Is cardiac rehabilitation still relevant in the new millennium?
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Cardiac rehabilitation is an evidence-based intervention which has evolved over time and incorporates physical, psycho-social and educational components with the aim of improving the patients' functioning following a cardiac event. The evidence base for cardiac rehabilitation following acute myocardial infarction has been growing over the past half a century. Individual randomized control trials were small and, therefore, mortality outcomes usually failed to reach significance; however, meta-analyses have proven consistently that participation in cardiac rehabilitation following a myocardial infarction is associated with a significant improvement in mortality. In the era of revascularization and improved drug therapies, observational studies still provide evidence that independent of other treatments, cardiac rehabilitation is a life-saving measure. Although early studies often only studied young males, more contemporary data include patients from all sectors of society and have found that groups such as women, the elderly and those with heart failure appear to have greater mortality benefits compared with the traditional young male cohort. Uptake remains a problem and one challenge for the future is ensuring improved uptake on to good-quality rehabilitation programmes and demonstrating these positive effects.


Keywords: acute coronary syndrome, acute myocardial infarction, cardiac rehabilitation, mortality

Introduction
Coronary heart disease is the principal cause of death in the European Union.\textsuperscript{1} It is also a major financial burden to the European economy.\textsuperscript{2} As such, cardiovascular disease remains very much part of the European Union healthcare and political agenda.\textsuperscript{3} Increasing emphasis has been placed on the prevention of both coronary artery disease (CAD) and its sequelae. Although the use of early revascularization has been enthusiastically embraced, resulting in significant reductions in mortality,\textsuperscript{4,5} more holistic evidence-based approaches to the care of patients with CAD that also reduce mortality, such as cardiac rehabilitation and health behaviour change programmes,\textsuperscript{6} are still frequently overlooked in preference to more expensive pharmacological and mechanical interventions. Moreover, although there are over 40 years of data from randomized controlled trials (RCT’s) that constitute the evidence base for cardiac rehabilitation, its relevance may be questioned by some in light of contemporary cardiac care and the changing face of the research available. This article explores the literature to ascertain whether there is evidence to suggest that the impact of cardiac rehabilitation on survival has changed with time.

Cardiac rehabilitation
Most patients admitted with an acute coronary syndrome (ACS) have acquired coronary heart disease, in part, due to maladaptive health behaviours. Often, hospitalization leaves patients with uncertainties about return to normal life and functioning. In turn, this may lead to psychological and physical sequelae with subsequent delay in return to work and/or adoption of abnormal health behaviours.\textsuperscript{7} Cardiac rehabilitation is an evidence-based intervention defined by the European Society of Cardiology as “co-ordinated multifaceted interventions designed to optimize a cardiac patient’s physical, psychological, and social functioning, in addition to stabilizing, slowing, or even reversing the progression of the underlying processes thereby reducing morbidity and mortality”.\textsuperscript{8} It complements secondary prevention, typically incorporating several methods of rehabilitation. These approaches differ between programmes and include exercise components, psycho-social interventions, education programmes and advice regarding smoking cessation, return to sexual activity and healthy eating.

The term comprehensive cardiac rehabilitation (CCR) has evolved over time and refers to programmes
containing elements of physical intervention alongside education and counselling. Many national and international organizations have published guidelines with frameworks for delivery of service. The National Institute for Health and Clinical Excellence is an example of a body based in the UK which offers best practice advice on secondary prevention for patients following a myocardial infarction. Accordingly, cardiac rehabilitation draws on a holistic approach to address the many aspects of a patient’s life – it encourages behavioural change that leads to improved survival.

Cardiac rehabilitation has evolved substantially since its inception in the 1950s when Levine and Lown first questioned the practice of prolonged bed rest following acute myocardial infarction (AMI). Meta-analyses have quantified the positive survival effects of cardiac rehabilitation and ‘mortality’. Recent guidelines and evidence-based reviews (such as the Cochrane library) were also used to identify suitable studies. One reviewer (L.E.D.) scanned all abstracts and titles to select those applicable to the review. All types of cardiac rehabilitation were included and studies not utilizing all-cause mortality as an outcome were excluded. Only studies including patients participating in cardiac rehabilitation following an admission with an ACS were chosen for review.

