Effect of inorganic nitrate or nitrite supplementation on exercise capacity for heart failure: a systematic review and meta-analysis of randomized controlled trials

He Zhang
National Clinical Research Center for Chinese Medicine Cardiology, China Academy of Chinese Medical Sciences
Yixuan Fan
National Clinical Research Center for Chinese Medicine Cardiology, China Academy of Chinese Medical Sciences
Qiuyi Li
National Clinical Research Center for Chinese Medicine Cardiology, China Academy of Chinese Medical Sciences
Anlu Wang
China Academy of Chinese Medical Sciences
Jie Zhang
National Clinical Research Center for Chinese Medicine Cardiology, China Academy of Chinese Medical Sciences
Jingen Li
Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine
Zhuo Chen
Department of Hematology, Xiyuan Hospital, China Academy of Chinese Medical Sciences
Hao Xu (xuhaotcm@hotmail.com)
National Clinical Research Center for Chinese Medicine Cardiology, China Academy of Chinese Medical Sciences

Article

Keywords: Inorganic nitrate, Inorganic nitrite, Heart Failure, Randomized clinical trials, Meta-analysis, Systematic review

Posted Date: June 2nd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1605412/v1

Abstract

Background: Some studies showed beneficial effects for exercise capacity of inorganic nitrates or nitrites (INNs) in heart failure (HF). However, the evidence is inconsistent.

Objective: We performed a meta-analysis to evaluate effects of INNs on exercise intolerance for heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).

Methods: Seven databases were searched from inception until September 2020 for randomized controlled trials (RCTs) assessing effects of INNs for HFrEF or HFpEF. RCTs comparing INNs with placebo, no treatment, or organic nitrates in patients. Primary outcomes were parameters of the exercise test. Secondary outcomes were N-terminal fragment of the prohormone brain natriuretic peptide (NT-Pro-BNP), cardiac function, and quality of life.

Results: Four RCTs with 43 patients in HFrEF and seven RCTs with 224 patients in HFpEF were included with high quality. The meta-analysis showed INNs didn't improve the muscle function of peak power in HFrEF, or peak oxygen uptake (VO_2 peak) in HFrEF; neither in HFpEF. In HFpEF group, INNs significantly decreased right atrial pressure, systolic blood pressure, pulmonary arterial pressure and pulmonary capillary wedge pressure during rest and exercise. No effect of INNs on NT-Pro-BNP, quality of life, or diastolic cardiac function. No serious adverse event was reported.

Conclusions: INNs don't improve exercise capacity in HF; however, they improved hemodynamic status, especially in HFpEF patients. More high-quality large-sample trials are needed to provide evidence for clinical application.

PROSPERO registration number: CRD42020210266

1. Introduction

Heart failure (HF) is the final stage of all cardiovascular disease, and it carries a high risk of mortality. In 2016, more than 6.2 million adults had HF in the United States. There were 8.9 million people with HF in China in 2019 [1]. HF with preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF) is characterized by exercise intolerance [4–5], which often leads to the decline of quality of life [3]. Patients with HF also exhibit decreased skeletal muscle strength, decreased peak oxygen consumption (VO_2) [5–6], and unstable hemodynamic changes.

Nitric oxide (NO) and other related molecules improve muscle movement ability, increase the delivery of oxygen and peak VO2 [7]. NO also influences endothelial function and hemodynamic stability, and therefore, the recovery of cardiopulmonary function [8]. The primary pathways of NO production in vivo include reducing inorganic nitrate to nitrite (nitrate-nitrite-NO pathway) and the aerobic pathway of L-arginine to NO and L-citrulline through nitric oxide synthase (the L-arginine-NO-synthase pathway). When the oxygen supply is insufficient, the intake of inorganic nitrates or nitrites (INNs) becomes an essential

route of NO supplementation. The anti-inflammatory and antioxidant properties of inorganic nitrates and the function of improving endothelial nitric oxide synthase have been demonstrated in animal experiments [9–10]. Impaired NO bioavailability or the increase of NO destruction and the destruction of endogenous NO pathway caused by oxidative stress in patients with HF lead to decreased exercise ability [11–12]. Studies showed that exogenous nitrate supplements are also effective sources of NO [13–15]. Although organic nitrates such as isosorbide mononitrate are used as supplements, their use is limited by the risk of hypotension and low oral bioavailability [13–15].

Moreover, organic nitrates failed to improve the quality of life in patients with HF [16]. INNs are abundant in green leafy vegetables and beet root juice [17]. Although studies have shown that INNs can improve HF's exercise ability or hemodynamic indexes [18–19], other studies showed inconsistent results [20]. These inconsistent findings may have resulted from different patient populations, as the bioavailability of NO in patients with HFrEF was lower than patients with HFpEF [21]. Researchers did not appear to note the effect of different ejection fractions. Therefore, the purpose of the present study was to determine the safety and effectiveness of INNs on exercise ability and cardiac function in both HFrEF and HFpEF using a meta-analysis.

2. Methods

2.1 Study registration

The study is registered in the international prospective register of systematic reviews (PROSPERO registration number CRD42020210266) and was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

2.2 Selection criteria

We included all randomized controlled trials (RCTs) comparing INNs with placebo, no treatment, or organic nitrates for patients with established HFrEF or HFpEF. When including crossover trials, carry-over effect from the first step was determined by whether the study described the washout period between the two steps. We excluded studies containing unavailable or incomplete data. There were no restrictions on language, population characteristics, or publication type. Duplicated publications reporting the same groups of participants were excluded. The primary outcomes were exercise testing, including muscle function of peak power, VO_2 peak, respiratory exchange ratio (RER), ventilation (Ve)/ carbon dioxide production (VCO_2) slope, and exercise time. Secondary outcomes included the following: N-terminal fragment of the prohormone brain natriuretic peptide (NT-pro-BNP); quality of life; and cardiac function measured by echocardiography, including E/A ratio, E/*e*' ratio (E: early mitral velocity; A: atrial mitral velocity; *e*': mitral annulus velocity), and right atrial pressure (RAP). Because ejection fraction was not included in the outcome index of the included articles, our study focused on the evaluation of cardiac diastolic function. The physiological outcomes included systolic blood pressure (SBP), diastolic blood pressure (DBP), pulmonary artery pressure (PAP), heart rate (HR), cardiac output (CO), and pulmonary

capillary wedge pressure (PCWP). The metabolism index after administering inorganic nitrate was the biochemical outcome. Adverse events were safety outcomes. Included trials needed to report at least one of the primary outcomes or at least two secondary outcomes or adverse events.

2.3 Search strategy

We conducted comprehensive literature searches of PubMed, the Cochrane Library, Embase, the China National Knowledge Infrastructure (CNKI), the Chinese Biomedical Literature Database (SinoMed), the Wanfang Database, and the Chongqing VIP Chinese Science and Technology Periodical Database (VIP). The search period was from database inception until September 2020. Search terms included “inorganic nitrates,” “inorganic nitrite,” “heart failure,” and “randomized controlled trials.” The complete search strategy is displayed in *Appendix 1*.

2.4 Study selection

Two authors (He Zhang and Yixuan Fan) independently screened the retrieved records using the same selection criteria. Non-relevant and repeated studies were removed by reviewing the titles and abstracts. All articles with potentially relevant trials were downloaded and reviewed before final inclusion. Disagreements were resolved by consultation with a third investigator (Hao Xu).

2.5 Data extraction and management

Two reviewers (He Zhang and Qiuyi Li) independently extracted the data from the selected studies. A standardized data extraction form was used to extract data, including the author names, year of publication, research type, age and sex of the participants, interventions, disease duration, outcomes, course of interventions, and follow-up. The data were imported into an electronic database by the two reviewers individually. Disagreements were resolved by consensus, including a third investigator. If the data in these RCTs were missing or not recorded clearly, we attempted to contact the authors for further information.

2.6 Quality assessment

Two authors (Yixuan Fan and Jie Zhang) independently evaluated the risk of bias of the included articles using the Cochrane Handbook for Systematic Reviews of Interventions [22]. The following aspects were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective outcome reporting, and other risk of bias (whether funds or institutions supported the study). According to the Cochrane Handbook, the risk of bias for each item was assessed as unclear, high, or low risk of bias. We also evaluated whether crossover interventions were grouped randomly, whether the crossover trial data were complete, and whether they showed advantages over parallel trials [22]. The method of bias evaluation of crossover trials was the same as for parallel trials. However, crossover tests generally use themselves as the control; therefore, it is necessary to evaluate the washout period and its rationale for data analysis. Disagreements were resolved through discussion. The third author evaluated the results that remained divergent.

2.7 Data analysis

All statistical analysis was performed using Review Manager version 5. software recommended by the Cochrane Collaboration. Data were summarized using risk ratio (RR) with 95% confidence intervals (CIs) for dichotomous outcomes and mean difference (MD) or standard mean difference (SMD) with 95% CI for continuous outcomes. Continuous variables generally use MD. However, SMD eliminates the influence of the absolute value of a study and eliminates the influence of the measurement unit on the results. According to the Cochrane Handbook [22], the reasonable reports of crossover trials are mostly SMD. Statistical heterogeneity was evaluated using the Cochrane chi-square and quantified with I^2. If $I^2 <= 50\%$, $P >= 0.1$, it means that there is low heterogeneity in the results, and the fixed effect model should be used. When $I^2 > 50\%$, $P < 0.1$, the results with heterogeneity were analyzed using a random-effects model [23, 24]. Sensitivity analysis or subgroup analysis to determine the stability of outcomes and heterogeneity. To measure differences in intervention effect of INNs in HF patients of different types, subgroup analysis was conducted according to whether the study involved patients with HFrEF or HFpEF. Publication bias was explored by funnel plot if sufficient studies were found ($n >= 10$).

