OPEN ACCESS

UNIVERSITY OF DUNDEE

University of Dundee

Exercise-Based Rehabilitation for Heart Failure

Taylor, Rod S .; Long, Linda; Mordi, Ify; Madsen, Michael Tvilling; Davies, Edward J.; Dalal, Hasnain M. ; Rees, Karen; Singh, Sally J.; Gluud, Christian; Olsen Zwisler, Ann-Dorthe

Published in:
JACC: Heart Failure

DOI:
10.1016/j.jchf.2019.04.023

Publication date:
2019

Document Version
Version created as part of publication process; publisher's layout; not normally made publicly available

Link to publication in Discovery Research Portal

Citation for published version (APA):
Taylor, R. S. ., Long, L., Mordi, I., Madsen, M. T., Davies, E. J., Dalal, H. M., ... Olsen Zwisler, A-D. (2019). Exercise-Based Rehabilitation for Heart Failure: Cochrane Systematic Review, MetaAnalysis, and Trial Sequential Analysis. *JACC: Heart Failure*, *7*(8), 691-705. https://doi.org/10.1016/j.jchf.2019.04.023

General rights
Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 10. Sep. 2019

JACC: HEART FAILURE VOL. ■, NO. ■, 2019
© 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/).

Exercise-Based Rehabilitation for Heart Failure

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

Rod S. Taylor, PhD,[a] Linda Long, PhD,[b] Ify R. Mordi, MD,[c] Michael Tvilling Madsen, PhD,[d] Edward J. Davies, MD,[e] Hasnain Dalal, MD,[f,g] Karen Rees, PhD,[h] Sally J. Singh, PhD,[i] Christian Gluud, DrMedSci,[j] Ann-Dorthe Zwisler, PhD[k]

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;■:■-■) © 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/).

From the [a]Institute of Health and Wellbeing, University of Glasgow, Glasgow, and Institute of Health Research, University of Exeter College of Medicine and Health, Exeter, United Kingdom; [b]Institute of Health Research, University of Exeter College of Medicine and Health, Exeter, United Kingdom; [c]Molecular and Clinical Medicine, University of Dundee, Dundee, United Kingdom; [d]Department of Surgery, Zealand University Hospital, Køge, Denmark, and University of Copenhagen, Koege, Denmark; [e]Cardiothoracic Department, University Hospital Plymouth, Plymouth, United Kingdom; [f]Department of Primary Care, University of Exeter Medical School, Truro Campus, Knowledge Spa, Royal Cornwall Hospitals Trust, Truro; [g]Institute of Health Research, Exeter College of Medicine and Health School, University of Exeter, Exeter, United Kingdom; [h]Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, United Kingdom; [i]Department of Respiratory Sciences, University of Leicester College of Life Sciences, National Institute for Health Research, Leicester Biomedical Research Center - Respiratory, Glenfield Hospital, Leicester, United Kingdom; [j]Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; and the [k]REHPA Danish Knowledge Center for Rehabilitation and Palliative Care, University of Southern and Odense University Hospital, Copenhagen, Denmark. Drs. Taylor, Singh, Zwisler, and Dalal received research funding from governmental research grants. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 15, 2019; revised manuscript received April 26, 2019, accepted April 29, 2019.

ISSN 2213-1779 https://doi.org/10.1016/j.jchf.2019.04.023

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).

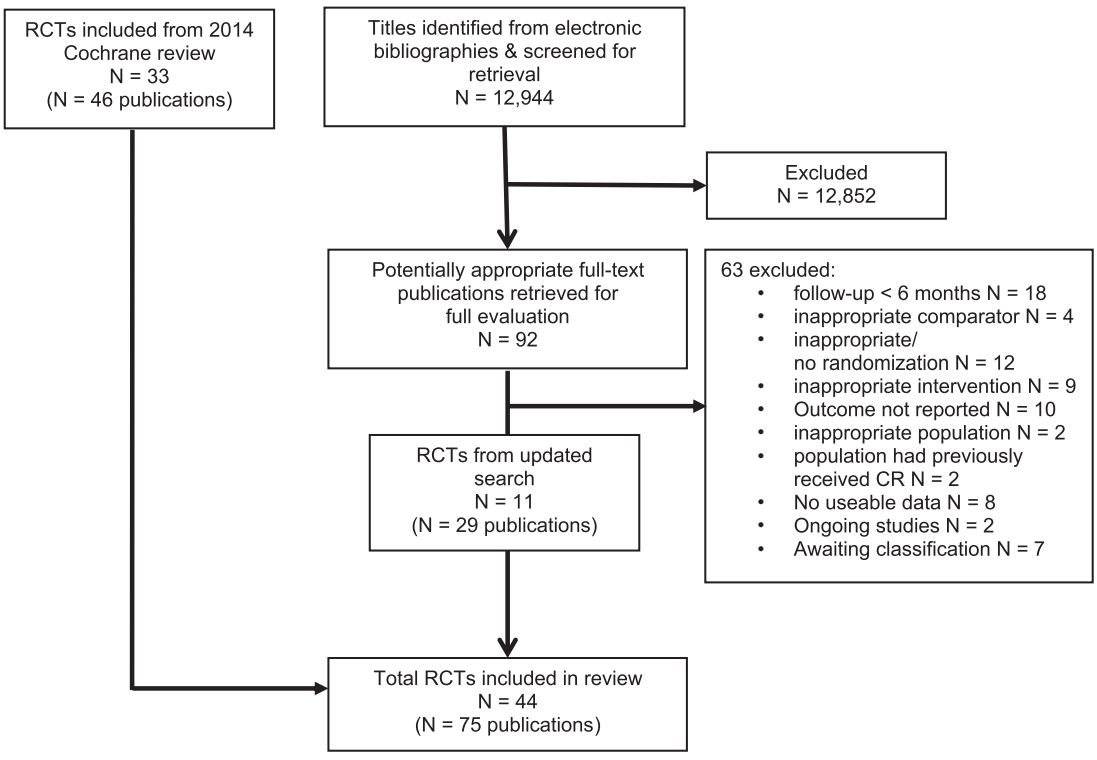
Meta-analyses of randomized trials over the last decade support the Class I recommendation of current national and international clinical guidelines that exercise-based cardiac rehabilitation (ExCR) should be offered to all patients with HF (5–7). However, the authors of the 2014 Cochrane ExCR review 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).

