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Exercise-based cardiac rehabilitation for coronary heart disease: a meta-analysis

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Introduction

✓Coronary heart disease (CHD) is the most common cause of death globally.

✓Exercise-based cardiac rehabilitation (**CR**) is recognized as a **key component** of comprehensive CHD **management** and is a **Class I Grade A** recommendation in international guidelines.
✓Although meta-analyses of randomized controlled trials (RCTs) have shown the beneficial effect of CR in patients with CHD.

کنفرانس علمی:

آشنایی با بازتوانی /توانبخشی قلبی در بیماران پس از سندروم حاد کرونری و عمل جراحی قلب

دکتر طوبی کاظمی

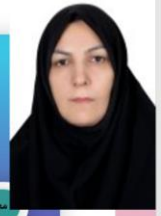
جنرال کاردیولوژیست

مرکز تحقیقات بیماری های قلب و عروق

دکتر سید علی معزی

اینترونشنال کاردیولوژیست

مرکز تحقیقات بیماری های قلب و عروق



محل برگزاری کنفرانس: سالن امفی تئاتر بیمارستان رازی

تاریخ برگزاری کنفرانس: ۱۴۰۱/۰۴/۲۳ - ساعت ۱۰-۸

گروه های هدف:

پرستاران – همکاران کاردرمان و فیزیوتراپ

پیشگیری ثالثیه در بیماران قلبی

- ✓ بازتوانی قلبی ،برنامه جامع و بلندمدت شامل ارزیابی پزشکی، ورزش تحت نظارت، اصلاح فاکتور خطر قلبی، آموزش و مشاوره است.

Value of Cardiac Rehab

Interventions	NNT	Lives saved per 1000 patients
Anti-platelets	153	6.5
ACE inhibitors	108	9.2
Statins	94	10.5
Beta blockers	42	24
Cardiac rehab	37	27

Sources: Created by Kaiser Permanente using the following sources. For anti-platelets, statins, beta blockers: HT Ong, "Beta Blockers in hypertension and cardiovascular disease", BMJ 2007. For ACE inhibitors: HT Ong, "Angiotensin-Converting Enzyme Inhibitors (ACEIs)...: A Meta-Analysis of 10 Randomised Placebo-Controlled Trials", ISRN Cardiology, 2013.

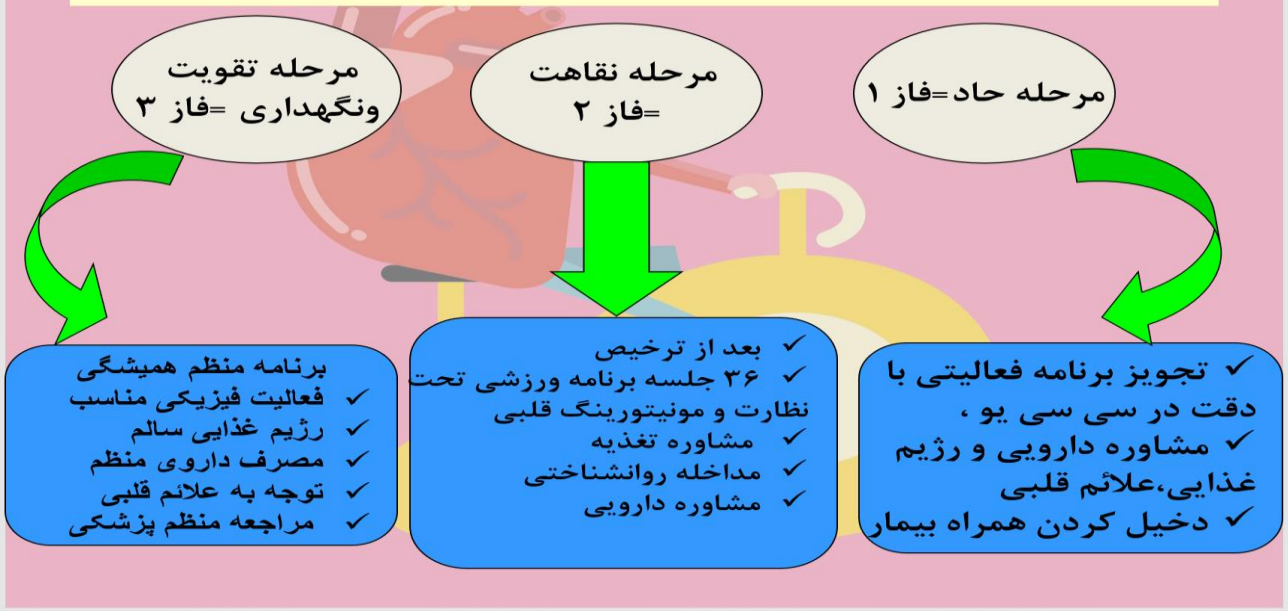
چه کسانی از بازتوانی سود می برند

- متعاقب انفارکتوس میوکارد
- آنژین صدری پایدار
- جراحی بای پس عروق کرونر(CABG)
- آنژیوپلاستی کرونر (PCI)
- نارسایی قلبی پایدار ناشی از اختلال عملکرد سیستولی یا دیاستولی (کاردیومیوپاتی)
- پیوند قلب
- جراحی دریچه های قلب
- بیماران عروق محیطی (PAD)
- بعد از هر عمل جراحی قلب
- بیماران با پیس میکر و ICD
- بیماران با فاکتور خطر قلبی مانند فشارخون و دیابت **جهت پیشگیری** از بیماری قلبی

زمان شروع بازتوانی قلبی

- ✓هر چه سریعتر بهتر
- ✓براساس استاندارد معاونت درمان وزارت بهداشت ایران :
  بیمارانی که بعد از PCI به عنوان مثال **۷۲ ساعت بعد از PCI** یا **دو هفته** بعد از CABG به شرطی که بیمار دچار عارضه ای نبوده و کاملا پایدار باشد.
- ✓بعد از **یکسال** از مداخله قلبی ، دیگر بیماران از بازتوانی قلبی سودی نمی برند.

مراحل بازتوانی بیماران قلبی



کنتراندیکاسیون بازتوانی قلبی

- ✓ آنژین صدری ناپایدار
- ✓ هیپرتانسیون کنترل نشده یعنی فشارخون سیستولی۱۸۰/۱۱۰< میلیمترجیوه
- ✓ افت ارتوستاتیک فشارخون بیش از ۲۰ میلیمتر جیوه همراه با علائم
- ✓ تنگی شدید آئورت (سطح دریچه آئورت کمتر از یک سانتی متر مربع)
- ✓ آریتمیهای دهلیزی یا بطنی کنترل نشده
- ✓ تاکیکاردی سینوسی کنترل نشده (بیش از ۱۲۰ ضربان در دقیقه)
- ✓ بلوک درجه ۳ دهلیزی بطنی بدون پیس میکر
- ✓ پریکاردیت یا میوکاردیت حاد
- ✓ آمبولی اخیر
- ✓ ترومبوفلبیت حاد
- ✓ بیماری سیستمیک یا تب حاد
- ✓ دیابت کنترل نشده
- ✓ اختلالات ارتوپدیک شدید که مانع ورزش می شوند
- ✓ سایر بیماریهای متابولیک نظیر تیروئیدیت حاد، هیپوکالمی، هیپرکالمی یا هیپوولمی (تا زمانی که به حد کافی درمان شوند.
- ✓ دپرسیون شدید

Introduction

This evidence base has been questioned on the grounds of:

✓ (i) **uncertainty** in the impact on **mortality**;

✓(ii) **lack** of data on health-related **quality of life** (HRQoL);

✓(iii) inclusion of **RCTs limited to** **low-risk** patients and conducted in **high-income** country settings,

✓(iv) **lack** of trials conducted during the era of **modern** CHD **therapy**.

Introduction

To address these uncertainties,

- ✓ we undertook a contemporary update
- ✓ of the Cochrane systematic review and meta-analyses of RCTs
- ✓ to assess the effects of exercise-based CR in patients with CHD on :

i. mortality
ii. clinical events
iii. HRQoL
iv. cost-effectiveness.

- ✓ We also sought to explore whether intervention effects varied with patient case mix, study and intervention characteristics, and CR delivery settings.

Methods: Search strategy and study selection

- ✓ We undertook update literature searches of

i. Cochrane Central Register of Controlled Trials (CENTRAL),
ii. MEDLINE
iii. Embase
iv. CINAHL
v. Science Citation Index

- ✓ Expanded from June 2014 to September 2020 (strategy provided in Supplementary material online, File S1).
- ✓ We also searched two clinical trials registers (World Health Organization's International Clinical Trials Registry Platform and ClinicalTrials.gov), and hand-searched reference lists of retrieved articles and recent systematic reviews.

Methods: Search strategy and study selection

- ✓ Records collected from trial registry searches were used to identify trials not picked up in database searches, as well as ongoing studies.
- ✓ We sought RCTs of exercise-based CR (exercise training alone or in combination with psychosocial or educational interventions) compared with no-exercise or usual care control
- ✓ with at least 6-month post-baseline follow-up outcome measures.
- ✓ All patients in both the intervention and control groups were generally reported to receive (local or national) guideline recommended medical treatment.
- ○ **Two** reviewers (G.O.D. and J.F.) independently confirmed trial eligibility. **Disagreements** were resolved by discussion or by a third reviewer (R.S.T.), if necessary.

Methods: Patient population

✓ We included

i. adults (≥18 years)

ii. in either hospital-or community-based settings

iii. who had a myocardial infarction (MI) , CABG , PCI), who had angina pectoris or coronary artery disease defined by angiography.