3. Results

3.1 Search results

We identified 190 potentially relevant articles: 11 from PubMed, 39 from the Cochrane Library, 50 from Embase, 70 from CNKI, five from SinoMed, and 15 from Wanfang Database. We excluded 94 duplicate records, and 59 articles were excluded after reading titles and abstracts. 26 trials were excluded in the process of full-text screening: eight trials lacked complete articles, six trials lacked data, six were only study protocols that did not report outcomes, two were subgroup analyses of the included studies, and four were repeated articles. Finally, 11 RCTs were included in the quantitative and qualitative analyses. The flow chart of the search is displayed in *Fig. 1*.

3.2 Characteristics of included trials

A total of 11 studies involving 267 participants were included in this analysis. All articles were published in English. Four [20–21, 25–26] of the 11 trials enrolled patients with HFrEF, and the remaining seven [27–33] included HFpEF patients. Eight [20, 25–29, 32–33] were registered and were provided with registration numbers. All RCTs were double-blind, and nine [20–21, 25–26, 29–33] of 11 included a crossover design. The mean ages of patients in all studies were over 47 years. The characteristics of other details of all trials are summarized in Table 1.

3.3 Risk of bias

All included articles [20–21, 25–33] used random sequence generation (n = 11, 100%) (*Appendix 2*). Eight studies [20–21, 25–26, 30–33] not reporting allocation concealment were labeled as having an unclear risk of selection bias. All studies blinded their participants or personnel. Five studies [20–21, 26, 29, 32]

(45%) masked outcome assessments to the treatment allocation. All 11 trials were assessed as having a low risk of selective reporting bias and other risks of bias. The summary of the risk of bias assessment is presented in *Fig. 2*.

(a)Graph of bias risk

(b)Summary of bias risk

3.4 Effect of inorganic nitrate or nitrite on HFrEF

3.4.1 Primary outcomes: effectiveness of the intervention on the exercise test

3.4.1.1 The muscle function of peak power

Two crossover trials [21, 25] involving 17 participants treated with inorganic nitrate and placebo reported muscle function of peak power. Pooled results showed no significant difference in peak power (W/kg) [SMD, 0.43; 95% CI, -0.26 to 1.11, P = 0.22; I^2 = 0%, P = 0.46] (Fig. 3).

3.4.1.2 VO_2 Peak

Two crossover trials [21, 26] involving 24 participants compared VO_2 peak (L/min, ml/kg/min). Pooled results showed INNs did not significantly improve VO_2 peak ove placebo [SMD, 0.03; 95% CI, -0.54 to 0.60, P = 0.91; I^2 = 17%, P = 0.27] (Fig. 3).

3.4.1.3 RER

One crossover trial [21] involving eight participants compared RER between inorganic nitrate and placebo. Pooled results showed INNs did not significantly improve RER [SMD, -0.00; 95% CI, -0.98 to 0.98, P = 1.00] (Fig. 3).

3.4.1.4 Ve/VCO_2 slope

One crossover trial [21] involving eight participants compared INNs and placebo in terms of Ve/VCO_2. Pooled results showed INNs did not significantly improve the reduction of Ve/VCO_2 [SMD, -0.07; 95% CI, -1.05 to 0.91, P = 0.89] (Fig. 3).

3.4.1.5 Exercise duration

Two crossover studies [21, 26] involving 24 patients compared INNs and placebo. Results of the meta-analysis showed no significant difference between the two interventions [SMD, -0.17; 95% CI, -0.75 to 0.40, P = 0.55; I^2 = 37%, P = 0.21] (Fig. 3).

3.4.2 Other secondary outcomes

3.4.2.1 Blood pressure (BP)

Two trials [25–26] involving 25 patients compared INNs and placebo in SBP during rest and DBP during rest (mmHg). There was no significant reduction of the SBP during rest in the INN groups [SMD, -0.07; 95% CI, -0.62 to 0.49, P = 0.82; I^2 = 0%, P = 0.40]; neither in the DBP during rest [SMD, -0.41; 95% CI, -0.97 to 0.16, P = 0.16; I^2 = 16%, P = 0.28]. Two trials [21, 25] involving 17 participants compared INNs and placebo in terms of SBP during exercise and DBP during exercise (mmHg). Pooled results showed INNs did not significantly lower SBP during exercise compared with placebo [SMD, -0.15; 95% CI, -0.82 to 0.53, P = 0.67; I^2 = 0%, P = 0.65]; neither in DBP during exercise (mmHg) [SMD, -0.38; 95% CI, -1.07 to 0.31, P = 0.28; I^2 = 31%, P = 0.23] (Fig. 4).

3.4.2.2 HR during rest and exercise

One trials [25] involving 9 patients compared INNs and placebo in terms of HR (bts/min) during rest. Pooled results showed no significant difference between the two interventions [SMD, 0.54; 95% CI, -0.41 to 1.48, P = 0.26] (Fig. 4). Two trials [21, 25] involving 17 participants compared INNs and placebo in HR (bts/min) during exercise. The meta-analysis showed significant reduction in the placebo group [SMD, 0.89; 95% CI, 0.18 to 1.61, P = 0.01; I^2 = 0%, P = 0.65] (Fig. 4).

3.5 Effect of inorganic nitrate or nitrite on HFpEF

3.5.1 Primary outcomes: effectiveness of the intervention on the exercise test

3.5.1.1 VO_2 Peak

Four crossover trials [29, 31–33] and one normal RCT trial [30] involving 168 participants with HFpEF compared effects of INNs and placebo on peak VO_2 (ml/kg/min, ml/min/kg). Pooled results showed INNs did not significantly improve VO_2 peak ove placebo [SMD, 0.04; 95% CI, -0.18 to 0.26, P = 0.73; I^2 = 0%, P = 0.63] (Fig. 5).

3.5.1.2 RER

One parallel-group trial [30], and three crossover trials [31–33] involving 63 participants with HFpEF compared RER between inorganic nitrate and placebo. Pooled results showed INNs did not significantly improve RER [SMD, 0.31; 95% CI, -0.07 to 0.70, P = 0.11; I^2 = 42%, P = 0.16] (Fig. 5).

3.5.1.3 Ve/VCO_2 slope

Two crossover trials [32–33] involving 26 participants with HFpEF compared INNs and placebo in terms of Ve/VCO_2. Pooled results showed INNs did not significantly improve the reduction of Ve/VCO_2 [SMD, 0.27; 95% CI, -0.28 to 0.82, P = 0.33; I^2 = 0%, P = 0.35]) (Fig. 5).

3.5.1.4 Exercise duration

Four crossover studies [29, 31–33] and one parallel study [30] involving 168 participants with HFpEF compared INNs and placebo. Results of the meta-analysis showed no significant difference between the two interventions [SMD, 0.05; 95% CI, -0.27 to 0.17, P = 0.66; I^2 = 43%, P = 0.14] (Fig. 5).

3.5.2 Main secondary outcomes

3.5.2.1 Effect of intervention on NT-pro-BNP

Two crossover trials [29, 33] involving 25 HFpEF patients compared INNs and placebo in terms of NT-pro-BNP (pg/ml) based on a fixed-effects model. Pooled results showed INNs did not significantly decrease NT-pro-BNP compared with placebo [SMD, 0.00; 95% CI, -0.26 to 0.26, P = 0.99; I^2 = 0%, P = 0.59] (Fig. 6).

3.5.2.2 Effect of intervention on quality of life

Two crossover trials [29, 33] involving 114 participants with HFpEF compared INNs and placebo in terms of KCCQ score based on a random-effects model. There was no significant difference between the interventions [SMD, 0.40; 95% CI, -0.50 to 1.29, P = 0.38; I^2 = 69%, P = 0.07] (Fig. 6).

3.5.2.3 Effect of intervention on cardiac function

3.5.2.3.1 E/A ratio and E/e’ ratio

Two RCTs, concluding one typical RCT [30] and one crossover trial [33] involving 26 participants compared inorganic nitrate and placebo in terms of E/A ratio. The meta-analysis showed that INNs did not significantly improve the E/A ratio compared with placebo [SMD, 0.45; 95% CI, -0.23 to 1.14, P = 0.19; I^2 = 17%, P = 0.27] (Fig. 6).

Three RCTs, including two typical RCTs [29, 30] and one crossover trial [33] involving 131 participants compared INNs and placebo in terms of E/e’ ratio based on a fixed-effects model. The pooled results showed no significant difference in the two interventions [SMD, 0.02; 95% CI, -0.23 to 0.27, P = 0.87; I^2 = 0%, P = 0.58] (Fig. 6).

3.5.2.3.2 RAP during rest and exercise

Two parallel controlled trials [27–28] involving 54 participants compared INNs and placebo in RAP (mmHg) during rest. High quality results showed INNs significantly reduced RAP compared with placebo [MD, -1.52; 95% CI, -2.36 to -0.68, P = 0.0004; I^2 = 26%, P = 0.25]. Two articles [27–28] involving 54 participants compared INNs and placebo in RAP (mmHg) during exercise and showed a significant reduction in RAP [MD, -3.71; 95% CI, -4.95 to -2.46, P < 0.00001; I^2 = 0%, P = 0.47] (Fig. 6). We could not conduct the Egger’s test for these positive outcomes because of a lack of sufficient articles [34].

