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Effect of exercise therapy on established and emerging circulating biomarkers in patients with heart failure: a systematic review and meta-analysis

Melissa J Pearson, Nicola King, Neil A Smart

ABSTRACT

Background Biomarkers are important in the diagnosis, risk stratification and management of patients with heart failure (HF). The established biomarkers of myocardial stretch, brain natriuretic peptide (BNP) and amino (N) portion of BNP (NT-proBNP) have been extensively studied, and early analyses have demonstrated response to exercise training. Several other biomarkers have been identified over the last decade and may provide valuable and complementary information which may guide treatment strategies, including exercise therapy.

Methods A systematic search of PubMed, EMBASE and Cochrane Trials Register to 31 October 2017 was conducted for exercise-based rehabilitation trials in HF. Randomised and controlled trials that reported biomarkers, BNP, NT-proBNP, soluble ST2, galectin-3, mid-regional atrial natriuretic peptide, mid-regional adrenomedullin and copeptin, were included.

Results Forty-three studies were included in the systematic review, with 27 studies suitable for meta-analyses. Data pooling was only possible for NT-proBNP and BNP. Meta-analyses of conventional training studies demonstrated a statistically significant improvement in NT-proBNP (pmol/L); mean difference (MD) −32.80 (95% CI −56.19 to −9.42), p=0.006 and in BNP (pmol/L); MD −17.17 (95% CI −29.56 to −4.78), p=0.007. Pooled data of non-conventional training failed to demonstrate any statistically significant improvements.

Conclusion Pooled data indicated a favourable effect of conventional exercise therapy on the established biomarkers, NT-proBNP and BNP; however, this was in contrast to a number of studies that could not be pooled. Limited evidence exists as to the effect of exercise training on emerging biomarkers.

INTRODUCTION

Heart failure (HF) is a complex syndrome resulting from multiple conditions and underlying disorders and continues to be a significant burden on the healthcare system. Over the past three decades, an increasing number of studies have provided evidence on a range of benefits of exercise training in patients with HF.

In patients with stable HF, exercise training is now a Class 1 recommendation in HF guidelines. Numerous pathways are involved in the development and progression of HF, and the discovery of biomarkers has and will hopefully continue to enhance our understanding of the pathophysiology. Circulating biomarkers are important in the diagnosis, risk stratification and management of patients with HF. HF biomarkers tend to be classified according to the associated pathophysiological processes. These include biomarkers of myocardial stretch, myocyte injury, fibrosis, matrix remodelling, inflammation,
oxidative stress, neurohumoral activation and renal dysfunction. Some biomarkers may bridge several pathophysiological processes. Currently, brain (B-type) natriuretic peptide (BNP) and its more stable inert form, the amino (N terminal) portion (NT-proBNP), markers of myocardial stretch, are recognised as the gold standard diagnostic and prognostic biomarkers in HF.

Over recent decades, the role of circulating biomarkers in HF has evolved, with the emergence of a number of novel biomarkers. Among these biomarkers, suppression of tumorigenicity 2 (ST2) and galectin-3 (Gal-3) have demonstrated prognostic value in HF and both are shown to be predictors of sudden cardiac death. In fact, the combination of the gold standard cardiac biomarkers of BNP/NT-proBNP with the newer biomarkers, such as soluble ST2 (sST2) and Gal-3, may improve risk stratification and prognosis.

Other emerging biomarkers, mid-regional atrial natriuretic peptide (MR-proANP), mid-regional adrenomedullin (MR-proADM) and copeptin (CT-proAVP), have also been shown to have prognostic value in HF.

In addition to their diagnostic and prognostic utility, biomarker profiles may prove beneficial in guiding HF therapy and improving treatment strategies, including the identification of patients with HF that may respond to exercise training. A 2010 meta-analysis suggested that exercise training had a favourable effect on both BNP and NT-proBNP. The results of which were confirmed by a 2011 individual patient data (IPD) meta-analysis, with a 37.4% and 28.3% reduction in NT-proBNP and BNP, respectively. Furthermore, BNP and NT-proBNP changes are correlated with changes in peak oxygen consumption (VO2peak).

The aim of this systematic review and meta-analysis was first to update the previous reviews as a number of additional studies have investigated BNP and/or NT-proBNP after training interventions. Second, given the emergence of new biomarkers in HF trials, we intended to add to the current literature the inclusion of a selected number of emerging biomarkers. Furthermore, differing to previous analyses, we expanded our review to include additional modalities of exercise therapy due to their increasing utilisation in cardiac rehabilitation programmes and trials, which may provide alternatives for subgroups of patients with HF.

METHODS

Search strategy

Potential studies were identified by conducting systematic searches of PubMed, EMBASE, CINHAL and the Cochrane Library of Controlled Trials up until 31 October 2017. Searches included a mix of MeSH and free-text terms related to the key concepts of HF, exercise training and biomarkers. Additionally, systematic reviews, meta-analyses and reference lists of papers were hand searched for additional studies. One reviewer (MJP) conducted the search, and full articles were assessed for eligibility by two reviewers (MJP and NAS). A sample search strategy is presented in online supplementary files. Additional information was requested from five authors, with three responses.

Study selection

Study type and participants

Randomised controlled trials (RCTs) and controlled trials of exercise therapy in patients with HF aged 18 years or older were included. HF type (ie, preserved, moderately reduced and reduced ejection fraction) was not considered as an inclusion or exclusion criteria. Only studies in which the authors specifically reported a patient diagnosis of HF were included. Studies assessing intervention effect on acute or decompensated HF were excluded.

Intervention

Exercise therapy included both conventional training, defined as aerobic training (AT), resistance training (RT) and combined AT and RT, and non-conventional modes of therapy, defined as Yoga, Tai Chi, stretching and the physical therapies of functional electrical stimulation (FES) and inspiratory muscle training (IMT). Studies must have compared an exercise intervention to a usual care or education control group, with no formally prescribed exercise, and the duration of the exercise training must have been for a minimum of 4 weeks. Studies in which the participants had participated within a formal exercise rehabilitation programme within the last 6 months were excluded.

