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REVIEW

Oral iron supplementation in patients with heart failure: a systematic review and meta-analysis

Zhiping Song[1†], Mingyang Tang[2†], Gang Tang[2†], Guoqi Fu[2], Dengke Ou[2], Fengyou Yao[2], Xingzhi Hou[1*] and Denghong Zhang[2*]

[1]*Department of Cardiovascular Medicine, Yuechi County People's Hospital, Guang'an, China; and* [2]*Geriatric Diseases Institute of Chengdu / Cancer Prevention and Treatment Institute of Chengdu, Department of Cardiology, Chengdu Fifth People's Hospital (The Second Clinical Medical College, Affiliated Fifth People's Hospital of Chengdu University of Traditional Chinese Medicine), Chengdu, China*

Abstract

Aims This review aimed to assess whether oral iron supplementation in a chronic heart failure (HF) population with iron deficiency (ID) or mild anaemia is safe and effective according to evidence-based medicine.

Methods We retrieved 1803 records from the PubMed, Embase, and the Cochrane Library databases from 1 January 1991 to 15 September 2021. The clinical outcome of oral iron supplementation for ID anaemia in patients with HF was the primary endpoint. The primary safety measures included adverse events and all-cause mortality, and efficacy measures included transferrin saturation (Tsat), ferritin levels, and the 6-min walk test (6MWT). The rate ratio (RR) was used to pool the efficacy measures.

Results Five randomized controlled trials that compared oral iron treatment for patients with the placebo group and included a combined total of 590 participants were analysed. No significant difference was found in all-cause death between oral iron treatment and placebo groups (RR = 0.77; 95% confidence intervals (CI), 0.46–1.29, Z = 0.98; P = 0.33). However, adverse events were not significantly higher in the iron treatment group (RR = 0.83; 95% CI, 0.60–1.16, Z = 1.07; P = 0.28). In addition, ferritin levels and Tsat were slightly increased after iron complex administration in patients with HF but were not statistically significant (ferritin: mean difference [MD] = 2.70, 95% CI, –2.41 to 7.81, Z = 1.04; P = 0.30; Tsat: MD = 27.42, 95% CI, –4.93 to 59.78, Z = 1.66; P = 0.10). No significant difference was found in exercise capacity, as indicated by the 6MWT results (MD = 59.60, 95% CI, –17.89 to 137.08, Z = 1.51; P = 0.13). We also analysed two non-randomized controlled trials with follow-up results showing that oral iron supplementation increased serum iron levels (MD = 28.87, 95% CI, 1.62–56.12, Z = 2.08; P = 0.04).

Conclusions Based on the current findings, oral iron supplementation can increase serum iron levels in patients with HF and ID or mild anaemia but does not improve Tsat and 6MWT. In addition, oral iron supplementation is relatively safe.

Keywords Heart failure; Oral iron; Iron deficiency; Anaemia; Efficacy; Safety

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**Correspondence to: Denghong Zhang, The Fifth People's Hospital of Chengdu, 33 Mashi Street, Wenjiang District, Chengdu 611100, China. Telephone: +86 18980705541. Email: 64518190@qq.com;*
Xingzhi Hou, Department of Cardiovascular Medicine, Yuechi County People's Hospital, 22 East Section of Jianshe Road, Yuechi County, Guang'an 638300, China. Email: 344179697@qq.com
† Contributed equally to the manuscript.

Introduction

Heart failure (HF) is a chronic disabling syndrome associated with a lower quality of life and shorter longevity, which could be described as a 'malignant condition' owing to its poor prognosis[1,2] and a 10% prevalence in people aged ≥65 years,[3,4] resulting in high mortality and a huge social burden.[5] Approximately 30–50% of stable patients with HF have iron deficiency (ID) or anaemia during the remainder of life,[6] which is an independent risk factor for patients with HF. ID can further reduce functional capacity, impair the quality of life, and ultimately increase the re-hospitalization rate and economic costs.[7–9] Therefore, the impact of iron treatment on patients with HF and ID or anaemia would be of clinical interest.