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Methods: Data abstraction and quality appraisal

- ✓ 2 reviewers (G.O.D. and J.F.) independently completed data extraction and assessed study quality using the Cochrane Risk of Bias (ROB) tool
- ✓ was checked by a third reviewer (R.S.T.).
- ✓ Trials were assessed based on

i. random sequence generation
ii. allocation concealment
iii. blinding of outcome assessment
iv. incomplete outcome data
v. selective reporting.

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Methods: Data abstraction and quality appraisal

✓ Information regarding

i. study methods (country, design, follow-up, and setting)
ii. participant characteristics (numbers randomized, age, sex, diagnosis, and inclusion/exclusion criteria)
iii. intervention (exercise mode, duration, frequency, intensity)
iv. control (description, i.e. usual care, no exercise)
v. outcomes
vi. funding sources
vii. notable author conflicts of interest

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Methods : Outcomes and certainty of evidence

✓ Clinical event outcomes included

i. overall mortality
ii. cardiovascular mortality
iii. fatal and/or non-fatal MI (as reported by studies)
iv. CABG, PCI
v. overall hospitalization
vi. CV hospitalization.

✓ Other outcomes included

i. HRQoL
ii. CR costs
iii. cost-effectiveness per quality-adjusted life year (QALY

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Methods : Outcomes and certainty of evidence

- ✓ One reviewer (G.O.D.) assessed the certainty of the evidence using Grading of Recommendations Assessment, evelopment, and Evaluation (GRADE)
- ✓ it checked by a second reviewer (R.S.T.).
- ✓ GRADE assessment was applied to clinical event outcomes (overall and CV mortality, fatal and/or non-fatal MI, CABG, PCI, overall hospitalization, and CV hospitalization) at 6–12 months follow-up, the most frequently reported follow-up time point across trials.
- ✓ Evidence was downgraded from high certainty by one level based on the following domains: limitations in study design or execution (ROB), inconsistency of results, indirectness of evidence, imprecision, and publication bias.

Statistical analysis

- ✓ Outcome data were pooled at the longest reported follow-up three separate time periods:

i. ‘short-term’ (6–12 months),
ii. ‘medium-term’ (13–36 months),
iii. a ‘long-term’ (>36 months) follow-up.

- ✓ Given the level of clinical heterogeneity (variation in CR interventions and populations), we purposively undertook random-effects meta-analyses, using the DerSimonian and Laird random-effects meta-analysis method, assuming that each study estimates a different underlying intervention effect.

Statistical analysis

- ✓ Dichotomous outcomes (overall and CV mortality, MI, CABG, PCI, and all-cause hospitalization, and CV hospitalization) are expressed as risk ratios (RRs) with 95% CI.
- ✓ For those clinical event outcomes with significant risk reductions, we calculated the number needed to treat for an additional beneficial outcome (NNT).

Statistical analysis

- ✓ Where ≥2 trials reported the same validated HRQoL measures and domains [i.e. Short-Form-36 (SF-36), EuroQol-5D (EQ-5D)], continuous outcomes were pooled separately by each scale and reported as the mean difference (MD) and 95% CI.
- ✓ Given the heterogeneity in HRQoL outcome measures and reporting, for comprehensiveness, we used a vote-counting approach to synthesis in addition to meta-analyses, where the number of positive, negative, and non-significant results was summed.
- ✓ Cost-effectiveness data were synthesized narratively.
- ✓ Statistical heterogeneity was considered substantial where I2 statistic >50%.
- ✓ For outcomes with ≥10 trials included in the meta-analysis, we used the funnel plot and Egger's test to examine small study bias.

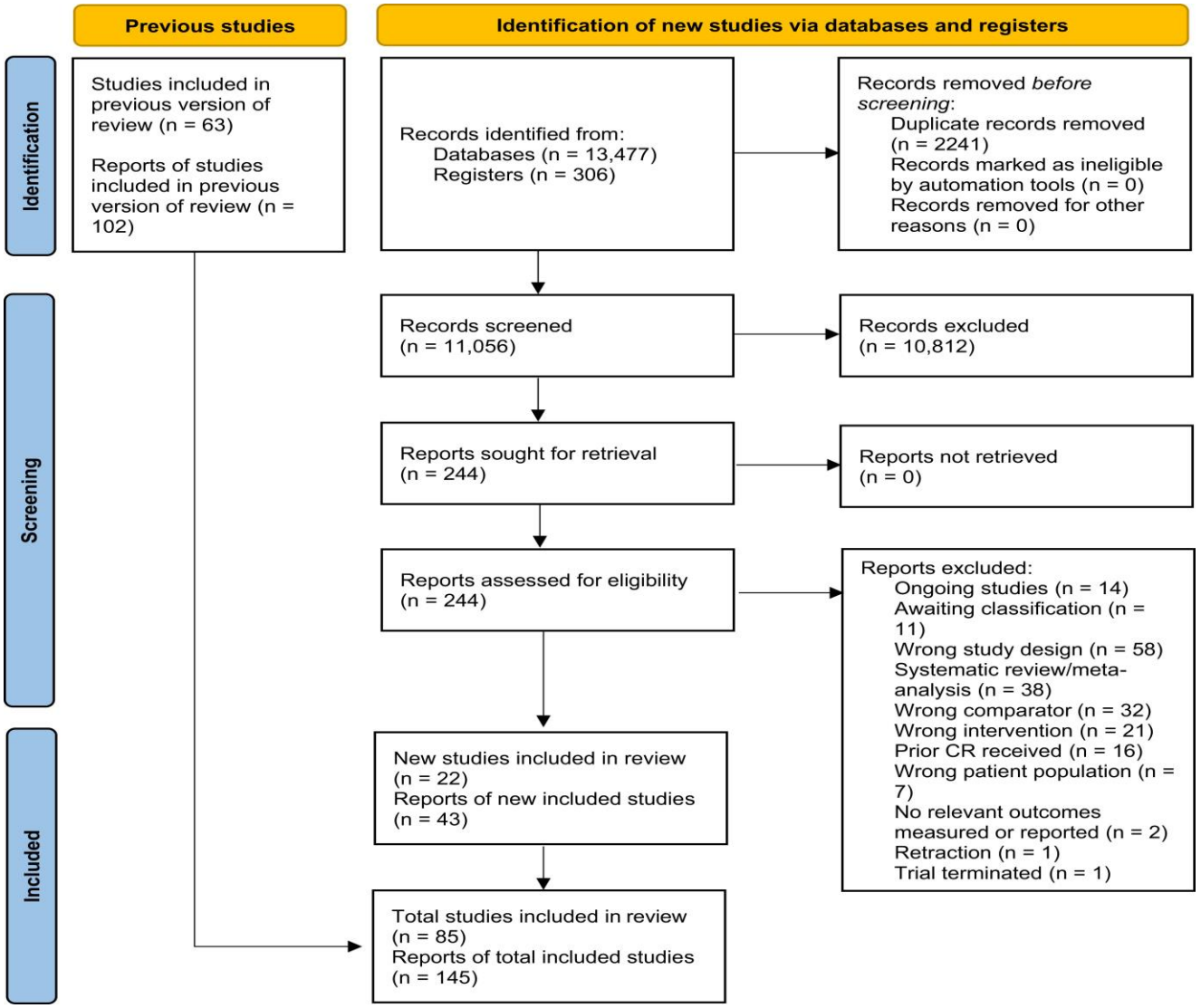
Statistical analysis

- ✓ The two-sided P-values <0.05 were considered statistically significant.
- ✓ A univariate random-effects meta-regression was used to explore heterogeneity and examine the following pre-defined treatment effect modifiers across clinical event outcomes only: (i) case mix (patients percentage presenting with MI), (ii) 'dose' of exercise [dose (units) = number of weeks of exercise training × average sessions per week × average duration of each session in min], (iii) type of CR (exercise only vs. comprehensive CR), (iv) length of follow-up (longest follow-up used where multiple time points are assessed), (v) publication year, (vi) sample size, (vii) CR setting (home or centre based), (viii) ROB (low in <3 of 5 domains), (ix) study continent (Europe, North America, Australia/Asia, or other), and (x) study country status [low-middle-income countries (LMICs) or high-income countries] according to the World Bank Group18. Given the number of statistical comparisons performed in this review, the results interpretation was primarily based on 95% CIs rather than P-values. Statistical analyses were performed in RevMan Web version 3.12.1 and STATA version 16.1.

Results : Search and selection of studies

- ✓ The search selection process is summarized in Figure 1.
- ✓ Updated database and trial registry searches resulted in a total of 13 783 hits, of which 11 056 unique records were identified, and 244 were selected for full-text review. The main reasons for exclusion were study design (e.g. non-RCT, <6-month follow-up), or use of exercise comparators. The 22 new RCTs (7795 participants; 43 publications),[19–40] identified in this update, provide a total evidence base of 85 RCTs (145 publications, 23 430 participants) comparing exercise-based CR with a no-exercise control group in patients with CHD.[19–103] The participants in the newly included trials represent about one-third of all participants included in this study (33%). A complete list of primary and associated supplementary references for included studies is provided in Supplementary material online, *File S2.*

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection process.



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Results : Search and selection of studies

- ✓ A summary of the study, participant, intervention, and comparator characteristics of the 85 included studies is presented in Table 1.
- ✓ Seventy-nine (93%) of the 85 studies were two-arm parallel RCTs, with four studies comparing more than two arms, (two types of CR vs. control).
- ✓ one study using quasi randomization methods
- ✓ one cluster RCT.
- ✓ 16 of the 22 new trials identified were undertaken in LMICs 0 resulting in a total of 21 RCTs in LMICs.
- ✓ 3 large multicentre trials contributed a total of 8956 participants (~40% overall).

