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Exercise-Based Rehabilitation for Heart Failure

Cochrane Systematic Review, Meta-Analysis, and Trial Sequential Analysis

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ABSTRACT

OBJECTIVES This study performed a contemporary systematic review and meta-analysis of exercise-based cardiac rehabilitation (ExCR) for heart failure (HF).

BACKGROUND There is an increasing call for trials of models of ExCR for patients with HF that provide alternatives to conventional center-based provision and recruitment of patients that reflect a broader HF population.

METHODS The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, and PsycINFO databases were searched between January 2013 and January 2018. Randomized trials comparing patients undergoing ExCR to control patients not undergoing exercise were included. Study outcomes were pooled using meta-analysis. Metaregression examined potential effect modification according to ExCR program characteristics, and risk of bias, trial sequential analysis (TSA), and Grading of Recommendations Assessment Development and Evaluation (GRADE) were applied.

RESULTS Across 44 trials (n = 5,783; median follow-up of 6 months), compared with control subjects, ExCR did not reduce the risk of all-cause mortality (relative risk [RR]: 0.89; 95% confidence interval [CI]: 0.66 to 1.21; TSA-adjusted CI: 0.26 to 3.10) but did reduce all-cause hospitalization (RR: 0.70; 95% CI: 0.60 to 0.83; TSA-adjusted CI: 0.54 to 0.92) and HF-specific hospitalization (RR: 0.59; 95% CI: 0.42 to 0.84; TSA-adjusted CI: 0.14 for 2.46), and patients reported improved Minnesota Living with Heart Failure questionnaire overall scores (mean difference: −7.1; 95% CI: −10.5 to −3.7; TSA-adjusted CI: −13.2 to −1.0). No evidence of differential effects across different models of delivery, including center- versus home-based programs, were found.

CONCLUSIONS This review supports the beneficial effects of ExCR on patient outcomes. These benefits appear to be consistent across ExCR program characteristics. GRADE and TSA assessments indicated that further high-quality randomized trials are needed. (J Am Coll Cardiol HF 2019;7:691–705) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

ExCR = exercise-based cardiac rehabilitation

HF = heart failure

HRQoL = health-related quality of life

MLWHF = Minnesota Living with Heart Failure

RR = relative risk

TSA = trial sequential analysis

Chronic heart failure (HF) represents a major health issue that affects 1% to 2% of adults in the Western world (1,2). Whereas survival after HF diagnosis has improved, prognosis remains poor; 30% to 40% of patients die within 1 year of diagnosis (1,2). Patients living with HF experience marked reductions in their exercise capacity, which has detrimental effects on their activities of daily living and health-related quality of life (HRQoL) (3,4).

Meta-analyses of randomized trials over the last decade support the Class I recommendation of current national and international clinical guidelines that exercise-based cardiac rehabilitation (ExCR) should be offered to all patients with HF (5–7). However, the authors of the 2014 Cochrane ExCR review raised concerns about the generalizability of their meta-analysis results given that trial participants were predominantly lower-risk male patients who had HF with reduced ejection fraction (8). Furthermore, recent surveys show that <10% of patients with HF in the United States and <20% in Europe participated in ExCR (9,10), prompting a call to explore more accessible alternatives to the conventional model of group supervised center-based ExCR, such as home-based and internet programs (8,9).

The present study undertook a review and meta-analyses of an updated Cochrane database in order to reassess the evidence base for ExCR in patients with HF, including recently performed randomized clinical trials. The updated review includes analysis of center-based compared to home-based programs. This update incorporates both a formal assessment of overall trial quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines and trial sequential analysis (TSA) to control for type I and type II errors of conventional meta-analysis methods (11).

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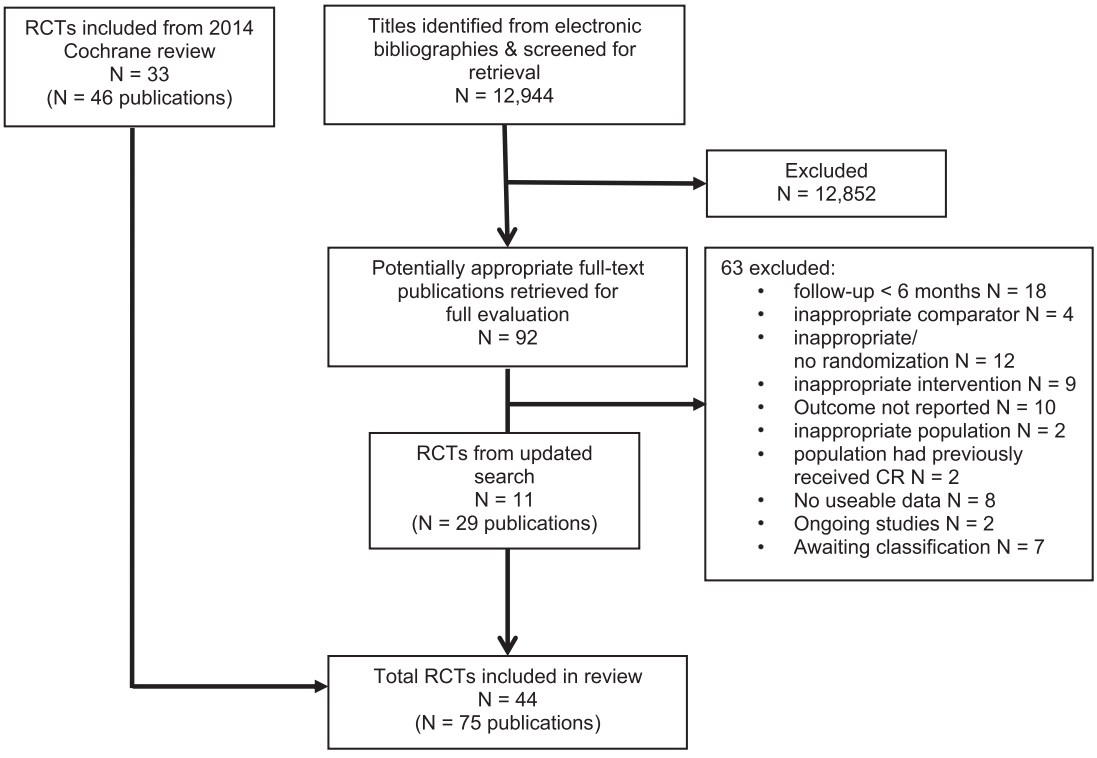
METHODS

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

FIGURE 1 Summary of the Study Selection Process



CR = cardiac rehabilitation; RCT = randomized control trial.

statement and the Cochrane Handbook for Interventional Reviews (12-14).

DATA SOURCES AND SEARCHES. Databases (Cochrane Central Register of Controlled Trials [CENTRAL], MEDLINE, EMBASE, CINAHL, and PsycINFO) were searched from January 2013 (the end date of the Cochrane 2014 review) to January 2018, without language restriction. Web of Science, bibliographies of systematic reviews, trial registers (e.g., the World Health Organization International Clinical Trials Registry Platform and the Clinical Trials.gov) were also checked, in addition to reference lists of all eligible studies and other published systematic reviews. A copy of the search strategy is available online (Online Appendix 1).

STUDY SELECTION. Studies were eligible, as follows, if they were: 1) randomized trials with ≥6 months follow-up; 2) had enrolled adult subjects (>18 years of age) with evidence of HF with reduced ejection fraction and HF with preserved ejection fraction; 3) compared ExCR interventions, either alone or as a component of a comprehensive ExCR program (plus education and/or psychological intervention); 4) included a control group that must not have received exercise training but might have received education, psychological intervention, or usual medical care alone; and 5) reported 1 or more of the following outcome measurements: mortality (all-cause and HF-related), hospitalization (all-cause or HF-related hospitalization), or HRQoL.

DATA EXTRACTION AND RISK OF BIAS ASSESSMENT. Trial information was extracted across studies. Study risk of bias was assessed using Cochrane standard criteria (14).