Iron supplementation is a better option for patients with HF and anaemia. Recent randomized controlled trials (RCTs) and meta-analyses have shown that intravenous iron administration contributes to increased iron bioavailability and exercise capacity, as well as decreased re-hospitalization.[10–13] However, intravenous iron is relatively expensive and inconvenient to administer at scale for non-hospitalized patients, particularly in many countries with limited healthcare resources.[14–16] Furthermore, the safety of intravenous iron is unclear. In contrast, oral iron supplementation is easily available and more economic. Thus, clinicians often recommend oral iron. The disadvantages of intravenous iron place oral iron as a good alternative therapeutic approach. Nevertheless, absorption problems with oral administration have impeded its widespread use.

The safety of oral iron remains to be established, as gastrointestinal side effects have been reported. Meanwhile, several clinical studies have inconsistent results about oral administration.[14,17–19] Partial clinical studies demonstrate that oral iron therapy can elevate haematological parameters and improve functional capacity,[14,19,20] whereas recent studies report that it is ineffective in improving cardiac function.[21] Two multicentre, double-blinded RCTs, IRON-HF and IRONOUT, have demonstrated that oral iron supplementation failed to raise the peak volume of oxygen consumption (VO_2) and the distance in the 6-min walk test (6MWT) compared with placebo, which suggests against oral iron supplementation in patients with HF with ID or mild anaemia.[16,17] Hence, we conducted a meta-analysis to establish the safety and efficacy of oral iron supplementation in the chronic HF population with ID or mild anaemia safe and effective.

Methods

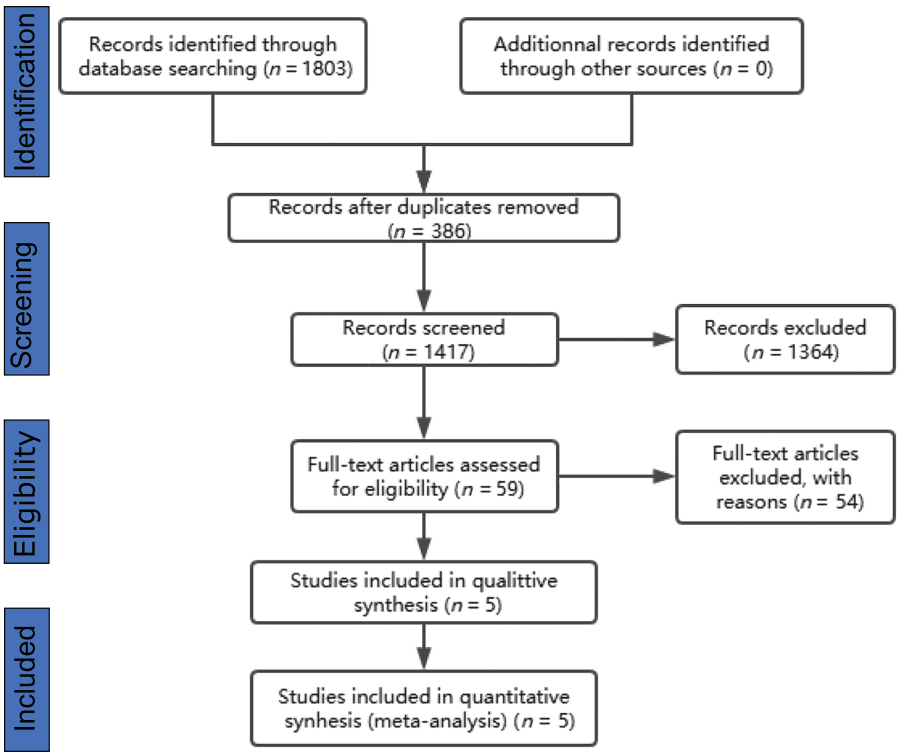
Data sources and search strategy

A literature search was conducted on the Cochrane Library, PubMed, and Embase databases. The Medical Subject Headings keywords and free words used for the search were 'anaemia' and 'heart failure'. Two researchers independently performed the search. When disparities occurred, consensus was reached through discussion and consultation. A flow chart of the literature search is shown in *Figure 1*.

