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REVIEW ARTICLE

Exercise-based cardiac rehabilitation for adults with heart failure – 2023 Cochrane systematic review and meta-analysis

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Aims

Despite strong evidence, access to exercise-based cardiac rehabilitation (ExCR) remains low across global healthcare systems. We provide a contemporary update of the Cochrane review randomized trial evidence for ExCR for adults with heart failure (HF) and compare different delivery modes: centre-based, home-based (including digital support), and both (hybrid).

Methods and results

Databases, bibliographies of previous systematic reviews and included trials, and trials registers were searched with no language restrictions. Randomized controlled trials, recruiting adults with HF, assigned to either ExCR or a no-exercise control group, with follow-up of ≥6 months were included. Two review authors independently screened titles for inclusion, extracted trial and patient characteristics, outcome data, and assessed risk of bias. Outcomes of mortality, hospitalization, and health-related quality of life (HRQoL) were pooled across trials using meta-analysis at short-term (≤12 months) and long-term follow-up (>12 months) and stratified by delivery mode. Sixty trials (8728 participants) were included. In the short term, compared to control, ExCR did not impact all-cause mortality (relative risk [RR] 0.93; 95% confidence interval [CI] 0.71–1.21), reduced all-cause hospitalization (RR 0.69; 95% CI 0.56–0.86, number needed to treat: 13, 95% CI 9–22), and was associated with a clinically important improvement in HRQoL measured by the Minnesota Living with Heart Failure Questionnaire (MLWHF) overall score (mean difference: −7.39; 95% CI −10.30 to −4.47). Improvements in outcomes with ExCR was seen across centre, home (including digitally supported), and hybrid settings. A similar pattern of results was seen in the long term (mortality: RR 0.87, 95% CI 0.72–1.04; all-cause hospitalization: RR 0.84, 95% CI 0.70–1.01, MLWHF: −9.59, 95% CI −17.48 to −1.50).

Conclusions

To improve global suboptimal levels of uptake for HF patients, global healthcare systems need to routinely recommend ExCR and offer a choice of mode of delivery, dependent on an individual patient's level of risk and complexity.

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Graphical Abstract

All-cause mortality	No. studies	ExCR	Control	Relative Risk (RR)* [95% confidence interval]	Interaction Test between delivery modes P-value ***
Centre	11	15/285	17/275	0.95 (0.48, 1.87)	
Home	10	30/761	36/752	0.86 (0.54, 1.39)	
Hybrid	14	55/912	59/879	0.96 (0.67, 1.38)	0.94
Overall	**35**	**100/1958**	**112/1906**	0.93 (0.71, 1.21)	
All-cause hospitalisation	**No. studies**	**ExCR**	**Control**	**Relative Risk (RR)* [95% confidence interval]**	**P-value*** **
Centre	5	19/123	21/123	0.83 (0.37, 1.86)	
Home	8	77/442	100/430	0.78 (0.59, 1.03)	
Hybrid	11	86/583	149/582	0.63 (0.46, 0.86)	0.55
Overall	**24**	**182/1148**	**270/1135**	0.69 (0.56, 0.86)	
MLWHF overall score	**No. studies**	**ExCR**	**Control**	**Mean difference (MD)** [95% confidence interval]**	**P-value*** **
Centre	4	-	-	-10.80 (-14.90, -6.70)	
Home	11	-	-	-6.90 (-11.30, -2.60)	
Hybrid	7	-	-	-6.40 (-11.80, -0.90)	0.31
Overall	**22**	**-**	**-**	-7.40 (-10.30, -4.50)	

This 2023 Cochrane review of 60 randomized trials in 8728 heart failure patients, confirms the benefits of participation in exercise-based cardiac rehabilitation (ExCR), including reduced risk of hospitalization and a clinically meaningful improvement in health-related quality of life. Leveraging on the development of alternative modes of rehabilitation delivery with the COVID-19 pandemic, we provide a contemporary evidence base to demonstrate patient outcome benefits of ExCR programmes whether delivered in home and digitally supported or centre-based (or hybrid) settings. MLWHF, Minnesota Living with Heart Failure Questionnaire. *RR <1.0 indicates reduced risk of event in favour of ExCR. **MD of <0.0 indicates improvement in MWHF total score in favour of ExCR. ***Interaction $p > 0.05$ indicates no significant difference in ExCR effect across centre, home, and hybrid mode of delivery trials.

Keywords Heart failure • Cardiac rehabilitation • Exercise training • Mortality • Hospitalization • Health-related quality of life

Introduction

Heart failure (HF) is a leading cause of mortality and morbidity globally.[1] Supported by class I evidence from meta-analyses of randomized trials,[2,3] exercise training is recognized as a key component of comprehensive HF management and a Grade A recommendation in international guidelines.[4,5]

Despite robust evidence and strong recommendation, the uptake remains low with less than 20% of patients with HF across United States and Europe receiving exercise-based cardiac rehabilitation (ExCR).[6–8] Whilst the reasons for poor access are complex and include system-, clinician-, and patient-level barriers, a key factor is setting of ExCR delivery.[9] Traditionally delivered in a supervised centre-based setting, access to ExCR has been further challenged during and following the COVID-19 pandemic.[10] As a result, there have been calls for healthcare systems to move to alternative ExCR delivery models that include home-based programmes that can be digitally supported, and hybrid programmes combining elements of both centre and home participation. Whilst such alternative delivery models have the advantages of overcoming inconvenience of travel, a dislike of group-based activities, and facilitating flexibility around work/life commitments, questions remain about the efficacy and safety of remotely delivered ExCR.[11]

This 2023 Cochrane systematic review and meta-analysis provides a timely update of the randomized trial evidence for effects of ExCR on mortality, hospitalization, and health-related quality of life (HRQoL) of adults with HF and the impact of ExCR across different modes of ExCR delivery (centre, home [including digitally supported], and hybrid).