Outcomes

Studies were eligible to be included in the review if they reported one or more of the following outcomes in serum or plasma: BNP, NT-proBNP, cardiac troponin (cTnT), sST2, Gal-3, MR-proANP, MR-proADM and CT-proAVP.

Exclusions

Abstracts and non-English studies were excluded.

Data extraction

One reviewer (MJP) extracted the data. For each study, the following information was extracted: (1) author, year of publication and study design, (2) demographic and clinical characteristics, (3) exercise intervention characteristics, (4) mean, SD, P value and main findings in regard to biomarkers and (5) details of assessment methodology for biomarkers.

Data synthesis

Statistical analyses were performed using Revman V.5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). Individual meta-analyses were completed for continuous data by using the change in the mean and SD. Where the change in mean and SD was not reported, the change in mean was calculated by subtracting the preintervention mean from the postintervention mean, and Revman V.5.3 enabled calculations of SD using number of participants in each group, within or between group p values or...
95% CI. Where p values were not provided, the SD of the mean difference (MD) was calculated using the formula: $SD = \sqrt{([SD_{pretreatment}]^2 + [SD_{post-treatment}]^2 - 2(2 \times r \times SD_{pretreatment} \times SD_{post-treatment})]}$, assuming a correlation coefficient ($r$)=0.5, which is considered a conservative estimate. Where data were not presented in text or tables and authors could not be reached, data presented in figures or reported in prior meta-analyses were extracted or accessed where possible.

Data were pooled for meta-analysis when two or more studies measured the same outcome and provided data in a format suitable for pooling. Where a study included multiple intervention groups and data were not provided for the combined intervention, data were entered separately for each group, and the sample size of the control group was divided by the number of intervention groups to eliminate overinflation of the sample size. A random-effects inverse variance was used with the effects to measure MD. We used a 5% level of significance and a 95% CI to report change in outcome measures. Both BNP and NT-proBNP are commonly reported in SI units (pmol/L) or conventional units (pg/mL). Owing to large values associated with NT-proBNP, change data were converted from pg/mL to pmol/L for both NT-proBNP and BNP for presentation. Data were converted using the following factors: for NT-proBNP pmol/L = pg/mL ×0.118 and BNP pmol/L = pg/mL ×0.289.

For meta-analysis, we did not pool studies in which participants were clearly identified as only having heart failure with preserved ejection fraction (HFpEF), with other studies. We grouped studies for analysis according to conventional or non-conventional training modalities. For studies where the mean or SD of outcomes was not reported, but median, IQR or median and range were reported or where only a descriptive result was reported in regard to postintervention changes, a table and descriptive analysis are used.

**Sensitivity analysis:** In order to evaluate the influence of each study on the overall effect size, sensitivity analysis using the leave-one-out approach was conducted. Where SD was imputed, additional analyses were also carried out with different values for the correlation coefficient ($r=0.75$ and $0.25$) to determine whether the overall results of the analyses were robust to the use of imputed correlation coefficients.

**Heterogeneity and publication bias**
Heterogeneity was quantified using the $I^2$ test. Values range from 0% (homogeneity) to 100% (high heterogeneity). Visual inspection of funnel plots assessed risk of publication bias.

**Study quality**
Study quality was assessed using the Tool for the Assessment of Study Quality and Reporting in Exercise (TESTEX) by two authors (MJP and NK). In case of discrepancies, a third author (NAS) was consulted.

**RESULTS**
The initial search generated a total of 3419 articles. After removal of duplicates and exclusion of articles based on abstract and title, 77 full-text articles remained for screening. Full screening resulted in 43 articles meeting the stated inclusion criteria (figure 1, Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement), of which 27 studies were included in meta-analyses. Details of full-text articles reviewed but excluded are provided, with reasons, in online supplementary table S1.

**Study and participant characteristics**
A general description of included studies is provided in table 1. Of the 43 included studies, two studies were from the same trial but provided different biomarker information, and two studies contained an overlap of some participants, and data were combined into one dataset for meta-analysis to eliminate data overlap. Four studies of the studies were controlled but not randomised, one study randomised participants between exercise intervention groups, but the control group was not randomised, one study was a retrospective analysis and all remaining studies were RCTs. Seven studies representing six trials, included participants with a mean left ventricular ejection fraction (LVEF) >50%, one of which also included participants with LVEF <50%. Thirty-six trials included participants with mean LVEF <50%, and the mean LVEF of at least three studies indicates the inclusion of participants with a range of ejection fractions, reduced, mid-range and/or preserved ejection fraction. Baseline NT-proBNP and BNP levels are provided in online supplementary table S2.

**Intervention details**
A detailed description of the interventions can be found in online supplementary table S3. Thirty-four studies used conventional exercise training, eight studies used non-conventional exercise training or therapy and one study combined non-conventional and conventional training. Intervention duration ranged from 4 weeks to 9 months.

**Biomarker assessment**
Biomarker assay details are provided in online supplementary table S4.

**Outcome measures**
Amino (N) portion of BNP
Twenty studies reported on NT-proBNP. Two studies contained an overlap of some participants; to avoid possible duplication of data, these studies are represented as one dataset in the meta-analysis.

**Meta-analysis**
Overall, exercise demonstrated a statistically significant improvement in NT-proBNP (pmol/L); MD $-47.83$ (95% CI $-77.23$ to $-18.43$), $p=0.001$ (figure 2).
Conventional training
Pooled data from 10 studies \( ^{32} \text{33} \text{35} \text{37} \text{43} \text{47} \text{52} \) (14 intervention groups, 315 exercise participants and 212 controls) demonstrated a statistically significant improvement in favour of exercise, on NT-proBNP (pmol/L); MD \(-32.80\) (95% CI \(-56.19\) to \(-9.42\)), \(p=0.006\) (figure 2). Removal of the two intervention groups from one \(^43\) study, that included patients with a mean ejection fraction of 50%, improved the MD and statistical significance; MD \(-54.62\) (95% CI \(-74.36\) to \(-34.87\)) pmol/L, \(p<0.00001\) (online supplementary table S5). Apart from the study by Aksoy et al., \(^43\) sensitivity analysis using the leave-one-out approach revealed that the results remained relatively stable (figure 3). Sensitivity analyses conducted for different correlation coefficients for SD imputation did not result in any significant variance in overall results.