Inclusion and exclusion criteria

Using the PICO model,[22] the potential clinical trials that met the following criteria were considered for inclusion in the

Figure 1 The clinical studies' selection process was presented in flow chart.



meta-analysis: (i) all symptomatic stages of HF [New York Heart Association (NYHA) Classes II–IV, with ejection fraction (LVEF) < 50%] with ID or anaemia (≥18 years old), (ii) oral iron administration to patients with HF, (iii) oral placebo or blank for control group, and (iv) evaluation of efficacy and safety of oral iron supplementation. The exclusion criteria were as follows: (i) studies on other diseases like chronic kidney disease, (ii) intravenous iron intervention or erythropoietin (EPO) combination treatment, and (iii) other research types, for example, retrospective study, review, systematic review, and meta-analysis.

Data extraction

The following data were independently extracted by two cardiologists: (i) population characteristics, including the number of participants, age, and sex; (ii) drug types, dosage, treatment duration, and the duration of follow-up; and (iii) the evaluation of results. When discrepancies occurred between the two cardiologists and could not be resolved, statistics experts were consulted or the original authors were sought for intervention by e-mail. In the process, a third reviewer supervised the work and censored the data to minimize mistakes and missing crucial information as much as possible.

Quality assessment

The risk of bias in this meta-analysis was assessed using the Cochrane Collaboration's tool.[23] Based on the standards specified in the manual, we graded each part as low risk for bias, unclear risk if lacking information or uncertain over the potential for bias, and high risk for bias. Furthermore, we assessed trials for methodological quality and examined bias for the following: selection bias, random sequence generation and allocation concealment; performance bias, blinding of participants and researchers; detection bias, blinding of outcome assessment; and attrition bias, incomplete outcome data, and other biases.[24]

Statistical analysis

Data analysis was performed using Review Manager Version 5.3 software. The continuous variables, namely, ferritin level, transferrin saturation (Tsat), and 6MWT distance, were analysed by calculating the mean difference (MD) with standard deviation (SD) of the mean. When the sample mean and SD could not be directly obtained, other statistical methods were applied to estimate the approximate effect sizes.[25] Dichotomous data were analysed using the rate ratio (RR), and each result was expressed with 95% confidence interval. Statistical heterogeneity was quantified via the I^2 statistic. An $I^2 > 50\%$ or $P < 0.1$ indicated significant heterogeneity. We used the random-effects model; otherwise, the fixed-effects model was applied. Sensitivity analysis was performed to estimate the statistical effect value with the addition of two studies. $P < 0.05$ was considered statistically significant.

Results

Article selection process

The article selection process is presented in *Figure 1*. A total of 1803 records were retrieved by electronic database search. After removing duplicates, 1417 records were included. After skimming the titles and abstracts, we removed 1364 studies that were irrelevant to our research topic. Subsequently, 59 potentially eligible studies were identified and recaptured for full-text scanning, but 54 articles did not match the inclusion criteria. Ultimately, five RCTs on oral iron administration to patients with HF with ID or mild anaemia were included in the meta-analysis.[16,17,20,21,26]

Patient baseline characteristics

The baseline characteristics are summarized in *Table 1*. A total of 590 participants were included, with the age ranging from 18 to 75 years and the duration of follow-up ranging from 8 to 26 weeks. All patients underwent standard HF therapy, with the treatment group placed under oral iron therapy, whereas the control group was given placebo or blank. Ferrous sulfate and polysaccharide iron complex were administered with the dose varying from 150 to 350 mg. All patients had established chronic HF with LVEF < 50% and NYHA Classes II–IV. ID or mild anaemia was diagnosed based on a haemoglobin level of 8–15 g/dL, ferritin <100 ng/mL or between 100 and 300 mg/L, and Tsat <20%.

Risk of bias assessment

We expressed the quality of each risk of bias item presented as percentages based on the Cochrane risk of bias assessment manuals. Briefly, the five studies underwent random sequence generation. Only one trial had reported adequate allocation. Furthermore, one trial did not use blinding, whereas two trials were double-blinded, one of which had merely completed a blinded assessment of the outcomes. In addition, two trials had incomplete outcome data, and selective reporting was identified. No other significant biases were noted during quality assessment (*Figure 2*).

