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# Meta-analysis of Exercise Training on Left Ventricular Ejection Fraction in Heart Failure with Reduced Ejection Fraction: A 10-year Update☆

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A R T I C L E   I N F O

*Keywords:*
Exercise therapy
Moderate-intensity continuous training
High-intensity interval training
Resistance training
Left ventricular ejection fraction

A B S T R A C T

*Background:* The role of exercise training modality to attenuate left ventricular (LV) remodeling in heart failure patients with reduced ejection fraction (HFrEF) remains uncertain. The authors performed a systematic review and meta-analysis of published reports on exercise training (moderate-intensity continuous aerobic, high-intensity interval aerobic, and resistance exercise) and LV remodeling in clinically stable HFrEF patients.
*Methods:* We searched MEDLINE, Cochrane Central Registry of Controlled Trials, CINAHL, and PubMed (2007 to 2017) for randomized controlled trials of exercise training on resting LV ejection fraction (EF) and end-diastolic and end-systolic volumes in HFrEF patients.
*Results:* 18 trials reported LV ejection fraction (LVEF) data, while 8 and 7 trials reported LV end-diastolic and LV end-systolic volumes, respectively. Overall, moderate-intensity continuous training (MICT) significantly increased LVEF (weighted mean difference, WMD = 3.79%; 95% confidence interval, CI, 2.08 to 5.50%) with no change in LV volumes versus control. In trials ≥6 months duration, MICT significantly improved LVEF (WMD = 6.26%; 95% CI 4.39 to 8.13%) while shorter duration (<6 months) trials modestly increased LVEF (WMD = 2.33%; 95% CI 0.84 to 3.82%). High-intensity interval training (HIIT) significantly increased LVEF compared to control (WMD = 3.70%; 95% CI 1.63 to 5.77%) but was not different than MICT (WMD = 3.17%; 95% CI −0.87 to 7.22%). Resistance training performed alone or combined with aerobic training (MICT or HIIT) did not significantly change LVEF.
*Conclusions:* In clinically stable HFrEF patients, MICT is an effective therapy to attenuate LV remodeling with the greatest benefits occurring with long-term (≥6 months) training. HIIT performed for 2 to 3 months is superior to control, but not MICT, for improvement of LVEF.



## Contents



*Abbreviations and acronyms:* EF, ejection fraction; ET, exercise training; HF, heart failure; HFrEF, heart failure with reduction ejection fraction; HIIT, high-intensity interval training; LV, left ventricle; MICT, moderate-intensity continuous training; Peak $VO_2$, peak oxygen consumption; WMD, weighted mean difference.

☆ Statement of Conflict of Interest: see page 171.

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Heart failure (HF) is a major health care problem associated with a high individual and societal health care burden.[1] Approximately 50% of HF patients have reduced ejection fraction (HFrEF) with structural cardiac remodeling characterized by left ventricular (LV) dilation and reduced function.[2] Given that LV remodeling is associated with increased mortality, therapies that attenuate this process are important therapeutic targets.[3,4]

Exercise training (ET) is an effective intervention to attenuate LV remodeling in clinically stable HFrEF patients.[5] However, the magnitude of this change may depend on the type of exercise undertaken.[6] In 2007, a meta-analysis by Haykowsky et al. found a significant increase in resting LV ejection fraction (LVEF) and reduction in LV volumes and improved peak oxygen uptake (peak $VO_2$) following aerobic moderate-intensity continuous training (MICT) but these changes were not replicated when aerobic and strength training were combined.[6] Wisloff et al. extended these findings by demonstrating significantly greater anti-remodeling benefits with high-intensity interval training (HIIT) (e.g. brief, intermittent bursts of vigorous aerobic exercise interspersed with short periods of low-intensity active recovery[7]) compared to MICT in older (mean age: 76 years) post-infarction HFrEF patients.[8] Yet in contrast, other investigators[9–11] have not found additional anti-remodeling benefits with HIIT versus MICT in HFrEF patients (mean age: 60 years). Given this continued uncertainty and importance of understanding optimal ET regimen for the large and vulnerable population with HFrEF, we performed a 10-year update of our prior systematic review and meta-analysis of randomized controlled trials that examined the effect of ET on LV remodeling and peak oxygen consumption (peak $VO_2$) in clinically stable HFrEF patients.