An additional six \(^{30} \text{34} \text{53} \text{55} \) studies (table 2) could not be pooled due to differences in data reporting. Five studies presented data as median (IQR) or median (range), and one \(^30\) study only included patients with HFpEF. Two studies \(^{34}\) reported preintervention to postintervention NT-proBNP changes in exercise participants, but only one study reported a significant difference compared with control participants.

Non-conventional training
Pooled data from two \(^45 \text{56} \) studies (55 exercise participants and 59 controls) failed to demonstrate a statistically significant improvement in NT-proBNP (pmol/L); MD \(-157.47\) (95% CI \(-327.64\) to \(12.70\)), \(p=0.07\) (figure 2). Notably, the large size of the improvement was due to the inclusion of one study \(^45\) (figure 4). One \(^42\) additional study, in patients with HFpEF, not pooled, failed to demonstrate any significant change (table 2).

Brain natriuretic peptide
Twenty-two studies reported on BNP. Two \(^{32} \text{33} \) studies contained an overlap of some participants; to avoid duplication of data, these studies are represented as one dataset in the meta-analysis.

Meta-analysis
Overall, exercise demonstrated a statistically significant improvement in BNP (pmol/L); MD \(-15.02\) (95% CI \(-25.06\) to \(-4.99\)), \(p=0.003\) (figure 5).

Conventional training
Pooled data from 11 studies \(^{32} \text{33} \text{38} \text{46} \text{57} \text{64} \) (12 intervention groups, 268 exercise participants and 192 controls)
| Study                      | Design          | Participant characteristics                                                                 | Intervention       |
|---------------------------|-----------------|-----------------------------------------------------------------------------------------------|--------------------|
| Ahmad et al<sup>53</sup>  | RCT             | n=928 analysed, biomarker substudy HF ACTION Trial  
E: n=477 (68% male), 59 (51–68) years, LVEF 25% (20–30)*  
C: n=451 (73% male), 59 (51–68) years, LVEF 25% (20–31)  
NYHA Class II–IV (<1% IV) | 3 months  
Aerobic                       |
| Aksoy et al<sup>43</sup>  | RCT             | n=57 randomised, n=45 analysed  
E1: n=15 (87% male), 64±9 years, LVEF 50%±7%  
E2: n=15 (87% male), 60±7 years, LVEF 52%±5%  
C: n=15 (87% male), 58±11 years, LVEF 52%±6%  
NYHA Class II–III            | 10 weeks  
Aerobic (E1: IAE, E2: CAE)   |
| Antonicelli et al<sup>44</sup> | RCT         | n=343 randomised, n=313 completed 6 months  
E: n=170 (61% male), 76±5 years, LVEF 48%±13%  
C: n=173 (53% male), 78±6 years, LVEF 49%±13%  
NYHA Class ≥2               | 6 months  
Aerobic                       |
| Van Berendoncks et al<sup>24</sup> | Non-RCT  
Cohort with control group | n=80 analysed  
E: n=46 (70% male), 58±10 years, LVEF 17% (14–22)*  
C: n=34 (59% male), 61±12 years, LVEF 19% (15–24)  
NYHA Class II–III            | 4 months  
Aerobic and combined          |
| Billebeau et al<sup>22</sup> | Non-RCT  
Cohort with control group | n=131 enrolled  
E: n=107 (86% male), 59 (52–66) years, LVEF 30% (25–39)*  
C: n=24 (79% male), 63 (53–72) years, LVEF 35% (30–40)  
NYHA Class II–IV             | 4–6 months  
Aerobic                       |
| Brubaker et al<sup>45</sup> | RCT             | n=59 randomised, n=44 analysed  
E: n=30 (63% male), 70±5 years, LVEF 32%±9%  
C: n=29 (69% male), 70±6 years, LVEF 30%±9%  
NYHA Class II–IV (n=1 Class IV) | 16 weeks  
Aerobic                       |
| Butterfield et al<sup>58</sup> | RCT          | n=19 randomised, n=17 analysed  
E: n=11 (82% male), 66±10 years, LVEF 34%±11%  
C: n=6 (50% male), 75±12 years, LVEF 35%±14%  
NYHA Class II–III            | 12 weeks  
Combined                      |
| Conraads et al<sup>48</sup> | RCT             | n=17 randomised and analysed  
E: n=8 (38% male), 57±2 years, LVEF 27%±5%  
C: n=9 (56% male), 61±4 years, LVEF 28%±5%  
NYHA Class III               | 4 months  
Aerobic                       |
| Conraads et al<sup>45</sup> (2004) | Non-RCT  
Cohort with control group | n=49 enrolled and analysed  
E: n=27 (78% male), 59±2 years, LVEF 26%±1%  
C: n=22 (68% male), 59±2 years, LVEF 26%±1%  
NYHA Class II–III            | 4 months  
Combined                      |
| Delagardelle et al<sup>37</sup> | RCT/non-RCT†   | n=60 randomised and analysed  
E: n=45 (84% male), 59±6 years, LVEF 24%±5%  
C: n=15 (87% male), 56±8 years, LVEF 25%±6%  
NYHA Class II                | ~13.3 weeks Combined,  
aerobic or strength           |
| Edelmann et al<sup>30</sup> | RCT             | n=67 randomised, n=64 analysed  
E: n=44 (45% male), 64±8 years, LVEF 68%±7%  
C: n=20 (40% male), 65±6 years, LVEF 67%±7%  
NYHA Class II and III         | 12 weeks  
Combined                      |
| Eleuteri et al<sup>44</sup>  | RCT             | n=21 randomised and analysed  
E: n=11 (100% male), 66±2 years, LVEF 28%±2%  
C: n=10 (100% male), 63±2 years, LVEF 30%±2%  
NYHA Class II                | 3 months  
Aerobic                       |
| Fernandes-Silva et al<sup>23</sup> | RCT       | n=52 randomised, n=40 analysed  
E: n=28 (50% male), 51±7 years, LVEF 30%±6%  
C: n=16 (62% male), 48±7 years, LVEF 29%±7%  
NYHA Class I–III             | 12 weeks  
Aerobic                       |