Table 1 The baseline characteristics of the studies included are presented

Study	Area	Female, total	Age (y)	EF; NYHA	Follow-up (w)	Drug; dosage	Iron deficiency and anaemia (ferritin; Tsat; Hb)	Results evaluation
Beck-da-Silva 2013	Porto Alegre, Brazil	4/13	63.5 ± 16.2[a]	LVEF < 40%; NYHA: II–IV	8	Ferrous sulfate; 200 mg, tid	<500 μg/L; Tsat <20%; Hb: 9–12 (g/dL)	Hb; ferritin, Tsat; VO_2
Suryani 2017	Jakarta, Indonesia	NA/54	18–75	LVEF < 50%; NYHA: II–III	12	Ferrous sulfate; 200 mg, tid	<100 μg/L, 100–300 μg/L (Tsat <20%); Hb: 8–13 g/dL (F: 12 g/dL)	Hb, ferritin, Tsat; NT-proBNP; 6MWT
Lewis 2017	Massachusetts, USA	80/225	63 (median)	LVEF ≤ 40%; NYHA: II–III	16	Iron polysaccharide; 150 mg, bid	<100 μg/L, 100–300 μg/l (Tsat <20%); Hb: 9–15 g/dL (F: 13.5 g/dL)	TIBC, Tsat, sTfR; NT-proBNP; VO_2, KCCQ, 6MWT
Sagita 2017	Jakarta, Indonesia	NA/37	NA	LVEF < 50%; NYHA: NA	12	Ferrous sulfate; NA	<100 μg/L, 100–300 μg/L (Tsat <20%); Hb: <13 g/dL	GLS
Snezana 2019	Nis, Serbia	79/201	73.31 ± 9.766 70.76 ± 9.811	NA NYHA: II–IV	26	Ferrous fumarate; 350 mg, bid	<100 mg/L (Tsat <20%) NA	Hb, ferritin, Tsat; 6MWT

6MWT, 6-min walk test; bid, bis in der; GLS, global longitudinal train; Hb, haemoglobin; Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NA, not available; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association functional class; sTfR, soluble transferrin receptor; TIBC, total iron binding capacity; tid, ter in der; Tsat, transferrin saturation; VO_2, volume of oxygen consumption.
[a]Mean ± standard deviation.

Adverse effects on oral iron supplementation

To evaluate the safety of oral iron therapy, we analysed all-cause death, adverse events, and gastrointestinal side effects. Three studies reported data for all-cause death, and no heterogeneity was observed across them (I^2 = 25%, P = 0.26). Assembling the evidence via the fixed-effects model revealed no significant difference in all-cause death between the oral iron and placebo groups (RR = 0.77; 95% CI, 0.46–1.29, Z = 0.98; P = 0.33) (*Figure 3A*). Two trials reported statistical data for adverse events, which showed no statistical heterogeneity (I^2 = 36%, P = 0.21). In summary, analysis of the safety outcome confirmed that the incidence rate of adverse effects was not statistically significant (RR = 0.83; 95% CI, 0.60–1.16, Z = 1.07; P = 0.28) (*Figure 3B*).

Iron storage status and cardiac function

We assessed whether haematological parameters were improved remarkably after oral iron supplementation. The ferritin levels and Tsat were pooled and showed a slight increase after iron complex administration (ferritin: MD = 2.70, 95% CI, −2.41–7.81, Z = 1.04; P = 0.30; Tsat: MD = 27.42, 95% CI, −4.93–59.78, Z = 1.66; P = 0.10) (*Figure 4A* and *4B*), but neither showed significant differences. The 6MWT, which was assessed in two trials, showed statistically significant heterogeneity (I^2 = 92%, P < 0.00001). After summarizing the results using the random-effects model, no significant difference was found (MD = 59.60, 95% CI, −17.89–137.08, Z = 1.51; P = 0.13) (*Figure 4C*).

