/L, body mass index >25 kg/m^2, physical activity ≤4 hours per week, diabetes, male sex, or a family history of IHD <60 years) were considered HR if they did not have CHF or IHD. The reasons for nonparticipation in the trial are listed in Figure 1; mental and social problems were defined as conditions with an HR of inadequate participation (eg, dementia, alcohol abuse), and severe illness was defined as terminal illness or comorbidity with an HR of death within 1 year (eg, terminal cancer).

Interventions

Hospital-based CCR. The patients randomized to CCR were offered a standardized cardiac rehabilitation program designed in accordance with the national guidelines,[6] the program was individually tailored and carried out by a multidisciplinary team. Patients were scheduled to consult with a physician within 1 week of randomization. The CCR physician was responsible for initiating or tritrating the medicine in accordance with guidelines. A 6-week intensive CCR program was planned, including patient education, 12 exercise training sessions, dietary counseling, smoking cessation, psychosocial support, risk factor management, and clinical assessment.[16] We assigned patients to follow up visits at 3, 6, and 12 months. Besides the planned follow-up, there was no contact between the CCR personnel and the CCR patients.

Usual care. The discharging physician in the outpatient clinic or a general practitioner offered the UC patients follow-up. The pharmaceutical treatment followed routine clinical practice based on guidelines. The physician who discharged the patient and saw the patient for follow-up was responsible for initiating or titrating the medicine. We informed the UC patients that they would be contacted after 12 months to assess outcomes. Besides the planned 12-month visit, there was no contact between the CCR personnel and the patients in the UC group.

Follow-up services received. Information on hospital-based outpatient clinic visits was sourced from the local administrative system. We obtained information on use of primary health care services from the National Health Insurance Registry. We collected information on medication, exercise training, dietary guidance, and structured smoking cessation received at the hospital and in the community at the 12-month interview.

Outcomes

Primary outcome. Our primary composite outcome measure included overall mortality, MI, or acute first-time readmission due to heart disease other than MI. This information was taken from central registries.[16] Myocardial infarction is defined as *International Classification of Diseases, 10th Revision* (*ICD-10*), codes I21–I22 (primary or secondary diagnosis). Acute first-time readmission due to heart disease is defined as the primary *ICD-10* codes I10–I15, I20, I23–I25, I46–I50, Z03.4, and Z03.5.

Other outcomes. Several secondary outcomes reflected the multifactorial nature of the intervention. We collected data using an adapted standardized interview questionnaire and a postal questionnaire (eg, SF-36, HADS), clinical examination, and blood tests.[16] We obtained information on health service utilization from the National Patient Registry[17] and by interview.

Sample size and stopping rules

The expected event rate was based on an unpublished pilot study. We estimated a 12-month composite primary outcome measure in the UC group of 20% and a relative risk reduction of 25% to 15% in the CCR group, power of 0.80, and 2-sided $P < .05$. We therefore aimed to include 1,810 patients. The duration of inclusion was fixed at maximum 3 years to minimize the influence of changing treatment trends on UC intervention over time and reduce costs. Our pilot study indicated that 900 patients would be eligible annually, enabling the 1,810 patients to be recruited within 3 years at the expected participation rate of 70%. The study design did not allow crossover in the full study period. No interim analyses or stopping rules were applied.

Recruitment and randomization

We screened all patients residing in the hospital catchment area (150,000 people) and discharged from the Department of Cardiology from March 2000 until February 2003. We reviewed patient records according to our inclusion and exclusion criteria. Reasons for not participating in the trial are listed in Figure 1. We screened eligible patients according to symptoms, discharge diagnosis, and risk factors using patient records and interview.[16]

The Copenhagen Trial Unit computer generated the allocation sequence and provided central secretary-staffed telephone randomization. We stratified the randomization according to the risk groups based on a random-permuted multiblock within-stratum method[16] and randomized patients 1:1 to CCR versus UC. The essential patient data were registered, and the result of the randomization was delivered to the research nurse, who informed the CCR team and the patient about the allocation.

