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Effects Of An Expanded Rehabilitation Programme In Patients With Ischemic Heart Disease

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# **EFFECTS OF AN EXPANDED REHABILITATION PROGRAMME IN PATIENTS WITH ISCHEMIC HEART DISEASE**

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*"Det viktigaste i livet  
kan man inte se med ögonen  
utan med hjärtat"*

*Antoine de Saint-Exupéry*



## ABSTRACT

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The effects of expanded cardiac rehabilitation (ECR) after coronary artery by-pass surgery or myocardial infarction (MI) on medical risk markers, cardiovascular (CV) morbidity and hospitalizations due to symptoms of CV disease, were evaluated in a prospective randomized trial. The project was performed at the Department of Cardiology, Danderyd Hospital, between 1999-2001. In total, 828 patients were screened and 224 patients <75 years were randomized to ECR or usual care (UC). The UC group was offered physical training, education and heart school with information/counselling on risk factor intervention. The patients met with a cardiac nurse on one or two occasions after the event and a cardiologist on one occasion, 6-8 weeks after the event. Patients who were randomized to ECR participated in all activities of the UC rehabilitation programme. In addition they spent one week at the patient hotel after discharge from the hospital. They also participated in a stress management programme in groups during one year, and in cooking sessions and diet counselling. All smokers in both treatment groups were offered a smoking cessation programme. In paper I, the effects of ECR on metabolic and inflammatory markers and other CV risk markers, as well as exercise performance, were evaluated after one year. Several biochemical risk markers such as total cholesterol and LDL cholesterol, fibrinogen and CRP improved similarly in both the ECR and the UC group. Both groups improved in exercise performance significantly over time. In summary, there was no further improvement in the ECR group in addition to what was observed in the UC group. In paper II, a five year follow-up was carried out using data from the National Board of Health and Welfare register. The primary composite endpoint was time to first cardiac event defined as CV death, MI or readmission due to CV disease. There was a significant reduction in the primary composite endpoint among those in the ECR as compared to UC group (47.7% vs. 60.2%; hazard ratio 0.69; 95% CI 0.48-0.99;  $p=0.049$ ). This was mainly due to a reduction in MI in the ECR group (10.8% vs. 20.3%; hazard ratio 0.47; 95% CI 0.21-0.97;  $p=0.047$ ). Readmission to hospital and days in hospital for CV reasons were significantly reduced in patients who received ECR as compared to UC ( $p<0.01$  and  $p=0.02$ , respectively). In conclusion, our results show that ECR, despite the absence of an incremental effect on risk markers, reduced the incidence of MI and reduced health care consumption due to CV causes in a long-term follow-up.

## LIST OF PUBLICATIONS

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- I. **Edström-Plüss C**, Rydell-Karlsson M, Wallen NH, Billing E, Held C  
Effects of an expanded cardiac rehabilitation programme in patients treated for an acute myocardial infarction or a coronary artery by-pass graft operation.  
*Clinical Rehabilitation* 2008;22:306-318
  
- II. **Edström-Plüss C**, Billing E, Held C, Henriksson P, Kiessling A, Rydell- Karlsson M, Wallen NH  
Long-term beneficial effects of expanded cardiac rehabilitation after an acute myocardial infarction or coronary artery by-pass grafting: A five year follow-up of a randomized controlled study  
*Submitted*

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## LIST OF ABBREVIATIONS

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|       |  |
|-------|--|
| ACE   | Angiotensin converting enzyme                      |
| AHA   | American Heart Association                         |
| ANOVA | Analysis of variance                               |
| BMI   | Body mass index                                    |
| CABG  | Coronary artery by-pass graft                      |
| CAD   | Coronary artery disease                            |
| CHD   | Coronary heart disease                             |
| CV    | Cardiovascular                                     |
| CVD   | Cardiovascular disease                             |
| CR    | Cardiac rehabilitation                             |
| ECR   | Expanded cardiac rehabilitation                    |
| ESC   | European Society of Cardiology                     |
| HDL   | High density lipoprotein                           |
| HR    | Hazard ratio                                       |
| ICD   | Implantable Cardioverter Defibrillator             |
| IHD   | Ischemic Heart Disease (synonymous to CHD and CAD) |
| LDL   | Low density lipoprotein                            |
| MI    | Myocardial infarction                              |
| PCI   | Percutaneous coronary intervention                 |
| UC    | Usual care   |
| WHO   | World Health Organisation                          |

# INTRODUCTION

---

## **Background**

Cardiovascular disease (CVD) i.e. diseases of the heart and the circulatory system, is the main cause of death in Europe. Almost half of all deaths are from CVD (55% of deaths in women and 43% deaths in men). The main components of CVD are coronary heart disease (CHD) and stroke, and of all deaths from CVD almost half are caused by CHD and nearly a third due to stroke (1).

## **Risk factors for cardiovascular disease**

In the literature there are several factors or markers identified that increase the risk of CVD. The term risk factor is generally defined as an aspect of personal behaviour or lifestyle, an environmental exposure, or an inborn or inherited characteristic, which by temporal sequence directly increases the probability to develop a certain disease. Furthermore, there should be a “dose-response” relationship between the risk factor and development of the disease. If the factor is reduced or removed, the probability of having the disease should be reduced (2). A risk marker, however, is an attribute or exposure that is associated with increased probability of disease, but is not necessarily a causal factor (2).

It has been shown that nine common and potentially modifiable “risk factors” accounts for about 90% of the population attributable risk for developing myocardial infarction (MI) in both men and women in different geographical areas of the world (3). These were: smoking, hypertension, low alcohol consumption, low physical activity, elevated blood lipoproteins, diabetes mellitus, obesity, low fruit and vegetable consumption and some psychosocial factors like stress and depression. Of note, risk factors are part of the casual chain, or expose the host of the causal chain, but once the disease occurs, removal of a risk factor may not necessarily result in cure from the disease (4).

However, in order to reduce the risk factor profile and eliminate or reduce several risk factors it has been stated that (5, 6) comprehensive cardiac rehabilitation (CR) programmes, which includes a cluster of activities and treatments, should be offered to patients with CVD (7, 8)

## **History of cardiac rehabilitation**

In US during the 1930s, patients with MI were advised to stay in bed for 6-8 weeks because physical activity was feared to lead to vascular complications and sudden death. Many members of the labour force were on disability pension because of heart problems, and this led to the establishment of cardiac work-evaluation units and rehabilitation centres in order to evaluate the physical and mental capacity of these patients (9). However, by the early 1950s, 3-5 minutes daily walking was advocated after MI, and clinicians gradually began to recognize that early ambulation avoided many of the complications in bed rest and that it did not increase the risk (9, 10). In 1968 Saltin et al (11) reported that the functional capacity of normal subjects confined to bed for 3 weeks decreased by about 33%. However, concerns about the safety of unsupervised exercise remained strong and led to the development of structured and physician-supervised rehabilitation programmes.