Continued
| Study                | Design | Participant characteristics | Intervention               |
|---------------------|--------|-------------------------------|----------------------------|
| Fu (2013)57         | RCT    | n=45 randomised, n=40 analysed | 12 weeks                   |
|                     |        | E1: n=15 (67% male), 68±5%, LVEF 38%±4% | Aerobic (E1: AIT, E2: MCT) |
|                     |        | E2: n=15 (60% male), 66±2 years, LVEF 39%±5% |                           |
|                     |        | C: n=15 (67% male), 68±3 years, LVEF 38%±4% |                           |
|                     |        | NYHA Class II–III              |                           |
| Gary et al69        | RCT    | n=24 randomised and analysed   | 12 weeks                   |
|                     |        | E: n=12 (58% male), 59±11 years, LVEF 23%±8% | Combined                  |
|                     |        | C: n=12 (42% male), 61±10 years, LVEF 27%±9% |                           |
| Guazzi et al69      | RCT    | n=26 randomised and analysed   | 24 weeks                   |
|                     |        | E: n=18, C: n=8, 68±6 years, LVEF 37%±5% | Aerobic                   |
|                     |        | NYHA Class II–III              |                           |
| Jónsdóttir et al66  | RCT    | n=51 randomised, n=43 analysed | 5 months                   |
|                     |        | E: n=21 (76% male), 68±7 years, LVEF 42%±14% | Combined                  |
|                     |        | C: n=22 (82% male), 69±5 years, LVEF 41%±14% |                           |
|                     |        | NYHA Class II–III              |                           |
| Karavidas et al66   | RCT    | n=30 randomised and analysed   | 6 weeks                    |
|                     |        | E: n=20 (80% male), 62±12 years, LVEF 28%±7% | FES                       |
|                     |        | C: n=10 (80% male), 64±8 years, LVEF 27%±5% |                           |
|                     |        | NYHA Class II–III              |                           |
| Karavidas et al41   | RCT    | n=30 randomised and analysed   | 6 weeks                    |
|                     |        | E: n=15 (60% male), 69±9 years, LVEF 64%±8% | FES                       |
|                     |        | C: n=15 (60% male), 69±8 years, LVEF 63%±5% |                           |
|                     |        | NYHA Class II–III              |                           |
| Kato et al67        | RCT    | n=50 randomised and analysed   | 4 weeks                    |
|                     |        | E: n=25 (80% male), 70±11 years, LVEF 28%±9% | Stretching                |
|                     |        | C: n=25 (76% male), 70±8 years, LVEF 29%±9% |                           |
|                     |        | NYHA Class II–IV               |                           |
| Kawauchi et al68    | RCT    | n=53 randomised, n=35 analysed | 8 weeks                    |
|                     |        | E1: n=13 (46% male), 54±10 years, LVEF 30%±6% | IMT+resistance            |
|                     |        | E2: n=13 (62% male), 56±7 years, LVEF 28%±5% |                           |
|                     |        | C: n=9 (56% male), 56±7 years, LVEF 29%±7% |                           |
|                     |        | NYHA Class II–III              |                           |
| Kitzman et al40     | RCT    | n=53 randomised, n=46 completed | 16 weeks                   |
|                     |        | E: n=26 (17% male), 70±6 years, LVEF 61%±5% | Aerobic                   |
|                     |        | C: n=27 (9% male), 69±5 years, LVEF 60%±10% |                           |
|                     |        | NYHA Class II–III              |                           |
| Kitzman et al39     | RCT    | n=51 randomised‡               | 20 weeks                   |
|                     |        | E: n=26 (19% male), 68±6 years, LVEF 61%±6% | Aerobic                   |
|                     |        | C: n=25 (20% male), 66%±5%, LVEF 63%±6% |                           |
|                     |        | NYHA Class II–III              |                           |
| Kobayashi et al61   | RCT    | n=28 randomised and analysed   | 12 weeks                   |
|                     |        | E: n=14 (86% male), 55±2 years, LVEF 29%±2% | Aerobic                   |
|                     |        | C: n=14 (57% male), 62±2 years, LVEF 33%±2% |                           |
|                     |        | NYHA Class II and III          |                           |
| Krishna et al45     | RCT    | n=130 randomised, n=92 analysed | 12 weeks                   |
|                     |        | E: n=44 (73% male), 49±6 years, LVEF 39%±5% | Yoga                      |
|                     |        | C: n=48 (67% male), 50±5 years, LVEF 40%±5% |                           |
|                     |        | NYHA Class I–II                |                           |
| Malfatto et al60    | RCT    | n=54 randomised and analysed   | 12 weeks                   |
|                     |        | E: n=27 (70% male), 65±11 years, LVEF 31%±6%, | Aerobic                   |
|                     |        | C: n=27 (74% male), 67±9 years, LVEF 33%±6%, |                           |
|                     |        | NYHA Class I and II            |                           |
| Study | Design | Participant characteristics | Intervention |
|------|--------|----------------------------|--------------|
| Marco et al<sup>56</sup> | RCT | n=22 randomised and analysed  
E: n=11 (64% male), 69±9 years, LVEF 38%±16%  
C: n=11 (91% male), 70±11 years, LVEF 36%±17%  
NYHA Class II–III | 4 weeks  
IMT |
| Meyer et al<sup>50</sup> | RCT | n=42 randomised and analysed  
E: n=19 (79% male), 58±10 years, LVEF 29%±13%  
C: n=23 (78% male), 54±9 years, LVEF 30%±11%  
NYHA Class II–III | 12 weeks  
Aerobic |
| Nilsson et al<sup>55</sup> | RCT | n=78 randomised, n=70 for BNP at follow-up  
E: n=39 (77% male), 69±8 years, LVEF 30%±8%  
C: n=39 (79% male), 72±8 years, LVEF 31%±10%  
NYHA Class II–III | 4 months  
Aerobic |
| Nishi et al<sup>58</sup> | Retrospective analysis | n=45 randomised, n=31 analysed BNP  
E: n=33 (88% male), 51±14 years, LVEF 18%±4%  
C: n=12 (83% male), 52±16 years, LVEF 18%±5%  
NYHA Class II–III | 3 months  
Aerobic |
| Norman et al<sup>53</sup> | RCT | n=42 randomised, n=39 analysed for BNP  
E: n=20 (55% male), 56±3 years, LVEF 34%±1%  
C: n=20 (60% male), 63±3 years, LVEF 32%±1%  
NYHA Class II–IV | 24 weeks  
Combined |
| Palau et al<sup>42</sup> | RCT | n=27 randomised, n=26 analysed  
E: n=14 (50% male), 68 (60–76) years, LVEF 69% (63–77)*  
C: n=12 (60% male), 74 (73–77) years, LVEF 76% (68–83)  
NYHA Class II–IV | 12 weeks  
IMT |
| Parrinello et al<sup>43</sup> | RCT | n=22 randomised and analysed  
E: n=11 (73% male), 62±5 years, LVEF 39%±4%  
C: n=11 (64% male), 63±5 years, LVEF 39%±4%  
NYHA Class II–III | 10 weeks  
Aerobic |
| Passino et al<sup>32</sup> | RCT | n=95 randomised, n=85 analysed  
E: n=44 (89% male), 60±2 years, LVEF 35%±2%  
C: n=41 (85% male), 61±2 years, LVEF 32%±2%  
NYHA Class II–III | 9 months  
Aerobic |
| Passino et al<sup>33</sup> | RCT | n=97 randomised, n=90 analysed  
E: n=71 (87% male), 61±2 years, LVEF 35%±1%  
C: n=19 (74% male), 63±2 years, LVEF 36%±2%  
NYHA Class I–III | 9 months  
Aerobic |
| Sandri et al<sup>51</sup> LEICA Study | RCT | n=60 randomised and analysed  
E1: n=15 (80% male), 50±5 years, LVEF 27%±1%  
C1: n=15 (87% male), 49±5 years, LVEF 28%±1%  
E2: n=15 (80% male), 72±4 years, LVEF 29%±2%  
C2: n=15 (80% male), 72±3 years, LVEF 28%±2%  
NYHA Class II–III | 4 weeks  
Aerobic |
| Maria Sarullo et al<sup>62</sup> | RCT | n=60 randomised and analysed  
E: n=30 (77% male), 53±6 years, LVEF 29%±5%  
C: n=30 (74% male), 53±5 years, LVEF 29%±4%  
NYHA Class II–III | 12 weeks  
Aerobic |
| Stevens et al<sup>64</sup> | RCT | n=28 randomised, n=22 analysed  
E: n=15 (67% male), 67±3 years, LVEF 39%±3%  
C: n=7 (86% male), 64±6 years, LVEF 35%±2%  
NYHA Class I–III | 12 weeks  
Combined |
| Trippel et al<sup>31</sup> Ex-DHF pilot study post hoc analysis | RCT | n=67 randomised, n=62 analysed for biomarkers  
E: n=44 (45% male), 64±8 years, LVEF 68%±7%  
C: n=20 (40% male), 65±6 years, LVEF 67%±7%  
NYHA Class II–III | 12 weeks  
Combined |

