Brief Report

Title: The Effects of Cardiac Rehabilitation on Mortality and Morbidity in Women: a Meta-Analysis Attempt

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Condensed Abstract

Cardiac rehabilitation (CR) reduces mortality and morbidity. However, there have been few women in CR trials, and no meta-analyses. Thirty-one potential trials were identified in recent systematic reviews. All authors were contacted for data by sex as this was rarely reported. Data were only available for 2 trials.

Structured Abstract

Background: Cardiac rehabilitation (CR) is associated with significant reductions in mortality and morbidity, but few women are included in trials. Therefore, a meta-analysis of the effects of CR in women is warranted.

Methods: Randomized controlled trials from recent systematic reviews that included women, attending comprehensive CR, and reporting the outcomes of mortality, morbidity (hospitalization, myocardial infarction, bypass surgery, percutaneous coronary intervention) were considered for inclusion. An updated search of the literature was performed from the end date of the last search, based on the Cochrane strategy. Authors were contacted to request results in women where not reported.

Results: Based on 2 recent systematic reviews, 80 trials were identified. Fifty (62.5%) were excluded, most-commonly due to lack of inclusion of women (n=18; 22.5%). One trial was identified through the search update. Of 31 potential trials meeting inclusion criteria, one reported results in women, and many were old and hence data by sex were no longer available. Ultimately, data for women were available in 2. Therefore, it was deemed inappropriate to undertake meta-analysis.

Conclusion: This review corroborates the dearth of data on CR in women, despite the fact that it is their leading cause of death. Given the totality of evidence, including reductions in mortality and morbidity in non-randomized studies, and evidence of benefit for other important outcomes such as functional capacity and quality of life, women should continue to be referred to CR.

Key words: cardiac rehabilitation; women; coronary heart disease; secondary prevention.

Introduction

Cardiovascular diseases (CVDs) are among the leading burdens of disease worldwide.[1] Approximately 2.4 million Canadians (aged 20 years and older) live with ischemic heart disease, with approximately 50% of these being women.[2] As there have been significant advances in acute treatment, there are many individuals living with this chronic condition, who require comprehensive management to optimize their quality and quantity of life. Cardiac rehabilitation (CR) is a recommended model of care to mitigate this burden.[3]

Meta-analysis of CR trials have demonstrated significant reductions in all-cause mortality and morbidity with participation.[3-5] Based on the evidence, CR referral is a recommendation in clinical practice guidelines for cardiac patients,[6] including those for women with CVD specifically.[7] However, there have been relatively few women in the randomized controlled trials (RCTs) of CR; in the last Cochrane review,[3] only 66% of included trials included women, and women accounted for <15% of total participants.

There have been numerous observational studies which have demonstrated that women achieve similar or even greater improvements than those noted in men with CR participation,[8-10] but these studies often report surrogate outcomes, such as risk factors or health behaviours. There are very few studies, and even fewer randomized studies, reporting the effect of CR on the so-called "hard outcomes" of mortality and morbidity in women.[8] Moreover, there have been several narrative reviews on the benefits of CR in women,[11-14] and a limited number of systematic reviews,[15-17] but a rapid search of the literature reveals no meta-analysis on the effects of CR in women. While it is expected that women would achieve comparable benefits with CR participation as men, it is known that there are some sex differences in terms of the pathophysiology of CVD,[18] the burden of risk factors, the access and impact of acute reperfusion

therapies,[19] and that women are less likely to adhere to CR programs (if they do access it).[19] Therefore a meta-analysis of the effects of CR on mortality and morbidity in women is warranted. The objective of this study was to describe the issues identified in the attempt to perform such a meta-analysis.

Methods

Search Strategy and Data Sources

Systematic reviews, undertaken using the most rigorous, currently-accepted methods, on the benefits of CR have been previously performed. A search for these reviews was performed by an information specialist. Medline (inception through to July 2017) was searched using terms such as "cardiac rehabilitation", "women" and "systematic review". One author (GG) considered the identified citations for inclusion, and another author (SLG) verified selection. Included RCTs in these reviews were considered for this study. The reviews with searches through to the most recent date were considered first, and so on until there was general saturation in identification of unique RCTs.

