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# Expanded cardiac rehabilitation in socially vulnerable patients with myocardial infarction: A 10-year follow-up study focusing on mortality and non-fatal events



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# TITLE PAGE (1/2)

## Title

Expanded cardiac rehabilitation in socially vulnerable patients with myocardial infarction: A 10-year follow-up study focusing on mortality and non-fatal events


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# TITLE PAGE (2/2)

## Contributorship statement

All authors contributed to the conception and design of the work. All authors contributed to acquisition, analysis and interpretation of data. KH and MLL drafted the manuscript. KMN, LKM, FBL, BC and CVN critically revised the manuscript. All authors approved the final version and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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## Competing interests

The authors declare that they have no conflicts of interest.

## Patient consent

A patient consent form has been signed by the patients.

## Ethics approval

The Danish Data Protection Agency (Case number: 1-16-02-684-14). Ethical approval is not required for register-based studies in Denmark.

## Data sharing statement

No additional data available.

## Trial registration number

None.

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# ABSTRACT

## Objective

Cardiac rehabilitation (CR) positively impacts on cardiovascular risk. A research project performed at a university hospital in Denmark, offered an expanded CR intervention to socially vulnerable patients. One-year follow-up showed significant improvements concerning medicine compliance, lipid profile, blood pressure and body mass index, when compared to socially vulnerable patients receiving standard CR. The aim of the study was to perform a long-term follow-up on the socially differentiated CR intervention and examine the impact of the intervention on all-cause mortality, cardiovascular mortality, non-fatal recurrent events and major cardiac events (MACE) 10 years after.

## Design

Prospective cohort study.

## Setting

The cardiac ward at a university hospital in Denmark from 2000 to 2004.

## Participants

379 patients < 70 years admitted with first episode myocardial infarction (MI). The patients were defined as socially vulnerable or non-socially vulnerable according to their educational level and their social network. A complete follow-up was achieved.

## Intervention

A socially differentiated CR intervention. The intervention consisted of standard CR and additionally a longer phase II course, more consultations, telephone follow-up and a better handover to phase III CR in the municipal sector, in general practice and in the patient association.

## Main outcome measures

All-cause mortality, cardiovascular mortality, non-fatal recurrent events and MACE.

## Results

There was no significant difference in all-cause mortality (95% CI 0.58;2,89), cardiovascular mortality (95% CI 0.31;2.09), non-fatal recurrent events (95% CI 0.67;3.92) or MACE (95% CI 0.53;2.42) measured at 10-year follow-up when comparing the expanded CR intervention to standard CR.

## Conclusions

Despite the significant results of the socially differentiated CR intervention at one-year follow-up, no long-term effects were seen regarding the main outcome measures at 10-year follow-up. Future research should focus on why it is not possible to lower the mortality and morbidity significantly among socially vulnerable patients admitted with first episode MI.

## KEYWORDS

Myocardial infarction, Angina pectoris, Cardiac rehabilitation, Social support, Educational status, Single person, Marital status, Vulnerable populations, Treatment outcome, Mortality.

# ARTICLE SUMMARY

## Strengths and limitations of this study

- This is the first longitudinal study to analyze the long-term effects of a socially differentiated cardiac rehabilitation intervention given to patients admitted with first episode myocardial infarction, which provide knowledge in better understanding how to reduce social inequalities in health.
- Highly valid Danish register data were used which combined with a unique personal 10-digit civil registration number that is given to all citizens living in Denmark, provides the study with a complete follow-up.
- The study was not carried out as a randomized controlled trial. To minimize potential confounding regression analysis was used. Moreover the patients were almost similar at baseline.
- The intervention given in the study was designed as a "realistic intervention". The aim was to create an intervention that would be affordable and applicable to most rehabilitation centers if proven effective.
- Patients from non-parallel time periods were being compared. All analyses were performed on both the socially and non-socially vulnerable patients. A difference between the non-socially vulnerable patients could have indicated that any changes among the socially vulnerable patients were just a general development in risk management and secondary prevention.

# INTRODUCTION

According to the European Association for Cardiovascular Prevention & Rehabilitation, cardiovascular disease (CVD) remains a leading cause of mortality and morbidity although CVD mortality has declined considerably in the past 20 years.[1] However, the one-year mortality rate is around 20 % in patients with myocardial infarction (MI). Among the patients who survive, 20 % will experience a recurrent MI within one year.[2]

It is estimated that recurrent events are caused by progression of coronary and systemic atherosclerosis.[2] Secondary prevention including cardiac rehabilitation (CR) is therefore essential to improve the long-term prognosis of patients with MI, and to improve their quality of life and functional capacity.[2,3] CR consists of multidisciplinary interventions with focus on risk assessment and management.[2]

A recent Cochrane meta-analysis examining the effect of exercise-based CR with at least six months follow-up found that CR significantly reduced cardiovascular mortality.[4] Another recent meta-analysis reported that CR significantly reduced recurrent events, all-cause and cardiovascular mortality if CR combined goal setting, self-monitoring, planning and feedback.[5] Two randomized controlled trials (RCT) examined the effect of an expanded CR intervention. At three- and five-year follow-up the patients randomized to receive expanded CR experienced fewer non-fatal recurrent events and a lower cardiovascular mortality compared to patients receiving standard CR.[6,7]

Socially vulnerable patients are less likely to participate in and complete CR.[8-10] This is also seen in patients with MI when focusing on mortality and non-fatal recurrent events.[11-14] Patients with a low educational level have a significantly higher long-term mortality than patients with a high educational level.[15] Likewise, patients living alone have a significantly higher long-term mortality risk compared to patients living with a partner.[16]

On a cardiac ward at a university hospital in Denmark a socially differentiated CR intervention was performed from 2000 to 2004. Patients defined as socially vulnerable received expanded CR and outcome was compared to socially vulnerable patients receiving standard CR according to international guidelines. At one-year follow-up, patients in the intervention group had significantly better results in relation to medicine compliance, lipid profile, blood pressure and body mass index (BMI).[17]

The aim of the present study was to perform a long-term follow-up on the socially differentiated CR intervention and examine the impact of the intervention on mortality and non-fatal recurrent events 10 years after.

# METHODS

## Study design

A prospective cohort study. Patients were followed from baseline, defined as time of admission with first episode of MI, and during the next 10 years. Follow-up was performed at the exact day 10 years after their admission.

The four-year socially differentiated CR intervention was carried out on a cardiac ward at a university hospital in Denmark between 2000 and 2004.

This study focuses on the socially vulnerable patients who received expanded CR compared to those who received standard CR.

## Patient population

From 1 April 2000 – 31 March 2002 all patients < 70 years admitted with first episode of MI were systematically identified. Of the 205 patients with MI, 171 were referred to standard CR; 133 patients gave informed consent to participate. Of these, 78 were categorized as socially vulnerable and 55 were categorized as non-socially vulnerable. All of the 133 patients received standard CR according to international guidelines.

From 1 September 2002 – 31 December 2004 all patients < 70 years admitted with first episode of MI were assessed by a project nurse and referred to either standard CR or expanded CR. A total of 303 patients were admitted; 270 patients were referred to CR of whom 246 patients gave informed consent to participate. Of these, 130 patients were categorized as socially vulnerable and received expanded CR and the remaining 116 patients were categorized as non-socially vulnerable and received standard CR.

Patients were defined as socially vulnerable if they had: 1) Low educational level (education classified 1-4 in The Danish Educational Nomenclature - DUN if age < 55 years and 1-3 if age

> 55 years) and / or 2) If they lived alone. Patients were defined as non-socially vulnerable if they did not meet the criteria above.

Patients were excluded if they suffered from severe comorbidities such as stroke, dementia, mental disorders, retardation or severe alcohol abuse. Patients suffering from depression or anxiety were not excluded.