**Methods**

RCTs were identified from meta-analyses and systematic reviews. The clinical databases MEDLINE and Embase were searched using the keywords ‘cardiac rehabilitation’ and ‘mortality’. Recent guidelines and evidence-based reviews (such as the Cochrane library) were also used to identify suitable studies. One reviewer (L.E.D.) scanned all abstracts and titles to select those applicable to the review. All types of cardiac rehabilitation were included and studies not utilizing all-cause mortality as an outcome were excluded. Only studies including patients participating in cardiac rehabilitation following an admission with an ACS were chosen for review.

**Results**

**Early cardiac rehabilitation**

One of the first multicentre studies investigating mortality following cardiac rehabilitation was published by the WHO in 1983.18 This non-blinded RCT followed 1735 men with AMI under the age of 65 (mean 53) years across 17 European centres recruited over a 2-year period from 1973 to 1975. The intervention group received CCR with or without an exercise component. The control group received usual care and both arms were followed up for 3 years. There was a non-significant trend toward reduced all-cause mortality in the intervention group [odds ratio (OR) 0.86, 95% confidence interval (CI) 0.7–1.05]. The study was not without bias, as randomization procedures were not robust, data collection inadequately standardized and the quality and content of the rehabilitation programme varied between centres (physical training, for example, was recommended as part of the CCR by the study organizers, but was not compulsory and, therefore, not offered by some centres).

In 1995, Hamalainen et al. studied 375 patients (301 men and 74 women) with AMI for 15 years. Although statistically significant reductions in cardiac and sudden death were seen in the group receiving CCR (n = 151), all-cause mortality was not significantly different. In 1982, Carson et al. recruited 330 men under the age of 70 years into an exercise programme or control group. The reduction in mortality in those participating in the exercise programme was not statistically different from those in the control group (8 versus 14%). The study excluded patients with heart failure, severe chronic obstructive pulmonary disease, hypertension and diabetes mellitus, and did not randomize until 6 weeks after AMI, potentially missing the benefits of early intervention and removing from the study patients at higher risk who had more to benefit from cardiac rehabilitation (such as the elderly and those with congestive cardiac failure) – a ‘risk-treatment paradox’ seen elsewhere in ACS management.

Wilhelmsen et al. followed 314 patients who were randomized to either an exercise-only rehabilitation programme (without any behavioural/educational programme) commencing 3 months following AMI or a control group. At 4 years, 35 patients in the control group had died compared with 28 in the intervention group (P = 0.40). A concern with this study was the low numbers of unrepresentative participants (predominantly males under the ages of 60 years) and the high attrition rate in the intervention arm.

In 1981, the National Exercise and Heart Disease Project randomized 651 men aged 30 to 64 years from five centres into a supervised exercise group (without a psycho-social or behavioural component) and a control group, and followed them up for 19 years. Participants were recruited up to 36 months after AMI (although the majority were recruited at least 6 months after AMI and back in full-time employment at study onset). At 3 years, the intervention arm had a relative risk (RR) of 0.69 (95% CI 0.39–1.25). The non-significant effect did not extend to 19 years follow-up (RR 1.09, 95% CI 0.87–1.36). The duration of the intervention, 8 weeks, was rather short and may have accounted for the lack of long-term benefit.

In 1993, Hedback et al. published the only prospective trial to date (albeit non-randomized) in which there was a statistically significant reduction in mortality in those receiving CCR. The intervention arm (n = 147) demonstrated reduced 10-year mortality rates when compared with the control arm (n = 158) (42.2 versus 57.6%, respectively, P < 0.01) which was accounted for predominantly by a reduction in cardiac mortality. As with many other earlier studies, the study population was predominantly of male sex (84%) and of ages less than...
65 years. In addition, those in the intervention group were less likely to smoke and had better control of their blood pressure at 5 years. It appears, therefore, that although a positive long-term survival effect was associated with this premillennium CCR programme, there were important biases in the selection of patients into the study.