Study selection, data extraction, and risk of bias assessment were carried out independently by 2 authors. Any disagreements were resolved by consensus, and decisions were independently checked by a third author.

DATA ANALYSIS AND EVIDENCE GRADING. Heterogeneity was explored among the studies qualitatively (by comparing the study characteristics) and quantitatively (using the chi-square test of heterogeneity and I^2 statistic). Where appropriate, an overall estimate of treatment effect was obtained for combining the results from included studies for each outcome. A random-effects model was used where there was formal evidence of statistical heterogeneity (i.e., chi-square test p value <0.10 and an I^2 statistic >50%). For outcomes with lower levels of statistical heterogeneity, both fixed-effects and random-effects models were applied, reporting fixed-effects results unless there were differences in statistical inference, where the most conservative random-effects model was reported. Where reported, outcome results were pooled at 2 time points: up to 12 months follow-up and >12 months follow-up.

TABLE 1 Summary of Trial, Patient, and Intervention Characteristics

	All Trials (N = 44)	Trials Published 2015-2018 (n = 10)
Publication year		
1990-1999	5 (11)	-
2000-2009	22 (50)	-
2010 onward	17 (39)	10 (10)
Study location		
Europe	26 (59)	5 (50)
North America	12 (27)	1 (10)
Other	6 (14)	4 (40)
Single center	38 (86)	7 (70)
Sample size	59 (19-2,331)	61 (27-343)
Population characteristics		
Sex		
Males	13 (30)	1 (10)
Females	0 (0)	0 (0)
Both males and females	33 (75)	9 (90)
Not reported	1 (2)	0 (0)
Age, yrs	63 (51-81)	67 (56-77)
Diagnosis		
Ejection fraction, %	32 (21-49)	36.5 (34-49)
HFpEF included†	6 (14)	3 (30)
Not reported	7 (16)	4 (40)
NYHA functional class IV included	7 (16)	1 (10)
Not reported	14 (31)	5 (50)
Intervention characteristics		
ExCR type		
Exercise-only programs	31 (68)‡	7 (70)
Comprehensive programs	14 (32)‡	3 (30)
Exercise type		
Aerobic only	32 (73)	10 (100)
Aerobic and resistance	12 (27)	0 (0)
Dose of exercise		
Duration, months	6 (2-30)	6 (2-8)
Frequency, sessions/week	1-7	1-3
Length, min/session	10-120	30-60
Intensity		
Maximal heart rate, %	40-80	40-80
Maximal oxygen uptake, % (VO_{2max})	50-85	60-70
Borg rating	11-18	6-20
Setting		
Center-based only	21 (47)*	5 (45)*
Both center- and home-based	14 (31)	2 (18)
Home-based only	9 (20)*	4 (36)*
Not reported	1 (2)	0 (0)
Duration of follow-up, months	6 (6-74)	6 (6-62)

Values are n (%) or median (range). Median of study means the study includes both exercise-only and comprehensive cardiac rehabilitation arms. *Includes 1 trial that had both separate center-based and home-based only arms. †Stated that patients with ejection fraction >40% or with diastolic HF included. ‡Includes 1 trial that had both separate exercise and comprehensive rehabilitation arms.

CHD = coronary heart disease; ExCR = exercise-based cardiac rehabilitation; HFpEF = heart failure with preserved ejection fraction; NYHA = New York Heart Association.

TABLE 2 Summary of Risk of Bias Assessment

	Low Risk of Bias	Unclear Risk of Bias	High Risk of Bias
Random sequence generation (selection bias)	16/44 (36)	27/44 (61)	1/44 (3)
Allocation concealment (selection bias)	10/44 (23)	34/44 (77)	0/44 (0)
Blinding of outcome assessment (detection bias)	16/44 (36)	25/44 (57)	3/44 (7)
Incomplete outcome data (attrition bias)	37/44 (84)	3/44 (7)	4/44 (9)
Selective reporting (reporting bias)	37/44 (84)	6/44 (14)	1/44 (3)
Groups balanced at baseline	40/44 (91)	2/44 (5)	2/44 (5)
Intention-to-treat analysis conducted	39/44 (89)	4/44 (9)	1/44 (3)
Groups received same treatment (apart from the intervention)	33/44 (77)	11/44 (23)	0/44 (0)

Values are n/N (%).

Random effects metaregression was used to examine the association between the effect of exercise on all-cause mortality, all-hospitalization, and HRQoL (e.g., using Minnesota Living with Heart Failure [MLWHF] or other measurements) up to 12 months (15). Covariates included dose of aerobic exercise (calculated as the overall number of weeks of training multiplied by the mean number of sessions per week multiplied by the mean duration of sessions in minutes); type of exercise (aerobic training alone or aerobic plus resistance training); setting (center only, home only, both center and home); type of rehabilitation (exercise only compared to comprehensive); overall risk of bias (where "low risk" of bias occurred on ≥5 of 8 items compared to "high risk" of bias which occurred on <5 of 8 items); single-center compared to multicenter; and publication date. Given the relatively small trial-to-covariate ratio, metaregression was limited to univariate analysis (14). This study sought to explore small-study bias and the potential for publication bias by using funnel plots and the Egger test (16). Meta-analysis results are presented stratified by risk of bias. Two post hoc sensitivity analyses were undertaken to examine, first, the measured impact of excluding trials that included diastolic/preserved ejection fraction patients with HF, and second, the measured impact of excluding the large HF-ACTION (Participants in Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training trial (17). Analyses were performed using RevMan version 5.2 software (Chocrane, London, United Kingdom) and STATA version 15.0 software (College Station, Texas). GRADE guidelines and TSA analysis methods are summarized in Online Appendixes 2 and 3, respectively.

RESULTS

DESCRIPTION OF STUDIES. The 2014 version of the Cochrane review contributed 33 trials (8). Searches for this update yielded 12,944 titles, of which 92 full-length papers were considered for inclusion. This updated review identified 11 new trials (see citations in Online Appendix 4) in a total of 1,092 patients and included a total of 44 trials. The study selection process is summarized in **Figure 1**. Four trials (18–21) included more than 1 comparison between patients with ExCR and control subjects, resulting in a total of 48 ExCR-versus-control comparisons.

STUDY, PATIENT, AND INTERVENTION CHARACTERISTICS. The included trials randomized a total of 5,783 patients, predominantly those with HF with reduced ejection fraction and New York Heart Association functional classes II and III (**Table 1**). Eight trials formally stated that they included patients with HF with preserved ejection fraction (defined as either an ejection fraction of >40% or a diagnosis of diastolic HF) (18,22–28). The median follow-up was 6 months, and 6 studies reported ≥12 months of follow-up. Most studies were small in sample size (median: n = 52), with 1 large multicenter trial (HF-ACTION) (17) contributing ~40% of all participants. The median age of participants across studies was 63 years old. Although 33 studies (75%) included women, the median proportion of women recruited was only 19%. More recent studies (published from 2013 to 2018) were more likely to recruit participants who were older, female, and had HF with preserved ejection fraction.

ExCR programs were typically delivered in a supervised hospital or center-based setting, either exclusively or in combination with some maintenance home-exercise sessions. Nine studies were conducted in an exclusively home-based setting (18,20,24,28–34). Whereas the primary mode of exercise training across all studies was aerobic, the overall or average duration, frequency, and intensity of sessions varied considerably across studies. Approximately two-thirds of trials were exercise-only programs. The control group of included studies received no formal exercise training but included a wide range of interventions. These interventions included education, psychological interventions, and usual medical care alone.

