A randomized clinical trial of hospital-based, comprehensive cardiac rehabilitation versus usual care for patients with congestive heart failure, ischemic heart disease, or high risk of ischemic heart disease (the DANREHAB trial)—design, intervention, and population

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Background Current guidelines broadly recommend comprehensive cardiac rehabilitation (CR), although evidence for this is still limited. It is not known whether evidence from before 1995 is still valid.

Study Design The DANish Cardiac REHABilitation (DANREHAB) trial was designed as a centrally randomized clinical trial to clarify whether hospital-based comprehensive CR is superior to usual care for patients with congestive heart failure, ischemic heart disease, or high risk for ischemic heart disease. A combined primary outcome measure included total mortality, myocardial infarction, or readmissions due to heart disease based on linkage to public registries. The CR was an individually tailored, multidisciplinary program (6 weeks of intensive CR and 12 months of follow-up) including patient education, exercise training, dietary counseling, smoking cessation, psychosocial support, risk factor management, and clinical assessment.

Study Population Of 5060 discharged patients, 1614 (32%) were eligible for the trial and 770 patients were randomized (47% of those eligible). Participants were younger ($P < .001$) and had less comorbidity than nonparticipants ($P < .03$).

Conclusion Our trial shows that a large-scale, centrally randomized clinical trial on comprehensive CR can be conducted among a broadly defined patient group, but reaching the stipulated number of 1800 patients was difficult. Although the study included relatively many women and older people, elderly patients and patients with high comorbidity were underrepresented, which may influence the external validity. (Am Heart J 2005;150:899.e7-899.e16.)

Background

Evidence shows that cardiac rehabilitation (CR) can reduce mortality, morbidity, and risk factors among patients with myocardial infarction (MI).[1-5] Furthermore, CR may increase the quality of life[6,7] and lead to fewer readmissions.[8,9]

According to current guidelines,[3,10-12] comprehensive CR including exercise training, patient education, psychological support, risk factor management, and clinical assessment is indicated for patients with congestive heart failure (CHF) and ischemic heart disease (IHD). Patients with a high risk of developing high risk for IHD (HR) may also be a target group.[10,13] Nevertheless, trials on CR have mostly included young men with MI,[4] and the effects of CR among more broadly defined patients are not fully known.[4] Studies indicate that women benefit as much as men[14] and that patients >75 years of age benefit,[15,16] but women and elderly patients have been underrepresented.[4]

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A Cochrane review[4] assessed the quality of CR trials: 82% did not describe the randomization clearly, and only 8% used blinded outcome evaluation. Such methodological problems may lead to exaggerated intervention benefits.[4,17] These findings stress the importance of conducting high-quality trials. Many of the randomized clinical trials on CR have poorly described interventions,[4,13] and detailed descriptions of evidence-based CR interventions have been sought.[4,13,18]

Many CR trials were carried out before 1995, and their effects may now be outstripped by new and highly effective treatments such as thrombolysis, acetylsalicylic acid, β-blockers, statins, angiotensin-converting enzyme (ACE) inhibitors, and acute invasive treatments. A recent review[5] indicated that the effect of CR is still valid in trials conducted after 1994, but the power of this subgroup analysis was not strong.

To ascertain whether hospital-based comprehensive CR is superior to usual care (UC) on broad indications, we designed a randomized clinical trial, the DANish Cardiac REHABilitation (DANREHAB) trial. This article presents the study design, interventions, and patient recruitment.

Table I. Inclusion and exclusion criteria of the DANREHAB trial

Inclusion criteria	Exclusion criteria
CHF	Fulfilling none of the inclusion criteria
Present symptoms of CHF and objective findings or effect of medication	Mental disorders and social problems (such as dementia, alcoholism, or drug addiction)
IHD	Transferred to other department or hospital at discharge
MI, PCI, CABG, or angina	Severe illness, including NYHA class IV
	Living at nursing home
	Did not speak Danish
	Refused consent
HR	
≥3 classic risk factors for IHD: current smoking, systolic blood pressure >140 mm Hg, total serum cholesterol >4.5 mmol/L, BMI >25, leisure activity ≤4 h weekly, diabetes, male sex, or family history of IHD at <60 y	

Study design

Trial design

This randomized clinical trial compared comprehensive CR versus UC for patients with CHF, IHD, or HR (defined as ≥3 classic risk factors for IHD). Table I outlines the inclusion and exclusion criteria, and Figure 1 summarizes the design.

Patients included in the trail were stratified in the 3 groups: CHF, IHD, or HR irrespective of admission diagnosis. The patients were stratified to the CHF group based on present symptoms and objective criteria of CHF in accordance with the European guidelines on CHF.[19] Patients not fulfilling the criteria of CHF were stratified to the IHD group if there were symptoms and objective criteria of MI or angina pectoris in accordance with the European guidelines[20,21] or if the patient had gone through percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). Patients not fulfilling the criteria of CHF or IHD who had the presence of ≥3 classic risk factors for IHD were stratified to the HR group. The risk factors included were current smoking, systolic blood pressure >140 mm Hg, total serum cholesterol >4.5 mmol/L, body mass index (BMI) >25, leisure activity ≤4 hours weekly, diabetes, male sex, or family history of IHD at <60 years.

