Exercise training and high-sensitivity cardiac troponin T in patients with heart failure with reduced ejection fraction

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Abstract

Aims

Whether an exercise training intervention is associated with reduction in long-term high-sensitivity cardiac troponin T concentration (hs-cTnT, a biomarker of subclinical myocardial injury) in patients with heart failure with reduced ejection fraction (HFrEF) is unknown. Aims were to determine (1) the effect of a 12-week endurance exercise training intervention with different training intensities on hs-cTnT in stable patients with HFrEF (LVEF ≤ 35%); (2) associations between hs-cTnT and peak oxygen uptake (VO_{2peak}).

Methods

In this sub-study of the SMARTEX-HF trial originally including 261 patients from 9 European centres, 213 eligible patients were included after withdrawals and appropriate exclusions (19% women, mean age 61.2 years (SD: 11.9)), randomized to High-Intensity Interval Training (HIIT, n=77), Moderate Continuous Training (MCT, n=63), or a Recommendation of Regular Exercise (RRE, n=73). Hs-cTnT measurements and clinical data acquired before (BL) and after a 12-week exercise training intervention (12w) and at 1-year follow-up (1yr) were analysed using multivariable mixed models.

Results

Baseline hs-cTnT was above the 99th percentile upper reference limit of 14 ng/L in 35 (48%), 35 (56%) and 49 (64%) patients in the RRE, MCT and HIIT group, respectively. Median hs-cTnT was 16 ng/L at BL, 14 ng/L at 12w and 14 ng/L at 1yr. Hs-cTnT was statistically significantly reduced at 12w in a model adjusted for randomization group, center and VO_{2peak}, and after further adjustment in the final model which also included age, sex, creatinine concentrations, NT-proBNP, smoking, and HF treatment. The mean reduction from BL to 12w in the final model was 1.1 ng/L (95% CI: 1.0 – 1.2 ng/L, p<0.001) and the reduction was maintained at 1yr with a mean reduction from BL to 1yr of 1.1 ng/L (95% CI: 1.0 – 1.1 ng/L, p=0.025). Randomization group was not associated with hs-cTnT at

any timepoint (overall test: p=0.20, MCT vs RRE: p=0.81, HIIT vs RRE: p=0.095, interaction time×randomization group: p=0.88). Independent of timepoint, higher VO_{2peak} correlated with lower hs-cTnT (mean reduction over all time-points: 0.2 ng/L per increasing $ml \cdot kg^{-1} \cdot min^{-1}$, p=0.002), without between-group differences (p=0.19).

Conclusions

In patients with stable HFrEF, a 12-week exercise intervention was associated with reduced hs-cTnT in all groups when adjusted for clinical variables. Higher VO_{2peak} correlated with lower hs-cTnT, suggesting a positive long-term effect of increasing VO_{2peak} on subclinical myocardial injury in HFrEF, independent of training program.

Keywords

Heart failure; Troponin T; Cardiorespiratory fitness; Exercise training interventions; Training intensity

Introduction

Although exercise training is part of current guidelines for the treatment of chronic heart failure (HF) (1), concerns have been raised that high-intensity exercise may increase myocardial injury in HF patients, where normal adaptive mechanisms malfunction. In contrast, some studies indicate that exercise as a therapeutic option is underused in HF patients. (2-4) Measurement of biomarkers of heart failure and myocardial injury may help to clarify these issues. Cardiac-specific troponin T (cTnT) is part of the contractile apparatus in cardiac muscle cells and leaks out of damaged cells. It is therefore used as a biomarker, and detection in serum plays an important role in the diagnostics of acute and chronic myocardial injury. (5) Chronic elevation of high-sensitivity (hs)-cTnT above the 99th percentile upper reference limit (URL) of 14 ng/L is associated with adverse cardiovascular events. (6, 7) In chronic HF, hs-cTnT also independently predicts more robust endpoints, including all-cause and cardiovascular death, as well as cardiovascular hospitalizations, with 18 ng/L as the preferred cut-off. (8)

In patients diagnosed with HF, the effects and safety of exercise training have been questioned. (9, 10) However, according to the European Society of Cardiology 2016 HF guideline, regular aerobic exercise training has the highest recommendation in stable HF patients with reduced ejection fraction (HFrEF), with level of evidence class IA. (4) An unresolved matter is the preferred training intensity in these patients. Peak oxygen uptake (VO_{2peak}) is associated with prognosis in HF (9, 11) and high intensity interval training (HIIT) has increased VO_{2peak} more efficiently than moderate continuous training (MCT) in stable HFrEF patients in some studies. (12) This was not confirmed in the index SMARTEX-HF study and the debate regarding training intensity is therefore still ongoing. (13)

There are few studies assessing the association between long-term cTnT concentrations and endurance exercise training in HFrEF patients. In the HF-ACTION study evaluating an exercise training program in patients with stable HFrEF, no changes were found in cTnT concentrations measured at baseline, after 3 months and after 12 months (14) However, the employed assay was not a

high-sensitivity assay (14% of patients had measurable cTnT). In addition, only MCT with a training duration of 15-35 minutes was performed, and the training effect was too small to draw definite conclusions. Accordingly, there is a need for studies using hs-cTnT assays and high-intensity exercise training programs with good adherence.

The randomized multicentre SMARTEX-HF Study compared 12 weeks of supervised intervention of HIIT, MCT or a recommendation of home-based regular exercise (RRE). Training intensity was measured objectively using heart rate (HR) at all supervised training sessions and myocardial injury was assessed with hs-cTnT. The compliance to number of supervised sessions was 93.3%. (13) Thus, this study data is well suited for a secondary analysis investigating the association between cTnT and endurance exercise training in patients with HFrEF.

The aim of the present study was to determine the long-term effect of a 12-week endurance exercise training intervention with different training intensities and modes on hs-cTnT in stable patients with HFrEF (left ventricular ejection fraction (LVEF) ≤ 35%) and to determine associations between hs-cTnT and VO_{2peak}. We hypothesized 1) that a 12-week endurance exercise training program is associated with reduced chronic myocardial injury, measured as a decline in hs-cTnT concentrations and that this association will last through the follow-up period; 2) that different training intensities and modes have different associations to hs-cTnT; and 3) that changes in hs-cTnT during the study period are associated with changes in VO_{2peak}.