The study population, categorization and CR characteristics are described in detail in Figure 1.

## Exposure

The expanded CR intervention consisted of standard CR and a longer phase II course, more consultations, telephone follow-up and a better handover to phase III CR in the municipal sector, in general practice and in the patient association.

The standard CR intervention was consistent with international guidelines.

The differences between the two CR interventions are described in detail in Table 1.

**Table 1.** Content of the socially differentiated cardiac rehabilitation intervention

| | Standard cardiac rehabilitation | Expanded cardiac rehabilitation |
|---|---|---|
| Phase I<br>Acute treatment until discharge | • Start of medical and acute surgical treatment<br>• Start of secondary prevention concerning medication, smoking, diet and exercise<br>• Psychological and social support to patients and relatives | Like standard cardiac rehabilitation |
| Phase II<br>Discharge from hospital until return to vocational activities | • 5-6 weeks of cardiac rehabilitation<br>• 3 consultations with medical doctor<br>• 4 consultations with nurse<br>• 2 consultations with dietician<br>• 6-12 weeks of exercise course<br>• Screening for depression and anxiety | Like standard cardiac rehabilitation and:<br>• Extra 2 weeks of cardiac rehabilitation<br>• 1 extra consultation with nurse<br>• Sharing of patient's own rehabilitation plan with general practice |
| Phase III<br>Further course after phase II | • Referral to general practice<br>• Information about activities in the municipal sector and in The Danish Heart Association | Like standard cardiac rehabilitation and:<br>• Referral to ½ hour of preventive consultation in general practice<br>• Referral to activities in the municipal sector and in The Danish Heart Association<br>• Telephone follow-up 2 months after completion of phase II |

## Study outcomes

The main outcome measures in the present study were all-cause mortality, cardiovascular mortality, non-fatal recurrent events (MI and unstable angina pectoris) and major cardiac events (MACE) defined as cardiovascular mortality and non-fatal recurrent events. The endpoints were adjusted for gender, age, diabetes and smoking status at baseline.

## Data sources

Baseline patient data were collected at admission from clinical databases and from questionnaires filled in by the patients. In 1968, The Danish Civil Registration System was introduced. The system provides all persons living in Denmark with a unique personal 10-digit civil registration number. This number was used to link the study population to different registers ensuring a high validity and completeness. Endpoint data concerning mortality was collected from The Danish Cause of Death Register established in 1970. Cardiovascular mortality was defined using The International Classification of Diseases (ICD-10). Data on non-fatal recurrent events were retrieved using the ICD-10 from The Danish National Patient Registry established in 1977.

## Statistics

Categorical variables are presented as numbers and percentages. Continuous variables are presented as mean with standard deviation. The Kaplan Meier estimate plots were used to evaluate survival probability and event-free probability. Logistic regression was applied when performing adjusted analyses. All endpoints are presented as odds ratios (OR) with 95% confidence intervals (CI) and *P*-values. A significance level of 0.05 was applied. When performing the adjusted analyses, the rule of ten was used. All statistical analyses were carried out using the statistics software program Stata version 14.1.

## Ethics

The study was approved by The Danish Data Protection Agency (Case number: 1-16-02-684-14). Ethical approval is not required for register-based studies in Denmark.

# RESULTS

## Baseline characteristics

From 1 April 2000 to 31 December 2004, 379 patients were referred to and participated in a socially differentiated CR intervention receiving either a standard or expanded CR intervention (Figure 1). Baseline characteristics of the patients are given in Table 2. A complete follow-up after 10 years was achieved.

**Table 2.** Baseline characteristics at patient admission with first episode myocardial infarction (N = 379)

| | Socially vulnerable patients | | Non-socially vulnerable patients | |
|---|---|---|---|---|
| | Rehabilitation type<br>N<br>Time periode | | Rehabilitation type<br>N<br>Time periode | |
| | Standard<br>N = 78<br>2000-2002<br>(% / standard deviation) | Expanded<br>N = 130<br>2002-2004<br>(% / standard deviation) | Standard<br>N = 55<br>2000-2002<br>(% / standard deviation) | Standard<br>N = 116<br>2002-2004<br>(% / standard deviation) |
| Age, years | 56 (8.15) | 55 (8.53) | 60 (7.56) | 57 (8.50) |
| Gender, male | 57 (73 %) | 93 (71 %) | 42 (76 %) | 94 (81 %) |
| Educational level, The Danish Educational Nomenclature | 3.18 (1.19) | 3.26 (1.39) | 4.80 (1.08) | 4.75 (1.19) |
| Living alone | 27 (35 %) | 51 (39 %) | 0 | 0 |
| Current smoker | 59 (76 %) | 83 (64 %) | 34 (62 %) | 60 (52 %) |
| Body mass index | 27.26 (4.35) | 26.26 (4.08) | 26.37 (3.99) | 26.54 (3.12) |
| Hypertension | 18 (23 %) | 28 (22 %) | 11 (20 %) | 23 (20 %) |
| Hyperlipidaemia | 20 (26 %) | 37 (28 %) | 13 (24 %) | 44 (38 %) |
| Diabetes mellitus | 10 (13 %) | 16 (12 %) | 6 (11 %) | 10 (9 %) |



## All-cause mortality

A total of 17 % of the vulnerable patients died during the 10 year follow-up period; 18 % of these patients had received expanded CR and 15 % had received standard CR, respectively. No significant differences were found between the two groups as an OR of 1.29 (95 % CI: 0.58;2.89) and a *P*-value of 0.53 was obtained (Table 3). As indicated in Figure 2, no

significant associations were found at 10-year follow-up among the non-socially vulnerable patients receiving standard CR.

**Table 3.** Endpoints at 10 year follow-up among socially vulnerable patients admitted with first episode myocardial infarction and participating in socially differentiated cardiac rehabilitation in the period from 2000-2004

| | Total (N = 208) | Expanded cardiac rehabilitation (N = 130) | Standard cardiac rehabilitation (N = 78) | Odds ratio (95 % CI) | *P*-value |
|---|---|---|---|---|---|
| All-cause Mortality* | 35 (17) | 23 (18) | 12 (15) | 1.29 (0.58;2.89) | 0.53 |
| Cardiovascular Mortality** | 19 (9) | 11 (8) | 8 (10) | 0.80 (0.31;2.09) | 0.65 |
| | Total (N = 176***) | Expanded cardiac rehabilitation (N = 115***) | Standard cardiac rehabilitation (N = 61***) | OR (95 % CI) | *P*-value |
| Non-fatal recurrent events* | 30 (17) | 22 (19) | 8 (13) | 1.62 (0.67;3.92) | 0.29 |
| Major cardiac events **** | 41 (23) | 27 (23) | 14 (23) | 1.31 (0.53;2.42) | 0.75 |

Data are given as numbers (percentage).
* Adusted for gender, age and diabetes mellitus.
** Adjusted for gender.
*** Only patients who did not suffer from a recurrent event during the first month after admission were included in the analysis.
**** Adjusted for gender, age, diabetes and smoking status.

## Cardiovascular mortality

Among the vulnerable patients 9 % suffered from cardiovascular mortality. Of the patients receiving expanded CR, 8 % died compared to 10 % among patients receiving standard CR. No significant differences were found at 10-year follow-up; OR 0.80 (95 % CI: 0.31;2.09) and *P*-

value 0.65 (Table 3). As indicated in figure 2 no significant associations were found at 10-year follow-up among the non-socially vulnerable patients receiving standard CR.

## Non-fatal recurrent events

Only patients who did not experience a non-fatal recurrent event during the first 30 days after admission were included in the analysis. A total of 17 % of the vulnerable patients experienced a non-fatal recurrent event during the 10-year follow-up; among these 19 % received expanded CR and 13 % received standard CR. No significant differences were found between the two groups; OR 1.62 (95 % CI: 0.67;3.92) and a *P*-value of 0.29 (Table 3). As indicated in figure 2 no significant associations were found at 10-year follow-up among the non-socially vulnerable patients receiving standard CR.