All patients discharged from the Department of Cardiology of H:S Bispebjerg Hospital from March 2000 until February 2003 and living in the hospital catchment area were screened. Patient records were reviewed for the predefined exclusion criteria (Table I). Patients not excluded were screened according to symptoms, discharge diagnosis, and risk factors using patient records and interview. Before randomization, baseline data were collected (Table II).

Randomization

Patients who gave informed consent were randomized using a centralized randomization procedure administered by the Copenhagen Trial Unit. The randomization was stratified according to risk group (CHF, IHD, or HR) based on a random-permuted multiblock within-stratum method. Within each risk group, randomization was stratified by sex, age, and the presence or absence of type 2 diabetes mellitus. For the IHD group, information on prior invasive procedures (CABG and/or PCI) was also included in stratification. Within each risk stratum, the block size, unknown to the investigators, alternated between 6 and 8 patients. Patients were randomized 1:1 to the CR and UC groups. Patients who refused participation were offered the same follow-up services as the UC group.

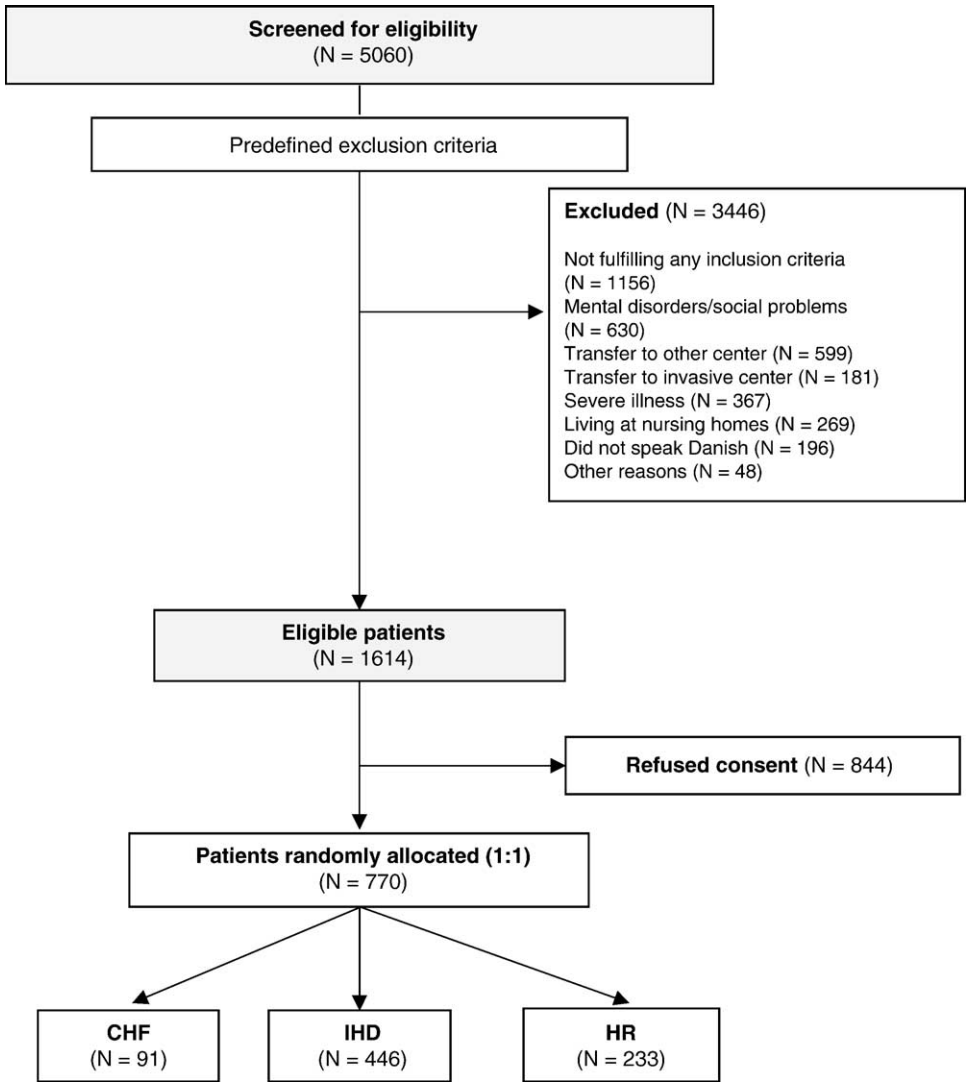
Blinding

Because of the nature of CR, the interventions were open to the investigators and the patients. Investigator-independent outcome data from registries were chosen to ensure blinded assessment and outcome analysis.