Results : Search and selection of studies

- ✓ The median age of participants across studies was 56 years
- ✓ over the last decade, the percentage of female patients included in trials increased from 11% to 17%.
- ✓ The median CR intervention duration and trial follow-up were 6 and 12 months, respectively.
- ✓ 38 of the 85 (45%) interventions were exercise only
- ✓ 47 (55%) involving multiple components including education (20 trials), psychosocial (7 trials),or a combination of both (16 trials), or other components (i.e. controlled diet, risk factor management, smoking cessation, relaxation;(4 trials).

Results : Search and selection of studies

- ✓ Exercise was typically aerobic, with the inclusion of resistance training reported in 27% trials (23 out of 85).
- ✓ The dose of exercise interventions varied widely, with frequency ranging between 1 and 7 sessions per week, length of sessions ranging between 20 and 90 min, and intensity ranging between 50% and 90% of maximal or peak heart rate, 50%–95% of aerobic capacity, or at a rating of perceived exertion.
- ✓ Of the 21 home-based exercise programmes , 4 were delivered electronically via mobile phones or the internet.

Results :Risk of bias and GRADE assessment

- ✓ The overall ROB of included trials was judged to be low or unclear (see Supplementary material online, Figure S1), and the quality of reporting improved since 2010 (80% of studies had <3 low-ROB domains pre-2010 vs. 55% post-2010).
- ✓ The 30 (35%) trials reported sufficient and appropriate details of random sequence generation,21–25,28–32,34–37,41,45,48,50,56,60,61,65,66,72,77,79,82,97,100,103 and 23 (27%) reported appropriate allocation concealment,21–25,29–31,34,36,45,50,61,65,68,72,77,79,82,85,96,98,103 with 24 (28%) reporting sufficient details of outcome assessment blinding.23–25,28,29,34–36,57,59,60,65,71–74,77,81,82,84,85,98,103 The 38 (44%) trials were assessed to have low-ROB for incomplete outcome data,19,25,26,28,29,32–37,40,42,45,49,50,54,59,60,67,69,70,72,73,75,77,79,83,84,86,95,97,98,101,103 and 62 (73%) had low-ROB for selective reporting.19,23–25,29,34–36,40–68,70–72,74–78,80,82–89,91,92,94–99,101–103 GRADE assessments for the clinical event outcomes at short-term follow-up ranged from low to high (Table 2), downgrading for imprecision (wide CIs), evidence of publication bias, or substantial statistical heterogeneity.

Results :Outcomes

- ✓ A summary of pooled clinical events across all four follow-up time points [longest reported follow-up, short-term (6–12 months), medium-term (13–36 months), and long-term (>36 months)] is presented in Table 2.
- ✓ GRADE assessments for certainty of evidence at short-term (6–12 months) follow-up across clinical event outcomes ranged from low-to-high certainty.
- ✓ We downgraded overall mortality, CV mortality, PCI, and CV hospitalization by one level for imprecision, due to wide CIs that overlapped the boundary with no effect.
- ✓ We downgraded MI and all-cause hospitalization by one level due to evidence of publication bias.
- ✓ We downgraded CV hospitalization by an additional level due to evidence of substantial heterogeneity.

Results :Outcomes

months)

Outcome follow-up time point	*n* participants	*n* studies	*n* events/participants		RR (95% CI)	Statistical heterogeneity I^2 statistic χ^2 test	GRADE assessment of certainty
			Intervention	Comparator			
Overall mortality							
Longest follow-up	16 829	47	919/8608	950/8221	0.96 (0.89–1.04)	0%	
â6–12 months	8823	25	228/4590	242/4233	0.87 (0.73–1.04)	35%	⊕⊕⊕⊖ Moderate[a]
â13–36 months	11 073	16	467/5611	498/5462	0.90 (0.80–1.02)	0%	
â>36 months	3828	11	476/1902	493/1926	0.91 (0.75–1.10)	35%	
CV mortality							
Longest follow-up	7762	26	296/3997	382/3765	0.74 (0.64–0.86)***	0%	
â6–12 months	5360	15	109/2799	114/2561	0.88 (0.68–1.14)	0%	⊕⊕⊕⊖ Moderate[a]
â13–36 months	3614	5	199/1861	39/1753	0.77 (0.63 to 0.93)**	5%	
â> 36 months	1392	8	56/690	100/702	0.58 (0.43–0.78)***	0%	
Fatal and/or non-fatal MI							
Longest follow-up	14 151	39	383/7181	437/6970	0.82 (0.70–0.96)*	9%	
â6–12 months	7423	22	140/3820	174/3603	0.72 (0.55–0.93)*	7%	⊕⊕⊕⊖ Moderate[b]
â13–36 months	9565	12	264/4830	237/4735	1.07 (0.91–1.27)	0%	
â>36 months	1560	10	65/776	102/784	0.67 (0.50–0.90)**	0%	
CABG							
Longest follow-up	5872	29	211/3028	215/2844	0.96 (0.80–1.15)	0%	

Results : Mortality

✓ Of the 60 trials (61 comparisons) that reported overall mortality

i. 13 trials reported zero events in both arms.
ii. There was no difference in risk of overall mortality at short-term follow-up (6–12 months; RR: 0.87, 95% CI: 0.73–1.04, I2 = 0%; moderate certainty evidence) or longest follow-up (47 trials, RR: 0.96, 95% CI: 0.89–1.04, I2 = 0%; Figure 2).

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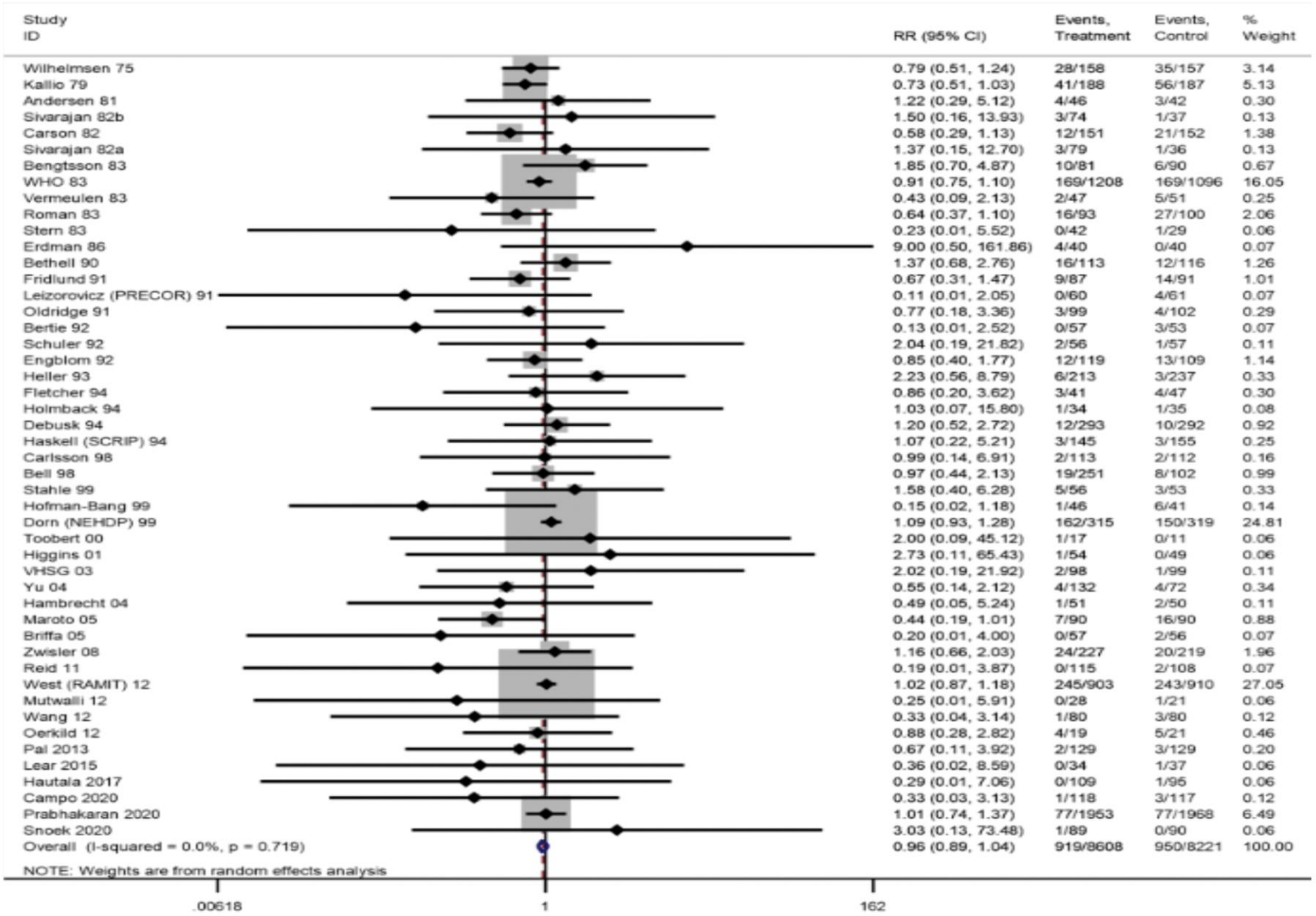
Figure 2 Forest plot: exercise-based cardiac rehabilitation vs. control for overall mortality.



Results : Mortality

✓ Across 33 trials (35 comparisons) reporting CV mortality:

i. 7 trials reported zero events in both arms.

ii. A 26% reduction in risk of CV mortality was seen at longest reported follow-up (26 trials, RR: 0.74, 95% CI: 0.64–0.86, I2 = 0%; Figure 3) with an NNT of 37.

iii. At short-term (6–12 months) follow-up, there was no significant difference in CV mortality (RR: 0.88, 95% CI: 0.68–1.14, I2 = 0%, moderate certainty).