In the 1950s, Hellerstein presented his methodology for the comprehensive rehabilitation of patients recovering from an acute cardiac event (12, 13). Hellerstein advocated a multidisciplinary approach and his idea was adopted by CR programmes throughout the world. Preventive strategies became more common during the late 1970s and 1980s in parallel with the growing evidence that such interventions could inhibit or reverse the underlying pathological process of atherosclerosis. During the same period, behavioural approaches to the treatment of IHD became recognized as a complement to traditional medical and surgical therapies (14). CR has since then gradually evolved into complex interventions based on several treatment modalities, including exercise training, patient education, behavioural and psychosocial counselling, risk factor management and pharmacological treatment and clinical assessment.

## **Clinical studies on cardiac rehabilitation**

The earliest randomized controlled studies investigating the effects of CR mainly included young men with MI, and varied substantially according to the time after index event until randomization, type and duration of intervention, and duration of follow-up (15, 16). Moreover, most studies were small with low power, and allocations were not concealed and the descriptions of the interventions have been poor or missing. Effects of CR have been systematically reviewed in meta-analyses and systematic reviews (17-19). Some of them review effects of exercise-based rehabilitation, and some examine effects of patient education and psychosocial interventions. Overall, the meta-analyses

conclude that exercise only, and comprehensive CR, reduce all-cause mortality by about 20% and cardiac mortality by about 25% (17-19). Furthermore, in one of these (17) a significant reduction in recurrent myocardial infarction was observed. In support of comprehensive CR, there are two prospective cohort studies presenting data on ten year follow-up after CABG and MI, respectively. The studies showed a significant reduction in total and CV death and also in the risk of non-fatal reinfarction (20, 21).

### **Definitions of modern cardiac rehabilitation**

As defined by the American Heart Association (AHA) in 2007, CR programmes should be comprehensive, long-term, involve medical evaluation, prescribe exercise, and include cardiac risk factor modifications, education and counselling (22). These programmes are designed to limit the physiologic and psychological effects of cardiac illness, to reduce the risk for sudden death or re-infarction, to control cardiac symptoms, stabilize or reverse the atherosclerotic process, and enhance psychosocial and vocational status of selected patients (8).

In the AACVPR/ACC/AHA 2007 Performance Measures on Cardiac Rehabilitation, it is stated that comprehensive CR should be offered to all patients after an MI/acute coronary syndrome, after coronary by-pass grafting (CABG), following percutaneous coronary angioplasty (PCI), in patients with stable chronic angina pectoris, after heart transplantation and in patients who have undergone heart valve surgical repair or replacement. CR should also aim to stabilize heart disease, improve physical capacity, limit physical and mental disability, prevent relapse and improve the overall quality of life (7, 8).

In the European Society of Cardiology (ESC) guidelines of 2007, the importance of secondary prevention is emphasized. Early identification of symptoms and disease is crucial as it may reduce progression and improve prognosis. The identification of patients at high risk of developing CVD and prevention of disease progression in these patients is also stressed (23).

In comprehensive CR programmes the following treatment modalities or core components, are recommended (7, 8):

- Physical activity and exercise training
- Patient education and behavioural intervention
- Smoking cessation
- Dietary guidance

- Psychosocial support
- Risk factor management and clinical assessment

### **Physical activity and exercise training**

Exercise training is one of the cornerstones of comprehensive CR. A 20% to 25% reduction in all cause mortality has been observed in patients with CHD disease who adhere to a regular physical activity regimen (15-19). According to the American College of Sports Medicine and AHA (24), recommendations are moderate physical activity for a minimum of 30 minutes up to 60 minutes on most, if not all days of the week. Strategies to incorporate increased physical activity into usual daily activities are recommended. The activity may be performed in a single session or accumulate in multiple bouts, each lasting at least 8-10 minutes. The intensity may be defined as a heart rate during peak exercise of 60-75% of the average maximum heart rate, i.e. 11-13 on the 6-20 Borg scale (25). It has also been stated that a majority of the patients will benefit from supervised physical exercise in group (17-19, 25).

### **Smoking cessation**

Tobacco smoking is perhaps the most important modifiable risk factor for CHD (3, 26). The benefits of smoking cessation have been extensively reported (see e.g. 27, 28) and stopping smoking after a MI is probably the most effective of all preventive actions. Thus all smokers should be professionally encouraged to permanently stop smoking all forms of tobacco. Guidelines (7, 8) recommend the five “As” to help:

ASK systematically - identify all smokers at every opportunity

ADVISE all smokers to quit

ASSESS the person's degree of addiction

ASSIST a smoking cessation strategy including behavioural counselling, nicotine replacement therapy, and/or pharmacological intervention

ARRANGE follow up visits

Additional smoking cessation therapy - both individual and group behavioural interventions - was reported to be effective in helping current smokers to quit in a recently published meta-analysis. Provided the therapy was of sufficient intensity and with a minimum length of one month, the quit rate was up to 48% (29).

## **Dietary guidance**

Today's recommendation on healthy eating is focused to reduce saturated fat, to increase omega-3 fat intake and to stay on a Mediterranean diet (30-32). Dietary counselling is an important part of risk management, and recommendations should be individualized, taking the patient's risk factors into account; such as dyslipidemia, hypertension, diabetes and obesity. The fourth joint Task Force of the ESC recommends the following (7):

- A wide variety of foods should be eaten
- Energy intake should be adjusted to avoid overweight
- Encourage intake of fruits, vegetables, wholegrain cereals and bread, fish, lean meat and low fat products
- Replace saturated fats with the above foods with monounsaturated and polyunsaturated fats from vegetables and marine sources to reduce total fat < 30% of energy, of which less than 1/3 is saturated
- Reduce salt intake, especially if blood pressure is elevated

## **Body weight**

Overweight is generally defined as body mass index (BMI)  $>25\text{kg/m}^2$  and obesity as BMI  $>30\text{ kg/m}^2$ . Obesity is reaching epidemic proportions globally. More than 60% of the US adult population is either overweight or obese (33). Clearly, increased BMI is associated with an increased risk of CVD (34, 35). In the WHO report on obesity (36) the use of waist circumference measurement is recommended as an additional indicator of metabolic risk. Importantly, in a substudy from the INTERHEART study, waist-hip ratio was found to be more strongly associated with the risk of MI than BMI (37).

