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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. Metare-gression 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

hronic 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 recom-

mendation 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

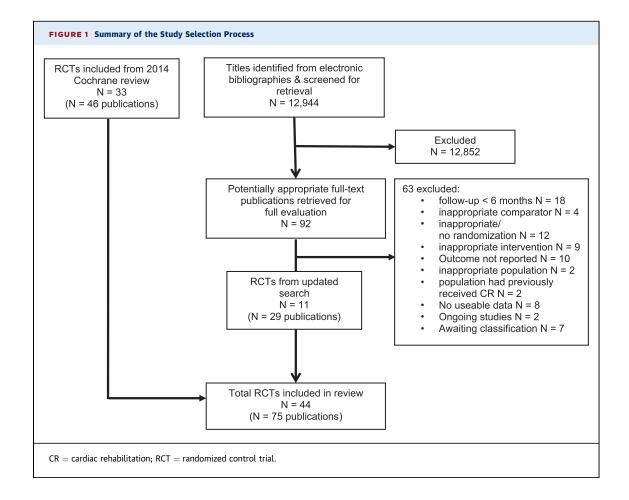
Europe participated in ExCR (9,10), prompting a call to explore more accessible alternatives to the conventional model of group supervised center-based ExCR, such as home-based and internet programs (8,9).

The present study undertook a review and metaanalyses 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)



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 \geq 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 I² 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 I² 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,

TABLE 1 Summary of Trial, Patient, and	Intervention Char	acteristics
	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 centerbased 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.

 $\label{eq:chi} CHD = \text{coronary heart disease; } ExCR = \text{exercise-based cardiac rehabilitation; } HFpEF = \text{heart} \\ failure with preserved ejection fraction; } NYHA = \text{New York Heart Association.} \end{cases}$

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.

	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)

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 \geq 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 fulllength 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 \geq 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

AL ILLUSTRA of Life Outcomes	TION Summ	nary of Meta-An	nalysis Effects	s on Clinical and H	lealth-Related		
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 (l 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)	l 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)	l 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)	l 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)	l 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)	l ² = 11%; p = 0.32	Low†‡	
MLWHF 6-12 months follow-up	17 (18)	-	-	MD: -7.1 (-10.5 to -3.7)	l ² = 82%; p < 0.0001	Low†#	
MLWHF ≥12 months follow-up	3 (3)	-	-	MD: -9.5 (-17.5 to -1.5)	l ² = 73%; p < 0.03	Low††***	
All HRQoL outcome 6-12 months follow-up	27 (29)	-	-	SMD: -0.60 (-0.82 to -0.39)	l ² = 87%; p < 0.0001	Low†**	

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*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 ($l^2 = 66\%$); 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 ($l^2 = 87\%$); therefore, certainty of evidence was downgraded by 1 level. \dagger three intervals in the substantial statistical heterogeneity ($l^2 = 73\%$); 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

	Exercis		Contr			Risk Ratio	Risk Ratio
tudy or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
.1.1 Low RoB							
ustin 2005	5	100	4	100	4.9%	1.25 [0.35, 4.52]	
hen 2018	0	31	2	31	3.1%	0.20 [0.01, 4.00]	
alal 2018	4	107	4	109	4.9%	1.02 [0.26, 3.97]	
ANREHAB 2008	4	45	3	46	3.6%	1.36 [0.32, 5.75]	
avidson 2010	4	53	11	52	13.6%	0.36 [0.12, 1.05]	
acup 2007	9	87	8	86	9.9%	1.11 [0.45, 2.75]	
u 2018	1	67	1	65	1.2%	0.97 [0.06, 15.19]	
ary 2010 (1)	1	20	0	17	0.7%	2.57 [0.11, 59.30]	
ary 2010 (2)	0	18	1	19	1.8%	0.35 [0.02, 8.09]	
ambrecht 1998	1	10	1	10	1.2%	1.00 [0.07, 13.87]	
ambrecht 2000	3	36	2	37	2.4%	1.54 [0.27, 8.69]	
olly 2009	7	84	5	85	6.1%	1.42 [0.47, 4.29]	
cKelvie 2002	9	90	8	91	9.8%	1.14 [0.46, 2.82]	
ehani 2013	0	20	2	20	3.1%	0.20 [0.01, 3.92]	
yers 2000	1	12	0	13	0.6%	3.23 [0.14, 72.46]	
lsson 2008	2	40	1	40	1.2%	2.00 [0.19, 21.18]	
orman 2012	1	22	0	20	0.6%	2.74 [0.12, 63.63]	
all 2010	1	9	1	10	1.2%	1.11 [0.08, 15.28]	
'illenheimer 2001	3	27	2	27	2.5%	1.50 [0.27, 8.28]	
itham 2005	1	41	3	41	3.7%	0.33 [0.04, 3.07]	
itham 2012	3	53	2	54	2.4%	1.53 [0.27, 8.78]	
eh 2011	0	50	3	50	4.3%	0.14 [0.01, 2.70]	
ubtotal (95% CI)		1022		1023	82.7%	0.94 [0.68, 1.31]	•
eterogeneity: Chi ² = [·] est for overall effect: : 1.2 High RoB		•		2 = 0%			
ntonicelli 2016	5	170	8	173	9.7%	0.64 [0.21, 1.91]	
iannuzzi 2003	0	45	1	45	1.8%	0.33 [0.01, 7.97]	
ottlieb 1999	1	17	0	18	0.6%	3.17 [0.14, 72.80]	
ambrecht 1995	1	12	0	10	0.7%	2.54 [0.11, 56.25]	
eteyian 1996	0	21	1	19	1.9%	0.30 [0.01, 7.02]	
zehl 2008	0	15	1	6	2.6%	0.15 [0.01, 3.16]	
ubtotal (95% CI)	÷	280		271	17.3%	0.65 [0.29, 1.46]	
tal events	7		11				-
eterogeneity: Chi ² = 3		5 (P = (0%			
est for overall effect:		•	, ·				
otal (95% CI)		1302		1294	100.0%	0.89 [0.66, 1.21]	◆
otal events	67		75				
	Z = 0.73 (F	P = 0.4	7)		.41), l² = 0	%	0.01 0.1 1 10 100 Favors exercise Favors control
est for overall effect:	rences: Cł						
est for overall effect: est for subgroup diffe	rences: Cl	. 0.					
eterogeneity: Chi ² = ⁻ est for overall effect: est for subgroup diffe <u>potnotes</u>) exercise alone	rences: Cl						

cause horizon at >12 months' follow-up. (b) Att-cause montanty at >12 months' follow-up. (c) Att-cause horizon at >12 months'

3	Exerci	se	Contr	ol		Risk Ratio	Risk	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fix	ed, 95% Cl
1.2.1 Low RoB								
Austin 2005	31	100	38	100	13.6%	0.82 [0.56, 1.20]		<u> </u>
Belardinelli 2012	4	63	10	60	3.7%	0.38 [0.13, 1.15]	•	
HF ACTION 2009 Subtotal (95% CI)	189	1159 1322	198	1171 1331	70.5% 87.8%	0.96 [0.80, 1.16] 0.92 [0.78, 1.08]	-	-
Total events	224		246					
Heterogeneity: Chi ² =	3.08, df =	2 (P = 0	0.21); l² =	35%				
Test for overall effect:	Z = 1.04 (Р = 0.3	0)					
1.2.2 High RoB								
Belardinelli 1999	9	50	20	49	7.2%	0.44 [0.22, 0.87]	-	
Jónsdóttir 2006a	2	21	2	22	0.7%	1.05 [0.16, 6.77]		•
Mueller 2007 Subtotal (95% CI)	9	25 96	12	25 96	4.3% 12.2%	0.75 [0.39, 1.46] 0.58 [0.37, 0.93]		<u> </u>
Total events	20		34					
Heterogeneity: Chi ² =	1.58, df =	2 (P = 0	0.45); l² =	0%				
Test for overall effect:	Z = 2.28 (P = 0.0	2)					
Total (95% CI)		1418		1427	100.0%	0.88 [0.75, 1.02]	•	
Total events	244		280					
			0.18); l² =					1 1 1

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 \geq 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).

