


Intravenous iron supplement for iron deficiency in patients with severe aortic stenosis scheduled for transcatheter aortic valve implantation: results of the IISAS randomised trial

Anette B. Kvaslerud^{1,2,3*}, Sara Bardan^{1†}, Kristoffer Andresen^{1,2}, Sophie F. Kløve², Morten W. Fagerland⁴, Thor Edvardsen^{1,2}, Lars Gullestad^{1,2,3}, and Kaspar Broch^{1,2,3}

¹Faculty of Medicine, University of Oslo, Oslo, Norway; ²Department of Cardiology, Rikshospitalet, Oslo University Hospital, Oslo, Norway; ³KG Jebsen Center for Cardiac Research and Center for Heart Failure Research, University of Oslo, Oslo, Norway; and ⁴Oslo Centre for Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, Oslo, Norway

Received 2 May 2022; revised 11 May 2022; accepted 14 May 2022; online publish-ahead-of-print 3 June 2022

Aims

The aim of this trial was to evaluate whether intravenous iron could provide benefit beyond transcatheter aortic valve implantation (TAVI) in iron-deficient patients with severe aortic stenosis.

Methods and results

In this randomised, placebo-controlled, double-blind, single-centre trial, we enrolled patients with severe aortic stenosis and iron deficiency (defined as ferritin <100 µg/L, or 100–299 µg/L with a transferrin saturation <20%) who were evaluated for TAVI. Patients were randomly assigned (1:1) to receive intravenous ferric derisomaltose or placebo ~3 months before TAVI. The primary endpoint was the between-group, baseline-adjusted 6-min walk distance measured 3 months after TAVI. Secondary outcomes included quality of life, iron stores, hand grip strength, New York Heart Association (NYHA) class, and safety. Between January 2020 and September 2021, we randomised 74 patients to ferric derisomaltose and 75 patients to placebo. The modified intention-to-treat population comprised the 104 patients who completed the 6-min walk test at baseline and 3 months after successful TAVI. Iron stores were restored in 76% of the patients allocated to iron and 13% of the patients allocated to placebo ($p < 0.001$). There was no difference in the baseline-adjusted 6-min walk distance between the two treatment arms ($p = 0.82$). The number of serious adverse events, quality of life, hand grip strength, and NYHA class did not differ between the treatment arms.

Conclusion

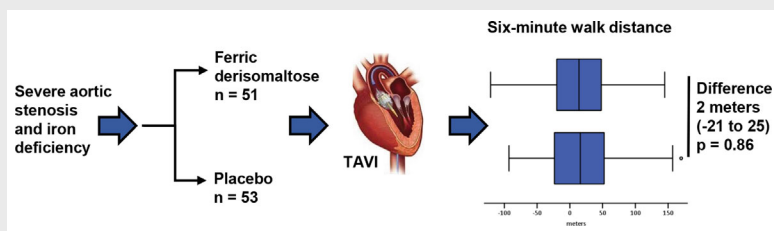
Treatment with intravenous iron did not provide clinical benefit beyond TAVI in iron-deficient patients with severe aortic stenosis.

Clinical Trial Registration: ClinicalTrials.gov NCT04206228.

*Corresponding author. Oslo University Hospital, Rikshospitalet, P.O. Box 4950 Nydalen, 0424 Oslo, Norway. Tel: +4723070000; Fax number: +4723070650; Email: a.b.kvaslerud@medisin.uio.no

†These authors contributed equally.

Graphical Abstract



In the IIISAS (Intravenous Iron supplement for Iron deficiency in patients with Severe Aortic Stenosis) trial, 149 patients with severe aortic stenosis and iron deficiency (defined as ferritin $<100 \mu\text{g/L}$, or $100\text{--}299 \mu\text{g/L}$ with a transferrin saturation $<20\%$) were randomised to intravenous ferric derisomaltose or placebo ~3 months before transcatheter aortic valve implantation (TAVI). The modified intention-to-treat population comprised the 104 patients who completed the 6-min walk test at baseline and 3 months after successful TAVI. As illustrated in the bar chart, the primary endpoint, the between-group, baseline-adjusted 6-min walk distance did not differ between the two treatment groups (between group difference 2 m [95% confidence interval -21 to 25], $p = 0.86$).

Keywords

Aortic stenosis • Iron deficiency • Safety • Randomized controlled trials

Introduction

Iron deficiency is present in ~50% of patients with severe aortic stenosis.^{1,2} Iron is an essential micronutrient, and while its fundamental role in oxygen transport through erythropoiesis is well recognised, it is equally critical for energy production and efficient functioning of all of the body's organs.^{3,4} Iron deficiency is a condition in which there is insufficient available iron to meet the body's needs.⁴

Patients who are scheduled for transcatheter aortic valve implantation (TAVI) are often elderly and have multiple comorbidities that may affect clinical outcomes after valve implantation. Approximately one third of patients undergoing TAVI do not experience an improvement in physical capacity and symptom burden – despite successful valve implantation.^{5,6} It is therefore relevant to address the comorbidities of these patients and to investigate whether we can identify therapeutic targets to optimise the effect of the TAVI procedure. In patients with heart failure, intravenous iron improves exercise capacity, quality of life, myocardial function, and reduce the risk of heart failure hospitalisations.^{7–12} In patients with severe aortic stenosis, observational data suggest that iron deficiency is associated with an unfavourable clinical profile and adverse outcomes.² Furthermore, the symptoms of iron deficiency, such as fatigue, dyspnoea, and reduced exercise capacity, are similar to the cardinal symptoms of symptomatic aortic stenosis.^{13,14} Iron deficiency may therefore contribute to a lack of improvement in symptoms after TAVI, and may thus represent a potential cost-effective treatment to improve outcomes after TAVI.