As overweight and obesity are mainly the result of an imbalance between energy intake and expenditure, restriction of total calorie intake and regular physical exercise are the cornerstones of weight control. Behaviour modification and long term lifestyle change in order to reduce weight loss is emphasized (38). Of note, reduction of initial body weight by only 5 - 10% has been shown to result in a significant cardiovascular risk reduction (39) and may also lead to other health benefits.

## **Blood pressure**

Hypertension is one of the leading preventable causes of premature death worldwide (40) and a risk factor for CVD. Treatment of hypertension includes treatment of all

reversible risk factors such as smoking, dyslipidemia, obesity, diabetes mellitus, alcohol consumption and, importantly, pharmacological treatment of the elevated blood pressure per se. The goal in patients with IHD is to obtain a blood pressure less than 130/80 (41).

### **Blood lipids**

In a recent meta-analysis, exercise based CR was associated with a significant reduction in total cholesterol and triglyceride levels, whereas there seemed not to be any significant effect on LDL or HDL cholesterol levels by the rehabilitation procedure (19). Lipid lowering therapy with statins is without any doubt one of the cornerstones in secondary prevention of CVD. A meta-analysis of the efficacy of cholesterol lowering treatment showed that statin therapy can reduce the 5 year incidence of major coronary events, coronary revascularization and stroke by about 20% per mmol/l reduction in plasma LDL cholesterol (42). The treatment target according to recent guidelines is to achieve a total cholesterol level of <4.5 mmol/l, (if feasible <4.0 mmol/l) and LDL cholesterol to <2.5 mmol/l, (if feasible < 2.0 mmol/l) (7).

### **Psychosocial management**

According to the INTERHEART study, psychosocial factors including psychosocial stress and depression are important (and potentially modifiable) “risk factors” for CHD (3). Psychological treatment has often been a part of comprehensive CR but the results have been controversial (17). However, Linden et al (43) recently claimed that psychological treatment offered - in addition to UC - reduced mortality by 28% for the first 2 years or less, and the effect was also shown after longer follow-up (11% reduction); recurrent events at longer follow-up (2 years) was reduced by 43 %. Somewhat puzzling, beneficial effects on cardiac mortality were only seen when patients were recruited and treated later than 2 months after the cardiac event, and with a significant mortality reduction of 72% in the 2 first years. However, no significant effect was seen when the psychological treatment was initiated within 2 months of the event (13% reduction - not significant). In addition, there were no mortality benefits in women. In the rather large ENRICHD study including 2481 patients (44), no significant effects of individual and group based cognitive behavioural therapy on the composite endpoint of death and non-fatal MI could be observed. The treatment started early (within one month after the event), and half of the patients were women.

In support of a lack of effect of behavioural therapy is a Cochrane Meta-analysis (45) which identified statistical evidence of publication bias and no significant effect on mortality. Taken together, there is at present limited documentation in support of behavioural therapy in the setting of CR.



**Patient education and behavioural intervention**

Patient education could be defined as the process by which health professionals and others impart information to patients that will alter their health behaviours or improve their health status. Important elements of patient education are skill building and responsibility, i.e. patients need to know when, how and why they need to make lifestyle changes.

A Finnish study provides some support of benefits of individual counselling (46). They studied patients with impaired glucose tolerance and who received individual counselling regarding weight loss, decreased fat intake, increased fibre intake and more physical activity. Over a 3.2 year long period of the lifestyle programme, the risk of developing diabetes mellitus was reduced by 58%.

In the ESC guidelines of 2003 (47) it is advised that intervention should integrate education on healthy lifestyle, medical resources, exercise and relaxation training, and smoking cessation. If required, individual or group counselling on psychosocial risk factors is recommended in order to improve coping with stress and illness.

## **AIMS**

---

Aims of the present study were:

- To investigate the effects of an expanded cardiac rehabilitation programme in a prospective randomized trial on metabolic and inflammatory markers, exercise performance and on established cardiovascular risk factors.
- To investigate the long-term effects of the expanded cardiac rehabilitation programme on cardiovascular morbidity and health care consumption.

## MATERIALS AND METHODS

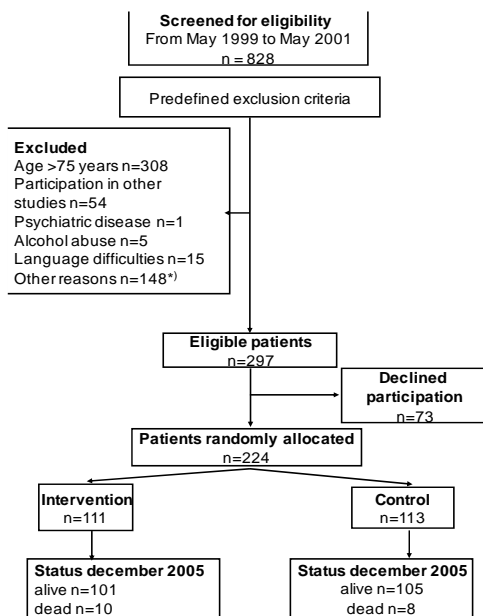
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### Patients

Between May 1999 to May 2001, 828 patients under the age of 75 years suffering either an acute myocardial infarction (MI) or who were planned for coronary artery bypass grafting (CABG) were screened at Danderyd Hospital for participation in the study. Five-hundred thirty-one patients did not fulfil the inclusion criteria and 73 patients declined to participate. The remaining 224 patients were randomized to expanded cardiac rehabilitation (ECR, in paper I called “intervention” (I); n=111) or usual care (UC, in paper I called “control” (C); n=113). Exclusion criteria were significant psychiatric disease, alcohol abuse, not speaking or understanding the Swedish language and/or participation in another randomized controlled trial. Patients who lived in another public health service area could not participate for health care administrative reasons. A few patients could not participate due to severe concomitant diseases such as severe disabling ischemic or hemorrhagic strokes, need for chronic haemodialysis or metastasizing cancer of the prostate.

All participants received written and verbal information on the study. After giving verbal consent to participate the baseline assessment was performed. Thereafter the research nurse opened a sealed numbered envelope containing the allocation: *expanded cardiac rehabilitation (ECR)* i.e. participation in the expanded rehabilitation programme, or *usual care (UC)* i.e. participation in the routine rehabilitation programme provided by the hospital. The randomization was performed by data selection in blocks of six. The MI patients were included during their hospital stay and the randomized rehabilitation programme started at the time of discharge from the hospital. The CABG patients were mainly randomized in association with the decision to perform surgery. However, the rehabilitation treatment programme started post-surgery. CABG surgery was normally performed a few weeks up to 2-3 months after the decision to perform CABG. In these patients we evaluated the effect of the randomized rehabilitation programme from the time-point at which the actual rehabilitation started, i.e. after the CABG had been performed. Participation in the different rehabilitation activities was on a voluntary basis but strongly encouraged. The patients were followed for one year. The screening procedure is shown in Figure 1. The study was approved by the Ethics committee of the Karolinska Hospital.