Usual care

Usual care patients were offered follow-up treatment prescribed by the discharging physician either as outpatient control or by the general practitioner. The pharmaceutical treatment followed routine clinical practice based on current national guidelines.[22-24] The

Figure 1



Flow of patients through the DANREHAB trial.

discharging nurse or physician determined whether patients were referred to smoking cessation and dietary counseling parallel to outpatient treatment. Selected patients with MI could be referred to exercise training at the Department of Rheumatology. Usual care patients were informed that they would be contacted after 12 months to assess the outcome.

Hospital-based comprehensive CR

The CR program was designed according to the national guidelines on CR.[10] The program was carried out by a multidisciplinary clinical team and individually tailored to each patient. Cardiac rehabilitation included patient education, exercise training, dietary counseling, smoking cessation, psychosocial support, and risk factor management and clinical assessment. All components included theoretical and practical approaches followed by individual follow-up and feedback. The lifestyle intervention strategy was based on the stages of change model[25] and self-efficacy theory.[26] The lifestyle intervention was designed as group intervention, but individual counseling was included.

The CR program involved and educated patients and got spouses to participate. The core clinical team comprised a physician trained in internal medicine with

Table II. Baseline data and outcome measures of the DANREHAB trial

	Baseline (all patients)	12 mo (all patients)	Registry* (all patients)
Background			
Age, sex	x	x	
Education, socioeconomics†	x	x	x
Working situation, sick leave†	x	x	x
Medical history			
Family history of IHD†	x		
IHD†‡	x		x
Intermittent claudication, stroke†	x		
Diabetes†‡	x		x
Comorbidity‡			x
Lifestyle			
Smoking†	x	x	
Carbon monoxide measurements§	x	x	
Leisure activity†	x	x	
6-min walking test§	x	x	
Diet†‖	x	x	
Weight, height§	x	x	
Waist and hip circumference§	x	x	
Risk factors			
Resting blood pressure§	x	x	
Fasting lipids§	x	x	
Fasting glucose§	x	x	
Health-related quality of life, anxiety, and depression			
SF-36 Health Survey[45]‖	x	x	
Hospital Anxiety and Depression Scale [33]§	x	x	
Antidepressants†‡	x	x	x
All medication			
ATC codes, dosages†‡	x	x	x
Readmissions			
Total number‡			x
CHF as primary diagnosis‡			x
IHD as primary diagnosis‡			x
MI as primary diagnosis‡			x
Deaths			
Total mortality‡			x
IHD mortality‡			x

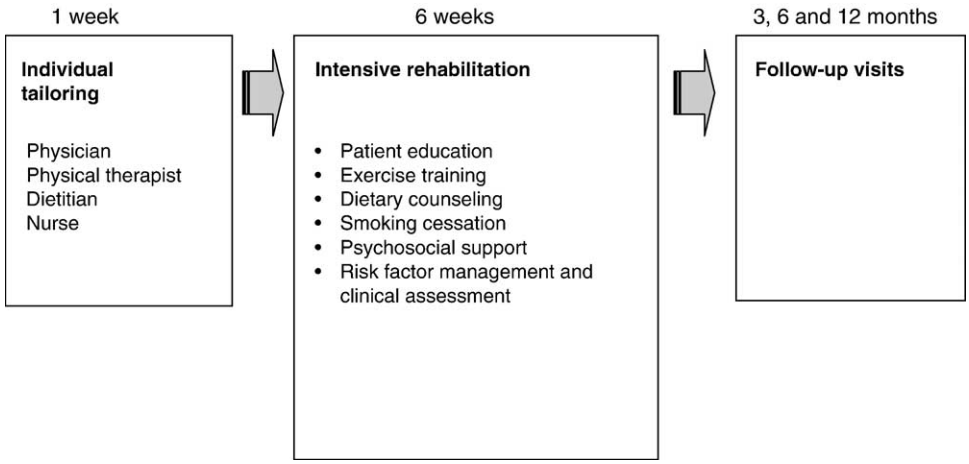
SF-36, Short Form 36. *ATC*, Anatomical Therapeutic Chemical Classification System.
*At 12 months and 3 years of follow-up.
†Interview.
‡Administrative information.
§Clinical examination.
‖Validated self-administrated questionnaire.

a special interest in CR, a nurse, a physical therapist, a clinical dietitian, and a secretary. Furthermore, a social worker and a liaison psychiatrist could be involved when needed. The core staff had been trained in cardiology but had limited experience with CR. All staff participated in motivational counseling training and team building before trial launch.

The comprehensive CR program used in here was first described in 1997. The CR methods were tested in a pilot study of 15 patients, and the program was finally adjusted. Effort was made to maintain the intervention as described throughout the study period; all education materials were standardized, and only minor adjustments were allowed. In March 2002, a substudy on type 2 diabetes mellitus was added with intensified focus on treating patients with diabetes in the CR arm following the originally described principles (The DANSUK trial). The design and population of the diabetes substudy will be described separately. The CR program (Figure 2) has been described in English in detail[27] and is summarized at www.cardiacrehabilitation.dk.