Bobbio et al. performed a meta-analysis of RCTs of cardiac rehabilitation with at least 2-year follow-up to quantify the effect of post-AMI rehabilitation on mortality. The study included eight RCTs and 2260 patients to conclude that cardiac rehabilitation was associated with a RR reduction of 0.68 (95% CI 0.48–0.82). In the same year (and including many of the same trials), O’Connor et al. studied 23 RCTs (4554 patients) to analyse the effects of cardiac rehabilitation (which included an exercise component) on mortality and found a pooled odds ratio at over 36-month follow-up of 0.80 (95% CI 0.66–0.96). Notably, similar reductions in all-cause mortality following post-AMI cardiac rehabilitation were suggested in a systematic review by Oldridge et al. (OR 0.76, 95% CI 0.62–0.92).

Contemporary cardiac rehabilitation data
An observational study published in 2010 by Junger et al. studied 4547 patients following ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI). Participation in cardiac rehabilitation was high with 60% of eligible patients taking part (compared with 15–30% reported elsewhere). Participation in cardiac rehabilitation was associated with a significant reduction in all-cause mortality at 1 year (STEMI: OR 0.41, 95% CI 0.28–0.60; NSTEMI: OR 0.53, 95% CI 0.38–0.76). In an observational study of 30161 Medicare beneficiaries over the age of 65 years who undertook an exercise-based cardiac rehabilitation programme between 2000 and 2005, Hammill et al. found that the completion of a prolonged programme of rehabilitation (36 sessions) was associated with a 47% lower risk of death at 4 years (hazard ratio 0.53, 95% CI 0.48–0.59). Because all those who completed at least one cardiac rehabilitation session, the true benefit of cardiac rehabilitation on survival may have been underestimated. A retrospective matched cohort study comparing 2042 cardiac rehabilitation participants with controls showed that, after a mean of 5.25-year follow-up, cardiac rehabilitation was associated with a 50% reduction in mortality (2.6 versus 5.1%, P < 0.001).

Suaya et al. published the largest study to date of cardiac rehabilitation in the elderly, evaluating 601 099 US Medicare beneficiaries aged 65 years and over who were coded as chronic stable angina, coronary revascularization [percutaneous coronary intervention (PCI)/coronary artery bypass grafting] and hospitalization for an ACS in 1997. Notably, only 12% of eligible patients participated in cardiac rehabilitation (n = 73 049) and the content of cardiac rehabilitation was not defined. Participants in cardiac rehabilitation were more likely to be white, male, younger and of higher socio-economic class. At 1-year and 5-year follow-up, there were statistically significant RR reductions of 58 and 34%, respectively, in favour of cardiac rehabilitation. The benefits were seen in all groups, including those with chronic heart failure (who gained greater benefit than those without heart failure) and those following revascularization procedures. Importantly, there was a ‘dose-dependent’ response – those who attended more sessions experienced a greater mortality reduction than those who attended fewer sessions. Mortality reductions were increased in older age groups (over 75 years of age) and women gained greater benefit than men across all age groups. A recently published retrospective analysis published in 2011 by Goel et al. analysed registry data relating to 964 patients undergoing cardiac rehabilitation following PCI between 1994 and 2008 for both stable CAD and ACS. Uptake for cardiac rehabilitation was 40% and median follow-up time 6.3 years. A propensity score matched-pair analysis found a significant reduction in all-cause mortality in those participating in cardiac rehabilitation (hazard ratio 0.54, 95% CI 0.41–0.71, P < 0.001) which translated to a number needed to treat with cardiac rehabilitation to prevent one death of 34 at 1 year and 22 at 5 years. There was no comparison of outcomes between the group undergoing cardiac rehabilitation following PCI for an ACS and stable CAD, but it was noted that cardiac rehabilitation uptake was higher in the ACS cohort. Table 1 outlines the important features of the major studies of cardiac rehabilitation following an ACS and Fig. 1 illustrates the impact of cardiac rehabilitation following an ACS on mortality over time.

Discussion
Typically, the 20th century RCTs were small; however, the pooled analysis of these data has shown that cardiac rehabilitation is associated with significantly reduced risk of death of 20–32%. Outputs from research studies undertaken in the 21st century report reductions in mortality which approach 50%. Yet, Taylor et al. who compared pooled pre-1995 and pooled post-1995 RCTs suggested that mortality was non-significantly reduced in the post-1995 pooled data (pre-1995 OR 0.84, 95% CI 0.73–0.97; post-1995 OR 0.62, 95% CI 0.38–1.04).