**Figure 1**



\*) Other reasons were: severe illness n=17, living in another public health service area n=101, primary aortic stenosis n=5, lost for screening n=2

## Study design

The ROC-study (Rehabilitation Of Cardiac patients) was a single centre prospective, randomized controlled study including patients with an acute MI or patients undergoing CABG. The original and overall aim of the study was to evaluate the effects of an multifactorial ECR on psychosocial and medical risk markers. In paper I we focus on medical risk markers. As the design of the study permitted a long-term follow-up, a registry based five-year follow-up was also performed (paper II).

### *Usual Care (UC; control rehabilitation programme)*

This programme included the following activities:

1. *Physical training:* The training was classified into three different training groups: light, modest, and heavy training. The physiotherapist who led the training groups decided the level of training intensity for each patient. Most patients started with modest physical training within two weeks after discharge. The training sessions lasted for 60 minutes, and consisted of 45 minutes of physical exercise, followed by 15 minutes of relaxation. After six weeks, the patients performed an exercise test, and based on the results it was decided whether the patient should increase training intensity. The training sessions were performed twice a week during 3 months.
2. *Information/counselling:* Patients and their spouses were invited to meet a cardiologist in an open forum for a “counselling hour”, which took place once a week in the hospital. Information was given orally and in conjunction with the training sessions during the light physical training period. The counselling included information on risk factors, pathophysiology and treatment options in an informal setting.
3. *Heart School:* The patients were invited, within two months after discharge, to participate in two information sessions, of which each was 90 minutes. During the first session, a nurse informed the patients about basic knowledge in CVD and cardiac risk factors. A dietician explained the importance of healthy diet and lifestyle for reducing the risk of new events. During the second session, a physiotherapist and a medical social worker informed the patients about the beneficial effects of physical training, and about the negative effects of mental stress on the cardiovascular system.
4. *Out-patient clinic:* The patients met a cardiac nurse on one or two occasions after the event and a cardiologist on one occasion, 6-8 weeks after the event. If the clinical recovery was uncomplicated, i.e. if there were no indications of reversible myocardial ischemia, severe arrhythmias or in compensated heart failure, the patients were then referred for long-term follow-up with their regular physicians.

5. Individual counselling on social insurance or other needs of the patient were organised by the medical social worker at the department.

*Expanded Cardiac Rehabilitation (ECR; participation in an expanded rehabilitation programme)*

The patients randomized to ECR participated in all activities of the UC programme (see table 1) and, in addition, in the following activities:

1. *A stress management programme*: This programme, which is based on cognitive behavioural therapy, has previously been evaluated (48) and comprised twenty group sessions, each two hours long, during the course of one year. The ten first sessions were held once a week and thereafter every third week. Each group consisted of 5-9 participants; women and men separately. Each session's agenda covered a specific theme and was presented using written texts, case illustrations, slides, films, audio and videotapes, and by specific exercises for a more detailed description of the programme. There was one group leader for the women's group and two leaders for the men's group. All group leaders had passed a structured training education led by the inventor of the stress management programme (48).

2. *A five day stay at the Patient Hotel* (located within the hospital area), directly after discharge from the hospital. At the hotel, the patients participated in physical training twice a day, including one outdoor walk led by a physiotherapist, and one training session with light gymnastic movements while the patients were sitting on a chair. During the stay, a cardiologist led an extra "counselling hour", to which also the patients' spouses were invited.

3. *Cooking sessions and counselling regarding diet*: The sessions were held once a week during three weeks under the supervision of a dietician. Each session lasted for 3 hours. At the first and third sessions the participants were cooking menus composed by the dietician. The second session was theoretical with information and counselling regarding cooking and preparing foods for the patients and also for their spouses. All three sessions emphasized low-fat cooking and a high intake of fibres.

### *Smoking cessation programme*

All patients who smoked (n=37) were offered to participate in a smoking cessation programme; individual, and/or in group sessions. Eleven patients participated. The patients received individual counselling with a specially educated and certified nurse once a week throughout a five weeks period. The group sessions were held twice a week during the first two weeks, and thereafter once a week during a four week period. The patients were allowed to call the nurses if they needed advice or support. During the individual counselling, the nurse assessed the patients' tobacco use, and his/her readiness to quit, gave advice on how to quit smoking, and set individual action plans.

**Table 1. Description of the components of (UC) and (ECR)**

| Components                                   | Usual Care (UC)   | Expanded Cardiac Rehabilitation (ECR)   |
|--|---|---|
| <i>Physical training</i>                     | Physical training with light, modest, or heavy intensity. Each session 60 minutes, twice a week during 3 months.  | Same as UC  |
| <i>Information/counselling</i>               | Counselling hour with cardiologist for patients and spouses.  | Same as UC  |
| <i>Heart School</i>                          | Two educational sessions (90 minutes each) lead by a nurse, physiotherapist, welfare officer and a dietician  | Same as UC  |
| <i>Individual counselling</i>                | Regarding social insurance or other needs, organized by the welfare officer at the department on demand. All smokers were offered to participate in a smoking cessation programme | Same as UC  |
| <i>Patient Hotel stay</i>                    | -   | Five day stay at the Patient Hotel with several activities including physical training and information.                                   |
| <i>Stress management programme</i>           | -   | Validated programme (48). Twenty group sessions during one year, each 2 hours long, 5-9 participants per group; women and men separately. |
| <i>Cooking sessions and diet counselling</i> | -   | Cooking sessions once a week during 3 weeks led by a dietician. Each session lasted for 3 hours.  |



### *Exercise testing*

A symptom limited exercise test was carried out at baseline, after 3 months and after one year, on an electrically braked bicycle ergometer (Marquette Case 8000 Ergometer bicycle). Work load was initiated at 30-50 W, depending on the expected maximal work load, with subsequent increments of 10-20 W every minute. The patients reported occurrence of chest pain as assessed by the 10-degree modified Borg scale. Rate of perceived exertion (RPE) during exercise was estimated according to the 20-grade Borg scale. Continuous single-averaged 12-lead ECG was recorded before, during and until 10 minutes after termination of exercise. Systolic blood pressure was measured at rest, at the end of each work load, and 3 and 10 minutes after exercise. According to standard criteria, a positive ischemic response was defined as  $\geq 0.1$  mV (1 mm) J-point depression with ST segment flat or down-sloping at peak exercise or during the recovery period in any lead.