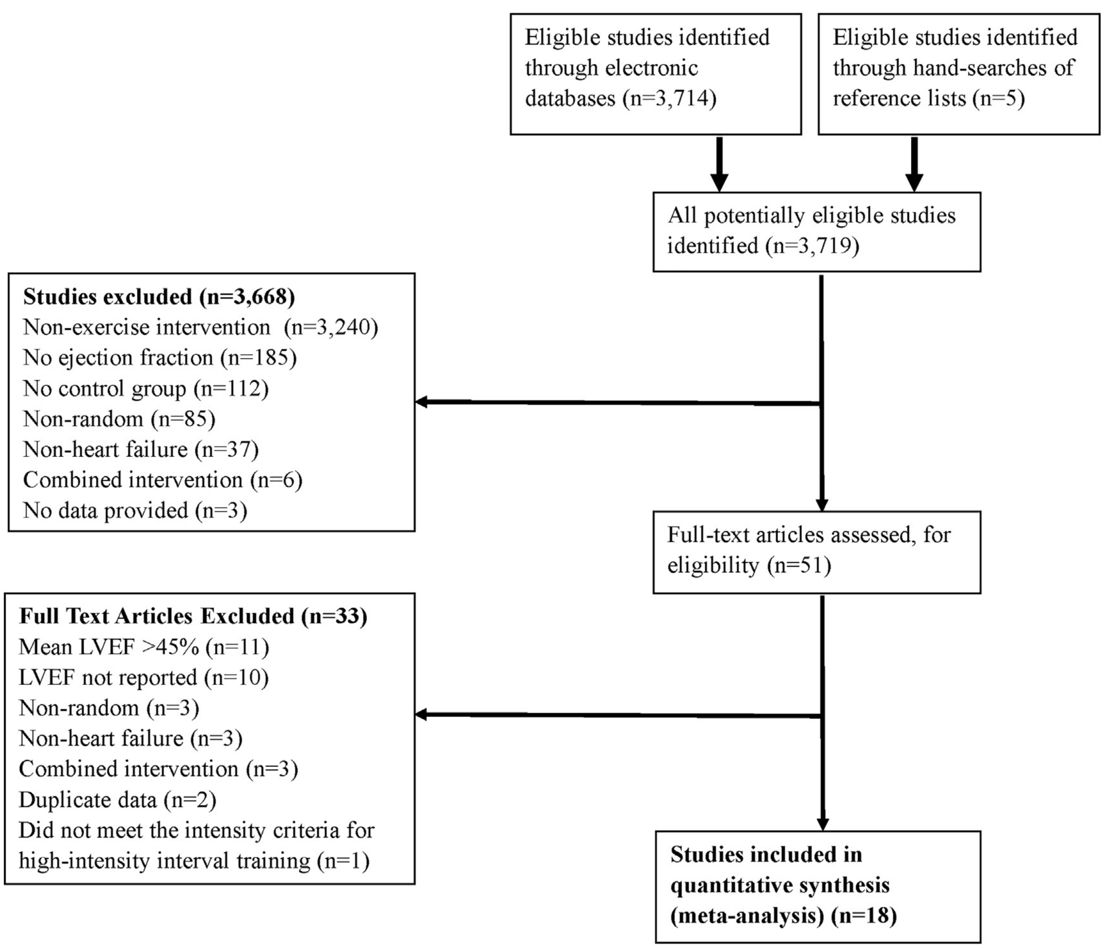


**Fig 1.** Flow of trials through the selection process. LVEF: left ventricle ejection fraction.

**Table 1**
Description of randomized controlled exercise training intervention studies included.

| Study, year (Ref.) | Study sample | Sample size, *n* | Men, % | Mean age, years | HFrEF etiology | Exercise training intervention | Intervention duration, months | EF measure | Drug therapy, % |
|---|---|---|---|---|---|---|---|---|---|
| Antunes-Correa 2014 [22] | NYHA class II–III HF, LVEF <40% | ET, 17 | 76 | 56 | Ischemic 35% Idiopathic 35% | RT + MICT 3 days/week, MICT 30–40 min at 60–72% $VO_{2peak}$ + 10 min RT strength training exercises | 3 | Echo, SBP | ACE: 100; BB: 100; DIU: 71; SPIRO: 82 |
| | | CNT, 17 | 88 | 54 | Ischemic 29% Idiopathic 35% | | 3 | | ACE: 100; BB: 100; DIU: 82; SPIRO: 82 |
| Belardinelli 2008 [9] | NYHA class II–III HF, LVEF <40% | ET, 44 | 82 | 60 | Prior MI 55% Prior CABG 77% | HIIT 3 days/week, 21 min/session, Dance 5 min slow, 3 min fast (88% $HR_{peak}$ reported) | 2 | Echo, modified SSP | ACE: 80; BB: 80; DIGI: 14; DIU: 73; NIT: 18 |
| | | ET, 44 | 86 | 59 | Prior MI 57% Prior CABG 82% | MICT 3 days/week, 30 min/session, 70% $VO_{2peak}$ | 2 | | ACE: 77; BB: 82; DIGI: 11; DIU: 77; NIT: 25 |
| | | CNT, 42 | 83 | 58 | Prior MI 50% Prior CABG 69% | | 2 | | ACE: 88; BB: 88; DIGI: 10; DIU: 69 |
| Belardinelli 2012 [23] | NYHA class II–III HF, LVEF <40% | ET, 63 | 78 | 60 | Ischemic 80% Non-ischemic 20% | MICT 3 days/week, 40 min/session, 60–70% $VO_{2peak}$ | 120 | Echo, not specified | ACE: 71; AIIA: 24; BB: 46; DIGI: 19; DIU: 52 |
| | | CNT, 60 | 78 | 59 | Ischemic 80% Non-ischemic 20% | | 120 | | ACE: 73; AIIA: 23; BB: 45; DIGI: 17; DIU: 52 |
| Brubaker 2009 [24] | LVEF <45% | ET, 30 | 63 | 70 | Not reported | MICT 3 days/week, 30–40 min/session, 40% HRR × 2 weeks followed by 60–70% HRR. | 4 | Echo, not specified | ACE: 80; BB: 20; CCB: 30; DIGI: 70; DIU: 87; NIT: 23 |
| | | CNT, 29 | 69 | 70 | | | 4 | | ACE: 86; BB: 14; CCB: 21; DIGI: 72; DIU: 86; NIT: 41 |
| Eleuteri 2013 [25] | NYHA class II HF, LVEF <40% | ET, 11 | 100 | 66 | Not reported | MICT 5 days/week, 30 min/session, 59–62% $VO_{2peak}$ | 3 | Echo, BP area-length | ACE: 100; BB: 100; NIT: 27 |
| | | CNT, 10 | 100 | 63 | | | 3 | | ACE: 100; BB: 100; NIT: 30 |
| Ellingsen 2017 [11] | NYHA class II–III HF, LVEF <35% | ET, 77 | 81 | 65 | Ischemic 60% Prior MI 57%, prior CABG 26%, prior PCI 46% | HIIT 3 days/week, 38 min/session, Intervals, 4 × 4 min at median 90% $HR_{max}$ reported (88–92%, 95% CI) 3 min active recovery between | 3 | Echo, Modified SBP | ACE: 92; BB: 95; DIGI: 22; DIU: 75 |
| | | ET, 65 | 82 | 60 | Ischemic 60% Prior MI 55%, prior CABG 22%, prior PCI 35% | MICT 3 days/week, 47 min/session, median 77% $HR_{max}$ reported (74–82%, 95% CI) | 3 | | ACE: 92; BB: 94; DIGI: 12; DIU: 75 |
| | | CNT, 73 | 81 | 60 | Ischemic 56% Prior MI 44%, prior CABG 23%, prior PCI 45% | MICT 1 day every 3 weeks, 47 min/session, 70% $HR_{max}$ prescribed | 3 | | ACE: 96; BB: 97; DIGI: 8; DIU: 70 |
| Fu 2013 [26] | NYHA class II–III HF, LVEF <40%, or LVEF >40% with episodes of acute pulmonary edema | ET, 14 | 64 | 68 | Ischemic 67% Non-ischemic 33% | HIIT 3 days/week, 30 min/session, Intervals, 5 × 3 min at 80% $VO_{2peak}$, 3 min recovery between | 3 | Echo, not specified | ACE: 79; BB: 93; CCB: 64; DIGI: 21; DIU: 50 |
| | | ET, 13 | 62 | 66 | Ischemic 60% Non-ischemic 40% | MICT 3 days/week, 30 min/session, 60% $VO_{2peak}$ | 3 | | ACE: 77; BB: 92; CCB: 62; DIGI: 31; DIU: 46 |
| | | CNT, 13 | 69 | 68 | Ischemic 67% Non-ischemic 33% | | 3 | | ACE: 77; BB: 92; CCB: 69; DIGI: 23; DIU: 46 |
| Hassanpour Dehkordi 2015 [27] | NYHA class II–III HF, LVEF <40% | ET, 30 | 60 | 60 | Ischemic 70% Non-ischemic 30% | MICT 3 days/week, 25–35 min/session, 60–70% HRR | 6 | Echo, not specified | ACE: 80; DIGI: 70; DIU: 93 |
| | | CNT, 31 | 74 | 58 | Ischemic 65% Non-ischemic 35% | | 6 | | ACE: 87; DIGI: 71; DIU: 90 |
| Hollriegel 2016 [28] | NYHA class IIIb HF, LVEF <30% | ET, 18 | 100 | 60 | Ischemic 56% DCM 44% | MICT 5 days/week, 30 min/session, 50–60% $VO_{2peak}$ | 12 | Echo, not specified | ACE: 100; BB: 94; DIGI: 56; DIU: 94 |