The Intravenous Iron supplement for Iron deficiency in Severe Aortic Stenosis (IIISAS) trial is the first randomised, clinical trial to assess the efficacy and safety of intravenous iron in patients with severe aortic stenosis. We hypothesised that in iron-deficient patients with severe aortic stenosis, intravenous iron

would improve physical performance, New York Heart Association (NYHA) functional class, muscle strength, and health-related quality of life beyond the effect of TAVI.

Methods

Study design and participants

The IIISAS trial was an investigator-initiated, single-centre, randomised, double-blind, placebo-controlled trial conducted at Oslo University Hospital, Rikshospitalet, Norway. We screened consecutive patients who were electively admitted for evaluation for aortic valve replacement due to severe aortic stenosis. We did not include patients who were referred for emergency TAVI. Eligible patients had severe aortic stenosis and iron deficiency defined as serum ferritin $<100 \mu\text{g/L}$, or between $100\text{--}299 \mu\text{g/L}$ with transferrin saturation (TSAT) $<20\%$.^{4,7,8} Exclusion criteria included haemoglobin $<10 \text{ g/dL}$, intravenous iron supplement within 6 months prior to inclusion, and inability to walk at least 100 m on the 6-min walk test (6MWT). The complete inclusion and exclusion criteria can be found in the statistical analyses plan in the [online supplementary material](#). All study participants provided written informed consent. Randomisation and study drug infusion were performed during admission for evaluation for aortic valve replacement, which was before the final decision was made by the heart team regarding valvular intervention. The next study visit was scheduled at hospitalisation for TAVI, ~3 months after inclusion. The last study visit was scheduled 3 months after TAVI, ~6 months after randomisation. The trial was approved by the South-East Regional Ethics Committee in Norway and the Norwegian Medicines Agency, and the investigation conforms to the principles outlined in the Declaration of Helsinki.

Randomisation and blinding

The Research Support Unit at Oslo University Hospital generated a balanced, permuted, variable block size (block size: four or six)

randomisation list. We did not include any stratification factors. A third-party nurse placed cards marked 'ferric derisomaltose 20 mg/kg' or 'placebo' in sealed and numbered envelopes. Once the informed consent form had been signed and the patient had been assigned a trial number, the corresponding envelope was opened, and the study drug was prepared. Because ferric derisomaltose is easily distinguishable from saline placebo, preparation and administration of the study drug were performed by third-party, unblinded personnel. To maintain double blinding, the infusion stand, intravenous line, syringe, and injection site were covered, and the patients' eyes were blindfolded. The infusion was administered over 30 min, and the patients were observed for adverse effects for 2 h following the infusion. All study investigators and study participants were blinded and did not participate in treatment allocation or administration of the study drug.

Study drug

The patients received the study intervention immediately after randomisation, and no more than 1 day after performing the baseline tests. The active drug, ferric derisomaltose (formerly known as iron isomaltoside 1000), was administered as a single, intravenous infusion of 20 mg/kg body weight (rounded off to the nearest 100 mg; the maximal dose was 2000 mg) dissolved in 100 ml NaCl 0.9%. This dosing regimen is in compliance with the European marketing authorisation. Patients allocated to placebo received an intravenous infusion of 100 ml NaCl 0.9%.

Study outcomes

The primary endpoint was the 6-min walk distance 3 months after TAVI adjusted for the baseline walk distance. Secondary endpoints were quality of life, NYHA class, and muscle strength. We also assessed safety and tolerability of the study drug, adverse events during follow-up, and complications during the TAVI procedure. Restoration of iron stores was an important explanatory endpoint.

Assessments

Before randomisation, the patients underwent echocardiography, left-sided heart catheterisation, electrocardiogram, assessment of NYHA class, and laboratory tests including markers of iron homeostasis (ferritin, TSAT, total iron binding capacity [TIBC], iron, transferrin and transferrin receptor). We also assessed cognitive function by the mini-cog test and frailty by the Essential Frailty Toolset (EFT),¹⁵ which includes a five-times sit to stand test.

At follow-up visits, markers of iron homeostasis were not analysed, but blood was drawn for storage in a biobank for subsequent analyses.

Six-minute walk test

The 6MWT measures the number of meters that the subject is able to walk over 6 min. The patients walked back and forth on a 30 m marked walking course in a hospital corridor. Turnaround points were marked with orange cones. Standardised encouragement was provided. We measured heart rate, blood pressure, and oxygen saturation before and after the 6MWT. The 4 m gait speed was measured between the first 1 m mark and the 5 m mark.