The test was terminated upon the occurrence of limiting symptoms (severe chest pain, shortness of breath, or fatigue i.e. RPE rating  $\geq 17$ ) or if indications of severe coronary ischemia such as a fall in systolic blood pressure ( $>10$  mm Hg), substantial ST-segment depression or if a severe arrhythmia on the ECG should occur.

Heart rate recovery was assessed and was defined as the difference between peak heart rate and the heart rate measured at 3 minutes of recovery (heart rate recovery = heart rate<sub>peak</sub> - heart rate<sub>3 min recovery</sub>). Further details are described in the methods section of paper I.

### *Laboratory variable:*

Blood samples were obtained between 8 and 10 am after an overnight fast, at baseline, after 3 months and at 12 months. All samples were analysed at the Clinical Chemistry Department of Karolinska University Hospital.

**Table 2. Baseline characteristics**

|   | <i>ECR</i><br>n=111  | <i>UC</i><br>n=113 |
|---|----------------------|--------------------|
| <b>Inclusion Diagnosis:</b>               |                      |                    |
| AMI (%)                                   | 47 (42)              | 50 (44)            |
| CABG (%)                                  | 64 (58)              | 63 (56)            |
| <b>Age (year)</b>                         | 63 ± 7.2             | 63 ± 7.3           |
| <b>Gender:</b>                            |                      |                    |
| Men (%)                                   | 85 (77)              | 88 (79)            |
| Women (%)                                 | 26 (23)              | 25 (22)            |
| <b>Patient history prior to inclusion</b> |                      |                    |
| Previous myocardial infarction (%)        | 31 (28)              | 35 (31)            |
| Angina pectoris (%)                       | 70 (63)              | 75 (66)            |
| Congestive heart failure (%)              | 28 (25)              | 26 (23)            |
| Hypertension (%)                          | 43 (39)              | 49 (43)            |
| Hyperlipidemia (%)                        | 86 (78)              | 83 (73)            |
| Diabetes mellitus (%)                     | 17 (15)              | 25 (22)            |
| <b>Smoking status;</b>                    |                      |                    |
| Never smoked (%)                          | 36 (32)              | 28 (25)            |
| Ex-smoker (%)                             | 52 (47)              | 60 (53)            |
| Current smoker (%)                        | 16 (14)              | 21 (19)            |
| <b>Education ≥ 12 years</b>               | 42 (38)              | 40 (35)            |
| <b>Physical status</b>                    |                      |                    |
| Body mass index (kg/m <sup>2</sup> )      | 26.4 ± 3.8           | 27.0 ± 3.9         |
| Blood pressure (SBP/DBP mmHg)             | 131 ( 21) / 76 ( 10) | 134 (21) / 78 (10) |
| Heart rate (beats/min)                    | 64 (10)              | 66 (11)            |
| <b>Cardiovascular drug treatment:</b>     |                      |                    |
| Acetyl salicylic acid (%)                 | 98 (88)              | 93 (82)            |
| Beta-blockers (%)                         | 105 (95)             | 103 (91)           |
| Lipid lowering drugs (%)                  | 93 (83)              | 86 (76)            |
| ACE-inhibitors (%)                        | 41 (40)              | 42 (37)            |

Continuous values are expressed as Mean (SD).

## **Data collection**

The patients were followed up by completing questionnaires, doing exercise tests and biochemical analyses at 3 and 12 months. The results of the clinical one-year follow-up is presented in paper I

Data for the presented five-year register follow up (paper II) was obtained from the National Board of Health and Welfare in Sweden. The Hospital Discharge Register includes all patients discharged from public hospitals in Sweden. The Cause of Death Register comprises all deaths, where the deceased was registered as a Swedish resident, whether or not the death occurred in Sweden. A report for each death is sent to the register from the physician in charge. The endpoint of the present follow-up was a composite endpoint including CV mortality, MI or readmission to hospital due to other CVD. Myocardial infarction was defined as International Classification of Disease, 10th Revision (ICD-10), codes I21-I22. Readmission due to CVD was defined as the primary ICD-10 codes I20, I25, I50, I63, G45, Z03.4, R07.4, Z95.1, and Z95.5. Data were collected from the registers mentioned above.

## **Statistical analyses**

Group data are presented as median (range) or mean ( $\pm$ SD), or proportions (%). To evaluate nominal data, the chi-square test was used. Analysis of variance (ANOVA) was used to evaluate temporal changes. Cox proportional-hazards analysis was used to compare the treatment groups. Cumulative incidence and 95% CI were calculated by the Kaplan-Meier method.

The number of patients (n=224) in the study was calculated to ensure a power of at least 90% to detect a 30% change in quality of life at alpha 0.05. A p-value of <0.05 was considered as statistically significant. Statistical analyses were performed by Statistica® software (StatSoft, Inc., Tulsa, USA).

# RESULTS

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## **Paper I**

Baseline characteristics of all patients are shown in table 2 (see above). There were no significant differences between patients in ECR as compared to patients in UC. In general, risk factors for coronary heart disease were common in both groups. A large proportion of patients were treated with aspirin, beta-blockers and lipid lowering drugs. Use of ACE-inhibitors was lower than today, but according to standard of care at the time of the study.

In this paper, we studied the effects of ECR on metabolic and inflammatory markers, exercise performance and other CV risk markers one year after starting CR.

### **Effects on exercise performance**

Table 3 describes exercise performance (bicycle ergometry) at baseline and after one year. Both groups improved in exercise performance significantly measured as maximal work load and exercise duration. However, there was no significant difference between the treatment groups.



**Table 3. Exercise performance**

| <i>Variable</i>  | <i>Baseline</i>    | <i>One year</i>    | <i>p-value<br/>time</i> | <i>p-value<br/>time*treatment</i> |
|--|--------------------|--------------------|-------------------------|-----------------------------------|
| Heart rate at rest / max exercise (beats/min)  |                    |                    |                         |                                   |
| ECR  | 65 (15) / 119 (22) | 62 (10) / 134 (21) | 0.088 / <0.001          | 0.667                             |
| UC   | 64 (12) / 114 (20) | 62 (9) / 126 (21)  | 0.148 / <0.001          | 0.571                             |
| Heart rate recovery (3 min) heart rate <sub>peak</sub> -heart rate <sub>3 min recovery</sub> (beats/min) |                    |                    |                         |                                   |
| ECR  | 40 (14)            | 51 (16)            | <0.001                  | 0.129                             |
| UC   | 40 (16)            | 46 (16)            | <0.001                  |                                   |
| Max watt   |                    |                    |                         |                                   |
| ECR  | 118 (35)           | 136 (34)           | <0.001                  | 0.848                             |
| UC   | 117 (36)           | 133 (39)           | <0.001                  |                                   |
| Exercise duration (seconds)  |                    |                    |                         |                                   |
| ECR  | 403 (130)          | 532 (154)          | <0.001                  | 0.339                             |
| UC   | 425 (129)          | 519 (160)          | <0.001                  |                                   |

Expanded Cardiac Rehabilitation (ECR) vs Usual Care (UC).