3.5.3 Other secondary outcomes

3.5.3.1 Blood pressure (BP)

Four trials [27–30] involving 178 patients compared INNs and placebo in SBP during rest (mmHg). There was a significant reduction of the SBP during rest in the INN groups [SMD, -0.27; 95% CI, -0.51 to -0.04, P = 0.02; I^2 = 0%, P = 0.43]. Two trials [29–30] involving 124 patients compared INNs and placebo in DBP during rest (mmHg). Pooled results showed INNs did not significantly lower DBP during rest compared with placebo [SMD, -0.18; 95% CI, -0.44 to 0.08, P = 0.17; I^2 = 0%, P = 0.68]. Five trials [27–28, 30–31, 33] involving 100 participants compared INNs and placebo in terms of SBP during exercise (mmHg). INNs significantly lowered SBP during exercise compared with placebo [SMD, -0.52; 95% CI, -0.88 to -0.16, P = 0.005; I^2 = 31%, P = 0.22]. Four trials [27, 30–31, 33] involving 74 participants compared INNs and placebo in DBP during exercise (mmHg). There was a significant reduction in DBP during exercise [SMD, -0.81; 95% CI, -1.56 to -0.07, P = 0.03; I^2 = 67%, P = 0.03] (Fig. 7). We conducted Egger's test to determine publication bias. For SBP during rest, there was no publication bias (P = 0.180 > 0.05). The same was found for SBP during exercise (P = 0.05 = 0.05) and DBP during exercise (P = 0.073 > 0.05).

3.5.3.2 PAP during rest and exercise

Two trials [27–28] involving 54 participants compared inorganic nitrite and placebo in terms of PAP (mmHg) during rest and exercise. There was a significant reduction in the two interventions (for PAP during rest [MD, -4.66; 95% CI, -6.46 to -2.86, P < 0.00001; I^2 = 0%, P = 0.61] and for PAP during exercise [MD, -6.96; 95% CI, -9.68 to -4.25, P < 0.00001; I^2 = 6%, P = 0.30]) (Fig. 7). We could not perform Egger's because there were only two articles in analysis.

3.5.3.3 HR during rest and exercise

Three trials [27–28, 32] involving 71 patients compared INNs and placebo in terms of HR (bts/min) during rest. Pooled results showed no significant difference between the two interventions [SMD, 0.21; 95% CI, -0.21 to 0.64, P = 0.32; I^2 = 0%, P = 0.44] (Fig. 7). Six trials [27–28, 30–33] involving 117 participants compared INNs and placebo in HR (bts/min) during exercise. The meta-analysis showed no significant difference [SMD, 0.06; 95% CI, -0.25 to 0.37, P = 0.69; I^2 = 0%, P = 0.89] (Fig. 7).

3.5.3.4 CO during rest and exercise

Three trials [27, 32–33] involving 40 HFpEF patients compared INNs and placebo in terms of CO (L/min) during rest and exercise. Pooled results showed INNs did not significantly improve CO during rest and exercise compared with placebo (for CO during rest [SMD, -0.18; 95% CI, -0.62 to 0.26, P = 0.43; I^2 = 0%, P = 0.89] and for CO during exercise [SMD, 0.52; 95% CI, -0.21 to 1.24, P = 0.16; I^2 = 59%, P = 0.09]) (Fig. 7).

3.5.3.5 PCWP during rest and exercise

Two trials [27–28] involving 54 participants compared inorganic nitrite and placebo in terms of PCWP (mmHg) during rest and exercise. INNs did not significantly lower PCWP during rest and exercise (for PCWP during rest [MD, -3.00; 95% CI, -4.27 to -1.73, P < 0.00001; I^2 = 0%, P = 1.00], and for PCWP during

exercise [MD, -7.7; 95% CI, -10.49 to -4.91, P < 0.00001; I^2 = 8%, P = 0.30]) (Fig. 7). PCWP during rest and exercise just included only two trials and Egger's test was not performed.

3.6 Sensitivity analysis

When studies were removed one by one, the following results remained stable in HFrEF and HFpEF groups: peak power, peak VO_2, VO_2 during rest, Ve/VCO_2 slope, exercise duration, NT-pro-BNP, E/A ratio, E/e' ratio and RAP during exercise, SBP during exercise, DBP during rest, PAP during rest and exercise, HR during rest, CO during rest and exercise, and PCWP during rest and exercise. The RER, SBP during rest and DBP during exercise in HFrEF group, and the HR during exercise in HFpEF were also stable. However, when one study [25] was removed, the significance of HR during exercise changed in HFrEF group. In HFpEF group, it changed in RER when one study [31] was removed. Another study [29] offered inadequate evidence for the unstable outcome of KCCQ score change. When one study [30] was removed, the significance of SBP during rest changed. When anyone study [27 or 30 or 33] was removed, the significance of DBP during exercise also changed. Sensitivity analysis affected the heterogeneity of the results of RER, exercise duration, DBP during exercise, and CO during exercise in HFpEF group..

3.7 Heterogeneity and subgroup analysis of outcomes

Heterogeneity of all outcomes was not significant except CO during exercise and KCCQ score in HFpEF group. We did not conduct subgroup analysis for CO during exercise and KCCQ score because few studies reported.

3.8 Adverse events and assessment of publication bias

Three crossover trials [25, 29, 33] reported adverse events, including headache, palpitations, and other symptoms. Pooled data analysis showed that there was no significant difference in safety between INNs and placebo [RR, 0.74; 95% CI, 0.37 to 1.48, P = 0.40; I^2 = 0%, P = 0.47] (Fig. 8). No outcome indicators contained more than ten relevant studies; therefore, it was unnecessary to analyze publication bias.

4. Discussion

To our knowledge, the present analysis is the first evaluation of the effectiveness and safety of INNs in patients with all types of HF using the most recent RCTs. Because HF is a chronic disease, the intervention time was relatively short, and the intervention measures were stable, clinical trials with crossover design were included. The data of all eight crossover trials were complete. Our meta-analysis demonstrated that, compared with placebo, there is insufficient evidence to prove that INNs improve exercise ability in patients with HFrEF and HFpEF. While in patients with HFpEF, INNs reduced RAP, SBP, PAP, PCWP during rest and exercise and DBP during exercise effectively.

Our finding that there is no clear evidence for improving exercise ability in patients with HF using INNs is consistent with the results of a previous meta-analysis [35]. However, there are some limitations in that study: the included studies rarely evaluated the effectiveness and safety of INNs for HF; some trials were

supported by pharmaceutical manufacturers or written by the same author teams; this may have resulted in bias. There were different routes of nitrate administration, and the included patients all had HFpEF, both of which limit the generalizability of the findings. There were no studies assessing INNs on the impact of hospitalization or mortality in patients with HF.

Because of the lack of large and longitudinal studies, the present meta-analysis has similar limitations; therefore, more studies are needed to validate our findings. We found that INNs were less effective in patients with HFrEF than in those with HFpEF. These two kinds of HF are different in terms of the mechanism during the absorption of NO and reaction of the INNs [26, 36]. Inflammatory reactions caused by various metabolic diseases promote oxidative stress of vascular endothelium in patients with HF [36–38]. The response of HFpEF patients to INNs is more pronounced due to the opposing mechanisms of myocardial remodeling in HFpEF patients [26, 39]. The effect of INN supplementation on BP may also lead to our positive outcomes of BP in HFpEF patients [26]. There was no significant heterogeneity in these outcomes, probably due to the small number of studies.

Some studies [25, 35, 40] showed that inorganic nitrates supplementation improved skeletal muscle strength; however, the present meta-analysis did not show similar results. This discrepancy may be due to the insufficient number of existing RCT, small sample sizes, and large amounts of bias.

VO_2 peak is related to the risk of HF and the cardiac function classification [41–43]. The current guidelines [44] recommend using VO_2 peak to evaluate the improvement of exercise capacity, which is the overall reflection of heart and lung function [45] and is beneficial to HF outcomes. Although few clinical trials [21, 30, 32–33] reported the increase of VO_2 peak after inorganic nitrate intake, the present meta-analysis results did not show the beneficial effect of inorganic nitrate on VO_2 peak. According to the current meta-analysis, there is insufficient evidence to support the use of INNs to improve exercise ability.

Cohort studies showed that, in patients with HF, adverse events such as bleeding and stroke are caused by higher baseline SBP and DBP [46]. Therefore, BP control is an essential part of HF management. Hemodynamic parameters of PAP are associated with adverse clinical events, and PCWP determines the volume reserve in patients with HF [47]. The atrial and ventricular pressure measured by echocardiography indicates cardiac function. RAP reflects the preload of the right ventricle and venous blood volume, which is related to right HF. Although inorganic nitrates did not significantly improve exercise capacity, they did improve SBP, DBP, PAP, RAP, and PCWP during rest and exercise, factors that affect the outcome in patients with HF.

Consistent with our finding, another meta-analysis [48] showed that dietary supplementation of inorganic nitrates in adults reduced SBP, which may be related to nitrates' vasodilator effect; there is no clear evidence of its long-term effectiveness and safety. This is consistent with our results, suggesting that inorganic nitrates reduce BP. Hypertension is associated with an increased risk of HF. Although organic nitrates (as opposed to inorganic nitrates) dilate blood vessels and reduce BP, the side effects of hypotension, headache, and cerebral vascular dilation restrict the use of organic nitrates in patients with

HF [16, 49], and long-term use may further reduce the utilization of NO [50]. There were no significant differences between inorganic nitrate and placebo in adverse events in the present meta-analysis. The evidence to support the clinical use of INNs is insufficient, although it may have potential applications owing to their safety profiles.

HF is a chronic disease, and the long-term outcome depends on long-term follow-up. This follow-up should include measurement of outcome-related indicators of HF in large-sample RCT trials. There are several clinical trials in progress (ClinicalTrials. gov: NCT02713126, NCT02840799, and NCT02918552). Results of these trials are expected to determine the safety and effectiveness of INNs. Although the present meta-analysis results did not show that supplementation with inorganic nitrate improved muscle strength or peak VO_2, studies found that supplementation with inorganic nitrate improves muscle strength and endurance in healthy people [39, 51]. In the included articles in the HFrEF group [19, 25], motor ability improvement was significant. The improvement of hemodynamic results suggests that INNs are helpful to patients with HF. Large-sample clinical trials are needed further to study the effect of INNs on patients with HF.