Sensitivity analysis

In addition to the clinical trials, we included two well-designed, non-random control trials for sensitivity analysis to increase statistical samples and acquire more reliable results.[19] Two articles described statistics on gastrointestinal adverse effects, and the heterogeneity from them diverged (I^2 = 79%, P = 0.03). Eleven (23.4%) candidates in the experimental group had gastrointestinal side effects, whereas the incidence in the control group is 18.4% (nine candidates). Synthesis analysis indicated that the oral iron administration group did not show a significant increase in gastrointestinal adverse effects. After adding the two studies, no changes were found in 6MWT and all adverse events. However, significant changes in ferritin levels were observed (I^2 = 88%, P < 0.0001) (MD = 28.87, 95% CI 1.62–56.12, Z = 2.08; P = 0.04) (*Figure 5*).

Figure 2 Risk bias assessment results.

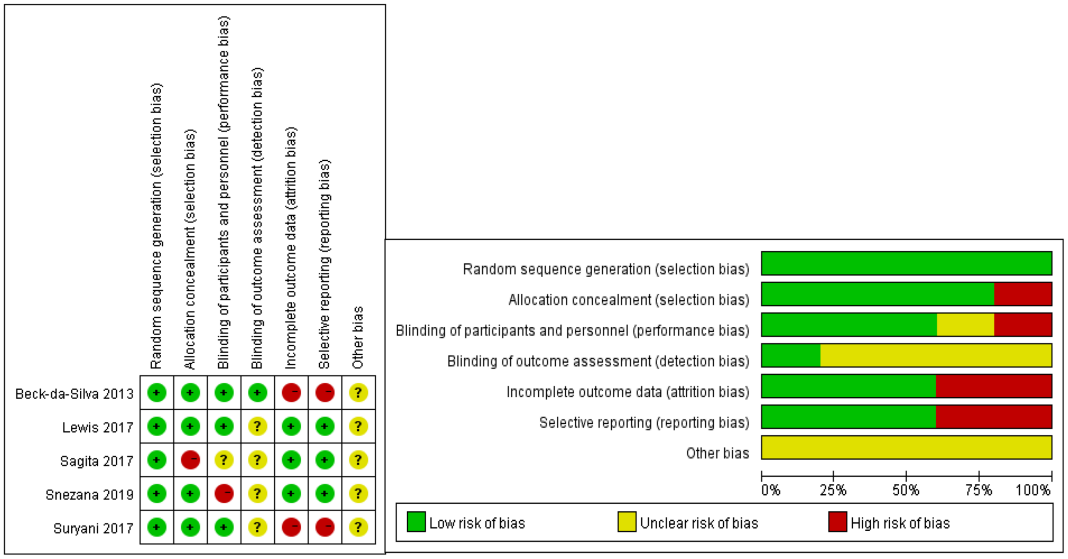
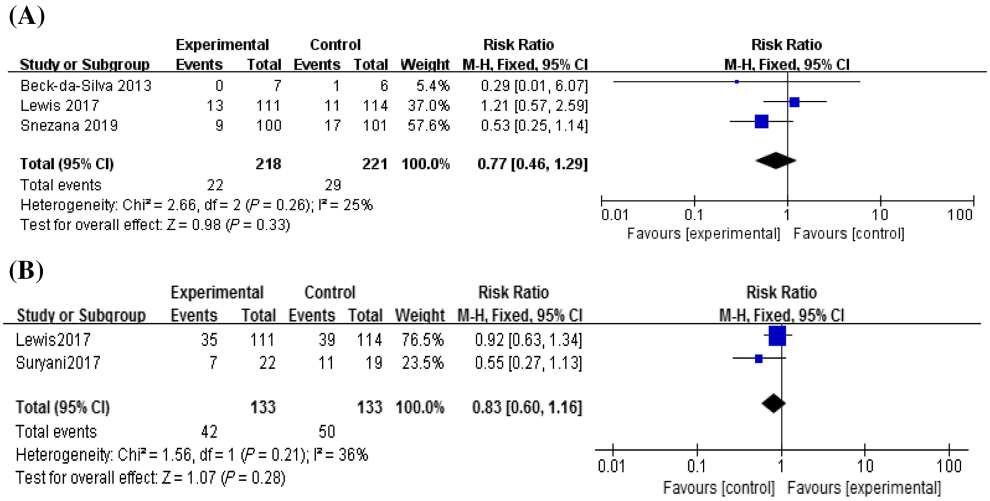


Figure 3 Forest plot displaying (A) all-cause death and (B) adverse events on oral iron administration to HF patients with ID or anaemia.