Data are expressed as Mean ( SD).

Statistical analyses were performed by 2-way ANOVA.

P-values reflect differences over time (baseline vs one year) and the interaction between time and treatment.

### **Effects on blood lipids, blood pressure and glucose metabolism**

Table 4 describes changes from baseline to one year of follow-up for clinical and biochemical variables. Systolic blood pressure (SBP) increased both in the ECR group and in those assigned to UC, but no difference between the treatment groups were noted (Table 3). Diastolic blood pressure (DBP) did not change over time in any treatment group. Total cholesterol, LDL cholesterol and triglycerides decreased in both the ECR and UC groups but with no significant difference between the groups. Among patients with known diabetes, the HbA1c levels were unchanged at one year follow-up in the ECR group whereas they increased slightly in the UC group. Again, there was no significant difference between treatments.

### **Effects on smoking and BMI**

Overall, the number of smokers decreased substantially during the study. In the ECR group, the number of active smokers was reduced from 16 patients at baseline to 7 after one year. In the UC group the corresponding numbers were 21 smokers at baseline and 11 patients after one year. Of note, both ECR and UC patients were offered participation in the smoking cessation programme. All patients were slightly overweight at baseline. BMI remained unchanged in both treatment groups during the study.

### **Effects on inflammation and cell counts**

Circulating inflammatory markers, including CRP and fibrinogen, were elevated at baseline (Table 4) and decreased significantly after one year. No significant difference between the two treatment groups was found.

**Table 4. Effects on metabolic and inflammatory variables**

| <i>Variable</i>            | <i>Baseline</i>                                 | <i>One year</i>                          | <i>p-value<br/>time</i>          | <i>p-value<br/>treatment*time</i> |
|----------------------------|---|--|----------------------------------|-----------------------------------|
| Total Cholesterol (mmol/l) | ECR 4.88 (1.12)<br>UC 5.10 (1.08)               | 4.38 (0.73)<br>4.47 (1.02)               | 0.001<br>0.001                   | 0.347                             |
| HDL cholesterol (mmol/l)   | ECR 1.17 (0.33)<br>UC 1.17 (0.33)               | 1.22 (0.28)<br>1.21 (0.32)               | 0.05<br>0.26                     | 0.649                             |
| LDL cholesterol (mmol/l)   | ECR 3.00 (0.97)<br>UC 3.20 (0.85)               | 2.54 (0.66)<br>2.54 (0.63)               | <0.001<br><0.001                 | 0.185                             |
| Triglycerides (mmol/l)     | ECR 1.59 (1.03)<br>UC 1.77 (1.09)               | 1.34 (0.59)<br>1.53 (1.24)               | <0.001<br><0.01                  | 0.923                             |
| HbA1c (%)                  | ECR 6.6 (1.8)<br>UC 6.3 (0.9)                   | 6.9 (2.0)<br>6.9 (1.3)                   | 0.11<br>0.02                     | 0.107                             |
| CRP (mg/l)*                | ECR 3.04 (2.79)<br>UC 4.01 (3.49)               | 2.09 (2.13)<br>2.39 (2.49)               | 0.007<br><0.001                  | 0.178                             |
| Fibrinogen (g/l)           | ECR 5.30 (2.00)<br>UC 5.29 (1.89)               | 4.25 (1.01)<br>4.22 (0.83)               | <0.001<br><0.001                 | 0.964                             |
| BMI (kg/m2)                | ECR 26.4 (3.7)<br>UC 27.0 (3.8)                 | 26.6 (3.8)<br>27.2 (3.9)                 | 0.32<br>0.22                     | 0.826                             |
| Blood pressure (mmHg)      | ECR 131 (20) / 76 (10)<br>UC 134 (21) / 78 (10) | 139 (23) / 77 (10)<br>142 (24) / 79 (11) | <0.001 / 0.576<br><0.001 / 0.250 | 0.753 / 0.961                     |

Expanded Cardiac Rehabilitation (ECR) vs Usual Care (UC).

Data are expressed as Mean (SD).

Statistical analyses were performed by 2-way ANOVA.

P-values given show changes over time (baseline vs one year) and the interaction between time and treatment.\*CRP values above 15mg/l were excluded (49)



## PAPER II

### Five-year follow-up data

During the five-year follow-up period, 53 patients (47.7%) in the ECR group and 68 patients (60.1%) in the UC group had a primary cardiac event (for a definition see above under the Data collection section). The absolute risk of the composite primary end-point was thus reduced by 12.4% (hazard ratio (HR) 0.69; 95% CI 0.48-0.99;  $p=0.049$ ) as compared to UC. This was mainly due to a reduction in any MI in the ECR group; 12 patients (10.8%) in the ECR group had an MI vs 23 patients (20.3%) in the UC group; (HR; 0.47; 95% CI 0.21-0.97;  $p=0.047$ ). The corresponding figures for ischemic stroke were 6 (5.4%) in the ECR group vs 9 (8.0%) in the UC group (HR 0.76; 95% CI, 0.25-2.18; ns).

During the five-year follow-up, 8 patients died a CV death, 5 patients in the ECR group and 3 patients in the UC group. However, none of the patients had death as a primary end-point. The number of revascularizations were similar in the two treatment groups, as regards both PCI (9 patients in the ECR group and 10 patients in the UC group) and CABG (10 and 14 patients, respectively). Only a few patients had an ICD (Implantable Cardioverter Defibrillator) implanted during follow-up (1 patient in the ECR group and 2 in the UC group).

Figure 2 shows Kaplan-Meier curves illustrating the reduction of primary events between the two groups ( $p<0.05$ ). The curves started to separate early, between 3 and 6 months from randomization.