Individual tailoring. Cardiac rehabilitation patients were scheduled for an individual consultation with the physician within 1 week. A 6-week intensive CR program was planned. The treatment goals were identified individually based on the current guidelines on pharmaceutical and nonpharmaceutical treatment (Table III). The CR interventions were coordinated by

Figure 2



Outline of the CR program in the DANREHAB trial.

Table III. Ideal treatment goals in the DANREHAB trial

	CHF[22]	IHD[23]	HR[24]
Symptomatic treatment	No angina NYHA classes I-II		–
Blood pressure (mm Hg)	<140/90		<140/90
Serum cholesterol			
Total (mmol/L)	<4.5		<5.0
LDL (mmol/L)	<2.6		<3.0
HDL (mmol/L)	>1.0		>1.0
Triglycerides (mmol/L)	<2.0		<2.0
Weight			
BMI	<25 kg/m^2		<25 kg/m^2
Waist (men/women)	<94 cm/<80 cm		<102 cm/<88 cm
Lifestyle			
Physical activity	>30 min/d*		
Dietary habits	Heart-healthy diet		
Smoking	Nonsmoker		
Level of functioning[10]			
Physical	Maximally optimized		
Psychological	Maximally optimized		
Social	Maximally optimized		

LDL, Low-density lipoprotein; *HDL*, high-density lipoprotein.
*The recommendation on physical activity changed during the study period from 4 hours of moderate physical activity a week to >30 min/d.[46]

systematic exchange of information using electronic patient records and at a weekly conference with all clinical team members.

Patient education. Patient education was offered in groups with 6 lectures of 60 to 90 minutes, individual education when needed, and practical training.

Exercise training. Exercise training included initial individual consultation with the physical therapist, supervised exercise training, a test of aerobic functioning before and after, a theoretical lecture during the patient education sessions, and individual follow-up with the physical therapist. The supervised exercise training was a 6-week group program of 90 minutes twice weekly. Of the 90 minutes, at least 30 minutes was conducted at an intensity of 60% to 85% of heart rate reserve based on an initial bike test and perceived exertion. The intensity, duration, and activity were individually tailored according to the initial test results, individual preferences, and current guidelines for exercise training.[28,29] The maximum heart rate to be attained in exercise training was reduced individually for patients with CHF (New York Heart Association [NYHA] class III). For this group of patients, exercise training was induced at about 50% of the theoretical maximum heart rate (under the maximum conversational level) with short intervals, frequent breaks, and slow progression,[29] and the supervised period was prolonged to 12 weeks. The training plan was highly individualized and the patients were monitored clinically for cardiopulmonary response to the exercise and by using pulse watches. The physical exercise was conducted as a mixture of endurance and strengthening training using various upper and lower body modalities easily implemented as activities that the patients could perform at home. Adherence to the advised increased level of physical activity was validated by self-administrated questionnaires, interviews, and tests. During the entire program, the patients were encouraged to exercise at home between the 2 weekly sessions and to continue exercising after the 6 weeks of supervised training.

Dietary counseling. Dietary counseling was based on the heart health principles of less fat (<30% of total energy intake), more fish, and more vegetables and fruit.[30] It included initial individual consultation with the

dietitian, 3 practical cooking classes, and individual courses for special dietary conditions when needed: hypercholesterolemia, diabetes, obesity, or risk of malnutrition.

Smoking cessation. Smoking cessation was introduced at the initial consultation with the nurse and included individual and group counseling, nicotine replacement therapy, and biofeedback using systematic carbon monoxide measurements. The group counseling was set up according to a national smoking cessation program for 6 weeks with 5 90-minute sessions.

Psychosocial support. Psychosocial support was an integrated part of the program. Patients were screened for anxiety and depression anxiety and sent to the liaison psychiatrist and treated pharmaceutically when needed. Vocational guidance was offered as individual consultations with the social worker. A 24-hour telephone hotline was set up.

Risk factor management and clinical assessment. Risk factor management and clinical assessment were given high priority during the intervention. At follow-up, the risk profile was systematically assessed, and the lifestyle changes achieved were supported and reinforced. The patient was assigned to follow-up at 3, 6, and 12 months with the physician responsible. If needed, a consultation with the dietitian, physical therapist, or nurse could be prescribed. At each visit, patients were informed of their results, and biofeedback and supervision were given. Pharmaceutical treatment was systematically examined, prescribed, and stabilized as part of the intervention to ensure optimal symptomatic and prophylactic treatment and pharmaceutical compliance (Table IV). A stepwise approach was applied; if there were no side effects, the patient was given the maximum dose of one drug before a new one was added to limit the daily intake of drugs and minimize the potential interactions.