Table I. Entry characteristics of the DANREHAB Trial

	Cardiac rehabilitation	Usual care
	n = 380	n = 390
Demographic data		
Female	36	37
Age, median (range), y	66 (33-91)	66 (29-94)
Living alone	47	47
Working	26	26
Highest level of education	12	13
Medical history		
Diagnosis groups		
CHF	12	12
IHD	58	58
HR	30	30
MI	42	41
Percutaneous coronary intervention	29	26
Coronary artery bypass grafting	16	20
Diabetes	20	20
Family history of IHD	50	49
Medication		
Antithrombotics	80	79
Lipid-lowering drugs	49	50
β-Blockers	43	44
Calcium antagonists	30	29
ACE inhibitors	29	27
Diuretics	42	47
Long-acting nitrates	17	17
Lifestyle and risk factors		
Current smoking	29	30
Low physical activity	51	53
Blood pressure systolic ≥140 mm Hg	32	29
Blood pressure diastolic ≥90 mm Hg	13	14
Total cholesterol >4.5 mmol/L	62	64
HDL cholesterol <1.0 mmol/L	34	39
LDL cholesterol >2.6 mmol/L	60	64
Triglycerides >2.0 mmol/L	24	24
Body mass index >25 kg/m^2	70	74
Numbers of modifiable risk factors and lifestyle items above target, mean (SD)	3.5 (1.69)	3.7 (1.58)
Quality of life and anxiety and depression		
SF-36 Health Survey, mean score (SD)		
Physical component	41 (10)	42 (10)
Mental component	44 (12)	46 (12)
HADS, mean score (SD)		
Anxiety	10 (2)	10 (2)
Depression	9 (2)	9 (2)

Values are expresses as percentage unless otherwise indicated. *ACE*, Angiotensin-converting enzyme; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein.

Blinding. The interventions were open to the patients and investigators. Investigator-independent outcome data from registries were chosen to ensure blinded outcome assessment. The scientific team and CCR team collected secondary outcome measures blinded to intervention at baseline and without blinding at 12 months. An independent statistician analyzed the primary outcome measure blinded to intervention arm.[18]

Statistical analysis

The trial conclusion was drawn from the intention-to-treat analysis of the proportion of the primary outcome measure (CCR vs UC). We analyzed differences in prevalence using Pearson χ^2 test. We considered 2-tailed $P < .05$ significant. We conducted further analysis using Cox regression models, including time to first event as an outcome variable. Because of the skewed distribution of length of stay and repeated measurements on admission of patients, we analyzed these registry-based outcomes simultaneously using multivariate random-effects modeling with patients as random effects.[19] We log-transformed changes in length of stay on the original scale $\frac{los_{CR}-los_{UC}}{los_{UC}}\times$-100%=(exp(-$\beta$)-1)×100%. We analyzed the intervention effect on medication, lifestyle, and risk factors with standard statistical methods based on data from patients attending the 12-month clinic visit. Because we lacked information on a number of these data at entry, the analysis cannot include individual changes for these outcomes. To analyze whether the groups differed in SF-36 and HADS at 12-month follow-up, we used a linear mixed model with patients as random effects. We imputed missing items for patients answering the questionnaire using age and sex as auxiliary variables under the assumption of the missing at random mechanism.

Ethics

We conducted the trial in accordance with the Declaration of Helsinki; all participants supplied written informed consent. The local ethics committee ((KF)11-121/01) and the Danish Data Protection Agency (RT-no. 1998-1200-353/2001-41-1313) approved the trial, which was registered as ISRCTN74601515.

Results

Study population

Among 1,614 eligible patients, 770 (47%) consented to participate. The 844 nonparticipants were older ($P <$ .001), had more often CHF ($P = .04$), and had less often IHD ($P < .001$) than participants. Adjusted for age and comorbidity, mortality was almost twice as high among the nonparticipants as compared with the participants at 12 months (relative risk 1.87, 95% confidence interval [CI] 1.19-2.85).

Of the 770 participants, 91 (12%) had CHF, 446 (58%) IHD, and 233 (30%) HR; 380 patients were randomly allocated to CCR versus 390 to UC. Two patients allocated to UC received CCR and one allocated to CCR received UC (Figure 1). The patients were well matched at entry both overall (Table I) and in the 3 subgroups (data not shown).