Methods

This meta-analysis was conducted and reported in accordance with the preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement[12] and the Cochrane Handbook for Interventional Reviews.[13]

Search strategy

Databases searched included CENTRAL, MEDLINE, Embase, CINAHL, PsycINFO, and Web of Science. Searches ran from 29 January 2018 (the end date of the previous 2019 version of this Cochrane review) to 13 December 2021. Also searched were the bibliographies of both identified systematic reviews and included trials, and trial registers (i.e. ClinicalTrials.gov and World Health Organization International Clinical Trials Registry). There were no language restrictions (search strategies listed in online *Appendix S1*).

Eligibility criteria

Trials were eligible for inclusion if they: (i) employed a randomized trial design with ≥6-month follow-up; (ii) included participants ≥18 years old with HF; (iii) employed ExCR; and (iv) included a control group not receiving a formal exercise programme. Trials were excluded if the participants had previously received exercise training.

Data extraction and risk of bias assessment

Data extracted from trials included: trial methods (design, setting, number of sites), participant characteristics (total number randomized, sex, age, diagnosis), interventions (duration, type of exercise, frequency, duration, intensity, modality, setting), control treatments, outcome data, funding sources and conflicts of interest. Outcomes included: all-cause mortality, all-cause hospitalization, HF-specific hospitalization and HRQoL. Risk of bias was determined using Cochrane Risk of Bias I tool[14] based on the following factors: random sequence generation, allocation concealment, blinding of outcome assessment, selective reporting, intention-to-treat analysis, incomplete outcome data, groups balanced at baseline, and groups receiving the same intervention. Trials were defined to be at an overall low risk of bias if they demonstrated low risk of bias for both random sequence generation and allocation concealment.

Two review authors (CDM and IRM) independently screened references, confirmed trial eligibility, and completed data extraction. Disagreements were resolved by a third review author (RST).

Statistical analysis and evidence grading

Outcome data were pooled across included trials at two time points: 'short-term' (≤12 months) and 'long-term' (>12 months) follow-up. Heterogeneity was assessed qualitatively by comparing trial characteristics and quantitatively by use of I^2 statistic and χ^2 test of heterogeneity. Given the heterogeneity in HF populations, ExCR interventions, and control groups, a random-effects model was used to pool outcome results across trials. Dichotomous outcomes are expressed as relative risk (RR) with 95% confidence intervals (CI). For those event outcomes that achieved statistically significant risk reductions, we also report the number needed to treat (NNT) for an additional beneficial outcome and 95% CI. HRQoL was expressed as mean difference (MD) and standardized mean difference (SMD) for Minnesota Living with Heart Failure Questionnaire (MLWHF) total score and all HRQoL scales, respectively. Due to variety of methods of reporting HRQoL findings, a vote-counting approach was also used, where results were categorized as 'positive' (ExCR better than control, $p < 0.05$), 'negative' (control better than ExCR, $p < 0.05$), or 'neutral' (ExCR and control difference, $p > 0.05$).[15] Small study bias was investigated using funnel plots and Egger's test.[16] In addition to an overall pooled analysis, meta-analyses were stratified by ExCR intervention setting, that is, centre, home (including digitally supported), and hybrid, and a χ^2 test was used to investigate potential subgroup differences. Meta-regression was used to examine the following pre-specified potential trial level treatment effect modifiers: type of rehabilitation (exercise only or comprehensive), type of exercise (aerobic only or aerobic and resistance), exercise dose (i.e. duration [weeks] × frequency [sessions per week] × length of session [h]), number of centres (single or multicentre), risk of bias (i.e. low risk for both random sequence generation and allocation concealment), geographical location (North America vs. Europe vs. other), follow-up (months), and sample size. Statistical analyses were performed in RevMan Web and STATA v17.0.[17] Two-sided $p < 0.05$ were considered statistically significant.

Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the certainty of evidence for each outcome at short-term follow-up. GRADE assessment includes consideration of trial limitations, consistency of effect, imprecision, indirectness, and publication bias. Two reviewers (CDM and LL) independently used the GRADE criteria for each short-term follow-up outcome. Any discrepancies were resolved by a third reviewer (RST).

Results

Study selection

Database searches for this update yielded a total of 4587 titles, of which 138 full-text publications were assessed for eligibility. An additional report was sourced by bibliographic searching of included studies. Sixteen new randomized controlled trials (8728 participants) were identified, resulting in a total of 60 trials (104 publications). As six trials were multi-arm, there were 66 ExCR versus control comparisons. The search and selection process are summarized in *Figure 1*.