Table IV. Ideal prophylactic pharmaceutical treatment in the DANREHAB trial

	CHF[22]	IHD[23]	HR[24]
Thrombotic inhibition[47]			
Acetylsalicylic acid 75* mg	+	+	+
Clopidogrel bisulfate 75 mg	Optional†,‡	Optional†,‡	Optional‡
β-Blockers	+	+	Optional
Calcium antagonist		Optional when β-blockers are not tolerated	
ACE inhibitors	+	Optional	Optional
Angiotensin II	Optional	Optional	Optional
Spironolactone	+	Not used	Not used
Statins	+	+	Optional

*150 mg of acetylsalicylic acid for previous stroke.
†12-month supplement to acetylsalicylic acid after PCI.
‡When allergic to or intolerant of acetylsalicylic acid.

Ethical considerations

The local ethics committee ([KF]11-121/01) and the Danish Data Protection Agency (RT-nr 1998-1200-353) approved the trial, registered as ISRCTN74601515. Although guidelines around the world recommend CR to patients with post-MI, the evidence on CR has been questioned because of poor quality of CR trials.[4,5] The extension of CR has been very limited in Denmark,[31] and the local ethics committee agreed in 1999 with the investigator group that we had a unique opportunity to conduct a high-quality trial with well-described randomization and blinded outcome evaluation.

All participants supplied written informed consent. The trial was conducted in accordance with the Helsinki Declaration[32] and the relevant regulatory requirements. No experimental treatment was introduced. The program may have introduced an unintended feeling of illness and symptoms of anxiety and depression. This was monitored using the Hospital Anxiety and Depression Scale[33] at baseline, at 12 months, and further among a subgroup of patients at 3 months.

Safety aspects

The risk of adverse events is low in supervised exercise training for patients with MI,[34] and guidelines in Denmark have no specific safety instructions.[10] Patient safety was given high priority because exercise training included patients with CHF. However, exercise training among patients with CHF is considered safe when guidelines for intensity and duration are followed.[29] All adverse events were registered.

Study outcome

The primary composite outcome measure included overall mortality, MI, or readmission due to heart disease. Several secondary outcomes reflected the multifactorial nature of the intervention (Table II).

Assessment methods

Information on the primary outcome will be drawn from central registries to reduce bias. Overall mortality will be drawn from the Civil Registration System, which records the vital status and addresses of all inhabitants in Denmark when all patients have been followed up for at least 12 months. Information on MI and admissions for heart disease will be drawn from the National Patient Registry, which registers information about all hospital admissions in Denmark.

The scientific staff and CR team members collected secondary outcome measures blinded to intervention at baseline and nonblinded at 12-month follow-up. Data were collected using standard procedures by interview, clinical examination, blood tests, and self-administered questionnaire.

Table V. Characteristics of eligible and consenting patients in the DANREHAB Trial tested by logistic regression with adjustment of other covariates

	Eligible	Consented			
	n	n (%)	Odds ratio	95% CI	*P*
Sex					.81
Women	656	281 (43)	0.97	0.76-1.22	
Men	958	489 (51)	1.00	–	
Age groups					<.001
20-64	676	389 (58)	6.54	4.13-10.36	
65-74	336	194 (58)	7.06	4.39-11.37	
75-85 y	429	157 (37)	3.00	1.88-4.76	
≥85	173	30 (17)	1.00	–	
Comorbidity score*					.03
0	885	420 (47)	2.72	0.75-9.90	
1	582	283 (48)	3.88	1.08-13.87	
≥2	20	3 (15)	1.00	–	
	1614	770 (47)			

*Modified Charlson index score.[37,38] Due not sum up to 100%, whereas some of the patients were not registered in the local administrative system because they were back referred from the invasive department.

Dropout was systematically registered. Information on UC patients was collected from the local administrative system and by interviews at 12-month follow-up.

Statistical power

The expected event rate was based on a pilot study. We estimated a 12-month composite outcome measure in the UC group of 20% and a reduction in the probability of a primary outcome event from 25% to 15% in the CR group, power of 0.80, and 2-sided *P* value <.05. We therefore aimed to include 1810 patients. The duration was fixed at a maximum of 3 years to minimize the influence of changing treatment trends on CR intervention over time. The pilot study indicated that 900 patients would be eligible annually, enabling the 1810 patients to be achieved within 3 years with the expected participation rate of about 70%.

Dropout was not included in the assumptions on power calculation due to the register-based design with very low dropout rate; only 0.05% of the Danish population are moving out of the country per year.[35] This percentage will tend to be even lower in a cohort of middle-aged people with severe disease. The study design did not allow crossover in the full study period running from March 2000 until March 2003, and crossovers were not included in the power calculation either.

Statistical analysis

Differences between the CR and UC groups and within the CR subgroups will be analyzed by survival analysis, including Cox regression. Two-tailed *P* value <.05 is considered significant. Patients lost during follow-up will be censored at dropout. Per-protocol analysis will only include the patients who received the planned intervention.