All 770 participants could be identified in the registries for assessment of the primary outcome measure (100%); 642 (84%) attended the 12-month visit, and 70% of these answered the postal questionnaire on SF-36 and HADS. Those who attended and those answering the

Table II. Follow-up services, lifestyle intervention, health care and medication during the 12-month follow-up period in the DANREHAB Trial

	Cardiac rehabilitation (n = 380)	Usual care (n = 390)	*P*
Hospital-based services			
Clinical follow-up by physicians	90	82	.02
Total number of physician visits (mean visits per patient)	1654 (5.3)	974 (3.2)	<.01
Nurse consultation	79	53	<.01
Total number of nurse visits (mean visits per patient)	893 (3.6)	1.330 (8.9)	<.01
Exercise training by a physical therapist	90	14	<.01
Structured smoking cessation *	50	18	<.01
Dietary guidance by a dietitian	83	28	<.01
Consultation with a social worker	20	2	<.01
Primary health care services			
Consultation by GP	98	98	.76
Total number of GP visits (mean visits per patient)	3331 (8.8)	4059 (10.4)	<.01
Consultation with a psychiatrist	2	3	.67
Consultation with a physical therapist	10	10	.81
Community-based or private services			
Physical exercise activities	33	6	<.01
Smoking cessation	13	9	.37
Private consultations with a dietitian	7	5	.27
Private consultations with a psychologist	8	6	.19
Medication			
Antithrombotics	85	81	.12
Lipid-lowering drugs	63	61	.56
β-Blockers	34	41	.07
Calcium antagonists	34	32	.56
ACE inhibitors	33	28	.23

Values are expresses as percentage unless otherwise indicated. *GP*, General practitioner; *ACE*, angiotensin-converting enzyme.
*Among smokers at entry.

questionnaire did not differ significantly regarding entry characteristics (data not shown).

Follow-up services and lifestyle intervention

Table II outlines the follow-up services and lifestyle intervention received at hospital, in the primary health care services, and in the community. The CCR patients consulted a hospital physician more often and had fewer general practitioner visits than the UC group. Significantly more CCR patients than UC patients received exercise training, smoking cessation, dietary guidance, and consultations with a social worker at the hospital and attended community physical exercise activities. The groups did not differ significantly regarding medication at follow-up.

Primary outcome

During the 12 months, 235 primary events occurred: 29 deaths, 21 MI, and 219 acute first-time readmissions due to heart disease, whichever came first. The CCR and UC groups did not differ significantly regarding the cumulative risk of the primary combined outcome, nor did the groups differ significantly regarding death, MI, or acute first-time readmission due to heart disease (Figure 2).

Other outcomes

Table III shows data on the other outcomes. During the 12 months, 209 (55%) CCR patients and 219 (56%) UC patients were hospitalized once or more. About 70% and 75% of the respective admissions were acute. Comprehensive cardiac rehabilitation patients had 15% lower average length of stay (95% CI 1.1%-27.1%, $P = .04$) for all readmissions and 17% lower length of stay (1.2%-31.0%, $P = .04$) for acute readmissions.

Comprehensive cardiac rehabilitation patients had significantly fewer modifiable risk factors and lifestyle items (smoking, physical activity, and dietary habits) above treatment target (4.1 [3.9-4.3] versus 4.5 [4.4-4.6], $P = .01$). Excluding dietary habits, the CCR group still had fewer risk factors and lifestyle items above treatment target (3.2 [3.0-3.4] vs 3.5 [3.4-3.6], $P = .03$). Significantly fewer CCR patients had systolic blood pressure above target (odds ratio 0.61 [0.44-0.84], $P = .003$), were physically inactive (0.66 [0.46-0.91], $P = .01$), or had 'heart-unhealthy' dietary habits (a sum-score of not consuming less fat, more vegetables, more fruit, and more fish; 0.34 [0.19-0.62], $P = .0003$). SF-36 and HADS did not differ significantly.

Complications

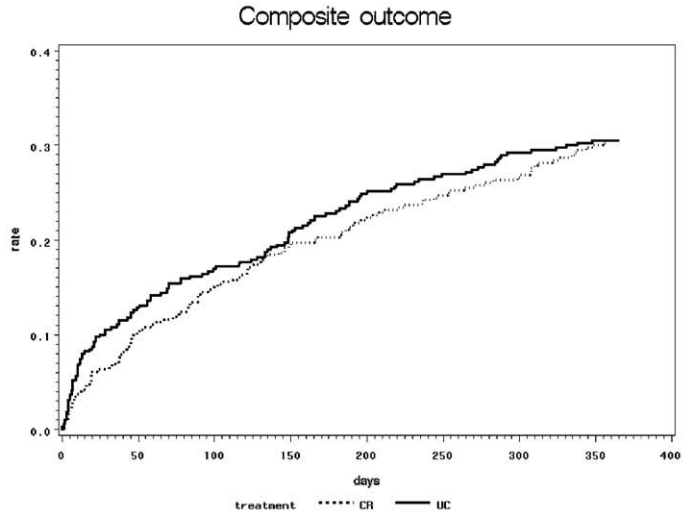
We systematically registered major clinical events during exercise training, defined as any adverse event causing exercise training to stop. The CCR group had 3 major events in 3 patients: sprained ankle; syncope in the waiting room caused by orthostatic hypotension; and hyperventilation due to anxiety during outdoor exercise. No events were reported for the UC group.