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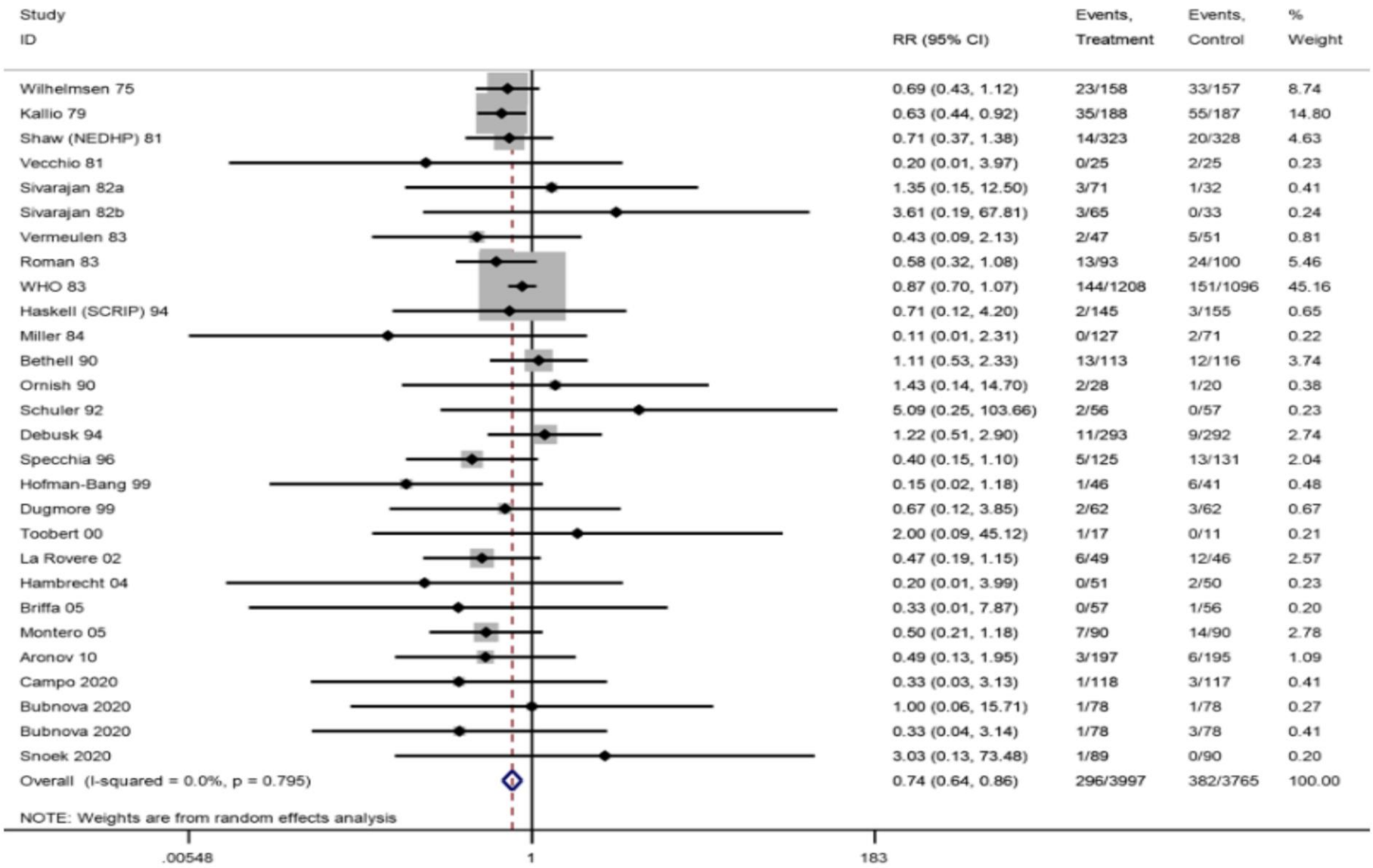
Figure 3 Forest plot: exercise-based cardiac rehabilitation vs. control for cardiovascular mortality.



Results : Fatal and/or non-fatal MI

- ✓ Across 42 trials (44 comparisons) reporting fatal and non-fatal MI:

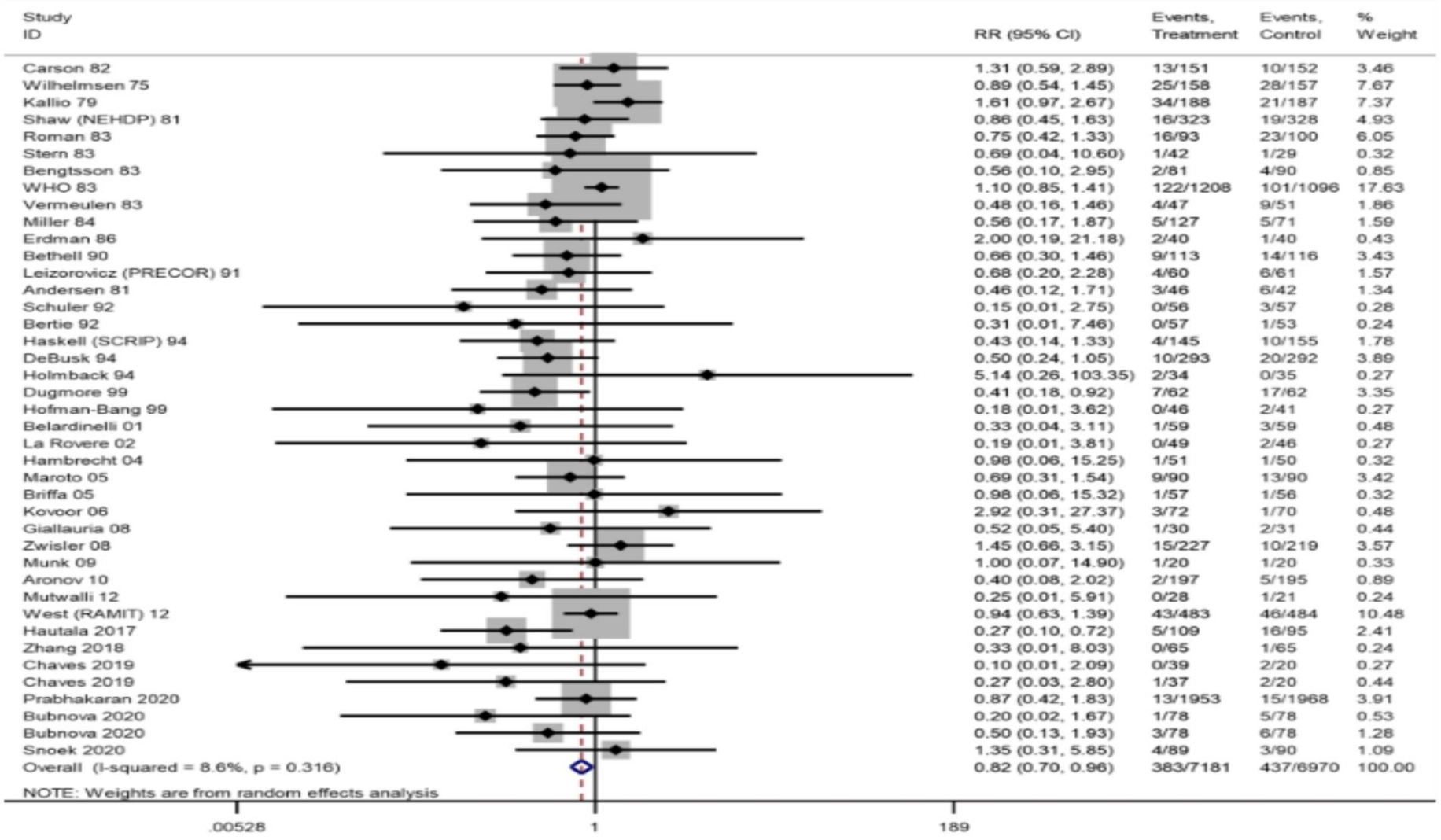
i. 3 trials reported zero events in both arms.

ii. An 18% reduction in risk was shown at longest follow-up (39 trials, RR: 0.82, 95% CI: 0.70–0.96, I2 = 9%; Figure 4) with an NNT of 100.

iii. The overall risk was driven by significant reductions in the short-term (6–12 months; RR: 0.72, 95% CI: 0.55– 0.93, I2 = 7%, high certainty evidence) and long-term (>36 months; RR: 0.67, 95% CI: 0.50–0.90, I2 = 0%)

iv. with no difference in the medium-term follow-up (13–36 months; RR: 1.07, 95% CI: 0.91–1.27, I2 = 0%).

Figure 4 Forest plot: exercise-based cardiac rehabilitation vs. control for myocardial infarction.



Results :Revascularization events

- ✓ Of 31 trials (33 comparisons) reporting CABG:
  - i. 2 trials reported zero events in both arms.
  - ii. There was no difference in risk of CABG at longest follow-up (29 trials, RR: 0.96, 95% CI: 0.80–1.15, I2 = 0%; Figure 5).
- ✓ Of the 20 trials (21 comparisons) reporting PCI:
  - i. 3 trials reported zero events in both arms.
  - ii. There was no significant difference in risk of PCI (17 trials, RR: 0.84, 95% CI: 0.69–1.02, I2 = 0%; Figure 6).

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Figure 5 Forest plot: exercise-based cardiac rehabilitation vs. control for coronary artery bypass graft.