Continued
demonstrated a statistically significant improvement in BNP (pmol/L) in favour of exercise; MD −17.17 (95% CI −29.56 to −4.78), p=0.007 (figure 5). Sensitivity analyses using the leave-one-out approach revealed that the study by Gary et al. impaired the size of the result, with an increase in MD and statistical significance with removal of this study (figure 6).

An additional five studies using conventional training (table 2) reported on BNP concentrations, but were not pooled due to differences in data reporting. Two studies reported data as median (IQR), two studies were in participants with HFpEF and one study did not provide post-data but noted no change. Of the five studies, two reported decreases post-training in

| Study | Design | Participant characteristics | Intervention |
|-------|--------|-----------------------------|--------------|
| Wisløff et al | RCT | n=27 randomised, n=26 analysed | 12 weeks |
|  | E1: n=9 (78% male), 77±9 years, LVEF 28%±7% | Aerobic (E1: AIT, E2: MCT) |
|  | E2: n=9 (78% male), 74±12 years, LVEF 33%±5% | |
|  | C: n=9 (67% male), 76±13 years, LVEF 26%±8% | |
| Yamamoto et al | Non-RCT | n=18 enrolled and analysed | 6 months |
|  | Cohort with control group | | Aerobic |
|  | E: n=10 (90% male), 68 (64–70) years, LVEF 40% (37–43)* | |
|  | C: n=8 (100% male), 70 (66–73) years, LVEF 37% (35–38) NYHA Class II–III | |
| Yeh et al | RCT | n=30 randomised and analysed | 12 weeks |
|  | E: n=15 (67% male), 66±12 years, LVEF 24%±7% NYHA Class I–IV | Tai Chi |
|  | C: n=15 (60% male), 81±14 years, LVEF 22%±8% | |
| Yeh et al | RCT | n=100 randomised and analysed | 12 weeks |
|  | E: n=50 (56% male), 68±12 years, LVEF 28%±8% NYHA Class I–III | Tai Chi |
|  | C: n=50 (72% male), 67±12 years, LVEF 30%±7% | |

*Median (IQR).
†Randomised between three exercise groups, but control group not randomised.
‡Excludes diet and diet and exercise groups.

AIT, aerobic interval training; BNP, brain natriuretic peptide; C, control; CAE, continuous aerobic training; DHF, diastolic heart failure; E, exercise; FES, functional electrical stimulation; IAE, aerobic interval training; IMT, inspiratory muscle training; LVEF, left ventricular ejection fraction; MCT, moderate continuous training; NHF, non-ischaemic heart failure; NT-proBNP, amino (N) portion of BNP.

Figure 2 Change (MD) in NT-proBNP (pmol/L) exercise versus control. For conversion to pg/mL=pmol/L divided by 0.118. AIT, aerobic interval training; CAE, continuous aerobic training; IAE, aerobic interval training; IHF, ischaemic heart failure; MCT, moderate continuous training; MD, mean difference; NHF, non-ischaemic heart failure; NT-proBNP, amino (N) portion of BNP.
exercise participants with no change in controls. The two \cite{39,40} studies with HFpEF patents failed to find any change.