	Exerci		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.3.1 Low RoB							
Austin 2005	9	100	19	100	7.3%	0.47 [0.23, 1.00]	_
Chen 2018	11	31	8	31	3.1%	1.38 [0.64, 2.95]	
Dalal 2018	19	107	24	109	9.2%	0.81 [0.47, 1.38]	
Davidson 2010	23	53	36	52	14.0%	0.63 [0.44, 0.90]	
Dracup 2007	35	87	37	86	14.4%	0.94 [0.66, 1.33]	
Du 2018	1	67	1	65	0.4%	0.97 [0.06, 15.19]	
Jolly 2009	16	84	20	85	7.7%	0.81 [0.45, 1.45]	
Jónsdóttir 2006a	2	21	5	22	1.9%	0.42 [0.09, 1.93]	
Lang 2018	4	25	7	25	2.7%	0.57 [0.19, 1.71]	
Mehani 2013	3	20	0	20	0.2%	7.00 [0.38, 127.32]	
Witham 2005	10	41	11	41	4.2%	0.91 [0.43, 1.90]	_ + _
Witham 2012	14	53	11	54	4.2%	1.30 [0.65, 2.59]	
Yeh 2011	2	50	4	50	1.5%	0.50 [0.10, 2.61]	
Subtotal (95% CI)		739		740	70.8%	0.81 [0.68, 0.98]	•
Total events	149		183				
Heterogeneity: Chi ² =	11.92, df =	12 (P	= 0.45); l ²	² = 0%			
Test for overall effect:	Z = 2.23 (F	⊃ = 0.0	3)				
1.3.2 High RoB							
-	25	170	60	173	22.9%	0 42 [0 28 0 64]	
Antonicelli 2016	25 0	170 22	60 3	173 20	22.9% 1.4%	0.42 [0.28, 0.64]	
Antonicelli 2016 Bocalini 2008	0	22	3	20	1.4%	0.13 [0.01, 2.38]	
Antonicelli 2016 Bocalini 2008 Giallauria 2008	0 3	22 30	3 7	20 31	1.4% 2.7%	0.13 [0.01, 2.38] 0.44 [0.13, 1.55]	
Antonicelli 2016 Bocalini 2008 Giallauria 2008 Giannuzzi 2003	0 3 2	22 30 45	3 7 1	20 31 45	1.4% 2.7% 0.4%	0.13 [0.01, 2.38] 0.44 [0.13, 1.55] 2.00 [0.19, 21.28]	
Antonicelli 2016 Bocalini 2008 Giallauria 2008 Giannuzzi 2003 Gielen 2003	0 3 2 1	22 30 45 10	3 7 1 0	20 31 45 10	1.4% 2.7% 0.4% 0.2%	0.13 [0.01, 2.38] 0.44 [0.13, 1.55] 2.00 [0.19, 21.28] 3.00 [0.14, 65.90]	
Antonicelli 2016 Bocalini 2008 Giallauria 2008 Giannuzzi 2003 Gielen 2003 Hambrecht 1995	0 3 2 1 0	22 30 45 10 12	3 7 1 0 1	20 31 45 10 10	1.4% 2.7% 0.4% 0.2% 0.6%	0.13 [0.01, 2.38] 0.44 [0.13, 1.55] 2.00 [0.19, 21.28] 3.00 [0.14, 65.90] 0.28 [0.01, 6.25]	
Antonicelli 2016 Bocalini 2008 Giallauria 2008 Giannuzzi 2003 Gielen 2003 Hambrecht 1995 Passino 2006	0 3 2 1	22 30 45 10	3 7 1 0	20 31 45 10	1.4% 2.7% 0.4% 0.2%	0.13 [0.01, 2.38] 0.44 [0.13, 1.55] 2.00 [0.19, 21.28] 3.00 [0.14, 65.90]	
Antonicelli 2016 Bocalini 2008 Giallauria 2008 Giannuzzi 2003 Gielen 2003 Hambrecht 1995 Passino 2006 Subtotal (95% CI)	0 3 2 1 0 0	22 30 45 10 12 44	3 7 1 0 1 2	20 31 45 10 10 41	1.4% 2.7% 0.4% 0.2% 0.6% 1.0%	0.13 [0.01, 2.38] 0.44 [0.13, 1.55] 2.00 [0.19, 21.28] 3.00 [0.14, 65.90] 0.28 [0.01, 6.25] 0.19 [0.01, 3.78]	
Antonicelli 2016 Bocalini 2008 Giallauria 2008 Giannuzzi 2003 Gielen 2003 Hambrecht 1995 Passino 2006 Subtotal (95% CI) Total events	0 3 2 1 0 0 31	22 30 45 10 12 44 333	3 7 1 0 1 2 74	20 31 45 10 10 41 330	1.4% 2.7% 0.4% 0.2% 0.6% 1.0%	0.13 [0.01, 2.38] 0.44 [0.13, 1.55] 2.00 [0.19, 21.28] 3.00 [0.14, 65.90] 0.28 [0.01, 6.25] 0.19 [0.01, 3.78]	
Antonicelli 2016 Bocalini 2008 Giallauria 2008 Giannuzzi 2003 Gielen 2003 Hambrecht 1995 Passino 2006 Subtotal (95% CI)	0 3 2 1 0 0 31 4.15, df = 6	22 30 45 10 12 44 333 6 (P = 0	3 7 1 0 1 2 74 74 0.66); ² =	20 31 45 10 10 41 330	1.4% 2.7% 0.4% 0.2% 0.6% 1.0%	0.13 [0.01, 2.38] 0.44 [0.13, 1.55] 2.00 [0.19, 21.28] 3.00 [0.14, 65.90] 0.28 [0.01, 6.25] 0.19 [0.01, 3.78]	
Antonicelli 2016 Bocalini 2008 Giallauria 2008 Giannuzzi 2003 Gielen 2003 Hambrecht 1995 Passino 2006 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	0 3 2 1 0 0 31 4.15, df = 6	22 30 45 10 12 44 333 6 (P = 0	3 7 1 0 1 2 74 74 0.66); ² =	20 31 45 10 10 41 330 0%	1.4% 2.7% 0.4% 0.2% 0.6% 1.0%	0.13 [0.01, 2.38] 0.44 [0.13, 1.55] 2.00 [0.19, 21.28] 3.00 [0.14, 65.90] 0.28 [0.01, 6.25] 0.19 [0.01, 3.78]	
Antonicelli 2016 Bocalini 2008 Giallauria 2008 Giannuzzi 2003 Gielen 2003 Hambrecht 1995 Passino 2006 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Total (95% CI)	0 3 2 1 0 0 31 4.15, df = 6 Z = 4.37 (F	22 30 45 10 12 44 333 6 (P = (> < 0.0	3 7 1 0 1 2 74 0.66); ² = 001)	20 31 45 10 10 41 330 0%	1.4% 2.7% 0.4% 0.2% 0.6% 1.0% 29.2%	0.13 [0.01, 2.38] 0.44 [0.13, 1.55] 2.00 [0.19, 21.28] 3.00 [0.14, 65.90] 0.28 [0.01, 6.25] 0.19 [0.01, 3.78] 0.44 [0.30, 0.63]	
Antonicelli 2016 Bocalini 2008 Giallauria 2008 Giannuzzi 2003 Gielen 2003 Hambrecht 1995 Passino 2006 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	0 3 2 1 0 0 31 4.15, df = 6 Z = 4.37 (F	22 30 45 10 12 44 333 6 (P = 0 P < 0.0 1072	3 7 1 0 1 2 74 0.66); I ² = 001) 257	20 31 45 10 10 41 330 0% 1070	1.4% 2.7% 0.4% 0.2% 0.6% 1.0% 29.2%	0.13 [0.01, 2.38] 0.44 [0.13, 1.55] 2.00 [0.19, 21.28] 3.00 [0.14, 65.90] 0.28 [0.01, 6.25] 0.19 [0.01, 3.78] 0.44 [0.30, 0.63]	

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) (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 followup (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 TSAadjusted 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,