The full-texts of all the included RCTs identified from the reviews were obtained for inclusion consideration. Where the RCT met criteria but data were not reported in women separately, the corresponding author was contacted to provide this information. The RCT was included where the data were provided.

The end date for the searches in the included reviews was ascertained. An information specialist performed an updated search of the literature from this date to the present in the Medline database. Search terms were derived from the 2016 Cochrane review,[3] but excluded psychotherapy, health education, counseling and self-care.

Inclusion and Exclusion Criteria

(1) Participants: adult women with a cardiac diagnosis indicated for CR as per clinical practice guidelines were included.[6,7]

(2) Intervention: only studies where comprehensive CR was offered were included. This was defined as a program which offered: (1) initial assessment, (2) structured exercise, and (3) at least one other strategy to control CV risk factors (i.e., nutrition counselling, smoking cessation, pharmacotherapy for hypertension or dyslipidemia, stress management). Patients had to receive at least 10 sessions.

(3) Comparison: studies had to include a control (e.g., enhanced usual care) or comparison (e.g., home-based provision of CR components) arm.

(4) Outcomes: all-cause and CV mortality, all-cause and CV hospitalization, non-fatal myocardial infarction (MI), and coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI).

Non-English publications were not considered. These criteria are consistent with those in the Cochrane review, however RCTs offering exercise-only CR were excluded, as were those comprised of all male samples.

Study Selection

One (GG) author considered trials identified in previous reviews for inclusion, and considered recent citations identified through the search for inclusions. The senior author was consulted where there was uncertainty or disagreement. Plans for data extraction, quality assessment and analysis are shown in the Supplemental Appendix.

Results

The initial search identified 11 systematic reviews which were considered. Ultimately 2 on the effects of CR on mortality and morbidity were selected,[3,5] from which RCTs were then considered.

Excluding duplicates, they included 80 unique RCTs (see supplemental appendix for citations). Of these, 30 met our inclusion criteria. Table 1 displays a list of these studies, and reasons for exclusion of the other 50 trials. As shown, 18 (22.5%) were excluded because they included only men in their sample, 10 (12.5%) were exercise-only CR, 9 (11.3%) for not reporting on the outcomes under investigation, 5 (6.3%) did not include any exercise component, in 3 (3.8%) patients were referred to CR in both arms, 3 (3.8%) did not offer CR, and 1 (1.3%) each was not in English and had < 10 sessions.

The searches from these reviews[3,5] went to July 2014. The new search from that point through to July 2017 yielded 694 records. Upon consideration of these citations, one trial was included.

Of the 31 trials that met our inclusion criteria, one reported data in women. All other corresponding authors were emailed, and non-responders re-emailed on four occasions, with an interval of 4 months between the first and the last contact. We searched for alternate email addresses through Google and ResearchGate where we received a delivery failure message. We attempted to contact co-authors where the corresponding author did not respond after 2 emails. For all studies, a valid email address was secured (i.e., no delivery failure message). As shown in Table 1, 21 (67.8%) did not respond following these multiple attempts, 8 (25.8%) responded that they did not have the data to provide, and 2 (6.5%) provided the data.[20,21] It was deemed inappropriate to pool the data with only two studies.

Discussion

This initial attempt at a meta-analysis on the benefits of CR in women on mortality and morbidity has corroborated the dearth of available data in this population. Granted herein only trials of comprehensive CR were considered (and perhaps in future criteria should be expanded to include exercise-only programs as herein 14 studies were excluded on this basis, however many were dated), but the lack of reporting of data by sex in any trial and provision of data in only 1 RCT is deplorable. Some of the trials were quite old, and hence data were likely destroyed in the interests of privacy or due to the fact that historically ethical regulations for data storage and retention were not as robust as they are contemporarily. It is assumed that many of the non-responding authors also did not have the data available by sex, given 16 (76.2%) of these studies were undertaken before 2010. However, given the open nature of science, it was discouraging that many authors failed to reply and that authors of recent trials did not have the data available by sex.

