Research Letter

Cardiac Rehabilitation Effectiveness for Coronary Artery Disease by Clinical Era: Trial Sequential Analysis

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Cardiac rehabilitation (CR) is an outpatient model of care for the secondary prevention of cardiovascular disease, which is widely and strongly recommended in international clinical guidelines. The latest update of the Cochrane systematic review on CR for patients with coronary artery disease[1] found that CR is effective in preventing cardiovascular death and hospital admissions, but not all-cause mortality, reinfarctions and other complications, as reported in the previous update. This could be due to the inclusion of more recent trials. Thanks to advances in medicine, patients now have access to acute revascularization treatments such as thrombolysis and angioplasty, and therefore achieve better outcomes, such that some have hypothesized that CR may have less impact in the current clinical era[2]. Although the Cochrane review included a meta-regression which showed no impact of the publication year on the effectiveness,[1] some others meta-analyses in the field that have included only recent trials,[2,3] have contradicted this finding.

In this context, we conducted a secondary analysis of these trials with the aim of examining whether there is sufficient data to determine effectiveness of CR on all-cause and cardiovascular mortality as well as hospitalization, and to test effectiveness over time, using trial sequential analysis (TSA) for the first time. With sequential analysis, it is possible to determine the need for more trials or whether the results are conclusive.[4] Such analysis allows the effect to be observed as the participants in the primary studies accumulate even if the optimal sample size has not been reached, adjusting the threshold of statistical significance as the sample size is accumulated. [5]

Randomized clinical trials (RCTs) of CR versus usual care were identified in previous reviews by Anderson 2016[1] and Powell 2018,[2] and an update of the same search strategy was performed to December 28, 2019 to identify further trials. Two reviewers independently screened citations identified by title and abstract, and then the full-text of potentially-eligible new trials.

Trial characteristics, risk of bias using the Cochrane tool (v1), and data related to the outcomes of interest were extracted for each RCT from the reviews.[1,2] The plan was to extract these same variables

from the RCTs identified in the search update. The GRADE approach was utilized for rating the overall evidence quality by outcome.[6] We defined three temporal eras considering the moment when the main therapeutic milestones were introduced: post-angioplasty era (2000 onwards RCTs), post-thrombolysis era (1990 onward RCTs), and all eras (all RCTs available).

In total, 9 TSAs were performed using the TSA Software© of the Copenhagen Trial Unit. For each of the 3 eras, a sequential analysis was conducted for each of the 3 outcomes of interest, using the data from the longest participant follow-up. For each, the analyses were performed as follows: First, the optimal sample size was calculated for each outcome and era. At this stage, the incidence of events per arm from the Anderson review[1] was considered, and the result was adjusted according to the sample size already available in each era. Next, to determine whether CR is effective, the effectiveness boundaries were assessed and adjusted using the O'Brien-Fleming α-spending function. To determine if there is no CR effectiveness, the futility boundaries were tested and established before the optimal sample size was reached by the data of the meta-analysis. For each, random-effects models were computed, and the relative risk (RR) was used as a measure of effect with its 95% confidence interval (CI). To manage groups with zero events, the method of the constant was used at a value of 0.5.

Fifty-nine RCTs were included (Supplement 1); none from the search update (Supplement 2). The RCTs comprised 15036 patients, of mean age ranging 47.5-76.9 years; participants were predominantly male (>75%). As per the previous reviews,[1] the overall risk of bias was low to moderate, with generally low risk of reporting bias, low or no clear risk of selection bias and high risk of attrition bias (Supplemental 3).

Results from this sequential analysis confirmed no effect of CR on all-cause mortality across time. CR was associated with reduced cardiovascular mortality, particularly in the angioplasty era [Relative Risk (RR) =0.48; 95%CI = 0.28-0.83 (10 RCTs; 1,314 participants; moderate quality of evidence)]

and confirmed for all eras [RR=0.75; 95%CI =0.65-0.86 (28 RCTs; 7,469 participants; low quality of evidence)]. Finally, a protective trend was observed for hospital admissions for all eras. A summary of findings is shown in Table 1 and Figure 1 displays all TSAs, by era and outcome of interest.