Because of the skewed distribution of length of stay and repeated measurements of admissions on patients, these register-based tertiary outcomes will be analyzed simultaneously using multivariate random effect modeling with patients as random effects.[36]

A study group–independent, "blinded" statistician will be conducting the statistical analysis. A detailed protocol for the statistical analysis has been planned in advance to ensure the blindness of the analysis available in English at the Web site: www.cardiacrehabilitation.dk.

The participation of patients was compared for sex, age, and comorbidity by standard statistical methods, including logistic regression.

A comorbidity index was calculated based on administrative data of discharge and primary and secondary diagnoses until 1 year before randomization, using the Manitoba-Dartmouth[37] modification of the Charlson index,[38] converted into *International Classification of Diseases, Tenth Revision (ICD-10)* and *ICD-17* independent risk factors. The comorbidity index scores were categorized in 3 groups according to increasing prognostic value.[39]

Current status of the trial

Patients were enrolled from March 2000 to February 2003. Enrollment ended when we reached the fixed duration of 3 years. Of the 5060 patients screened, 1614 patients (32%) met the inclusion criteria and none of the exclusion criteria (Figure 1). A total of 1156 did not meet the inclusion criteria. Among the 1614 eligible

Table VI. Demographic data, history of disease, and risk factors at baseline in the DANREHAB trial

	CHF	IHD	HR
	n = 91	n = 446	n = 233
Demographic data			
Age (y) (mean)	70.3	65.9	60.1
Women	37.4	33.4	41.6
Living alone	62.6	45.5	44.6
Working	7.7	24.9	35.6
History of disease			
IHD presentation:			
MI	51.7	62.6	–
Coronary artery bypass grafting	19.8	25.6	–
Percutaneous coronary intervention	22.0	41.6	–
Atrial fibrillation	25.3	12.1	23.6
Hypertension	47.3	41.5	59.7
Hypercholesterolemia	42.8	66.6	49.4
Diabetes	30.8	18.4	18.9
Modifiable risk factors			
Blood pressure			
High systolic*	13.2	27.6	39.9
High diastolic†	5.5	9.6	22.8
Cholesterol			
High total cholesterol†	41.8	45.7	47.2
High LDL cholesterol†	40.7	41.9	45.9
Low HDL cholesterol†	55.0	50.0	55.4
High triglycerides†	6.6	17.5	23.2
Weight			
BMI $\geq$30 kg/m^2	31.9	20.2	38.2
Lifestyle			
Moderate physical activity†	69.2	48.2	52.8
Current smoking	20.9	24.9	40.4
Medication			
Lipid lowering drugs	43.9	68.0	17.1
Antithrombotics	82.9	92.1	59.5
β-Blockers	36.6	55.6	27.2
Calcium antagonists	22.1	32.0	31.6
ACE inhibitors	54.9	28.9	16.5
Diuretics	93.9	37.1	38.6
Prolonged nitrates	20.7	22.8	5.7
Antipsychotics/anxiolytics	18.3	9.0	7.6
Antirheumatics	2.4	7.3	7.0

Values are presented as percentages unless otherwise stated.
*Defined according to target treatment goals listed in Table 3.
†<4 hours of leisure activity per week.

patients, 770 (48%) consented to participate and 844 (52%) refused.

Table V outlines the characteristics of the eligible patients and the consenting patients according to sex, age, and comorbidity. In univariate analysis, men were more likely to consent than women (51% vs 43% [P = .002]). This sex difference disappears when other covariates are corrected in multivariate logistic regression analysis (odds ratio 0.97, 95% CI 0.76-1.22). Patients who consented were younger (P < .0001), and more had a low comorbidity score (P = .03) than patients who did not consent.

Table VI summarizes the demographic data, history of disease, risk factors, and medication among patients with CHF, IHD, and HR at baseline.

Discussion

Current guidelines recommend comprehensive CR to a broad spectrum of patients[10-12]; the evidence on comprehensive CR, however, is still limited. The trials have primarily included younger patients with MI.[1-5] The quality of the trials has been questioned because of poorly reported randomization, lack of blinded outcome assessment, and insufficient program description.[4,5]

The DANREHAB trial included a broad spectrum of patients, but older patients and patients with high comorbidity were underrepresented. This may limit the external validity. Our trial, however, included more elderly patients and more women than previous trials on comprehensive CR[4]: mean age 63.4 versus 56.3 years and 37% versus 11% women.

The investigators randomized each patient by a centralized randomization procedure to avoid selection bias.[40] Blinded outcome assessment is especially relevant in CR trials where blinding to the intervention is not possible. The existence of a national system of unique personal identification and data on all somatic hospital admissions in a population with relative demographic stability enables blinded assessment of primary outcome. The validity of the data on somatic hospitals is high for administrative data on admissions, identification, and discharges (97%-98%).[41] However, the validity of data on diagnosis is lower, 66% to 93%, depending on the diagnosis.[41,42] A study from Ontario showed that sensitivity and positive predictive value of the MI diagnosis (*ICD-9* 410) were 88.8% and 88.5%, respectively.[43] Similar figures were found in a validation study from Denmark on the MI diagnosis (primary and secondary) (*ICD-8* 410) (96.6% and 78.8%).[42] Thus, several studies have shown high validity for coding of acute MI in administrative databases, however, with lesser validity for heart failure. Potential misclassification of diagnoses is believed to be independent of randomization; further nondifferential misclassification will tend to move the register-based results toward the null hypothesis, with no difference between groups.