Methods

Patients

Hs-cTnT was measured in a sub-study of the SMARTEX-HF Study that included 261 patients from nine different testing centres. Inclusion criteria and interventions have been described in detail previously. (15) Participants were randomized to three groups: HIIT (n=90), MCT (n=85) and RRE (n=86), stratified by testing centre and ischemic vs. non-ischemic aetiology of HF. 215 patients

completed the 12-week follow-up, i.e. n=77 in HIIT, n=65 in MCT, and 73 in RRE. For the present study, two patients were excluded due to missing blood samples (both from the MCT group, n=63 eligible patients). Data were analysed according to the Intention-to-treat principle, comprising 213 patients at baseline (BL) and 12 weeks (12w), and 191 patients at 52-week follow-up (1yr). Study enrolment, randomization and loss to follow-up have been detailed earlier. (13) In brief, 14 patients had LVEF > 40% and did not fulfil the inclusion criteria, 16 withdrew, died or were hospitalized before starting the training intervention, and 16 were excluded during the training intervention (2 died, 7 stopped due to serious adverse events, 5 withdrew and 2 were lost to follow-up). At 1yr, 5 had died, 6 missed follow-up due to serious adverse events, 1 withdrew, 1 was lost to follow-up and 11 patients had missing blood samples. (13) In the present sub-study, total loss to follow-up due to all causes was similar in the three groups (HIIT: n=10, MCT: n=7, RRE: n=7, p=0.80).

Samples and tests

Blood samples were drawn after an overnight fast before starting the training intervention (BL), after completion of the exercise program (12w), and at 52-week follow-up (1yr). Sampling was done more than 48 h after the last exercise training. Serum hs-cTnT was measured in all samples in a single batch at a core lab using a commercially available assay (Elecsys TnT hs STAT, cobas e 801, Roche Diagnostics). The analytical range was 3 ng/L to 10,000 ng/L, and the inter- and intra-assay coefficients of variation (CV) in the relevant concentration ranges were 2.1-3.5 % and 2.2-3.9%, respectively. The samples were analysed by order of randomization number with the three samples from each person in the same run, and the laboratory personnel were blinded to randomization group. All samples had hs-cTnT concentrations within the analytical range.

Cardiopulmonary exercise testing (CPET) was performed after blood samples were drawn. As detailed in previous publications, CPET was performed on either a bicycle or a treadmill, using an incremental protocol with 10W or 20W increase in workload per minute until exhaustion, starting at 20W or 40W, respectively. Standard equipment for indirect calorimetry was used to measure the maximal oxygen uptake. VO_{2peak} is the highest measured oxygen uptake during CPET when maximal

oxygen uptake is not reached. The mean of the three highest 10-second consecutive measurements was identified as VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$), and for simplicity, the term is used for all test results in the present study. (13, 15) BL, 12w and 1yr tests were performed using the same protocol and exercise modality (treadmill or bicycle) as the training. Left ventricular end-diastolic diameter (LVEDD) and LVEF was assessed by echocardiography according to standard procedure, as detailed previously. (13)

Participants in the MCT and HIIT groups had three supervised exercise training sessions per week, on a treadmill or bicycle. Exercise protocols have been described elsewhere. (12, 13, 15) In brief, the HIIT group was targeted to exercise at ≥90% of HR_{peak} during the high intensity intervals and 60-70% of HR_{peak} between these intervals. The MCT group was targeted to exercise at 60-70% of HR_{peak}. The number of participants was calculated based on the primary endpoint in the index SMARTEX-HF Study. (15)

The investigation was conducted in conformity with the principles outlined in the *Declaration of Helsinki*. (16) The study was approved by national or institutional ethics committees for medical research in all countries. All patients gave written informed consent.

Statistics

This is a post-hoc analysis of the SMARTEX-HF trial. Descriptive data are given as median (25 and 75 percentile). Due to non-normality and to improve model fit, hs-cTnT concentrations were logarithmically transformed during analysis and back-transformed to the original scale for data presentation. The changes in hs-cTnT and association to VO_{2peak} during the study were investigated using multivariable mixed model analyses. This approach allows for variations in the dependent and independent variables due to the repeated measurements during the study and accounts for different number of cases at each timepoint. A basic model included hs-cTnT as dependent variable and VO_{2peak}, randomization group and testing centre (by a categorical variable) as independent variables. The model was then further adjusted with predefined clinical variables selected based on previous literature, i.e. age (1, 5), sex (1, 5), creatinine concentration (1, 17), N-terminal pro-brain natriuretic

peptide (NT-proBNP) (1), LVEDD (13), New York Heart Association functional class (NYHA) (18), LVEF (18), HR_{peak} (18), workload (18) and HF treatment, defined as treatment (yes/no) with angiotensin II receptor blockers, angiotensin converting enzyme inhibitors and/or betablockers. For adjustment variables with repeated measurements, i.e. creatinine, NT-proBNP, LVEDD, LVEF, HR_{peak} and workload, the values for each timepoint were included. Sex was a better explanatory variable than body surface area. Non-significant variables were excluded from the final model.

To assess the robustness of the results, two sensitivity analyses were performed. Sensitivity analysis 1 investigated whether supervised training had a different effect on hs-cTnT than recommendation of exercise. Thus, data from the exercise training groups were pooled, making one intervention group (MCT + HIIT, n=142) and one control group (RRE, n=73) in the analysis. In sensitivity analysis 2, we included patients training "on target", i.e. 60-70% of HR_{peak} in the MCT group and ≥90% of HR_{peak} in the HIIT group, to better assess the effect of the target intensity difference between the two training groups. All patients in the RRE group were included in order to permit comparisons among the three randomization groups.

Two-sided p-values <0.05 were considered significant, and Sidak adjustment was used where necessary for comparison among the three randomization groups. Model fit was assessed by checking residuals and using the Akaike information criterion (AIC) and Bayesian information criterion (BIC). These criteria indicate how well different models represent the pattern in the data and penalize unnecessary variables and interactions. Statistical analyses were performed using Stata, version 16 (StataCorp, College Station, TX).

Results

Hs-cTnT concentrations

Descriptive data are shown in Table 1. Baseline concentrations of hs-cTnT were above the 99th percentile URL in 35 (48%), 35 (56%) and 49 (64%) patients in the RRE, MCT and HIIT group,

respectively. Hs-cTnT at any timepoint and changes in hs-cTnT during the study period were not significantly associated with randomization group in the adjusted analysis (overall test for randomization group: p=0.20, MCT vs RRE: p=0.81, HIIT vs RRE: p=0.095, interaction by time and randomization group: p=0.88) (figure 1). Hs-cTnT concentrations decreased significantly by time, independently of randomization group in both the basic and adjusted models (overall test: basic model: p=0.014, adjusted model: p<0.001). From BL to 12w, mean reduction of hs-cTnT was 1.1 ng/L (95% CI: 1.0 - 1.2; p<0.001) in the model adjusted for clinical variables. The reduction was maintained at 1yr in the adjusted model (from BL to 1yr: 1.1 ng/L, 95% CI: 1.0 - 1.1; p=0.025). There was no significant difference between 12w and 1yr regarding hs-cTnT (p=0.82).