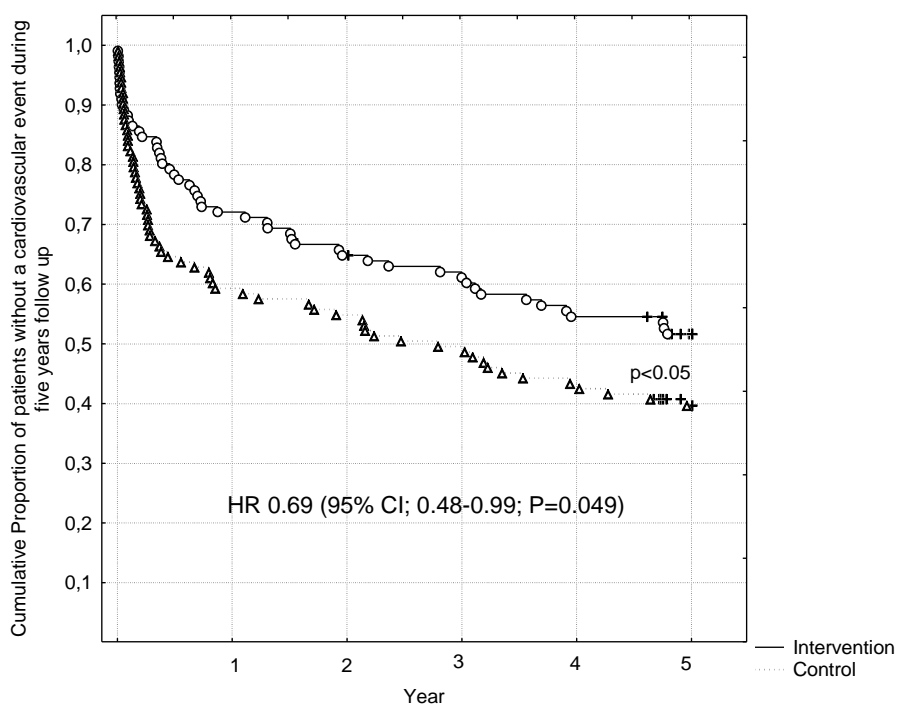
During the five-year follow-up, there was a reduction in the total number of hospitalizations and in the number of days of hospitalization in the ECR group (table 5).

**Table 5. Data on hospitalisation during the 5-year follow-up**

|                           | Expanded cardiac rehabilitation | Usual care   |
|---------------------------|---------------------------------|--------------|
| Hospitalization (numbers) | 1**<br>(1-8)                    | 2<br>(1-8)   |
| Number of days            | 6*<br>(1-51)                    | 10<br>(1-69) |

Data are expressed as median (range); \* $p < 0.02$  \*\* $p < 0.01$  comparisons between treatments (Mann-Whitney U-test)

**Figure 2**



## DISCUSSION

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In this prospective randomized controlled study we evaluated the effects of an ECR programme in patients with a history of a recent MI or after CABG surgery. Several cardiac risk markers or risk factors, such as lipid profile, markers of inflammation and exercise parameters, improved similarly in both treatment groups after one year of follow-up. There was no significant incremental benefit in cardiac risk parameters among patients undergoing the ECR as compared to the control group which received the UC, a rehabilitation programme which was quite extensive in our study. However, at the five year follow-up, patients in the ECR programme showed a reduction in CV morbidity and in days in hospital for CV reasons. The ECR was multifactorial and comprised several components, such as increased exercise training, psychosocial behavioural change support with a one-year cognitive-behavioural stress management programme (48), increased counselling/education, cooking sessions and further risk factor management. These components may altogether contribute to the beneficial effects of the ECR programme but the specific importance of each component can not be determined from our study.

Patients suffering from an acute MI were randomized during the hospitalization for the acute event. The randomized rehabilitation programme started after discharge from the hospital. The CABG patients were mainly randomized in association with the decision to perform surgery. This was normally performed a few weeks or up to 2-3 months after the actual decision as the patients were put on a waiting list. However, the actual randomized ECR programme started after the CABG procedure. Thus, there was a time delay from randomization to the start of the ECR programme. Slightly more than half (57%) of the patients were included based on a planned CABG.

The strengths of our study are several. It was a single centre study, which provides better homogeneity in patient handling. In total, 75% of eligible patients were included, and we used a successful randomization procedure which led to comparable patient characteristics at baseline. Furthermore, by using the national registries, we achieved a 100% complete follow-up of all events. No patients were lost to follow-up in our study. We have a fairly long registry based follow-up time resulting in almost 1000 patient years in total. The Danrehab study (50) which was a single-centre trial included 770

patients (48% of eligible patients) and the inclusion criteria of the study were wider. The study allowed inclusion of “patients at high risk” thus making the patient population more heterogeneous. In the Gospel trial (51), which was a larger Italian multi-centre trial, 85% of the eligible patients were included, and lost to follow up was 5% in both the intervention and the control arm. They included patients post infarction, irrespectively of revascularization procedures. The design and performance of our study is thus good but the study is, in comparison to Danrehab and Gospel, smaller in size.

In Paper I, we demonstrated that several biochemical predictors of recurrent events, such as plasma concentrations of total cholesterol, LDL cholesterol, fibrinogen and CRP improved similarly in both treatment groups. Furthermore, exercise performance factors, such as exercise duration, heart rate recovery and maximal exercise tolerance, were improved but without a significant difference between the ECR group and UC group. In a recent meta-analysis, evaluating 63 randomized CR trials, it was concluded that “usual care” was often close to optimal treatment, thus making it hard to show incremental benefits in such settings (17). This conclusion is clearly in line with the present findings. The impact of the ECR programme in our study was not great enough to cause significant improvements on factors such as physical performance, anthropometrics, or blood pressure in the intervention group, as compared to the well treated UC group. However, we found beneficial long-term effects on new MI:s and in-hospital health-care consumption, data which are presented in paper II. Until recently, few randomized controlled studies on CR programmes available have reported significant reductions of primary end-points such as CV death, non-fatal MI, non-fatal stroke or hospitalization due to CV disease (50, 51). The Italian Gospel study, which included patients post MI of whom more than half had performed a PCI or CABG before randomization, made observations similar to ours. They found a significant reduction in non-fatal MI with a risk reduction expressed as HR of 0.51 (95% CI; 0.31-0.86), which is close to the HR which we observed in the present study (HR 0.47; 95% CI 0.21-0.97). The Gospel study was a multicenter study and, as mentioned above, considerably larger than ours (3241 patients) and with a continued reinforced intervention of three years compared to one year in our study. The smaller size of our study compared to Gospel could explain the wider confidence interval observed, but the point estimate of the HR is very similar between the two trials. The previously mentioned Danrehab (50) study had a shorter intervention (6 weeks) and a shorter follow-up time (12 months) than in our study. Danrehab included both patients with

established heart disease (congestive heart failure or ischemic heart disease) and patients at high risk of ischemic heart disease. The study did not show a difference between expanded rehabilitation and UC for the primary outcome (registry based composite of total mortality, MI or acute first time readmission due to heart disease). However, they found a significant reduction in length of stay in hospital for patients randomized to expanded rehabilitation during the follow-up. Interestingly, we found similar effects of our ECR programme, with both a reduced number of readmissions to hospital and a reduced number of days in hospital. This important finding supports previous studies suggesting that ECR may reduce health-care consumption and health-care costs (52).