Muscle strength

We measured hand grip strength by the Kern MAP hand-held dynamometer. The patients' dominant hand was tested three times, and the best result was registered. Men and women were tested at a resistance of 40 and 20 kg, respectively.

Health-related quality of life

The principal measure of quality of life was the change in the overall summary score from the Kansas City Cardiomyopathy Questionnaire (KCCQ). For in-depth analyses of the impact of intravenous iron on quality of life, we also assessed the number of patients whose summary scores increased or decreased by more than five points, as well as quality of life assessed by the EuroQol (EQ) 5D-3L (converted to a summary index using the Swedish based value set¹⁶), the EQ-VAS, and the SF-36v2 tools with norm-based summary scores for mental and physical component scores.

Statistical analysis

Data analyses were performed with IBM SPSS V.28. Baseline data are expressed as means \pm standard deviation, medians with interquartile range, and numbers with percentages depending on distribution. For continuous variables, we assessed the effect of the intervention using one-way analysis of covariance (ANCOVA), in which we treated the baseline value of the endpoint in question as a covariate. For dichotomous endpoints, we applied the Newcombe hybrid score interval and the Fisher mid-P test (Fisher–Irwin). Categorical endpoints with more than two outcome categories (NYHA class) were analysed with the Wilcoxon–Mann–Whitney test. We assessed the effect on the primary endpoint across prespecified subgroups by adding an interaction term between the subgroup variable and the treatment variable in the linear regression. To determine the robustness of the analysis of the primary endpoint, we performed best-case, worst-case and no-change sensitivity analyses with imputations for missing data. The statistical analysis plan can be found in the supplementary material. All analyses were performed according to the intention-to-treat principle.

Sample size calculation

This trial was designed to assess the effect of intravenous iron on the baseline-adjusted 6-min walk distance. We considered an increase of 30 m to represent a clinically meaningful improvement.⁷ We expected a repeat-measurement standard deviation of 50 m. With a power of 80% and a significance level of 5%, we would need at least 44 patients in each group. To ensure adequate power, we performed a prespecified, interim, blinded estimation of the standard deviation of the repeat measurement 6-min walk distance after 50 patients had completed the last study visit. The measured standard deviation was 53 m. In the revised sample size calculations, we would need at least 49 patients in each group. Due to a higher number of patient dropouts than expected, we aimed to include 145 patients to ensure sufficient power.

Results

Study population

Between 13 January 2020 and 13 September 2021, we screened 684 consecutive patients of whom 369 (54%) had iron deficiency.