RISK OF BIAS ASSESSMENT. Several trials failed to give details sufficient to allow complete assessment of their potential risk of bias. Details of generation and concealment of random allocation sequences and blinding of outcomes were particularly poorly reported (**Table 2**). However, the other 5 items (incomplete outcome data, selective reporting, groups balanced at baseline, intention-to-treat analysis conducted, and groups who received the same treatment apart from the ExCR intervention) were generally judged to be at low risk of bias. There was no

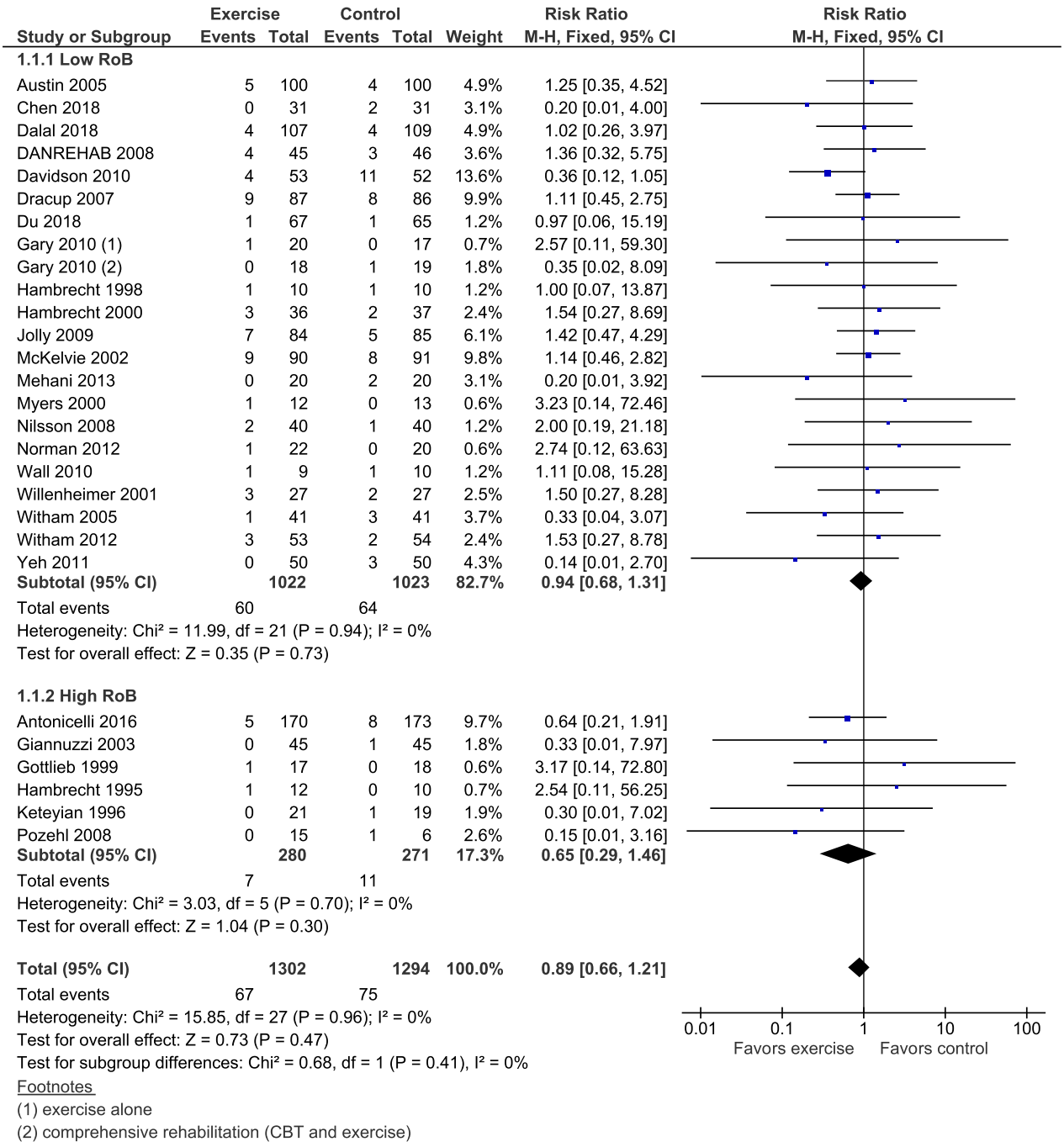
CENTRAL ILLUSTRATION Summary of Meta-Analysis Effects on Clinical and Health-Related Quality of Life Outcomes

Outcome	n Trials (n comparisons)	Number of ExCR patient events/ total patients	Control (Number of control patient events/total patients)	Mean Treatment Effect (95% CI)	Statistical Heterogeneity (I^2 statistic; chi-square p value)	GRADE Quality Rating
All-cause mortality 6-12 months follow-up	27 (28)	67/1,302	75/1,294	RR: 0.89 (0.66-1.21)	I^2 = 0%; p = 0.97	Low*†
All-cause mortality ≥12 months follow-up	6 (6)	244/1,418	280/1,427	RR: 0.88 (0.75-1.02)	I^2 = 34%; p = 0.18	High
All-cause hospitalization 6-12 months follow-up	21 (21)	180/1,093	258/1,089	RR: 0.70 (0.60-0.83)	I^2 = 19%; p = 0.22	Moderate‡
All-cause hospitalization ≥12 months follow-up	6 (7)	772/1,348	825/1,343	RR: 0.70 (0.47-1.05)	I^2 = 66%; p = 0.007	Very low ‖¶
HF-related hospitalization 6-12 months follow-up	14 (15)	40/562	61/552	RR: 0.59 (0.42-0.84)	I^2 = 11%; p = 0.32	Low†‡
MLWHF 6-12 months follow-up	17 (18)	-	-	MD: −7.1 (−10.5 to −3.7)	I^2 = 82%; p < 0.0001	Low†#
MLWHF ≥12 months follow-up	3 (3)	-	-	MD: −9.5 (−17.5 to −1.5)	I^2 = 73%; p < 0.03	Low††***
All HRQoL outcome 6-12 months follow-up	27 (29)	-	-	SMD: −0.60 (−0.82 to −0.39)	I^2 = 87%; p < 0.0001	Low†**

Taylor, R.S. et al. J Am Coll Cardiol HF. 2019;7(8):691–705.

*Some concerns arose with random sequence generation and allocation concealment; bias likely, therefore the quality of evidence was downgraded by 1 level. †Imprecise due to small numbers of events (<300); therefore, certainty of evidence was downgraded by 1 level. ‡Some concerns appeared with random sequence generation, allocation concealment, and blinding of outcome assessment; bias likely, therefore, certainty of evidence was downgraded by 1 level. ‖Inconsistent directions of effect and substantial statistical heterogeneity (I^2 = 66%); therefore, certainty of evidence was downgraded by 1 level. ¶Imprecise due to confidence intervals, including potential for no benefit and important benefit, as 95% CI crosses RR of 0.75; therefore, certainty of evidence was downgraded by 1 level. #Inconsistency with considerable statistical heterogeneity (I^2 = 82%); therefore, certainty of evidence was downgraded by 1 level. **Inconsistency with considerable statistical heterogeneity (I^2 = 87%); therefore, certainty of evidence was downgraded by 1 level. ††Inconsistency with substantial statistical heterogeneity (I^2 = 73%); therefore, certainty of evidence was downgraded by 1 level. §§Imprecise due to small number of participants (<400); therefore, certainty of evidence was downgraded by 1 level. ***Some concerns with random sequence generation, allocation concealment, and groups balanced at baseline; bias likely, therefore, certainty of evidence was downgraded by 1 level. CI = confidence interval; ExCR = exercise-based cardiac rehabilitation; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HRQoL = health-related quality of life; MD = mean difference; RR = relative risk; SMD = standardized mean difference; MLWHF: Minnesota Living with Heart Failure questionnaire; RR = relative risk.

FIGURE 2 Meta-Analyses of Events and HRQoL Outcomes



(A) All-cause mortality at 6- to 12-months' follow-up. **(B)** All-cause mortality at >12 months' follow-up. **(C)** Hospital admissions at 6- to 12-months" follow-up. **(D)** All-cause hospital admissions at >12 months' follow-up. **(E)** HF-specific hospital admissions. **(F)** MLWHF at ≤12 months' follow-up. **(G)** All HRQoL scales at ≤12 months' follow-up. **(H)** MLWHF at >12 months' follow-up.