*(continued on next page)*

**Table 1** (*continued*)

| Study, year (Ref.) | Study sample | Sample size, *n* | Men, % | Mean age, years | HFrEF etiology | Exercise training intervention | Intervention duration, months | EF measure | Drug therapy, % |
|---|---|---|---|---|---|---|---|---|---|
| | | CNT, 19 | 100 | 62 | Ischemic 53%<br>DCM 47% | | 12 | | ACE: 100; BB: 100; DIGI: 21; DIU: 100 |
| Klecha 2007 [29] | NYHA class II–III HF, LVEF <35% | ET, 25 | 80 | 60 | Ischemic 100% | MICT<br>3 days/week,<br>25 min/session, 80% $HR_{max}$ | 6 | MRI, not specified | ACE: 100; BB: 100; DIGI: 36; DIU: 64; NIT: 36 |
| | | CNT, 25 | 72 | 61 | Ischemic 100% | | 6 | | ACE: 100; BB: 100; DIGI: 32; DIU: 68<br>NIT: 68 |
| Malfatto 2009 [30] | DCM | ET, 27 | 70 | 65 | Ischemic 52%<br>Non-ischemic 48% | MICT<br>3 days/week,<br>40 min/session, 60% $VO_{2peak}$ | 3 | Echo, not specified | ACE: 89; BB: 81; DIGI: 4; DIU: 67; SPIRO: 52 |
| | | CNT, 27 | 74 | 67 | Ischemic 59%<br>Non-ischemic 41% | | 3 | | ACE: 81; BB: 78; DIGI: 7; DIU: 70; SPIRO: 48 |
| Muller 2009 [31] | LVEF <40% | ET, 8 | 100 | 47 | Not reported | MICT<br>5 days/week,<br>30 min/session, +45 min walk twice daily, | 1 | MRI, Stack | ACE: 100; BB: 75; DIGI: 38; DIU: 88 |
| | | CNT, 8 | 100 | 56 | | 60–80% HRR | 1 | | ACE: 88; BB: 50; DIGI: 25; DIU: 75 |
| Palevo 2009 [32] | NYHA class II–III HF, LVEF <40% | ET, 10 | 94[a] | 70 | Ischemic 100% | RT<br>3 days/week, | 2 | Echo, not specific | ACE: 100; BB: 100 |
| | | CNT, 6 | | 65 | Ischemic 100% | 12 strength exercises, 2 sets, 12–15 reps, 60% 1RM | 2 | | ACE: 100; BB: 100 |
| Passino 2008 [13] | NYHA class <IV HF, LVEF <45% | ET, 71 | 87 | 61 | Ischemic 55%<br>Idiopathic 45% | MICT<br>3 days/week,<br>30 min/session, 65% $VO_{2peak}$ | 9 | Echo, not specific | ACE: 75; BB: 73; DIU: 79; SPIRO: 38 |
| | | CNT, 19 | 74 | 63 | Ischemic 42%<br>Idiopathic 58% | | 9 | | ACE: 74; BB: 74; DIU: 84; SPIRO: 37 |
| Sandri 2012 [33] | NYHA class II–III HF, LVEF <40% | ET, 30 | 80 | 61 | Ischemic 60%<br>DCM 40% | MICT<br>4 days/week,<br>4 sessions/day, | 1 | Echo, 4C Simpson Disk | ACE: 83<br>BB: 100; DIU: 83; SPIRO: 43 |
| | | CNT, 30 | 83 | 61 | Ischemic 67%<br>DCM 33% | 20 min/session, 70% $VO_{2peak}$ | 1 | | ACE: 83, BB: 100, DIU: 83, SPIRO: 50 |
| Santos 2010 [14] | LVEF <45% | ET, 13 | 69 | 53 | Not reported | RT + MICT<br>3 days/week,<br>MICT 25–40 min per session at HR of AT + RT 10 | 4 | Echo, modified SBP | ACE: 100, BB: 100, DIGI: 38, DIU: 85 |
| | | CNT, 10 | 40 | 59.4 | | min of strength exercises | 4 | | ACE: 70, BB: 100, DIGI: 0, DIU: 40 |
| Stevens 2015 [34] | NYHA class III HF | ET, 15 | 67 | 67 | Ischemic 40% | RT + HIIT<br>5 sessions every 2 weeks, 24–60 min/session, | 3 | Echo, modified SBP | ACE: 87, BB: 93, DIU: 80 |
| | | CNT, 7 | 86 | 64 | Ischemic 57% | HIIT 4 bouts of 6–10 min cycle/walk at critical power (~80% $VO_{2peak}$) with 2 min rest between bouts RT 2–3 sets, 10–15 reps 50–70% 1RM | 3 | | ACE: 100, BB: 100, DIU: 86 |
| Wisloff 2007 [8] | >12 months post-MI, LVEF <40% | ET, 9 | 78 | 77 | Post-MI 100% | HIIT<br>3 days/week,<br>38 min/session, Intervals, 4 × 4 min at mean 92 ± 2% $HR_{max}$ reported, 3 min active recovery between. | 3 | Echo, modified SBP | ACE: 100, BB: 100, DIU: 56<br>NIT: 44 |
| | | ET, 9 | 78 | 74 | Post-MI 100% | MICT<br>3 days/week,<br>47 min/session, mean 74 ± 2% $HR_{max}$ reported | 3 | | ACE: 100, BB: 100, DIU: 44, NIT: 56 |
| | | CNT, 9 | 67 | 76 | Post-MI 100% | MICT<br>1 day ever 3 weeks,<br>47 min/session, mean 71 ± 2% $HR_{max}$ reported | 3 | | ACE: 100, BB: 100, DIU: 56, NIT: 44 |