## MACE

The percentage of vulnerable patients who either experienced cardiovascular mortality or experienced a non-fatal recurrent event within 30 days after admission until 10-year follow-up was 23 % in total and in each group. No significant differences were seen between the two groups; OR 1.31 (95 % CI: 0.53;2.42) and a *P*-value of 0.63 (Table 3). As indicated in figure 2 no significant associations were found at 10-year follow-up among the non-socially vulnerable patients receiving standard CR.

# DISCUSSION

## Study findings

There were no significant differences between socially vulnerable patients admitted with first episode MI receiving expanded CR and socially vulnerable patients receiving standard CR concerning the four endpoints; all-cause mortality, cardiovascular mortality, non-fatal recurrent events and MACE at 10-year follow-up (Table 3). Moreover, no significant results were found at 10-year follow-up among the non-socially vulnerable patients who all received standard CR.

## Comparison with other studies

A number of studies have examined the effect of an expanded CR intervention. In 2008, a Swedish RCT by Plüss et al. [6] including 224 patients < 75 years with recent MI and / or CABG were randomized to either expanded CR or standard CR between 1999 and 2002 and followed for five years. Patients were excluded if suffering from a significant psychiatric disease or alcohol abuse. All patients received three months of standard CR including consultations with health professionals and a social worker, physical exercise, patient education and advice on smoking cessation. The patients receiving the expanded intervention also stayed five days at a patient hotel after discharge, where they participated in a cooking school for three weeks and attended a stress management course for one year. The study had an almost complete follow-up and a significantly lower number of the patients in the intervention group suffered a non-fatal recurrent event at five-year follow-up (Hazard rate 0.47, 95% CI 0.21;0.97, *P*-value 0.04). No significant results were found regarding all-cause and cardiovascular mortality.[6]

The study by Plüss et al.[6] has many similarities with the present study. Sweden and Denmark have similar welfare states with the same access to free health care and social services. The patients in the two studies were recruited in the same time period and had comparable characteristics concerning disease and age. Furthermore, exclusion criteria were the same. However, the Swedish in contrast to the present study found significant results. This could be

explained by the Swedish intervention being more pervasive and lasting a whole year and thereby constituting a major part of the long-term secondary prevention. Furthermore, the Swedish intervention was not socially differentiated. It could thus be speculated that the patients who profited the most from the intervention, were the patients who were not socially vulnerable.

## Strengths, limitations and external value of the study

One of the strengths of the present study is the complete follow-up. This is partly because the patients were identified by their unique personal 10-digit civil registration number and partly because of the use of highly valide Danish register data. The information concerning mortality and morbidity were registered by health professionals using ICD-10 and did thus not rely on the memory of patients or relatives. Another strength is that the patients were almost similar at baseline. The only variables with considerable variation were educational level and whether the patients lived alone. This could be explained by these variables defining whether patients were socially vulnerable or not. It should, however, be noted that smoking status and the presence of hyperlipidaemia also varied.

The fact that patients from non-parallel time periods were being compared raises some methodological issues. All analyses were performed on both the socially and non-socially vulnerable patients. A difference between the non-socially vulnerable patients could have indicated that any changes among the socially vulnerable patients were just a general development in risk management and secondary prevention. However, no significant differences were found.

The present study was carried out as a prospective cohort study and not as a RCT, thus there is a risk of confounding and bias. An attempt to minimize potential confounding was made by using logistic regression analysis. Potential information bias cannot be ruled out concerning the self-reported questionnaires. However, it must be expected that potential bias must be non-

differentiated and thereby changing the results towards the null-hypothesis. A risk of selection bias could occur as attendance rates were significantly higher in the time period of the intervention than in the period where the control group received standard CR. If more highly socially vulnerable patients participated in the intervention it could be difficult to see any significant results of the intervention if they were compared to the low-risk part of the socially vulnerable patients in the group receiving standard CR.

A reason that no significant changes were found between the socially vulnerable patients receiving expanded CR and the ones receiving standard CR could be that standard CR is an evidence-based, structured and multidisciplinary intervention of high quality that any significant changes due to the expanded CR would be hard to detect. The mean age of the patients were around late fifties. Any changes in hard endpoints such as mortality and non-fatal recurrent events could be lacking because it must be expected that the patients have had an unhealthy life style for many years resulting in severe irreversible atherosclerosis. Also, the non-significant results could indicate the importance of phase III CR. More focus should be placed on supporting the patients in the long-term CR similar to the study by Plüss et al.[6] and trying to maintain and strengthen the knowledge that the patients obtain during phase II CR.

The external validity of the present study could be applied to CR in a hospital setting in most western countries, especially countries with free health care and a wide access to social services.

## Future research

Future research should focus on why it was not possible to lower the mortality and morbidity significantly among socially vulnerable patients admitted with first episode MI. The authors suggest at least three plausible explanations which could be helpful when designing new interventions. 1) Maybe it is not possible to lower social inequality in mortality and morbidity by using socially differentiated interventions. 2) Maybe the expanded CR should have focused

on other things such as stress reduction, mindfulness or coping like it was the case in Plüss et al.[6] 3) Perhaps the intensity and the time frame were wrong. In Plüss et al.[6] the expanded intervention lasted one year and the patients therefore received support not only in phase II, but also in phase III as a part of the long-term secondary prevention.[6]

## CONCLUSION

Despite the significantly improved results of the socially differentiated CR intervention at one-year follow-up, no long-term significant effects were seen regarding mortality and non-fatal recurrent events at follow-up after 10 years.

# TABLE LEGENDS

**Table 1.** Content of the socially differentiated cardiac rehabilitation intervention.

**Table 2.** Baseline characteristics at patient admission with first episode myocardial infarction (N = 379).

**Table 3.** Endpoints at 10 year follow-up among socially vulnerable patients admitted with first episode myocardial infarction and participating in socially differentiated cardiac rehabilitation in the period from 2000-2004.

## CONTRIBUTORSHIP STATEMENT

All authors contributed to the conception and design of the work. All authors contributed to acquisition, analysis and interpretation of data. KH and MLL drafted the manuscript. KMN, LKM, FBL, BC and CVN critically revised the manuscript. All authors approved the final version and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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## COMPETING INTERESTS

The authors declare that they have no conflicts of interest.

## PATIENT CONSENT

A patient consent form has been signed by the patients.

## ETHICS APPROVAL

The Danish Data Protection Agency (Case number: 1-16-02-684-14). Ethical approval is not required for register-based studies in Denmark.

## DATA SHARING STATEMENT

No additional data available.