The establishment of the safety of INNs is critical. Because about three-quarters of inorganic nitrates are first metabolized through the kidney, patients with renal insufficiency require surveillance [52, 53]. Because these products are oral preparations, the effect on the gastrointestinal tract also requires attention. Inhaled forms may also be considered. However, the safety of the inhaled forms [27, 29] has not been demonstrated.

The strength of the current study is that we comprehensively searched all relevant literature in Chinese and English databases based on pooled results of all eligible RCTs assessing the effects of INNs on patients with HF (including HFrEF and HFpEF). We developed a comprehensive search strategy, strictly included the standard RCT, and strictly evaluated the trials' quality. Second, we divided patients into subgroups to determine the various effects of interventions on HF with reduced and preserved ejection fractions. In terms of outcome evaluation, the choice of different calculation models for parallel RCTs and crossover trials was helpful to reduce the errors of the trial outcome. These patients were compared before and after taking inorganic nitrate in crossover trials [33] without randomization and washout phase. We extracted the first phase data for analysis, which had no significant impact on the overall results. The other seven crossover trials [20–21, 25–26, 29, 31–32] explained the washout period, which eliminated the effect of the first stage intervention. Results of sensitivity analysis indicated the robustness of our findings. There was no evidence that INNs improve exercise ability, although our analysis provides the basis for future research.

Although we strictly followed the provisions of PRISMA and Cochrane manuals, there remain some limitations. First, there are always problems in comparisons among RCT because of differences in included patients, the blinding methods used, differences of randomization content, differences of outcome evaluation index, and varying sample sizes. Because of the large number of crossover trials, we used standardized mean difference, which may compromise the inherent heterogeneity. Second, the

number of included studies was limited, and the sample sizes were small. Most studies suffered from the risk of bias, especially performance and detection bias. Therefore, our results should be interpreted with caution. Third, the present meta-analysis only included patients with HFrEF and HFpEF, and patients with heart failure with median ejection fraction were not included. This omission may have affected the generalizability of our findings. Finally, because of the short follow-up periods of the included trials, we could not assess the long-term effects of inorganic nitrate on patients with HF. Further studies assessing the long-term effects of inorganic nitrate on HF are needed.

5. Conclusion

INNs do not improve exercise capacity in patients with HF; however, they improve hemodynamic status, especially in HFpEF patients. Further large and long-term studies are needed to confirm our findings and assess the long-term effects of INNs on HF.

Declarations

Funding

The work was supported by the National Key R&D Program of China (grant number 2018YFC2002502) and the Fundamental Research Funds for the Central public welfare research institutes (ZZ13-YQ-002).

Author contributions

Conceptualization: He Zhang, Yixuan Fan, Hao Xu.

Data curation: He Zhang, Yixuan Fan, Qiuyi Li.

Formal analysis: He Zhang, Yixuan Fan, Zhuo Chen.

Methodology: Yixuan Fan, Jingen Li.

Project administration: Hao Xu.

Supervision: Hao Xu.

Writing - original draft: He Zhang, Yixuan Fan, Anlu Wang, Jingen Li.

Writing - review & editing: He Zhang, Yixuan Fan, Jie Zhang, Hao Xu.

Author Disclosure Statement

No competing financial interests exist.

References

1. Hu shengshou. Summary of cardiovascular health and disease report 2019 in China [J]. Chinese journal of circulation,2020,35(9):833–854.
2. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Shay CM, Spartano NL, Stokes A, Tirschwell DL, VanWagner LB, Tsao CW; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation. 2020 Mar 3;141(9):e139-e596. doi: 10.1161/CIR.0000000000000757.
3. Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, Brosnihan B, Morgan TM, Stewart KP. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA. 2002 Nov 6;288(17):2144–50. doi: 10.1001/jama.288.17.2144.
4. Haykowsky MJ, Kitzman DW. Exercise physiology in heart failure and preserved ejection fraction. Heart Fail Clin. 2014;10(3):445–452. doi:10.1016/j.hfc.2014.04.001.
5. Haykowsky MJ, Tomczak CR, Scott JM, Paterson DI, Kitzman DW. Determinants of exercise intolerance in patients with heart failure and reduced or preserved ejection fraction. J Appl Physiol (1985). 2015 Sep 15;119(6):739 – 44. doi: 10.1152/japplphysiol.00049.2015.
6. Okita K, Kinugawa S, Tsutsui H. Exercise intolerance in chronic heart failure–skeletal muscle dysfunction and potential therapies. Circ J. 2013;77(2):293–300. doi: 10.1253/circj.cj-12-1235.
7. Stamler JS, Meissner G. Physiology of nitric oxide in skeletal muscle. Physiol Rev. 2001 Jan;81(1):209–237. doi: 10.1152/physrev.2001.81.1.209.
8. Rush JW, Denniss SG, Graham DA. Vascular nitric oxide and oxidative stress: determinants of endothelial adaptations to cardiovascular disease and to physical activity. Can J Appl Physiol. 2005 Aug;30(4):442–74. doi: 10.1139/h05-133.
9. Ling WC, Murugan DD, Lau YS, Vanhoutte PM, Mustafa MR. Sodium nitrite exerts an antihypertensive effect and improves endothelial function through activation of eNOS in the SHR. Sci Rep. 2016 Sep 12;6:33048. doi: 10.1038/srep33048.
10. Jädert C, Petersson J, Massena S, Ahl D, Grapensparr L, Holm L, Lundberg JO, Phillipson M. Decreased leukocyte recruitment by inorganic nitrate and nitrite in microvascular inflammation and NSAID-induced intestinal injury. Free Radic Biol Med. 2012 Feb 1;52(3):683–692. doi: 10.1016/j.freeradbiomed.2011.11.018.
11. Tang L, Wang H, Ziolo MT. Targeting NOS as a therapeutic approach for heart failure. Pharmacol Ther. 2014 Jun;142(3):306–15. doi: 10.1016/j.pharmthera.2013.12.013.
12. Münzel T, Gori T, Keaney JF, Jr, Maack C, Daiber A. Pathophysiological role of oxidative stress in systolic and diastolic heart failure and its therapeutic implications. Eur Heart J. 2015 7;36:2555–2564. doi: 10.1093/eurheartj/ehv305.

13. Münzel T, Daiber A, Gori T. Nitrate therapy: new aspects concerning molecular action and tolerance. Circulation. 2011 May 17;123(19):2132-44. doi: 10.1161/CIRCULATIONAHA.110.981407.
14. Schwartzenberg S, Redfield MM, From AM, Sorajja P, Nishimura RA, Borlaug BA. Effects of vasodilation in heart failure with preserved or reduced ejection fraction implications of distinct pathophysiologies on response to therapy. J Am Coll Cardiol. 2012 Jan 31;59(5):442 – 51. doi: 10.1016/j.jacc.2011.09.062.
15. Chirinos JA, Zamani P. The Nitrate-Nitrite-NO Pathway and Its Implications for Heart Failure and Preserved Ejection Fraction. Curr Heart Fail Rep. 2016 Feb;13(1):47–59. doi: 10.1007/s11897-016-0277-9.
16. Redfield MM, Anstrom KJ, Levine JA, Koepp GA, Borlaug BA, Chen HH, LeWinter MM, Joseph SM, Shah SJ, Semigran MJ, Felker GM, Cole RT, Reeves GR, Tedford RJ, Tang WH, McNulty SE, Velazquez EJ, Shah MR, Braunwald E; NHLBI Heart Failure Clinical Research Network. Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2015 Dec 10;373(24):2314–24. doi: 10.1056/NEJMoa1510774.
17. Hord NG, Tang Y, Bryan NS. Food sources of nitrates and nitrites: the physiologic context for potential health benefits. Am J Clin Nutr. 2009 Jul;90(1):1–10. doi: 10.3945/ajcn.2008.27131.
18. Ferguson SK, Holdsworth CT, Colburn TD, Wright JL, Craig JC, Fees A, Jones AM, Allen JD, Musch TI, Poole DC. Dietary nitrate supplementation: impact on skeletal muscle vascular control in exercising rats with chronic heart failure. J Appl Physiol (1985). 2016 Sep 1;121(3):661-9. doi: 10.1152/japplphysiol.00014.2016.
19. Bhushan S, Kondo K, Polhemus DJ, Otsuka H, Nicholson CK, Tao YX, Huang H, Georgiopoulou VV, Murohara T, Calvert JW, Butler J, Lefer DJ. Nitrite therapy improves left ventricular function during heart failure via restoration of nitric oxide-mediated cytoprotective signaling. Circ Res. 2014 Apr 11;114(8):1281-91. doi: 10.1161/CIRCRESAHA.114.301475.
20. Hirai DM, Zelt JT, Jones JH, Castanhas LG, Bentley RF, Earle W, Staples P, Tschakovsky ME, McCans J, O'Donnell DE, Neder JA. Dietary nitrate supplementation and exercise tolerance in patients with heart failure with reduced ejection fraction. Am J Physiol Regul Integr Comp Physiol. 2017 Jan 1;312(1):R13-R22. doi: 10.1152/ajpregu.00263.2016.
21. Coggan AR, Broadstreet SR, Mahmood K, Mikhalkova D, Madigan M, Bole I, Park S, Leibowitz JL, Kadkhodayan A, Thomas DP, Thies D, Peterson LR. Dietary Nitrate Increases VO_2 peak and Performance but Does Not Alter Ventilation or Efficiency in Patients With Heart Failure With Reduced Ejection Fraction. J Card Fail. 2018 Feb;24(2):65–73. doi: 10.1016/j.cardfail.2017.09.004.
22. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020.
23. Cheung MW, Vijayakumar R. A Guide to Conducting a Meta-Analysis. Neuropsychol Rev. 2016 Jun;26(2):121–8. doi: 10.1007/s11065-016-9319-z.