All data are mean values unless otherwise indicated. *Abbreviations*: ACE: angiotensin converting enzyme inhibitor, AIA: angiotensin 1 antagonist, AIIA: angiotensin 2 antagonist, AT: anaerobic threshold, BB: beta-blocker, CABG: coronary artery bypass graft, CCB: calcium channel blocker, CI: confidence interval, CNT: control, DCM: dilated cardiomyopathy, DIGI: digoxin, DIU: diuretic, EF: ejection fraction, ET: exercise training, HF: heart failure, HIIT: high-intensity interval training, $HR_{max}$: heart rate max, HRR: heart rate reserve, LVEF: left ventricular ejection fraction, MI: myocardial infarction, MICT: moderate-intensity continuous training, NIT: nitrates, NYHA: New York Heart Association, PCI: percutaneous coronary intervention, RT: resistance training, SBP: Simpson's Biplane, SPIRO: spironolactone, SSP: Simpson's Single Plane, $VO_{2peak}$: peak oxygen consumption, 1RM: 1-repetition maximum, 4C: 4-chamber.

[a] Median values.

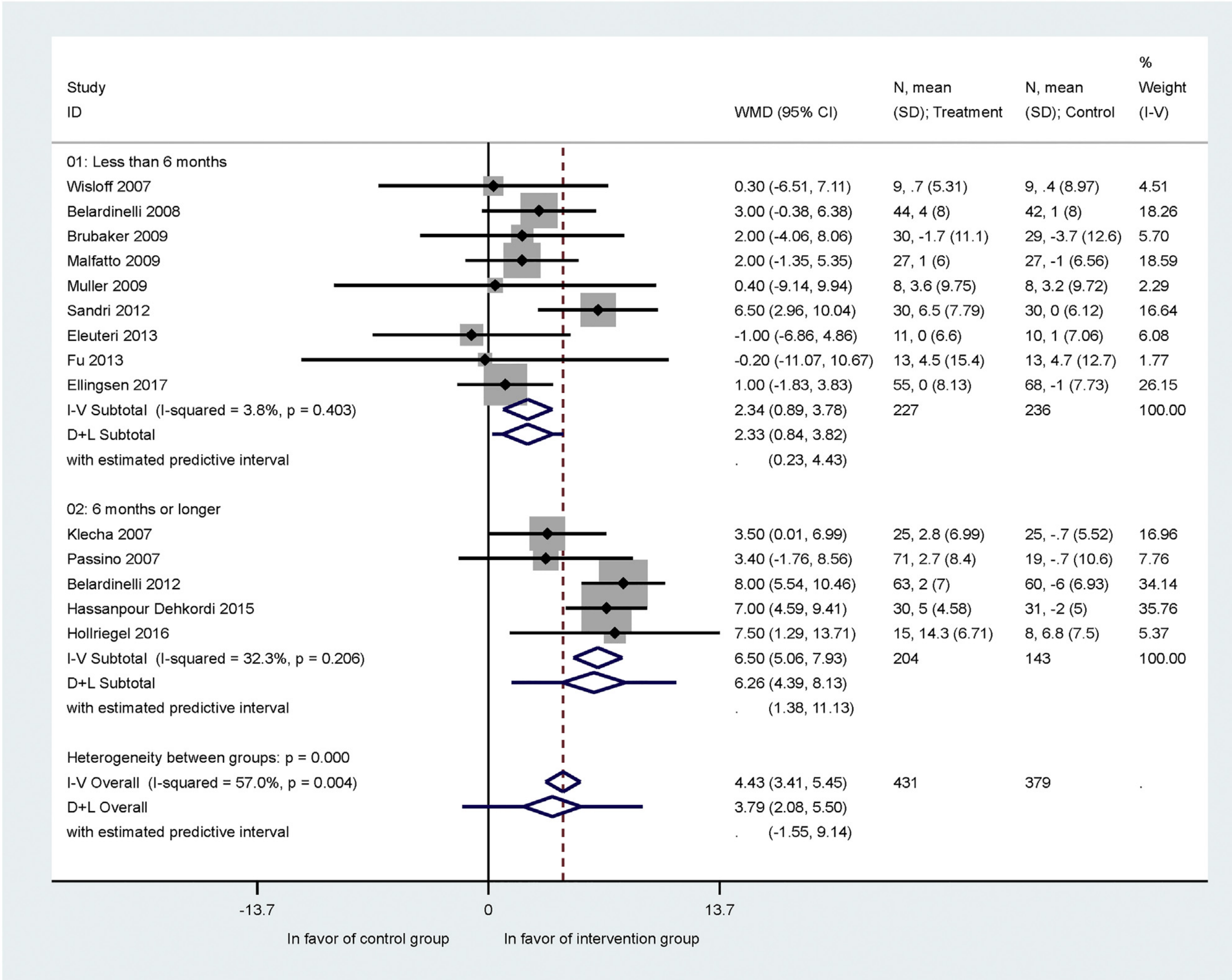


**Fig 2.** Moderate-intensity continuous training (MICT) and left ventricle ejection fraction (LVEF) in all trials and split by intervention duration (<6 months or ≥6 months).

## Methods

### *Data sources*

The authors searched (Jan 2007 to Jan 2017) MEDLINE, Cochrane Central Register of Controlled Trials, CINAHL, and PubMed using the following MESH terms and text words used in our original meta-analysis[6]: *heart failure, exercise, exercise therapy, exercise test, therapeutic exercise, cardiac rehabilitation, and kinesiotherapy*. We also hand-searched reference lists of all identified studies, and previous systematic reviews. We excluded non-English articles.