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 (range)	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	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 Participants in Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) 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

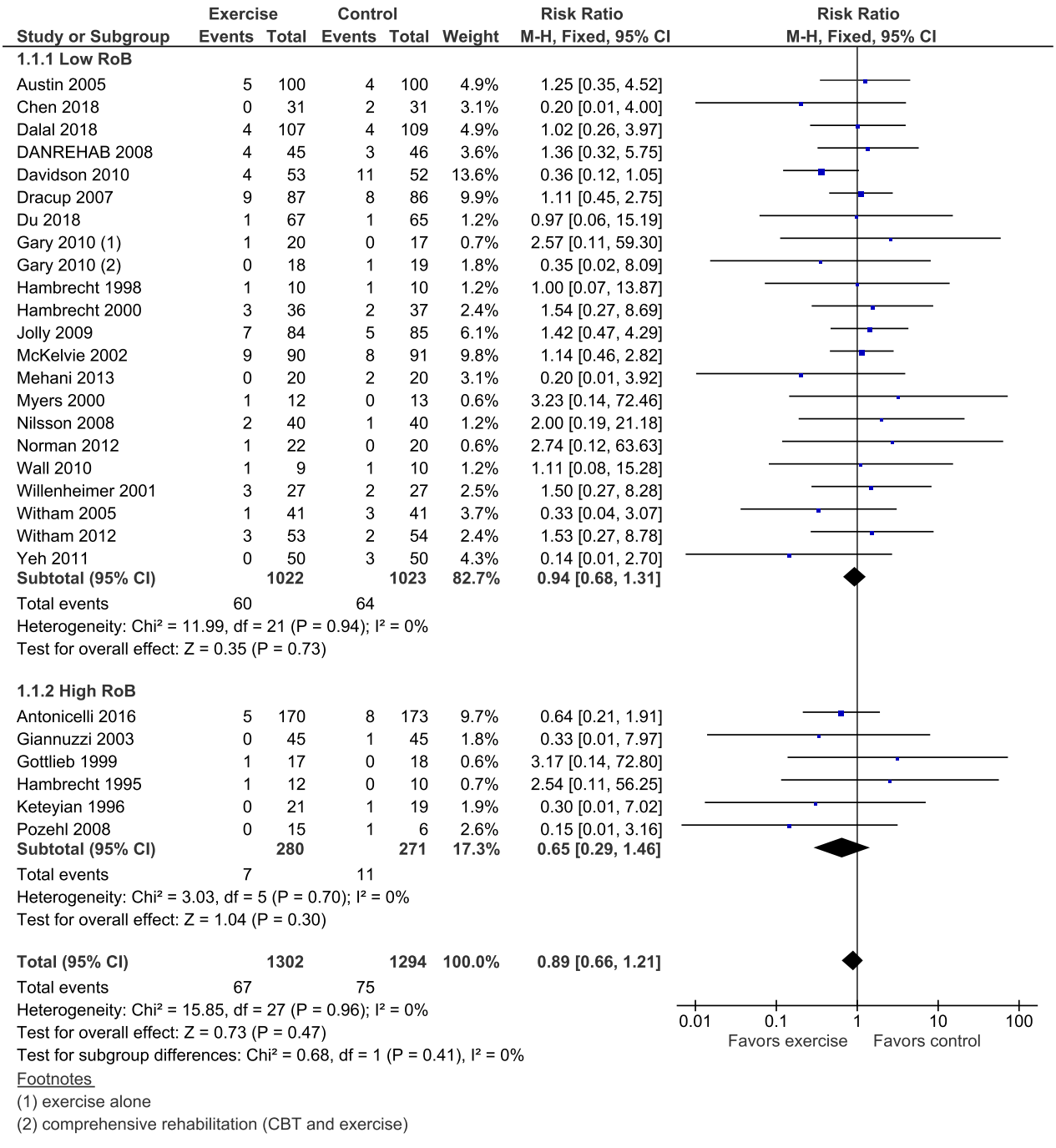
CENTRAL ILLUSTRATION Summary of Meta-Analysis Effects on Clinical and Health-Related Quality of Life Outcomes

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 ≥12 months follow-up	27 (28) 6 (6)	67/1,302 244/1,418	75/1,294 280/1,427	RR: 0.89 (0.66-1.21) RR: 0.88 (0.75-1.02)	I^2 = 0%; p = 0.97 I^2 = 34%; p = 0.18	Low*† High
All-cause hospitalization 6-12 months follow-up ≥12 months follow-up	21 (21) 6 (7)	180/1,093 772/1,348	258/1,089 825/1,343	RR: 0.70 (0.60-0.83) RR: 0.70 (0.47-1.05)	I^2 = 19%; p = 0.22 I^2 = 66%; p = 0.007	Moderate‡ 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 ≥12 months follow-up	17 (18) 3 (3)	-	-	MD: −7.1 (−10.5 to −3.7) MD: −9.5 (−17.5 to −1.5)	I^2 = 82%; p < 0.0001 I^2 = 73%; p < 0.03	Low†# 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;■(■):■-■.