Correlation between hs-cTnT and VO_{2peak}

Higher VO_{2peak} correlated with lower hs-cTnT concentrations for all timepoints, i.e. BL, 12w and 1yr (mean reduction of hs-cTnT over all timepoints: 0.2 ng/L per increasing $ml \cdot kg^{-1} \cdot min^{-1}$, p=0.002, interaction by time: p=0.88), independent of randomization group (interaction by randomization group: p=0.19) (figure 2). Because data for each of the repeated measurements were included in the mixed model, the design ensured that changes in VO_{2peak} for each patient were considered in parallel with changes in hs-cTnT.

Clinical adjustment variables associated with higher hs-cTnT were higher creatinine concentrations (p=0.001), higher age (p<0.001) and higher NT-proBNP (p<0.001). Variables associated with lower hs-cTnT were female sex (p<0.001), ever smoking (p=0.034) and treatment with betablockers (p=0.028). LVEDD (p=0.098), LVEF (p=0.097), HR_{peak} (p=0.39), NYHA (p=0.59) and other HF medications (p=0.90) were not significantly associated with hs-cTnT and were therefore not included in the final model. Higher maximal workload during CPET was associated with lower hs-cTnT when VO_{2peak} was not included in the model (p=0.004), but VO_{2peak} was a better explanatory variable. Thus, to avoid collinearity, maximal workload was not included in the final model. Model fit was considered acceptable.

Sensitivity analyses

In the first sensitivity analysis, pooling of the two supervised exercise training groups did not change the results: Hs-cTnT at any timepoint was not associated with randomization group (p=0.24), i.e. there was no difference between participants randomized to supervised exercise training and those in the control group. In the second sensitivity analysis, only including participants who trained "on target", there was no significant difference between the two training groups (p=0.76) and no significant difference between the training groups and the control group (p=0.83). However, only 8 patients (12.7%) in the MCT group trained on target at 60-70% of HR_{peak}, and only 38 patients (49.4%) in the HIIT group trained on target at ≥90% of HR_{peak}. As previously reported, 55 (86.3%) in the MCT group trained above the target, whereas 39 (50.6%) in the HIIT group trained below the target. (13)

Discussion

In this SMARTEX-HF sub-study of 213 HFrEF patients undergoing a 12-week endurance exercise training program or given recommendations for regular exercise, hs-cTnT concentrations were reduced at 12w in all randomization groups when adjusted for clinical variables. This reduction was maintained at 1yr. Higher VO_{2peak} correlated with lower hs-cTnT concentrations independently of randomization group and timepoint, suggesting reduced chronic subclinical myocardial injury with increasing VO_{2peak}. In other words, the exercise program by which the participants increased their VO_{2peak} was not decisive for the decrease in hs-cTnT concentration.

Morris and Chen (2019) recently stated that cardiac rehabilitation and exercise are underused in HFrEF patients, despite robust scientific proof concerning safety and inclusion in current guidelines. (4) Other studies of cardiac rehabilitation from European hospitals have shown that cardiac rehabilitation is not offered to all eligible patients. Reasons given are primarily logistics and lack of resources, but in some cases the perception of lack of safety has been stated. (2, 3) If HIIT were harmful to HFrEF patients over time, one would expect increases in chronic myocardial injury, i.e. hs-cTnT in this group, which was not the case in the present study. Exercise training is generally

recommended in chronic HF. However, transient increases in hs-cTnT after exercise training have been demonstrated and there is an ongoing discussion whether this represents a physiological response or a pathological process indicating increased risk for future cardiovascular events. (19) In the present study, sampling was performed more than 48h after exercise training to avoid confounding the evaluation of chronic myocardial injury with such transient increases. Thus, differences in acute transient increases of hs-cTnT among the randomization groups cannot be assessed. The present study did not have the necessary power to assess associations to serious adverse events. Occurrence of serious adverse events has been reported previously and a brief summary is given in the supporting information. (13)

As previously reported, many participants in the HIIT group exercised below their prescribed target HR, whereas many participants in the MCT group trained above their prescribed target HR. (13) This made the two supervised training interventions more similar than intended and could thereby confound the results. The sensitivity analyses supported the main results regarding associations between hs-cTnT and randomization groups. They are also in line with a recent meta-analysis, which found HIIT not to be superior to MCT regarding improvements in VO_{2peak} in patients with HFrEF when isocaloric protocols were compared. (20)

Published data showed that the RRE group also had an improvement in VO_{2peak}, (13) suggesting that many of the patients in the control group performed exercise as recommended during the study period. However, there are no objective data on how and how much the RRE group exercised. There are several possible explanations why patients in the RRE group also increased their VO_{2peak}. Recommendations of regular exercise may be sufficient for some patients to increase their daily activity. Additionally, being part of a research study in which VO_{2peak} was measured three times in one year may be an extra motivational factor. This is supported by a recent study in a general population of older adults, which showed that the control group exercised with higher intensity than the MCT group. (21) Assuming that the RRE group followed the recommendations they were given, the present study therefore indicates that performing activities leading to improved VO_{2peak}, including supervised exercise training but not excluding other activities, is accompanied by reductions in hs-

cTnT in HFrEF patients. The study also confirmed the hypothesis that exercise training could lead to reduced chronic subclinical myocardial injury as measured by hs-cTnT, even if the mean absolute reduction was numerically small. This may be related to the fact that the patients were optimally medically treated or that the average potential for cardiac improvement in the included patients was not very large. Furthermore, there were individual differences with larger effects in some patients and hs-cTnT increases in others. Despite the findings of reduced mean myocardial injury, the present study did not show differences among HIIT, MCT and RRE, suggesting that training intensity and mode (supervised vs. home-based training) did not affect chronic myocardial injury. These findings are in line with the well-known positive effects of exercise training on contractility and remodelling in skeletal muscle. (22)

The SMARTEX-HF trial found that exercise training increased VO_{2peak} and reduced LVEDD. (13) The increase in VO_{2peak} was also associated with increased HR_{peak} from BL to 12w, the ability to increase workload during the training period, lower NYHA class, higher LVEF, and lower age. Thus, younger and less symptomatic patients had a better training response than older and more symptomatic patients. (18) Of the factors previously associated with increased VO_{2peak}, only age was independently associated with hs-cTnT concentrations in the present analysis. Effects on hs-cTnT by the other mentioned factors could seem to be mediated or confounded by VO_{2peak}.