### *Study selection*

After removal of all duplicate citations, two investigators (W.J.T. and R.I.B.) independently reviewed the titles and abstracts of all potentially eligible citations reporting the effect of ET on LVEF (primary outcome) and/or volumes in HFrEF patients. Both investigators obtained the full text of potentially relevant articles and independently reviewed those using pre-standardized data abstraction forms and eligibility criteria that were defined a priori. Studies were excluded that were: non-randomized, non-HFrEF, did not contain an ET intervention, did not report EF, LVEF >45%, did not have a usual care control group, had an ET intervention that also received a drug intervention, or had HF patients who were not clinically stable for at least 1 month prior to starting the ET intervention. In addition, studies that did not meet the Weston et al.[12] criteria of HIIT (e.g. 85%–95% peak heart rate or 80–100% peak work rate/peak $VO_2$) were excluded.

### *Data extraction and quality assessment*

Two investigators (W.J.T. and R.I.B.) extracted all outcome data independently. When necessary, original investigators were contacted to clarify data or provide data in the required format (mean ± SD). Authors for 3 studies provided additional data.[11,13,14] Quality was assessed using the previously validated Jadad scale[15] (a 5-point scale used to assess the methodological quality of clinical trials by evaluating the adequacy of reporting for study randomization, double-blinding, and disclosure of withdrawals and dropouts) and adequacy of allocation concealment.

### *Data synthesis and analysis*

Data were analyzed using the change score (post–pre) from baseline for both the exercise and control groups and the corresponding standard deviation was estimated using standard statistical methods assuming a correlation of 0.5 between pre and post measures.[16] To pool the effect sizes, two models were used: 1) a fixed effect model using the inverse variance (IV) method; and 2) a random effects model using the method of DerSimonian and Laird (D + L), with the estimate of heterogeneity being taken from the IV fixed-effect model.[17,18] Results were reported as weighted mean differences (WMD) with 95%

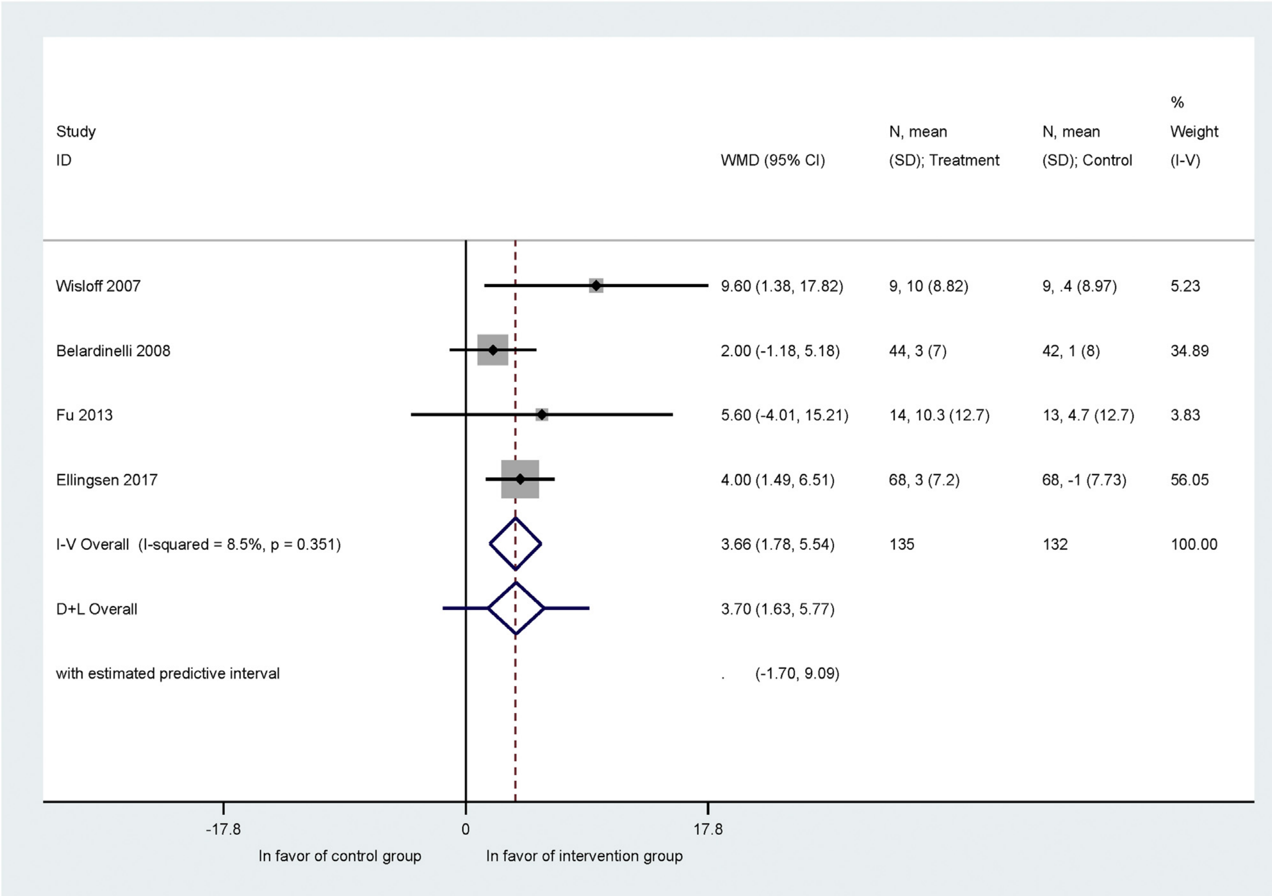


**Fig 3.** High-intensity interval training (HIIT) and left ventricle ejection fraction (LVEF).

confidence intervals (CIs) using random effects model. Heterogeneity was quantified using the $I^2$ statistic and a value of $I^2 > 50\%$ is considered substantial heterogeneity.[18] Subgroup analyses by the length of exercise program (≥6 months vs. <6 months) were conducted to investigate possible sources of heterogeneity. Publication bias was tested visually using funnel plots[19] and quantitatively using the Begg adjusted-rank correlation test[20] and Egger regression asymmetry test.[21] There was no evidence of publication bias identified. All analyses were performed using Stata/SE 15 (StataCorp, College Station, Texas).