24. Lee YH. An overview of meta-analysis for clinicians. Korean J Intern Med. 2018 Mar;33(2):277–283. doi: 10.3904/kjim.2016.195.
25. Coggan AR, Leibowitz JL, Spearie CA, Kadkhodayan A, Thomas DP, Ramamurthy S, Mahmood K, Park S, Waller S, Farmer M, Peterson LR. Acute Dietary Nitrate Intake Improves Muscle Contractile Function in Patients With Heart Failure: A Double-Blind, Placebo-Controlled, Randomized Trial. Circ Heart Fail. 2015 Sep;8(5):914–20. doi: 10.1161/CIRCHEARTFAILURE.115.002141.
26. Woessner MN, Neil C, Saner NJ, Goodman CA, McIlvenna LC, Ortiz de Zevallos J, Garnham A, Levinger I, Allen JD. Effect of inorganic nitrate on exercise capacity, mitochondria respiration, and vascular function in heart failure with reduced ejection fraction. J Appl Physiol (1985). 2020 May 1;128(5):1355–1364. doi: 10.1152/japplphysiol.00850.2019.
27. Borlaug BA, Koepp KE, Melenovsky V. Sodium Nitrite Improves Exercise Hemodynamics and Ventricular Performance in Heart Failure With Preserved Ejection Fraction. J Am Coll Cardiol. 2015 Oct 13;66(15):1672-82. doi: 10.1016/j.jacc.2015.07.067.
28. Borlaug BA, Melenovsky V, Koepp KE. Inhaled Sodium Nitrite Improves Rest and Exercise Hemodynamics in Heart Failure With Preserved Ejection Fraction. Circ Res. 2016 Sep 16;119(7):880–6. doi: 10.1161/CIRCRESAHA.116.309184.
29. Borlaug BA, Anstrom KJ, Lewis GD, Shah SJ, Levine JA, Koepp GA, Givertz MM, Felker GM, LeWinter MM, Mann DL, Margulies KB, Smith AL, Tang WHW, Whellan DJ, Chen HH, Davila-Roman VG, McNulty S, Desvigne-Nickens P, Hernandez AF, Braunwald E, Redfield MM; National Heart, Lung, and Blood Institute Heart Failure Clinical Research Network. Effect of Inorganic Nitrite vs Placebo on Exercise Capacity Among Patients With Heart Failure With Preserved Ejection Fraction: The INDIE-HFpEF Randomized Clinical Trial. JAMA. 2018 Nov 6;320(17):1764–1773. doi: 10.1001/jama.2018.14852.
30. Shaltout HA, Eggebeen J, Marsh AP, Brubaker PH, Laurienti PJ, Burdette JH, Basu S, Morgan A, Dos Santos PC, Norris JL, Morgan TM, Miller GD, Rejeski WJ, Hawfield AT, Diz DI, Becton JT, Kim-Shapiro DB, Kitzman DW. Effects of supervised exercise and dietary nitrate in older adults with controlled hypertension and/or heart failure with preserved ejection fraction. Nitric Oxide. 2017 Sep 30;69:78–90. doi: 10.1016/j.niox.2017.05.005.
31. Eggebeen J, Kim-Shapiro DB, Haykowsky M, Morgan TM, Basu S, Brubaker P, Rejeski J, Kitzman DW. One Week of Daily Dosing With Beetroot Juice Improves Submaximal Endurance and Blood Pressure in Older Patients With Heart Failure and Preserved Ejection Fraction. JACC Heart Fail. 2016 Jun;4(6):428–37. doi: 10.1016/j.jchf.2015.12.013.
32. Zamani P, Rawat D, Shiva-Kumar P, Geraci S, Bhuva R, Konda P, Doulias PT, Ischiropoulos H, Townsend RR, Margulies KB, Cappola TP, Poole DC, Chirinos JA. Effect of inorganic nitrate on exercise capacity in heart failure with preserved ejection fraction. Circulation. 2015 Jan 27;131(4):371 – 80; discussion 380. doi: 10.1161/CIRCULATIONAHA.114.012957. Epub 2014 Dec 22.

33. Zamani P, Tan V, Soto-Calderon H, Beraun M, Brandimarto JA, Trieu L, Varakantam S, Doulias PT, Townsend RR, Chittams J, Margulies KB, Cappola TP, Poole DC, Ischiropoulos H, Chirinos JA. Pharmacokinetics and Pharmacodynamics of Inorganic Nitrate in Heart Failure With Preserved Ejection Fraction. Circ Res. 2017 Mar 31;120(7):1151–1161. doi: 10.1161/CIRCRESAHA.116.309832.
34. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol. 2000 Nov;53(11):1119-29. doi: 10.1016/s0895-4356(00)00242-0. PMID: 11106885.
35. Gui Y, Chen J, Hu J, Ouyang M, Deng L, Liu L, Sun K, Tang Y, Xiang Q, Xu J, Zhu L, Peng Z, Zou P, Li B, Zheng Z, Xu D. Efficacy and Safety of Inorganic Nitrate Versus Placebo Treatment in Heart Failure with Preserved Ejection Fraction. Cardiovasc Drugs Ther. 2020 Aug;34(4):503–513. doi: 10.1007/s10557-020-06980-4.
36. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013;62(4):263–71. Epub 2013/05/21. doi: 10.1016/j.jacc.2013.02.092. PubMed PMID: 23684677.
37. Franssen C, Chen S, Unger A, Korkmaz HI, De Keulenaer GW, Tschope C, et al. Myocardial Microvascular Inflammatory Endothelial Activation in Heart Failure With Preserved Ejection Fraction. JACC Heart Fail. 2016;4(4):312–24. Epub 2015/12/20. doi: 10.1016/j.jchf.2015.10.007. PubMed PMID: 26682792.
38. Borlaug BA, Olson TP, Lam CS, Flood KS, Lerman A, Johnson BD, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2010;56(11):845–54. Epub 2010/09/04. doi: 10.1016/j.jacc.2010.03.077. PubMed PMID: 20813282; PubMed Central PMCID: PMCPMC2950645.
39. Reddy YNV, Andersen MJ, Obokata M, Koepp KE, Kane GC, Melenovsky V, et al. Arterial Stiffening With Exercise in Patients With Heart Failure and Preserved Ejection Fraction. J Am Coll Cardiol. 2017;70(2):136–48. Epub 2017/07/08. doi: 10.1016/j.jacc.2017.05.029. PubMed PMID: 28683960; PubMed Central PMCID: PMCPMC5520668.
40. San Juan AF, Dominguez R, Lago-Rodríguez Á, Montoya JJ, Tan R, Bailey SJ. Effects of Dietary Nitrate Supplementation on Weightlifting Exercise Performance in Healthy Adults: A Systematic Review. Nutrients. 2020 Jul 26;12(8):2227. doi: 10.3390/nu12082227.
41. Coggan AR, Broadstreet SR, Mikhalkova D, Bole I, Leibowitz JL, Kadkhodayan A, Park S, Thomas DP, Thies D, Peterson LR. Dietary nitrate-induced increases in human muscle power: high versus low responders. Physiol Rep. 2018 Jan;6(2):e13575. doi: 10.14814/phy2.13575.
42. Malhotra R, Bakken K, D'Elia E, Lewis GD. Cardiopulmonary Exercise Testing in Heart Failure. JACC Heart Fail. 2016 Aug;4(8):607–16. doi: 10.1016/j.jchf.2016.03.022.
43. Weber KT, Kinasewitz GT, Janicki JS, Fishman AP. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. Circulation. 1982 Jun;65(6):1213–23. doi: 10.1161/01.cir.65.6.1213.