In the HF-ACTION study, no associations between cTnT and exercise training were found when comparing a training program comprising 36 supervised sessions with usual care. (14) However, whereas the training program in the present study included 3 supervised exercise sessions per week, each session lasting 37-48 minutes depending on the training method, the 36 sessions in the HF-ACTION study took place over a median time of 3.8 months and the participants exercised a median time of 76 minutes per week during the first 3 months. (14) Thus, there is reason to believe that the participants in the present study had a higher training load between baseline and follow-up at 12w. Myocardial injury in HF-ACTION was measured using a contemporary cTnT analysis and not the high-sensitivity assay. The combination of higher compliance and intensity of the training

program and the use of hs-cTnT in the present study enabled the detection of small changes in cTnT concentrations during the training period.

Clinical implications

Motivating patients with HFrEF to improve their VO_{2peak} may help reduce chronic myocardial injury as indicated by hs-cTnT. HIIT did not seem to differ from MCT or RRE in this respect, revealing that exercise intensity did not influence hs-cTnT. Thus, cardiac rehabilitation in HFrEF should aim at finding the optimal way to increase VO_{2peak} for each individual patient, including motivation and practical implementation as important aspects.

Strengths and limitations

This was a large multicentre randomized controlled trial with two different intervention groups and a control group where the patients were recommended to perform exercise. The intervention groups were closely followed and had good adherence to number of sessions. However, the differences between the training groups were smaller than anticipated due to variability in training intensity and exercise response. Physical activity data from the RRE group were limited. We cannot exclude that these participants also trained with high intensity. Blood samples were collected at times when the potential interference from recent exercise was small, i.e. measured hs-cTnT was not biased from possible transient increase related to exercise, as demonstrated in other studies. (23, 24) Myocardial injury was measured using a highly sensitive biomarker with high analytical precision. Because samples were analysed in random order, small variations due to measurement accuracy would not systematically affect the results. The cardiac form of troponin T may be expressed in damaged and regenerating skeletal muscle (25), which may result from exercise training. However, this would tend to increase concentrations, contrary to the study results showing decreased concentrations following the exercise intervention.

Conclusion

In patients with stable HFrEF, a 12-week exercise training intervention was associated with reduced serum hs-cTnT concentrations in all randomization groups (HIIT, MCT and RRE) when adjusted for clinical variables. The effect was maintained at 1yr follow-up. There was no significant difference in chronic myocardial injury among patients performing supervised training at high or moderate intensity and those being recommended to exercise at home. Those with higher VO_{2peak} had lower hs-cTnT at all timepoints. Increases in VO_{2peak} were associated with reductions of myocardial injury, measured as hs-cTnT. The effect was independent of randomization group and was maintained at 1-year follow-up, suggesting a long-term positive effect of increasing VO_{2peak} in HFrEF regardless of training method.

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Conflicts of Interest

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Figure legends:

Figure 1: Mean hs-cardiac Troponin T for each randomization group

Panel A: Measured concentrations

Panel B: Concentrations following adjustment for testing centre, randomization group, age, sex, creatinine, VO_{2peak}, NT-proBNP, LVEDD and HF treatment.

There were no significant differences among the groups. Hs-cTnT is back-transformed from logarithmic values.

* $p<0.05$ compared to baseline in the same group

RRE, recommendation of regular exercise; MCT, moderate continuous training; HIIT, high-intensity interval training; hs-cTnT, high-sensitivity cardiac Troponin T; VO_{2peak}, peak oxygen uptake; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEDD, left ventricular end-diastolic diameter; HF, heart failure

Figure 2: Association between hs-cardiac troponin T and peak oxygen uptake

The five groups correspond to the 10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th} percentile of VO_{2peak}. Hs-cTnT is back-transformed from logarithmic values.

* $p<0.05$ compared to baseline in the same group

Hs-cTnT, high-sensitivity cardiac troponin T; VO_{2peak}, peak oxygen uptake

Figure 3: Associations between hs-cardiac troponin T and selected adjustment variables

Panel A: Age

Panel B: N-terminal pro-brain natriuretic peptide

The five groups correspond to the 10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th} percentile of the respective adjustment variable. Hs-cTnT is back-transformed from logarithmic values.

* $p<0.05$ compared to baseline in the same group

Hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide

Table 1: Baseline characteristics

Characteristics	**RRE (n=73)**	**MCT (n=63)**	**HIIT (n=77)**
Age, years	60 (51 – 70)	60 (54 – 67)	65 (55 – 72)
Women, n (%)	14 (19.2 %)	12 (19.1 %)	14 (18.2 %)
Heart failure <12 months, n (%)	14 (19.4 %)	7 (11.1 %)	14 (18.2 %)
New York Heart Association class, n (%)			
II	54 (74.0 %)	40 (63.5 %)	55 (71.4 %)
III	19 (26.0 %)	23 (36.5 %)	22 (28.6 %)
Left ventricular ejection fraction, %	30.0 (23.9 – 33.9)	29.1 (23.5 – 34.0)	29.3 (24.0 – 34.0)
Ischaemic aetiology, n (%)	41 (56.2 %)	37 (58.7 %)	46 (59.7 %)
History of myocardial infarction, n (%)	32 (43.8 %)	34 (54.0 %)	44 (57.1 %)
History of coronary artery bypass surgery, n (%)	17 (23.3 %)	13 (20.6 %)	20 (26.0 %)
History of percutaneous coronary intervention, n (%)	33 (45.2 %)	21 (33.3 %)	32 (41.6 %)
Device therapy, n (%)			
Pacemaker	2 (2.7 %)	0 (0 %)	2 (2.6 %)
Implantable cardioverter defibrillator	31 (42.5 %)	36 (57.1 %)	27 (35.1 %)
Cardiac resynchronization therapy	13 (17.8 %)	4 (6.4 %)	14 (18.2 %)
Atrial fibrillation, n (%)			
Paroxysmal	13 (17.8 %)	5 (7.9 %)	11 (14.3 %)
Persistent	6 (8.2 %)	8 (12.7 %)	14 (18.2 %)
History of hypertension, n (%)	36 (49.3 %)	23 (36.5 %)	22 (29.0 %)
History of diabetes mellitus, n (%)	14 (19.2 %)	20 (31.8 %)	16 (20.8 %)