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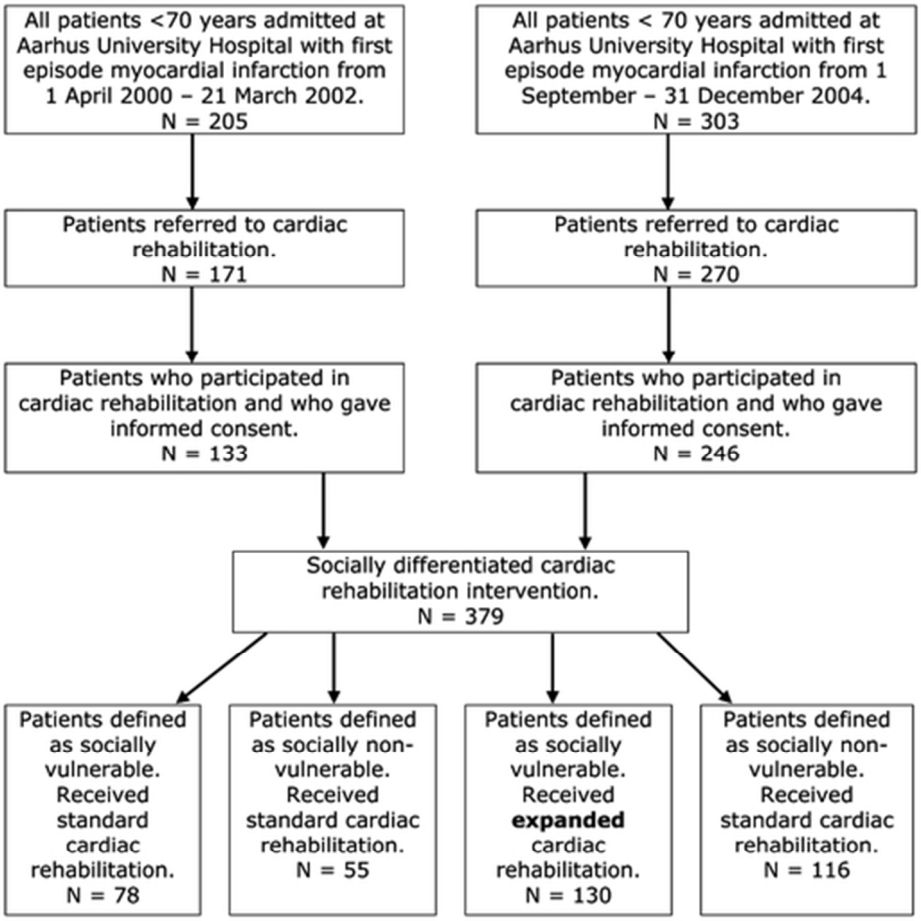


**Figure 1.** Flowchart of study participants

Flowchart of study participants

23x25mm (600 x 600 DPI)

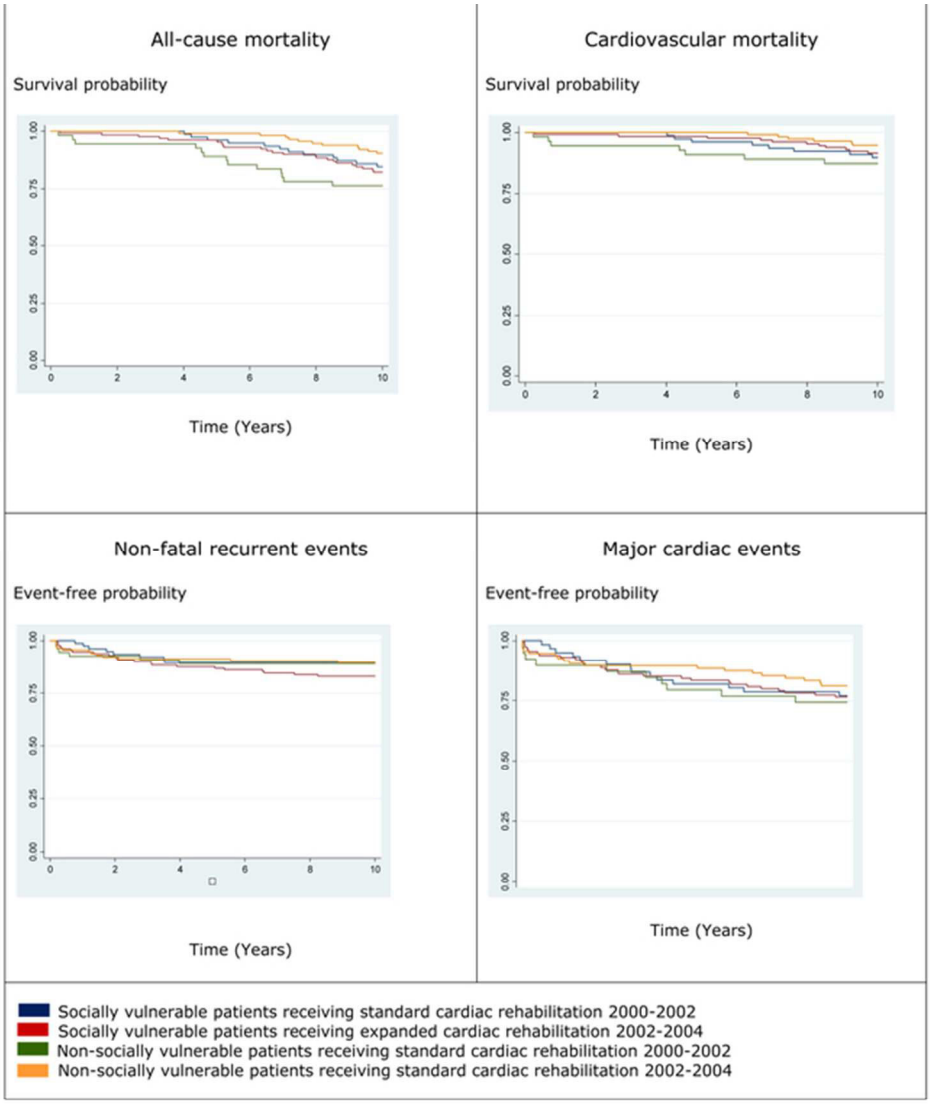


**Figure 2.** Kaplan Meier estimates of the probability of all-cause mortality, cardiovascular mortality, non-fatal recurrent events and major cardiac events.

Kaplan Meier estimates of the probability of all-cause mortality, cardiovascular mortality, non-fatal recurrent events and major cardiac events

27x35mm (600 x 600 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No. | Recommendation | Page No. | Relevant text from manuscript |
|---|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 3 | |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 3-4 | |
| **Introduction** | | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 7-8 | |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 8 | |
| **Methods** | | | | |
| Study design | 4 | Present key elements of study design early in the paper | 9 | |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 9-12 | |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 9-12 | |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | Not a matched study. | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 11 - 12 | |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 11 - 12 | |
| Bias | 9 | Describe any efforts to address potential sources of bias | 12 | |
| Study size | 10 | Explain how the study size was arrived at | 9 | |

Continued on next page

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|---|---|---|---|
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 12 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 12 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | No subgroup analyses |
| | | (*c*) Explain how missing data were addressed | No missing data |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | No loss to follow-up |
| | | (*e*) Describe any sensitivity analyses | No sensitivity analyses |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Figur 1 |
| | | (b) Give reasons for non-participation at each stage | Figur 1 |
| | | (c) Consider use of a flow diagram | Figure 1 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 13 and Table 2 |
| | | (b) Indicate number of participants with missing data for each variable of interest | No missing data |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | 14-16 |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | 14-16 |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 14-16 |
| | | (*b*) Report category boundaries when continuous variables were categorized | Not relevant. |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Not relevant |

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| | | | |
|---|---|---|---|
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | No subgroup analyses |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 17 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 18-19 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 17-20 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 19 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 24 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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# Expanded cardiac rehabilitation in socially vulnerable patients with myocardial infarction: A 10-year follow-up study focusing on mortality and non-fatal events



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# TITLE PAGE (1/2)

## Title

Expanded cardiac rehabilitation in socially vulnerable patients with myocardial infarction: A 10-year follow-up study focusing on mortality and non-fatal events


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# TITLE PAGE (2/2)

## Contributorship statement

All authors contributed to the conception and design of the work. All authors contributed to acquisition, analysis and interpretation of data. KH and MLL drafted the manuscript. KMN, LKM, FBL, BC and CVN critically revised the manuscript. All authors approved the final version and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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## Competing interests

The authors declare that they have no conflicts of interest.

## Patient consent

A patient consent form has been signed by the patients.

## Ethics approval

The Danish Data Protection Agency (Case number: 1-16-02-684-14). Ethical approval is not required for register-based studies in Denmark.

## Data sharing statement

No additional data available.

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None.