## Results

### *Study screening, selection and evaluation*

After removing duplicates, our search yielded 3714 citations from electronic databases. In addition, five citations were identified through hand-searches of reference lists. After initial screening, 51 full manuscripts were reviewed of which 33 were excluded for reasons highlighted in (Fig 1). Screening consistency between independent evaluators was $\kappa = 0.88$ for interrater reliability.

### *Studies included in the systematic review*

Eighteen unique randomized controlled ET trials were identified (Table 1).[8,9,11,13,14,22–34] The trials included clinically stable older (mean age: 63 years, 77% male, predominantly ischemic etiology) HFrEF patients. Fourteen trials incorporated MICT,[8,9,11,13,23–31,33] four trials compared HIIT with MICT or control,[8,9,11,26] and four trials examined the effects of resistance training performed alone or in combination with aerobic training (resistance training alone, $n = 1$; combined aerobic and resistance training, $n = 3$).[14,22,32,34] The training duration varied between 1 month and 10 years, with most of the trials lasting between 3 and 6 months.

Given the nature of the intervention, no trial was double-blind. Although all trials were randomized, only 6 (32%) described the randomization procedures or allocation concealment. Thirteen trials (68%) adequately detailed subject withdrawals/dropouts and 14 trials (74%) blinded ascertainment of LV remodeling outcomes. Accordingly, trials scored relatively poorly on the Jadad Scale: 5 received a score of 1 out of 5, 9 received a score of 2 out of 5, and 5 received a score of 3 out of 5.

### *Quantitative data synthesis*

*ET and LVEF*

Compared to controls, MICT significantly improved LVEF (14 trials; 810 patients; WMD = 3.79%, 95% CI 2.08 to 5.50, Fig 2), however substantial heterogeneity across trials was found ($I^2 = 57.0\%$). Accordingly, further analysis based on ET program length (<6 months versus ≥6 months) revealed that MICT lasting <6 months modestly increased LVEF (9 trials; 463 patients; WMD = 2.33%, 95% CI 0.84 to 3.82%; $I^2 = 3.8\%$) while ET performed for 6 months or longer resulted in large significant increases in LVEF (5 trials; 347 patients; WMD = 6.26%; 95% CI 4.39 to 8.13%; $I^2 = 32.3\%$).

HIIT significantly increased LVEF compared to control (4 trials; 267 patients; WMD = 3.70%; 95% CI 1.63 to 5.77%; $I^2 = 8.5\%$, Fig 3) but no significant difference occurred with resistance training performed alone or in combination with aerobic training (4 trials; 95 patients; WMD = 1.94%; 95% CI −2.04 to 5.92%; $I^2 = 0.0\%$, Fig 4). Finally, in the 4 trials comparing HIIT and MICT, the increase in LVEF was not

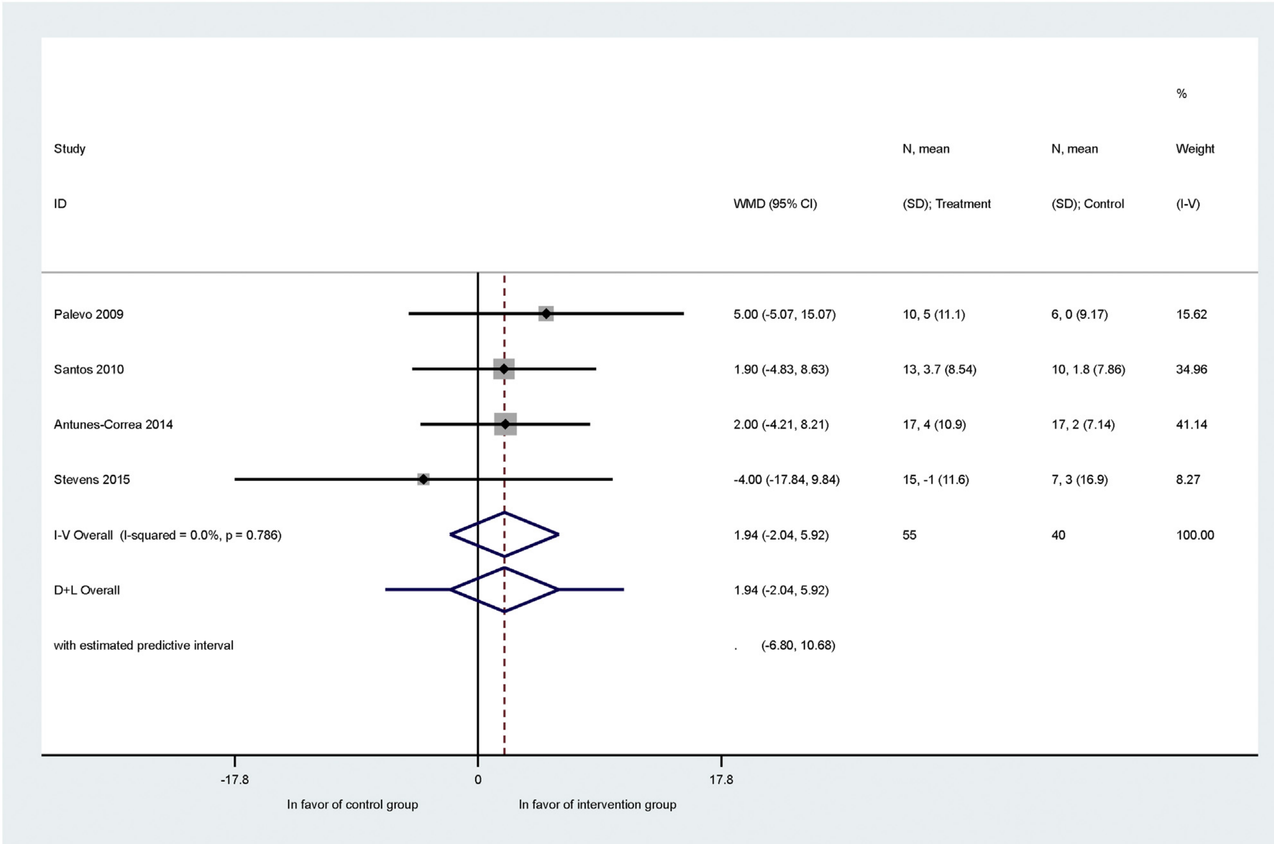


**Fig 4.** Resistance training performed alone or combined with aerobic training and left ventricle ejection fraction (LVEF).

significantly different between groups (256 patients; WMD = 3.17%; 95% CI −0.87 to 7.22%; $I^2 = 66.7\%$, Fig 5).