History of chronic obstructive pulmonary disease, n (%)	4 (5.5 %)	7 (11.1 %)	4 (5.2 %)
Smoking			
Previous smoker	35 (48.0 %)	30 (47.6 %)	38 (49.4 %)
Present smoker	18 (24.7 %)	6 (9.5 %)	14 (18.2 %)
Alcohol consumption, units per week	1 (0 – 4)	2 (0 – 6)	1 (0 – 7)
Medications, n (%)			
ACE inhibitor/ARB	70 (95.9 %)	58 (92.1 %)	71 (92.2 %)
Betablockers	71 (97.3%)	59 (93.7 %)	73 (94.8 %)
Diuretics	51 (69.9 %)	47 (74.6 %)	58 (75.3 %)
Digoxin or digitoxin	6 (8.2 %)	7 (11.1 %)	17 (22.1 %)
Statins	45 (61.6 %)	45 (71.4 %)	50 (64.9 %)
Anticoagulation	28 (38.4 %)	20 (31.8 %)	27 (35.1 %)
Body mass index, kg/m^2	27.7 (24.6 – 31.4)	27.5 (25.0 – 32.3)	27.6 (24.9 – 31.3)
Systolic blood pressure, mmHg	120 (110 – 131)	120 (110 – 131)	115 (105 – 129)
Diastolic blood pressure, mmHg	75 (70 – 82)	73 (65 – 80)	71 (65 – 80)
N-Terminal pro-Brain Natriuretic Peptide, ng/L	895 (407 – 1618)	976 (462 – 1635)	1052 (435 – 2285)
Left ventricular end-diastolic diameter, mm	68 (63 – 72)	69 (64 – 74)	68 (62 – 74)

Data are given as median (25 and 75 percentiles) due to mostly nonnormally distributed data, or number (percent) as indicated.

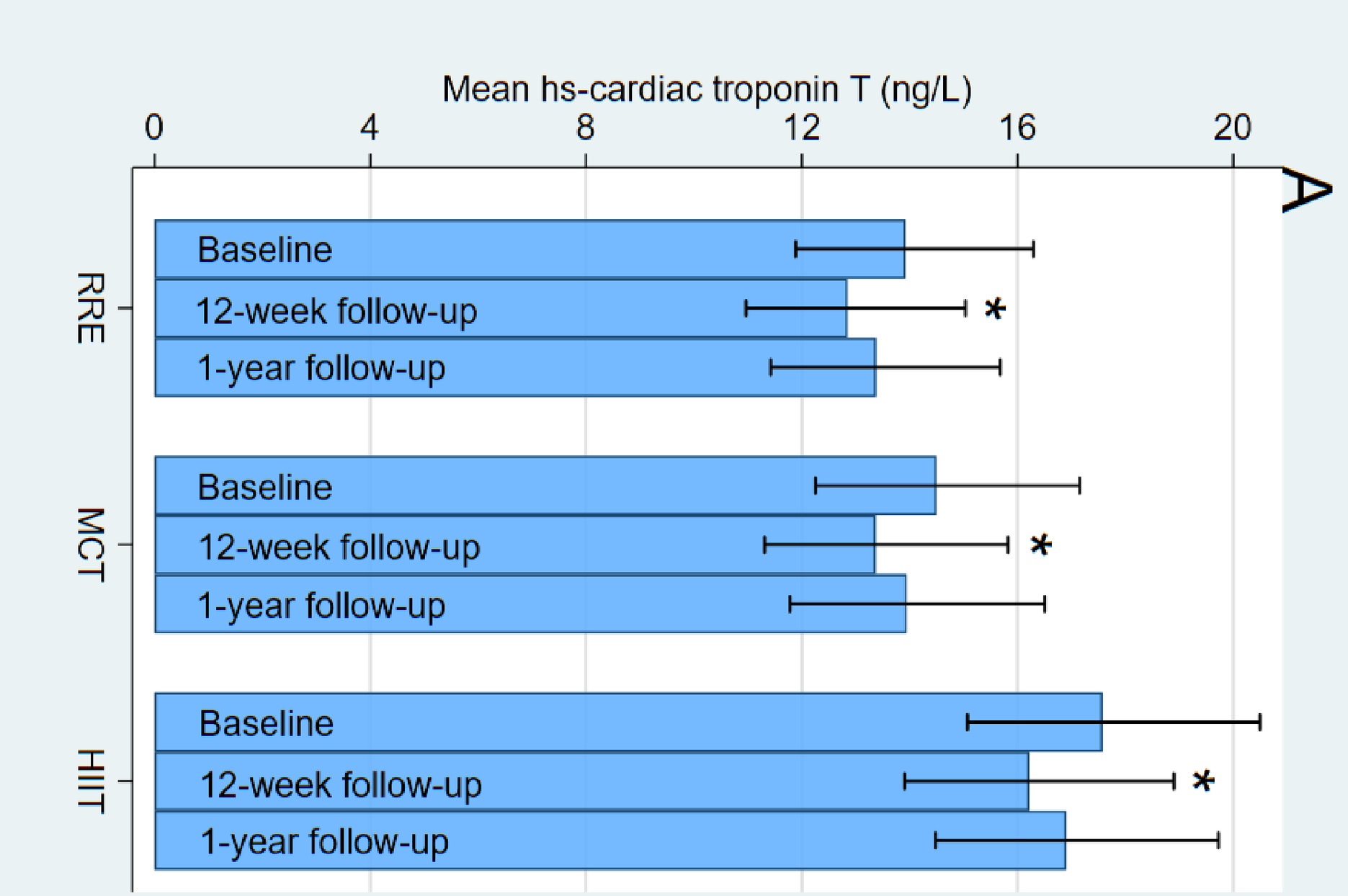
RRE, recommendations of regular exercise; MCT, moderate continuous training; HIIT, high-intensity interval training; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers

Table 2: Main testing measures at baseline, 12 weeks and 1 year with unadjusted changes