D Exercise Control Risk Ratio Hisk Ratio 1.4.1 Low RoB Belardinelli 2012 8 63 25 60 13.7% 0.30 [0.15, 0.62] HF ACTION 2009 7.29 1159 760 1171 25.3% 0.37 [0.91, 1.03] Jönsdöttir 2006a 7 2.1 1 1.9 1.4% 0.30 [0.01, 7, 02] HF ACTION 2009 7.9 1.289 1.297 63.5% 0.72 [0.41, 1.27] Jönsdöttir 2006a 7 2.1 1.9 1.4% 0.30 [0.01, 7, 02] Mueller 2007 8 2.5 5.2 9.8% 1.60 [0.61, 4.22] Subtotal (95% CI) 1289 1297 63.5% 0.72 [0.41, 1.27] Total events 752 802 Heterogeneity: Tau ² = 0.23; Chi ² = 12.78, df = 4 (P = 0.01); l ² = 69% Test for overall effect: Z = 1.12 (P = 0.26) Cowie 2014 (1) 6 15 5 8 14.3% 0.96 [0.49, 1.89] 0.64 [0.35, 1.17] Total events 702 8.26 1.43% <	FIGURE 2 Continued							
Belardinelli 2012 8 63 25 60 13.7% 0.30 [0.15, 0.62] HF ACTION 2009 729 1159 760 1171 25.3% 0.97 [0.91, 1.03] Jónsdóttir 2006a 7 21 11 22 13.3% 0.67 [0.32, 1.39] Keteyian 1996 0 21 1 19 1.4% 0.30 [0.01, 7.02] Mueller 2007 8 25 5 25 9.8% 1.60 [0.61, 4.22] Subtotal (95% CI) 1289 1297 63.5% 0.72 [0.41, 1.27] Total events 752 802 Heterogeneity: Tau ² = 0.23; Chi ² = 12.78, df = 4 (P = 0.01); l ² = 69% Test for overall effect: Z = 1.12 (P = 0.26) 1.4.2 High RoB Belardinelli 1999 5 50 14 49 10.2% 0.35 [0.14, 0.90] Cowie 2014 (1) 6 15 5 8 11.9% 0.64 [0.28, 1.45] Cowie 2014 (2) 9 15 5 8 14.3% 0.96 [0.49, 1.89] Subtotal (95% CI) 80 65 36.5% 0.64 [0.28, 1.45] Cowie 2014 (2) 9 15 5 8 14.3% 0.96 [0.49, 1.89] Subtotal (95% CI) 80 65 36.5% 0.64 [0.35, 1.17] Total events 20 24 Heterogeneity: Tau ² = 0.12; Chi ² = 3.42, df = 2 (P = 0.18); l ² = 42% Test for overall effect: Z = 1.45 (P = 0.15) Total (95% CI) 1369 1362 100.0% 0.70 [0.47, 1.03] Total events 772 826 Heterogeneity: Tau ² = 0.15; Chi ² = 18.36, df = 7 (P = 0.01); l ² = 62% Test for overall effect: Z = 1.82 (P = 0.07) Test for subgroup differences: Chi ² = 0.09, df = 1 (P = 0.76), l ² = 0% <u>Footnotes</u> (1) centre (hospital) - based intervention	Study or Subgroup					Weight		
HF ACTION 2009 729 1159 760 1171 25.3% 0.97 [0.91, 1.03] Jónsdóttir 2006a 7 21 11 22 13.3% 0.67 [0.32, 1.39] Keteyian 1996 0 21 1 19 1.4% 0.30 [0.01, 7.02] Mueller 2007 8 25 25 9.8% 1.60 [0.61, 4.22] Subtotal (95% Cl) 1289 1297 63.5% 0.72 [0.41, 1.27] Total events 752 802 Heterogeneity: Tau ² = 0.23; Chi ² = 12.78, df = 4 (P = 0.01); l ² = 69% Test for overall effect: Z = 1.12 (P = 0.26) 1.4.2 High RoB Belardinelli 1999 5 50 14 49 10.2% 0.35 [0.14, 0.90] Cowie 2014 (1) 6 15 5 8 11.9% 0.64 [0.28, 1.45] Cowie 2014 (2) 9 15 5 8 14.3% 0.96 [0.49, 1.89] Subtotal (95% Cl) 1369 1362 100.0% 0.70 [0.47, 1.03] Total events 772 826 Heterogeneity: Tau ² = 0.15; Chi ² = 18.36, df = 7 (P = 0.01); l ² = 62% Test for overall effect: Z = 1.45 (P = 0.17) Total (95% Cl) 1369 1362 100.0% 0.70 [0.47, 1.03] Total events 772 826 Heterogeneity: Tau ² = 0.15; Chi ² = 18.36, df = 7 (P = 0.01); l ² = 62% Test for overall effect: Z = 1.82 (P = 0.07) Test for supprup differences: Chi ² = 0.09, df = 1 (P = 0.76), l ² = 0% <u>Footnotes</u> (1) centre (hospital) - based intervention	1.4.1 Low RoB							
Jónsdóttir 2006a 7 21 11 22 13.3% 0.67 [0.32, 1.39] Keteyian 1996 0 21 1 19 1.4% 0.30 [0.01, 7.02] Mueller 2007 8 25 5 25 9.8% 1.60 [0.61, 4.22] Subtotal [95% CI) 1289 1297 63.5% 0.72 [0.41, 1.27] Total events 752 802 Heterogeneity: Tau ² = 0.23; Chi ² = 12.78, df = 4 (P = 0.01); l ² = 69% Test for overall effect: $Z = 1.12$ (P = 0.26) 1.4.2 High RoB Belardinelli 1999 5 50 14 49 10.2% 0.35 [0.14, 0.90] Cowie 2014 (1) 6 15 5 8 11.9% 0.64 [0.28, 1.45] Cowie 2014 (2) 9 15 5 8 14.3% 0.96 [0.49, 1.89] Subtotal [95% CI) 80 65 36.5% 0.64 [0.35, 1.17] Total events 20 24 Heterogeneity: Tau ² = 0.12; Chi ² = 3.42, df = 2 (P = 0.18); l ² = 42% Test for overall effect: $Z = 1.45$ (P = 0.15) Total events 772 826 Heterogeneity: Tau ² = 0.15; Chi ² = 18.36, df = 7 (P = 0.01); l ² = 62% Test for overall effect: $Z = 1.82$ (P = 0.07) Test for subgroup differences: Chi ² = 0.09, df = 1 (P = 0.76), l ² = 0% <u>Footnotes</u> (1) centre (hospital) - based intervention		-					. , ,	_ _
Keteyian 1996 0 21 1 19 1.4% 0.30 [0.01, 7.02] Mueller 2007 8 25 5 25 9.8% 1.60 [0.61, 4.22] Subtotal (95% Cl) 1289 1297 63.5% 0.72 [0.41, 1.27] Total events 752 802 Heterogeneity: Tau ² = 0.23; Chi ² = 12.78, df = 4 (P = 0.01); l ² = 69% Test for overall effect: Z = 1.12 (P = 0.26) 1.4.2 High RoB Belardinelli 1999 5 50 14 49 10.2% 0.35 [0.14, 0.90] Cowie 2014 (1) 6 15 5 8 14.3% 0.96 [0.49, 1.89] Subtotal (95% Cl) 80 65 36.5% 0.64 [0.35, 1.17] Total events 20 24 Heterogeneity: Tau ² = 0.12; Chi ² = 3.42, df = 2 (P = 0.18); l ² = 42% Test for overall effect: Z = 1.45 (P = 0.15) Total events 772 826 Heterogeneity: Tau ² = 0.15; Chi ² = 18.36, df = 7 (P = 0.01); l ² = 62% Test for overall effect: Z = 1.82 (P = 0.07) Favors exercise Favors control Favors exercise Favors control Favors control Favors control </td <td></td> <td>729</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>•</td>		729						•
Mueller 2007 8 25 5 25 9.8% 1.60 [0.61, 4.22] Subtotal (95% CI) 1289 1297 63.5% 0.72 [0.41, 1.27] Total events 752 802 Heterogeneity: Tau ² = 0.23; Chi ² = 12.78, df = 4 (P = 0.01); l ² = 69% 0.72 [0.41, 1.27] Total events 752 802 Belardinelli 1999 5 50 14 49 10.2% 0.35 [0.14, 0.90] Cowie 2014 (1) 6 15 5 8 14.3% 0.96 [0.49, 1.45] Cowie 2014 (2) 9 15 5 8 14.3% 0.96 [0.49, 1.89] Subtotal (95% CI) 80 65 36.5% 0.64 [0.35, 1.17] 10 Total events 20 24 24 24 24 24 Heterogeneity: Tau ² = 0.12; Chi ² = 3.42; df = 2 (P = 0.18); l ² = 42% 0.70 [0.47, 1.03] 0.02 0.1 10 50 Total (95% CI) 1369 1362 100.0% 0.70 [0.47, 1.03] 10 50 Test for overall effect: Z = 1.82 (P = 0.07) 28		7		11				
Subtotal (95% Cl) 1289 1297 63.5% 0.72 $[0.41, 1.27]$ Total events 752 802 Heterogeneity: Tau ² = 0.23; Chi ² = 12.78, df = 4 (P = 0.01); l ² = 69% Test for overall effect: Z = 1.12 (P = 0.26) 1.4.2 High RoB Belardinelli 1999 5 50 14 49 10.2% 0.35 [0.14, 0.90] Cowie 2014 (1) 6 15 5 8 11.9% 0.64 [0.28, 1.45] Cowie 2014 (2) 9 15 5 8 14.3% 0.96 [0.49, 1.89] Subtotal (95% Cl) 80 65 36.5% 0.64 [0.35, 1.17] Total events 20 24 Heterogeneity: Tau ² = 0.12; Chi ² = 3.42, df = 2 (P = 0.18); l ² = 42% Test for overall effect: Z = 1.45 (P = 0.15) Total events 772 826 Heterogeneity: Tau ² = 0.15; Chi ² = 18.36, df = 7 (P = 0.01); l ² = 62% 0.02 0.1 1 0 50 Test for overall effect: Z = 1.82 (P = 0.07) Test for overall effect: Z = 1.82 (P = 0.07) Favors exercise Favors control Favors exercise Favors control Favors control Favors control		0		1	19			· · · · · · · · · · · · · · · · · · ·
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Heterogeneity: Tau ² = 0.23; Chi ² = 12.78, df = 4 (P = 0.01); l ² = 69% Test for overall effect: $Z = 1.12$ (P = 0.26) 1.4.2 High RoB Belardinelli 1999 5 50 14 49 10.2% 0.35 [0.14, 0.90] Cowie 2014 (1) 6 15 5 8 11.9% 0.64 [0.28, 1.45] Cowie 2014 (2) 9 15 5 8 14.3% 0.96 [0.49, 1.89] Subtotal (95% Cl) 80 65 36.5% 0.64 [0.35, 1.17] Total events 20 24 Heterogeneity: Tau ² = 0.12; Chi ² = 3.42, df = 2 (P = 0.18); l ² = 42% Test for overall effect: $Z = 1.45$ (P = 0.15) Total (95% Cl) 1369 1362 100.0% 0.70 [0.47, 1.03] Total events 772 826 Heterogeneity: Tau ² = 0.15; Chi ² = 18.36, df = 7 (P = 0.01); l ² = 62% Test for overall effect: $Z = 1.82$ (P = 0.09, df = 1 (P = 0.76), l ² = 0% Footnotes (1) centre (hospital) - based intervention	Subtotal (95% CI)	1	1289		1297	63.5%	0.72 [0.41, 1.27]	
Test for overall effect: $Z = 1.12$ (P = 0.26) 1.4.2 High RoB Belardinelli 1999 5 50 14 49 10.2% 0.35 [0.14, 0.90] Cowie 2014 (1) 6 15 5 8 11.9% 0.64 [0.28, 1.45] Cowie 2014 (2) 9 15 5 8 14.3% 0.96 [0.49, 1.89] Subtotal (95% CI) 80 65 36.5% 0.64 [0.35, 1.17] Total events 20 24 Heterogeneity: Tau ² = 0.12; Chi ² = 3.42, df = 2 (P = 0.18); l ² = 42% Test for overall effect: $Z = 1.45$ (P = 0.15) Total (95% CI) 1369 1362 100.0% 0.70 [0.47, 1.03] Total events 772 826 Heterogeneity: Tau ² = 0.15; Chi ² = 18.36, df = 7 (P = 0.01); l ² = 62% Test for overall effect: $Z = 1.82$ (P = 0.07) Test for overall effect: $Z = 1.82$ (P = 0.09, df = 1 (P = 0.76), l ² = 0% Footnotes (1) centre (hospital) - based intervention	Total events	752		802				
1.4.2 High RoB Belardinelli 1999 5 50 14 49 10.2% 0.35 [0.14, 0.90] Cowie 2014 (1) 6 15 5 8 11.9% 0.64 [0.28, 1.45] Cowie 2014 (2) 9 15 5 8 14.3% 0.96 [0.49, 1.89] Subtotal (95% CI) 80 65 36.5% 0.64 [0.35, 1.17] Total events 20 24 Heterogeneity: Tau ² = 0.12; Chi ² = 3.42, df = 2 (P = 0.18); l ² = 42% Test for overall effect: Z = 1.45 (P = 0.15) Total events 772 826 Heterogeneity: Tau ² = 0.15; Chi ² = 18.36, df = 7 (P = 0.01); l ² = 62% 0.70 [0.47, 1.03] Test for overall effect: Z = 1.82 (P = 0.07) 0.70 [0.47, 1.03] Test for subgroup differences: Chi ² = 0.09, df = 1 (P = 0.76), l ² = 0% Favors exercise Footnotes (1) centre (hospital) - based intervention	Heterogeneity: Tau ² = 0	0.23; Chi² =	= 12.78	3, df = 4 (P = 0.0	01); I² = 69	%	
Belardinelli 1999 5 50 14 49 10.2% 0.35 [0.14, 0.90] Cowie 2014 (1) 6 15 5 8 11.9% 0.64 [0.28, 1.45] Cowie 2014 (2) 9 15 5 8 14.3% 0.96 [0.49, 1.89] Subtotal (95% CI) 80 65 36.5% 0.64 [0.35, 1.17] Total events 20 24 Heterogeneity: Tau ² = 0.12; Chi ² = 3.42, df = 2 (P = 0.18); l ² = 42% Test for overall effect: $Z = 1.45$ (P = 0.15) Total (95% CI) 1369 1362 100.0% 0.70 [0.47, 1.03] Total events 772 826 Heterogeneity: Tau ² = 0.15; Chi ² = 18.36, df = 7 (P = 0.01); l ² = 62% Test for overall effect: $Z = 1.82$ (P = 0.07) Test for subgroup differences: Chi ² = 0.09, df = 1 (P = 0.76), l ² = 0% <u>Footnotes</u> (1) centre (hospital) - based intervention	Test for overall effect: 2	Z = 1.12 (P	= 0.26	5)				
Belardinelli 1999 5 50 14 49 10.2% 0.35 [0.14, 0.90] Cowie 2014 (1) 6 15 5 8 11.9% 0.64 [0.28, 1.45] Cowie 2014 (2) 9 15 5 8 14.3% 0.96 [0.49, 1.89] Subtotal (95% CI) 80 65 36.5% 0.64 [0.35, 1.17] Total events 20 24 Heterogeneity: Tau ² = 0.12; Chi ² = 3.42, df = 2 (P = 0.18); l ² = 42% Test for overall effect: $Z = 1.45$ (P = 0.15) Total (95% CI) 1369 1362 100.0% 0.70 [0.47, 1.03] Total events 772 826 Heterogeneity: Tau ² = 0.15; Chi ² = 18.36, df = 7 (P = 0.01); l ² = 62% Test for overall effect: $Z = 1.82$ (P = 0.07) Test for subgroup differences: Chi ² = 0.09, df = 1 (P = 0.76), l ² = 0% <u>Footnotes</u> (1) centre (hospital) - based intervention								
Cowie 2014 (1) 6 15 5 8 11.9% 0.64 [0.28, 1.45] Cowie 2014 (2) 9 15 5 8 14.3% 0.96 [0.49, 1.89] Subtotal (95% CI) 80 65 36.5% 0.64 [0.35, 1.17] Total events 20 24 Heterogeneity: Tau ² = 0.12; Chi ² = 3.42, df = 2 (P = 0.18); l ² = 42% Test for overall effect: $Z = 1.45$ (P = 0.15) Total (95% CI) 1369 1362 100.0% 0.70 [0.47, 1.03] Total events 772 826 Heterogeneity: Tau ² = 0.15; Chi ² = 18.36, df = 7 (P = 0.01); l ² = 62% Test for overall effect: $Z = 1.82$ (P = 0.07) Test for subgroup differences: Chi ² = 0.09, df = 1 (P = 0.76), l ² = 0% <u>Footnotes</u> (1) centre (hospital) - based intervention	1.4.2 High RoB							
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Subtotal (95% CI) 80 65 36.5% 0.64 [0.35, 1.17] Total events 20 24 Heterogeneity: Tau ² = 0.12; Chi ² = 3.42, df = 2 (P = 0.18); l ² = 42% Test for overall effect: Z = 1.45 (P = 0.15) Total (95% CI) 1369 1362 100.0% Total events 772 826 Heterogeneity: Tau ² = 0.15; Chi ² = 18.36, df = 7 (P = 0.01); l ² = 62% 0.02 0.1 1 10 50 Test for overall effect: Z = 1.82 (P = 0.07) Test for subgroup differences: Chi ² = 0.09, df = 1 (P = 0.76), l ² = 0% Favors exercise Favors control Footnotes (1) centre (hospital) - based intervention 1 Passed intervention	Cowie 2014 (1)	6	15	5	8	11.9%	0.64 [0.28, 1.45]	
Total events 20 24 Heterogeneity: Tau ² = 0.12; Chi ² = 3.42, df = 2 (P = 0.18); l ² = 42% Test for overall effect: Z = 1.45 (P = 0.15) Total (95% CI) 1369 1362 100.0% 0.70 [0.47, 1.03] Total events 772 826 Heterogeneity: Tau ² = 0.15; Chi ² = 18.36, df = 7 (P = 0.01); l ² = 62% Test for overall effect: Z = 1.82 (P = 0.07) Test for subgroup differences: Chi ² = 0.09, df = 1 (P = 0.76), l ² = 0% <u>Footnotes</u> (1) centre (hospital) - based intervention	Cowie 2014 (2)	9	15	5	8	14.3%	0.96 [0.49, 1.89]	
Heterogeneity: Tau ² = 0.12; Chi ² = 3.42, df = 2 (P = 0.18); l ² = 42% Test for overall effect: Z = 1.45 (P = 0.15) Total (95% CI) 1369 1362 100.0% 0.70 [0.47, 1.03] Total events 772 826 Heterogeneity: Tau ² = 0.15; Chi ² = 18.36, df = 7 (P = 0.01); l ² = 62% Test for overall effect: Z = 1.82 (P = 0.07) Test for subgroup differences: Chi ² = 0.09, df = 1 (P = 0.76), l ² = 0% <u>Footnotes</u> (1) centre (hospital) - based intervention	Subtotal (95% CI)		80		65	36.5%	0.64 [0.35, 1.17]	\bullet
Test for overall effect: $Z = 1.45$ (P = 0.15) Total (95% CI) 1369 1362 100.0% 0.70 [0.47, 1.03] Total events 772 826 Heterogeneity: Tau ² = 0.15; Chi ² = 18.36, df = 7 (P = 0.01); l ² = 62% 0.02 0.1 1 10 50 Test for overall effect: Z = 1.82 (P = 0.07) Test for subgroup differences: Chi ² = 0.09, df = 1 (P = 0.76), l ² = 0% Favors exercise Favors control Footnotes (1) centre (hospital) - based intervention 6 1 1 10 50	Total events	20		24				
Total (95% CI) 1369 1362 100.0% 0.70 [0.47, 1.03] Total events 772 826 Heterogeneity: Tau ² = 0.15; Chi ² = 18.36, df = 7 (P = 0.01); l ² = 62% 0.02 0.1 1 10 50 Test for overall effect: Z = 1.82 (P = 0.07) Test for subgroup differences: Chi ² = 0.09, df = 1 (P = 0.76), l ² = 0% $Favors exercise$ Favors control Footnotes (1) centre (hospital) - based intervention 0.70 0.47 , 1.03 0.70 0.47 , 1.03	Heterogeneity: Tau ² = 0	0.12; Chi² =	= 3.42,	df = 2 (F	9 = 0.18	3); I ² = 42%)	
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Footnotes (1) centre (hospital) - based intervention		· ·		,	(P = 0	76) $l^2 = 0$	%	Favors exercise Favors control
(1) centre (hospital) - based intervention	0 1	onoos. on	. 0.0	, ui – T	(i = 0.		70	
		asad intony	ontion					
(2) norm - based intervention			CINUUI					
	(2) HUITE - DASEU IIILEN	CILIUII						