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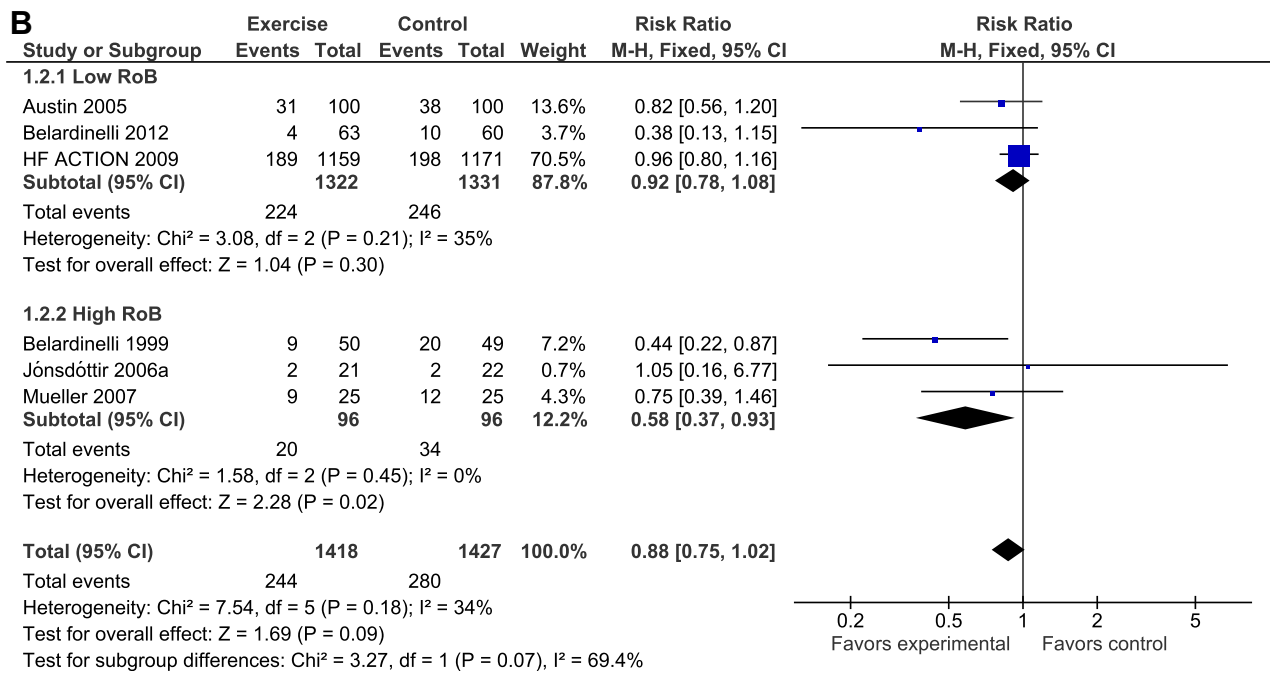
FIGURE 2 Continued



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evidence that trials published from 2013 to 2018 were overall better reported than those published before 2013 (20 of 34 trials [69%] with ≥5 items published before 2013 were judged to be of low bias compared to 7 of 10 trials [70%] published between 2013 and later).

OUTCOMES AND GRADE ASSESSMENT. Outcome results are summarized in the **Central Illustration** and discussed later.

Mortality. There were no significant differences in total mortality up to 12 months follow-up between the ExCR and control groups (fixed-effects, 27 trials, 28 comparisons, n = 2,596: relative risk [RR]: 0.89; 95% confidence interval [CI]: 0.66 to 1.21) (**Figure 2A**) (low certainty). The GRADE rating was downgraded due to high risk of bias and imprecision (number of events: <300).

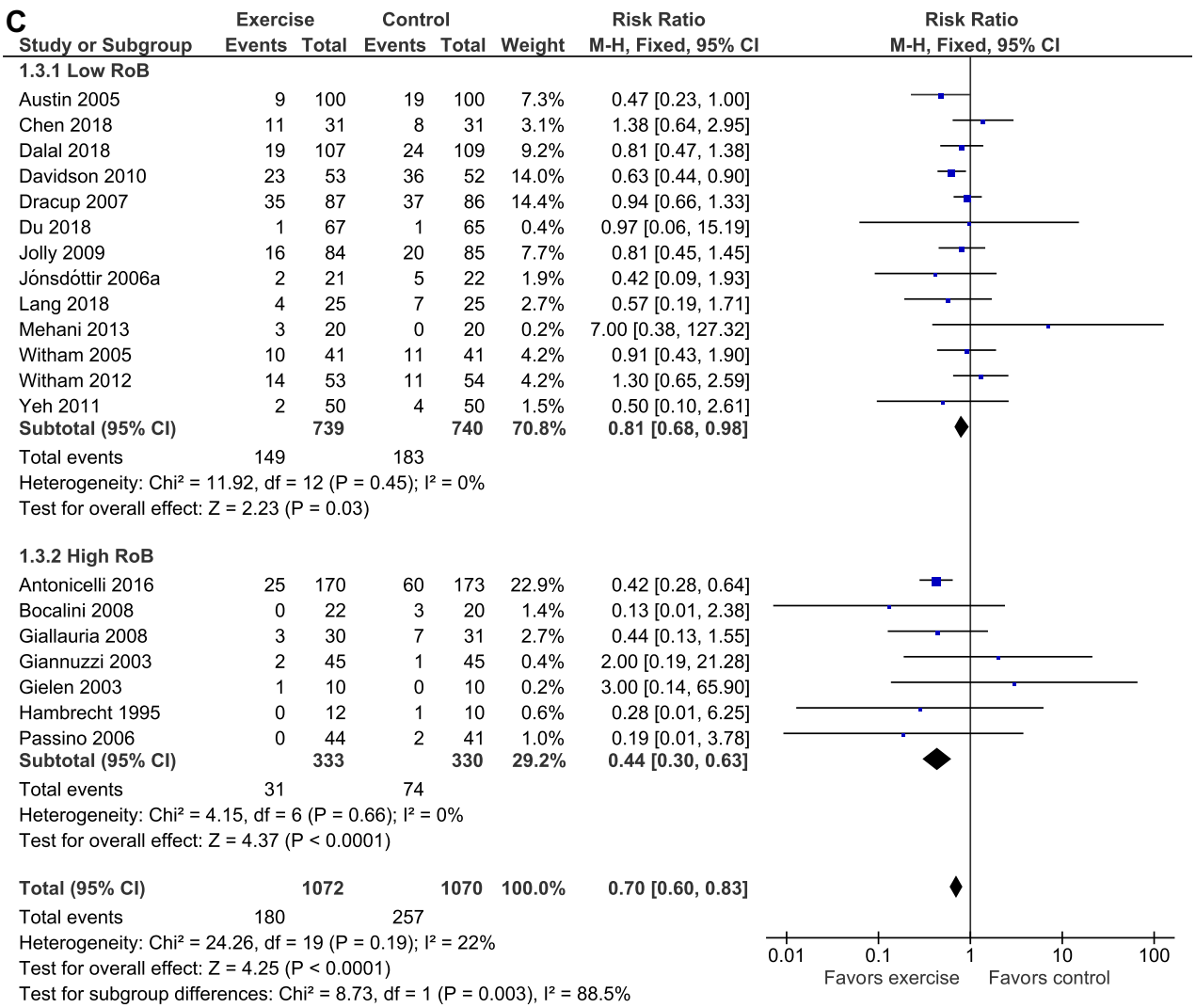
ExCR versus control did not affect mortality with >12 months follow-up (fixed-effects, 6 trials/comparisons, n = 2,845: RR: 0.88; 95% CI: 0.75 to 1.02) (**Figure 2B**) (high certainty). Studies did not consistently report deaths due to HF or sudden death.