Trial and patient characteristics

Included trials randomized a total of 8728 patients, predominantly with HF with reduced ejection fraction (HFrEF) and New York Heart Association (NYHA) classes II and III (*Table 1*). Nine trials included an (undefined) proportion of people with HF with preserved ejection fraction (HFpEF).[18–25] Most trials were small and single centre, with two large trials (HF-ACTION and TELEREH-HF) contributing approximately 40% of all included participants.[25,26] Most trials reported only in the short-term; nine trials reporting follow-up >12 months.[18,26–33] Median follow-up was 6 months. Participants mean age across trials ranged from 51 to 81 years. Although trials predominantly recruited males, most recent trials recruited a higher proportion of females. Ethnicity was not reported consistently. Fifteen trials were conducted exclusively at home (some including digital support), the remainder with centre-based (22 trials), or hybrid (23 trials). A comprehensive rehabilitation intervention was reported in 18 trials,[18,21–23,25,27,31,34–41] including an educational or psychological component alongside exercise training programme. As shown in *Table 1*, exercise prescription focused on aerobic training and ranged widely between trials.

Risk of bias assessment

The risk of bias criteria was judged to be either low, unclear, or high (*Figure 2*). Trials frequently failed to report methods of sequence generation, allocation concealment, and outcome blinding. Two (3%) trials[42,43] had a high risk of bias for random sequence generation. One (2%) trial[44] had a high risk of bias for allocation concealment. Twelve (20%) trials[22,23,26,28,34,36,38,40,45–48] were defined to be at overall low risk of bias.

Outcome findings

Outcomes results are summarized in *Table 2*.

Mortality

There was no difference between ExCR and control in the risk of mortality in the short-term (RR 0.93; 95% CI 0.71–1.21;

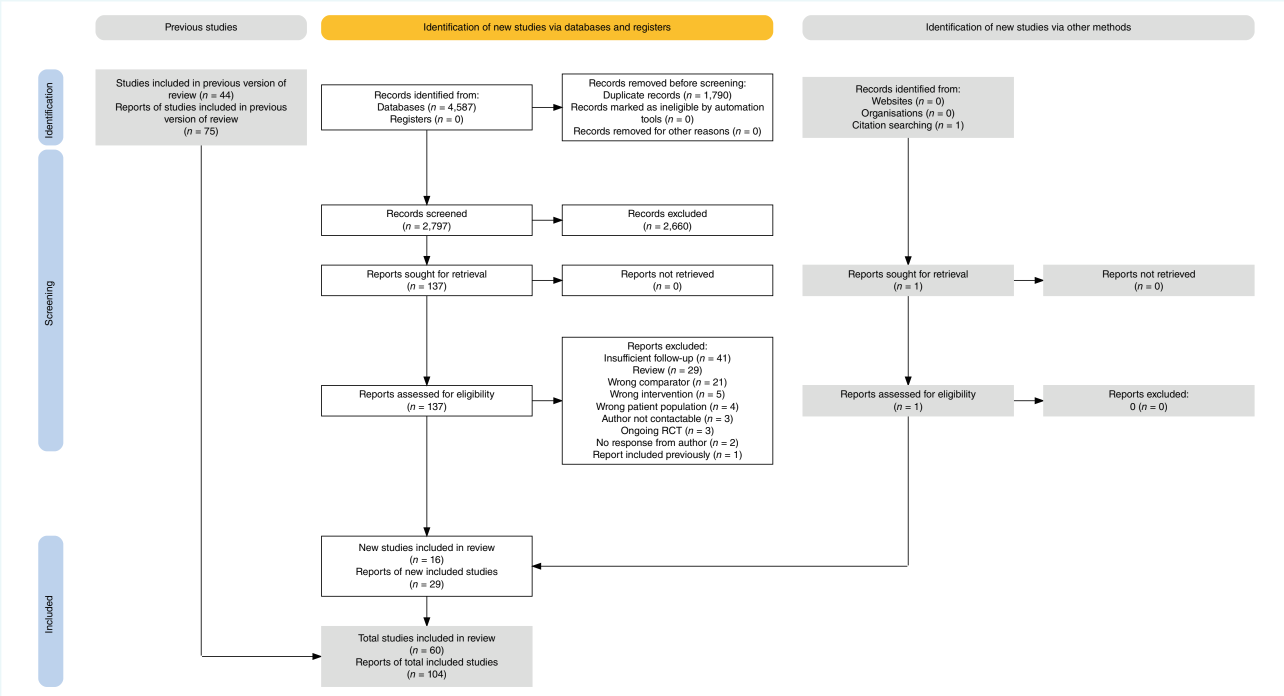

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection process. RCT, randomized controlled trial.

GRADE: low certainty) (*Figure 3A*). Similar results were seen in the long-term (RR 0.87; 95% CI 0.72–1.04; online supplementary *Appendix 2A*). There was no difference in ExCR effect across delivery settings (subgroup *p*-value for short- and long-term: 0.94 and 0.18, respectively). Trials did not report information on cause of death, such HF-related.

Hospitalization

Exercise-based cardiac rehabilitation reduced the risk of all-cause hospitalization in the short-term (RR 0.69; 95% CI 0.56–0.86; GRADE: moderate certainty, with an NNT of 13 [95% CI 9–22]) (*Figure 3B*); long-term (RR 0.84; 95% CI 0.70–1.01; online supplementary *Appendix 2B*). There was no difference in ExCR effect across delivery settings (subgroup *p*-value for short- and long-term: 0.55 and 0.51, respectively). There was no significant difference between ExCR and control for HF-related hospitalization in either the short-term (RR 0.80; 95% CI 0.60–1.06; moderate certainty) (*Figure 3C*) or the long-term (RR 0.90; 95% CI 0.73–1.10) (online supplementary *Appendix 2C*). There was some evidence a larger reduction with centre compared to home in the long-term (subgroup *p*-value for short- and long-term: 0.286 and 0.007, respectively).