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# ABSTRACT

## Objective

Cardiac rehabilitation (CR) has been shown to reduce cardiovascular risk. A research project performed at a university hospital in Denmark, offered an expanded CR intervention to socially vulnerable patients. One-year follow-up showed significant improvements concerning medicine compliance, lipid profile, blood pressure and body mass index, when compared to socially vulnerable patients receiving standard CR. The aim of the study was to perform a long-term follow-up on the socially differentiated CR intervention and examine the impact of the intervention on all-cause mortality, cardiovascular mortality, non-fatal recurrent events and major cardiac events (MACE) 10 years after.

## Design

Prospective cohort study.

## Setting

The cardiac ward at a university hospital in Denmark from 2000 to 2004.

## Participants

379 patients < 70 years admitted with first episode myocardial infarction (MI). The patients were defined as socially vulnerable or non-socially vulnerable according to their educational level and their social network. A complete follow-up was achieved.

## Intervention

A socially differentiated CR intervention. The intervention consisted of standard CR and additionally a longer phase II course, more consultations, telephone follow-up and a better handover to phase III CR in the municipal sector, in general practice and in the patient association.

## Main outcome measures

All-cause mortality, cardiovascular mortality, non-fatal recurrent events and MACE.

## Results

There was no significant difference in all-cause mortality (OR:1.29, 95%-CI 0.58;2,89), cardiovascular mortality (OR:0.80, 95%-CI 0.31;2.09), non-fatal recurrent events (OR:1.62, 95%-CI 0.67;3.92) or MACE (OR:1.31, 95%-CI 0.53;2.42) measured at 10-year follow-up when comparing the expanded CR intervention to standard CR.

## Conclusions

Despite the significant results of the socially differentiated CR intervention at one-year follow-up, no long-term effects were seen regarding the main outcome measures at 10-year follow-up. Future research should focus on why it is not possible to lower the mortality and morbidity significantly among socially vulnerable patients admitted with first episode MI.

## KEYWORDS

Myocardial infarction, Angina pectoris, Cardiac rehabilitation, Social support, Educational status, Single person, Marital status, Vulnerable populations, Treatment outcome, Mortality.

# ARTICLE SUMMARY

## Strengths and limitations of this study

- This is the first longitudinal study to analyze the long-term effects of a socially differentiated cardiac rehabilitation intervention given to patients admitted with first episode myocardial infarction, which provide knowledge in better understanding how to reduce social inequalities in health.
- Highly valid Danish register data were used which combined with a unique personal 10-digit civil registration number that is given to all citizens living in Denmark, provides the study with a complete follow-up.
- The study was not carried out as a randomized controlled trial. To minimize potential confounding regression analysis was used. Moreover the patients were almost similar at baseline.
- The intervention given in the study was designed as a "realistic intervention". The aim was to create an intervention that would be affordable and applicable to most rehabilitation centers if proven effective.
- Patients from non-parallel time periods were being compared. All analyses were performed on both the socially and non-socially vulnerable patients. A difference between the non-socially vulnerable patients could have indicated that any changes among the socially vulnerable patients were just a general development in risk management and secondary prevention.

# INTRODUCTION

According to the European Association for Cardiovascular Prevention & Rehabilitation, cardiovascular disease (CVD) remains a leading cause of mortality and morbidity although CVD mortality has declined considerably in the past 20 years.[1] However, the one-year mortality rate is around 20 % in patients with myocardial infarction (MI). Among the patients who survive, 20 % will experience a recurrent MI within one year.[2] It is estimated that recurrent events are caused by progression of coronary and systemic atherosclerosis.[2] Secondary prevention including cardiac rehabilitation (CR) is therefore essential to improve the long-term prognosis of patients with MI, and to improve their quality of life and functional capacity.[2,3] CR consists of multidisciplinary interventions with focus on risk assessment and management.[2]

A recent Cochrane meta-analysis and a review examining the effect of exercise-based CR with at least six months follow-up found that CR significantly improved psychological function and reduced cardiovascular mortality.[4,5] Another recent meta-analysis reported that CR containing lifestyle modification programmes significantly reduced recurrent events, all-cause and cardiovascular mortality if CR combined goal setting, self-monitoring, planning and feedback.[6] Two randomized controlled trials (RCT) examined the effect of an expanded CR intervention. One of the interventions consisted of different lifestyle modification activities as well as stress management therapy. The other of the interventions consisted of exercise-based CR. At three- and five-year follow-up the patients randomized to receive expanded CR experienced fewer non-fatal recurrent events and a lower cardiovascular mortality compared to patients receiving standard CR.[7,8]

Patients with low socioeconomic status, defined by their social class, educational level, income, occupation and marital status, are less likely to participate in and complete CR.[9-11] This is also seen in patients with MI when focusing on mortality and non-fatal recurrent events.[12-15] Patients with a low educational level have a significantly higher long-term mortality than

patients with a high educational level.[16] Likewise, patients living alone have a significantly higher long-term mortality risk compared to patients living with a partner.[17]

On a cardiac ward at a university hospital in Denmark a socially differentiated CR intervention was performed from 2000 to 2004. The aim of the intervention was to target the social groups at highest risk of not participating in CR, not completing CR and who have the poorest long-term outcomes. The intervention was designed as a 'realistic intervention' based on the health professionals experiences. The idea of the 'realistic intervention' was that it should be affordable and practical to implement if proven effective. Patients defined as socially vulnerable received expanded CR and outcome was compared to socially vulnerable patients receiving standard CR according to international guidelines. At one-year follow-up, patients in the intervention group had significantly better results in relation to medicine compliance, lipid profile, blood pressure and body mass index (BMI).[18]

The aim of the present study was to perform a long-term follow-up on the socially differentiated CR intervention and examine the impact of the intervention on mortality and non-fatal recurrent events 10 years after.

# METHODS

## Study design

A prospective cohort study. Patients were followed from baseline, defined as time of admission with first episode of MI, and during the next 10 years. Follow-up was performed at the exact day 10 years after their admission.

The four-year socially differentiated CR intervention was carried out on a cardiac ward at a university hospital in Denmark between 2000 and 2004.

This study focuses on the socially vulnerable patients who received expanded CR compared to those who received standard CR.

## Patient population

From 1 April 2000 – 31 March 2002 all patients < 70 years admitted with first episode of MI were systematically identified. Of the 205 patients with MI, 171 were referred to standard CR; 133 patients gave informed consent to participate. Of these, 78 were categorized as socially vulnerable and 55 were categorized as non-socially vulnerable. All of the 133 patients received standard CR according to international guidelines.

From 1 September 2002 – 31 December 2004 all patients < 70 years admitted with first episode of MI were assessed by a project nurse and referred to either standard CR or expanded CR. A total of 303 patients were admitted; 270 patients were referred to CR of whom 246 patients gave informed consent to participate. Of these, 130 patients were categorized as socially vulnerable and received expanded CR and the remaining 116 patients were categorized as non-socially vulnerable and received standard CR.

Patients were defined as socially vulnerable if they had: 1) Low educational level (education classified 1-4 in The Danish Educational Nomenclature - DUN if age < 55 years and 1-3 if age

> 55 years) and / or 2) If they lived alone. Patients were defined as non-socially vulnerable if they did not meet the criteria above.

Patients were excluded if they suffered from severe comorbidities such as stroke, dementia, mental disorders, retardation or severe alcohol abuse. Patients suffering from depression or anxiety were not excluded.

The study population, categorization and CR characteristics are described in detail in Figure 1.

## Exposure

The expanded CR intervention consisted of standard CR and a longer phase II course, more consultations, telephone follow-up and a better handover to phase III CR in the municipal sector, in general practice and in the patient association.

The standard CR intervention was consistent with international guidelines.

The differences between the two CR interventions are described in detail in Table 1.

