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ORIGINAL ARTICLE

Cardiac rehabilitation in patients with acute coronary syndrome with primary percutaneous coronary intervention is associated with improved 10-year survival

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Aims We aimed to assess the effects of a multidisciplinary cardiac rehabilitation (CR) program on survival after treatment with primary percutaneous coronary intervention (pPCI) for acute coronary syndrome (ACS).

Methods and results Using propensity matching analysis, a total of 1159 patients undergoing CR were 1:1 matched with ACS patients who did not undergo CR and survived at least 60 days. The Kaplan–Meier analyses and multivariate Cox regression analysis were applied to study differences in survival. During follow-up, a total of 335 (14.5%) patients had died. Cumulative mortality rates at 5 and 10 years were 6.4% and 14.7% after CR and 10.4% and 23.5% in the no CR group ($P < 0.001$). Cardiac rehabilitation patients had 39% lower mortality than non-CR controls [10-year mortality 14.7% vs. 23.5%; adjusted hazard ratio (HR) 0.61; 95% confidence interval (CI) 0.46–0.81]. A total of 915 (78.9%) patients completed CR and had 46% lower mortality than those who did not complete CR (10-year mortality 13.6% vs. 18.9%; adjusted HR 0.54; 95% CI 0.42–0.70).

Conclusion Patients who underwent pPCI for ACS, with a CR program had lower mortality than their non-CR counterparts. Mortality was particularly low in patients who completed the program. In conclusion, CR is still beneficial in terms of survival.

Keywords Cardiac rehabilitation • Prognosis • PCI

Introduction

The beneficial effects of cardiac rehabilitation (CR) that have been reported for more than 40 years[1] are not universally accepted. In particular, early reported mortality effects are disputed. Recently, West *et al.*[2] argued that pooled data of studies published after the landmark WHO European multicentre collaborative trial (early 1970s) did not evidently show a mortality reduction by CR in myocardial infarction (MI) patients. Also, in the recent Rehabilitation After Myocardial Infarction Trial (RAMIT), conducted in Great Britain, no beneficial effects of CR on short-term and long-term mortality were seen in MI patients mainly treated with thrombolysis.[2]

An additional concern for the need of CR in modern era acute coronary syndrome (ACS) patients may be the excellent overall prognosis of treated patients with an ACS with clear improvements in invasive and non-invasive medical treatment. Modern era AMI patients are in particular at lower risk because treatment with primary percutaneous coronary intervention (pPCI) has substantially reduced mortality.[3,4] On top of this, nowadays medical therapy is (close) to optimal from peri- and post-pPCI, including standard

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treatment with statins and dual antiplatelet therapy.[5] So, it may be expected that such patients even less benefit from CR.[6] Therefore, Taylor *et al.*[6] suggested to focus on seeking for the evidence of reduction in hospital readmission and health-related quality of life, rather than on a reduction of mortality. But, surprisingly, de Vries *et al.*[7] recently reported in a retrospective analysis, beneficial effects of CR on mortality in a subset of patients with an ACS, included from 2007 to 2010. It might be that because of the early discharge of this relatively low-risk modern-time ACS patients, CR can be valuable to guide patients towards a personal health plan, for which there is little time during the short hospitalization.[8] Also, a major flaw in many CR trials that may explain contradictory findings is that it is not clear what part of the CR program was actually followed by the patient because the definition of participation was lacking[2] or attendance of at least only one session was already defined participation. Because of the concerns and contradictory findings of the beneficial effects of CR on mortality in the modern era ACS patient, we conducted a large study to assess the effects of CR in patients after ACS treated with pPCI on long-term mortality, in particular in patients who completed the CR program, compared with those patients who did not complete the CR program.

Methods

Patients

The Erasmus Medical Centre (EMC) is one of the two hospitals in the Rotterdam, Rijnmond area that offers a 24/7 pPCI service for MI patients. Capri Cardiac Rehabilitation (Capri CR) Centre, Rotterdam provides dedicated CR at five different locations in the city of Rotterdam (www.caprihr.nl).

Capri CR provides standardized outpatient CR according to the European Society of Cardiology (ESC) guidelines.[9] In the database at Capri CR 1159 consecutive patients were identified with pPCI after an ACS between 2003 and 2011. Matching patients were found in the database of EMC: in total 3958 patients. Patients with cardiogenic shock (2.3%) were excluded: also patients with early (within 60 days post-PCI) death (5.2%). Early death was defined as death within 60 days post-PCI, because patients in the CR group started CR 4–6 weeks post-PCI (median period): so none of the early death could be caused by CR participation This study was not subjected to the Dutch Medical Research Involving Human Subjects Act no approval was required. Moreover, the study was conducted according to the Helsinki Declaration. All patients consented participation in this study.