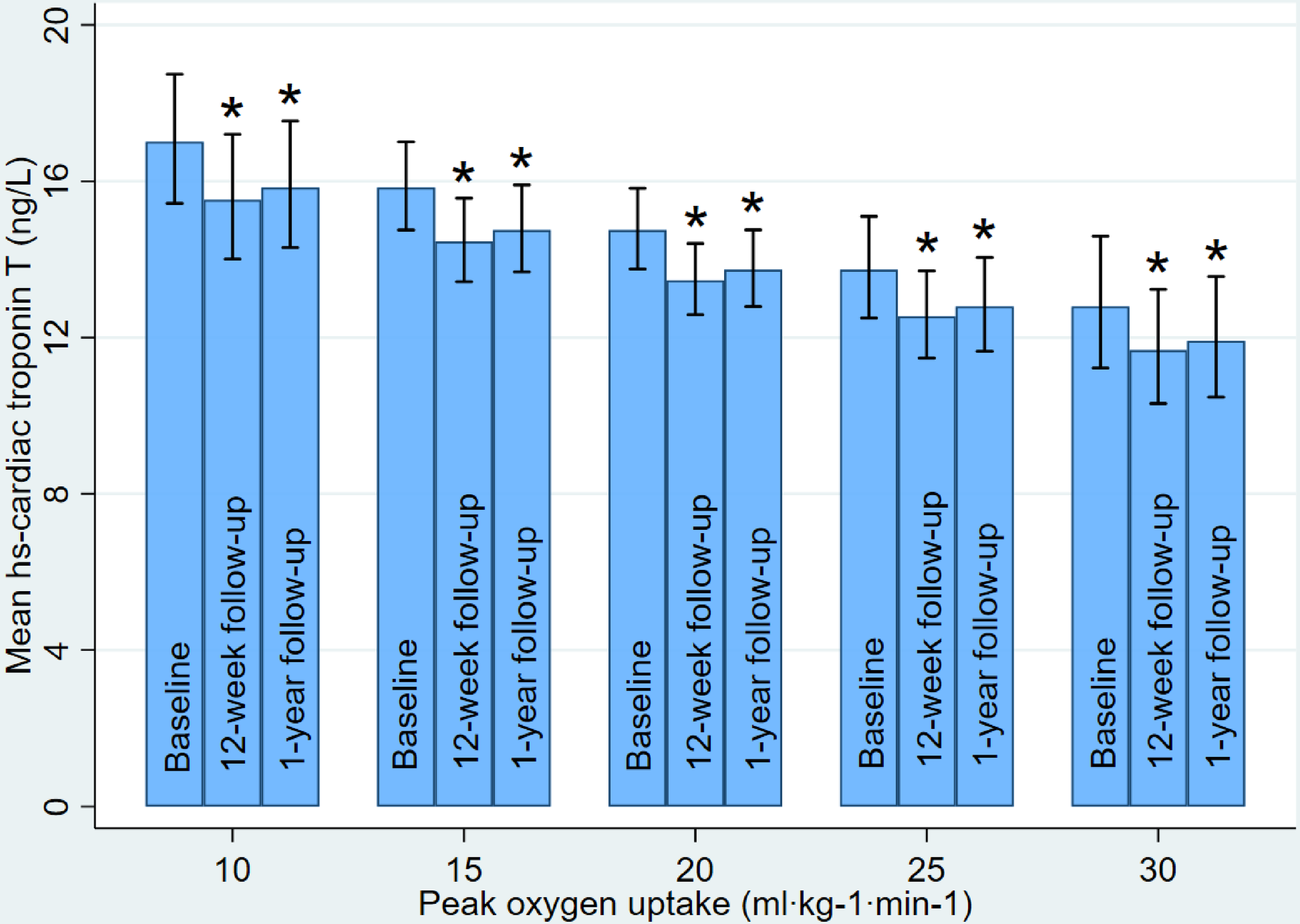
	RRE (n=73)	**MCT (n=63)**	**HIIT (n=77)**
Hs-cTnT, ng/L (95% CI)			
Baseline	14 (12, 18)	15 (14, 18)	17 (15, 20)
12-week follow-up	12 (10, 15)	15 (13, 17)	16 (13, 19)
1-year follow-up	12 (10, 16)	14 (12, 17)	15 (12, 20)
Delta hs-cTnT, ng/L			
Baseline – 12-week follow-up	0 (-1, 0)	-1 (-2, 0)	-1 (-2, 0)
Baseline – 1-year follow-up	0 (-1, 1)	-1 (-1, 0)	-1 (-1, 1)
VO_{2peak}, $ml \cdot kg^{-1} \cdot min^{-1}$ (95% CI)			
Baseline	18.4 (16.8, 19.6)	16.2 (15.3, 18.7)	16.8 (15.8, 17.8)
12-week follow-up	17.4 (15.7, 19.8)	17.0 (15.7, 19.8)	18.2 (16.3, 20.0)
1-year follow-up	18.2 (15.8, 20.0)	16.2 (15.0, 18.6)	17.1 (15.5, 18.6)
Delta VO_{2peak}, $ml \cdot kg^{-1} \cdot min^{-1}$ (95% CI)			
Baseline – 12-week follow-up	-0.1 (-0.9, 0.4)	1.1 (0.5, 1.8)	0.9 (0.0, 1.4)
Baseline – 1-year follow-up	-0.4 (-1.3, 0.4)	1.2 (-0.2, 1.4)	0.1 (-0.4, 1.0)

Data are given as median with 95% confidence interval of the median due to nonnormally distributed data.

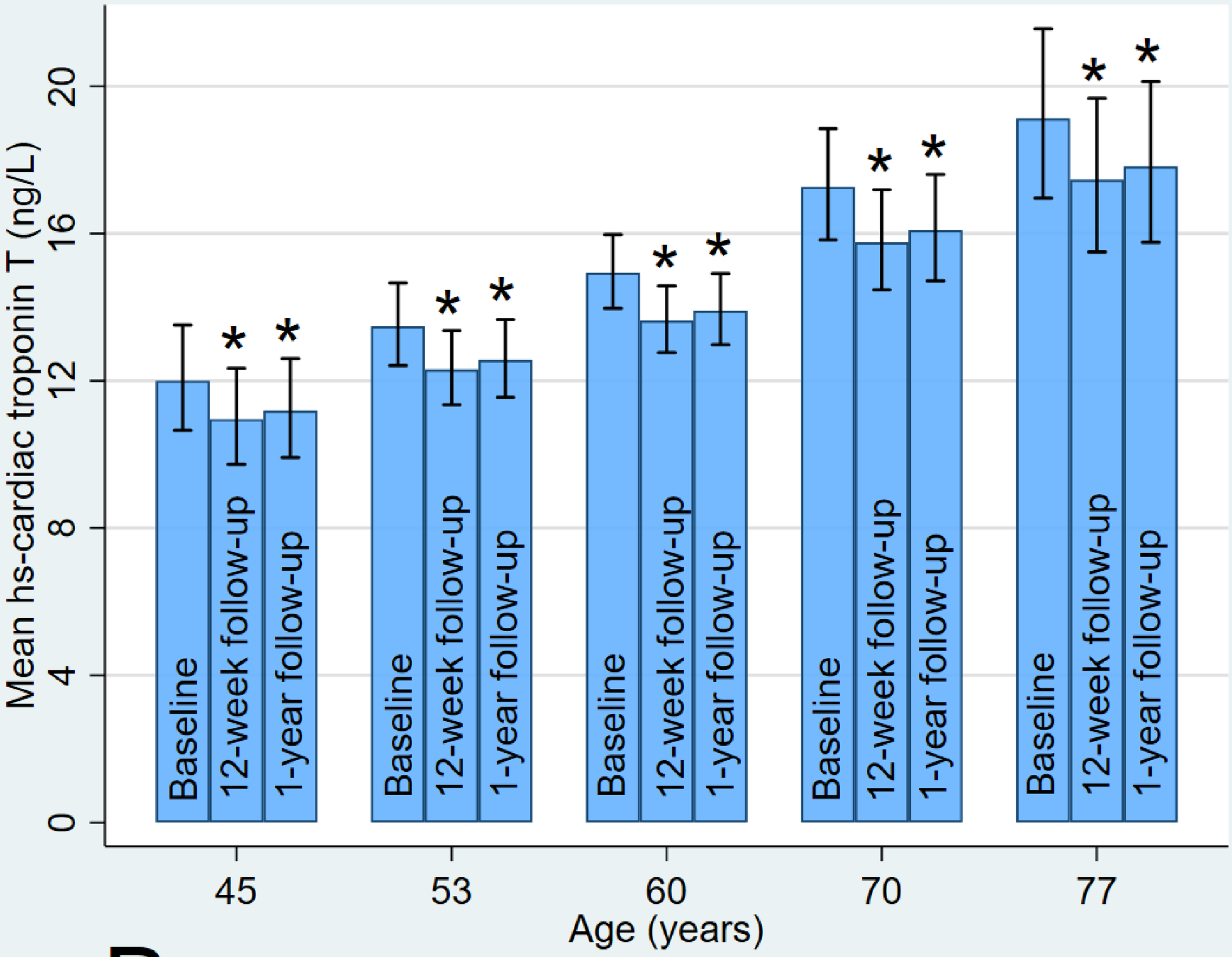
RRE, recommendations of regular exercise; MCT, moderate continuous training; HIIT, high-intensity interval training; Hs-cTnT, high-sensitivity cardiac troponin T; VO_{2peak}, peak oxygen uptake.