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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 allcause 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 \geq 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						
E	Exercise	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events To	otal Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
1.5.1 Low RoB					· ·	
Chen 2018	12	31 9	31	13.5%	1.33 [0.66, 2.70]	- -
Dalal 2018	3 -	107 6		8.9%	0.51 [0.13, 1.98]	
Giannuzzi 2003	2	45 1	45	1.5%	2.00 [0.19, 21.28]	
Hambrecht 1995	0	12 1	10	2.4%	0.28 [0.01, 6.25]	
Jolly 2009	4	84 2	85	3.0%	2.02 [0.38, 10.75]	
Jónsdóttir 2006a	0	21 3		5.1%	0.15 [0.01, 2.73]	
Lang 2018	0	25 4	25	6.7%	0.11 [0.01, 1.96]	
Myers 2000	0	12 2	13	3.6%	0.22 [0.01, 4.08]	· · · · · · · · · · · · · · · · · · ·
Passino 2006	0	44 2		3.9%	0.19 [0.01, 3.78]	
Willenheimer 2001	0	23 3		4.8%	0.17 [0.01, 3.07]	
Witham 2012	1	53 1	54	1.5%	1.02 [0.07, 15.87]	
Subtotal (95% CI)	4	457	462	54.9%	0.68 [0.43, 1.10]	\bullet
Total events	22	34				
Heterogeneity: Chi ² = 1	1.23, df = 10	O(P = 0.34);	l² = 11%	, D		
Test for overall effect: Z	. = 1.58 (P =	: 0.11)				
1.5.2 High RoB						
Belardinelli 1999	5	50 14	49	21.1%	0.35 [0.14, 0.90]	_
Cowie 2014 (1)	3	15 5	8	9.8%	0.32 [0.10, 1.01]	
Cowie 2014 (2)	8	15 5		9.8%	0.85 [0.42, 1.75]	
Mueller 2007	2	25 3	25	4.5%	0.67 [0.12, 3.65]	
Subtotal (95% CI)	1	105	90	45.1%	0.48 [0.29, 0.81]	\bullet
Total events	18	27				
Heterogeneity: Chi ² = 3.	.51, df = 3 (F	P = 0.32); I ² :	= 14%			
Test for overall effect: Z	2 = 2.78 (P =	• 0.006)				
Total (95% CI)	5	562	552	100.0%	0.59 [0.42, 0.84]	•
Total events	40	61				
Heterogeneity: Chi ² = 1			² = 11%	, D		
Test for overall effect: Z		· /·				0.01 0.1 1 10 100
Test for subgroup different			1 (P = 0	.33), I² = 0	%	Favors exercise Favors control
Footnotes			· -	,, -		
(1) centre (hospital) - ba	ased interve	ntion				
(2) home-based interve						
· · · · · · · · · · · · · · · · · · ·						

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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