Cardiac rehabilitation

The program focuses on improving physical condition, self-confidence, and social integration. The multidisciplinary CR program is led by a physician, specialized physiotherapists, nurses, and social workers. The core of the program consists of 1.5 h group exercise sessions 2 times a week during a maximum of 12 weeks at local sport's accommodations. Besides the exercise program, both verbal and written instructions are given on how to deal with exercise, diet, smoking cessation, and stress management. The aim is to improve adherence to lifestyle modification and to help patients to adopt a positive role in the care of their own health. If necessary, individual consultations with psychiatrist, psychologist, social workers, and dieticians are provided. The exact length of a CR program is determined by a multidisciplinary team together with the patient but with a minimum of 6 weeks. Upon completion of the CR program, a maximum (symptom-limited) bicycle stress test is performed. Patients who had completed CR program had attended at least 75% of the physical program: this was our definition of 'completed CR'.[10]

Table 1 Baseline characteristics of patients who did and did not undergo cardiac rehabilitation

	CR	no CR	*P*-value
Age (years), mean (SD)	59.0 (9.9)	58.8 (11.83)	0.91
Male, *n* (%)	892 (77)	898 (78)	0.80
STEMI, *n* (%)	760 (66)	754 (65)	0.83
MVD, *n* (%)	476 (41)	465 (40)	0.67
Smoking, *n* (%)	447 (39)	481 (42)	0.16
Diabetes, *n* (%)	158 (14)	153 (13)	0.81
Hypercholesterolaemia, *n* (%)	522 (45)	519 (45)	0.93
Hypertension, *n* (%)	489 (42)	484 (42)	0.87
Family history, *n* (%)	418 (36)	422 (36)	0.90
Prior MI, *n* (%)	8 (2)	6 (1)	0.88
Prior PCI, *n* (%)	151 (13)	153 (13)	0.95
Prior CABG, *n* (%)	30 (3)	18 (2)	0.11
Proximal LAD lesion, *n* (%)	475 (41)	484 (42)	0.74
Socioeconomic status, *n* (%)			
Upper class	172 (15)	162 (14)	0.84
Upper middle class	143 (12)	150 (13)	
Lower middle class	262 (23)	252 (22)	
Lower class	580 (50)	594 (51)	
Use of medication, *n* (%)			
Aspirin	1112 (96)	1093 (94)	0.07
Statins	1107 (95)	1096 (94)	0.3
B blockers	1113 (96)	1099 (95)	0.1
ACE	1127 (97)	1122 (97)	0.5
Diuretics	15 (1.3)	27 (2.3)	0.06
Anticoagulants	2 (0.2)	5 (0.4)	0.2

ACE, angiotensin-converting-enzyme inhibitors; CABG, coronary artery bypass graft; LAD, left anterior descending; MVD, multi-vessel disease; SD, standard deviation.

Statistical analysis

Continuous variables are presented as mean ± standard deviation, whereas categorical variables are expressed as percentages. Comparisons among groups were performed by the independent *t*-test for continuous variables and Pearson's χ^2 test for categorical variables. All statistical tests were two-tailed and a *P*-value of <0.05 was considered statistically significant. The incidence of events over time was studied with the use of the Kaplan–Meier method, whilst log-rank tests were applied to evaluate differences between the treatment groups. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Cox regression analysis was performed to adjust CR effect for the following potential confounders: to generate a propensity score for CR participation using the following characteristics (*Table 1*): age, sex, ST-segment elevation myocardial infarction (STEMI), hypertension, hypercholesterolaemia, diabetes, family history of coronary artery disease, current smoking, prior MI, prior history of PCI, or coronary artery bypass graft, proximal left anterior descending lesion, and socioeconomic status.[11,12] Using the generated propensity score, each patient from the CR group was 1:1 matched with a patient without CR. Statistical analysis was performed with SPSS 16 for Windows (SPSS Inc., Chicago,

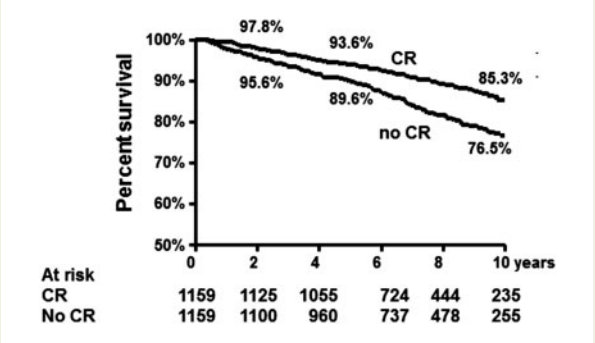

Figure 1 Cumulative survival after percutaneous coronary intervention according to cardiac rehabilitation. CR, cardiac rehabilitation.