At 20% relative risk reduction (RRR), the trial sequential analysis (TSA)-adjusted CI was 0.26 to 3.10 for mortality to 12 months follow-up and 0.67 to 1.14 for mortality at >12 months (Online Appendix 5). In both cases, the z-curve did not cross the conventional CON and TSMB boundaries (Online Figures 1.1c and 1.2c). In conclusion, the total sample size in the meta-analysis was underpowered to identify a difference in mortality with patients with ExCR compared with control participants in both short- and long-term follow-up.

Hospital admissions. Overall hospital admissions (fixed-effect, 21 trials/comparisons, n = 2,218: RR: 0.70; 95% CI: 0.60 to 0.83) (**Figure 2C**) (GRADE showed moderate certainty) up to 12 months follow-up were reduced with ExCR compared with control with an associated reduction in HF-specific hospitalizations (fixed effect, 14 trials, 15 comparisons, n = 1,114: RR: 0.59; 95% CI: 0.42 to 0.84) (**Figure 2D**) (low certainty). The 6 trials (7 comparisons, n = 2,691) with >12 months follow-up showed weak evidence of a reduction in overall hospital admissions (random effects, RR: 0.70; 95% CI: 0.47 to 1.05) (**Figure 2E**, very low certainty). The GRADE rating was downgraded due to high risk of bias, inconsistency, and imprecision.

At 20% RRR, the TSA-adjusted CI was 0.54 to 0.92 for all-cause hospitalization up to 12 months, 0.14 to 2.46 for all-cause hospitalization >12 months, and 0.14 to 3.56 for HF-specific hospitalization (Online Table 3, Online Figures 1.3c, 1.4c, and 1.5c). This effect was lost when limited to trials at low risk of bias (Online Figure 1.3e).

FIGURE 2 Continued



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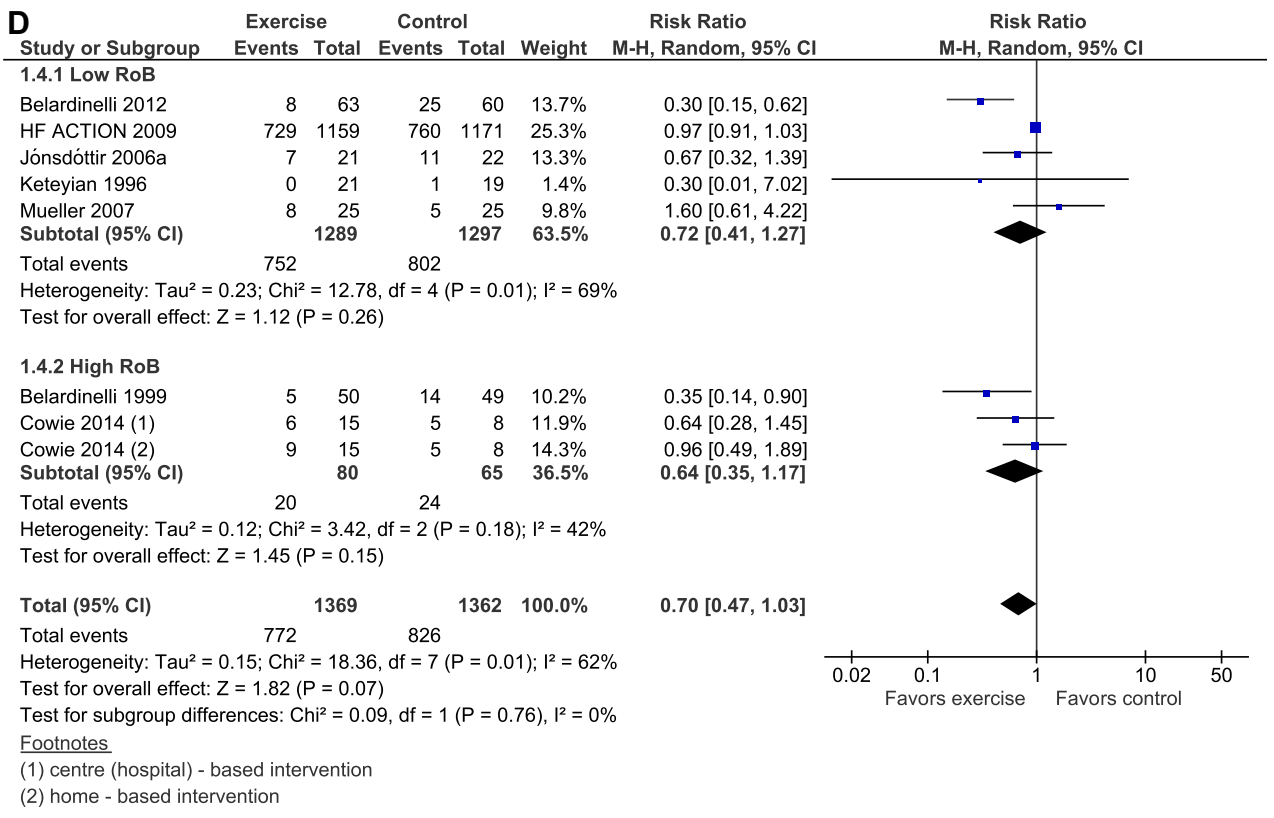
Health-related quality of life. A total of 28 trials assessed HRQoL by using a range of validated generic or disease-specific outcome measurements. Across the studies reporting the MLWHF questionnaire total score up to 12 months follow-up, there was evidence of a clinically important improvement with exercise (random effects, 17 trials, 18 comparisons, n = 1,995, mean difference: −7.1; 95% CI: −10.5 to −3.7) (very low certainty) (**Figure 2F**). An improvement in MLWHF score was also seen in the 3 trials (329 patients) that reported total MLWHF score beyond 12 months follow-up (random effects mean difference: −9.5; 95% CI: −17.5 to −1.5) (low certainty) (**Figure 2H**). Pooling studies regardless of outcome measurement used showed that there may be a significant improvement in HRQoL with exercise at ≤12 months follow-up (random effects, 26 trials, 29 comparisons, 3,833 patients: standardized mean difference [SMD]: −0.60; 95% CI: −0.82 to −0.39) (GRADE: very low certainty) (**Figure 2G**). GRADE rating was downgrading due to high risk of bias and inconsistency.

For MLWHF up to 12 months follow-up, the TSA-adjusted CI was −13.2 to −1.0 and −42.10 to 23.12 for trials with longer follow-up (Online Table 3, Online Figures 1.6b and 1.8a). Across all HRQoL outcomes with conversion to MLWHF, mean difference: −1.7; 95% CI: −9.3 to −4.9 and TSA-adjusted CI was −9.9 to −4.3 (Online Figure 1.7b). Although the MLWHF effect estimate of −7.1 favors ExCR and is larger than the minimal important clinical difference of 5 points,

FIGURE 2 Continued



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the TSA-adjusted CI is wide, diversity-adjusted required information size was not reached, and approximately 45% of the weight in analysis were from trials at high risk of bias. TSA analysis of trials at low risk of bias across different HRQoL scores (Online Table 3, Online Figure 1.7c) present effect estimates of mean differences: −4.72 TSA-adjusted CI: −9.36 to −0.08.

A total of 18 of 31 comparisons (55%) reported statistical superiority ($p < 0.05$) in 1 or more HRQoL domains for ExCR compared with control (Online Appendix 6). No trials reported a lower HRQoL domain score with ExCR than control.

SENSITIVITY ANALYSIS. Pooled outcomes for all-cause mortality, hospital admissions, and HRQoL were largely insensitive to exclusion of trials that included patients with HF with diastolic or preserved ejection fraction or the exclusion of the HF-ACTION trial (Online Appendix 7).