ustin 2005 22.9 14.7 85 36.9 21.3 94 6.7% -14.00 [-19.32, -8.68] then 2018 19.4 12.2 31 34.3 14.4 29 6.1% -14.00 [-21.68, -8.12] alal 2018 24.1 20.9 92 27.5 23.2 93 6.3% -3.40 [-9.76, 2.96] varidson 2010 52.9 15.7 50 56.4 18.3 42 6.0% -3.50 [-10.54, 3.54] tracup 2007 35.7 23.7 86 43.2 27.3 87 5.7% -7.50 [-15.2, 0.12] u 2018 36.9 21.59 67 41 22.4 65 5.8% -4.10 [-11.61, 3.41] aray 2010 (1) 25.6 19.7 17 28.9 29.9 14 2.4% -3.30 [-21.55, 14.95] aray 2010 (2) 24.2 16.3 15 34.3 23.6 16 3.3% -10.10 [-24.30, 4.10] olly 2009 37.6 21 77 34.9 24.8 80 5.9% 2.70 [-4.48, 9.88] arg 2018 29.2 25.8 22 38.7 30.1 23 2.8% -9.50 [-52.86, 6.68] likson 2008 23 14 35 28 20 37 5.6% -5.00 [-12.94, 2.94] who tal (95% C1) 727 741 77.4% -4.91 [-7.93, -1.90] ubtotal (95% C1) 727 741 77.4% -4.91 [-7.93, -1.90] teterogeneity: Tau ² = 18.17; Ch ² = 37.91, df = 13 (P = 0.0003); P = 66% est for overall effect: Z = 3.19 (P = 0.001) 6.2 High RoB ntonicelli 2016 28.6 12.3 150 44.5 12.3 163 7.6% -15.90 [-18.63, -13.17] elearGinelli 732 = 20.75; Ch ² = 3.19, df = 3 (P = 0.36); P = 66% est for overall effect: Z = 10.78 (P < 0.0001) 6.2 High RoB ntonicelli 2016 28.6 12.3 150 44.5 12.3 163 7.6% -15.90 [-18.63, -13.17] elearGinelli 732 = 0.55; Ch ² = 3.19, df = 3 (P = 0.36); P = 66% est for overall effect: Z = 10.78 (P < 0.0001) 6.2 High RoB ntonicelli 2016 28.6 12.3 150 44.5 12.3 163 7.6% -15.90 [-18.63, -13.17] elearGinelli Y. Tau ² = 36.91; Ch ² = 37.92, df = 17 (P < 0.00001); P = 82% est for overall effect: Z = 10.78 (P < 0.00001) 6.2 High RoB ntonicelli 69% C1) 985 1010 100.0% -7.11 [-10.49, -3.73] eletrogeneity: Tau ² = 36.91; Ch ² = 93.22, df = 17 (P < 0.00001); P = 82% est for overall effect: Z = 10.78 (P < 0.00001) est for overall effect: Z = 4.12 (P < 0.0001) est for overall effect: Z = 4.12 (P < 0.0001) est for overall effect: Z = 4.12 (P < 0.0001) est for overall effect: Z = 4.12 (P < 0.0001) est for subgroup differences: Ch ² = 23.74, df = 1 (P < 0.00001); P = 95.8% outnotes		E	ercise		С	ontrol			Mean Difference	Mean Difference
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bavidson 2010 52.9 15.7 50 56.4 18.3 42 6.0% -3.50 [-10.54, 3.54] bracup 2007 35.7 23.7 86 43.2 27.3 87 5.7% -7.50 [-15.12, 0.12] bu 2018 36.9 21.59 67 41 22.4 65 5.8% -4.10 [-11.61, 3.41] sary 2010 (1) 25.6 19.7 17 28.9 29.9 14 2.4% -3.30 [-21.55, 14.95] bary 2010 (2) 24.2 16.3 15 34.3 23.6 16 3.3% -10.10 [-24.30, 4.10] olly 2009 37.6 21 77 34.9 24.8 80 5.9% 2.70 [-4.48, 9.86] ang 2018 29.2 25.8 22 38.7 30.1 23 2.8% -9.50 [-25.86, 6.86] likeson 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 [-15.9, 9.79] ehe 2011 13 4 50 18 6 50 7.8% -5.00 [-7.00, -3.00] bubtotal (95% CI) 727 741 77.4% -4.91 [-7.93, -1.90] Heterogeneity: Tau ² = 18.17; Chi ² = 37.91, df = 13 (P = 0.0003); l ² = 66% test for overall effect: Z = 3.19 (P = 0.001) .6.2 High RoB untonicelli 2016 28.6 12.3 150 44.5 12.3 163 7.6% -15.90 [-18.63, -13.17] beterogeneity: Tau ² = 10.78 (P < 0.0001) .6.2 High RoB untonicelli 2016 28.6 12.3 150 44.5 12.3 163 7.6% -15.90 [-18.63, -13.17] beterogeneity: Tau ² = 0.75; Chi ² = 3.19, df = 3 (P = 0.36); l ² = 6% test for overall effect: Z = 10.78 (P < 0.00001) .6.2 High RoB untonicelli 2016 28.6 12.3 150 44.5 12.9 19 5.7% -11.10 [-18.65, -3.55] beterogeneity: Tau ² = 0.75; Chi ² = 3.19, df = 3 (P = 0.36); l ² = 6% test for overall effect: Z = 10.78 (P < 0.00001) .6.2 High RoB teterogeneity: Tau ² = 0.75; Chi ² = 3.19, df = 3 (P = 0.36); l ² = 6% test for overall effect: Z = 4.12 (P < 0.00001) .6.2 High RoB teterogeneity: Tau ² = 36.91; Chi ² = 93.22, df = 17 (P < 0.00001); l ² = 82% test for overall effect: Z = 4.12 (P < 0.00001) .6.2 High columnation .6.3 High columnation .6.4 High columnation .6.4 High columnation .6.6 High columnation .6.7 High columnation .6.7 High columnation .6.7 High columnation .6.8 High columnation .6.9 High columnation .6.9 High columnation .6.9 High columnation .6.9 High columnation .6.9 High columnation .6.10 High columnation .6.10 H	hen 2018	19.4	12.2	31	34.3	14.4	29	6.1%	-14.90 [-21.68, -8.12]	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	alal 2018	24.1	20.9	92	27.5	23.2	93	6.3%	-3.40 [-9.76, 2.96]	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	avidson 2010	52.9	15.7	50	56.4	18.3	42	6.0%	-3.50 [-10.54, 3.54]	
Sary 2010 (1) 25.6 19.7 17 28.9 29.9 14 2.4% -3.30 [-21.55, 14.95] Sary 2010 (2) 24.2 16.3 15 34.3 23.6 16 3.3% -10.10 [-24.30, 4.10] olly 2009 37.6 21 77 34.9 24.8 80 5.9% 2.70 [-4.48, 9.88] ang 2018 29.2 25.8 22 38.7 30.1 23 2.8% -9.50 [-5.86, 6.86] KcKelvie 2002 -3.4 18.1 57 -3.3 13.9 67 6.5% -0.10 [-5.86, 5.66] Hilsson 2008 23 14 35 28 20 37 5.6% -5.00 [-12.94, 2.94] Vilham 2012 15.4 14.8 43 11.3 12.1 44 6.6% 4.10 [-1.59, 9.79] Geh 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: Tau ² = 18.17; Chi ² = 37.91, df = 13 (P = 0.0003); l ² = 66% est for overall effect: Z = 3.19 (P = 0.011) 6.2 High RoB Intonicelli 2016 28.6 12.3 150 44.5 12.3 163 7.6% -15.90 [-18.63, -13.17] Sassino 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: Tau ² = 0.75; Chi ² = 3.19, df = 3 (P = 0.36); l ² = 6% est for overall effect: Z = 10.78 (P < 0.00001) Total (95% CI) 985 1010 100.0% -7.11 [-10.49, -3.73] Heterogeneity: Tau ² = 36.91; Chi ² = 3.22, df = 17 (P < 0.00001); l ² = 95.8% cost for overall effect: Z = 10.78 (P < 0.00001) Total (95% CI) 985 1010 100.0% -7.11 [-10.49, -3.73] Heterogeneity: Tau ² = 36.91; Chi ² = 3.22, df = 17 (P < 0.00001); l ² = 95.8% cost for overall effect: Z = 10.78 (P < 0.00001) Total (95% CI) 985 1010 100.0% -7.11 [-10.49, -3.73] Heterogeneity: Tau ² = 36.91; Chi ² = 23.74, df = 1 (P < 0.00001); l ² = 95.8% Controles	racup 2007	35.7	23.7	86	43.2	27.3	87	5.7%	-7.50 [-15.12, 0.12]	
Sary 2010 (2) 24.2 16.3 15 34.3 23.6 16 3.3% -10.10 [-24.30, 4.10] olly 2009 37.6 21 77 34.9 24.8 80 5.9% 2.70 [-4.48, 9.88] ang 2018 29.2 25.8 22 38.7 30.1 23 2.8% -9.50 [-25.86, 6.86] (K6Keive 2002 -3.4 18.1 57 -3.3 13.9 67 6.5% -0.10 [-5.86, 5.66] lilisson 2008 23 14 35 28 20 37 5.6% -5.00 [-12.94, 2.94] Vitham 2012 15.4 14.8 43 11.3 12.1 44 6.6% 4.10 [-1.59, 9.79] (eh 2011 13 4 50 18 6 50 7.8% -5.00 [-7.00, -3.00] libitotal (95% CI) 727 741 77.4% -4.91 [-7.93, -1.90] teterogeneity: Tau ² = 18.17; Chi ² = 37.91, df = 13 (P = 0.0003); l ² = 66% est for overall effect: Z = 3.19 (P = 0.001) .6.2 High RoB untonicelli 2016 28.6 12.3 150 44.5 12.3 163 7.6% -15.90 [-18.63, -13.17] ioukouvou 2004 34.1 13 16 45.2 9 19 5.7% -11.00 [-19.33, -2.67] ioukouvou 2004 34.1 13 16 45.2 9 19 5.7% -11.00 [-18.63, -13.17] ioukouvou 2004 34.1 13 16 45.2 9 19 5.7% -11.00 [-18.63, -13.17] ioukouvou 2004 34.1 13 16 45.2 9 19 5.7% -11.00 [-18.63, -13.17] ioukouvou 2006 32 26.5 44 53 32 41 3.8% -21.00 [-33.54, -8.46] ibutotal (95% CI) 258 269 22.6% -15.03 [-17.76, -12.30] teterogeneity: Tau ² = 0.75; Chi ² = 3.19, df = 3 (P = 0.36); l ² = 6% est for overall effect: Z = 10.78 (P < 0.00001) iotal (95% CI) 985 1010 100.0% -7.11 [-10.49, -3.73] teterogeneity: Tau ² = 36.91; Chi ² = 93.22, df = 17 (P < 0.00001); l ² = 82% est for overall effect: Z = 4.12 (P < 0.0001) est for subgroup differences: Chi ² = 23.74, df = 1 (P < 0.00001), l ² = 95.8% controls	u 2018	36.9	21.59	67	41	22.4	65	5.8%	-4.10 [-11.61, 3.41]	
olly 2009 37.6 21 77 34.9 24.8 80 5.9% 2.70 [4.48, 9.88] ang 2018 29.2 25.8 22 38.7 30.1 23 2.8% -9.50 [-25.86, 6.86] tcKelvie 2002 -3.4 18.1 57 -3.3 13.9 67 6.5% -0.10 [-5.86, 5.66] lilisson 2008 23 14 35 28 20 37 5.6% -5.00 [-1.2.94, 2.94] Vitham 2012 15.4 14.8 43 11.3 12.1 44 6.6% 4.10 [-1.59, 9.79] feh 2011 13 4 50 18 6 50 7.8% -5.00 [-7.00, -3.00] riubtotal (95% CI) 727 741 77.4% -4.91 [-7.93, -1.90] teterogeneity: Tau ² = 18.17; Chi ² = 37.91, df = 13 (P = 0.0003); l ² = 66% fest for overall effect: Z = 3.19 (P = 0.001) .6.2 High RoB Intonicelli 2016 28.6 12.3 150 44.5 12.3 163 7.6% -15.90 [-18.63, -13.17] telardinelli 1999 40 19 48 51 22 46 5.4% -11.00 [-19.33, -2.67] coukouvou 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] viabtotal (95% CI) 258 269 22.6% -15.03 [-17.76, -12.30] teterogeneity: Tau ² = 0.75; Chi ² = 3.19, df = 3 (P = 0.36); l ² = 6% fest for overall effect: Z = 10.78 (P < 0.00001) fotal (95% CI) 985 1010 100.0% -7.11 [-10.49, -3.73] teterogeneity: Tau ² = 36.91; Chi ² = 93.22, df = 17 (P < 0.00001); l ² = 82% fest for overall effect: Z = 4.12 (P < 0.00001) fotal (95% CI) 985 1010 100.0% -7.11 [-10.49, -3.73] teterogeneity: Tau ² = 36.91; Chi ² = 23.74, df = 1 (P < 0.00001); l ² = 95.8% footnotes	ary 2010 (1)	25.6	19.7	17	28.9	29.9	14	2.4%	-3.30 [-21.55, 14.95]	