Although the primary outcome measure will be assessed blindly, we are well aware of the risk of bias due to collateral intervention given to both arms during the trial, as well as bias in the assessment of secondary outcome measures.[17] This will tend to negatively bias the primary outcome measure because of more admissions due to closer follow-up.

We stipulated a sample size of about 1800 patients. However, we only included 770 patients. This increases the risk of not finding a statistically

significant difference, although it may exist (a type II error). Although the trial "only" includes 770 patients, the DANREHAB trial is still the largest trial on comprehensive CR published so far. Thus, adding the results of this high-quality trial to the meta-analysis on CR[5] will extend the total study population of the meta-analysis significantly.

It has been repeatedly found that the effect of CR is a long-term effect.[5,44] Thus, conducting long-term follow-up in this trial is highly relevant and might strengthen the power of the trial. In the DANREHAB trial, the long-term follow-up will be conducted by 3 years. Doing the long-term, register-based follow-up, we will be aware of crossover.

Comprehensive CR is built up from several components, including behavior modification and methods of organizing and delivering that are believed to act both independently and interdependently, posing difficulty in defining which components are active. In the DANREHAB trial, the effect of the single component cannot be separated. Analysis will determine whether there has been a learning-curve effect in the DANREHAB trial, given that complex interventions usually evolve over time, as providers become more experienced and evidence changes.[18]

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References

1. O'Connor GT, Buring JE, Yusuf S, et al. An overview of randomized trials of rehabilitation with exercise after myocardial infarction. Circulation 1989;80:234-44.
2. Oldridge NB, Guyatt GH, Fischer ME, et al. Cardiac rehabilitation after myocardial infarction. Combined experience of randomized clinical trials. JAMA 1988;260:945-50.
3. Wenger NK, Froelicher ES, Smith LK, et al. Cardiac rehabilitation as secondary prevention. Agency for Health Care Policy and Research and National Heart, Lung, and Blood Institute. Clin Pract Guidel Quick Ref Guide Clin 1995;17:1-23.
4. Jolliffe JA, Rees K, Taylor RS, et al. Exercise-based rehabilitation for coronary heart disease. The Cochrane Library. Issue 1. Chichester (UK): John Wiley & Sons, Ltd; 2004 [Cochrane Review].
5. Taylor RS, Brown A, Ebrahim S, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. Am J Med 2004;116:682-92.
6. Oldridge N, Guyatt G, Jones N, et al. Effects on quality of life with comprehensive rehabilitation after acute myocardial infarction. Am J Cardiol 1995;67:1084-9.
7. Lavie CJ, Milani RV. Effects of cardiac rehabilitation programs on exercise capacity, coronary risk factors, behavioral characteristics, and quality of life in a large elderly cohort. Am J Cardiol 1995;76:177-9.
8. Hedback B, Perk J, Hornblad M, et al. Cardiac rehabilitation after coronary artery bypass surgery: 10-year results on mortality, morbidity and readmissions to hospital. J Cardiovasc Risk 2001;8:153-8.
9. McAlister F, Lawson FM, Teo KK, et al. Randomised trials of secondary prevention programmes in coronary heart disease: systematic review. BMJ 2001;323:957-61.
10. Rehabilitation of people with heart disease—Danish clinical guidelines. Copenhagen: Danish Heart Foundation and Danish Society of Cardiology; 1997.
11. Vanhees L, Mc Gee HM, Dugmore LD, et al. The Carinex Survey. Current guidelines and practices in cardiac rehabilitation within Europe. Leuven: Acco; 1999. p. 1.
12. Leon AS, Franklin BA, Costa F, et al. Cardiac rehabilitation and secondary prevention of coronary heart disease: an American Heart Association scientific statement from the Council on Clinical Cardiology (subcommittee on exercise, cardiac rehabilitation, and prevention) and the Council on Nutrition, Physical Activity, and Metabolism (subcommittee on physical activity), in collaboration with the American Association of Cardiovascular and Pulmonary Rehabilitation. Circulation 2005;111:369-76.
13. Giannuzzi P, Saner H, Bjornstad H, et al. Secondary prevention through cardiac rehabilitation: position paper of the Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology. Eur Heart J 2003;24:1273-8.
14. Todaro JF, Shen BJ, Niaura R, et al. Do men and women achieve similar benefits from cardiac rehabilitation? J Cardiopulm Rehabil 2004;24:45-51.
15. Pasquali SK, Alexander KP, Peterson ED. Cardiac rehabilitation in the elderly. Am Heart J 2001;142:748-55.
16. Lavie CJ, Milani RV. Benefits of cardiac rehabilitation and exercise training programs in elderly coronary patients. Am J Geriatr Cardiol 2001;10:323-7.
17. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Ann Intern Med 2001;135:982-9.
18. UK Medical Research Counsil. A framework for development and evaluation of RCTs for complex interventions to improve health. United Kingdom: Medical Research Council; http://www.mrc.ac.uk/pdf-mrc_cpr.pdf [accessed March 31, 2004].
19. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001;22:1527-60.
20. Acute myocardial infarction: prehospital and inhospital management. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 1996;17:43-63.
21. Bertrand ME, Simoons ML, Fox KA, et al. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2002;23:1809-40.