### Non-conventional training

Pooled data from 4 studies \cite{66-69} (5 intervention groups, 86 exercise participants and 59 controls) failed to

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**Table 2** Summary of findings of studies for NT-proBNP and BNP not pooled for meta-analysis

| Study              | Design       | Intervention | Analysed E/C | Result                          |
|--------------------|--------------|--------------|--------------|--------------------------------|
| **NT-proBNP**      |              |              |              |                                |
| Conventional training |             |              |              |                                |
| Ahmad et al \cite{19} | RCT         | Aerobic      | 477/451      | ↔ between groups                |
| Antonicelli et al \cite{44} | RCT         | Aerobic      | 170/173      | ↓ in E and significantly different to C |
| Van Berendoncks et al \cite{44} | Controlled  | Aerobic and combined | 46/34 | ↓ in E, but ↔ for Δ between E and C |
| Edelmann et al \cite{30} | RCT         | Combined     | 44/20        | ↔ in E or C                     |
| Eleuteri et al \cite{54} | RCT         | Aerobic      | 11/10        | ↔ in E or C                     |
| Nilsson et al \cite{55} | RCT         | Aerobic      | 37/33        | ↔ in E or C or between E and C  |
| Non-conventional   |              |              |              |                                |
| Palau et al \cite{42} | RCT         | IMT          | 14/12        | ↔ in E or C or between E and C  |
| **BNP**            |              |              |              |                                |
| Conventional training |             |              |              |                                |
| Billebeau et al \cite{22} | Controlled  | Aerobic      | 107/24       | ↓ in E, ↔ in C                  |
| Brubaker et al \cite{65} | RCT         | Aerobic      | 23/21        | ↔ between E and C               |
| Kitzman et al \cite{30} | RCT         | Aerobic      | 26/25        | ↔ between E and C               |
| Kitzman et al \cite{29} | RCT         | Aerobic      | 26/25        | ↓ in E or C                     |
| Yamamoto et al \cite{36} | Controlled  | Aerobic      | 10/8         | ↓ in E, ↔ in C                  |
| Non-conventional   |              |              |              |                                |
| Karavidas et al \cite{41} | RCT         | FES          | 15/15        | ↔ for Δ between E and C         |
| Yeh et al \cite{70}  | RCT         | Tai Chi      | 50/50        | ↔ for Δ between E and C         |

↓ statistically significant, ↔ no statistically significant change.

BNP, brain natriuretic peptide; C, control; E, exercise; FES, functional electrical stimulation; IMT, inspiratory muscle training; NT-proBNP, amino (N) portion of BNP; RCT, randomised controlled trial.

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demonstrate a statistically significant improvement in BNP (pmol/L) exercise versus control; MD −9.92 (95% CI −28.03 to −8.20), p=0.28 (figure 5). Sensitivity analysis indicated that the study by Kawauchi et al 68 affected the magnitude of the result (figure 7). Sensitivity analyses conducted for different correlation coefficients for SD imputation did not result in any significant variance in overall results. Two 41 70 additional studies, using non-conventional training, were not pooled. One 70 reported data as median (IQR), and one 41 was in patients with HFpEF, and both failed to demonstrate any significant change (table 2).

Cardiac troponin

Only a substudy of the HF ACTION trial reported on the effect of exercise training on cTnT levels compared with control participants, with no decreases in detectable levels of cTnT found in a cohort of participants from the trial. 53

Galectin-3

Two studies compared Gal-3 in exercising and control participants. However, differences in data reporting did not allow for data pooling. Billebeau et al 22 observed a statistically significant (p<0.001) median decrease of 6.3% in the exercise group (n=107) with no change in control patients. While Fernandes-Silva et al 23 reported no statistically significant difference in the mean change between exercise and control groups (p=0.69).

Soluble ST2

One study reported predata and postdata in regard to the effect of exercise training on sST2 levels. A statistically
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Pearson MJ, et al. Open Heart 2018; 5:e000819. doi:10.1136/openhrt-2018-000819

Meta-analysis

### BNP (Conventional)

| Study name     | Statistics with study removed | Mean (95% CI) with study removed |
|----------------|-------------------------------|----------------------------------|
|                | Point | Standard error | Lower limit | Upper limit | p-Value |                                    |
| Butterfield 2008 | -16.883 | 6.631 | -29.880 | -3.886 | 0.011 |
| Fu (AIT) 2013   | -15.754 | 6.406 | -26.090 | -5.199 | 0.014 |
| Fu (M CT) 2013  | -17.175 | 6.095 | -30.122 | -4.228 | 0.009 |
| Gary 2011       | -21.790 | 3.631 | -28.906 | -14.674 | 0.000 |
| Jendričová 2006| -19.181 | 6.759 | -32.429 | -6.934 | 0.005 |
| Kobayashi 2003  | -17.456 | 6.542 | -30.312 | -4.566 | 0.008 |
| Montanaro 2009  | -13.598 | 6.669 | -26.668 | -0.527 | 0.041 |
| Nishi 2011      | -15.559 | 6.131 | -27.505 | -3.572 | 0.011 |
| Norman 2012     | -17.816 | 6.908 | -31.514 | -4.117 | 0.011 |
| Parrinello 2009 | -16.716 | 6.223 | -22.533 | -0.959 | 0.042 |
| Passino 2008/2006| -16.667 | 7.688 | -32.129 | -0.214 | 0.025 |
| Stevens 2015    | -16.568 | 6.551 | -22.979 | -4.110 | 0.010 |
|                | -17.174 | 6.322 | -28.356 | -4.782 | 0.007 |

Figure 6  Sensitivity analysis BNP (conventional training) with study removed. AIT, aerobic interval training; BNP, brain natriuretic peptide; MCT, moderate continuous training.

significant (p=0.035) median decrease of 7.4% was observed post-training (n=97) by Billebeau et al, with no change in controls.