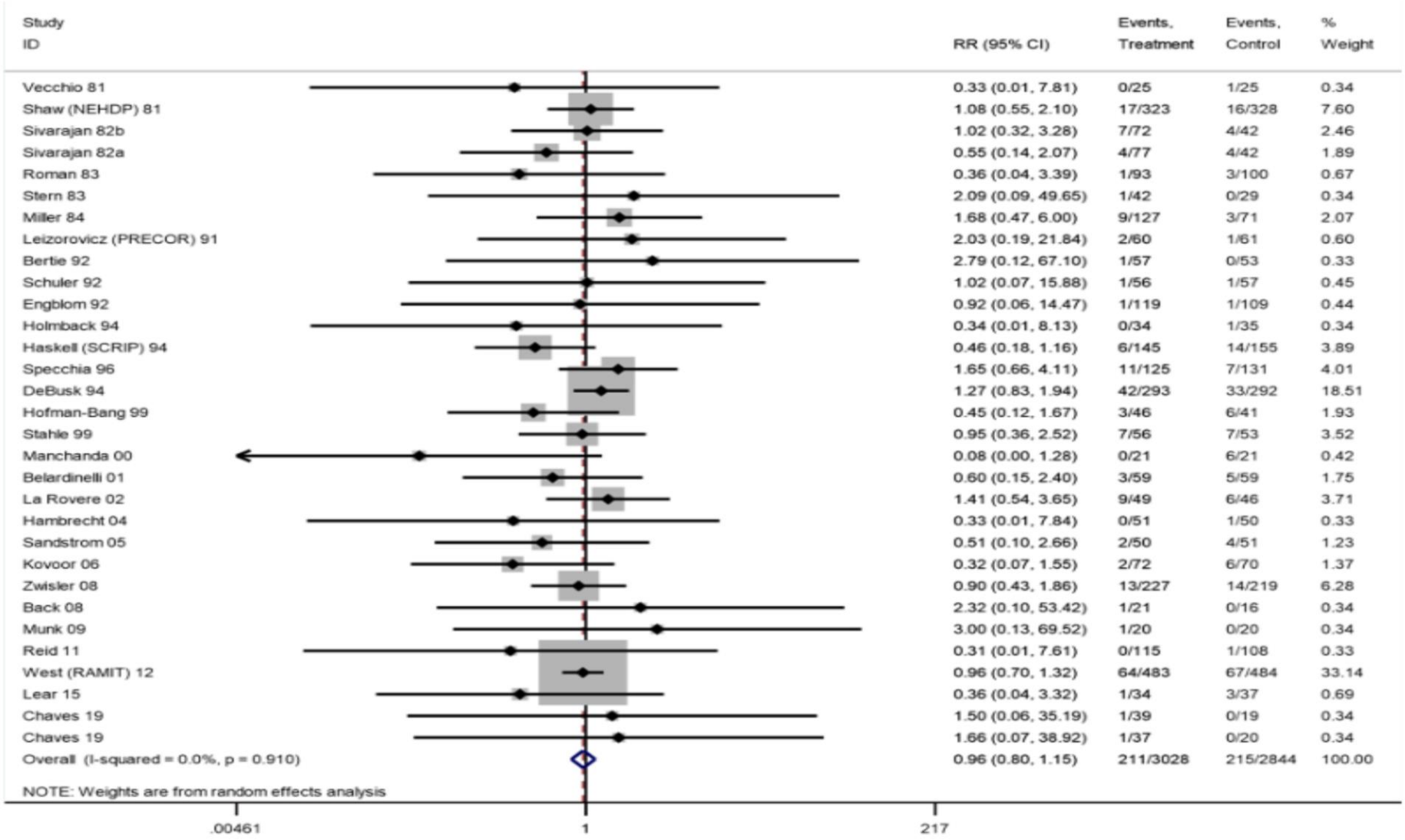
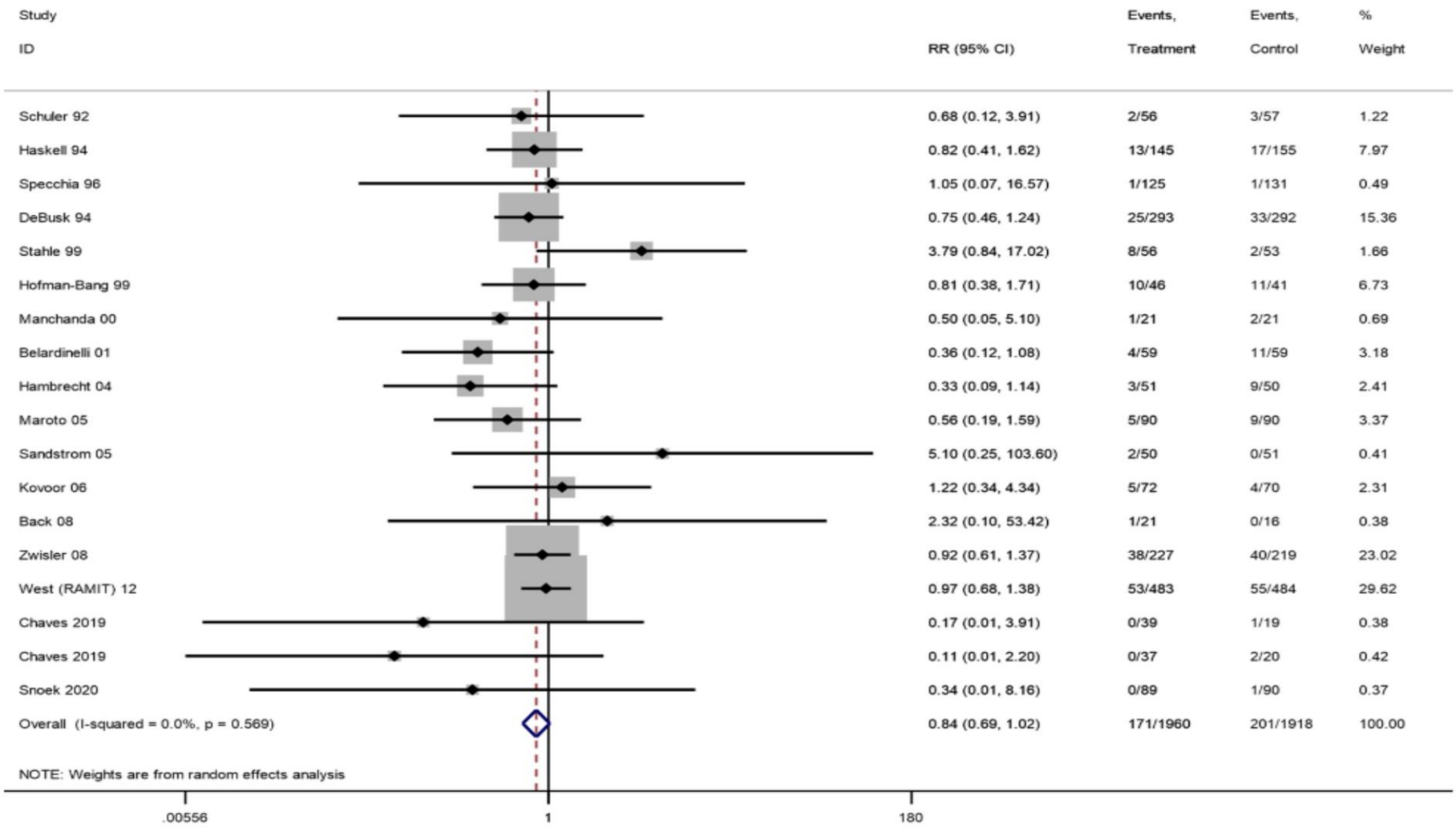


Figure 6 Forest plot: exercise-based cardiac rehabilitation vs. control for percutaneous coronary intervention.



Results : Hospitalization

- ✓ Across 22 trials (24 comparisons) that reported overall hospitalization:

i. 1 trial reported zero events in both arms.

ii. A 23% reduction in overall hospitalization risk with participation in exercise-based CR was shown at the longest follow-up (21 trials, RR: 0.77, 95% CI: 0.67–0.89, I2 = 32%; Figure 7) with an NNT of 37.

- ✓ 9 trials reported CV hospitalizations

i. 1 trial reported zero events in both arms.

ii. There was no significant difference in CV hospitalization at longest follow-up (eight trials, RR: 0.85, 95% CI: 0.67–1.08, I2 = 12%; Figure 8).

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Figure 7 Forest plot: exercise-based cardiac rehabilitation vs. control for overall hospitalization.