Health-related quality of life

Exercise-based cardiac rehabilitation participation resulted in improved HRQoL measured by MLWHF total score, and all HRQoL scales in the short-term (MD: −7.39; 95% CI −10.30 to −4.47; GRADE: moderate certainty; *Figure 3D*; and SMD: −0.53; 95% CI −0.71 to −0.35; GRADE very low certainty; *Figure 3E*). There was no difference in ExCR effect across delivery settings (subgroup *p*-value for HRQoL by MLWHF total score and all HRQoL scales: 0.31 and 0.96, respectively). ExCR also improved MLWHF total score in the long-term (MD: −9.49; CI −17.48 to −1.50; online supplementary *Appendix 2D*). There was no difference in ExCR effect across delivery settings (subgroup $p = 0.88$). Out of 106 comparisons, 40 (38%) reported a positive impact of ExCR compared to control, 63 (59%) reported a neutral effect, and three (3%) comparisons reported a negative (control better than ExCR) impact on HRQoL (online supplementary *Appendix 3*).

Meta-regression

There were no differential treatment effects across trial-level characteristics and outcomes in univariate meta-regression, except for the following: larger improvement in ExCR–control MLWHF total score in single centre trials compared with multicentre trials (MD: −11.53 vs. −3.57, $p = 0.046$); reduced reduction in HF hospitalization with more recent publication date that is, more recent trials had a smaller RR reduction (trial publication 1999 or before, RR: 0.34 vs. trial publication 2000 or later, RR 0.94, $p = 0.05$); larger mortality benefit in trials in Europe and other, than in North America (RR 0.64 vs. 0.67 vs. 0.90, respectively, $p = 0.05$); and higher risk of bias was associated with a larger ExCR–control

Table 1 Summary of included trial characteristics

	All trials (*n* = 60)	New trials in update (*n* = 16)	Centre-based trials (*n* = 22)	Home-based (digitally supported) trials (*n* = 15)	Hybrid trials (*n* = 23)
Population characteristics					
Male sex, %	78	59	79	68	73.5
Age, years, mean	63.3	63.9	61.7	64.9	64.5
HF type					
HFpEF included, *n* (%)	8 (13)	2 (25)	2 (9)	4 (27)	2 (9)
NYHA class IV, *n* (%)	15 (25)	8 (50)	6 (27)	4 (27)	5 (22)
Mean LVEF, %	32.3	32.2	33.2	32.3	29.1
Intervention characteristics					
ExCR type, *n* (%)					
Exercise only	42 (70)	11 (69)	16 (73)	10 (67)	16 (70)
Comprehensive	18 (30)	54 (31)	6 (27)	5 (33)	7 (30)
Aerobic only	42 (70)	10 (62)	16 (73)	10 (67)	11 (48)
Exercise type					
Aerobic and resistance	18 (30)	6 (38)	6 (27)	5 (33)	12 (52)
Exercise prescription					
Mean session duration, min	38	41	41.4	31.5	40.3
Session frequency, per week, mean	3.2	3.4	2.8	3.4	3.6
Programme length, weeks, mean	27	27	24.5	24.6	29.4
Follow-up, months, median	6	10	6	12	6
Study characteristics					
Publication year, *n* (%)					
1990 to 1999	5 (8)	0 (0)	3 (14)	0 (0)	2 (9)
2000 to 2009	22 (37)	0 (0)	9 (41)	3 (5)	10 (44)
2010 to 2019	26 (43)	9 (56)	9 (41)	10 (17)	7 (12)
2020 onwards	7 (12)	7 (43)	1 (2)	2 (3)	4 (30)
Study location, *n* (%)					
Europe	30 (50)	5 (8)	13 (59)	6 (10)	11 (48)
North America	16 (27)	4 (7)	4 (18)	5 (8)	7 (30)
Other	14 (23)	8 (13)	5 (23)	4 (7)	5 (22)
Single centre, *n* (%)	47 (78)	10 (63)	22 (100)	12 (80)	13 (57)

ExCR, exercise-based cardiac rehabilitation; HF, heart failure; HFpEF, heart failure with preserved ejection fraction, LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

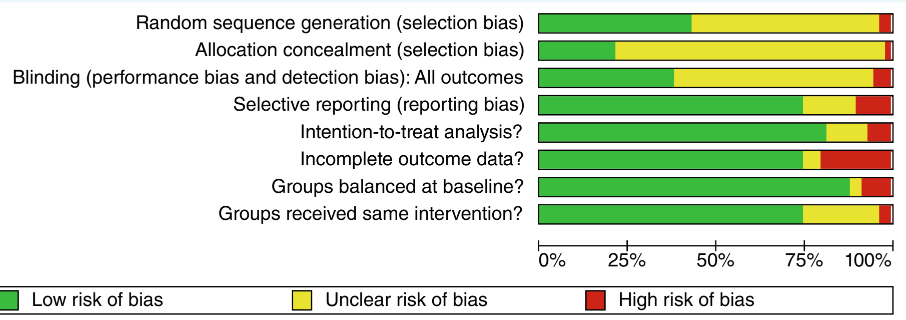

Figure 2 Summary of risk of bias assessment across included trials.