**Table 1.** Content of the socially differentiated cardiac rehabilitation intervention

| | Standard cardiac rehabilitation | Expanded cardiac rehabilitation |
|---|---|---|
| Phase I<br>Acute treatment until discharge | • Start of medical and acute surgical treatment<br>• Start of secondary prevention concerning medication, smoking, diet and exercise<br>• Psychological and social support to patients and relatives | Like standard cardiac rehabilitation |
| Phase II<br>Discharge from hospital until return to vocational activities | • 5-6 weeks of cardiac rehabilitation<br>• 3 consultations with medical doctor<br>• 4 consultations with nurse<br>• 2 consultations with dietician<br>• 6-12 weeks of exercise course<br>• Screening for depression and anxiety | Like standard cardiac rehabilitation and:<br>• Extra 2 weeks of cardiac rehabilitation<br>• 1 extra consultation with nurse<br>• Sharing of patient's own rehabilitation plan with general practice |
| Phase III<br>Further course after phase II | • Referral to general practice<br>• Information about activities in the municipal sector and in The Danish Heart Association | Like standard cardiac rehabilitation and:<br>• Referral to ½ hour of preventive consultation in general practice<br>• Referral to activities in the municipal sector and in The Danish Heart Association<br>• Telephone follow-up 2 months after completion of phase II |

## Study outcomes

The main outcome measures in the present study were all-cause mortality, cardiovascular mortality, non-fatal recurrent events (MI and unstable angina pectoris) and major cardiac events (MACE) defined as cardiovascular mortality and non-fatal recurrent events. The endpoints were adjusted for gender, age, diabetes and smoking status at baseline.

## Data sources

Baseline patient data were collected at admission from clinical databases and from questionnaires filled in by the patients. In 1968, The Danish Civil Registration System was introduced. The system provides all persons living in Denmark with a unique personal 10-digit civil registration number. This number was used to link the study population to different registers ensuring a high validity and completeness. Endpoint data concerning mortality was collected from The Danish Cause of Death Register established in 1970. Cardiovascular mortality was defined using The International Classification of Diseases (ICD-10). Data on non-fatal recurrent events were retrieved using the ICD-10 from The Danish National Patient Registry established in 1977.

## Statistics

Categorical variables are presented as numbers and percentages. Continuous variables are presented as mean with standard deviation. The Kaplan Meier estimate plots were used to evaluate survival probability and event-free probability. Logistic regression was applied when performing adjusted analyses. All endpoints are presented as odds ratios (OR) with 95% confidence intervals (CI) and *P*-values. A significance level of 0.05 was applied. When performing the adjusted analyses, the rule of ten was used. All statistical analyses were carried out using the statistics software program Stata version 14.1.

## Ethics

The study was approved by The Danish Data Protection Agency (Case number: 1-16-02-684-14). Ethical approval is not required for register-based studies in Denmark.

# RESULTS

## Baseline characteristics

From 1 April 2000 to 31 December 2004, 379 patients were referred to and participated in a socially differentiated CR intervention receiving either a standard or expanded CR intervention (Figure 1). Baseline characteristics of the patients are given in Table 2. A complete follow-up after 10 years was achieved.

**Table 2.** Baseline characteristics at patient admission with first episode myocardial infarction (N = 379)

| | Socially vulnerable patients | | Non-socially vulnerable patients | |
|---|---|---|---|---|
| | Rehabilitation type<br>N<br>Time periode | | Rehabilitation type<br>N<br>Time periode | |
| | Standard<br>N = 78<br>2000-2002<br>(% / standard deviation) | Expanded<br>N = 130<br>2002-2004<br>(% / standard deviation) | Standard<br>N = 55<br>2000-2002<br>(% / standard deviation) | Standard<br>N = 116<br>2002-2004<br>(% / standard deviation) |
| Age, years | 56 (8.15) | 55 (8.53) | 60 (7.56) | 57 (8.50) |
| Gender, male | 57 (73 %) | 93 (71 %) | 42 (76 %) | 94 (81 %) |
| Educational level, The Danish Educational Nomenclature | 3.18 (1.19) | 3.26 (1.39) | 4.80 (1.08) | 4.75 (1.19) |
| Living alone | 27 (35 %) | 51 (39 %) | 0 | 0 |
| Current smoker | 59 (76 %) | 83 (64 %) | 34 (62 %) | 60 (52 %) |
| Body mass index | 27.26 (4.35) | 26.26 (4.08) | 26.37 (3.99) | 26.54 (3.12) |
| Hypertension | 18 (23 %) | 28 (22 %) | 11 (20 %) | 23 (20 %) |
| Hyperlipidaemia | 20 (26 %) | 37 (28 %) | 13 (24 %) | 44 (38 %) |
| Diabetes mellitus | 10 (13 %) | 16 (12 %) | 6 (11 %) | 10 (9 %) |



## All-cause mortality

A total of 17 % of the vulnerable patients died during the 10 year follow-up period; 18 % of these patients had received expanded CR and 15 % had received standard CR, respectively. No significant differences were found between the two groups as an OR of 1.29 (95 % CI: 0.58;2.89) and a *P*-value of 0.53 was obtained (Table 3). As indicated in Figure 2, no

significant associations were found at 10-year follow-up among the non-socially vulnerable patients receiving standard CR.

**Table 3.** Endpoints at 10 year follow-up among socially vulnerable patients admitted with first episode myocardial infarction and participating in socially differentiated cardiac rehabilitation in the period from 2000-2004

| | Total (N = 208) | Expanded cardiac rehabilitation (N = 130) | Standard cardiac rehabilitation (N = 78) | Odds ratio (95 % CI) | *P*-value |
|---|---|---|---|---|---|
| All-cause Mortality* | 35 (17) | 23 (18) | 12 (15) | 1.29 (0.58;2.89) | 0.53 |
| Cardiovascular Mortality** | 19 (9) | 11 (8) | 8 (10) | 0.80 (0.31;2.09) | 0.65 |
| | Total (N = 176***) | Expanded cardiac rehabilitation (N = 115***) | Standard cardiac rehabilitation (N = 61***) | OR (95 % CI) | *P*-value |
| Non-fatal recurrent events* | 30 (17) | 22 (19) | 8 (13) | 1.62 (0.67;3.92) | 0.29 |
| Major cardiac events **** | 41 (23) | 27 (23) | 14 (23) | 1.31 (0.53;2.42) | 0.75 |

Data are given as numbers (percentage).
* Adusted for gender, age and diabetes mellitus.
** Adjusted for gender.
*** Only patients who did not suffer from a recurrent event during the first month after admission were included in the analysis.
**** Adjusted for gender, age, diabetes and smoking status.

## Cardiovascular mortality

Among the vulnerable patients 9 % suffered from cardiovascular mortality. Of the patients receiving expanded CR, 8 % died compared to 10 % among patients receiving standard CR. No significant differences were found at 10-year follow-up; OR 0.80 (95 % CI: 0.31;2.09) and *P*-

value 0.65 (Table 3). As indicated in figure 2 no significant associations were found at 10-year follow-up among the non-socially vulnerable patients receiving standard CR.

## Non-fatal recurrent events

Only patients who did not experience a non-fatal recurrent event during the first 30 days after admission were included in the analysis. A total of 17 % of the vulnerable patients experienced a non-fatal recurrent event during the 10-year follow-up; among these 19 % received expanded CR and 13 % received standard CR. No significant differences were found between the two groups; OR 1.62 (95 % CI: 0.67;3.92) and a *P*-value of 0.29 (Table 3). As indicated in figure 2 no significant associations were found at 10-year follow-up among the non-socially vulnerable patients receiving standard CR.