*ET and LV volumes*

Compared to controls, ET was not associated with a significant change in LV end-diastolic volume (MICT, 6 trials,[8,9,11,28,30,31] $n = 317$; WMD: 1.85 ml; 95% CI −5.03 to 8.73 ml, $I^2 = 0.0\%$; HIIT, 3 trials,[8,9,11] $n = 235$; WMD: −2.13 ml, CI −9.57 to 5.32 ml, $I^2 = 0.0\%$; Resistance training performed alone or in combination with aerobic training, 2 trials,[14,32] $n = 39$, WMD: −1.24 ml; 95% CI −31.64 to 29.16, $I^2 = 0.0\%$). No significant difference was found between HIIT and MICT for end-diastolic volume (3 trials,[8,9,11] $n = 227$; WMD: −4.17 ml, CI −11.08 to 2.75 ml, $I^2 = 0.0\%$).

LV end-systolic volume did not significantly differ between MICT or resistance training performed alone or combined with aerobic training versus controls (MICT, 5 trials,[8,9,11,28,31] $n = 324$; WMD: −6.14 ml; 95% CI −12.83 to 0.54 ml, $I^2 = 0.0\%$; Resistance training performed alone or in combination with aerobic training, 2 trials[14,32]; $n = 39$, WMD: −6.34 ml; 95% CI −34.78 to 22.09 ml, $I^2 = 0.0\%$). However, a significant decrease in LV end-systolic volume was found between HIIT and control (3 trials,[8,9,11] $n = 235$; WMD: −10.66 ml, 95% CI −17.73 to −3.58 ml, $I^2 = 0.0\%$) but not versus MICT (3 trials,[8,9,11] $n = 235$; WMD: −4.77 ml, 95% CI −10.90 to 1.37 ml, $I^2 = 0.0\%$).

*ET and peak $VO_2$*

MICT significantly increased peak $VO_2$ compared to controls (13 trials[8,9,11,13,23–26,28–31,33]; 749 patients, WMD = 2.67 $ml \cdot kg \cdot min^{-1}$; 95% CI 1.81 to 3.53 $ml \cdot kg \cdot min^{-1}$; $I^2 = 70.6\%$). Given heterogeneity across trials, further analysis by training length revealed that MICT performed for <6 months was associated with a modest increase in peak $VO_2$ (9 trials,[8,9,11,24–26,30,31,33] 463 patients; WMD = 2.01 $ml \cdot kg \cdot min^{-1}$; 95% CI 1.06 to 2.96 $ml \cdot kg \cdot min^{-1}$; $I^2 = 54.0\%$) while a larger increase occurred with ET ≥6 months (4 trials,[13,23,28,29] 286 patients, WMD = 3.88 $ml \cdot kg \cdot min^{-1}$; 95% CI 2.79 to 4.98 $ml \cdot kg \cdot min^{-1}$; $I^2 = 48.4\%$).

Compared to control, peak $VO_2$ was significantly higher with HIIT (4 trials,[8,9,11,26] $n = 267$ patients; WMD = 3.63 $ml \cdot kg \cdot min^{-1}$; 95% CI 1.99 to 5.28 $ml \cdot kg \cdot min^{-1}$; $I^2 = 71.6\%$) and resistance training performed alone or in combination with aerobic training (3 trials[14,22,34]; 79 patients; WMD = 3.19 $ml \cdot kg \cdot min^{-1}$; 95% CI 1.22 to 5.17 $ml \cdot kg \cdot min^{-1}$; $I^2 = 0.0\%$). Finally, the improvement in peak $VO_2$ was not different between HIIT and MICT (4 trials[8,9,11,26]; 256 patients; WMD = 1.89 $ml \cdot kg \cdot min^{-1}$; 95% CI −0.39 to 4.16 $ml \cdot kg \cdot min^{-1}$; $I^2 = 86.7\%$).

## Discussion

This 10-year review of ET trials in patients with HFrEF identified three major new findings: 1) In clinically stable HFrEF patients, MICT significantly improves LVEF compared to control with the greatest improvement occurring with long-term (≥6 months) training; 2) The increase in LVEF is significantly greater with HIIT compared to control but not compared to MICT; and 3) Resistance training performed alone or with aerobic training (MICT or HIIT) does not improve LVEF.

A 2007 meta-analysis by Haykowsky et al. found that MICT significantly increased LVEF (WMD: +2.6%) and decreased LV volumes in clinically stable HFrEF patients.[6] We extend these findings here to clinically stable HFrEF patients who are on optimal HF therapy, and show that the anti-remodeling benefit with MICT is dependent on the length of the ET program. The mechanisms underpinning this favorable adaptation could be attributed to a reduction in LV afterload which is associated with improved vascular endothelial function.[35,36] Specifically, Hambrecht et al. reported a significant reduction in resting and peak exercise total peripheral resistance after 6-months of MICT compared to control.[36] The change in resting total peripheral resistance