Discussion

Main findings

Our meta-analysis included studies comparing oral iron treatment with placebo or blank treatment in populations with HF with ID or mild anaemia. Our results reveal that oral iron is ineffective in improving the quality of life and exercise capacity of patients with HF with ID or mild anaemia. However, oral iron supplementation can improve iron storage status. More importantly, our findings indicate that oral iron therapy had no impact on adverse effects and all-cause death.

This study is the first to examine the safety and efficacy of oral iron in patients with HF with ID anaemia. The gastrointestinal canal of patients with HF is more susceptible to injury, and iron itself may have a negative effect on the gastrointestinal tract.[27] However, compared with the control arm, no increase in adverse events was observed after oral iron intervention in the experimental group. Hence, the results indicate that oral iron supplementation is sufficiently harmless to patients with HF and can be considered safe for use.

Iron, as the essential component of haemoglobin and the mitochondrial electron transport chain complex, plays an indispensable role in the oxygen-carrying function and electron transport for ATP generation of the blood.[28,29]

Figure 4 Forest plot displaying (A) the Tsat and (B) the ferritin level after oral iron supplementation. (C) The 6MWT in HF patients with ID or anaemia.

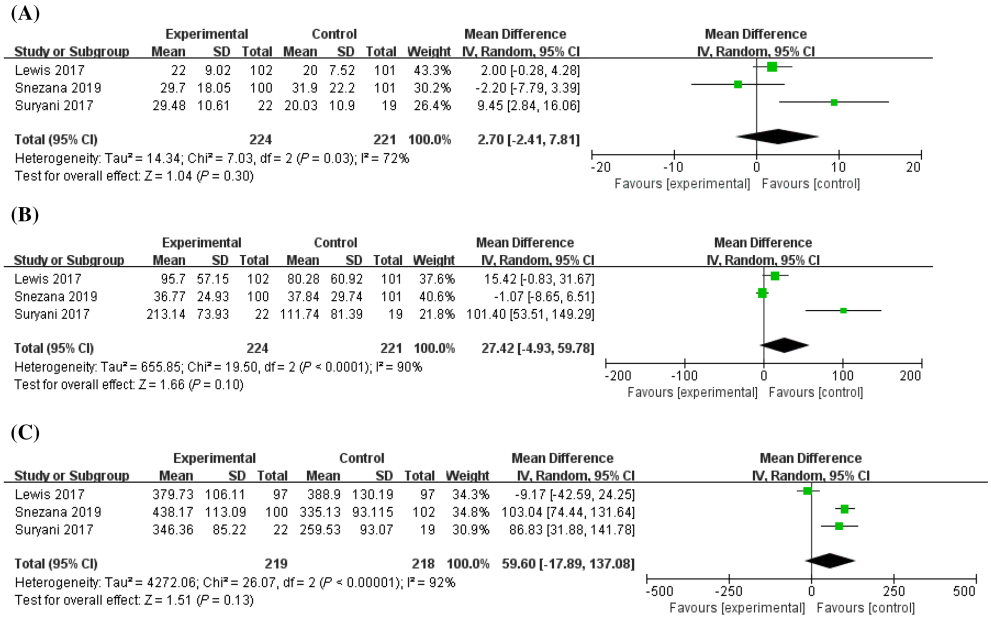
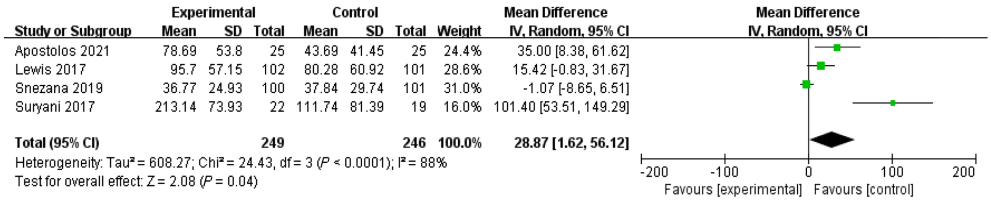


Figure 5 Forest plot showing the sensitivity analysis on the ferritin level at the end of follow-up.