Given the benefits of CR demonstrated in women in non-randomized studies with larger sample sizes (which also have greater external validity), and on proximate (e.g., risk factors, functional capacity) and patient-reported outcomes (e.g., mental health, quality of life),[15-17], it is contended that CR does improve outcomes in women. Thus, recommendations for women to participate in CR should remain.[7] Women continue to be significantly less likely than men to be referred (39.6% versus 49.4%, respectively),[22] enrol (38.5% versus 45.0%),[23] and adhere (64.2% of prescribed sessions versus 68.6%)[19] to CR. Proven strategies to increase CR utilization in men and women include structured contacts or counselling by healthcare providers, motivational letters, and early access.[24] Strategies to increase utilization in women include systematic referral,[25] peer navigation, physician endorsement, gender-tailored programming, alternative delivery settings, and motivational letters.[15]

There is a growing recognition in Canada and beyond that the integration of sex and gender into health research strengthens the overall health evidence base, facilitates specificity in health policies and planning, allows clinicians to better tailor care to individuals, and in so doing, contributes to the attainment of health equity goals globally.[26-28] Clearly there is an urgent need to undertake CR trials where women are better-represented, and in which data are reported by sex.

Given the level of evidence of benefit of CR (Class I, Level A),[6,29] it is no longer ethical to undertake a trial where patients are randomized to usual care. This would not be approved by a research ethics board in Canada, or other jurisdictions where CR is appropriately implemented. Trials with comparison arms where CR is offered in an alternate setting such as home-based with the use of information and communications technology is an option, but the required power to show benefit would be impracticable. To amass needed evidence, perhaps trials should be undertaken in under-resourced countries where the majority of patients cannot access CR.[29,30] By offering such a trial, more patients would actually receive guideline-recommended CR care through randomization. In addition, the benefits of this cost-effective model of care could be more strongly established in these settings where the burden of CVD has been growing to epidemic proportions,[1] which would support broader delivery.

In conclusion, this review corroborates the dearth of women in CR trials and the lack of reporting of outcomes by sex. We were unable to collate sufficient data to test the benefit of comprehensive CR participation on mortality and morbidity in women, despite the fact that it is their leading cause of death. Given the totality of evidence, however, including reductions in mortality and morbidity in non-randomized studies, and evidence of benefit for other important outcomes such as functional capacity and quality of life, it is contended that CR does improve

outcomes in women. Therefore, women should continue to be referred and encouraged to enrol and adhere to these programs. Ethically-conducted trials are needed to rigorously establish the benefits of CR on mortality and morbidity in women.

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Declaration

All authors have read and approved of the manuscript.

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Table 1: Potentially-eligible trials, N=80

Reference	Reason for exclusion
Astengo (2010)*	Not comprehensive CR
Brotons (2011)*	Intervention consisted of individual counselling sessions only (no exercise)
Carrington (2013)* ‖	Patients in both arms referred to CR, and outcome reporting does not take this into consideration
Cohen (2014)*	Not comprehensive CR
Haglin (2011)* §	Authors did not provide data for women only
Hawkes (2013)* §	Authors replied the data are not available
He (2012)*	Article in Chinese
Janssen (2014)*	Motivational counselling (no exercise)
Jorstad (2013)* §	Authors replied the data are not available
Krebs (2013)* §	Authors did not provide data for women only
Moreno-Palanco (2011)*	Nurse-led visits with education and counselling (no exercise)
Mosca (2010)* ‖	Patients in both arms referred to CR, and outcome reporting does not take this into consideration
Pinto (2011)*	Interventions after CR
Reid (2012) online programme*	Online programme for patients who did not want to participate in CR
Reid (2012) phone counselling*	Motivational counselling intervention to patients not intending to attend CR
Saffi (2014)*	Nurse-led lifestyle counselling (no exercise)
Stewart (2015)* ‖	Patients in both arms were not restricted from attending CR, and outcome reporting does not take this into consideration
West (2012) *†	Insufficient CR dose
Andersen (1981)†	Only men
Aronov (2010) † §	Authors did not provide data for women only