44. Janicki JS, Weber KT, McElroy PA. Use of the cardiopulmonary exercise test to evaluate the patient with chronic heart failure. Eur Heart J. 1988 Jun;9 Suppl H:55 – 8. doi: 10.1093/eurheartj/9.suppl_h.55.
45. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Rev Esp Cardiol (Engl Ed). 2016 Dec;69(12):1167. English, Spanish. doi: 10.1016/j.rec.2016.11.005.
46. Santoro C, Sorrentino R, Esposito R, Lembo M, Capone V, Rozza F, Romano M, Trimarco B, Galderisi M. Cardiopulmonary exercise testing and echocardiographic exam: an useful interaction. Cardiovasc Ultrasound. 2019 Dec 3;17(1):29. doi: 10.1186/s12947-019-0180-0.
47. Lip GY, Skjøth F, Overvad K, Rasmussen LH, Larsen TB. Blood pressure and prognosis in patients with incident heart failure: the Diet, Cancer and Health (DCH) cohort study. Clin Res Cardiol. 2015 Dec;104(12):1088–96. doi: 10.1007/s00392-015-0878-4.
48. Maron BA, Kovacs G, Vaidya A, Bhatt DL, Nishimura RA, Mak S, Guazzi M, Tedford RJ. Cardiopulmonary Hemodynamics in Pulmonary Hypertension and Heart Failure: JACC Review Topic of the Week. J Am Coll Cardiol. 2020 Dec 1;76(22):2671–2681. doi: 10.1016/j.jacc.2020.10.007.
49. Siervo M, Lara J, Ogbonmwan I, Mathers JC. Inorganic nitrate and beetroot juice supplementation reduces blood pressure in adults: a systematic review and meta-analysis. J Nutr. 2013 Jun;143(6):818–26. doi: 10.3945/jn.112.170233.49
50. Zamani P, Akers S, Soto-Calderon H, Beraun M, Koppula MR, Varakantam S, Rawat D, Shiva-Kumar P, Haines PG, Chittams J, Townsend RR, Witschey WR, Segers P, Chirinos JA. Isosorbide Dinitrate, With or Without Hydralazine, Does Not Reduce Wave Reflections, Left Ventricular Hypertrophy, or Myocardial Fibrosis in Patients With Heart Failure With Preserved Ejection Fraction. J Am Heart Assoc. 2017 Feb 20;6(2):e004262. doi: 10.1161/JAHA.116.004262.
51. Gori T, Mak SS, Kelly S, Parker JD. Evidence supporting abnormalities in nitric oxide synthase function induced by nitroglycerin in humans. J Am Coll Cardiol. 2001 Oct;38(4):1096–101. doi: 10.1016/s0735-1097(01)01510-8.
52. Ranchal-Sanchez A, Diaz-Bernier VM, De La Florida-Villagran CA, Llorente-Cantarero FJ, Campos-Perez J, Jurado-Castro JM. Acute Effects of Beetroot Juice Supplements on Resistance Training: A Randomized Double-Blind Crossover. Nutrients. 2020 Jun 28;12(7):1912. doi: 10.3390/nu12071912.
53. Lundberg JO, Weitzberg E, Gladwin MT. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. Nat Rev Drug Discov. 2008 Feb;7(2):156–67. doi: 10.1038/nrd2466.
54. Ivy JL. Inorganic Nitrate Supplementation for Cardiovascular Health. Methodist Debakey Cardiovasc J. 2019 Jul-Sep;15(3):200–206. doi: 10.14797/mdcj-15-3-200.

Table

Table 1 is available in the Supplementary Files section.

Figures

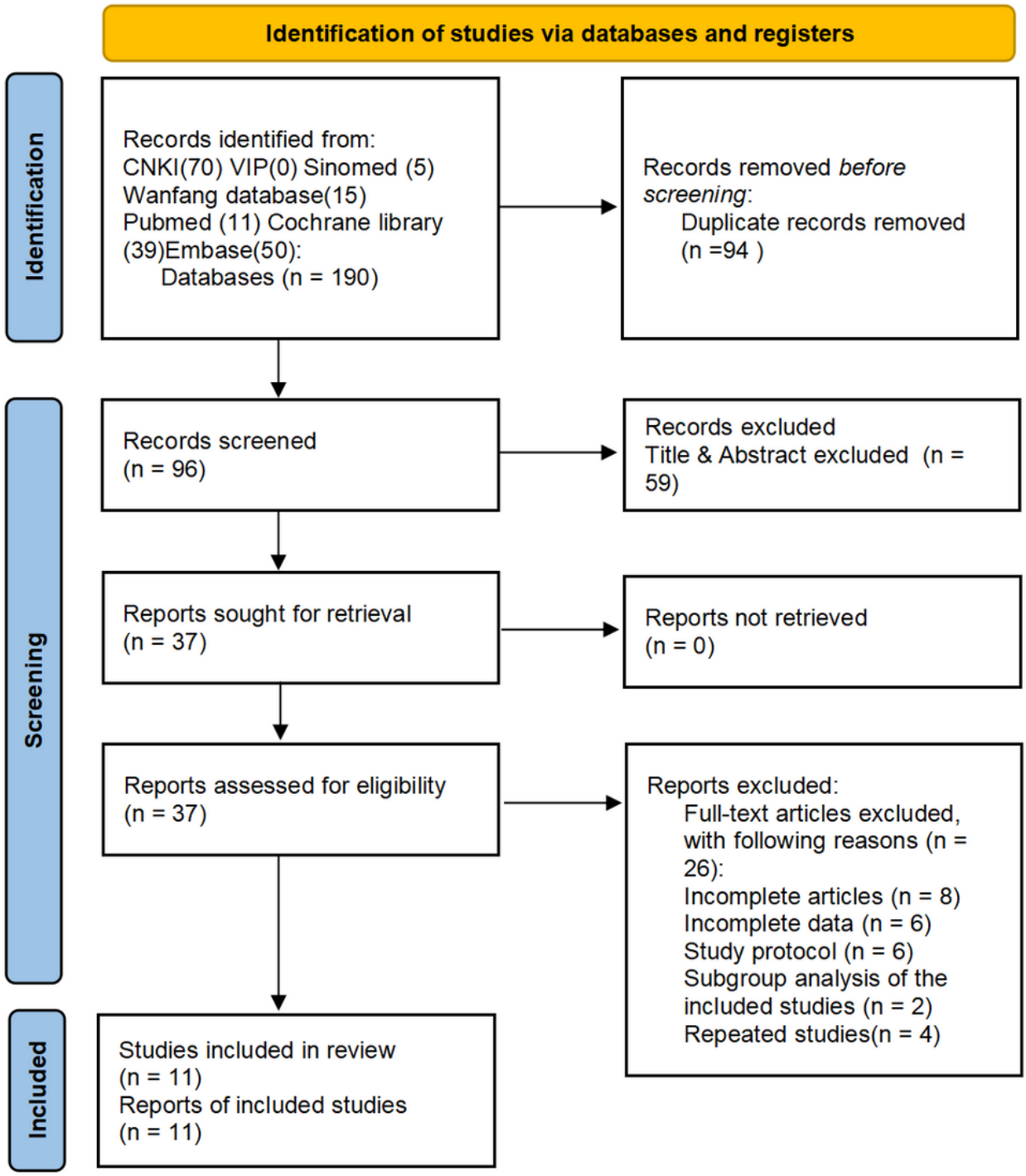
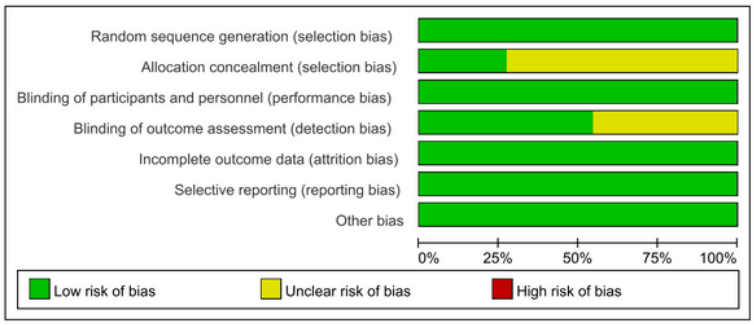


Figure 1

PRISMA 2020 Flow Diagram

A



B

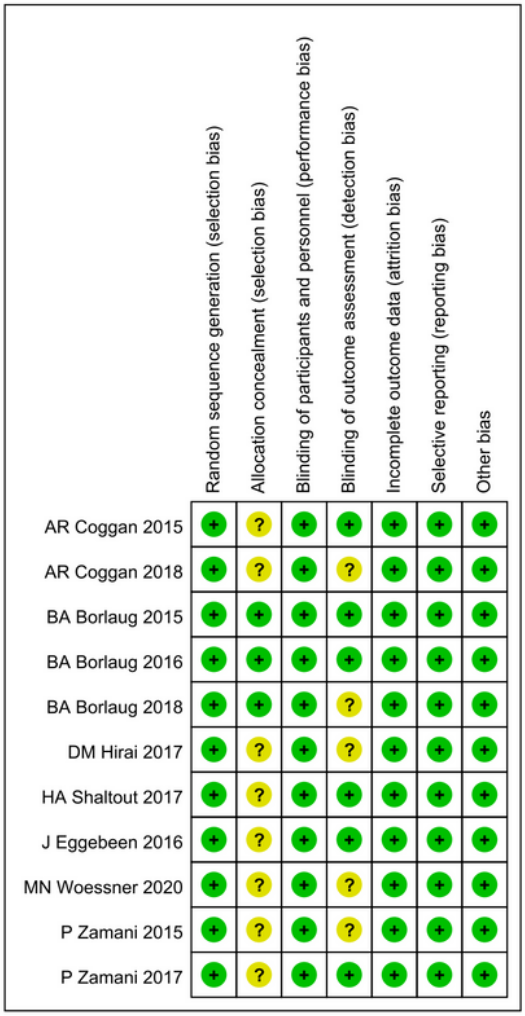


Figure 2

Graph of bias risk (a) and summary of bias risk (b).