The most recent data cannot, however, be compared fully with earlier research – the studies are very different. Earlier trials almost exclusively studied (usually white) males aged less than 65 years who had few comorbidities, whereas more recent studies utilized data from a ‘real world’ cohort of patients including the elderly, women, those with heart failure and ethnic minorities. Also, cardiac rehabilitation programmes have changed over the years. Home-based rehabilitation programmes, national guidelines setting minimum agreed standards.
Table 1  Studies of cardiac rehabilitation for acute coronary syndrome/AMI

<table>
<thead>
<tr>
<th>Study year</th>
<th>Study reference</th>
<th>Study design</th>
<th>Number</th>
<th>Outcome</th>
<th>Comment</th>
<th>Mortality effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td>Wilhelmsen et al.(^{23})</td>
<td>RCT</td>
<td>314</td>
<td>Non-significant trend toward reduced all-cause mortality in the intervention arm</td>
<td>High dropout rate in intervention arm, predominately males under 60 years, recruited 3 months after AMI</td>
<td>OR at 4-year follow-up 0.75; 95% CI 0.43–1.71</td>
</tr>
<tr>
<td>1981</td>
<td>Shaw(^{24})</td>
<td>RCT, multicentre</td>
<td>651</td>
<td>Non-significant trend toward improved all-cause mortality</td>
<td>Men aged 30–64, randomized 2 months, 3 years following AMI, short-term intervention</td>
<td>OR at 36-month follow-up 0.69; 95% CI 0.39–1.25</td>
</tr>
<tr>
<td>1982</td>
<td>Carson et al.(^{20})</td>
<td>RCT</td>
<td>303</td>
<td>Non-significant improvement in mortality</td>
<td>Men &lt; 70 years, patients with significant comorbidities excluded, randomized 6 weeks following AMI</td>
<td>OR at 25-month follow-up 0.54; 99% CI 0.25–1.14</td>
</tr>
<tr>
<td>1983</td>
<td>WHO(^{18})</td>
<td>RCT, multicentre</td>
<td>1735</td>
<td>Non-significant improvement in mortality</td>
<td>Survivors of AMI randomized at hospital discharge, male ≤65 years, 3-year follow-up, randomization not robust, intervention not standardized</td>
<td>OR at 3-year follow-up 0.86; 95% CI 0.7–1.05</td>
</tr>
<tr>
<td>1993</td>
<td>Hedback et al.(^{26})</td>
<td>Non-RCT</td>
<td>305</td>
<td>Significant reduction in mortality in control arm</td>
<td>Patients at one centre offered CR compared with those in a neighbouring centre receiving usual care, men and women &lt;65 years post-AMI</td>
<td>At 10-year follow-up, mortality 42.2 (CR) versus 57.6% (control) (P &lt; 0.001)</td>
</tr>
<tr>
<td>1995</td>
<td>Hanslainen et al.(^{19})</td>
<td>RCT</td>
<td>375</td>
<td>No significant difference in all-cause mortality, significant reduction sudden death</td>
<td>15-year follow-up following AMI small proportion of patients ≤65 years</td>
<td>At 15-year follow-up, mortality 64.4 (CR) versus 66.8% (control) (NS)</td>
</tr>
<tr>
<td>2009</td>
<td>Alter et al.(^{20})</td>
<td>Retrospective matched cohort study</td>
<td>4084</td>
<td>Significant mortality reduction in CR participants</td>
<td>CR participants with acute cardiac hospitalization retrospectively matched with control, follow up at 5 years</td>
<td>Mortality at 5-year follow-up 2.6 (CR) versus 5.1% (control) (P &lt; 0.0001)</td>
</tr>
<tr>
<td>2009</td>
<td>Skaya et al.(^{21})</td>
<td>Retrospective matched cohort study</td>
<td>73,049</td>
<td>Significant reduction in mortality at 1-year and 5-year follow up</td>
<td>Large study size with diverse socio-demographic and clinical characteristics, men and women aged ≥65, included ACS/AMI patients and those following revascularization alongside admissions for stable coronary syndrome and chronic ischaemic heart disease conditions</td>
<td>1-year RRR 58%; 5-year RRR 34%; P &lt; 0.001</td>
</tr>
<tr>
<td>2010</td>
<td>Junger et al.(^{27})</td>
<td>Prospective, observational</td>
<td>4547</td>
<td>Participation in CR associated with significant improvement in all-cause mortality</td>
<td>High participation rate, recruited consecutive patients hospitalized for ACS between 2000–2002 with 12-month follow-up period</td>
<td>At 12-month follow-up: STEMI OR 0.41, 99% CI 0.28–0.60; NSTEMI OR 0.53, 99% CI 0.38–0.76 HR at 4-year follow-up 0.53, 95% CI 0.48–0.59 P &lt; 0.001</td>
</tr>
<tr>
<td>2010</td>
<td>Hammill et al.(^{29})</td>
<td>Observational</td>
<td>30,161</td>
<td>Participation in an increased number of CR sessions associated with significant improvement in mortality</td>
<td>Comparison of those attending 1 session of CR with those attending prolonged programme (38 sessions), men and women &gt; 65 years, mainly post-CABG/AMI with some (15%) angina</td>
<td>HR at a median of 63 years of follow-up 0.54, 95% CI 0.41–0.71 P &lt; 0.001</td>
</tr>
<tr>
<td>2011</td>
<td>Goel et al.(^{17})</td>
<td>Retrospective matched analysis</td>
<td>964</td>
<td>Significant reduction in all-cause mortality in CR participants following PCI</td>
<td>Analysed all patients attending at least one session of CR following PCI for ACS or stable CAD, no comparison of outcomes between those receiving CR following PCI for ACS/AMI and stable CAD</td>
<td>HR at a median of 63 years of follow-up 0.54, 95% CI 0.41–0.71 P &lt; 0.001</td>
</tr>
</tbody>
</table>