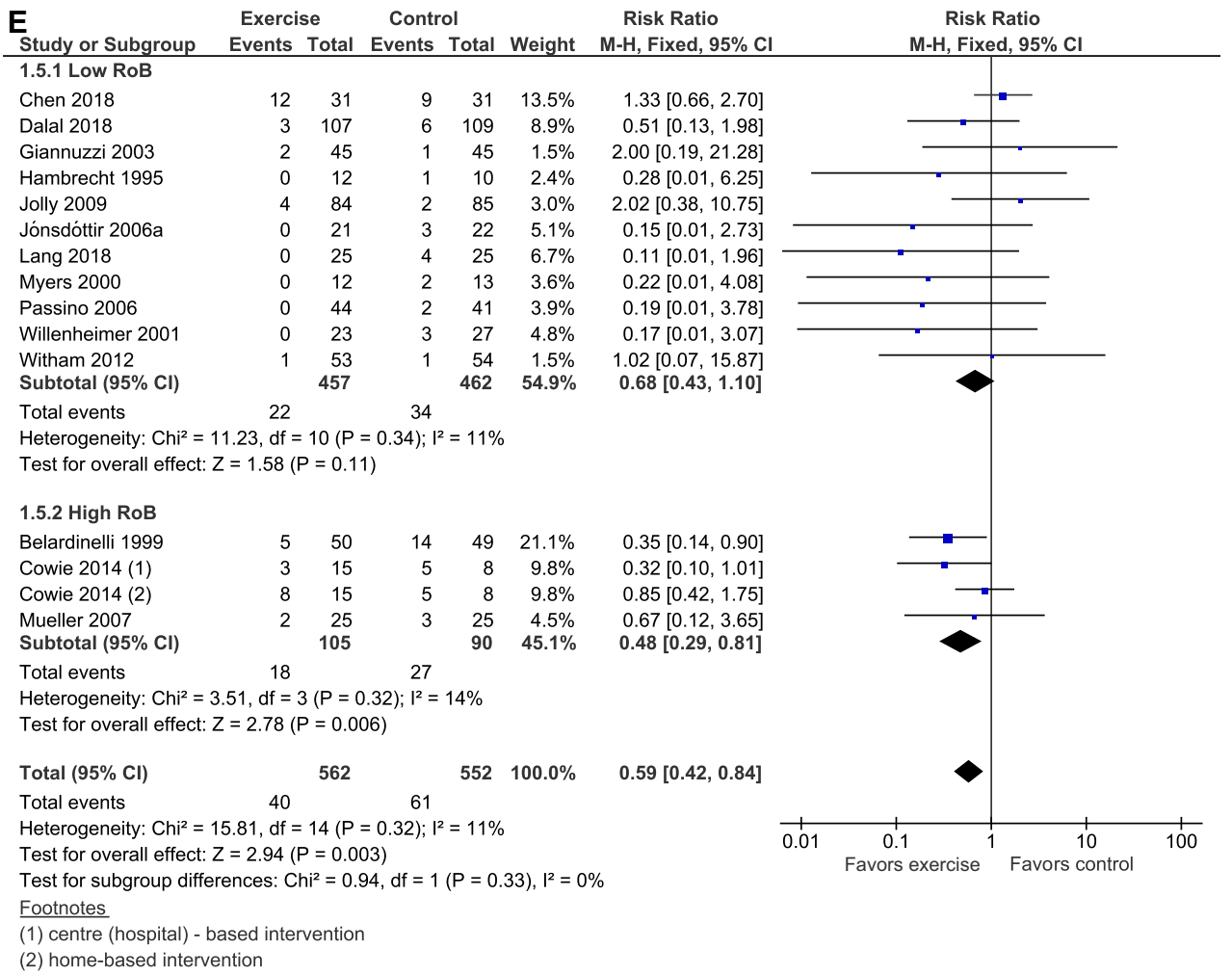
METAREGRESSION. There were no differential treatment effects across trial level characteristics and outcomes in univariate metaregression, except for the overall level of risk of bias and all-cause hospitalization, MLWHF, and HRQoL outcomes (Table 3). Trials at overall low risk of bias (low risk of bias on ≥5 of 8 items) had evidence of a smaller ExCR effect than trials at overall high risk of bias (low risk on bias on <5 of 8 items), that is, all-cause hospitalizations (RR: 0.89; 95% CI: 0.67 to 0.96; vs. RR: 0.48; 95% CI: 0.34 to 0.68), MLWHF (mean difference: −5.0; 95% CI: −8.0 to −1.9; vs. mean difference: −15.0; 95% CI: −17.8 to −12.3), and all HRQoL (SMD: −1.00; 95% CI: −1.33 to −0.66; vs. SMD: −0.48; 95% CI: −0.70 to −0.27).

SMALL STUDY BIAS. There was no evidence of funnel plot asymmetry, expect for all HRQoL measurements (Egger test p value <0.0001) (Online Figure 2). This asymmetry appeared to be due to an absence of small- to medium-sized studies with poorer HRQoL results for ExCR.

DISCUSSION

An updated systematic review and meta-analysis of ExCR was conducted in adults with HF. This study shows that, compared with no exercise control, ExCR does not appear to reduce or increase mortality.

FIGURE 2 Continued



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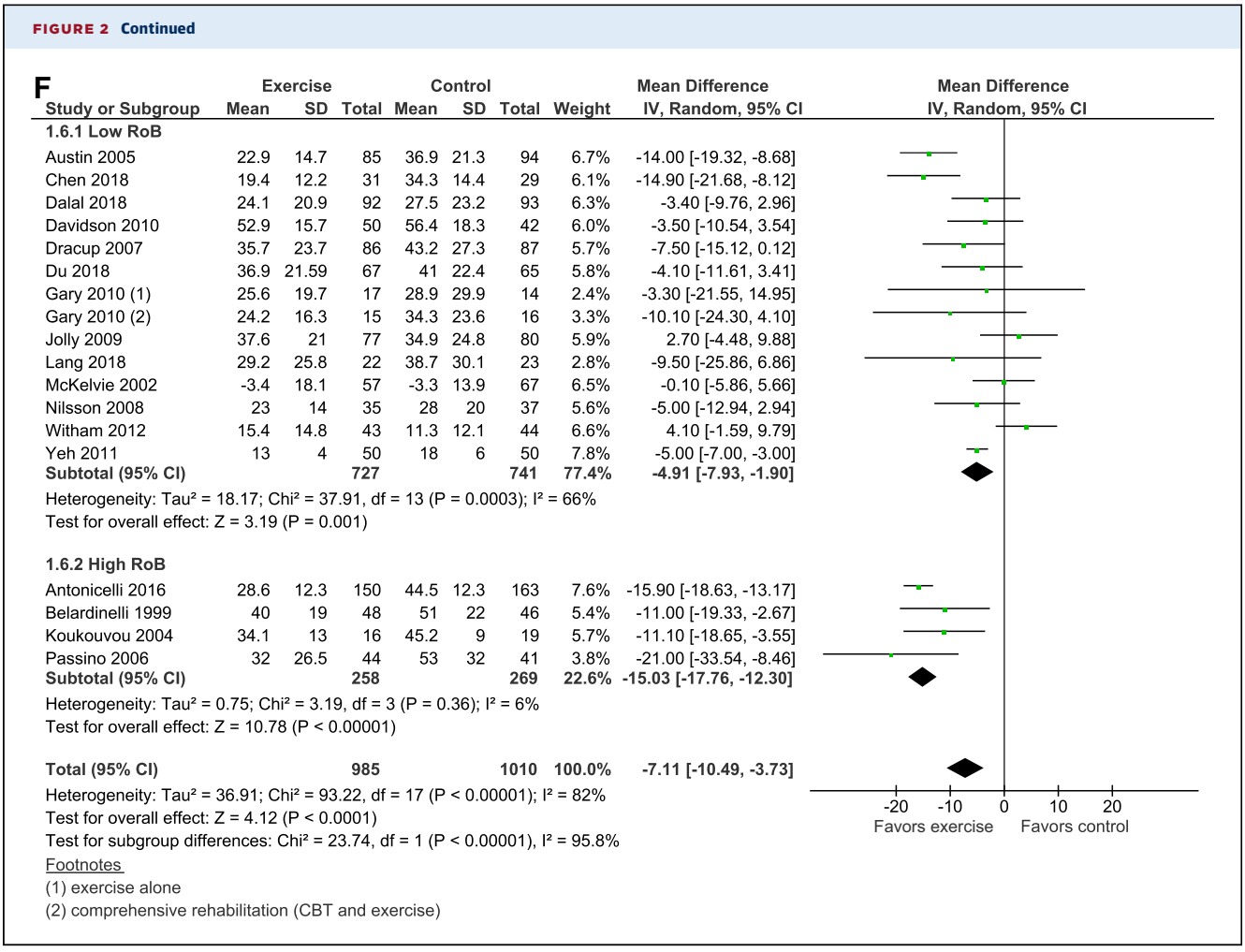
Potential differences were observed in the risk of all-cause hospitalization and hospitalization due to HF and improvements in HRQoL following exercise interventions. In trials reporting MLWHF questionnaire scores, those undertaking ExCR may have better disease-specific HRQoL by 7.1 points higher, on average, than controls. This exceeds the reported clinically important, meaningful difference of 5 points on the MLWHF questionnaire (15). These improvements in outcomes with ExCR were consistent across trials regardless of the nature or type of program (exercise only vs. comprehensive exercise; dose of exercise intervention) and setting of the program (center- vs. home-based) and other trial level characteristics (length of follow-up, year of publication). However, some of these outcome results are based on low GRADE rating evidence and may be prone to bias. The TSA showed that for all clinical event outcomes, the number of included patients remained too small to draw definitive conclusions. However, the fact that TSA of trials at low risk of bias showed an effect estimate for HRQoL close to a meaningful difference indicates the importance of future high-quality trials trials of ExCR collecting and reporting HRQoL outcomes.