*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.

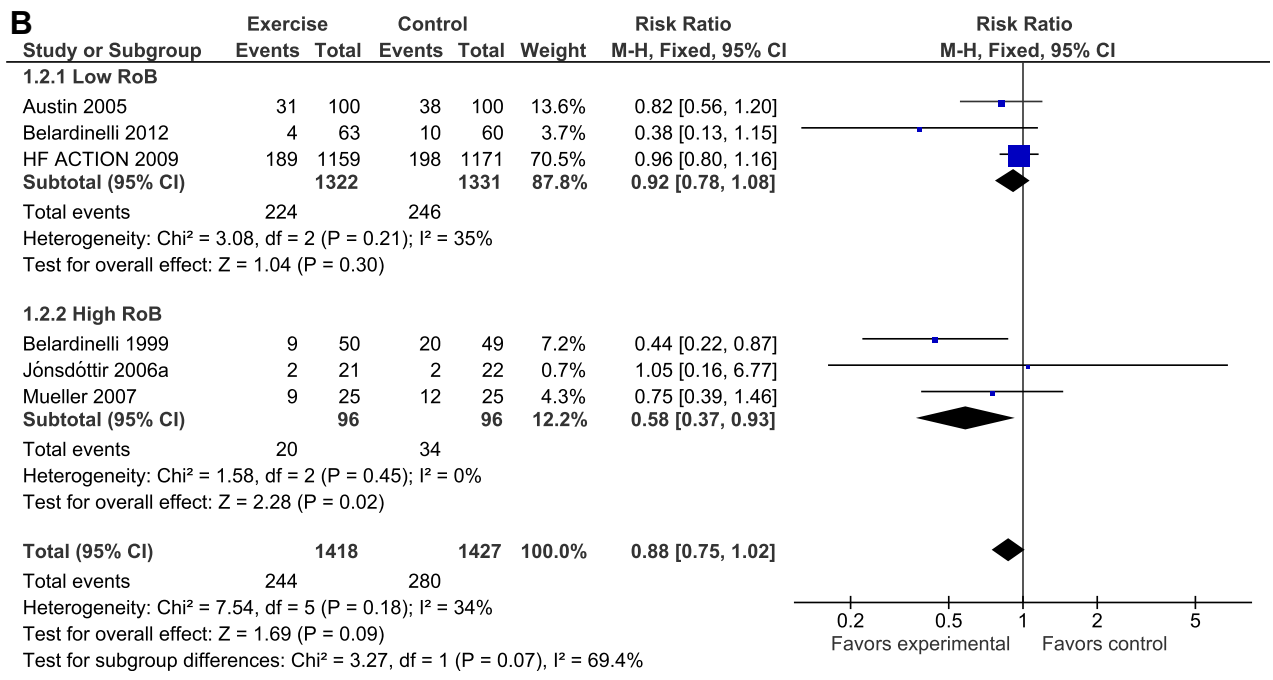
FIGURE 2 **Meta-Analyses of Events and HRQoL Outcomes**



(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.

Continued on the next page

FIGURE 2 Continued



Continued on the next page

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).