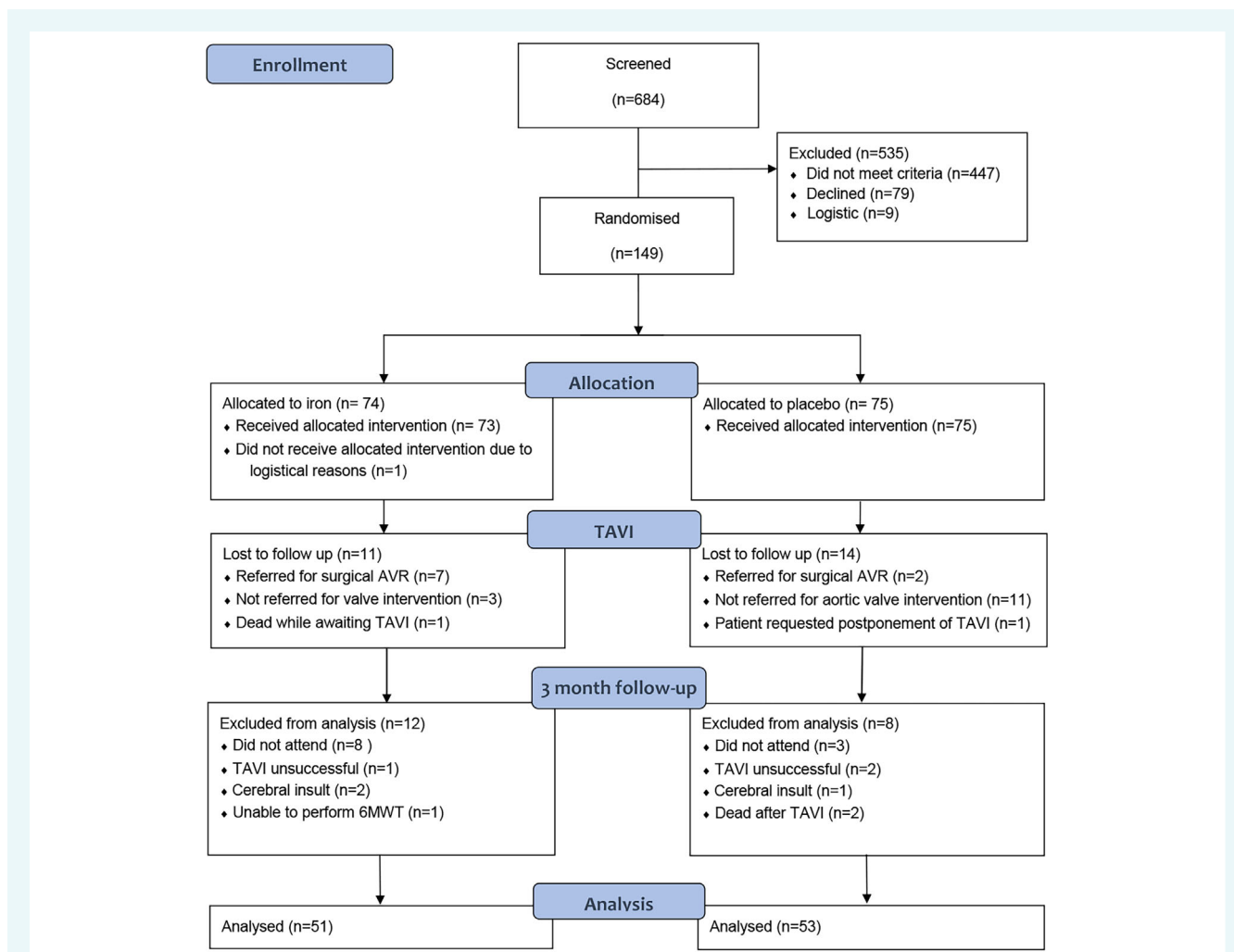


Figure 1 Flowchart of the IIISAS study population. AVR, aortic valve replacement; TAVI, transcatheter aortic valve implantation.

As illustrated in *Figure 1*, 149 patients were included and allocated to treatment, of whom 74 patients were randomised to ferric derisomaltose and 75 patients received placebo. Among the included patients, 14 patients were advised against TAVI due to either low symptomatic burden or high risk, nine patients were referred for surgical aortic valve replacement, one patient died 1 month after inclusion while waiting for TAVI due to pneumonia, and one patient had not received TAVI when the trial was finalised because the patient requested postponement of the procedure. The remaining 124 patients were scheduled for TAVI. In three patients, a new valve was not inserted due to complications during TAVI (occlusion of coronary arteries, perforation of the left ventricle with subsequent open-heart surgery, and difficult access due to calcification in the aortae). Two patients died after TAVI and before the final follow-up. Three patients were unable to attend the final visit due to sequela after perioperative cerebral infarction during TAVI. Eleven patients did not wish to attend the final visit, mainly due to fear of contracting COVID-19 during the early phase of the pandemic, and one patient was unable to perform 6MWT at follow-up because of a knee injury. The modified intention-to-treat

population comprised 104 patients for analysis of the primary end-point, where 53 received placebo and 51 patients were allocated to ferric derisomaltose.

During follow-up, three patients in the placebo group received intravenous iron infusion at their local hospital after TAVI due to iron deficiency anaemia. Another two patients in the placebo group and four patients in the ferric derisomaltose group were recommended per oral iron supplementation by their general practitioner or local hospital.

Table 1 shows the baseline data for the modified intention-to-treat population ($n = 104$) who performed a 6MWT at the final visit. The baseline data were well balanced between the study arms. Online supplementary *Table S2* shows the baseline data for the patients who were excluded from the modified intention-to-treat population ($n = 45$) and the modified-intention-to-treat population.

Six-minute walk test

There was no difference in the baseline-adjusted 6-min walk distance between the two treatment arms. The mean difference

Table 1 Demographic characteristics of the modified intention-to-treat population at baseline according to study groups