Mean hs-cardiac troponin T (ng/L)
0
4
8
12
16
20
A
RRE
Baseline
12-week follow-up
1-year follow-up
*
MCT
Baseline
12-week follow-up
1-year follow-up
*
HIIT
Baseline
12-week follow-up
1-year follow-up
*

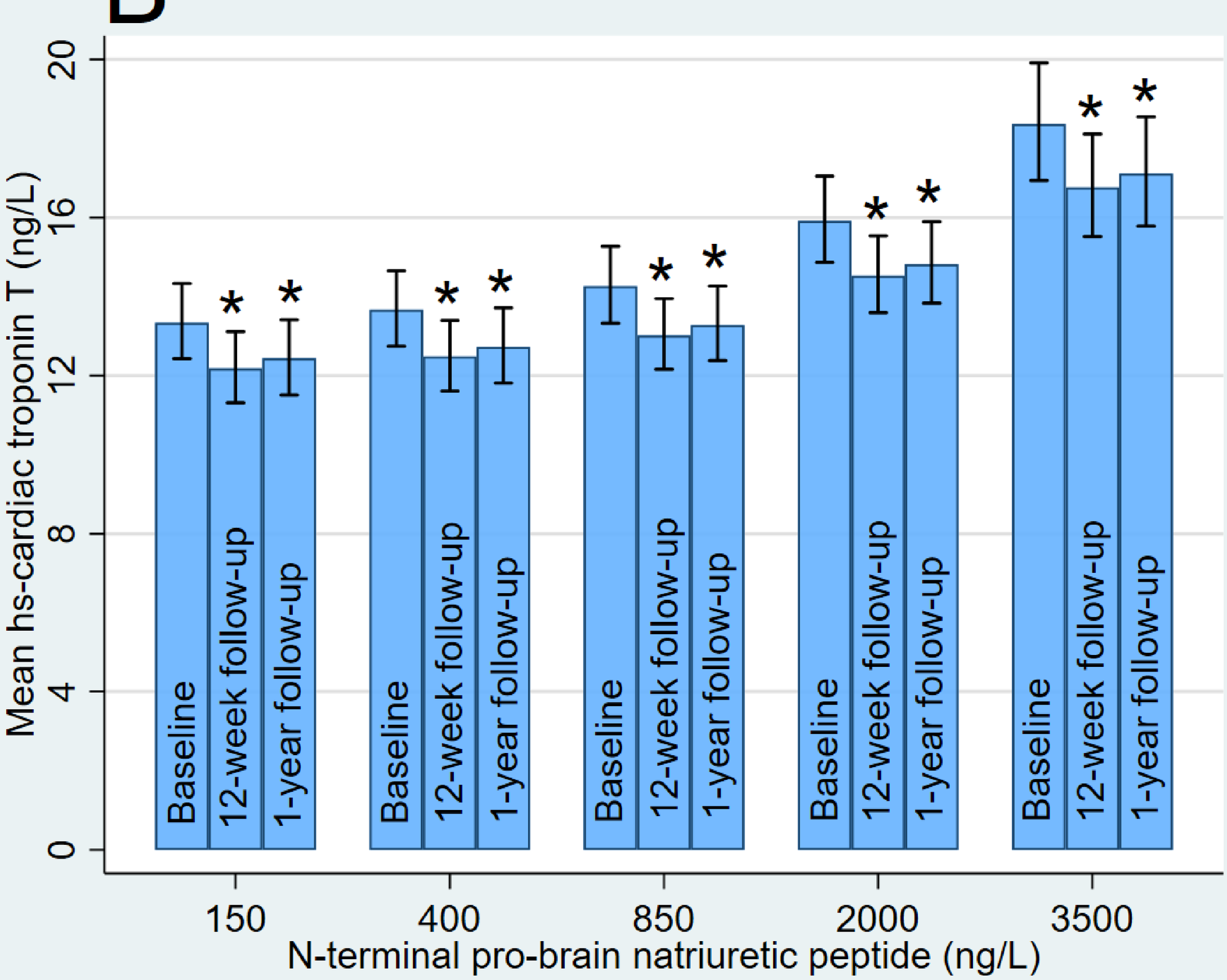
Mean hs-cardiac troponin T (ng/L)
0
4
8
12
16
20
B
RRE
Baseline
12-week follow-up
1-year follow-up
*
*
MCT
Baseline
12-week follow-up
1-year follow-up
*
*
HIIT
Baseline
12-week follow-up
1-year follow-up
*
*