The present findings are broadly consistent with the recently updated individual participant data pooled analyses of the ExtraMATCH II (Exercise Training Meta-Analysis of Trials for Chronic Heart Failure; NCT03799354) collaborative group (35,36). ExTraMATCH II reported that ExCR had no impact on overall mortality (hazard ratio: 0.83; 95% CI: 0.67 to 1.04) and improved MLWHF (mean of 5.9 points; 95% CI: 1.0 to 10.9). However, in

FIGURE 2 Continued



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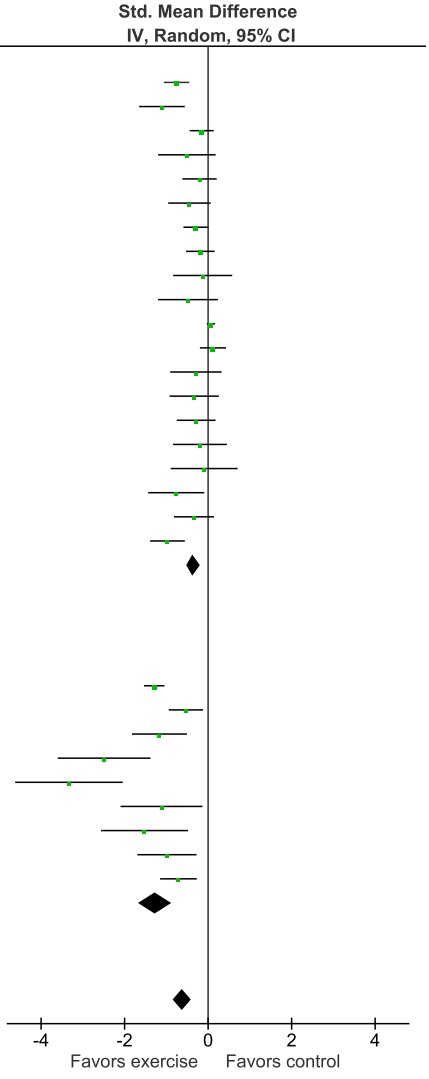
contrast to the present study, no reduction with ExCR was found in either all-cause hospitalization (hazard ratio of 0.90; 95% CI: 0.76 to 1.06) or HF-specific hospitalization (hazard ratio of 0.98; 95% CI: 0.72 to 1.35). Although individual participant data meta-analysis is recognized as the gold standard approach for assessing intervention subgroup effects (37), this discrepancy in the impact of ExCR on hospitalization may reflect limitations with the analytic approach in this case. The ExTraMATCH II authors highlighted 2 key limitations in their analyses; the first was a lack of consistency in how included trials defined time-to-event outcomes; and the second was that many included trials did not collect patient data for the time-to-event outcomes (35). The present findings are consistent with those of other systematic reviews and meta-analyses of randomized controlled trials (RCTs) of CR for HF published since the 2014 version of the present review. Zhang et al. (38) collated trial-level data from 2,533 patients with HF enrolled in 28 published RCTs. Based on the MLWHF questionnaire responses, study authors reported a similar magnitude of pooled improvement in HRQoL (mean: −6.8; 95% CI: −3.9 to −9.7; $p < 0.0001$). Similarly, based on 8 RCTs including 317 participants with HF with preserved ejection fraction, Chan et al. (39) reported a pooled improvement in mean MLWHF score of −6.8 (95% CI: −9.7 to −3.8; $p < 0.0001$) (39).

STUDY LIMITATIONS. The present authors believe this is the most comprehensive systematic review of aggregated data to date of randomized trial evidence for the impact of ExCR for people with HF. This is the first version of this Cochrane review to incorporate a formal assessment of quality by using GRADE rating and TSA that can better control for type I and type II errors of conventional meta-analysis methods. A