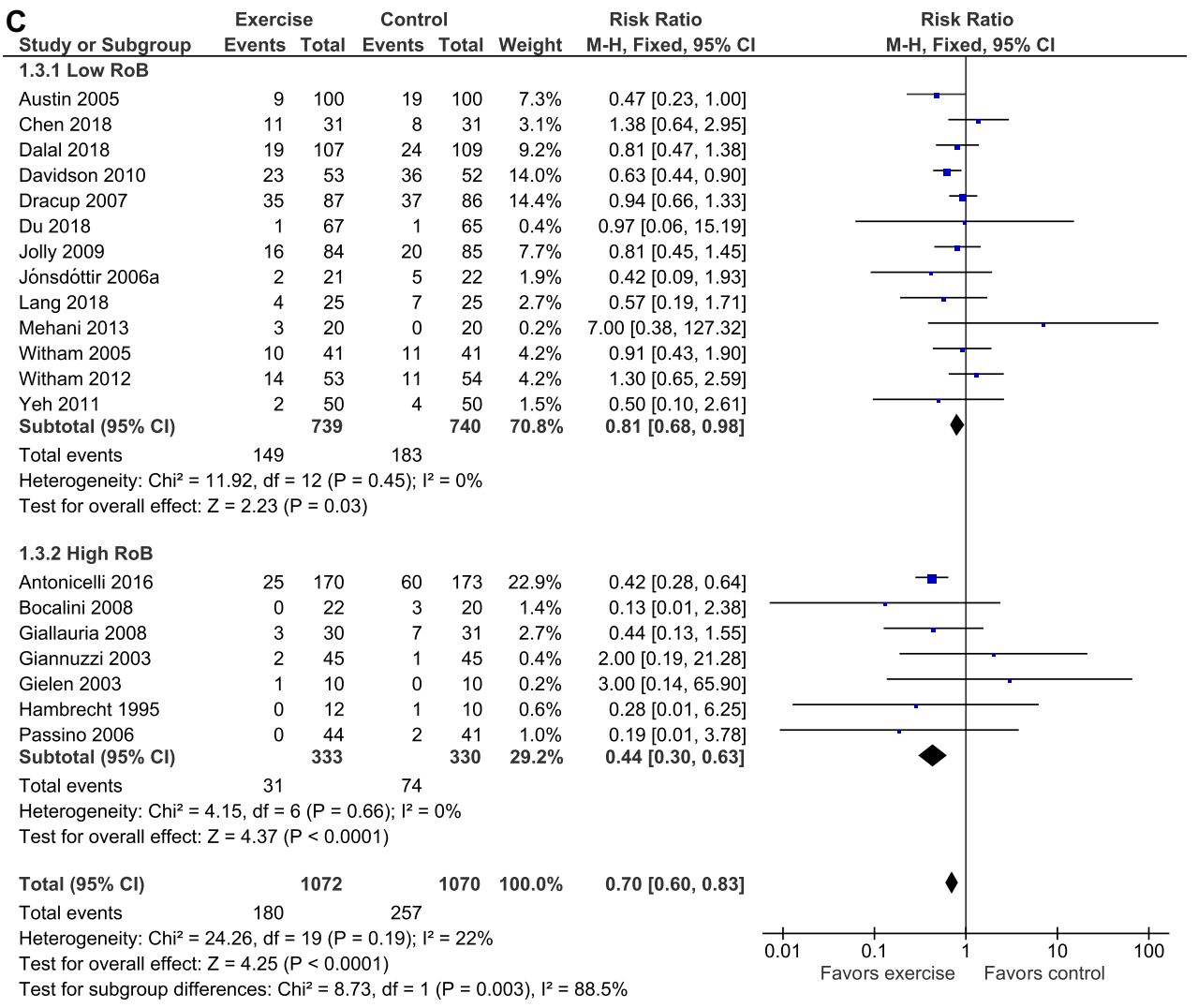
ExCR versus control did not affect mortality with >12 months follow-up (fixed-effects, 6 trials/comparisons, n = 2,845: RR: 0.88; 95% CI: 0.75 to 1.02) (**Figure 2B**) (high certainty). Studies did not consistently report deaths due to HF or sudden death.

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

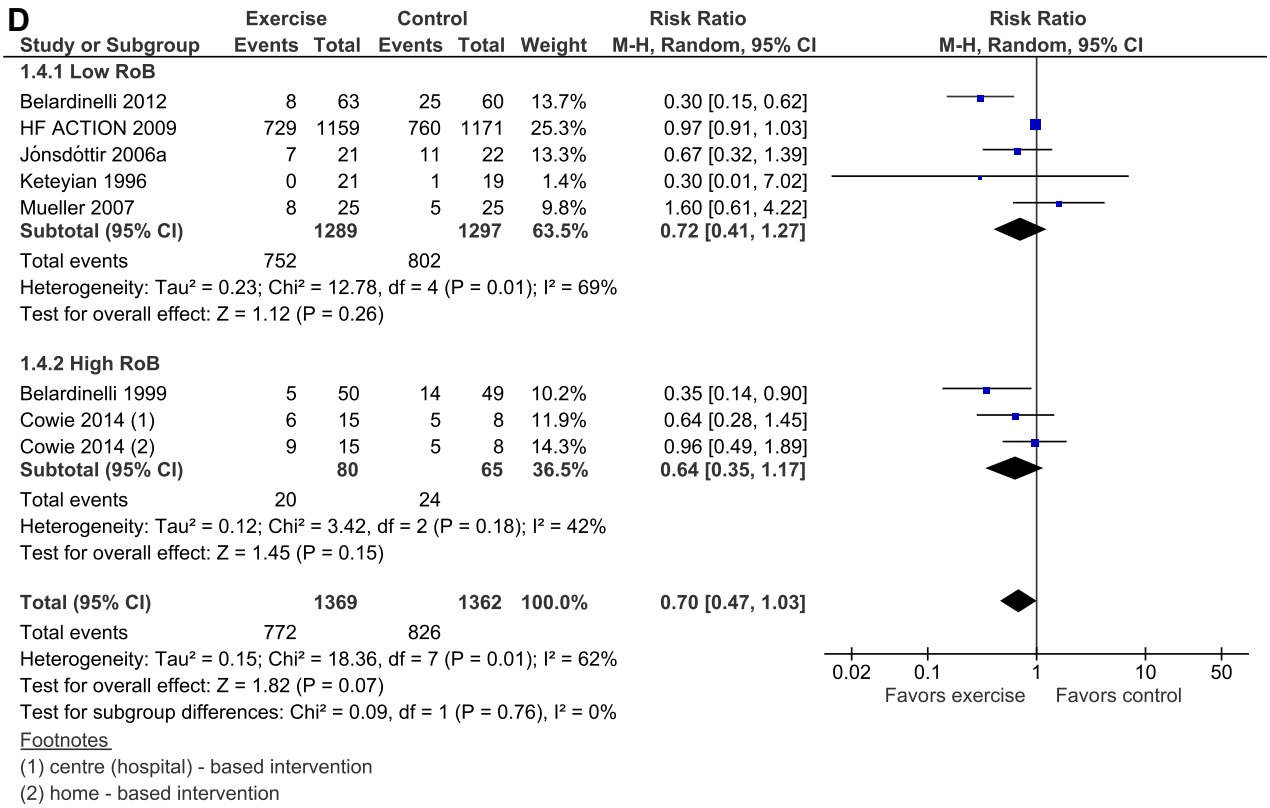


Continued on the next page

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) (**Figure 2F**, very low certainty). 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) (**Figure 2H**, low certainty). 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) (**Figure 2G**, GRADE: very low certainty). 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

FIGURE 2 Continued



Continued on the next page

the minimal important clinical difference of 5 points, 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).