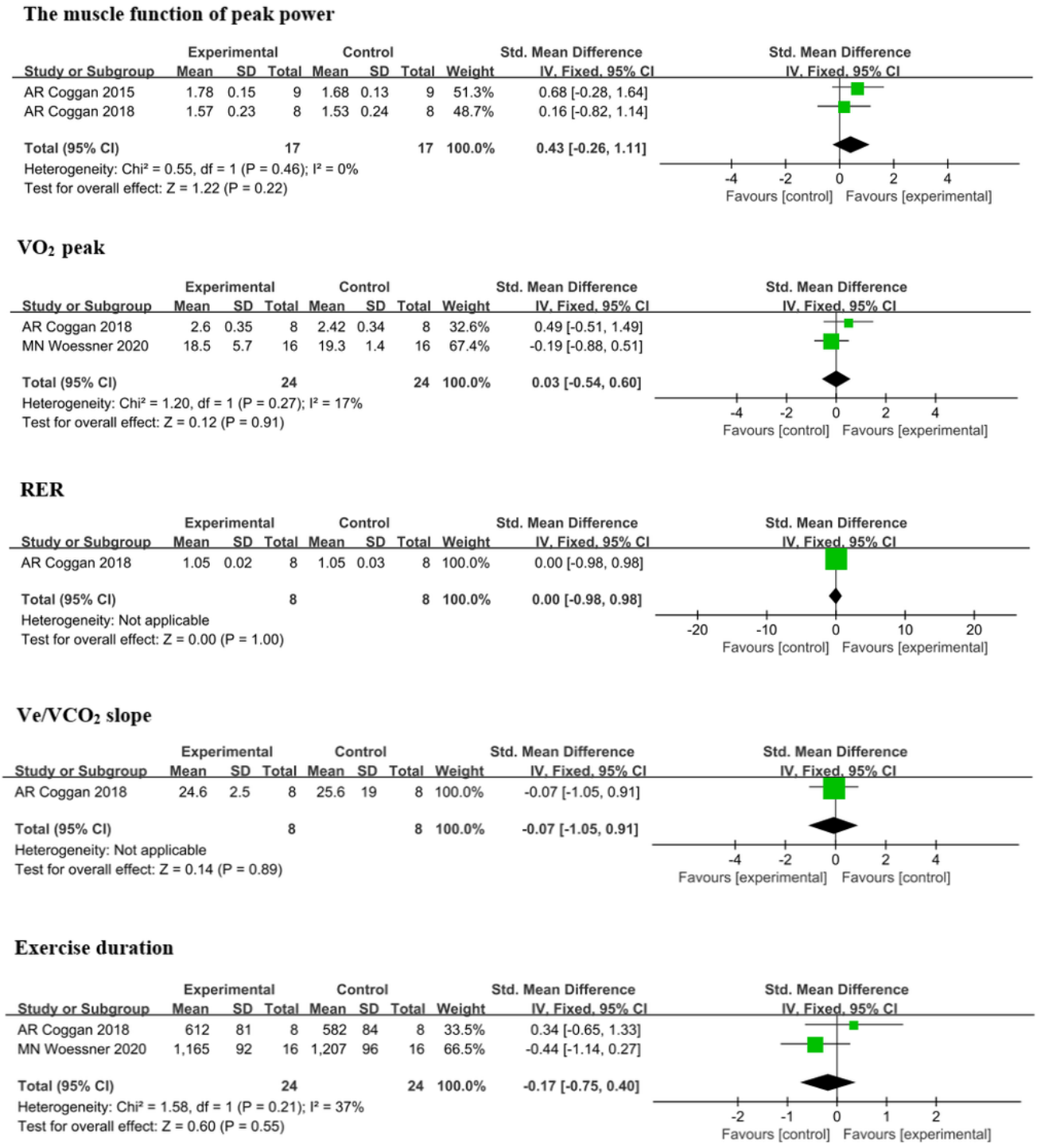
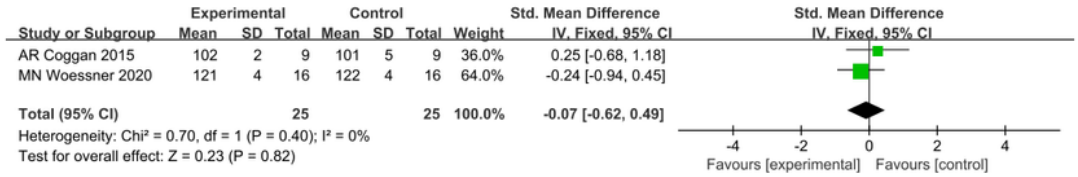


Figure 3

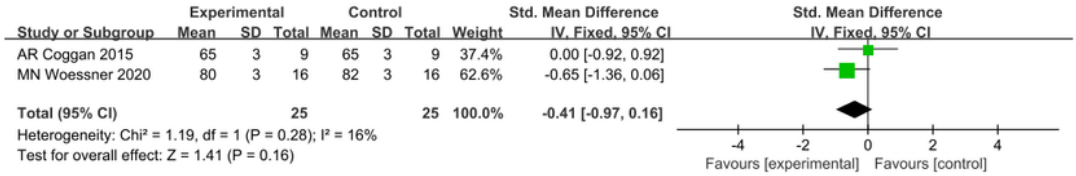
Forest plot showing effect of INNs and placebo on peak power, VO_2 peak, RER, Ve/VCO_2 slope and exercise duration in HFrEF.

BP

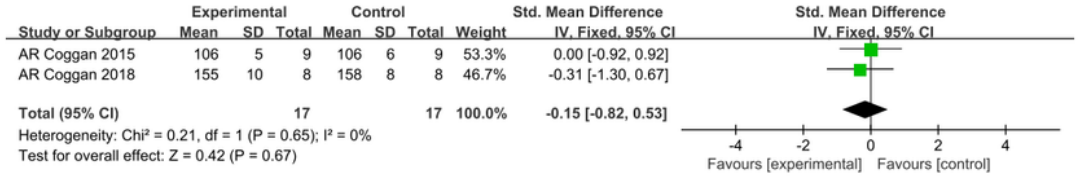
SBP during rest



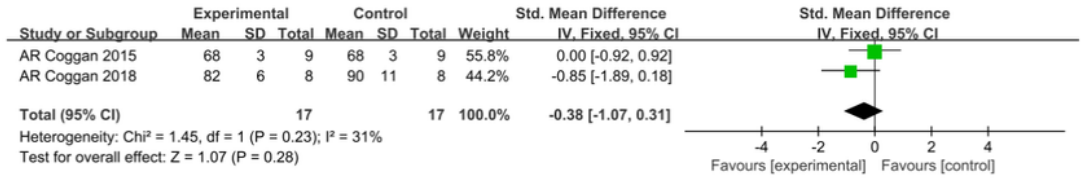
DBP during rest



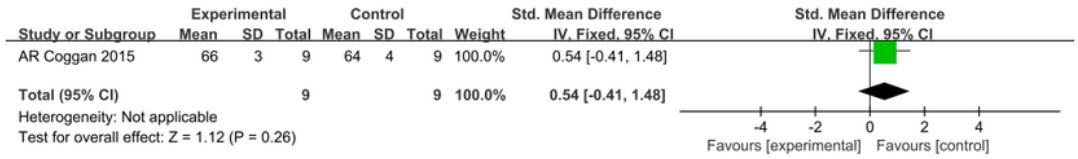
SBP during exercise



DBP during exercise



HR during rest



HR during exercise

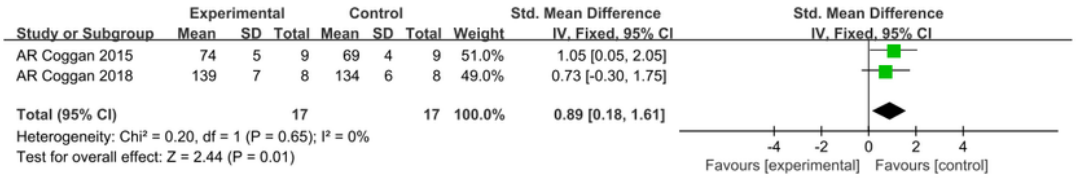


Figure 4

Forest plot showing effect of INNs and placebo on BP, HR during rest and exercise in HFrEF.

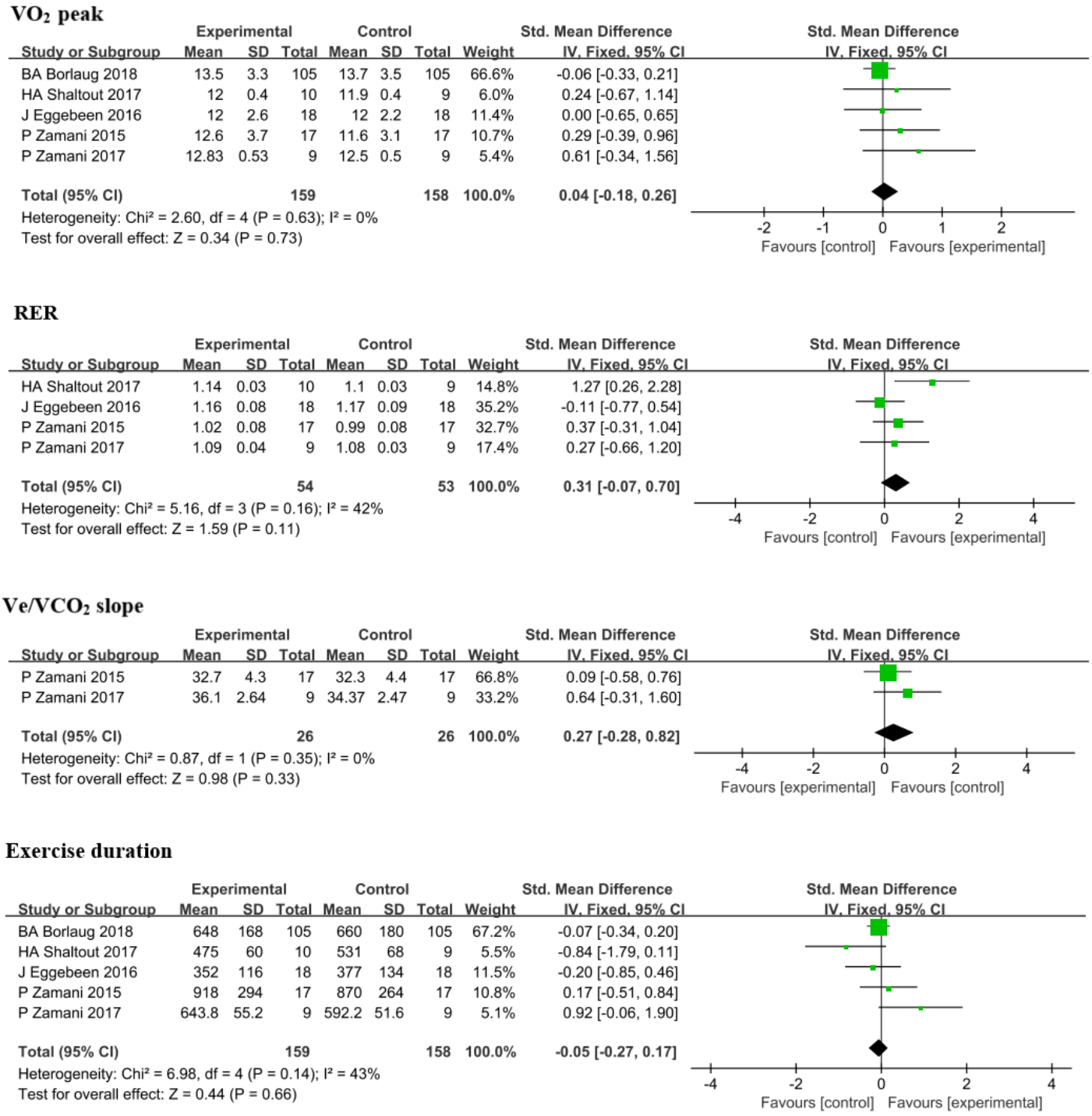


Figure 5

Forest plot showing effect of INNs and placebo on VO_2 peak, RER, Ve/VCO_2 slope and exercise duration in HFpEF.