Table 2 Summary of meta-analysis results

Outcome	N. trials (comparisons)	Patients, *n*	Intervention, *n* events/*n* patients (%)	Control, *n* events/N patients (%)	Treatment effect, RR (95% CI)	GRADE quality rating	Statistical heterogeneity (I^2 statistic; *p*-value)	Setting subgroup analysis *p*-value
All-cause mortality								
Short-term	35 (35)	3864	100/1958 (5.1)	112/1906 (5.9)	0.93 (0.71–1.21)	Low	I^2 = 0%, 0.95	0.94
Centre	11	560	15/285 (5.3)	17/275 (6.2)	0.95 (0.48–1.87)		I^2 = 0%, 0.65	
Home	10	1513	30/761 (3.9)	36/752 (4.7)	0.86 (0.54–1.39)		I^2 = 0%, 0.88	
Hybrid	14	1791	55/912 (6.0)	59/879 (6.7)	0.96 (0.67–1.38)		I^2 = 0%, 0.74	
Long-term	8	3780	300/1887 (16)	334/1893 (18)	0.87 (0.72–1.04)	High	I^2 = 16%, 0.31	0.18
Centre	3	192	20/96 (21)	34/96 (35)	0.60 (0.38–0.95)		I^2 = 0%, 0.46	
Home	2	935	56/469 (12)	54/466 (12)	1.03 (0.73–1.47)		I^2 = 0%, 0.91	
Hybrid	3	2653	224/1322 (17)	246/1331 (17)	0.87 (0.72–1.03)		I^2 = 16%, 0.31	
All-cause hospitalization								
Short-term	24 (24)	2283	182/1148 (16)	270/1135 (24)	0.69 (0.56–0.86)	Moderate	I^2 = 24%, 0.14	0.55
Centre	5	246	19/123 (15)	21/123 (9.8)	0.83 (0.37–1.86)		I^2 = 30%, 0.22	
Home	8	872	77/442 (17)	100/430 (23)	0.78 (0.59–1.03)		I^2 = 6%, 0.38	
Hybrid	11	1165	86/583 (15)	149/582 (26)	0.63 (0.46–0.86)		I^2 = 26%, 0.20	
Long-term	7 (8)	3509	1004/1757 (57)	1079/1752 (62)	0.84 (0.70–1.01)	Moderate	I^2 = 62%, 0.01	0.51
Centre	3	192	20/96 (21)	30/96 (31)	0.71 (0.32–1.58)		I^2 = 59%, 0.09	
Home	1	818	232/409 (57)	254/409 (62)	0.91 (0.82–1.02)		Not applicable	
Hybrid	4 (5)	2504	752/1252 (60)	795/1252 (63)	0.69 (0.41–1.17)		I^2 = 62%, 0.01	
HF-related hospitalization								
Short-term	16	1967	153/992	171/975	0.80 (0.60–1.06)	Moderate	I^2 = 14%, 0.12	0.29
Centre	6	302	22/154	36/148	0.52 (0.25–1.08)		I^2 = 43%, 0.29	
Home	6	1423	120/713	127/710	0.94 (0.70–1.26)		I^2 = 5%, 0.39	
Hybrid	4	242	11/125	8/117	0.88 (0.46–1.68)		I^2 = 0%, 0.80	
Long-term	6	1098	131/558	140/540	0.71 (0.50–1.08)	Low	I^2 = 38%, 0.15	0.007
Centre	3	926	121/468	118/458	0.98 (0.79–1.22)		I^2 = 0%, 0.84	
Home	3	172	10/90	22/82	0.38 (0.19–0.73)		I^2 = 0%, 0.80	
Hybrid	0							
HRQoL-MLWHF total score								
Short-term	17 (17)	2699			MD: −7.39 (−10.30 to −4.47)	Moderate	I^2 = 82%, <0.01	0.94
Centre	4	261			MD: −10.82 (−14.90 to −6.74)		I^2 = 13%, 0.33	
Home	11	1445			MD: −6.90 (−11.26 to −2.55)		I^2 = 74%, <0.01	
Hybrid	2	993			MD: −6.37 (−11.84 to −0.89)		I^2 = 92%, <0.01	
Long-term	3 (3)	329			MD: −9.49 (−17.84 to −1.50)	Very low	I^2 = 73%, 0.03	0.18
Centre	1	94			MD: −10.00 (−18.70 to −1.30)			
Home	0							
Hybrid	2	235			MD: −8.82 (−21.91 to 4.27)		I^2 = 86%, <0.01	
HRQoL – all outcome measures								
Short-term	37 (38)	4769			SMD: −0.53 (−0.71 to −0.35)	Very low	I^2 = 87%, <0.0001	0.94
Centre	13	565			SMD: −0.45 (−0.79 to −0.11)		I^2 = 72%, 0.01	
Home	12 (13)	1496			SMD: −0.61 (−0.92 to −0.30)		I^2 = 86%, 0.01	
Hybrid	12	2708			SMD: −0.53 (−0.71 to −0.35)		I^2 = 87%, <0.01	

CI, confidence interval; HF, heart failure; HRQoL, health-related quality of life; MD, mean difference; MLWHF, Minnesota Living with Heart Failure Questionnaire; RR, relative risk; SMD, standardized mean difference.