IL, USA). The results are presented as unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs).

Primary endpoint

For information about mortality municipality live registries were studied. Nine patients were lost to follow-up (0.9%).

Results

Cardiac rehabilitation participants vs. non-cardiac rehabilitation participants

After 1:1 propensity matching no differences in clinical characteristics between CR patients and controls were found (*Table 1*). The mean age of the study patients was 58.8 years and 77% were men. During a median (25th–75th percentile) follow-up of 10 (range 4–12) years a total of 335 out of 2318 (14.5%) patients had died: 211 in the no CR group (18.2%) and 124 in the CR group (10.7%). Throughout the entire follow-up period, mortality was lower in patients with CR and continued to diverge (*Figure 1*). Cumulative mortality rates at 5 and 10 years were 6.4% and 14.7% after CR and 10.4% and 23.5% in the no CR group. Patients with CR had a 44% lower 10-year mortality than non-CR controls (HR 0.56, 95% CI 0.43–0.73). After adjustment CR patients had a 39% lower 10-year mortality (HR 0.61, 95% CI 0.46–0.81; *P*-value < 0.001) than non-CR controls. Ten-year mortality 14.7% vs. 23.5%.

Cardiac rehabilitation participants: complete vs. non-complete Cardiac rehabilitation

Nine-hundred and fifteen (78.9%) patients completed CR. Clinical characteristics between complete CR and non-complete CR patients are displayed in *Table 2*. Patients who did not complete CR had more often diabetes (12.3% vs. 18.4%). Cumulative mortality rates at 5 and 10 years were 5.5% and 13.6% in the complete CR and 8.6% and 18.9% in the non-complete CR patients group (*Figure 2*). Complete CR patients had a 48% lower 10-year mortality than non-complete CR patients (HR 0.521, 95% CI 0.405–0.672). After adjustment complete CR patients had a 46% lower 10-year mortality (HR 0.54, 95% CI 0.42–0.70; *P* < 0.001) than non-complete CR patients.

Table 2 Baseline characteristics of patients who completed and who did not complete cardiac rehabilitation

	Complete CR (*n* = 915)	Non-complete CR (*n* = 244)	*P*-value
Age (years), mean (SD)	59.0 (9.9)	58.2 (11.2)	
Male, *n* (%)	711 (77.7)	181 (74.2)	0.24
STEMI, *n* (%)	611 (66.8)	149 (61.1)	0.09
MVD, *n* (%)	363 (39.7)	113 (46.3)	0.06
Smoking, *n* (%)	340 (37.2)	107 (43.9)	0.06
Diabetes, *n* (%)	113 (12.3)	45 (18.4)	0.01
Hypercholesterolaemia, *n* (%)	405 (44.3)	117 (48.0)	0.30
Hypertension, *n* (%)	384 (39.5)	105 (43.0)	0.76
Family history, *n* (%)	338 (36.9)	80 (32.8)	0.23
Prior MI, *n* (%)	6 (0.7)	2 (0.8)	0.15
Prior PCI, *n* (%)	110 (12.0)	41 (16.8)	0.05
Prior CABG, *n* (%)	23 (2.5)	7 (2.9)	0.76
Proximal LAD lesion, *n* (%)	380 (41.5)	95 (38.9)	0.46
Socioeconomic status, *n* (%)			
High	143 (15.7)	29 (11.9)	0.23
Less high	117 (12.8)	26 (10.7)	
Less low	208 (22.8)	54 (22.1)	
Low	445 (48.7)	135 (55.3)	

CABG, coronary artery bypass graft; LAD, left anterior descending; MVD, multivessel disease; SD, standard deviation.