95% CI, 95% confidence interval; ACS, acute coronary syndrome; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CR, cardiac rehabilitation; HR, hazard ratio; NSTEMI, non-ST-elevation myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; RRR, relative risk reduction; STEMI, ST-elevation myocardial infarction.
for programme quality, psycho-social interventions, development of phase IV programmes and a trend toward community-based programmes may have had an impact alongside improved scientific knowledge around smoking cessation techniques, the merits of a Mediterranean diet and the harmful effects of binge drinking.

Even so, there are data to suggest that these ‘real world’, more representative groups of participants who have been studied in recent trials have greater mortality benefits compared with the traditional young male cohort. It is worth noting that patients enrolled in the more recent observational studies may have been more compliant with secondary prevention medications (through improved education programmes), although there is evidence to suggest that the benefit derived from cardiac rehabilitation is independent of this. What is clear is that more research is required to more carefully evaluate whether improvements in cardiac rehabilitation care for ACS/AMI are evident over time. With the advent of national cardiovascular databases for contemporary observational research, this is now possible.

**Conclusion**

Cardiac rehabilitation is an effective intervention with a large and increasing evidence base – it is estimated that one 5-year death would be averted for every 12 patients receiving cardiac rehabilitation – a statistic not easily rivalled by most modern drug therapies. Observational studies in the new millennium consistently conclude that cardiac rehabilitation does significantly reduce mortality even in the context of improved medical and revascularization strategies and, therefore, it could be argued that its relevance is more apparent than ever before. Meta-analyses have proven the worth of cardiac rehabilitation in the last millennium and although RCT’s are no longer ethically possible to conduct, it is important that research into the mortality benefits of cardiac rehabilitation following AMI are ongoing to prove its value alongside contemporary medical care. It is anticipated that...
advances in the quality of cardiac rehabilitation programs and European-wide guidelines have led to improved survival. Presently, it is estimated that worldwide, cardiac rehabilitation is attended by 15–30% of those eligible. In light of evidence favouring the beneficial effects of cardiac rehabilitation (not only for mortality but also in terms of improved health behaviours, self-confidence and return to work), one of the main challenges for this century is improving cardiac rehabilitation uptake of good-quality cardiac rehabilitation programmes, especially in minority groups, and demonstrating these positive effects.

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References