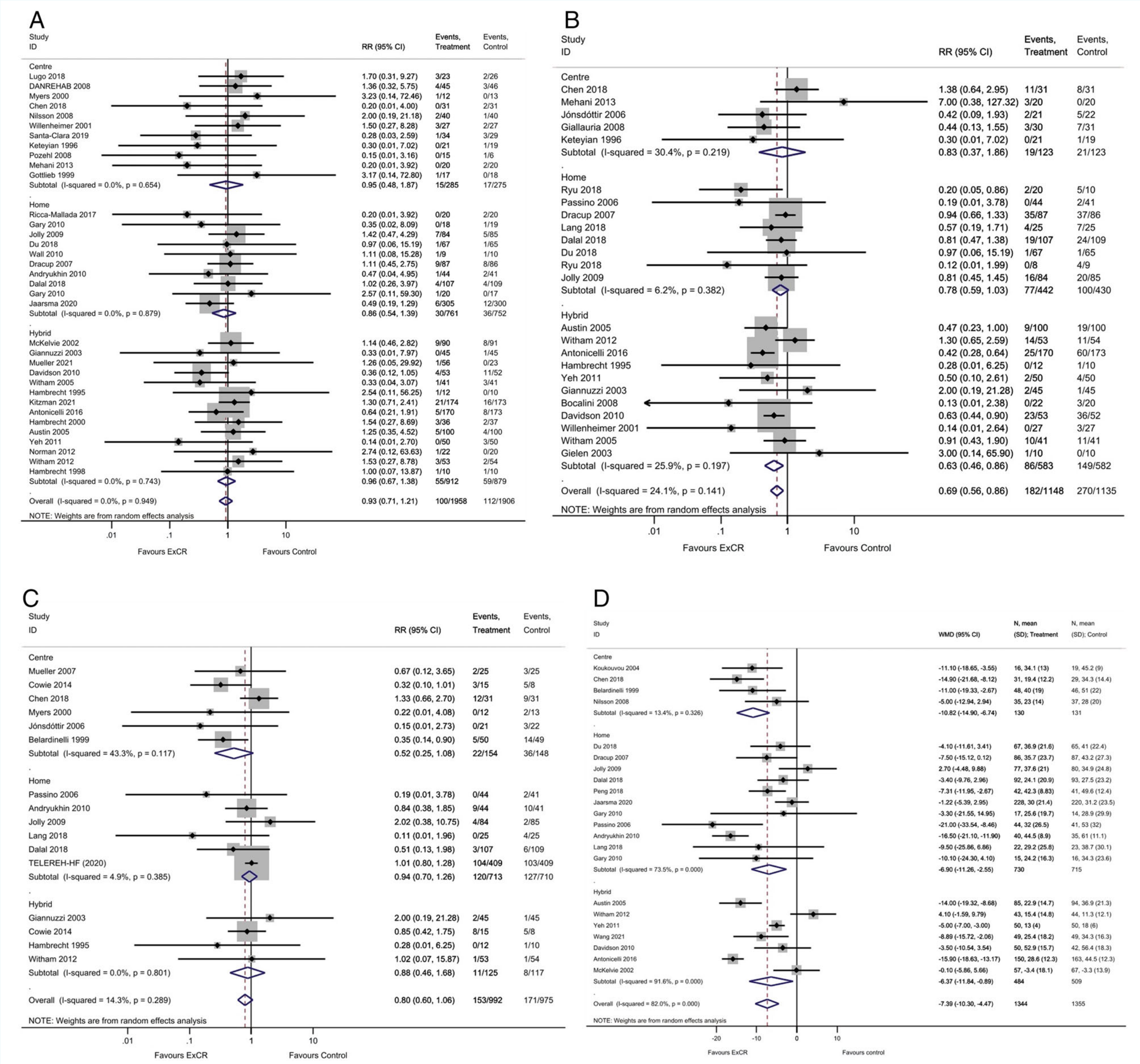

Figure 3 Forest plot of exercise-based cardiac rehabilitation (ExCR) versus control for (*A*) overall mortality in the short-term (≤12-month follow-up), (*B*) overall hospitalizations in the short-term (≤12-month follow-up), (*C*) HF hospitalizations in the short-term (≤12-month follow-up), (*D*) overall Minnesota Living with Heart Failure Questionnaire (MLWHF) score in the short-term (≤12-month follow up), and (*E*) all HRQoL outcomes in the short-term (≤12-month follow-up). CI, confidence interval; RR, relative risk; SD, standard deviation; SMD, standardized mean difference; WMD, weighted mean difference.

difference versus low risk of bias on both all-cause mortality (RR 0.70 vs. 1.26) and MLWHF (MD: −9.59 vs. −3.32, $p = 0.03$) (online supplementary *Appendix 4*).

Small study bias

There was evidence of small study bias for HF-related hospitalizations (Egger's test $p = 0.015$) and HRQoL by all scales (Egger's test $p = 0.001$). Other outcomes showed no evidence of funnel plot asymmetry (online supplementary *Appendix 5*).