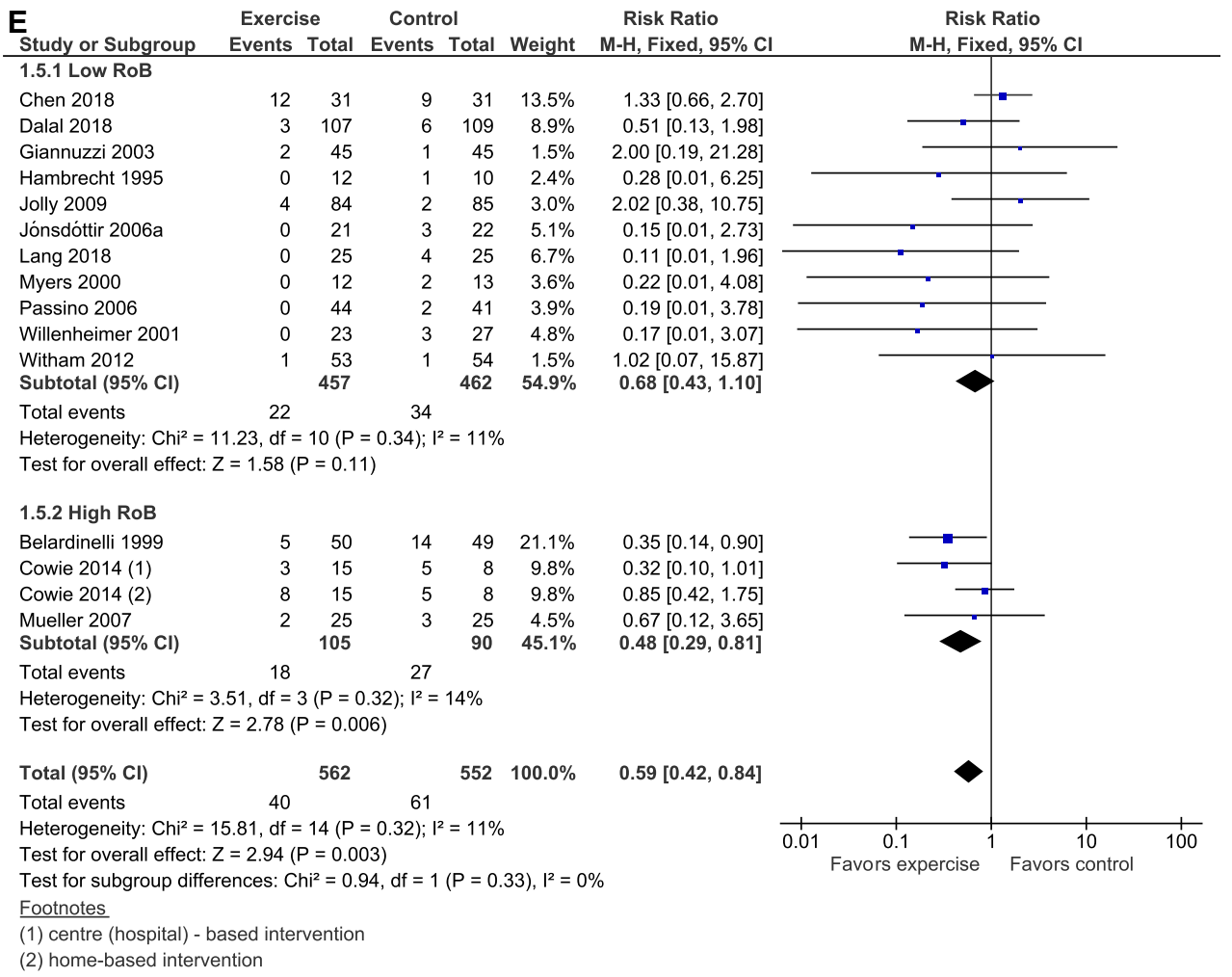
METAREGRESSION. There were no differential treatment effects across trial level characteristics and outcomes in univariate metaregression, except for the overall level of risk of bias and all-cause hospitalization, MLWHF, and HRQoL outcomes (Table 3). Trials at overall low risk of bias (low risk of bias 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