	Modified intention-to-treat population (n = 104)	
	Ferric derisomaltose (n = 51)	Placebo (n = 53)
Age, years	80.0 ± 7.8	79.2 ± 6.5
Male sex	28 (55)	32 (60)
History of smoking (previous or current)	11 (22)	19 (36)
Body mass index, kg/m ²	28.1 ± 5.0	27.7 ± 5.2
Systolic blood pressure, mmHg	147 ± 24	148 ± 26
Diastolic blood pressure, mmHg	76 ± 10	73 ± 11
Heart rate, bpm	75 ± 12	73 ± 14
EuroSCORE II, %	2.3 (1.5 to 3.5)	2.1 (1.4 to 3.2)
Medical history		
Hypertension	29 (57)	25 (47)
Previous cardiac arrest	0 (0)	1 (2)
Diabetes mellitus	11 (19)	8 (16)
Previous or current history of coronary artery disease	22 (42)	19 (37)
Intervention to coronary arteries during work-up before TAVI	8 (16)	6 (11)
Atrial fibrillation	18 (35)	18 (34)
Previous stroke or transient ischaemic attack	2 (4)	8 (15)
Peripheral vascular disease	2 (4)	0 (0)
Chronic obstructive pulmonary disease	4 (8)	3 (6)
Medication		
Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker	33 (65)	26 (49)
Beta-blocker	25 (49)	24 (45)
ASA	22 (43)	20 (38)
Non-ASA platelet inhibitors	5 (10)	3 (6)
Anticoagulation (warfarin or direct oral anticoagulation)	18 (35)	27 (51)
Cholesterol lowering agent	35 (69)	45 (85)
Loop diuretic	12 (24)	12 (23)
Oral iron supplementation prior to inclusion	1 (2)	1 (2)
Echocardiography		
Left ventricular ejection fraction, %	53 ± 7	52 ± 8
Aortic peak velocity, m/s	4.4 ± 0.4	4.2 ± 0.5
Aortic mean gradient, mmHg	48.7 ± 13.1	47.1 ± 16.1
Aortic valve area, cm ²	0.72 ± 0.16	0.78 ± 0.23
Concomitant moderate/severe valvular disease	12 (24)	10 (19)
Biochemistry		
Haemoglobin, g/dl	13.3 ± 1.2	13.3 ± 1.3
Cholesterol, mmol/L	4.1 ± 1.0	4.3 ± 1.1
LDL cholesterol, mmol/L	2.3 ± 0.74	2.4 ± 0.88
Creatinine, µmol/L	91.2 ± 29.1	90.2 ± 26.0
Estimated glomerular filtration rate, ml/min	64.3 ± 18.2	65.3 ± 17.0
C-reactive protein, mg/L	1.8 (0.9 to 5.7)	1.9 (1.0 to 5.8)
N-terminal pro-B-type natriuretic peptide, ng/L	825 (317 to 1644)	1039 (620 to 2469)
Troponin T, ng/L	18 (12 to 26)	20 (13 to 32)
Ferritin, µg/L	58 (46 to 80)	49 (33 to 94)
TSAT, %	19 (15 to 23)	16 (12 to 25)
Transferrin receptor, ng/ml	3.4 (2.8 to 4.0)	3.6 (3.1 to 4.6)
TIBC, µmol/L	66.1 ± 9.8	68.4 ± 10.1
Transferrin, g/L	2.6 ± 0.40	2.7 ± 0.40
Iron, µmol/L	12 (10 to 15)	11 (9 to 16)

Table 1 (Continued)

	Modified intention-to-treat population (n = 104)	
	Ferric derisomaltose (n = 51)	Placebo (n = 53)
Presence of iron deficiency		
Absolute (ferritin <100 µg/L)	44 (86)	43 (81)
Functional (ferritin 100–299 µg/L and TSAT <20%)	7 (14)	10 (19)
Ferritin <30 µg/L	6 (12)	8 (15)
TSAT <20%	32 (63)	37 (70)
Study outcome measures at baseline		
NYHA class		
I	1 (2)	2 (4)
II	27 (53)	27 (51)
III	22 (43)	23 (43)
IV	1 (2)	2 (2)
6-min walk test, m	355 ± 113	367 ± 129
Gait speed, m/s	0.94 ± 0.33	0.88 ± 0.31
Handgrip strength, kg	28.1 ± 10.1	31.3 ± 11.5
KCCQ overall summary score	69 (56 to 81)	64 (35 to 81)
KCCQ functional summary score	78 (56 to 86)	70 (50 to 86)
SF36v2 summary PCS	39 (33 to 47)	36 (31 to 44)
SF36v2 summary MCS	51 (44 to 55)	38 (36 to 51)
EQ-5D3L	0.83 (0.77 to 0.93)	0.81 (0.74 to 0.93)
EQ-VAS	67 (50 to 80)	50 (40 to 73)
Essential Frailty Toolset score		
0	20 (39)	21 (40)
1	26 (51)	19 (36)
2	4 (8)	12 (23)
3	1 (2)	1 (2)
4	0	0
5	0	0

Values are mean ± standard deviation, n (%), or median (interquartile range).

ASA, acetylsalicylic acid; EQ-5D, EuroQol-5 dimension; EQ-VAS, EuroQol-visual analogue scale; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; SF36v2, 36-item short form health survey; TAVI, transcatheter aortic valve implantation; TSAT, transferrin saturation.

The modified intention-to-treat population refers to the patients who were included, received a transcatheter aortic valve implantation, and performed an acceptable 6-min walk test at 3-month follow-up.

between the iron and placebo arm was 2 m (95% confidence interval [CI] –21 to 25) ($p = 0.86$) (Figure 2, right panel). Table 2 shows the main results of the IISAS trial. For all patients, irrespective of randomisation, the mean change in the 6-min walk distance from baseline to 3-month follow-up after TAVI was 19.1 ± 58.9 m. Of these patients, 38 patients (36.5%) failed to improve their 6-min walk distance.

Secondary endpoints

Iron status and haemoglobin

In the ferric derisomaltose group, iron stores were restored in 39 patients (76%) versus 8 patients (13%) in the placebo group ($p < 0.001$) (Figure 2, left panel). At 3 months after TAVI, haemoglobin was 0.6 g/dl (95% CI 0.1 to 1.0) higher in the ferric derisomaltose arm, ($p = 0.015$). Online supplementary Figure S1 shows the development in haemoglobin stratified by treatment. Red blood cell transfusion was administered during TAVI in five

patients in the ferric derisomaltose arm and in three patients receiving placebo. No patient received more than two units of red blood cell transfusion.