**MR-proANP**

Two studies reported on postintervention MR-proANP concentrations. Billebeau et al observed a statistically significant (p<0.001) median decrease of 16% post-training (n=105), with no changes in control participants. In contrast, the post hoc analysis of the Ex-DHF pilot trial by Trippel et al noted no significant treatment effect in patients with HFpEF.

**Mid-regional adrenomedullin**

Two studies reported on postintervention MR-proADM concentrations. Billebeau et al observed a statistically significant (p=0.001) 6.4% median decrease in MR-proADM (n=103), with no changes in control participants. In contrast, Trippel et al noted no significant treatment effect in patients with HFpEF.

**Copeptin**

One study by Trippel et al reported on CT-proAVP levels and failed to find any statistically significant change post-training or compared with the control group in patients with HFpEF.

### BNP (Non Conventional)

| Study name     | Statistics with study removed | Mean (95% CI) with study removed |
|----------------|-------------------------------|----------------------------------|
|                | Point | Standard error | Lower limit | Upper limit | p-Value |                                    |
| Karavias 2008  | -8.312 | 13.139 | -34.771 | 16.946 | 0.499 |
| Kato 2017      | -8.286 | 12.137 | -32.053 | 15.523 | 0.496 |
| Kawabuchi (LIPRT) 2017 | -11.713 | 11.211 | -33.687 | 10.280 | 0.296 |
| Kawabuchi (MIPRT) 2017 | -15.284 | 7.823 | -30.617 | -0.049 | 0.051 |
| Yen 2004       | -3.431 | 8.111 | -20.236 | 11.586 | 0.592 |
|                | -9.916 | 9.241 | -28.082 | 8.196 | 0.283 |

Figure 7  Sensitivity analysis BNP (non-conventional training) with study removed. BNP, brain natriuretic peptide; LIPRT, low-intensity inspiratory training and peripheral resistance training; MIPRT, moderate-intensity inspiratory and peripheral resistance training.
Study quality and reporting
A median TESTEX score of 8.5 out of 15 was obtained (range 6–12) (online supplementary table S6). Details of randomisation procedures, activity monitoring of control groups, adjustment of relative exercise intensity and provision of adequate details to calculate exercise energy expenditure were frequently lacking.

Heterogeneity and publication bias
Meta-analyses indicated a moderate level of heterogeneity. Visual inspection of the funnel plot showed slight asymmetry (online supplementary figures 1A,B).

DISCUSSION
This systematic review and meta-analysis compiled evidence from a large volume of studies assessing the effect of exercise therapy on established and a selected number of emerging biomarkers in patients with HF. Different to previous analyses, both conventional and non-conventional modes of training were examined. When analysed separately, conventional training demonstrated a statistically significant improvement in NT-proBNP and BNP, while pooled analyses of non-conventional training failed to demonstrate any significance. While BNP and NT-proBNP are raised across the HF spectrum, as levels may be lower in HFpEF, and in some instances close to normal, we excluded studies from pooled analyses that only included patients with HFpEF. However, it is highly likely that a number of other studies included in the analyses with mean ejection fractions >40% would have also included patients with HFpEF, and it is possible that this could be reflected in the variability of the results.

The favourable result demonstrated in pooled analyses of conventional training is consistent with previous reviews and a 2011 IPD meta-analysis. However, in contrast to our pooled results, of studies unable to be pooled, only two of seven studies for BNP, and two of the seven studies for NT-proBNP, indicated any significant change post-training or compared with controls. Furthermore, one of these studies was a sub-analysis of a large cohort from the HF ACTION trial, which found that levels of plasma NT-proBNP did not significantly improve after 3 months of AT, clearly contrasting with our result and previous analyses. However, adherence and participant crossover issues may have confounded the results of the HF ACTION trial. It is also possible that a longer intervention duration may have resulted in significant changes, as seen after 9 months by Passino et al., although Sandri et al. demonstrated significant decreases after only 4 weeks of endurance training.

Emerging biomarkers
While BNP/NT-proBNP remains the gold standard HF biomarkers, with proven prognostic value, there are limitations. Age, gender, arrhythmias, obesity, renal function and comorbidities may all affect concentrations; hence, biomarkers less affected by these issues can provide valuable information. Furthermore, as biomarkers of myocardial stretch, BNP/NT-proBNP is only reflective of one pathophysiological pathway involved in HF; hence, biomarkers reflecting other pathways may provide new and valuable information and complement BNP/NT-proBNP. Both Gal-3 and sST2 have been studied as emerging biomarkers in HF, and now have a Class IIB recommendation for risk stratification by the American College of Cardiology/American Heart Association (ACC/AHA) (2013) guideline for HF management. Gal-3, a β-galactoside-binding lectin, plays a dominant role in inflammation, fibrosis and cardiac remodelling. Initial evidence also indicates that other novel biomarkers, such as CT-proAVP and MR-proADM, both biomarkers of neurohormonal activation, also have prognostic value in HF.

Current evidence does not allow for any conclusion as to the effect of exercise training on emerging biomarkers. However, the recent studies of Fernandes-Silva et al. and Billebeau et al. provide an interesting and perhaps promising platform on which future research can expand. Billebeau et al. in a non-randomised trial, observed a significant decrease in BNP, MR-proANP, MR-proADM, Gal-3 and sST2 in exercise training participants with no change in controls. Analysis according to change in VO2peak demonstrated that patients with an increase in VO2peak ≥ 14.5% (based on the median increase) experienced a significant decrease in Gal-3, sST2, MR-proADM and MR-proANP compared with no significant biomarker change in participants with change in VO2peak < 14.5%. Furthermore, given that BNP improved regardless of the change in VO2peak, they concluded that the addition of the newer biomarkers improved the clinical follow-up of rehabilitation. Overall, their results demonstrated that exercise training improves neurohormonal, inflammatory and fibrotic processes. Fernandes-Silva et al. observed no significant difference between exercise and control patients for change in Gal-3 or the proinflammatory markers (IL-6 and tumour necrosis factor-α); however, VO2peak significantly improved in participants with low baseline Gal-3 levels, compared with patients with high levels, with similar findings for the proinflammatory markers. These results suggesting biomarkers may predict a patient’s response to training. Interestingly, in a sub-study of the HF ACTION trial, higher baseline ST2 levels were associated with a greater improvement in VO2peak at 3 months.