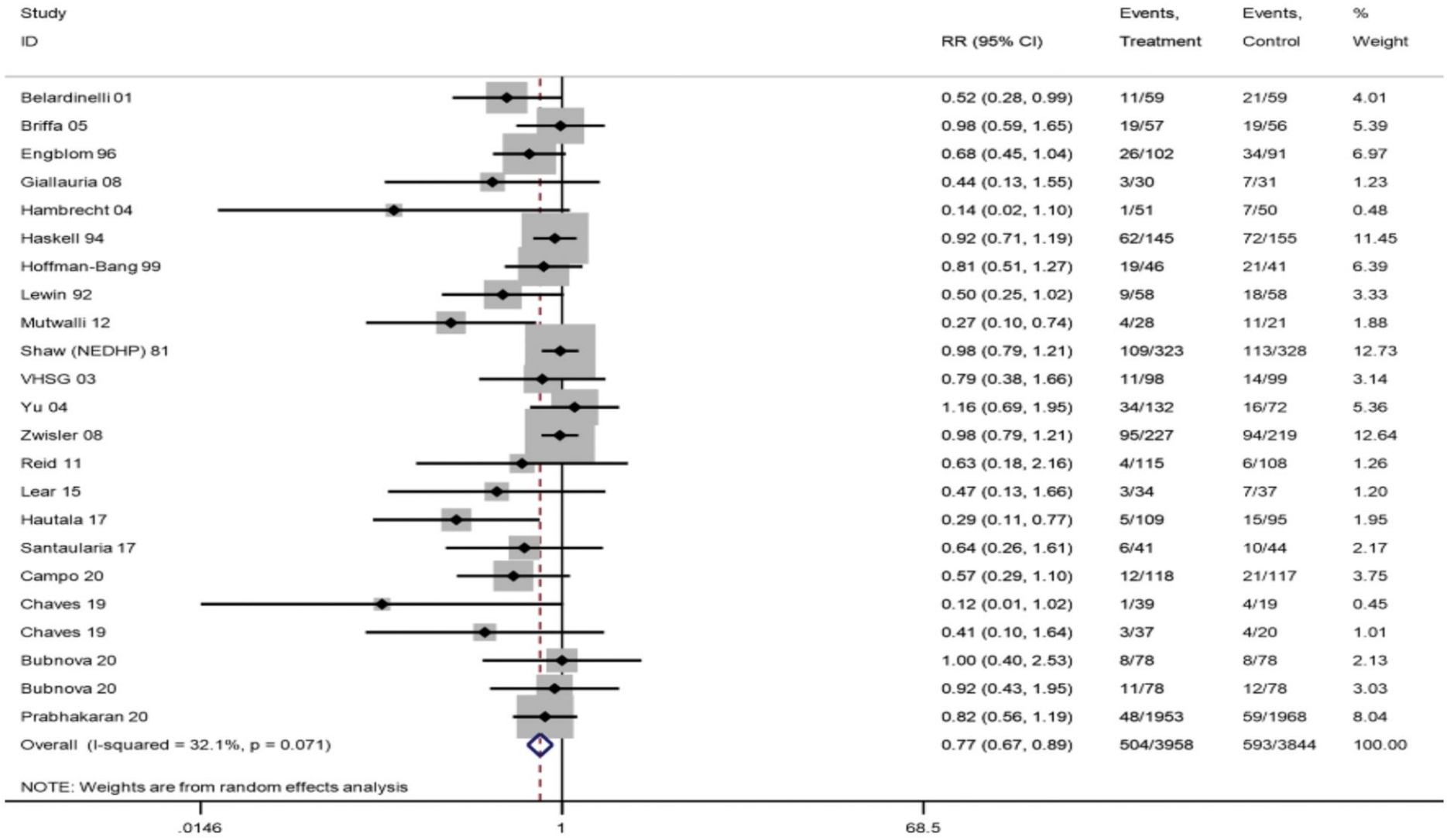
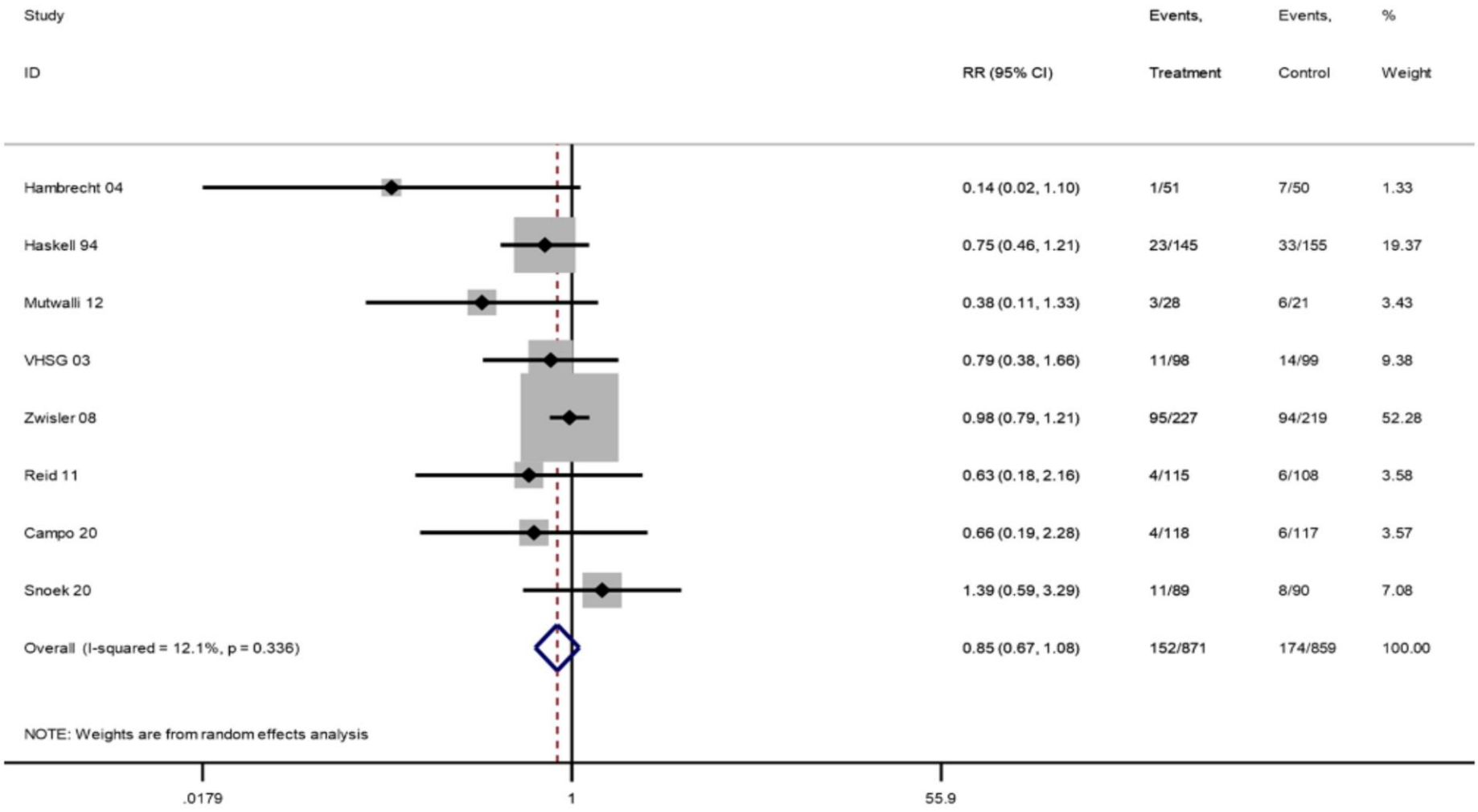


Figure 8 Forest plot: exercise-based cardiac rehabilitation vs. control for cardiovascular hospitalization.



Results :Health-related quality of life

- ✓ 6 trials reported SF-36 summary component scores with up to 12-month follow-up (Figure 9).

i. There was evidence of increases in both the mental component score (MD: 2.14, 95% CI: 1.07–3.22, I2 = 21%) and the physical component score (MD: 1.70, 95% CI: −0.08–3.47, I2 = 73%) with exercise-based CR.

- ✓ These findings were supported by improvements in selected SF-36 individual domain scores (Figure 10) that included physical functioning, physical performance, general health, vitality, social functioning, and mental health.

i. There was no evidence of an improvement in pooled EQ-5D visual analogue scores (VASs; MD 0.05, 95% CI −0.01–0.10, I2 = 69%; Figure 11).

Figure 9 Forest plot: exercise-based cardiac rehabilitation vs. control for health-related quality of life ...