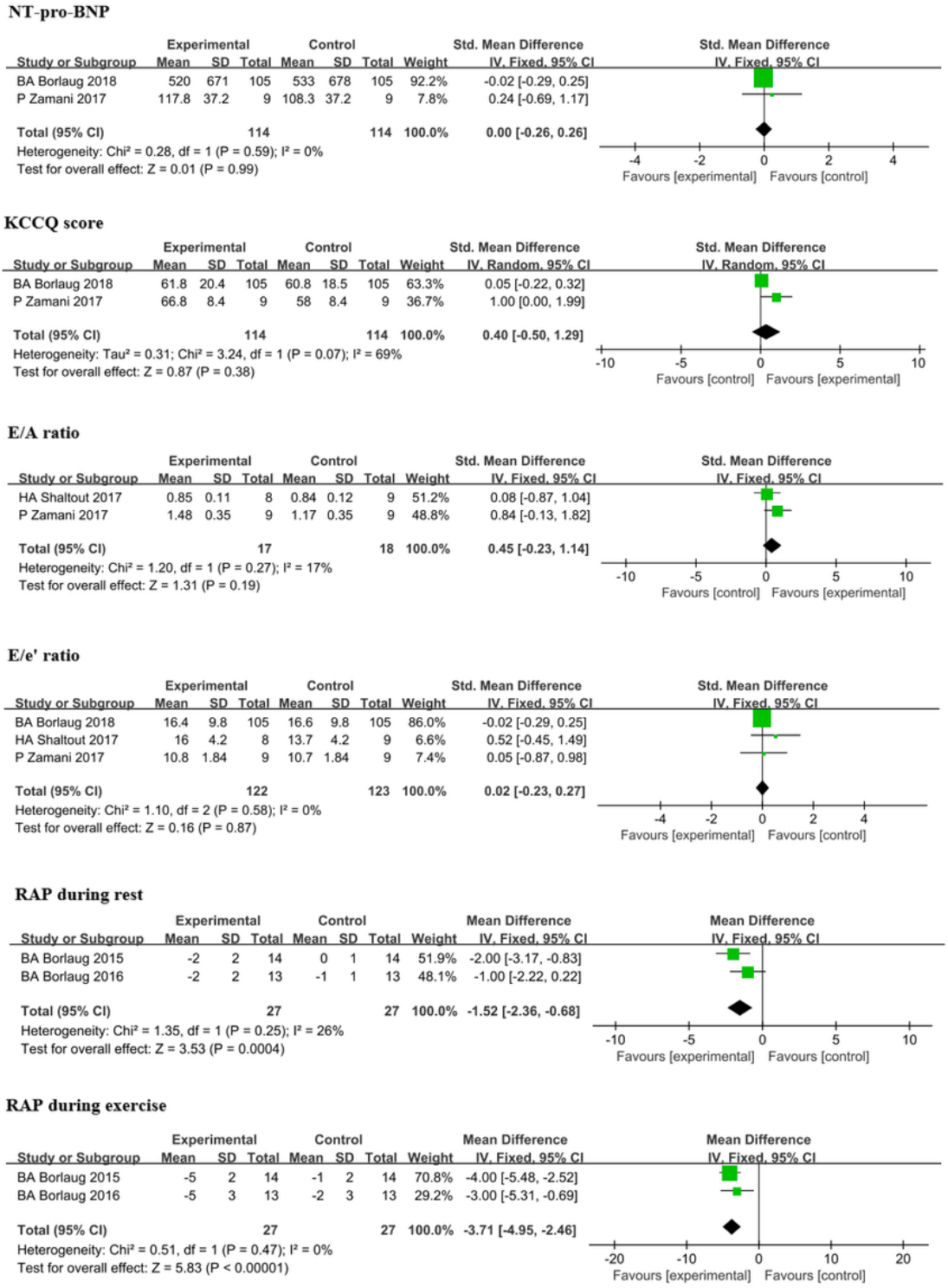


Figure 6

Forest plot showing effect of INNs and placebo on NT-pro-BNP, KCCQ score, E/A ratio, E/e' ratio, RAP during rest and exercise in HFpEF.

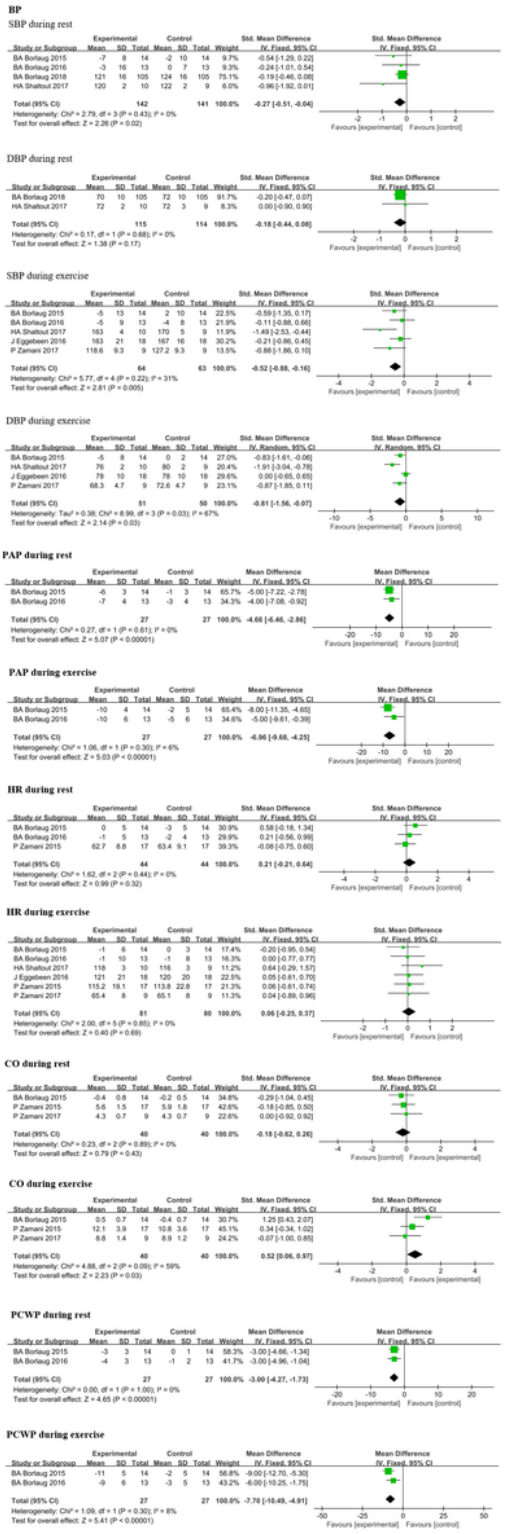


Figure 7

Forest plot showing effect of inorganic nitrate or nitrite and placebo on BP, PAP, HR, CO and PCWP during rest and exercise in HFpEF.

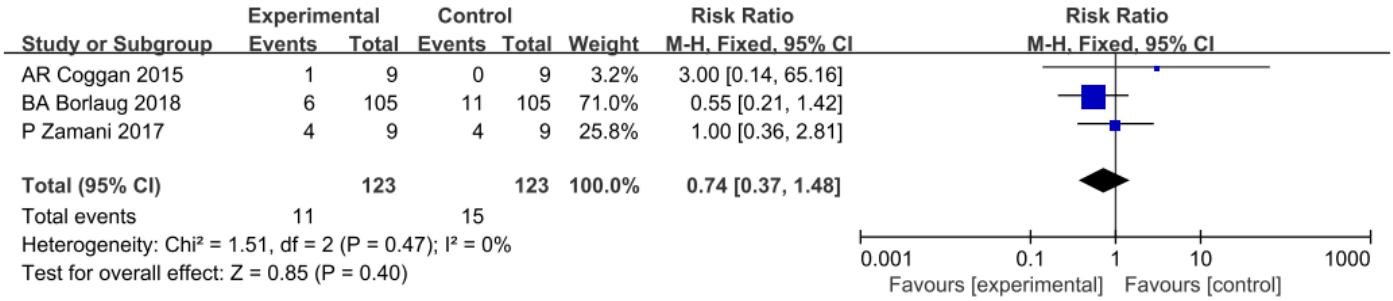


Figure 8

Forest plot showing the incidence of adverse events in the INNs and placebo group.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Datasheet1.docx
- Datasheet2.docx
- Datasheet3.docx
- Table1.docx