## MACE

The percentage of vulnerable patients who either experienced cardiovascular mortality or experienced a non-fatal recurrent event within 30 days after admission until 10-year follow-up was 23 % in total and in each group. No significant differences were seen between the two groups; OR 1.31 (95 % CI: 0.53;2.42) and a *P*-value of 0.63 (Table 3). As indicated in figure 2 no significant associations were found at 10-year follow-up among the non-socially vulnerable patients receiving standard CR.

# DISCUSSION

## Study findings

There were no significant differences between socially vulnerable patients admitted with first episode MI receiving expanded CR and socially vulnerable patients receiving standard CR concerning the four endpoints; all-cause mortality, cardiovascular mortality, non-fatal recurrent events and MACE at 10-year follow-up (Table 3). Moreover, no significant results were found at 10-year follow-up among the non-socially vulnerable patients who all received standard CR.

## Comparison with other studies

Two studies have examined the effect of an expanded CR intervention. In a Swedish RCT by Plüss et al.[7] 224 patients < 75 years with recent MI and / or CABG were randomized to either expanded CR or standard CR between 1999 and 2002 and followed for five years. Patients were excluded if suffering from a significant psychiatric disease or alcohol abuse. All patients received three months of standard CR including consultations with health professionals and a social worker, physical exercise, patient education and advice on smoking cessation. The patients receiving the expanded intervention also stayed five days at a patient hotel after discharge, where they participated in a cooking school for three weeks and attended a stress management course for one year. The study had an almost complete follow-up and a significantly lower number of the patients in the intervention group suffered a non-fatal recurrent event at five-year follow-up (Hazard rate 0.47, 95% CI 0.21;0.97, *P*-value 0.04). No significant results were found regarding all-cause and cardiovascular mortality.[7]

The study by Plüss et al.[7] has many similarities with the present study. Sweden and Denmark have similar welfare states with the same access to free health care and social services. The patients in the two studies were recruited in the same time period and had comparable characteristics concerning disease and age. Furthermore, exclusion criteria were the same. However, the Swedish in contrast to the present study found significant results. This could be

explained by the Swedish intervention being more pervasive and lasting a whole year and thereby constituting a major part of the long-term secondary prevention. Furthermore, the Swedish intervention was not socially differentiated. It could thus be speculated that the patients who profited the most from the intervention, were the patients who were not socially vulnerable.

In an Italian RCT by Giannuzzi et al.[8] 3241 patients ≤ 75 years with recent MI were randomized to either expanded CR or usual care. At first all patients received the same standard CR for one month consisting of physical training, lifestyle consultations and medical therapy. Hereafter 1621 patients continued in usual care and 1620 patients received an expanded CR intervention. The expanded CR intervention consisted of two hours of counseling and physical training every month for half a year and thereafter every six months for three years. Compared to usual care the expanded CR intervention showed significant improvements concerning cardiovascular mortality and recurrent events. The study by Giannuzzi et al.[8] differs from the present study regarding to the time frame of the intervention. The intervention lasted for three years and thus it was an important part of the long-term secondary prevention like Plüss et al.[7] Also, the outcomes was collected at the end of the three-year intervention and do not hold any information about the long-term effects.[8]

## Strengths, limitations and external value of the study

One of the strengths of the present study is the complete follow-up. This is partly because the patients were identified by their unique personal 10-digit civil registration number and partly because of the use of highly valid Danish register data. The information concerning mortality and morbidity were registered by health professionals using ICD-10 and did thus not rely on the memory of patients or relatives. Another strength is that the patients were almost similar at baseline. The only variables with considerable variation were educational level and whether the patients lived alone. This could be explained by these variables defining whether patients were socially vulnerable or not. It should, however, be noted that smoking status and the presence of hyperlipidaemia also varied.

The fact that patients from non-parallel time periods were being compared raises some methodological issues. All analyses were performed on both the socially and non-socially vulnerable patients. A difference between the non-socially vulnerable patients could have indicated that any changes among the socially vulnerable patients were just a general development in risk management and secondary prevention. However, no significant differences were found.

The present study was carried out as a prospective cohort study and not as a RCT, thus there is a risk of confounding and bias. An attempt to minimize potential confounding was made by using logistic regression analysis. Potential information bias cannot be ruled out concerning the self-reported questionnaires. However, it must be expected that potential bias must be non-differentiated and thereby changing the results towards the null-hypothesis. A risk of selection bias could occur as attendance rates were significantly higher in the time period of the intervention than in the period where the control group received standard CR. If more highly socially vulnerable patients participated in the intervention it could be difficult to see any significant results of the intervention if they were compared to the low-risk part of the socially vulnerable patients in the group receiving standard CR.

A reason that no significant changes were found between the socially vulnerable patients receiving expanded CR and the ones receiving standard CR could be that standard CR is an evidence-based, structured and multidisciplinary intervention of high quality that any significant changes due to the expanded CR would be hard to detect. The mean age of the patients were around late fifties. Any changes in hard endpoints such as mortality and non-fatal recurrent events could be lacking because it must be expected that the patients have had an unhealthy life style for many years resulting in severe irreversible atherosclerosis. Also, the non-significant results could indicate the importance of phase III CR. More focus should be

placed on supporting the patients in the long-term CR similar to the study by Plüss et al.[7] and trying to maintain and strengthen the knowledge that the patients obtain during phase II CR.

The external validity of the present study could be applied to CR in a hospital setting in most western countries, especially countries with free health care and a wide access to social services.

## Future research

Future research should focus on why it was not possible to lower the mortality and morbidity significantly among socially vulnerable patients admitted with first episode MI. The authors suggest at least three plausible explanations which could be helpful when designing new interventions. 1) Maybe it is not possible to lower social inequality in mortality and morbidity by using socially differentiated interventions. 2) Maybe the expanded CR should have focused on other things such as stress reduction, mindfulness or coping like it was the case in Plüss et al[7] and in another recent published RCT focusing on stress management training.[19] 3) Perhaps the intensity and the time frame were wrong. In Plüss et al.[7] the expanded intervention lasted one year and the patients therefore received support not only in phase II, but also in phase III as a part of the long-term secondary prevention.[7] In order to minimize the costs and maximize the benefit of a more intense and longer CR program alternate low-resource settings and interventions such as digital devices and home-based CR must be considered as well as a focus on those patients who will benefit mostly on participation.[20,21]

## CONCLUSION

Despite the significantly improved results of the socially differentiated CR intervention at one-year follow-up, no long-term significant effects were seen regarding mortality and non-fatal recurrent events at follow-up after 10 years.

# TABLE LEGENDS

**Table 1.** Content of the socially differentiated cardiac rehabilitation intervention.

**Table 2.** Baseline characteristics at patient admission with first episode myocardial infarction (N = 379).

**Table 3.** Endpoints at 10 year follow-up among socially vulnerable patients admitted with first episode myocardial infarction and participating in socially differentiated cardiac rehabilitation in the period from 2000-2004.

# FIGURE LEGENDS

**Figure 1.** Flowchart of study participants.

**Figure 2.** Kaplan Meier estimates of the probability of all-cause mortality, cardiovascular mortality, non-fatal recurrent events and major cardiac events.

## CONTRIBUTORSHIP STATEMENT

All authors contributed to the conception and design of the work. All authors contributed to acquisition, analysis and interpretation of data. KH and MLL drafted the manuscript. KMN, LKM, FBL, BC and CVN critically revised the manuscript. All authors approved the final version and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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## COMPETING INTERESTS

The authors declare that they have no conflicts of interest.

## PATIENT CONSENT

A patient consent form has been signed by the patients.

## ETHICS APPROVAL

The Danish Data Protection Agency (Case number: 1-16-02-684-14). Ethical approval is not required for register-based studies in Denmark.

## DATA SHARING STATEMENT

No additional data available.