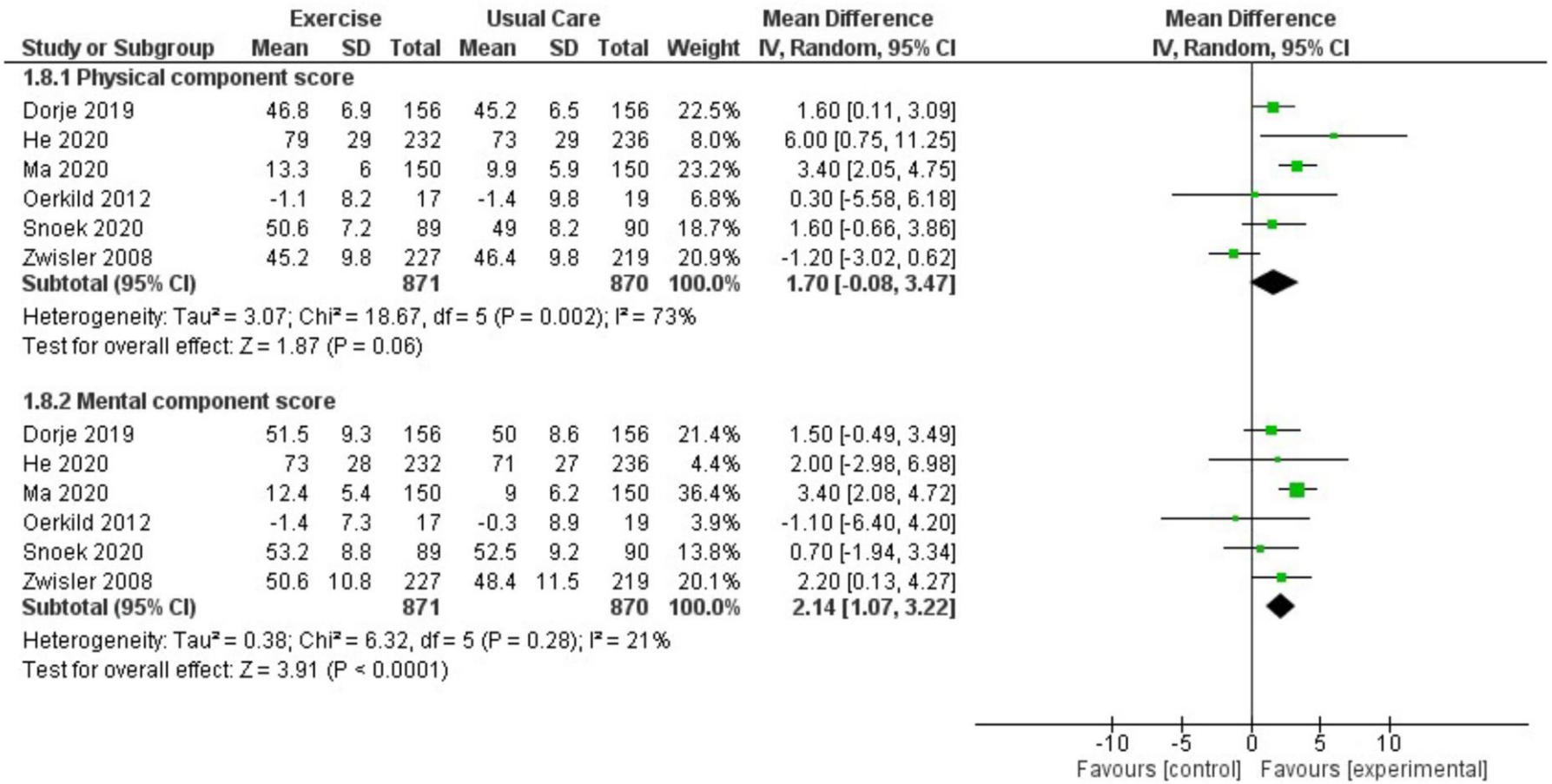


Figure 10 Forest plot: exercise-based cardiac rehabilitation vs. control for health-related quality of life ...

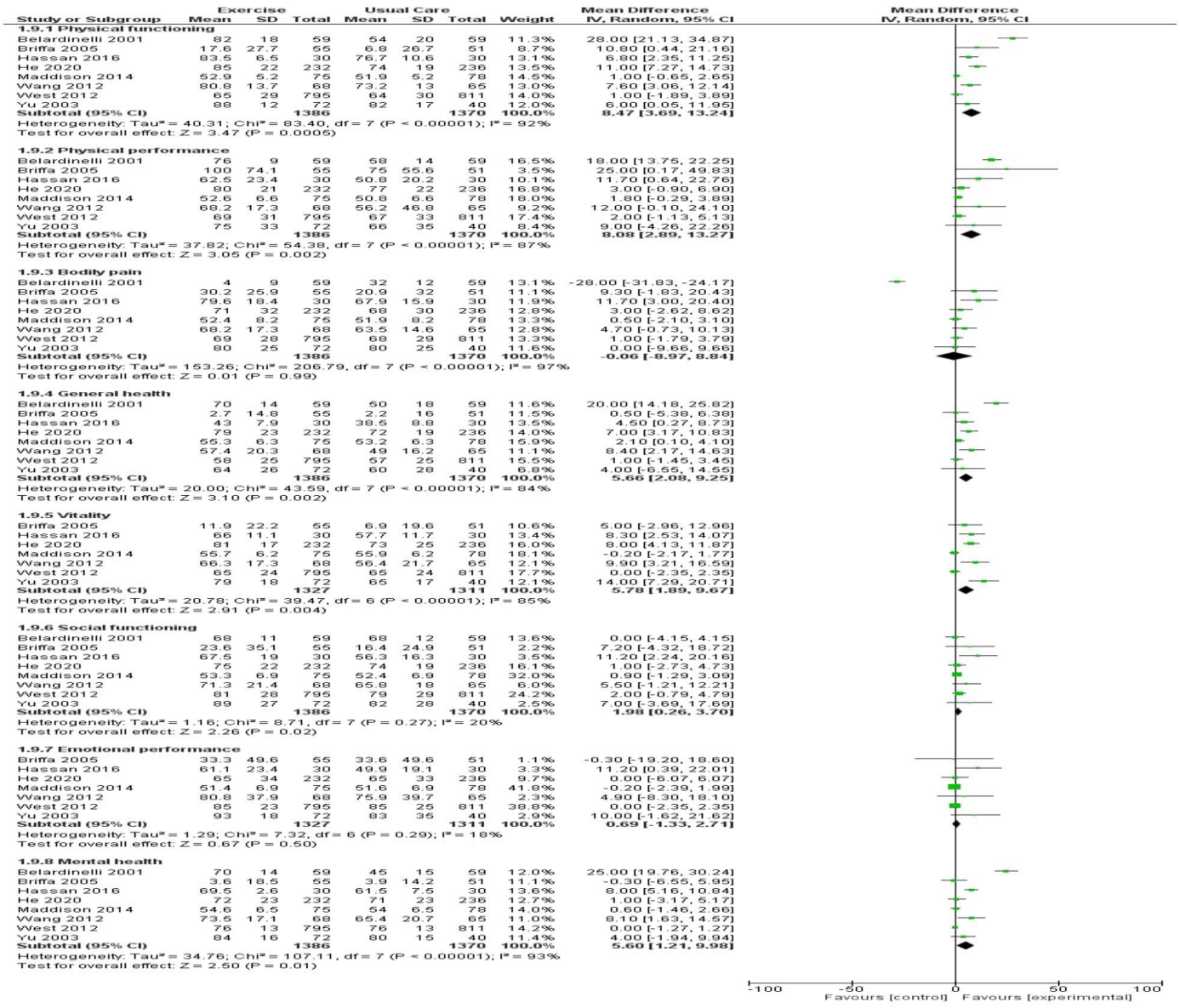
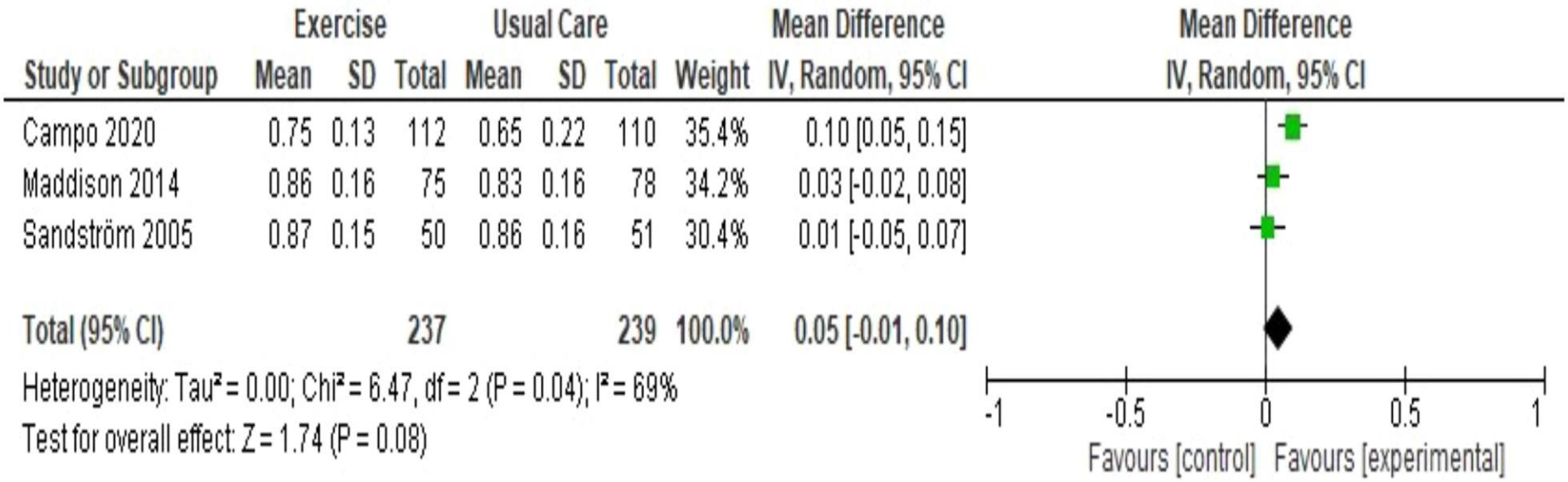


Figure 11 Forest plot: exercise-based cardiac rehabilitation vs. control for health-related quality of life (EQ-5D).



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Results : Costs and cost-effectiveness

- ✓ Only 8 of the 85 studies reported data on healthcare costs of CR with 5 studies reporting overall healthcare costs in both groups (Table 3).

i. Total healthcare costs were lower with exercise-based CR than usual care in 3 studies (mean US$2378,60 €1083,27 and US$415102 less per patient)

ii. higher healthcare costs were reported for exercise-based CR than usual care in 3 studies (mean US$395,50 US$4,839,72 and US$48080 more per patient),

iii. no difference was reported in 1 study.

iv. However, the difference was significant in only 1 (mean US$2378/patient; $P < 0.001$).

v. Acceptable cost-effectiveness ratios per QALY in favour of exercise-based CR were reported in 3 trials (US$42,535,50 €15,247,72 and US$9,20080).

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Results Small study bias

Egger's tests and visual inspection of funnel plots indicated there was no evidence of small study bias for overall mortality (Egger's test: *P* = 0.05; Supplementary material online, *Figure S2*), CV mortality (Egger's test: *P* = 0.20; Supplementary material online, *Figure S3*), CABG (Egger's test: *P* = 0.12; Supplementary material online, *Figure S4*), and PCI (Egger's test: *P* = 0.39; Supplementary material online, *Figure S5*). However, there was evidence of small study bias with funnel plot asymmetry and significant Egger's tests for MI (Egger's test: *P* = 0.001; Supplementary material online, *Figure S6*) and all-cause hospitalization (Egger's test: *P* < 0.001; Supplementary material online, *Figure S7*).

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Results Meta-regression

There was no evidence of significant differences in treatment effects across patient, intervention, and study characteristics for all clinical event outcomes (see Supplementary material online, *Table S2*).