An important component of our ECR programme was the stress management programme, previously described and validated by Burell et al (48). Of note, in a recent study on CR in women with CV disease, a similar stress management programme was associated with a significant reduction in mortality (53). Furthermore, in a recent meta-analysis (54) anger and hostility - both factors that may be affected by stress management (43) - came out as predictors of increased CV risk in both healthy individuals and in patients with IHD. We also investigated effects on psychosocial factors and quality of life in the present study, findings which have been presented elsewhere (55). Interestingly, patients with type D personality - a risk marker of CV complications (56) - and who received ECR, reported reduced anxiety, depressive symptoms and lower type D score compared to the UC group (55). Given that such factors are important for health-care consumption and recurrence of MI:s this may also be a possible explanation for the beneficial long-term effects of our ECR programme. It should also be realized that the ECR programme, which included several activities with considerable additional attention and care of the patients, could exert beneficial effects through the so called "Hawthorne effect" (57). Thus the awareness of "something extraordinary going on" (such as participating in our study and receiving ECR) could act as a trigger for long-term change in behaviour which in turn results in less health-care consumption and fewer new MI:s. Furthermore, in our study patients in the ECR group had a higher compliance to the routine rehabilitation parts of the programme, as compared to patients in the UC. Thus, participation in physical training sessions was 78% in ECR group and 54% in UC, and regarding "counselling hour with cardiologist for patients and spouses" the corresponding figures were 84% and 43% in the ECR and UC groups, respectively (55). It seems that having been openly

randomized to an “expanded treatment group” improves the willingness to comply with the treatment.

A limitation of our study is that it was primarily designed to evaluate effects on psychosocial variables and measures of quality of life. The power is thus limited to preclude smaller differences between the treatment groups in CV events. However, by using a long-term follow-up in our national registries, this problem has a reduced importance. We have evaluated patients with established IHD and include both patients with acute MI and post CABG which increase the population heterogeneity somewhat. However the underlying disease is the same and thus preventive actions should not differ.

### *Challenges for the future*

It is a well-known fact that there is a gap between recommended therapies in many fields of cardiology and what is provided in the real world. This is true also for CR. The Swedish secondary preventive registry (SEPHIA) (58), captures patients <75 years of age with a discharge diagnosis of MI. This registry has shown large regional variations of what components of CR is provided, despite existing national guidelines (59).

The challenge for the future is to minimize regional differences that are not explained by different patient populations. In the ideal world, there should be equity in the provision of health care across regions for the same patients, regardless of age, sex, ethnic origin and hospital region. Quality care improvement programmes on CR will be of potentially great importance in order to achieve these goals. Furthermore, research is needed on factors explaining the great variability among patients on accepting the rehabilitation, and on the relative importance of the respective components of CR, such as the stress management programme. Health economy issues will also be of great importance.

## CONCLUSION

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In the current expanded cardiac rehabilitation programme, several cardiac risk markers such as lipid profile, markers of inflammation and exercise parameters improved similarly in both treatment groups. There was no significant incremental benefit among patients undergoing the expanded rehabilitation as compared to the control group which received usual cardiac rehabilitation.

Despite the absence of an incremental effect on cardiac risk markers, this expanded cardiac rehabilitation programme reduced cardiovascular morbidity and reduced readmissions and days in hospital for cardiovascular reasons at five years of follow-up.

## POPULÄRVETENSKAPLIG SAMMANFATTNING

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I denna studie undersöktes effekterna av ett utvidgat hjärtrehabiliterings-program efter hjärtinfarkt eller en by-pass operation av hjärtat. Medicinska riskmarkörer för sjukdomen studerades, liksom återinsjuknande i hjärt-kärlsjukdom och återinläggning på sjukhus pga hjärt-kärlsjukdom. Projektet genomfördes på Hjärtkliniken, Danderyds Sjukhus. Av 828 patienter som "screenades" för deltagande lottades 224 patienter till utökad rehabilitering (111 patienter) eller till vanlig rehabilitering (113 patienter). I den vanliga rehabiliteringen ingick hjärtträning ("Kom-igång-grupper"), läkarledd frågestund samt "hjärtskola" med information om motion, enklare stresshanteringsråd, rökning och dietrådgivning. Dessutom ingick mottagning hos infarktsjuksköterska samt återbesök hos läkare. Patienterna i den utökade hjärtrehabiliteringen erbjöds förutom allt det som ingick i den vanliga rehabiliteringen även: 1) vistelse på patienthotellet första veckan efter utskrivning från sjukhuset; 2) utökad hjärtträning 3) läkarledd frågestund samt 4) stressbehandling i grupp (en gång/vecka under 10 veckor och därefter en gång/månad de följande 10 månaderna), och 5) dietrådgivning med individuell kostanamnes och deltagande i matlagningsgrupp vid tre tillfällen. Samtliga patienter erbjöds rökavvänjning. I den första artikeln studerades hur riskmarkörer för sjukdomen såsom blodfetter, blodsocker, och inflammationsfaktorer påverkades efter ett år. Flera av dessa faktorer förbättrades, men det var ingen skillnad mellan gruppen med utökad hjärtrehabilitering och gruppen som fick vanlig rehabilitering. Fysisk arbetsförmåga förbättrades också likartat i de båda behandlingsgrupperna.

I den andra artikeln gjordes en uppföljning efter fem år med hjälp av register från Socialstyrelsen. Död eller återinsjuknande i hjärt-kärlsjukdom eller inläggning på sjukhus pga symtom på hjärt-kärlsjukdom registrerades. Vi fann att totalt 121 patienter hade drabbats. De patienter som lottats till den utökade hjärtrehabiliteringen hade emellertid drabbats i mindre utsträckning (47 %) jämfört med de som deltagit i den vanliga hjärtrehabiliteringen (60.2%;  $p < 0.05$ ). Detta berodde främst på en reduktion av antalet hjärtinfarkter; 10.8% av patienterna drabbades i gruppen som fått utökad rehabilitering jämfört med 20.3% i kontrollgruppen ( $p < 0.05$ ). En minskad inläggning på sjukhus bland patienter som deltog i den utökade hjärtrehabiliteringen observerades också. Antalet sjukhusvistelser minskade; median värdet var 1 bland patienter som fått utökad rehabilitering jämfört med medianvärde 2 bland dem med



vanlig rehabilitering ( $p < 0.01$ ) Antalet vård dagar per inläggning var också lägre (median 6 dagar vs median 10 dagar;  $p < 0.05$ ).

Sammanfattningsvis visar studien att en utökad hjärtrehabilitering, trots uteblivna förändringar på traditionella medicinska riskmarkörer efter ett år, på längre sikt reducerar återinsjuknandet i hjärtinfarkt och minskar antalet inläggningar på sjukhus pga symtom på hjärt-kärlsjukdom.

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---

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