Discussion

Main findings

Our trial demonstrated that CCR can be safely delivered to a motivated, broadly defined group of patients with CHF, IHD, and HR attending the same program. Comprehensive cardiac rehabilitation did not significantly affect the composite primary outcome compared with UC during the 12 months. The lack of effect may be due to the low number of patients included, too short

Figure 2



Outcome	CCR n = 380		UC n = 390					
	n	(%)	*n*	(%)	*P*	RR	95% CI	*P*
Composite outcome	116	30.5	119	30.5	1.00	0.96	(0.78–1.26)	0.85
Death	14	3.7	15	3.9	1.00	0.96	(0.46–1.98)	0.90
Myocardial infarction	8	2.1	13	3.3	0.38	0.63	(0.26–1.52)	0.30
Acute first-time readmissions due to heart disease	108	28.4	111	28.5	1.00	0.97	(0.75–1.28)	0.87

Proportion with clinical outcomes at 12-month follow-up, analysis of time to event, and curves showing cumulative event rates for the primary composite outcome measure of death, MI, or acute first-time readmission due to heart disease among patients receiving CCR or UC.

follow-up, or too small 'a dose' of CCR. We found that CCR patients had significantly shorter length of stay during readmissions and fewer risk factors and lifestyle items above the treatment targets. Quality of life and anxiety and depression did not differ significantly.

Strengths and weaknesses

Our trial has several strengths. We used computer-generated central randomization, which reduces selection bias.[14,20,21] We used registry-based follow-up, which ensured close to 100% follow-up and blinded assessment of the outcome measure. This reduced attrition bias and assessment bias.[14,20,21] Our trial was a single-center trial. In single-center trials, less heterogeneity in the distribution of interventions and cointerventions occurs. Therefore, a more precise intervention effect (explanatory effect) may be detected. The weakness, however, is that single-center trials may have les external validity (pragmatic effect). Our trial also has several limitations. The major drawback is that we did not reach the stipulated sample size of 1,810 patients. The number of eligible patients was fewer (1,614 compared to 2,700 expected) and the enrolment rate lower (47% compared to 70% expected). This increases the risk of not finding a statistically significant difference, although it may exist (type II error). Follow-up was only 12 months, and longer observation time seems necessary to demonstrate differences between the groups. A 3-year follow-up is planned according to the protocol.[16] Although we only included 770 patients, this is still the largest single-center CCR trial published. Further, our trial included more older people (median age 65 vs 56 years) and more women (37% vs 11%) than previous trials on CCR.[10] When looking at age and sex separately, we found no significant differences between the groups; results from subgroup analysis must though be interpreted with caution because of limited power. Several secondary outcome measures were assessed without blinding of the intervention. Hence, bias may influence some of our significant observations.[14,20,21] The duration of the CCR intervention of 6 weeks in our trial was short as compared with the current recommendations of 8 to 12 weeks.[7,8] This may be one explanation of the limited effect at 12-month follow-up. Comprehensive cardiac