Bäck (2008) † §	Authors replied the data are not available
Belardinelli (2001) †§	Authors did not provide data for women only
Bell (1998) †§	Authors did not provide data for women only
Bengtsson (1983) † §	Authors did not provide data for women only
Bertie (1992) †	Not comprehensive CR
Bethell (1990) †	Only men
Bettencourt (2005) †	Mortality or morbidity not reported
Briffa (2005) †	Authors did not provide data for women only
Carlsson (1998) †§	Authors did not provide data for women only
Carson (1982) †	Only men
DeBusk (1994) †§	Authors did not provide data for women only
Dugmore (1999) †	Not comprehensive CR
Engblom (1996) †	Mortality or morbidity not reported
Erdman (1986) †	Only men
Fletcher (1994) †	Only men
Fridlund (1991) †§	Authors did not provide data for women only
Giallauria (2008) †§	Authors did not provide data for women only
Hambrecht (2004) †	Only men
Haskell (1994) †§	Authors replied the data are not available
Heller (1993) †§	Authors replied the data are not available
Higgins (2001) †§	Authors did not provide data for women only
Hofman-Bang (1999) †§	Authors did not provide data for women only
Holmbäck (1994) †	Not comprehensive CR
Houle (2012) †‖	Mortality or morbidity not reported and not comprehensive CR
Kallio (1979) †§	Authors did not provide data for women only
Kovoor (2006) †§	Authors did not provide data for women only
La Rovere (2002) †	Only men
Leizorovicz (1991) †	Only men
Lewin (1992) †	Mortality or morbidity not reported
Maddison (2014) †	Mortality or morbidity not reported

Manchanda (2000) †	Only men
Marchionni (2003) †	Mortality or morbidity not reported
Maroto (2005) †	Only men
Miller (1984) †	Only men
Munk (2009) †§	Authors did not provide data for women only
Mutwalli (2012) †	Only men
Oerkild (2012) †§	Authors did not provide data for women only
Oldridge (1991) †§	Authors did not provide data for women only
Ornish (1990) †§	Authors replied the data are not available
Reid (2012) †	Not comprehensive CR
Roman (1983) †	Not comprehensive CR
Sandström (2005) †	Not comprehensive CR
Schuler (1992) †	Only men
Seki (2003) †	Only men
Seki (2008) †	Only men
Shaw (1981) †	Not comprehensive CR
Sivarajan (1982) †§	Authors did not provide data for women only
Specchia (1996) †§	Authors did not provide data for women only
Ståhle (1999) †	Not comprehensive CR
Stern (1983) †	Not comprehensive CR
Toobert (2000) †§	Not applicable
Vecchio (1981) † ‖	Only men + Not comprehensive CR
Vermeulen (1983) †	Only men
Vestfold Heartcare Study Group (2003) †§	Not applicable
Wang (2012) †§	Authors did not provide data for women only
WHO (1983) †	Only men
Wilhelmsen (1975) †	Not comprehensive CR
Yu (2003) †	Mortality or morbidity not reported

Yu (2004) †§	Authors did not provide data for women only
Zwisler (2008) †§	Authors replied the data are not available

*Trial from van Halewijn et al. (2017)[5]
†Trial from Anderson et al. (2016)[3]
§considered for inclusion
||more than one reason for exclusion
CR: cardiac rehabilitation

Supplemental Appendix

Data Extraction Process and Quality Assessment

It was planned that one (GG) author would extract data from included studies. A second author would check the data extraction (GC). The senior author would be consulted where there was uncertainty or disagreement.

Risk of bias in included studies was to be considered as per the Cochrane approach,[1] except blinding of participants and personnel was not going to be considered (not possible in CR trials). Ratings made for the previously-identified trials were going to be adopted.

Data Analysis

We planned to analyze outcomes as risk ratios (RR) using 95% confidence intervals (CIs). To perform the meta-analysis, we planned to use RevMan 5.3[2]. Where heterogeneity was determined to be moderate or greater, as indicated by an I^2 greater than 40%, we planned to perform a random-effects model with the DerSimonian-Laird method.[3] Otherwise, a fixed-effect model was planned.

Heterogeneity of study results was to be evaluated by looking at the forest plots in order to detect non-overlapping CIs, with the application of the Chi^2 test (with a p-value < 0.10 to indicate statistical significance) and by applying the I^2 statistic. According to the Cochrane Handbook[25] values up to 40% indicate that the heterogeneity may not be important, while values between 30% and 60% indicate moderate heterogeneity, between 50% and 90% substantial heterogeneity, and between 75% and 100% considerable heterogeneity.

Subgroup analysis was planned to explore significant heterogeneity, performed in a consistent manner with the latest Cochrane review in this area.[4] Finally, to examine small study bias, an examination of funnel plots was planned and the Egger test.[3]

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