Continued on the next page

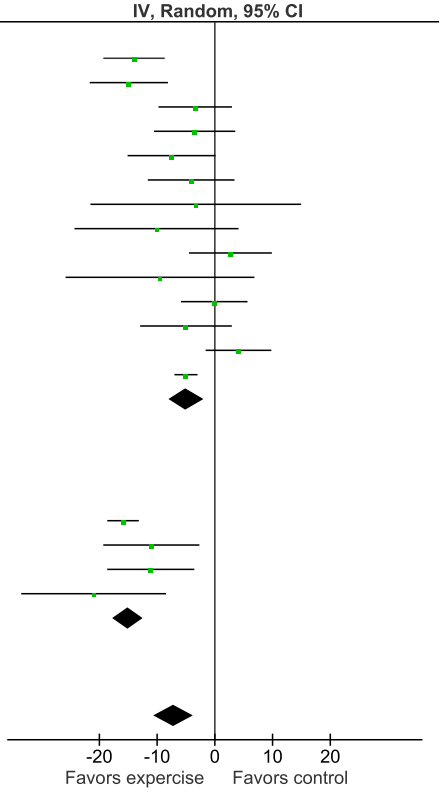
Potential differences were observed in the risk of all-cause hospitalization and hospitalization due to HF and improvements in HRQoL following exercise interventions. In trials reporting MLWHF questionnaire scores, those undertaking ExCR may have better disease-specific HRQoL by 7.1 points higher, on 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 versus 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

F

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.6.1 Low RoB								
Austin 2005	22.9	14.7	85	36.9	21.3	94	6.7%	-14.00 [-19.32, -8.68]
Chen 2018	19.4	12.2	31	34.3	14.4	29	6.1%	-14.90 [-21.68, -8.12]
Dalal 2018	24.1	20.9	92	27.5	23.2	93	6.3%	-3.40 [-9.76, 2.96]
Davidson 2010	52.9	15.7	50	56.4	18.3	42	6.0%	-3.50 [-10.54, 3.54]
Dracup 2007	35.7	23.7	86	43.2	27.3	87	5.7%	-7.50 [-15.12, 0.12]
Du 2018	36.9	21.59	67	41	22.4	65	5.8%	-4.10 [-11.61, 3.41]
Gary 2010 (1)	25.6	19.7	17	28.9	29.9	14	2.4%	-3.30 [-21.55, 14.95]
Gary 2010 (2)	24.2	16.3	15	34.3	23.6	16	3.3%	-10.10 [-24.30, 4.10]
Jolly 2009	37.6	21	77	34.9	24.8	80	5.9%	2.70 [-4.48, 9.88]
Lang 2018	29.2	25.8	22	38.7	30.1	23	2.8%	-9.50 [-25.86, 6.86]
McKelvie 2002	-3.4	18.1	57	-3.3	13.9	67	6.5%	-0.10 [-5.86, 5.66]
Nilsson 2008	23	14	35	28	20	37	5.6%	-5.00 [-12.94, 2.94]
Witham 2012	15.4	14.8	43	11.3	12.1	44	6.6%	4.10 [-1.59, 9.79]
Yeh 2011	13	4	50	18	6	50	7.8%	-5.00 [-7.00, -3.00]
Subtotal (95% CI)			**727**			**741**	**77.4%**	**-4.91 [-7.93, -1.90]**
Heterogeneity: Tau² = 18.17; Chi² = 37.91, df = 13 (P = 0.0003); I² = 66%								
Test for overall effect: Z = 3.19 (P = 0.001)								
1.6.2 High RoB								
Antonicelli 2016	28.6	12.3	150	44.5	12.3	163	7.6%	-15.90 [-18.63, -13.17]
Belardinelli 1999	40	19	48	51	22	46	5.4%	-11.00 [-19.33, -2.67]
Koukouvou 2004	34.1	13	16	45.2	9	19	5.7%	-11.10 [-18.65, -3.55]
Passino 2006	32	26.5	44	53	32	41	3.8%	-21.00 [-33.54, -8.46]
Subtotal (95% CI)			**258**			**269**	**22.6%**	**-15.03 [-17.76, -12.30]**
Heterogeneity: Tau² = 0.75; Chi² = 3.19, df = 3 (P = 0.36); I² = 6%								
Test for overall effect: Z = 10.78 (P < 0.00001)								
Total (95% CI)			**985**			**1010**	**100.0%**	**-7.11 [-10.49, -3.73]**
Heterogeneity: Tau² = 36.91; Chi² = 93.22, df = 17 (P < 0.00001); I² = 82%								
Test for overall effect: Z = 4.12 (P < 0.0001)								
Test for subgroup differences: Chi² = 23.74, df = 1 (P < 0.00001), I² = 95.8%								



Footnotes
(1) exercise alone
(2) comprehensive rehabilitation (CBT and exercise)

Continued on the next page

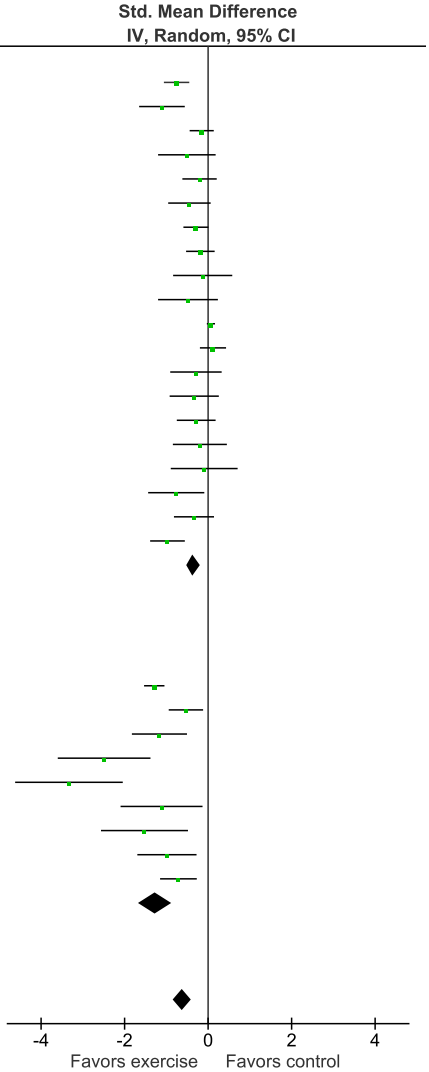
contrast to the present study, no reduction with ExCR was found in either all-cause hospitalization (hazard ratio of 0.90; 95% CI: 0.76 to 1.06) or HF-specific hospitalization (hazard ratio of 0.98; 95% CI 0.72 to 1.35). Although individual participant data meta-analysis is recognized as the gold standard 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