Caution is warranted in interpreting these results. Some included trials comprised only exercise, some had quite low dose, considerable follow-up losses, or short follow-up among other limitations, which may have impacted all-cause mortality findings. Moreover, many trials had quite active usual care arms, where CR components are offered,[7] which would minimize the difference between groups. Indeed, a recent network meta-analysis where components in intervention and comparison arms were carefully coded revealed a significant effect of CR in reducing all-cause mortality;[8] similarly the review by van Halewijn et al.[3] showed that more comprehensive programs were effective in reducing all-cause mortality. Another factor to be taken into account is that implementation of thrombolysis and angioplasty likely varied somewhat in the various countries where the trials were performed.[8] Finally, the context of most of the trials included in this analysis was tertiary care centers in high-income countries, limiting generalizability.

Given the current state of knowledge, it may be wasteful[9] to continue conducting clinical trials that compare effects of standard CR versus usual care on mortality in western/ high-income contexts or predominantly male samples, the setting and sample to which these trials generalize. On the other hand, there is insufficient data to demonstrate the impact of CR on hospital admission in general and on mortality and morbidity in women.[10]

In conclusion, the results of this first sequential analysis buttress the recommendations in multiple international clinical guidelines to refer patients with coronary artery disease to CR, as it is an effective intervention in robustly preventing cardiovascular mortality (including in the current era) and probably re-hospitalization.

DECLARATIONS OF INTEREST

All authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

MJO and PS contributed to the conception or design of the work. DB contributed to the acquisition and searching of studies. PS and MJO contributed to the acquisition, analysis and interpretation of data and drafted the manuscript. SG contributed to the drafted manuscript and critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Table 1. Summary of results by era and outcome**.**

		Post- Angioplasty Era (since 2000)	Post-Thrombolysis Era (since 1990)	All Eras
All-Cause Mortality	Number of RCTs	19	36	47
	Actual Sample Size	4235	8285	11931
	Relative Risk (95% CI)	0.79 (0.49 to 1.26)	0.89 (0.65 to 1.22)	0.96 (0.89 to 1.04)
	Inconsistency (I^2)	0.0	0.0	0.0
	Optimal Sample Size	6039	15039	16039
	Reaches effectiveness boundary	NO	NO	NO
	Reaches Futility Limit	YES (18° RCT of 19)	YES (34° RCT of 36)	YES (42° RCT of 47)
	Evidence Certainty (GRADE)	⊕◯◯◯ VERY LOW[1-2]	⊕◯◯◯ VERY LOW[1-2-3]	⊕⊕◯◯ LOW[1]
Cardiovascular Mortality	Number of RCTs	10	18	27
	Actual Sample Size	1314	3282	7469
	Relative Risk (95% CI)	0.48 (0.28 to 0.83)	0.67 (0.48 to 0.94)	0.75 (0.65 to 0.86)
	Inconsistency (I^2)	0.0	0.0	0.0
	Optimal Sample Size	2000	4650	11714
	Reaches effectiveness boundary	YES (10° RCT of 10)	NO	YES (15° RCT of 29)
	Reaches Futility Limit	NO	NO	NO
	Evidence Certainty (GRADE)	⊕⊕⊕◯ MODERATE[3]	⊕⊕◯◯ LOW[1-3]	⊕⊕◯◯ LOW[1-3]
Hospital Admission	Number of RCTs	10	14	15
	Actual Sample Size	1597	2293	2944
	Relative Risk (95% CI)	0.76 (0.57 to 1.00)	0.79 (0.66 to 0.94)	0.83 (0.71 to 0.96)
	Inconsistency (I^2)	0.4	0.3	0.3
	Optimal Sample Size	2850	3850	3850
	Reaches effectiveness boundary	NO	NO	YES (15° RCT of 15)
	Reaches Futility Limit	NO	NO	NO
	Evidence Certainty (GRADE)	⊕⊕⊕◯ MODERATE[1]	⊕⊕◯◯ LOW[1-3]	⊕⊕◯◯ LOW[1-3]

RCT= Randomized Clinical Trial

Explanations to degrade the quality of evidence (GRADE):

1 *The domains: incomplete data, intention to treat analysis and without co-interventions were frequently underreported or assessed as high risk of bias.*

2 *Although the sample size is very large, the CI overlaps no effect rate and fails to exclude important benefit or important harm*

3 *Random sequence generation, allocation concealment or blinding of outcome assessors were poorly described in around 50% of included studies.*

Figure 1. Trial sequential analysis by era for all-cause mortality (A), for cardiovascular mortality (B), and for hospital admission (C).