Discussion

This 2023 Cochrane systematic review of 60 randomized trials in over 8500 HF patients confirms the benefits of participation in ExCR. Meta-analyses showed ExCR to be associated with a reduction in the risk of hospitalization and improvement in HRQoL in both the short-term (trials with follow-up to 12 months) and long-term (trials with follow-up >12 months) (*Graphical Abstract*). For example, compared to control, there was an overall reduction of 31% (95% CI 14–44%) in the RR of all-cause hospitalization

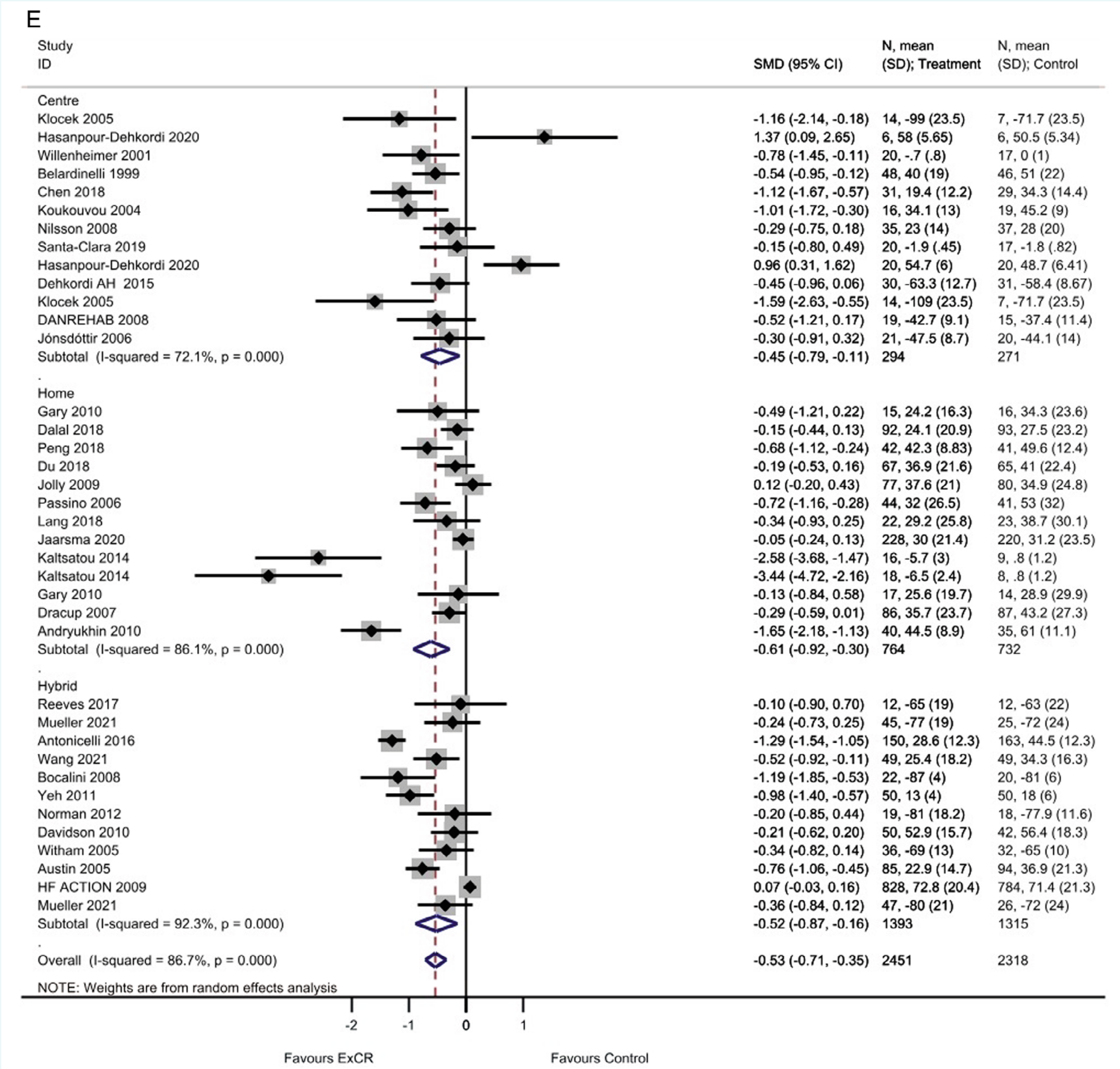

Figure 3 Continued.

(NNT of 13, 95% CI 9–22) and as improvement in disease-specific HRQoL assessed by the total MLWHF score of −7.4 (95% CI −10.3 to −4.5) in trials with short-term follow-up. A change in MLWHF total score of ≥5 points is considered clinically meaningful.[49] That recent trials recruited a wider range of patients (i.e. women, NYHA class IV, HFpEF and HF with mildly reduced ejection fraction [HFmrEF], and acute decompensated HF), increases the potential applicability of these benefits of ExCR to real-world clinical practice.

Our review included a number of trials evaluating alternative modes of ExCR delivery to the traditional supervised centre-based delivery. Fifteen trials were delivered remotely in a home setting that could include digital support and 23 trials with a mix of both centre and home-based sessions (hybrid). Given the urgent need to improve rehabilitation access and participation, our finding of gains in HF patient outcomes with ExCR, irrespective of delivery mode, is an important one. Our meta-regression findings of no difference in HF patient outcomes between trials employing an ExCR only intervention compared with trials of comprehensive cardiac rehabilitation (including education or psychological support or both) and trials of aerobic exercise training versus aerobic and resistance exercise, are consistent with the stratified meta-analysis findings of the CROS-HF systematic review.[50] It is also important to note that whilst the CROS-HF study reported no statistically significance reduction in hospitalization (either all-cause or HF) this likely reflects their inclusion of a smaller number of trials and, therefore, less events. This is reflected in their wide 95% CIs, but their mean pooled treatment effects are comparable to those seen in the present analysis (i.e. all-cause hospitalization: RR 0.79, 95% CI 0.41–1.53; HF hospitalization: RR 0.84, 95% CI 0.07–9.71).