Current experimental evidence indicates that appropriate iron supplementation can ameliorate muscle function and exercise capacity in animals, suggesting the function of iron as a co-factor in skeletal and cardiac muscles.[30,31] The results of the analysis reveal that ferritin levels and Tsat showed a slight but non-significant increase. Therefore, oral iron treatment has a negligible effect on complementing iron stores, which can help improve aerobic exercise and increase high quality of life. However, the sensitivity analysis showed that oral iron significantly improved patients' ferritin levels. Recent studies have reported that oral iron is effective in treating ID symptoms in patients with HF compared with intravenous iron supplementation.[32,33]

In addition, clinical trials have confirmed that ID may damage O_2 transport and utilization and decrease peak O_2 consumption, eventually leading to exercise intolerance and cardiac function decline in patients with HF. These situations were reversed with intravenous iron therapy.[34–36] However, this is inconsistent with our current findings indicating no significant difference in peak O_2 consumption, which is a strong predictive factor of exercise capacity in the HF population.[37] Furthermore, the 6MWT and the Kansas City Cardiomyopathy Questionnaire (KCCQ) are unchanged after oral iron administration. To expand the sample size, we included two non-randomized controlled studies for sensitivity analysis, and the findings were the same. In consequence, the evidence reveals that the application of oral iron fails to alleviate clinical symptoms, increase exercise capacity, and improve quality of life in HF with ID or mild anaemia. Apart from that, indicators of cardiac structure and systolic function were not ameliorated after oral iron administration, for example.[38]

In the studies analysed, oral iron supplementation was administered at 200–600 mg per day, which is 10–20-fold the absorption capacity for oral iron after accounting for limited gastrointestinal tract intake. More surprisingly, the total oral iron dosage in the IRON-HF trial was approximately 38-fold that for intravenous iron.[16,17] Nevertheless, the efficacy of oral iron supplementation on iron storage status lags far behind intra-

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venous iron.[39] Regarding the failure of oral iron to promote exercise function and iron storage status, several possible reasons may contribute to the phenomenon. As previously stated, gastrointestinal tract digestive and absorptive functions are impaired in the HF population, and massive oral iron can aggravate the injury, leading to excessive iron loss. Hepcidin is a crucial factor regulating iron absorption, and increased hepcidin levels will inhibit iron absorption and utilization.[40,41] The IRONOUT trial showed very high baseline levels of hepcidin, which may suppress the Tsat and ferritin increase after oral iron supplementation, thereby restricting iron uptake in the skeletal muscle and cardiomyocytes.[42] In addition, a follow-up duration of 2–4 months is short, which may have limited our evaluation.

Limitations

Our meta-analysis has some limitations. First, only a small number of studies were included, and high-quality trials are lacking. In addition, we were unable to gather more information for the assessment of prognosis as expected, for example, LVEF, re-hospitalization and long-term mortality. In addition, the definition of mild anaemia and ID is one of the limitations varied across the studies, and no standard recommendations exist on target Tsat, ferritin, and haemoglobin levels. Furthermore, we were unable to conduct sub-group analyses on anaemia status and NYHA class due to the limited data.

Conclusions

Our findings show that oral iron supplementation can safely improve iron storage status. However, oral iron supplementation in the HF population with ID or mild anaemia is ineffective in improving Tsat and 6MWT. The clinical trials on oral iron administration in HF with ID or anaemia are still very few. Therefore, further well-designed RCTs involving multiple centres and nationalities are still required. Furthermore, as our findings indicate, we recommend that ongoing and future trials should have long-term follow-up and should examine anaemic status, ID levels (based on ferritin and Tsat), NYHA class, and LVEF.

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Conflict of interest

None declared.

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