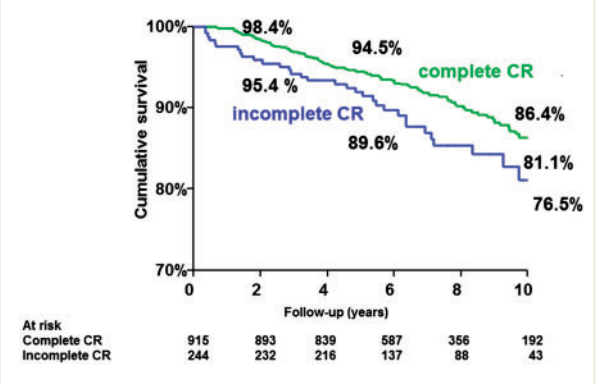

Figure 2 Cumulative survival after completing or not completing cardiac rehabilitation after percutaneous coronary intervention. CR, cardiac rehabilitation.

Discussion

The main findings of this study in ACS patients treated with pPCI are (i) patients who attended a CR program had significantly lower

10-year mortality than their no-CR counterparts and (ii) patients who completed CR had a lower 10-year mortality when compared with patients who started but did not complete CR. This confirms that despite major changes in ACS treatment, CR programs may still be beneficial in terms of 10-year survival in the pPCI era.

To the best of our knowledge our propensity matched study is the first which studied the relationship between long-term effects of CR on mortality in ACS patients treated with pPCI which is the currently recommend treatment for not only STEMI patients but also in most patients with non-STEMI.[13,14] Despite these major changes in treatment in the acute phase of ACS beneficial effects of CR seem still prominent, evidenced by a 39% reduction in mortality. One of the reasons for failure to demonstrate positive effects on mortality by others in different populations may be the existing different definitions and lengths of CR programs attendance.[7] Sometimes, attendance of only one session was already defined as participation. Therefore, we also assessed the outcome of patients who did and did not complete CR. Patients who completed CR had a 10-year mortality of 13.6% against 18.9% in patients who did not complete CR. Thus, there seems to be a 'dose response curve' with greater reduction in mortality with full completion of CR. This was already mentioned by Beauchamp *et al.*[10] who studied patients undergoing bypass surgery. Patients who attended less than 25% of the CR program had a mortality risk over twice that of patients who attended more than 75% of the program. In our experience, patient motivation is the most important reason in completing CR, although we cannot substantiate this with scientific evidence. When compared with the recent study by de Vries *et al.*,[15,16] we did have information on cardiovascular risk factors whereas they did not: but this was not a major confounder in our study. Logistic reasons such as transportation facilities and the distance to the nearest CR centre have shown to be crucial in CR participation. Finally, the expected effects of CR by the patient may play an important role.

One of the main challenges in post-ACS management is to increase patient participation in CR programs. As we recently demonstrated, in the Rotterdam-Rijnmond region, only 39% of eligible patients participated in CR, which is exemplary for a broad range of clinical practices.[15,17] Target populations including women, elderly and patients with low socioeconomic status have poorer than average participation rates and need specific attention.[18] Therefore, before patients can get the benefits of CR and even better completion of CR, they first have to be referred by their cardiologists. This is still a challenge worldwide.

Since there seems to be a 'dose response curve' with greater reduction in mortality with full completion of CR, we strongly advocate a strict definition of CR. Rauch *et al.*[19] in their systematic review and meta-analysis ('Cardiac Rehabilitation Outcome Study—analysis') already emphasize the need for defining internationally accepted CR standards, since they found a wide heterogeneity of CR programmes. Given the results of our current study, we plea that CR be defined 'complete' if a patient participated in at least 75% of the full multidisciplinary CR program. Our work can be considered a valuable contribution to review by Rauch *et al.*,[19] as our follow-up period was much longer and even then survival benefit was sustained. Furthermore, our patients constituted a more homogeneous population. In particular, all patients had ACS that was treated with pPCI, and there were no differences in the use of guideline-recommended 'optimal' medical therapy between the patients with complete and incomplete CR. Even in such a homogeneous group, CR in the new millennium showed to be beneficial for long-term survival.

Limitations

Our study had an observational retrospective design. Although we performed propensity matching and multivariate Cox regression, we could not control for all confounders.

Conclusion

Acute coronary syndrome patients treated with pPCI who attended a CR program had significantly lower 10-year mortality than their no-CR counterparts. Also, patients who completed CR had a better prognosis when compared with patients who started but did not complete CR. This suggests that despite changes in treatment of ACS, CR programs are still beneficial. However, only a formal Randomized Controlled Trial (RCT) can provide definite evidence.

Conflict of interest: none declared.

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