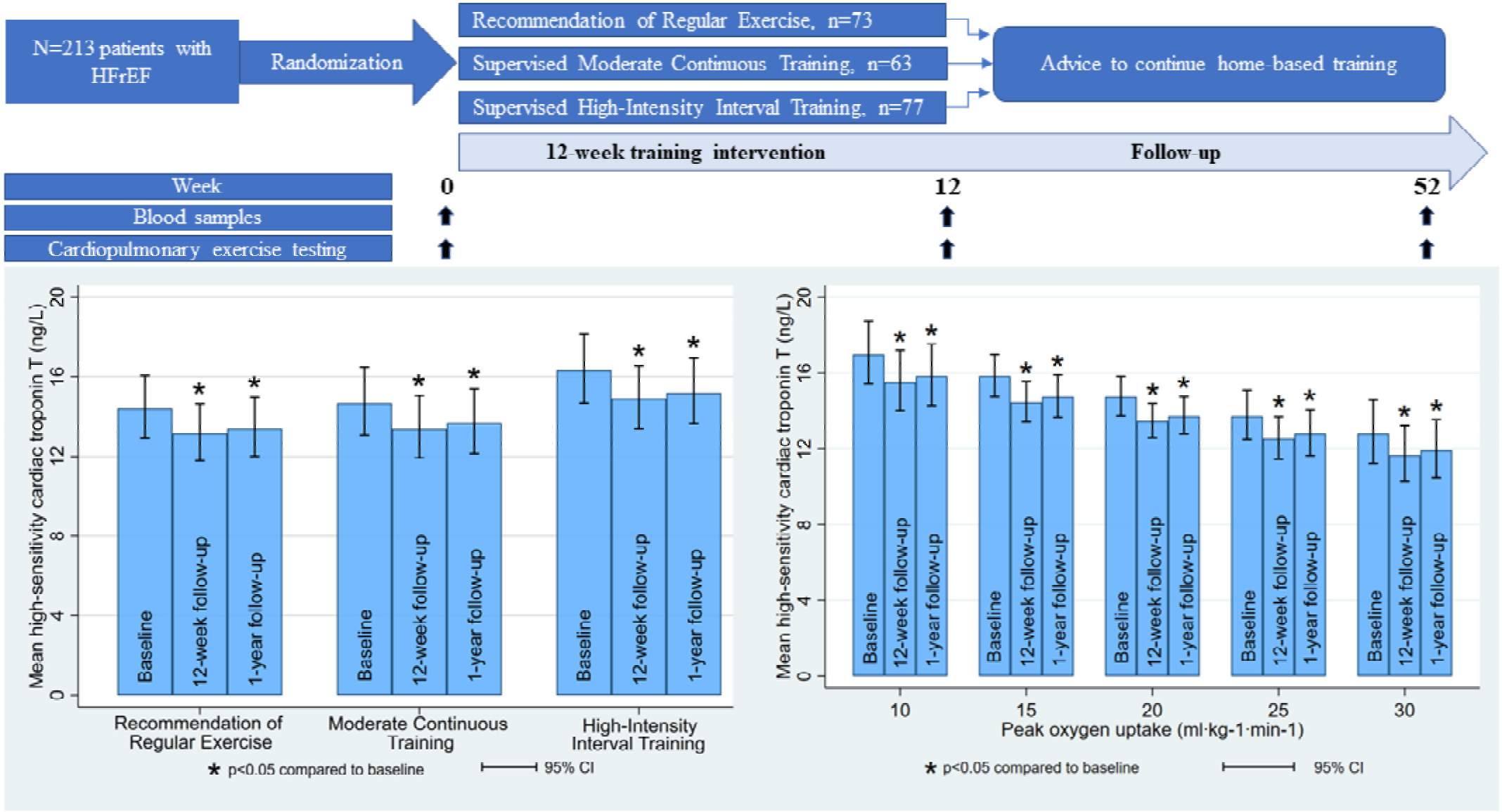

Mean hs-cardiac troponin T (ng/L)
0
4
8
12
16
20
Baseline
12-week follow-up
1-year follow-up
10
15
20
25
30
Peak oxygen uptake (ml·kg-1·min-1)

A


Mean hs-cardiac troponin T (ng/L)
0
4
8
12
16
20
Baseline
12-week follow-up
1-year follow-up
45
53
60
70
77
Age (years)

B


Mean hs-cardiac troponin T (ng/L)
0
4
8
12
16
20
Baseline
12-week follow-up
1-year follow-up
150
400
850
2000
3500
N-terminal pro-brain natriuretic peptide (ng/L)



In 213 patients with heart failure with reduced ejection fraction participating in a 12-week exercise intervention, all randomization groups had similar reductions in hs-cardiac troponin T, and higher peak oxygen uptake was associated with lower hs-cardiac troponin T at all timepoints and without between-group differences.

Supporting information

Manuscript title: Exercise training and high-sensitivity cardiac troponin T in patients with heart failure with reduced ejection fraction

First author: Koppen, E.

S1 Summary of serious adverse events in patients starting the 12-week training intervention (n=231)

	RRE (n=76)	MCT (n=73)	HIIT (n=82)
Cardiovascular events, n (%)			
Total cardiovascular SAE 1yr	21 (28 %)	13 (18 %)	24 (29 %)
Non-cardiovascular events, n (%)			
Total non-cardiovascular events	8 (11 %)	5 (7 %)	9 (11 %)
Total events, n (%)	26 (34 %)	18 (25 %)	32 (39 %)
Total fatal events 1yr, n	1	3	3

RRE, recommendation of regular exercise; MCT, moderate continuous training; HIIT, high-intensity interval training; SAE, serious adverse events; 1yr, 1-year follow-up. As detailed in (1), there was no significant difference between the groups in SAE during the 12-week training intervention (x^2 test for cardiovascular, non-cardiovascular and total number of events: p=0.61, 0.37 and 0.33, respectively).

S2 Mean hs-cTnT concentrations in eligible patients (n=213)

	RRE (n=73)	MCT (n=63)	HIIT (n=77)
Hs-cTnT (ng/L)			
Baseline	17.3 (14.6 – 20.1)	16.7 (14.4 – 19.1)	22.9 (18.2 – 27.7)
12-week follow-up	16.2 (13.3 – 19.1)	15.7 (13.4 – 18.0)	21.5 (17.0 – 25.9)
52-week follow-up	25.0 (8.7 – 41.4)	17.9 (12.1 – 23.8)	21.1 (16.6 – 25.5)

RRE, recommendation of regular exercise; MCT, moderate continuous training; HIIT, high-intensity interval training. Data are given as mean with 95% confidence intervals. Hs-cTnT concentrations were non-normally distributed and median concentrations are given in Table 2 of the main manuscript. Baseline concentrations were similar between RRE and MCT (p=0.63). However, there was a statistically significant difference at baseline between MCT and HIIT (p=0.01) and between RRE and HIIT (p=0.02).

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