Health-related quality of life

There were no differences in the KCCQ overall summary score (online supplementary Figure S2) or the KCCQ functional summary score, nor in the number of patients who improved or decreased their overall summary score with more than five points. Furthermore, there were no differences between the two groups in the other quality of life assessments: Equation 5D-3L, EQ-VAS, and the SF-36v2.

NYHA class

There was no difference in NYHA class between the patients who received ferric derisomaltose and those who received placebo at follow-up ($p = 0.18$). However, irrespective of randomisation, 76%

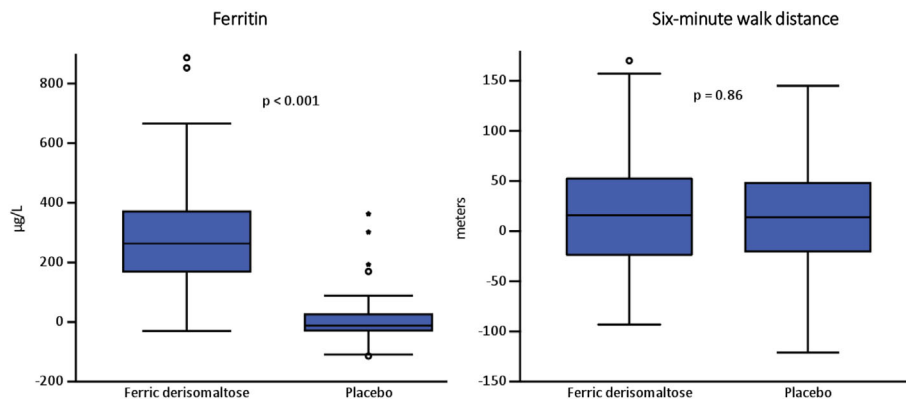


Figure 2 Changes in ferritin and 6-min walk distance. The left panel illustrates the change in ferritin ($\mu\text{g/L}$) stratified by treatment allocation. The right panel illustrates the change in the 6-min walk distance (m) stratified by treatment allocation. *P*-value for the between-treatment group difference in the baseline adjusted values of ferritin and walk distance. Boxes: 25–75 percentiles; whiskers: 10–90 percentiles.

of the patients who received TAVI improved their NYHA functional class by at least one point (online supplementary Figure S3).

Muscle strength and cardiac biomarkers

There were no differences in muscle strength, N-terminal pro-B-type natriuretic peptide (NT-proBNP), or troponin T between the two treatments arms.

Subgroup analyses

The effect of the intervention on the primary endpoint was not affected by age above or below median of 79 years ($p = 0.60$); gender ($p = 0.66$); ferritin above or below $30 \mu\text{g/L}$ ($p = 0.83$); TSAT above or below 20% ($p = 0.36$); or whether or not the patients had anaemia at baseline, defined as haemoglobin $<130 \text{ g/L}$ in men and $<120 \text{ g/L}$ in women ($p = 0.78$; Figure 3).

Safety

One patient had a hypersensitivity reaction with a transient decline in systolic blood pressure and skin itching during treatment with ferric derisomaltose. Another patient experienced chest pain 2.5 h after the infusion of ferric derisomaltose. Both patients recovered fully. One patient allocated to placebo was treated for pulmonary oedema 45 min after the infusion had finished, most likely due to a transient supraventricular tachycardia. Minor infusion reactions occurred in three patients who received ferric derisomaltose (transient taste of iron in two, headache in one) and in two patients who received NaCl (nausea, pre-syncope). In the ferric derisomaltose arm, there were 37 serious adverse events versus 49 in the placebo arm ($p = 0.071$). However, the analysis of adverse events are biased due to the relationship with TAVI and most of the serious adverse events were complications related to the TAVI procedure. Except for the aforementioned hypersensitivity reaction and episode of chest pain, all serious adverse events were deemed unrelated to the study drug, infusion procedure, and study

testing. There was no between-group difference in the number of infections treated with antibiotics during follow-up. Five patients in the placebo arm and two patients in the ferric derisomaltose arm died. Table 3 summarises the adverse events according to study drug treatment and online supplementary Table S3 gives further details on the serious adverse events.

Sensitivity analyses

Best-case, worst-case, and no-change scenario imputations for missing data did not affect the results of the analysis of the primary endpoint ($p = 0.055$, $p = 0.13$ and $p = 0.84$, respectively).

Discussion

The main finding of the IISAS trial was that treatment with ferric derisomaltose did not provide benefit beyond TAVI in terms of 6-min walk distance (Graphical Abstract), NYHA class, muscle strength, or quality of life in iron-deficient patients with severe aortic stenosis. Intravenous iron led to repletion of iron stores in 79% of the patients and except for one hypersensitivity reaction which resolved quickly after adequate treatment, the treatment was safe.