ang 2018 29.2 25.8 22 38.7 30.1 23 2.8% -9.50 [-25.86, 6.86] AcKelvie 2002 -3.4 18.1 57 -3.3 13.9 67 6.5% -0.10 [-5.86, 5.66] AcKelvie 2002 -3.4 18.1 57 -3.3 13.9 67 6.5% -0.10 [-5.86, 5.66] AcKelvie 2002 -3.4 18.1 57 -3.3 13.9 67 6.5% -0.10 [-2.94, 2.94] AcKelvie 2002 15.4 14.8 43 11.3 12.1 44 6.6% -4.10 [-1.59, 9.79] ehe 2011 13 4 50 18 6 50 7.8% -5.00 [-7.00, -3.00] Biubtotal (95% CI) 727 741 77.4% -4.91 [-7.93, -1.90] Heterogeneity: Tau ² = 18.17; Chi ² = 37.91, df = 13 (P = 0.0003); l ² = 66% Test for overall effect: Z = 3.19 (P = 0.001) .6.2 High RoB Intonicelli 2016 28.6 12.3 150 44.5 12.3 163 7.6% -15.90 [-18.63, -13.17] Delardinelli 1999 40 19 48 51 22 46 5.4% -11.00 [-19.33, -2.67] Coukouvou 2004 34.1 13 16 45.2 9 19 5.7% -11.10 [-18.65, -3.55] Taussino 2006 32 26.5 44 53 32 41 3.8% -21.00 [-33.54, -8.46] Bubtotal (95% CI) 258 269 22.6% -15.03 [-17.76, -12.30] Heterogeneity: Tau ² = 36.91; Chi ² = 3.19, df = 3 (P = 0.36); l ² = 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: Tau ² = 36.91; Chi ² = 93.22, df = 17 (P < 0.00001); l ² = 82% Test for overall effect: Z = 4.12 (P < 0.0001) Total (95% CI) 985 1010 100.0% -7.11 [-10.49, -3.73] Heterogeneity: Tau ² = 36.91; Chi ² = 23.74, df = 1 (P < 0.00001); l ² = 95.8% Toolnotes	ary 2010 (2)	24.2	16.3	15	34.3	23.6	16	3.3%	-10.10 [-24.30, 4.10]	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	olly 2009	37.6	21	77	34.9	24.8	80	5.9%	2.70 [-4.48, 9.88]	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	ang 2018	29.2	25.8	22	38.7	30.1	23	2.8%	-9.50 [-25.86, 6.86]	
Vitham 2012 15.4 14.8 43 11.3 12.1 44 6.6% 4.10 [-1.59, 9.79] (eh 2011 13 4 50 18 6 50 7.8% -5.00 [-7.00, -3.00] (bubtotal (95% CI) 727 741 77.4% -4.91 [-7.93, -1.90] (eterogeneity: Tau ² = 18.17; Chi ² = 37.91, df = 13 (P = 0.0003); l ² = 66% (est for overall effect: Z = 3.19 (P = 0.001) .6.2 High RoB Intonicelli 2016 28.6 12.3 150 44.5 12.3 163 7.6% -15.90 [-18.63, -13.17] (coukouvou 2004 34.1 13 16 45.2 9 19 5.7% -11.10 [-19.33, -2.67] (coukouvou 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] (coukouvou 2004 34.1 13 16 45.2 9 19 5.7% -11.00 [-19.33, -4.67] (coukouvou 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] (coukototal (95% CI) 258 269 22.6% -15.03 [-17.76, -12.30] (eterogeneity: Tau ² = 0.75; Chi ² = 3.19, df = 3 (P = 0.36); l ² = 6% (est for overall effect: Z = 10.78 (P < 0.00001) (rotal (95% CI) 985 1010 100.0% -7.11 [-10.49, -3.73] (eterogeneity: Tau ² = 36.91; Chi ² = 93.22, df = 17 (P < 0.00001); l ² = 82% (est for subgroup differences: Chi ² = 23.74, df = 1 (P < 0.00001), l ² = 95.8% (cootnotes (cootnotes)	cKelvie 2002	-3.4	18.1	57	-3.3	13.9	67	6.5%	-0.10 [-5.86, 5.66]	
The probability of the probabil	ilsson 2008	23	14	35	28	20	37	5.6%	-5.00 [-12.94, 2.94]	
Subtotal (95% Cl) 727 741 77.4% -4.91 [-7.93, -1.90] Heterogeneity: Tau ² = 18.17; Chi ² = 37.91, df = 13 (P = 0.0003); l ² = 66% eest for overall effect: Z = 3.19 (P = 0.001) .6.2 High RoB untonicelli 2016 28.6 12.3 150 44.5 12.3 163 7.6% -15.90 [-18.63, -13.17] Jelardinelli 1999 40 19 48 51 22 46 5.4% -11.00 [-19.33, -2.67] Coukouvou 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 [-3.5.4, -8.46] Subtotal (95% Cl) 258 269 22.6% -15.03 [-17.76, -12.30] - Heterogeneity: Tau ² = 0.75; Chi ² = 3.19, df = 3 (P = 0.36); l ² = 6% -7.01 -0 10 20 Fest for overall effect: Z = 10.78 (P < 0.00001)	itham 2012	15.4	14.8	43	11.3	12.1	44	6.6%	4.10 [-1.59, 9.79]	+
Atterogeneity: $Tau^2 = 18.17$; $Chi^2 = 37.91$, $df = 13$ (P = 0.0003); I ² = 66% Test for overall effect: Z = 3.19 (P = 0.001) .6.2 High RoB untonicelli 2016 28.6 12.3 150 44.5 12.3 163 7.6% -15.90 [-18.63, -13.17] telardinelli 1999 40 19 48 51 22 46 5.4% -11.00 [-19.33, -2.67] (oukouvou 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% Cl) 258 269 22.6% -15.03 [-17.76, -12.30] Heterogeneity: $Tau^2 = 0.75$; $Chi^2 = 3.19$, $df = 3$ (P = 0.36); I ² = 6% Test for overall effect: Z = 10.78 (P < 0.00001) Fotal (95% Cl) 985 1010 100.0% -7.11 [-10.49, -3.73] Heterogeneity: $Tau^2 = 36.91$; $Chi^2 = 93.22$, $df = 17$ (P < 0.00001); I ² = 82% Test for overall effect: Z = 4.12 (P < 0.0001) Test for subgroup differences: $Chi^2 = 23.74$, $df = 1$ (P < 0.00001), I ² = 95.8% Teators control		13	4		18	6				<u>→</u>
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	• •				= 13 (P	9 = 0.00	003); I²	= 66%		
Soukouvou 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: Tau ² = 0.75; Chi ² = 3.19, df = 3 (P = 0.36); l ² = 6% feest for overall effect: Z = 10.78 (P < 0.00001)	est for overall effect				= 13 (P	9 = 0.00	003); I²	= 66%		
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Subtotal (95% Cl) 258 269 22.6% -15.03 [-17.76, -12.30] Heterogeneity: Tau ² = 0.75; Chi ² = 3.19, df = 3 (P = 0.36); l ² = 6% • • • Fest for overall effect: Z = 10.78 (P < 0.00001)	est for overall effect 6.2 High RoB ntonicelli 2016	: Z = 3.19 28.6	(P = 0.9	001) 150	44.5	12.3	163	7.6%		<u> </u>
Heterogeneity: Tau ² = 0.75; Chi ² = 3.19, df = 3 (P = 0.36); I ² = 6% Fest for overall effect: Z = 10.78 (P < 0.00001)	est for overall effect: 6.2 High RoB ntonicelli 2016 elardinelli 1999	28.6 28	(P = 0.0 12.3 19	001) 150 48	44.5 51	12.3 22	163 46	7.6% 5.4%	-11.00 [-19.33, -2.67]	<u></u>
Heterogeneity: Tau ² = 36.91; Chi ² = 93.22, df = 17 (P < 0.00001); I ² = 82% Fest for overall effect: Z = 4.12 (P < 0.0001)	est for overall effect 6.2 High RoB ntonicelli 2016 elardinelli 1999 oukouvou 2004 assino 2006	28.6 28.6 40 34.1	(P = 0.0 12.3 19 13	001) 150 48 16 44	44.5 51 45.2	12.3 22 9	163 46 19 41	7.6% 5.4% 5.7% 3.8%	-11.00 [-19.33, -2.67] -11.10 [-18.65, -3.55] -21.00 [-33.54, -8.46]	
Test for overall effect: Z = 4.12 (P < 0.0001)	est for overall effect 6.2 High RoB ntonicelli 2016 elardinelli 1999 oukouvou 2004 assino 2006 ubtotal (95% CI) eterogeneity: Tau ² =	: Z = 3.19 28.6 40 34.1 32 = 0.75; Cr	(P = 0.0) 12.3 19 13 26.5 $H^2 = 3.19$	001) 150 48 16 44 258 9, df = 1	44.5 51 45.2 53 3 (P = 0	12.3 22 9 32	163 46 19 41 269	7.6% 5.4% 5.7% 3.8%	-11.00 [-19.33, -2.67] -11.10 [-18.65, -3.55] -21.00 [-33.54, -8.46]	
iest for overall effect: Z = 4.12 (P < 0.0001)Favors exerciseFavors controliest for subgroup differences: Chi² = 23.74, df = 1 (P < 0.00001), l² = 95.8%	est for overall effect 6.2 High RoB ntonicelli 2016 elardinelli 1999 oukouvou 2004 assino 2006 ubtotal (95% CI) eterogeneity: Tau ² = est for overall effect	: Z = 3.19 28.6 40 34.1 32 = 0.75; Cr	(P = 0.0) 12.3 19 13 26.5 $H^2 = 3.19$	001) 150 48 16 44 258 9, df = 3 000001	44.5 51 45.2 53 3 (P = 0	12.3 22 9 32	163 46 19 41 269 ² = 6%	7.6% 5.4% 5.7% 3.8% 22.6%	-11.00 [-19.33, -2.67] -11.10 [-18.65, -3.55] -21.00 [-33.54, -8.46] -15.03 [-17.76, -12.30]	
est for subgroup differences: Chi ² = 23.74, df = 1 (P < 0.00001), l ² = 95.8% ootnotes	est for overall effect 6.2 High RoB ntonicelli 2016 elardinelli 1999 oukouvou 2004 assino 2006 ubtotal (95% CI) eterogeneity: Tau ² = est for overall effect otal (95% CI)	: Z = 3.19 28.6 40 34.1 32 = 0.75; CP : Z = 10.7	(P = 0.0 12.3 19 13 26.5 si ² = 3.19 8 (P < 0	150 48 16 44 258 9, df = 3 0.00001 985	44.5 51 45.2 53 3 (P = 0	12.3 22 9 32 0.36); F	163 46 19 41 269 ² = 6% 1010	7.6% 5.4% 5.7% 3.8% 22.6%	-11.00 [-19.33, -2.67] -11.10 [-18.65, -3.55] -21.00 [-33.54, -8.46] -15.03 [-17.76, -12.30]	
	est for overall effect 6.2 High RoB ntonicelli 2016 elardinelli 1999 oukouvou 2004 assino 2006 ubtotal (95% CI) eterogeneity: Tau ² = est for overall effect otal (95% CI) eterogeneity: Tau ² =	: Z = 3.19 28.6 40 34.1 32 = 0.75; Ch : Z = 10.7	$(P = 0.0)$ 12.3 19 13 26.5 $ii^{2} = 3.19$ $8 (P < C)$ $chi^{2} = 93$	2001) 150 48 16 44 258 9, df = 3 0.00001 985 5.22, df	44.5 51 45.2 53 3 (P = 0	12.3 22 9 32 0.36); F	163 46 19 41 269 ² = 6% 1010	7.6% 5.4% 5.7% 3.8% 22.6%	-11.00 [-19.33, -2.67] -11.10 [-18.65, -3.55] -21.00 [-33.54, -8.46] -15.03 [-17.76, -12.30]	
1) exercise alone	est for overall effect 6.2 High RoB ntonicelli 2016 elardinelli 1999 oukouvou 2004 aassino 2006 ubtotal (95% CI) eterogeneity: Tau ² = est for overall effect otal (95% CI) eterogeneity: Tau ² = est for overall effect	: Z = 3.19 28.6 40 34.1 32 = 0.75; Ch : Z = 10.7 = 36.91; C : Z = 4.12	$(P = 0.4)$ 12.3 19 13 26.5 $ii^{2} = 3.19$ $8 (P < 0.4)$ $ihi^{2} = 93$ $(P < 0.4)$	150 48 16 44 258 9, df = 1 000001 985 0.22, df 0001)	44.5 51 45.2 53 3 (P = C) = 17 (P	12.3 22 9 32 0.36); F	163 46 19 41 269 ² = 6% 1010 0001); I	7.6% 5.4% 5.7% 3.8% 22.6% 100.0% ² = 82%	-11.00 [-19.33, -2.67] -11.10 [-18.65, -3.55] -21.00 [-33.54, -8.46] -15.03 [-17.76, -12.30] -7.11 [-10.49, -3.73]	
	est for overall effect 6.2 High RoB ntonicelli 2016 elardinelli 1999 oukouvou 2004 aassino 2006 ubtotal (95% CI) eterogeneity: Tau ² = est for overall effect otal (95% CI) eterogeneity: Tau ² = est for overall effect ast for overall effect	: Z = 3.19 28.6 40 34.1 32 = 0.75; Ch : Z = 10.7 = 36.91; C : Z = 4.12	$(P = 0.4)$ 12.3 19 13 26.5 $ii^{2} = 3.19$ $8 (P < 0.4)$ $ihi^{2} = 93$ $(P < 0.4)$	150 48 16 44 258 9, df = 1 000001 985 0.22, df 0001)	44.5 51 45.2 53 3 (P = C) = 17 (P	12.3 22 9 32 0.36); F	163 46 19 41 269 ² = 6% 1010 0001); I	7.6% 5.4% 5.7% 3.8% 22.6% 100.0% ² = 82%	-11.00 [-19.33, -2.67] -11.10 [-18.65, -3.55] -21.00 [-33.54, -8.46] -15.03 [-17.76, -12.30] -7.11 [-10.49, -3.73]	