FIGURE 2 Continued

G

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.7.1 Low RoB								
Austin 2005	22.9	14.7	85	36.9	21.3	94	4.2%	-0.76 [-1.06, -0.45]
Chen 2018	19.4	12.2	31	34.3	14.4	29	3.5%	-1.11 [-1.65, -0.56]
Dalal 2018	24.1	20.9	92	27.5	23.2	93	4.2%	-0.15 [-0.44, 0.14]
DANREHAB 2008	-42.7	9.1	19	-37.4	11.4	15	3.1%	-0.51 [-1.20, 0.18]
Davidson 2010	52.9	15.7	50	56.4	18.3	42	3.9%	-0.20 [-0.62, 0.21]
Dehkordi AH 2015	-63.34	12.69	30	-58.43	8.67	31	3.7%	-0.45 [-0.96, 0.06]
Dracup 2007	35.7	23.7	86	43.2	27.3	87	4.2%	-0.29 [-0.59, 0.01]
Du 2018	36.9	21.59	67	41	22.4	65	4.1%	-0.19 [-0.53, 0.16]
Gary 2010 (1)	25.6	19.7	17	28.9	29.9	14	3.1%	-0.13 [-0.84, 0.58]
Gary 2010 (2)	24.2	16.3	15	34.3	23.6	16	3.0%	-0.48 [-1.20, 0.23]
HF ACTION 2009	72.8	20.4	828	71.4	21.3	784	4.6%	0.07 [-0.03, 0.16]
Jolly 2009	37.6	21	77	34.9	24.8	80	4.2%	0.12 [-0.20, 0.43]
Jónsdóttir 2006a	-47.55	8.7	21	-44.1	14.04	20	3.3%	-0.29 [-0.91, 0.32]
Lang 2018	29.2	25.8	22	38.7	30.1	23	3.4%	-0.33 [-0.92, 0.26]
Nilsson 2008	23	14	35	28	20	37	3.8%	-0.29 [-0.75, 0.18]
Norman 2012	-81	18.2	19	-77.9	11.6	18	3.2%	-0.20 [-0.84, 0.45]
Reeves 2017	-65	19	12	-63	22	12	2.8%	-0.09 [-0.89, 0.71]
Willenheimer 2001	-0.7	0.8	20	0	1	17	3.2%	-0.76 [-1.44, -0.09]
Witham 2005	-69	13	36	-65	10	32	3.7%	-0.34 [-0.82, 0.14]
Yeh 2011	13	4	50	18	6	50	3.9%	-0.97 [-1.39, -0.56]
Subtotal (95% CI)			**1612**			**1559**	**73.3%**	**-0.35 [-0.52, -0.18]**
Heterogeneity: Tau² = 0.10; Chi² = 72.59, df = 19 (P < 0.00001); I² = 74%								
Test for overall effect: Z = 3.94 (P < 0.0001)								
1.7.2 High RoB								
Antonicelli 2016	28.6	12.3	150	44.5	12.3	163	4.3%	-1.29 [-1.53, -1.05]
Belardinelli 1999	40	19	48	51	22	46	3.9%	-0.53 [-0.94, -0.12]
Bocalini 2008	-87	4	22	-81	6	20	3.2%	-1.17 [-1.83, -0.51]
Kaltsatou 2014 (3)	-5.7	3	16	0.8	1.2	9	2.1%	-2.49 [-3.60, -1.38]
Kaltsatou 2014 (4)	-6.5	2.4	18	0.8	1.2	8	1.7%	-3.33 [-4.62, -2.04]
Klocek 2005 (5)	-99	23.5	14	-71.7	23.5	7	2.3%	-1.12 [-2.10, -0.13]
Klocek 2005 (6)	-109	23.5	14	-71.7	23.5	7	2.2%	-1.52 [-2.57, -0.48]
Koukouvou 2004	34.1	13	16	45.2	9	19	3.1%	-0.99 [-1.69, -0.28]
Passino 2006	32	26.5	44	53	32	41	3.9%	-0.71 [-1.15, -0.27]
Subtotal (95% CI)			**342**			**320**	**26.7%**	**-1.26 [-1.66, -0.86]**
Heterogeneity: Tau² = 0.23; Chi² = 30.94, df = 8 (P = 0.0001); I² = 74%								
Test for overall effect: Z = 6.20 (P < 0.00001)								
Total (95% CI)			**1954**			**1879**	**100.0%**	**-0.60 [-0.82, -0.39]**
Heterogeneity: Tau² = 0.26; Chi² = 215.03, df = 28 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 5.54 (P < 0.00001)								
Test for subgroup differences: Chi² = 16.94, df = 1 (P < 0.0001), I² = 94.1%								



Footnotes
(1) exercise alone
(2) comprehensive (CBT and exercise)
(3) formal exercise
(4) dance
(5) progressive exercise
(6) constant exercise

Continued on the next page

number of the new trials included in this update were based on home-based ExCR models as opposed to the conventional model groups of supervised center-based ExCR provision. More evidence was identified in patients with HF with preserved ejection fraction.

The general lack of reporting of methods in the included trial reports made it difficult to assess their methodological quality and thereby judge their risk of bias. Although larger HRQoL gains with ExCR were associated with higher risk of bias, improvement in HRQoL were still observed when meta-analyses were carried out in trials at low risk of bias but now at or under a minimal clinical important difference of 5 points. Funnel plot asymmetry for HRQoL is indicative of small-study bias and signals possible publication bias.

FIGURE 2 Continued

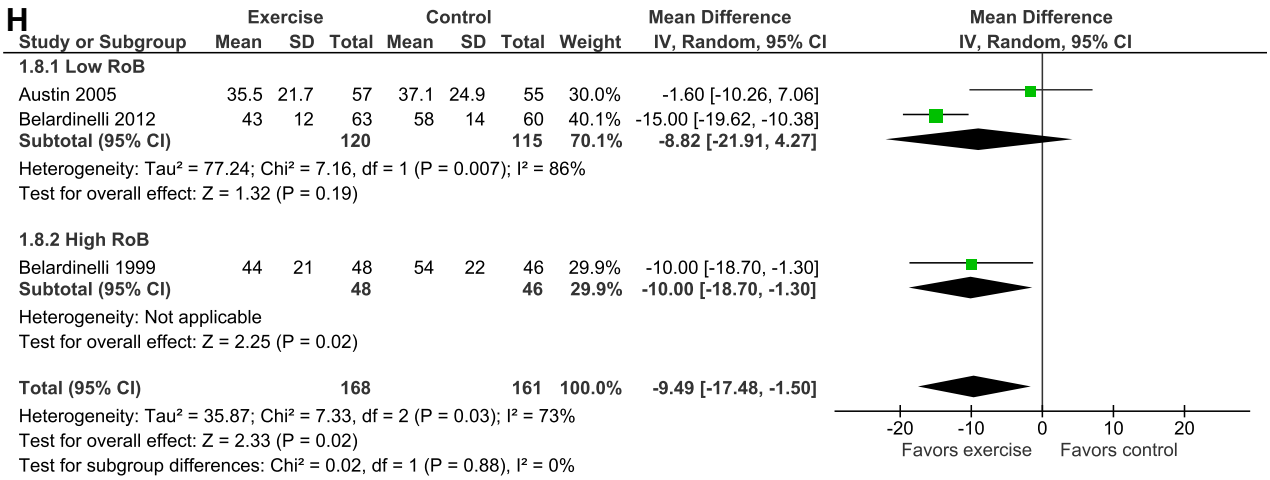


TABLE 3 Univariate Meta-Regression Analysis*

	p Values			
	All-Cause Mortality at 6-12 Months Follow-Up	All Hospitalizations at 6-12 Months Follow-Up	MLWHF at ≤12 Months Follow-Up	All HRQoL Outcomes at ≤12 Months Follow-Up
Type of ExCR†	0.72	0.55	0.22	0.49
Type of exercise‡	0.93	0.06	0.15	0.66
Exercise dose‖	0.10	0.44	0.89	0.71
Setting¶	0.09	0.60	0.62	0.08
Single vs multicenter	0.46	0.60	0.09	0.06
Publication date	0.20	0.76	0.67	0.74
Risk of bias#	0.28	0.05	0.01	0.01

*Based on "Metareg" and "Permute" option in Stata software, correcting for multiple testing. †Exercise only vs. comprehensive. ‡Aerobic training alone vs. aerobic plus resistance training. ‖Number of weeks × number of sessions/week × average duration of session in hours. ¶Hospital only, home only, or both hospital and home. #Low risk of bias on ≥5 of 8 items.

ExCR = exercise-based cardiac rehabilitation; HRQoL = health-related quality of life; MLWHF = Minnesota Living with Heart Failure questionnaire.

CONCLUSIONS

The findings of this latest updated Cochrane systematic review support the benefits of ExCR in terms of probable reductions in the risk of all-cause and HF-specific hospitalization and potential important gains in HRQoL in people with HF. With inclusion of more women, older patients, people with HF with preserved ejection fraction in recent trials, and more trials of ExCR delivered in a home-based setting, the findings of this updated review have potentially greater external validity and applicability. The benefits of ExCR appear to be consistent across trial settings (i.e., center- compared to home-based ExCR), type of rehabilitation (i.e., comprehensive compared to exercise-only ExCR program), and dose of ExCR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Exercise-based cardiac rehabilitation can improve the outcome of patients with heart failure by reducing their risk of hospital admission and by enhancing their quality of life.

TRANSLATIONAL OUTLOOK 1: Heart failure patients should be routinely offered and encouraged to participate in a cardiac rehabilitation program. Uptake of cardiac rehabilitation is likely to be enhanced if patients can be offered the choice of alternative models of provision that include not only (conventional) center-based programs but also home-based programs.

TRANSLATIONAL OUTLOOK 2: Additional research is needed to better understand approaches to the improve the uptake of longer-term adherence to cardiac rehabilitation of heart failure patients.

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KEY WORDS exercise training, heart failure, meta-analysis, randomized controlled trials, rehabilitation, trial sequential analysis

APPENDIX For supplemental figures and tables, please see the online version of this paper.