In patients with heart failure, iron deficiency regardless of haemoglobin status is a recommended treatment target based on the results of randomised trials.^{7,8,17} In patients with severe aortic stenosis, only a few studies have examined the association between iron deficiency regardless of haemoglobin levels and adverse events following TAVI.^{1,2} In an observational study on 495 patients undergoing TAVI, preprocedural iron deficiency was associated with adverse outcomes after TAVI. In a subgroup of patients ($n = 56$), intravenous iron resulted in improvements in both iron markers and symptoms at 30-day follow-up.² Consequently, many have emphasized the need for clinical trials to investigate the potential benefit of intravenous iron in patients with severe aortic stenosis.^{2,18–20}

Table 2 Outcomes in the ILLSAS trial (n = 104)

Variables	Ferric derisomaltose (n = 51)		Placebo (n = 53)		Mean difference between groups with 95% CI for difference	p-value
	Baseline	Follow-up	Baseline	Follow-up		
6MWT distance, m	355 ± 113	375 ± 132	367 ± 129	384 ± 128	2 (−21 to 25)	0.86
NYHA class						
I	1 (2%)	35 (69%)	2 (4%)	30 (57%)		0.18 ^a
II	27 (53%)	15 (29%)	27 (51%)	20 (40%)		
III	22 (43%)	1 (2%)	23 (43%)	3 (6%)		
IV	1 (2%)	0	1 (2%)	0		
Hand grip strength, kg	28.1 ± 10.1	27.9 ± 10.4	31.3 ± 11.5	31.5 ± 12.2	−0.5 (−2.2 to 1.1)	0.53
KCCQ overall summary score	69 (56 to 81)	88 (71 to 95)	64 (35 to 81)	82 (65 to 94)	0.6 (−6.4 to 7.7)	0.86
KCCQ functional summary score	78 (56 to 86)	88 (68 to 96)	70 (50 to 86)	89 (69 to 95)	−0.6 (−7.1 to 6.0)	0.86
No. of patients improving or decreasing their KCCQ overall summary score >5 points		35 (69%)		33 (62%)	−6.4% (−24% to 12%)	0.48 ^b
		6 (12%)		8 (15%)	3.3% (−10% to 17%)	0.68 ^b
EQ-5D3L index	0.83 (0.77 to 0.93)	0.91 (0.82 to 0.97)	0.81 (0.74 to 0.93)	0.91 (0.78 to 0.97)	−0.001 (−0.4 to 0.4)	0.97
EQ-5D VAS	67 (50 to 80)	70 (48 to 84)	50 (40 to 73)	75 (60 to 85)	−7.8 (−16.5 to 0.86)	0.077
SF36v2 summary PCS	39 (33 to 47)	45 (35 to 51)	36 (31 to 44)	43 (36 to 51)	−0.5 (−4.0 to 2.9)	0.76
SF36v2 summary MCS	51 (44 to 55)	50 (44 to 56)	48 (38 to 55)	53 (43 to 56)	3.0 (−0.2 to 6.3)	0.067
Ferritin	74.3 ± 57	361 ± 221	69 ± 52	79 ± 86	276 (216 to 336)	<0.001
TSAT	19.3 ± 7.0	26.4 ± 9.6	18.7 ± 9.8	20.3 ± 11.4	6.0 (1.9 to 10.1)	0.004
Haemoglobin, g/L	13.3 ± 1.2	13.7 ± 1.4	13.3 ± 1.3	13.1 ± 1.5	0.6 (0.1 to 1.0)	0.015
NT-proBNP	825 (317 to 1644)	611 (338 to 1561)	1039 (620 to 2469)	873 (451 to 1265)	83 (−242 to 408)	0.61
Troponin T	18 (12 to 26)	19 (13 to 30)	20 (13 to 32)	22 (14 to 35)	−0.4 (−0.8 to 7.4)	0.92
ID	51 (100%)	12 (24%)	53 (100%)	46 (87%)	63% (46% to 75%)	<0.00001 ^b
Absolute ID	44 (86%)	7 (14%)	43 (81%)	44 (83%)	69% (52% to 80%)	<0.00001 ^b
Functional ID	7 (14%)	5 (10%)	10 (19%)	2 (4%)	−6% (−18% to 45%)	0.19 ^b
No. of patients with ferritin <30 µg/L	6 (12%)	1 (2%)	8 (15%)	15 (28%)	26% (13% to 40%)	0.00013 ^b

6MWT, 6-min walk test; CI, confidence interval; EQ-5D, EuroQol-5 dimension; EQ-VAS, EuroQol visual analogue scale; ID, iron deficiency; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SF36v2, 36-item short form health survey; TSAT, transferrin saturation.

All p-values are ANCOVA except from: ^aWilcoxon–Mann–Whitney test; ^bFisher mid-P test (Fisher–Irwin), and Newcombe hybrid score interval.