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 HFspecific 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

		ercise	_		ontrol	_		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
.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]	
IF ACTION 2009	72.8	20.4	828	71.4	21.3	784	4.6%	0.07 [-0.03, 0.16]	The second se
olly 2009	37.6	21	77	34.9	24.8	80	4.2%	0.12 [-0.20, 0.43]	
ónsdóttir 2006a	-47.55	8.7	21	-44.1		20	3.3%	-0.29 [-0.91, 0.32]	
ang 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]	
orman 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]	
Villenheimer 2001	-0.7	0.8	20	0	1	17	3.2%	-0.76 [-1.44, -0.09]	
Vitham 2005	-69	13	36	-65	10	32	3.7%	-0.34 [-0.82, 0.14]	
'eh 2011 Subtotal (95% CI)	13	4	50 1612	18	6	50 1559	3.9% 73.3%	-0.97 [-1.39, -0.56] - 0.35 [-0.52, -0.18]	
1.7.2 High RoB									
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]	-
Antonicelli 2016 Belardinelli 1999	40	19	48	51	22	46	3.9%	-0.53 [-0.94, -0.12]	
Antonicelli 2016 Belardinelli 1999 Bocalini 2008	40 -87	19 4	48 22	51 -81	22 6	46 20	3.9% 3.2%	-0.53 [-0.94, -0.12] -1.17 [-1.83, -0.51]	
Antonicelli 2016 Belardinelli 1999 Bocalini 2008 Kaltsatou 2014 (3)	40 -87 -5.7	19 4 3	48 22 16	51 -81 0.8	22 6 1.2	46 20 9	3.9% 3.2% 2.1%	-0.53 [-0.94, -0.12] -1.17 [-1.83, -0.51] -2.49 [-3.60, -1.38]	
Antonicelli 2016 Belardinelli 1999 Bocalini 2008 Kaltsatou 2014 (3) Kaltsatou 2014 (4)	40 -87 -5.7 -6.5	19 4 3 2.4	48 22 16 18	51 -81 0.8 0.8	22 6 1.2 1.2	46 20 9 8	3.9% 3.2% 2.1% 1.7%	-0.53 [-0.94, -0.12] -1.17 [-1.83, -0.51] -2.49 [-3.60, -1.38] -3.33 [-4.62, -2.04]	
Antonicelli 2016 Belardinelli 1999 Bocalini 2008 Kaltsatou 2014 (3) Kaltsatou 2014 (4) Klocek 2005 (5)	40 -87 -5.7 -6.5 -99	19 4 3 2.4 23.5	48 22 16 18 14	51 -81 0.8 0.8 -71.7	22 6 1.2 1.2 23.5	46 20 9 8 7	3.9% 3.2% 2.1% 1.7% 2.3%	-0.53 [-0.94, -0.12] -1.17 [-1.83, -0.51] -2.49 [-3.60, -1.38] -3.33 [-4.62, -2.04] -1.12 [-2.10, -0.13]	
Antonicelli 2016 Belardinelli 1999 Bocalini 2008 Kaltsatou 2014 (3) Kaltsatou 2014 (4) Klocek 2005 (5) Klocek 2005 (6)	40 -87 -5.7 -6.5 -99 -109	19 4 3 2.4 23.5 23.5	48 22 16 18 14 14	51 -81 0.8 0.8 -71.7 -71.7	22 6 1.2 1.2 23.5 23.5	46 20 9 8 7 7	3.9% 3.2% 2.1% 1.7% 2.3% 2.2%	-0.53 [-0.94, -0.12] -1.17 [-1.83, -0.51] -2.49 [-3.60, -1.38] -3.33 [-4.62, -2.04] -1.12 [-2.10, -0.13] -1.52 [-2.57, -0.48]	
Antonicelli 2016 Belardinelli 1999 Bocalini 2008 Kaltsatou 2014 (3) Kaltsatou 2014 (4) Klocek 2005 (5) Klocek 2005 (6) Koukouvou 2004	40 -87 -5.7 -6.5 -99 -109 34.1	19 4 3 2.4 23.5 23.5 13	48 22 16 18 14 14 16	51 -81 0.8 -71.7 -71.7 45.2	22 6 1.2 23.5 23.5 9	46 20 9 8 7 7 19	3.9% 3.2% 2.1% 1.7% 2.3% 2.2% 3.1%	-0.53 [-0.94, -0.12] -1.17 [-1.83, -0.51] -2.49 [-3.60, -1.38] -3.33 [-4.62, -2.04] -1.12 [-2.10, -0.13] -1.52 [-2.57, -0.48] -0.99 [-1.69, -0.28]	
Antonicelli 2016 Belardinelli 1999 Bocalini 2008 Kaltsatou 2014 (3) Kaltsatou 2014 (4) Klocek 2005 (5) Klocek 2005 (6) Koukouvou 2004 Passino 2006	40 -87 -5.7 -6.5 -99 -109	19 4 3 2.4 23.5 23.5	48 22 16 18 14 14 16 44	51 -81 0.8 0.8 -71.7 -71.7	22 6 1.2 1.2 23.5 23.5	46 20 9 8 7 7 19 41	3.9% 3.2% 2.1% 1.7% 2.3% 2.2% 3.1% 3.9%	-0.53 [-0.94, -0.12] -1.17 [-1.83, -0.51] -2.49 [-3.60, -1.38] -3.33 [-4.62, -2.04] -1.12 [-2.10, -0.13] -1.52 [-2.57, -0.48] -0.99 [-1.69, -0.28] -0.71 [-1.15, -0.27]	
Antonicelli 2016 Belardinelli 1999 Bocalini 2008 Kaltsatou 2014 (3) Kaltsatou 2014 (4) Klocek 2005 (5) Klocek 2005 (6) Koukouvou 2004 Passino 2006 Bubtotal (95% CI)	40 -87 -5.7 -6.5 -99 -109 34.1 32	19 4 3 2.4 23.5 23.5 13 26.5	48 22 16 18 14 14 16 44 342	51 -81 0.8 -71.7 -71.7 45.2 53	22 6 1.2 23.5 23.5 9 32	46 20 9 8 7 7 19 41 320	3.9% 3.2% 2.1% 1.7% 2.3% 2.2% 3.1% 3.9% 26.7%	-0.53 [-0.94, -0.12] -1.17 [-1.83, -0.51] -2.49 [-3.60, -1.38] -3.33 [-4.62, -2.04] -1.12 [-2.10, -0.13] -1.52 [-2.57, -0.48] -0.99 [-1.69, -0.28]	
Antonicelli 2016 Belardinelli 1999 Bocalini 2008 Kaltsatou 2014 (3) Kaltsatou 2014 (4) Klocek 2005 (5) Klocek 2005 (6) Koukouvou 2004 Passino 2006 Bubtotal (95% CI) Heterogeneity: Tau ² =	40 -87 -5.7 -6.5 -99 -109 34.1 32 0.23; Chi	19 4 3 2.4 23.5 23.5 13 26.5 ² = 30.9	48 22 16 18 14 14 16 44 342 44, df =	51 -81 0.8 -71.7 -71.7 45.2 53	22 6 1.2 23.5 23.5 9 32	46 20 9 8 7 7 19 41 320	3.9% 3.2% 2.1% 1.7% 2.3% 2.2% 3.1% 3.9% 26.7%	-0.53 [-0.94, -0.12] -1.17 [-1.83, -0.51] -2.49 [-3.60, -1.38] -3.33 [-4.62, -2.04] -1.12 [-2.10, -0.13] -1.52 [-2.57, -0.48] -0.99 [-1.69, -0.28] -0.71 [-1.15, -0.27]	
Antonicelli 2016 Belardinelli 1999 Bocalini 2008 Caltsatou 2014 (3) Caltsatou 2014 (4) Clocek 2005 (5) Clocek 2005 (6) Coukouvou 2004 Passino 2006 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect:	40 -87 -5.7 -6.5 -99 -109 34.1 32 0.23; Chi Z = 6.20	19 4 3 2.4 23.5 23.5 13 26.5 ² = 30.9 (P < 0.0	48 22 16 18 14 14 16 44 342 44, df = 00001) 1954	51 -81 0.8 0.8 -71.7 -71.7 45.2 53 8 (P = 0.	22 6 1.2 23.5 23.5 9 32 .0001);	46 20 9 8 7 7 19 41 320 ² = 749	3.9% 3.2% 2.1% 1.7% 2.3% 2.2% 3.1% 3.9% 26.7% %	-0.53 [-0.94, -0.12] -1.17 [-1.83, -0.51] -2.49 [-3.60, -1.38] -3.33 [-4.62, -2.04] -1.12 [-2.10, -0.13] -1.52 [-2.57, -0.48] -0.99 [-1.69, -0.28] -0.71 [-1.15, -0.27]	
Antonicelli 2016 Belardinelli 1999 Bocalini 2008 Caltsatou 2014 (3) Caltsatou 2014 (4) Clocek 2005 (5) Clocek 2005 (6) Coukouvou 2004 Passino 2006 Bubtotal (95% CI) Heterogeneity: Tau ² = Total (95% CI) Heterogeneity: Tau ² =	40 -87 -5.7 -6.5 -99 -109 34.1 32 0.23; Chi Z = 6.20	19 4 3 2.4 23.5 23.5 13 26.5 ² = 30.9 (P < 0.0 ² = 215.	48 22 16 18 14 14 4 342 14, df = 00001) 1954 03, df =	51 -81 0.8 0.8 -71.7 -71.7 45.2 53 8 (P = 0.	22 6 1.2 23.5 23.5 9 32 .0001);	46 20 9 8 7 7 19 41 320 ² = 749	3.9% 3.2% 2.1% 1.7% 2.3% 2.2% 3.1% 3.9% 26.7% %	-0.53 [-0.94, -0.12] -1.17 [-1.83, -0.51] -2.49 [-3.60, -1.38] -3.33 [-4.62, -2.04] -1.12 [-2.10, -0.13] -1.52 [-2.57, -0.48] -0.99 [-1.69, -0.28] -0.71 [-1.15, -0.27] -1.26 [-1.66, -0.86]	
Antonicelli 2016 Belardinelli 1999 Bocalini 2008 Kaltsatou 2014 (3) Kaltsatou 2014 (4) Klocek 2005 (5) Klocek 2005 (6) Koukouvou 2004 Passino 2006 Bubtotal (95% CI) Heterogeneity: Tau ² = Total (95% CI)	40 -87 -5.7 -6.5 -99 -109 34.1 32 0.23; Chi Z = 6.20 0.26; Chi Z = 5.54	19 4 3 2.4 23.5 23.5 13 26.5 2 = 30.9 (P < 0.0 2 = 215. (P < 0.0	48 22 16 18 14 14 4 342 0001) 1954 03, df = 0001)	51 -81 0.8 0.8 -71.7 -71.7 45.2 53 8 (P = 0.	22 6 1.2 23.5 23.5 9 32 .0001);	46 20 9 8 7 7 19 41 320 ² = 749 1879 01); ² =	3.9% 3.2% 2.1% 1.7% 2.3% 2.2% 3.1% 3.9% 26.7% %	-0.53 [-0.94, -0.12] -1.17 [-1.83, -0.51] -2.49 [-3.60, -1.38] -3.33 [-4.62, -2.04] -1.12 [-2.10, -0.13] -1.52 [-2.57, -0.48] -0.99 [-1.69, -0.28] -0.71 [-1.15, -0.27] -1.26 [-1.66, -0.86]	← ← ← ← ← ← Favors exercise Favors control
Antonicelli 2016 Belardinelli 1999 Bocalini 2008 Kaltsatou 2014 (3) Kaltsatou 2014 (4) Klocek 2005 (5) Klocek 2005 (6) Koukouvou 2004 Passino 2006 Bubtotal (95% CI) Heterogeneity: Tau ² = Total (95% CI) Heterogeneity: Tau ² = T	40 -87 -5.7 -6.5 -99 -109 34.1 32 0.23; Chi Z = 6.20 0.26; Chi Z = 5.54	19 4 3 2.4 23.5 23.5 13 26.5 2 = 30.9 (P < 0.0 2 = 215. (P < 0.0	48 22 16 18 14 14 4 342 0001) 1954 03, df = 0001)	51 -81 0.8 0.8 -71.7 -71.7 45.2 53 8 (P = 0.	22 6 1.2 23.5 23.5 9 32 .0001);	46 20 9 8 7 7 19 41 320 ² = 749 1879 01); ² =	3.9% 3.2% 2.1% 1.7% 2.3% 2.2% 3.1% 3.9% 26.7% %	-0.53 [-0.94, -0.12] -1.17 [-1.83, -0.51] -2.49 [-3.60, -1.38] -3.33 [-4.62, -2.04] -1.12 [-2.10, -0.13] -1.52 [-2.57, -0.48] -0.99 [-1.69, -0.28] -0.71 [-1.15, -0.27] -1.26 [-1.66, -0.86]	
-	40 -87 -5.7 -6.5 -99 -109 34.1 32 0.23; Chi Z = 6.20 0.26; Chi Z = 5.54	19 4 3 2.4 23.5 23.5 13 26.5 2 = 30.9 (P < 0.0 2 = 215. (P < 0.0	48 22 16 18 14 14 4 342 0001) 1954 03, df = 0001)	51 -81 0.8 0.8 -71.7 -71.7 45.2 53 8 (P = 0.	22 6 1.2 23.5 23.5 9 32 .0001);	46 20 9 8 7 7 19 41 320 ² = 749 1879 01); ² =	3.9% 3.2% 2.1% 1.7% 2.3% 2.2% 3.1% 3.9% 26.7% %	-0.53 [-0.94, -0.12] -1.17 [-1.83, -0.51] -2.49 [-3.60, -1.38] -3.33 [-4.62, -2.04] -1.12 [-2.10, -0.13] -1.52 [-2.57, -0.48] -0.99 [-1.69, -0.28] -0.71 [-1.15, -0.27] -1.26 [-1.66, -0.86]	
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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 centerbased 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.