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Discussion

- ✓ This updated Cochrane review and meta-analysis of RCTs incorporated data from >23 000 CHD patients and confirmed the benefits of participation in exercise-based CR that include reductions in risk of CV mortality, MI, and all-cause hospitalization at a median follow-up of 12 months (Structured graphical abstract).
- ✓ No significant differences in effect were found across patient case mix, the type or set of CR programme, the dose of exercise prescribed, study sample size, location, length of follow-up, year of publication, and ROB.
- ✓ Reduced hospitalizations are likely to have benefits for both healthcare services as well as for patients in terms of health resource usage and associated costs, and early return home to families and community support networks.

Discussion

- ✓ Importantly, this updated review demonstrates that the benefits of CR extend across recent trials that are more representative of the modern therapeutic approach in CHD, the expanded CHD population, and low- and middle-income settings (21 trials undertaken in LMICs with 7851 participants), where the prevalence of CHD continues to rise.
- ✓ Additionally, we found gains in HRQoL with increased scores across six of the eight SF-36 domains, mental component scores, EQ-5D VAS, and synthesis without meta-analysis across 32 trials reporting HRQoL data. Based on the minimally important clinical differences, the increases in the individual domain scores were not clinically important, but increases in EQ-5D VAS scores could be clinically meaningful.

Discussion

- ✓ Minimally important clinical differences for the summary component scores are yet to be published for CHD patients.
- ✓ Although HRQoL is important to patients and improvements have been demonstrated in generic measures, this finding might have been more convincing if a generic measure had been accompanied by the additional use of a CHD disease-specific HRQoL measure.
- ✓ To provide more persuasive evidence, **we recommend that future trials** consider routinely incorporating both types of HRQoL outcome measures for at least 12 months to delineate which, if any, aspects of HRQoL may yield an improvement.
- ✓ Trial-based economic evaluations showed that CR is a cost-effective use of healthcare resources compared with usual care.

Discussion

Coronary heart disease is clinically changing from a life-threatening disease to a chronic disease trajectory, as reflected in the terminology of current clinical guidelines on chronic coronary syndromes.4 This crucial shift strongly calls for interventions that contribute to improvements in the rehospitalization rate and the well-being and HRQoL of people living with chronic diseases. Thus, this latest Cochrane review of RCTs still reinforces the importance of exercise-based CR as part of integrated CHD care alongside modern invasive and pharmacological therapy.

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Limitations

- ✓ Our review has a number of potential limitations.

i. First, although we found that the methodological quality and reporting of studies have improved over the last decade and that poor reporting did not appear to alter the review findings, several ROB assessments across trials were judged to be unclear, with many studies inadequately reporting methodologies.

ii. Second, this update sought to combine evidence across a range of CHD indications and studies that employed exercise-based CR interventions with varying doses of exercise, delivery settings, and durations of follow-up. However, we applied random-effect meta-analysis to take account of this potential clinical heterogeneity across studies. Furthermore, the GRADE assessment framework also considers heterogeneity in the evidence. For example, the outcomes all-cause mortality, CV mortality, PCI, and CV hospitalization were downgraded in GRADE due to wide CIs that crossed the boundary with no effect. Cardiovascular hospitalization was downgraded due to evidence of statistical heterogeneity (I2 statistic >50%).

Limitations

✓ Our review has a number of potential limitations.

i. First,.

ii. Second

iii. Thirdly, while studies reported a prescribed dose of exercise, few, if any, reported the actual level of exercise undertaken by participants. So, we were not able to assess the impact of intervention adherence.

iv. Fourth, the number of trials reporting follow-up data beyond 12 months has decreased over the last decade, from 48% (between 2000 and 2009) to 23% (between 2010 and 2020). Consequently, the number of deaths and clinical events reported in several trials were low or zero, and these data were often reported within descriptions of trial loss to follow-up rather than as primary or secondary outcomes, which also means that trials would not have been powered for these outcomes. Additionally, hazard ratios were inconsistently reported across trials; therefore, no analyses using these data were possible.

v. Finally, we also found evidence of reporting bias. For example, although 60 trials reported all-cause mortality, only 33 of these same trials reported CV mortality. Sensitivity analysis of the subgroup group of 16 trials that reported both mortality outcomes (see Supplementary material online, Figures S8 and S9) showed improvements in both pooled overall (RR 0.85, 95% CI: 0.74–0.98) and CV mortality (RR 0.79, 95% CI: 0.68–0.92). This sensitivity analysis is in contrast with our main

Conclusions

The findings of this latest Cochrane review of 85 RCTs in 23 430 CHD patients confirm the clinical outcome benefits of reduced CV mortality, MI, and hospitalization with participation in exercise-based CR and also provide timely evidence that supports the generalizability of these benefits across patients, in the context of contemporary medical management, and across healthcare settings, including LMICs. This updated review also provides meta-analytic evidence that CR participation improves patient quality of life-based on validated HRQoL data. Our findings reinforce the need to improve access to CR for patients with CHD across the globe.

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Structured graphical abstract Exercise-based CR is recognized as a key component of comprehensive disease management. CABG, coronary artery ...

Key Question

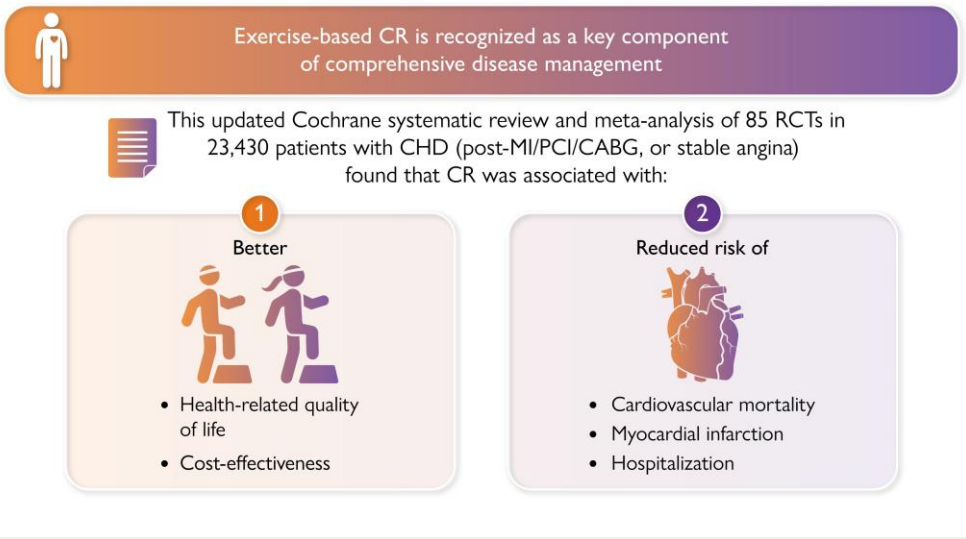
Compared to no exercise control, what are the clinical benefits of exercise-based cardiac rehabilitation (CR) for patients with coronary heart disease (CHD)?

Key Finding

In this meta-analysis of 85 randomized controlled trials of 23,430 CHD patients, exercise-based CR reduced the risk of cardiovascular mortality, recurrent cardiac events, and hospitalizations, improved health-related quality of life and was cost-effective.

Take Home Message

Exercise-based CR provides important benefits to CHD patients including improved quality of life, and better cardiovascular outcomes across different patient groups. In addition, it is cost-effective.



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Commentary (similar article)

European Heart Journal

ESC European Society of Cardiology

Volume 44, Issue 6
7 February 2023

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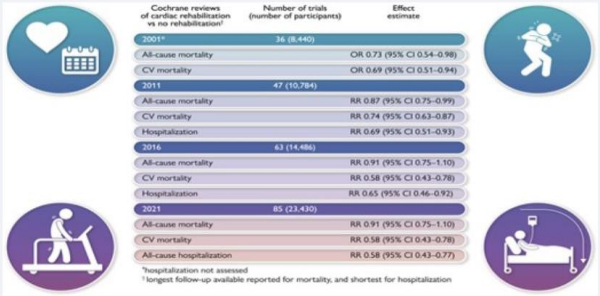
JOURNAL ARTICLE

Evidence is indisputable that cardiac rehabilitation provides health benefits and event reduction: time for policy action FREE

Sherry L Grace Author Notes

European Heart Journal, Volume 44, Issue 6, 7 February 2023, Pages 470–472,
https://doi.org/10.1093/eurheartj/ehac690
Published: 02 January 2023

Graphical Abstract



CITATIONS VIEWS ALTMETRIC

Graphical Abstract The benefits of cardiac rehabilitation have supported continually through Cochrane reviews since 2001. OR, ...

Cochrane reviews of cardiac rehabilitation vs no rehabilitation†	Number of trials (number of participants)	Effect estimate
2001*	36 (8,440)	
All-cause mortality		OR 0.73 (95% CI 0.54–0.98)
CV mortality		OR 0.69 (95% CI 0.51–0.94)
2011	47 (10,784)	
All-cause mortality		RR 0.87 (95% CI 0.75–0.99)
CV mortality		RR 0.74 (95% CI 0.63–0.87)
Hospitalization		RR 0.69 (95% CI 0.51–0.93)
2016	63 (14,486)	
All-cause mortality		RR 0.91 (95% CI 0.75–1.10)
CV mortality		RR 0.58 (95% CI 0.43–0.78)
Hospitalization		RR 0.65 (95% CI 0.46–0.92)
2021	85 (23,430)	
All-cause mortality		RR 0.91 (95% CI 0.75–1.10)
CV mortality		RR 0.58 (95% CI 0.43–0.78)
All-cause hospitalization		RR 0.58 (95% CI 0.43–0.77)

*hospitalization not assessed
† longest follow-up available reported for mortality, and shortest for hospitalization

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