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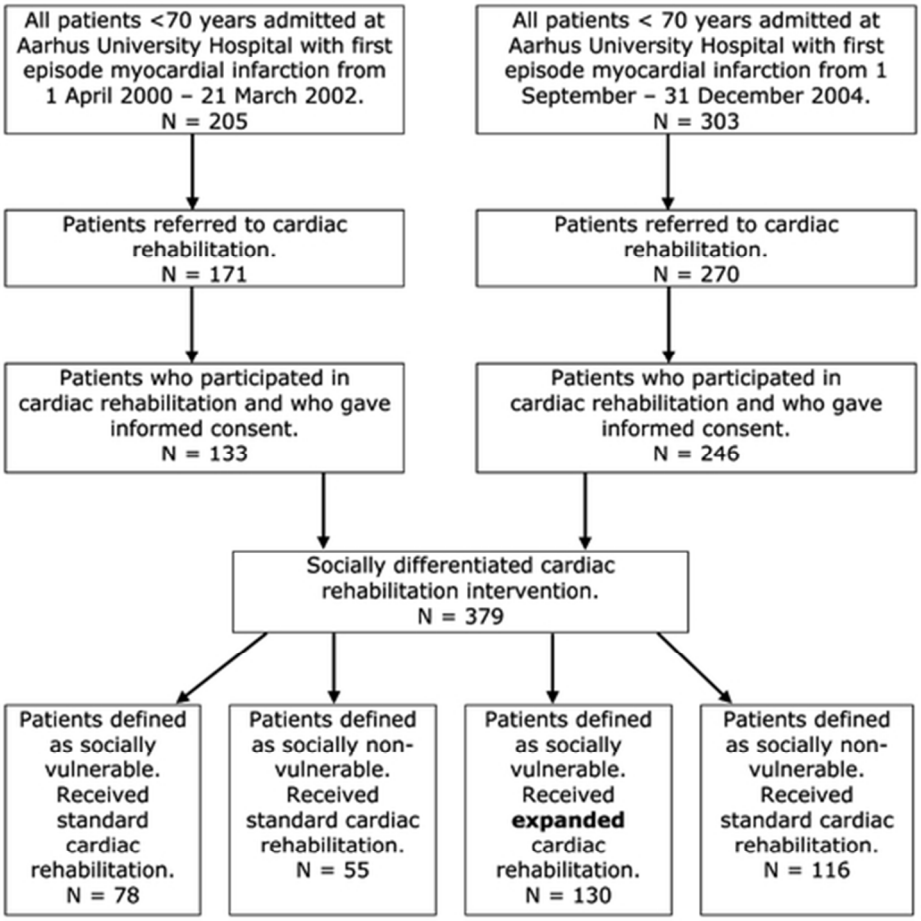


**Figure 1.** Flowchart of study participants

Flowchart of study participants

23x25mm (600 x 600 DPI)

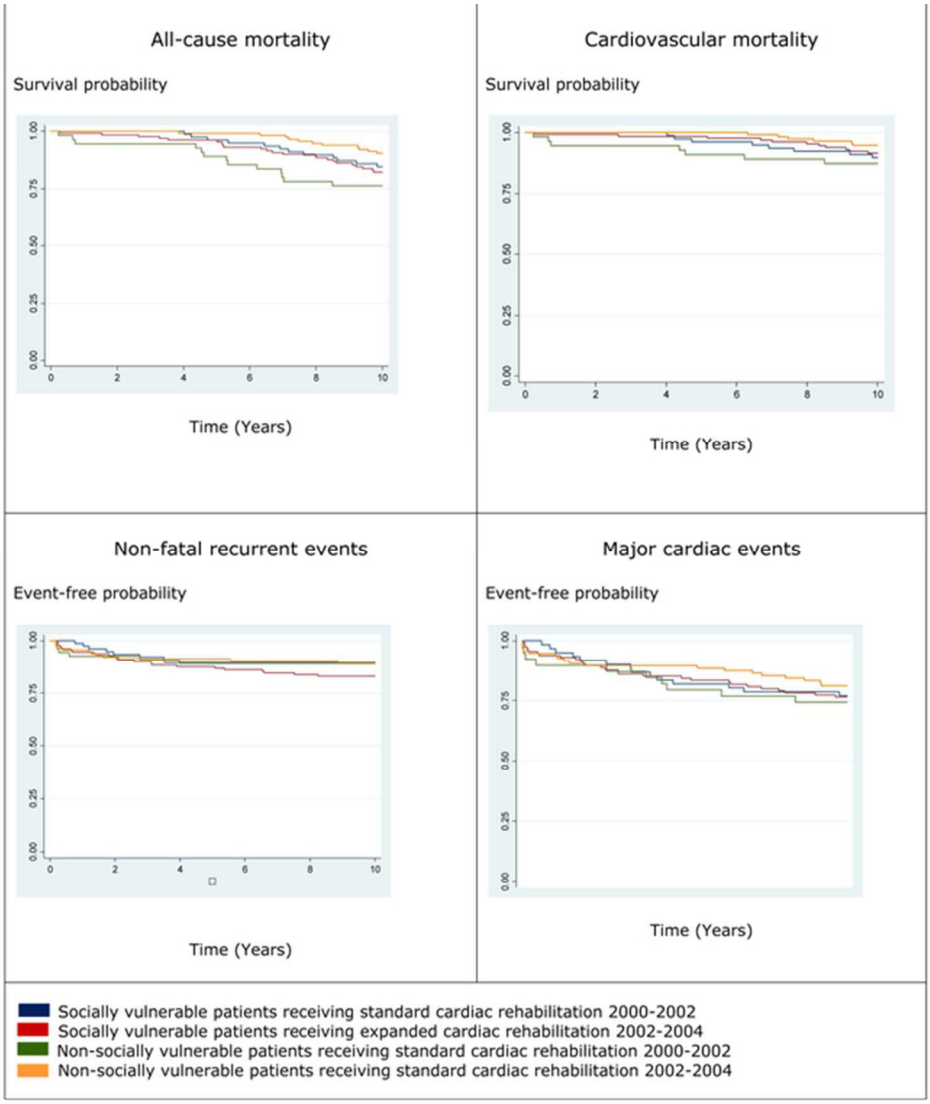


**Figure 2.** Kaplan Meier estimates of the probability of all-cause mortality, cardiovascular mortality, non-fatal recurrent events and major cardiac events.

Kaplan Meier estimates of the probability of all-cause mortality, cardiovascular mortality, non-fatal recurrent events and major cardiac events

27x35mm (600 x 600 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No. | Recommendation | Page No. | Relevant text from manuscript |
|---|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 3 | |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 3-4 | |
| **Introduction** | | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 7-8 | |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 8 | |
| **Methods** | | | | |
| Study design | 4 | Present key elements of study design early in the paper | 9 | |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 9-12 | |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 9-12 | |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | Not a matched study. | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 11 - 12 | |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 11 - 12 | |
| Bias | 9 | Describe any efforts to address potential sources of bias | 12 | |
| Study size | 10 | Explain how the study size was arrived at | 9 | |

Continued on next page

| | | | |
|---|---|---|---|
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 12 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 12 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | No subgroup analyses |
| | | (*c*) Explain how missing data were addressed | No missing data |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | No loss to follow-up |
| | | (*e*) Describe any sensitivity analyses | No sensitivity analyses |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Figure 1 |
| | | (b) Give reasons for non-participation at each stage | Figure 1 |
| | | (c) Consider use of a flow diagram | Figure 1 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 13 and Table 2 |
| | | (b) Indicate number of participants with missing data for each variable of interest | No missing data |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | 14-16 |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | 14-16 |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 14-16 |
| | | (*b*) Report category boundaries when continuous variables were categorized | Not relevant. |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Not relevant |

Continued on next page

| | | | |
|---|---|---|---|
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | No subgroup analyses |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 17 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 18-19 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 17-20 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 19 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 24 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.