22. Kühn Madsen B, Johannessen A, Thomassen A, et al. CopenhagenDanish Society of Cardiology and Danish Society of Internal Medicine: diagnosis and treatment of cardiac insufficiency. Overview and guidelines; 1997. p. 9. www.dadlnet.dk/klaringsrapporter/1997-09/1997-09.HTM [accessed April 1, 2004].
23. Hildebrandt P, Gøtzsche CO. Acute coronary syndrome. Guidelines for diagnosis and treatment Copenhagen: Danish Society of Cardiology; 2001. p. 3. www.dadlnet.dk/klaringsrapporter/2001-03/2001-03.htm [accessed March 22, 2004].
24. Færgeman O, Christensen B, SteenHansen H, et al. Secondary and primary prevention of coronary heart disease with special emphasis on dyslipidemia. Copenhagen: Danish Society of Cardiology; 2000. p. 7. www.dadlnet.dk/klaringsrapporter/2000-07/2000-07.htm [accessed April 1, 2004].
25. Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: toward an integrative model of change. J Consult Clin Psychol 1983;51:390-5.
26. Jeng C, Braun LT. Bandura's self-efficacy theory: a guide for cardiac rehabilitation nursing practice. J Holist Nurs 1994;12:425-36.
27. Zwisler ADO, Schou L, Vind-Sørensen L. Cardiac Rehabilitation—rationale, working methods and clinical experiences from Bispebjerg Hospital. Copenhagen: Bispebjerg Hospital and National Institute of Public Health; 2003. http://www.cardiacrehabilitation.dk/rehab_uk/ [accessed May 1, 2005].
28. Fletcher GF, Balady GJ, Amsterdam EA, et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. Circulation 2001;104:1694-740.
29. Recommendations for exercise training in chronic heart failure patients. Eur Heart J 2001;22:125-35.
30. Stender S, Astrup AV, Dyerberg J, et al. Significance of food for patients with ischemic heart disease. Ugeskr Laeger 1996;158:6885-91.
31. Zwisler ADO, Traeden UI, Videbaek J, et al. Cardiac rehabilitation services in Denmark—still room for expansion. Scand J Public Health 2005 [in press].
32. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. JAMA 2000;284:3043-5.
33. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.
34. Foster C, Porcari JP. The risks of exercise training. J Cardiopulm Rehabil 2001;21:347-52.
35. Statistical Yearbook. Copenhagen: National Statistics Denmark; 2004. http://www.dst.dk/Yearbook.aspx [accessed May 1, 2005].
36. Tooze JA, Grunwald GK, Jones RH. Analysis of repeated measures data with clumping at zero. Stat Methods Med Res 2002;11:341-55.
37. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. J Clin Epidemiol 1993;46:1075-9.
38. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
39. Sachdev M, Sun JL, Tsiatis AA, et al. The prognostic importance of comorbidity for mortality in patients with stable coronary artery disease. J Am Coll Cardiol 2004;43:576-82.
40. Schulz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;273:408-12.
41. Nickelsen TN. Data validity and coverage in the Danish National Health Registry. A literature review. Ugeskr Laeger 2001;164:33-7.
42. Madsen M, Davidsen M, Rasmussen S, et al. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. J Clin Epidemiol 2003;56:124-30.
43. Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. Am Heart J 2002;144:290-6.
44. Lisspers J, Sundin O, Ohman A, et al. Long-term effects of lifestyle behavior change in coronary artery disease: effects on recurrent coronary events after percutaneous coronary intervention. Health Psychol 2005;24:41-8.
45. McHorney CA, Ware Jr JE, Lu JF, et al. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care 1994;32:40-66.
46. National Board of Health. Physical activity and health. Copenhagen: National Board of Health; 2001. http://www.sst.dk/publ/Publ2001/Fysisk_aktivitet_sundhed/index.htm [accessed April 1, 2004].
47. Godtfredsen J, Sandbjerg Hansen M, Elkjær Husted S, et al. Antithrombotic treatment in cardiovascular diseases. Copenhagen: Danish Society of Cardiology and Danish Society of Clinical Chemistry; 1997. p. 5. www.dadlnet.dk/klaringsrapporter/1997-05/1997-05.htm [accessed April 1, 2004].