Exercise capacity
Reduced exercise capacity is a major hallmark of HF, and NT-proBNP is a strong predictor of VO2peak. Changes in BNP and NT-proBNP have been correlated with changes in VO2peak and suggested therefore as a possible surrogate for evaluating training responses. Only a minimal number of studies included in the review...
reported associations between change in peak VO$_{2peak}$ and biomarkers. Ahmad et al$^{53}$ did however observe that in patients in whom NT-proBNP levels decreased, there was an increase in VO$_{2peak}$, despite finding no significant change in NT-proBNP. While Passino et al$^{62}$ observed that changes in VO$_{2peak}$ correlated significantly with decreases in NT-proBNP and BNP. Recently, Billebeau et al found that of all the biomarkers they tested, for predicting change in exercise capacity, MR-proADM best correlated with VO$_{2peak}$.$^{22}$ Given that adrenomedullin originates not only from the heart but also from multiple organs, tissues and blood vessels$^{28}$ and that the mechanisms associated with improved exercise capacity in HF involve cardiac, vascular and skeletal muscle adaptations,$^{79}$ a relationship between MR-proADM and improved exercise capacity makes sense.

**Phenotype**

Levels of BNP and NT-proBNP are elevated irrespective of ejection fraction; although they are generally lower in HFpEF compared with heart failure with reduced ejection fraction (HFrEF).$^{80-82}$ Patients also present with elevated levels of a number of other biomarkers reflective of different pathophysiological pathways. Currently, there are limited data on the role of exercise training and biomarkers in HFpEF, and none of the HFpEF studies included in the review reported any significant changes in the biomarkers. Furthermore, it is likely that there exist different biomarker profiles for HFrEF and HFpEF.$^{83,84}$ Moving forward, these different biomarker profiles may provide valuable information for treatment strategies, including exercise.

**Exercise prescription**

While moderate continuous training (MCT) has been the cornerstone of conventional HF training, over the past decade, the interest in high-intensity interval training (HIIT) has grown.$^{85}$ Two studies included in the review that specifically incorporated HIIT and MCT groups for comparative purposes observed significant improvements in BNP$^{57}$ and NT-proBNP$^{47}$ from HIIT, with no significant change from MCT. However, this is in contrast to the recent results of the larger, multicentre SMARTEX HF study, which failed to demonstrate any significant difference between HIIT and MCT after 12 weeks.$^{86}$ However, for comparisons, difficulty arises in regard to actual training intensities attained, and in SMARTEX, both actual HIIT and MCT intensities attained may have impacted the results, with patients training at lower and higher intensities than prescribed.$^{86}$

To date, the majority of HF training studies have used conventional modes of training; however, not all patients can or are willing to participate in these activities. Women, for example, may be more likely to attend mind–body interventions, such as Tai Chi and Yoga, for cardiac rehabilitation purposes.$^{87,88}$ Furthermore, both FES and IMT offer alternative modes of physical therapy, particularly in patients unable to participate in more conventional modalities. Individually, the included studies investigating FES and IMT failed to demonstrate any significant change in BNP or NT-proBNP compared with control groups. However, the combination of these non-conventional modes with conventional training may provide possible synergistic effects$^{89}$ as demonstrated by Caminiti et al$^{86}$ with combined Tai Chi/endurance training and Adamopoulos et al$^{89}$ with combined IMT/AT. Furthermore, other modes of non-conventional exercise therapy, such as weight-supported$^{91}$ and robot-assisted$^{92}$ exercise training, have demonstrated improvements in BNP and NT-proBNP in patients with HF and may be beneficial in some subgroups.

**Clinical significance and future research**

Biomarkers are used in HF clinical trials for a number of reasons,$^{10}$ including establishment of inclusion criteria, outcome measures, explaining therapeutic efficacy and as a target for therapy.$^{53}$ Biomarkers and biomarker panels may aid in identifying subgroups of patients with HF who may have a more favourable response to exercise therapy, distinguishing responders and non-responders.$^{21,23}$ in terms of specified outcomes including functional and long-term outcomes. Different biomarkers may provide further insight into the downstream molecular mechanisms associated with improvements from exercise training.$^{21}$ It could be possible that different biomarker profiles respond differently to different intervention characteristics, such as intensity, perhaps allowing further tailoring of the exercise to the individual. Furthermore, biomarkers, with their prognostic utility, may provide useful postintervention information, indicating improvements when other favourable outcomes may be absent. It remains premature to draw too many conclusions about the relationship between changes in emerging biomarkers and exercise training, and the utility of these biomarkers in HF is yet to be fully established, but it presents as an interesting and important area for future research.

Future research also needs to consider the clinical interpretation of changes in biomarkers given their biological variation.$^{94}$ While NT-proBNP is considered to have high biological variation, the newer markers of sST2 and Gal-3 demonstrate a lower variation and therefore add value to their use.$^{94}$ However, from an individual perspective in interpreting clinically meaningful changes in biomarkers, it is suggested that reference change values which indicate the percentage change necessary within an individual, reflective of a true change as opposed to biological variation, be used.$^{94}$

**Strengths and limitations in the systematic review and meta-analysis**

To our knowledge, this is the first meta-analysis of BNP and NT-proBNP to include training studies beyond the conventional AT and RT modalities and the first review to consider exercise therapy and emerging biomarkers in HF. We aimed to provide a meta-analysis of studies.
CONCLUSION

Pooled data of conventional training modalities indicated a favourable effect on the established HF biomarkers, NT-proBNP and BNP, contrasting with information from a number of non-pooled studies. Limited evidence exists in regard to exercise training and emerging biomarkers. Given the complex pathways involved in the onset and progression of HF, more research is required to establish exactly how established and emerging biomarkers can be used in exercise training in this population. The use of multiple biomarkers is an area of active research in HF, and future studies using biomarker panels may prove beneficial in guiding non-pharmacological therapy such as exercise by facilitating a more precise approach to exercise for subgroups of patients.

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