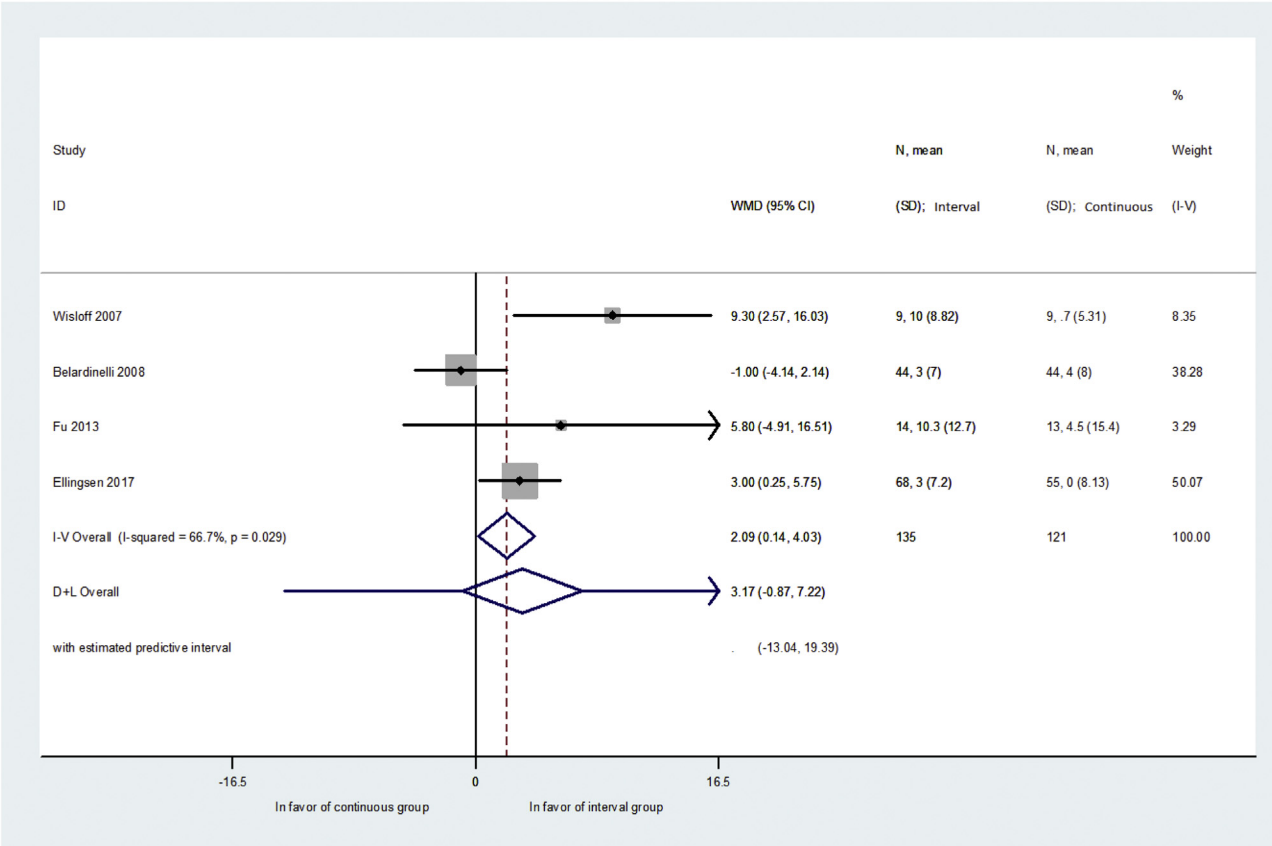


**Fig 5.** High-intensity interval training (HIIT) versus moderate-intensity continuous training (MICT) and left ventricle ejection fraction (LVEF).

was also positively related to the change in LV end-diastolic diameter while changes in resting and peak exercise total peripheral resistance were inversely related to the changes in stroke volume.[36] In a subgroup of patients studied, the improvement in leg blood flow in response to intra-arterial acetylcholine infusion (endothelial-dependent vasodilator) after MICT was inversely related to changes in peak exercise total peripheral resistance and positively related to the increase in peak $VO_2$.[35,36] Finally, our finding that peak $VO_2$ was significantly greater after long versus short-duration MICT is likely due to "central" adaptations as the change in maximal cardiac output is 3.5-fold higher after 6 months compared to 2 to 3 months of training in clinically stable HFrEF patients.[26,36–39]

Four trials in this review compared the effects of HIIT versus MICT (2 to 3 months in duration, Table 1) or control on LV remodeling and peak $VO_2$ in clinically stable HFrEF patients.[8,9,11,26] Our finding that HIIT was not associated with a greater improvement in LVEF and peak $VO_2$ compared to MICT may be related to the underlying intensity of the interval training exercise stimulus. For example, Wisloff et al. reported a superior increase in resting systolic mitral annulus excursion and velocity, LV outflow tract peak ejection velocity, isovolumic relaxation time, peak annular velocity during early filling, brachial artery endothelial function, mitochondrial function and peak $VO_2$ after 12 weeks of HIIT ($n = 9$) compared to MICT ($n = 9$) and controls ($n = 9$).[8] Importantly, subjects in the HIIT group exercised at 92% of their peak heart rate while the MICT group exercised at 74% of their peak heart rate. In contrast, in the SMARTEX trial, no significant difference was found between HIIT and MICT for resting LVEF and peak $VO_2$, however 51% of the HIIT participants exercised below their prescribed ET intensity while 80% of the MICT participants exercised above their prescribed intensity level.[11] Therefore, the interval training intensity may be an important determinant driving physiological benefit to LV function and peak $VO_2$.

Our finding that resistance training performed alone or combined with aerobic training (MICT or HIIT) significantly increased peak $VO_2$ compared to control but was not associated with a significant change in LVEF is consistent with a recent meta-analysis in HFrEF patients.[40] The failure of this form of exercise to attenuate LV remodeling may be due to the increased pressure load associated with resistance exercise.[41,42]

## Study limitations

The trials in this review compared HIIT to MICT over ≤12 weeks in duration, consequently the long-term effects of HIIT on LV remodeling and peak $VO_2$ and its determinants remain unknown. Secondly, few studies compared the effects on LV remodeling of resistance training alone or resistance combined with aerobic training (MICT or HIIT). However, our results confirm our prior finding that this form of ET does not attenuate LV remodeling in clinically stable HFrEF patients.[6] Not all studies included LV volume measures, however LVEF has been used extensively as a remodeling index[43], and a decrease in this outcome can occur via a reduction in end-diastolic and/or end-systolic volume. A final limitation common to cardiac rehabilitation and ET trials was that a majority of HFrEF patients in this analysis were males (77%).[44,45] Thus, it is unclear if these findings extend to older female HFrEF patients. Despite these limitations, and unlike our 2007 meta-analysis using the same search strategy,[6] the majority of the subjects in the trials included in this updated analysis were on evidence-based HF therapy, and most of the investigators performing the outcome measure analysis were blinded to group allocation.

## Conclusions

In clinically stable HFrEF patients, MICT is an effective therapy to attenuate LV remodeling and improve peak $VO_2$ compared to control with the greatest benefits occurring with long-term (≥6 months) training. HIIT performed for 2 to 3 months is superior to control, but not MICT, for the improvement in LVEF and peak $VO_2$. Finally, resistance training performed alone or combined with aerobic training (MICT or HIIT) significantly improved peak $VO_2$ without a change in LVEF.

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## Statement of conflict of interest

None of the authors have any conflicts of interests with regard to this publication.

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