Strengths and limitations

This review has several major strengths. We believe it to be the most comprehensive and contemporary overview of randomized trial evidence of ExCR in adults with HF to date. Importantly, given the stubbornly poor uptake of ExCR across global healthcare systems, our meta-analyses assess the impact of ExCR across different delivery settings: centre, home (including digitally supported), and hybrid. We also undertook a meta-regression analysis to explore the potential impact other trial level characteristics on the impact of cardiac rehabilitation. However, we acknowledge limitations in the review methods and included trials. Firstly, our comparison of centre-based ExCR versus alternative modes of delivery is indirect. In other words, we compared modes of delivery from separate trials, in contrast to a direct ('head-to-head') comparison of ExCR modes within a randomized trial. This indirect comparison therefore needs to be interpreted with caution. Although we found patient populations across trials in three delivery modes not to differ substantially, there was a paucity of reporting on key HF characteristics, such as time after the index event/diagnosis. Nevertheless, the recently updated Cochrane review of randomized trials directly comparing home (and digitally supported) versus centre-based ExCR supports our finding of similar improvement in outcome HF patients irrespective of delivery mode.[51] Our findings of similar improvements in HRQoL across models of ExCR delivery are also supported by the network meta-analysis of Tegegne *et al.*,[52] although this analysis did not consider mortality or hospitalization. Secondly, several included trials failed to report methodological details (including generation and concealment of the method of random allocation, and outcome blinding) and may therefore be subject to risk of bias. Meta-regression analysis showed that only the outcome of all-cause mortality and HRQoL were impacted by risk of bias, and the benefit of ExCR on MLWHF total score remained when we restricted meta-analysis to low risk of bias trials (MD: −3.32, 95% CI −8.20 to 1.57, seven trials). Thirdly, statistical heterogeneity was high (I^2 >50%) for many outcomes, likely arising from the broad inclusion criteria of this systematic review resulting in trials with a range of ExCR interventions and control regimes. To account for this heterogeneity, we employed a more conservative random-effects model of meta-analysis, sought to fully explore the possible causes of heterogeneity using stratified meta-analysis and meta-regression and downgraded the strength of evidence in GRADE. Fourthly, while trials reported a prescribed dose of exercise, few, if any, reported the actual level of exercise undertaken by participants. So, we were not able to formally assess the impact of intervention adherence. Fifthly, given that most trials that included HFpEF patients, were mixed populations including HFrEF and HFmrEF, we were not able to formally contrast the impact of ExCR across these subgroups. Finally, given background HF medication was not consistently across cardiac rehabilitation trials, especially in older trials, we were not able to undertake a formal analysis of the impact of specific medications on the impact of cardiac rehabilitation. However, as we demonstrated in a previous Cochrane review, year of trial publication can be used as proxy of the quality of medical care that is, more recently published trials are likely to reflect a better standard of background of HF care than older trials.[53] Interestingly, our meta-regression analysis did show some evidence ($p = 0.05$) of a smaller relative risk reduction in HF hospitalization with cardiac rehabilitation in trials published since 2000, raising the hypothesis that contemporary improvements in medical HF therapy may mediate the impact of cardiac rehabilitation on HF outcomes.

Implications for clinical practice and future research

Increasing recognition, not only of the need to reduce the risk of clinical events and improve survival of HF patients, but also to optimize HRQoL, underscores the importance of rehabilitation.[54,55] As proposed by a recent state of the art review, evidence for ExCR, supports its place as a 'fifth pillar' of HF management and alongside the four classes of drugs, that is, angiotensin receptor–neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium–glucose cotransporter 2 inhibitors.[9] Whilst this review found the patient characteristics to be broadly similar across trials, irrespective of the mode of delivery, given their less intensive supervision, patients should be carefully selected for home-based (and digitally supported) programmes. The scientific statement from the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Heart Association, and the American College of Cardiology recommend the use of home-based models, should be limited to patients who are clinically stable, at low to moderate risk, and who cannot attend a traditional supervised centre-based programme.[11] Future trials need to focus their recruitment on HF phenotypes less represented in current trials (i.e. HFpEF, HFmrEF, and acute HF) and patient subgroups at high risk of not accessing rehabilitation (e.g. ethnic minorities, more complex patients, including those with multimorbidity) and evaluate of the impact of alternative modes of ExCR delivery (including home, digitally supported, and hybrid programmes) using well designed 'head-to-head' studies.[9]

Conclusions

The 2023 Cochrane systematic review and meta-analysis provides a comprehensive and contemporary update of the randomized trial evidence base confirming the benefits of ExCR that includes both reduced hospitalization risk and a clinically important improvement in HRQoL for HF patients. Importantly, this meta-analysis shows that home-based, digitally supported, and centre-based (and hybrid) programmes are all associated with improvements in health outcomes. To improve suboptimal levels of ExCR uptake, global healthcare systems need to develop their services, so rehabilitation is routinely recommended for people with HF as part of routine care. Dependent on their level of risk and complexity, individual patients should be offered a choice of the mode of ExCR programme – centre, home (with or without digital support), or hybrid.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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