	Ex	ercise		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean			Mean			Weight	IV, Random, 95% CI	IV, Random, 95% Cl
1.8.1 Low RoB									
Austin 2005	35.5	21.7	57	37.1	24.9	55	30.0%	-1.60 [-10.26, 7.06]	
Belardinelli 2012 Subtotal (95% CI)	43	12	63 120	58	14	60 115	40.1% 70.1%	-15.00 [-19.62, -10.38] -8.82 [-21.91, 4.27]	
Heterogeneity: Tau ² =	77.24: 0	2hi² = 7	.16. df	= 1 (P :	= 0.00	7): $ ^2 = 1$	86%		
Test for overall effect:				V					
1.8.2 High RoB									
Belardinelli 1999	44	21	48	54	22	46	29.9%	-10.00 [-18.70, -1.30]	
Subtotal (95% CI)			48			46	29.9%	-10.00 [-18.70, -1.30]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 2.25	(P = 0).02)						
Total (95% CI)			168			161	100.0%	-9.49 [-17.48, -1.50]	
Heterogeneity: Tau ² =	35.87; C	Chi² = 7	7.33, df	= 2 (P =	= 0.03); l ² = 7	3%		-20 -10 0 10 20
Test for overall effect:	Z = 2.33	(P = 0)).02)						Favors exercise Favors control

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. \ddagger Exercise only vs. comprehensive. \ddagger Aerobic training alone vs. aerobic plus resistance training. \parallel Number of weeks \times number of sessions/week \times average duration of session in hours. \P Hospital only, home only, or both hospital and home. #Low risk of bias on \geq 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: Exercisebased 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.