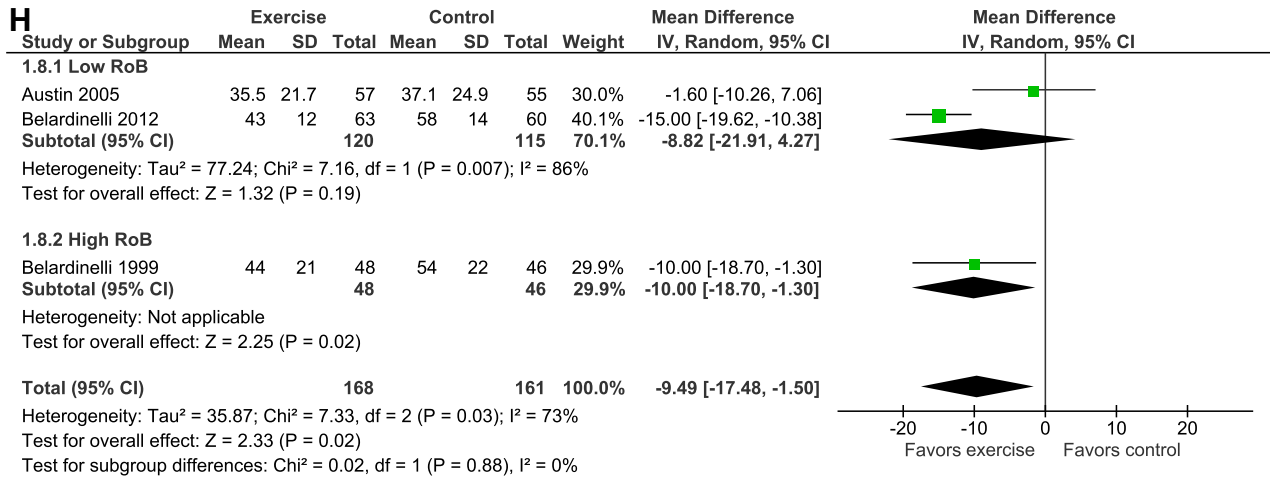


TABLE 3 Univariate Meta-Regression Analysis*

	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.

ACKNOWLEDGEMENTS The authors thank the Cochrane Heart Group, the reviewers for comments on drafts of the Cochrane review, information specialist Charlene Bridges for running updated database searches, and co-authors Dr. Viral Sagar and Fiona Lough for previous updates of this review.

ADDRESS FOR CORRESPONDENCE: Prof. Rod Taylor, MRC/CSO Social and Public Health Sciences Unit, University of Glasgow, Top floor, 200 Renfield Street, Glasgow G2 3AX, United Kingdom. E-mail: rod.taylor@gla.ac.uk.

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.

REFERENCES

1. Braunwald E. The war against heart failure: the Lancet lecture. Lancet 2015;385:812–24.

2. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. Nat Rev Cardiol 2016;13:368–78.

3. Calvert MJ, Freemantle N, Cleland JGF. The impact of chronic heart failure on health-related quality of life data acquired in the baseline phase of the CARE-HF study. Eur J Heart Fail 2007;7:243–51.

4. Wingate S. Quality of life research: more than ever. J Card Fail 2016;22:851–2.

5. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association. Task force on practice guidelines. J Am Coll Cardiol 2013;62:e147–239.

6. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891–975.

7. National Institute for Health and Care Excellence. Chronic heart failure in adults: diagnosis and management (NICE guideline NG106) 2018. Available at: https://www.nice.org.uk/guidance/ng106. Accessed June 5, 2019.

8. Taylor RS, Sagar VA, Davies EJ, et al. Exercise-based rehabilitation for heart failure. Cochrane Database Syst Rev 2014 Apr 27;(4):CD003331.

9. Golwala H, Pandey A, Ju C, et al. Temporal trends and factors associated with cardiac rehabilitation referral among patients hospitalized with heart failure: findings from Get With The Guidelines-Heart Failure Registry. J Am Coll Cardiol 2015;66:917–26.

10. Bjarnason-Wehrens B, McGee H, Zwisler AD, et al. Cardiac rehabilitation in Europe: results from the European Cardiac Rehabilitation Inventory Survey. Eur J Cardiovasc Prev Rehabil 2010;17:410–8.

11. Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential Analysis in systematic reviews with meta-analysis. BMC Med Res Methodol 2017;17:39.

12. Moher D, Liberati A, Tetzlaff J, Altman DG, for the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Brit Med J 2009;339:b2535.

13. Long L, Anderson L, Dewhirst AM, He J, Bridges C, Gandhi M, Taylor RS. Exercise-based cardiac rehabilitation for adults with stable angina. Cochrane Database Syst Rev 2018 Feb 2;2:CD012786.

14. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (updated March 2011). Available at: https://training.cochrane.org/handbook. Accessed June 5, 2019.

15. American Thoracic Society. Minnesota Living with Heart Failure Questionnaire. 2004. New York: American Thoracic Society; 2004. Available at: http://qol.thoracic.org/sections/instruments/ko/pages/MLWHFq.html. Accessed June 15, 2018.

16. Egger M, Davey Smith G, Schneiger M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Brit Med J 1997;315:629–34.

17. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439–50.

18. Gary RA, Dunbar SB, Higgins MK, Musselman DL, Smith AL. Combined exercise and cognitive behavioral therapy improves outcomes in patients with heart failure. J Psychosom Res 2010;69:119–31.

19. Klocek M, Kubinyi A, Bacior B, Kawecka-Jaszcz K. Effect of physical training on quality of life and oxygen consumption in patients with congestive heart failure. Int J Cardiol 2005;103:323–9.

20. Cowie A, Thow MK, Granat MH, Mitchell SL. Effects of home versus hospital-based exercise training in chronic heart failure. Int J Cardiol 2012;158:295–8.

21. Kalsatou ACH, Kouidi EI, Anifanti MA, Douka SI, Deligiannis AP. Functional and psychosocial effects of either a traditional dancing or a formal exercising training program in patients with chronic heart failure: a comparative randomized controlled study. Clin Rehab 2014;28:128–38.

22. Davidson PM, Cockburn J, Newton PJ, et al. Can a heart failure-specific cardiac rehabilitation program decrease hospitalizations and improve outcomes in high-risk patients? Eur J Cardiovasc Prevent Rehab 2010;17:393–402.

23. Nilsson BB, Westheim A, Risberg MA. Long-term effects of a group-based high-intensity aerobic interval-training program in patients with chronic heart failure. Am J Cardiol 2008;102:1220–4.

24. Wall HK, Ballard J, Troped P, Njike VY, Katz DL. Impact of home-based, supervised exercise on congestive heart failure. Int J Cardiol 2010;145:267–70.

25. Antonicelli R, Spazzafumo L, Scalvini S, et al. Exercise: a "new drug" for elderly patients with chronic heart failure. Aging 2016;8:860–72.

26. Reeves GR, Whellan DJ, O"Conner CM, et al. A novel rehabilitation intervention for older patients with acute decompensated heart failure: The REHAB-HF pilot study. J Am Coll Cardiol HF 2017;5:359–66.

27. Chen Y, Funk M, Wen J, Tang X, He G, Liu H. Effectiveness of a multidisciplinary disease management program on outcomes in patients with heart failure in China: A randomized controlled single center study. Heart Lung 2018;47:24–31.

28. Lang CC, Smith K, Wingham J, Eyre V, et al. A randomized controlled trial of a facilitated home-based rehabilitation intervention in patients with heart failure with preserved ejection fraction and their caregivers: REACH-HFpEF Pilot Study. BMJ Open 2018;8:e019649.

29. Dracup K, Evangelista LS, Hamilton MA, et al. Effects of a home-based exercise program on clinical outcomes in heart failure. Am Heart J 2007;154:877–83.

30. Jolly K, Taylor RS, Lip GY, et al. A randomized trial of the addition of home-based exercise to

specialist heart failure nurse care: the Birmingham Rehabilitation Uptake Maximisation study for patients with Congestive Heart Failure (BRUM-CHF) study. Eur J Heart Fail 2009;11:205–13.

31. Keteyian SJ, Levine AB, Brawner CA, et al. Exercise training in patients with heart failure. A randomized, controlled trial. Ann Int Med 1996; 124:1051–7.

32. Passino C, Severino S, Poletti R, et al. Aerobic training decreases B-type natriuretic peptide expression and adrenergic activation in patients with heart failure. J Am Coll Cardiol 2006;47:1835–9.

33. Du H, Newton PJ, Budhathoki C, et al. The Home-Heart-Walk study, the effect of a self-administered walk test on perceived physical functioning and self-care behaviour in people with stable chronic heart failure: a randomized controlled trial. Eur J Cardiovasc Nurs 2018;17:235–45.

34. Dalal H, Taylor RS, Jolly K, et al. Facilitated self-care and rehabilitation for people with heart failure with reduced ejection fraction: the REACH-HF (Rehabilitation EnAblement in CHronic Heart Failure) multicenter randomized controlled trial. Eur J Prev Cardiol 2019;26:262–72.

35. Taylor RS, Walker S, Smart NA, et al. Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalization: an individual patient data meta-analysis of randomized trials. Eur J Heart Fail 2018;20:1735–43.

36. Taylor RS, Walker S, Smart NA, et al. Impact of exercise-based rehabilitation in patients with heart failure (ExTraMATCH II) on exercise capacity and health-related quality of life: a meta-analysis of individual participant data from randomized trials. J Am Coll Cardiol 2019;73: 1430–43.

37. Stewart LA, Clarke M, Rovers M, et al. Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. JAMA 2015;313: 1657–65.

38. Zhang Y, Xu L, Yao Y, et al. Effect of short-term exercise intervention on cardiovascular functions and quality of life of chronic heart failure patients: a meta-analysis. J Exer Sci Fitness 2016; 14:67–75.

39. Chan E, Giallauria F, Vigorito C, Smart NA. Exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis. Monaldi Arch Chest Dis 2016; 86:759.

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.