Table III. Other outcomes at 12-month follow-up

	Cardiac rehabilitation	Usual care	P*
Hospitalization and invasive treatment			
Total number of readmissions (mean admissions)	531 (2.5)	630 (2.9)	.54
Total length of stay (mean days)	2634 (5.0)	3880 (6.2)	.04
Percutaneous coronary intervention	7	8	.47
Coronary artery bypass grafting	2	4	.34
Lifestyle and risk factors			
Current smoking	29	29	.97
Physical activity <4 hours per week	34	43	.01
Dietary habits			
Eat more fat	29	49	<.01
Eat less vegetables	46	58	<.01
Eat less fruit	67	83	<.01
Eat less fish	63	71	.03
Blood pressure, systolic ≥140 mm Hg	32	43	<.01
Blood pressure, diastolic ≥90 mm Hg	12	15	.38
Total cholesterol >4.5 mmol/L	56	60	.17
HDL cholesterol <1.0 mmol/L	14	15	.69
LDL cholesterol >2.6 mmol/L	48	51	.46
Triglycerides >2.0 mmol/L	26	26	.97
Body mass index >25 kg/m^2	72	76	.34
Numbers of modifiable risk factors and lifestyle items above the target, mean (SD)	4.1 (1.80)	4.5 (1.72)	.01
Quality of life and anxiety and depression			
SF-36, mean score (SD), P†			
Physical component	46 (10)	45 (10)	.56
Mental component	48 (12.3)	50 (11)	.65
HADS, mean score (SD), P†			
Anxiety	9 (2)	9 (2)	.79
Depression	9 (2)	9 (2)	.40

Values are expresses as percentage unless otherwise indicated. *HDL*, High-density lipoprotein; *LDL*, low-density lipoprotein.
*The analyses are adjusted for diagnostic group, age, and sex.
†Test for difference from baseline data.

rehabilitation was compared with UC. Usual care is not identical to a control group receiving no intervention. Usual care included smoking cessation, dietary counseling, and exercise training for some patients (Table II). Accordingly, UC patients were also offered elements of rehabilitation, creating difficulty in showing any differences between the groups. Nevertheless, CCR follow-up services were substantially more intensive than UC services (Table II). Comprehensive cardiac rehabilitation is a complex intervention[15] based on several components, including behavior modification and methods of organizing and delivering components that are believed to act both independently and interdependently, posing difficulty in defining which components are active. The effects of the single components in our trial cannot be separated.

Results compared with other studies

We found no effect on the composite primary outcome after 12 months or on any component thereof. Adding our 12-month data to the most recent published meta-analysis[1] does not change the estimated effect of CCR on mortality (odds ratio 0.82, 95% CI 0.70-0.95). Other studies have shown that cardiac rehabilitation has a long-term effect[22]; this has been explained by the nature of CCR. Follow-up of 3 years will determine whether CCR in our trial had a long-term effect. We found no difference between the subgroups: CHF, IHD, or HR at 12 month follow-up; these findings must be interpreted with caution due to the low number of patients in each subgroup.

The CCR reduced the length of stay by 15% for all readmissions and 17% for acute readmissions. To test sensitivity for possible outliers, we excluded the hospitalizations for the 5 patients with the most extreme length of stay in each group. This did not influence the reduction in overall hospitalizations between CCR versus UC: 15% (95% CI 1.5%-26.8%, $P = .03$). Thus, our trial supports current evidence[4,5] that CCR positively affects length of stay. We should acknowledge that the increased number of out-of-hospital visits during CCR might explain the decrease in length of stay. In Denmark, the physicians are solely employed at the hospital. They are very seldom involved in referring patients for acute admissions, which is administered by general practitioners or acute ward physicians. We only observed a decrease in the acute readmissions. This may therefore reflect a lower rate of acute illness.

Similar to other trials,[1] we only demonstrated a modest reduction in risk factors. The groups differed significantly in self-reported physical activity, self-reported dietary habits, and systolic blood pressure. Data on dietary habits and physical activities were collected by interview using standardized Danish questionnaires.[16] There is a high risk of these results being biased toward the CCR patients in the affirmative given the intense counseling and physical activity. The results on physical activity reflect exercise adherence at 12-month follow-up, where the patients were no longer training in the CCR program. The results primarily reflect a higher adherence to home exercise, whereas there was no significant difference in the numbers of patients' participation in structured activities (data not shown).

Comprehensive cardiac rehabilitation did not affect quality of life measured by SF-36. We used a generic questionnaire instead of a disease-specific questionnaire,

which is claimed to be more responsive.[23] This may partly explain why we did not find an effect. Twelve trials in the most recent meta-analysis[1] assessed quality of life. The meta-analysis found that although most trials reported improved quality of life scores, only 2 exceeded the improvement in the UC groups. It therefore remains to be proven whether CCR significantly improves quality of life.

Conclusion

At 12 months, the CCR and UC groups did not differ regarding the primary composite outcome: death, MI, or acute first-time readmission due to heart disease. Comprehensive cardiac rehabilitation was associated with a significant reduction in length of hospital stay and improved cardiac risk factors.

We thank the 770 patients and the staff who participated in the DANREHAB Trial.

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