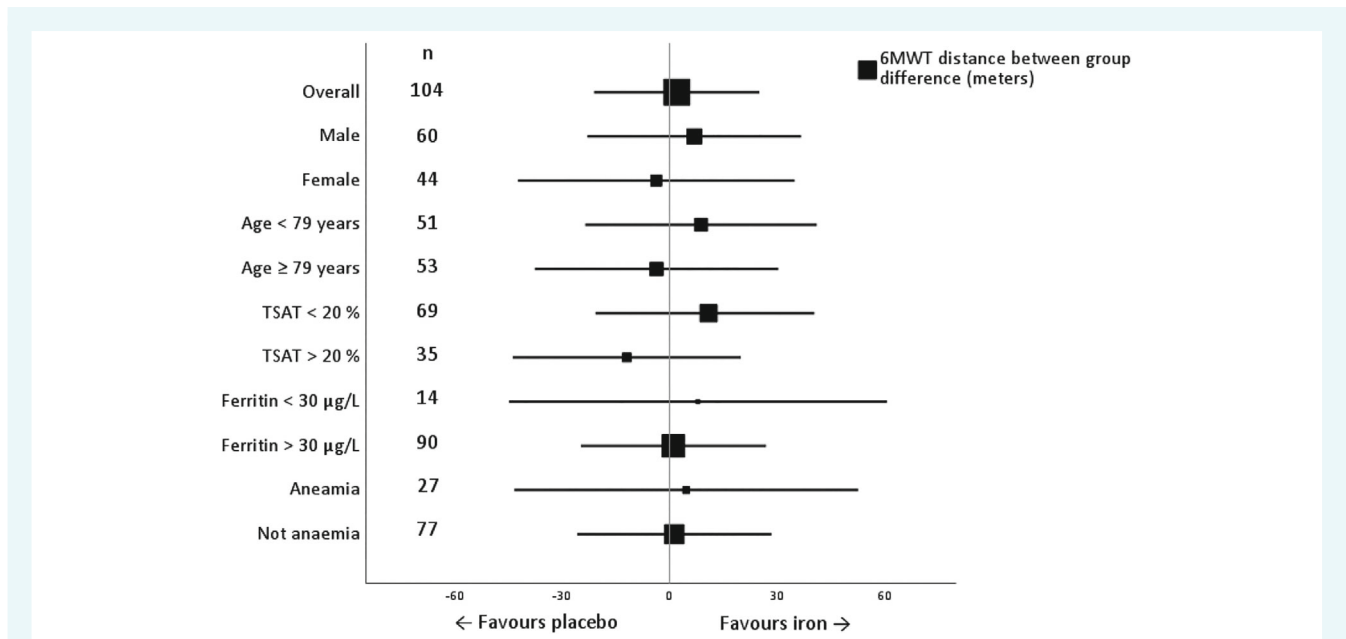


Figure 3 Subgroup analyses. The plot shows the impact of intravenous iron on the 6-min walk distance in five prespecified subgroups. The boxes represent the between-group difference in the 6-min walk distance and the lines indicate the lower and upper boundaries for the confidence intervals. Box sizes are proportional to the number of patients in each subgroup. 6MWT, 6-min walk test; TSAT, transferrin saturation.

The IIISAS trial included patients with iron deficiency, but only a few patients had anaemia, and severe anaemia was an exclusion criterion. Consequently, it cannot be concluded that intravenous iron does not have a position in the treatment of anaemic patients with severe aortic stenosis. However, prespecified subpopulation analyses on patients with and without anaemia indicated no benefit in anaemic patients. This suggests that anaemia and iron deficiency may serve as markers of poor outcomes, rather than cause these outcomes. Frailty is a multidimensional, dynamic state that makes the individual more vulnerable to the effect of stressors.¹⁷ Aortic stenosis and frailty are two distinct yet commonly associated conditions, and the presence of frailty in patients undergoing TAVI is associated with adverse outcomes.¹⁵

To assess the effect of one intervention when the patient undergoes another intervention is challenging. TAVI is a complex procedure that can be associated with severe complications. On the other hand, the benefit provided by successful intervention may eclipse the potential benefits of intravenous iron in the preoperative setting. In our population, the success and complication rates following TAVI were comparable between the two treatment arms. The relatively high drop-out rate is also a relevant issue. However, the similarities between the patients who were excluded from and included in the modified intention-to-treat population and the fact that imputation analyses did not change the results increase the robustness of the findings despite the drop-outs.

The overall change in the 6MWT after TAVI was moderate and 38 patients failed to improve their 6-min walk distance after TAVI. These results are comparable to those found in a recent study on patients who performed a 6MWT before and 6 months

after TAVI.⁵ In this study, the sub-group of 152 'fast walkers', who had a baseline walk distance that was comparable to that of our population, improved their walk distance by a mean of 20 m. The limited effect of TAVI on the 6-min walk distance raises the question of whether any intervention can be expected to improve the 6-min walk distance in a contemporary population of patients with severe aortic stenosis. The NT-proBNP levels in our population were moderately elevated, consistent with the low EuroSCORE and the inclusion criteria requiring a minimum 6-min walk distance of 100 m.

The IIISAS trial screened consecutive patients with severe aortic stenosis who were evaluated for TAVI and confirmed the high prevalence of iron deficiency observed in two previous studies.^{1,2} The administration of intravenous iron led to repletion of iron stores in most patients (76%), suggesting that the missing effect on clinical endpoints was not caused by inefficient treatment of the pre-existing iron deficiency. We have no reason to believe that the blood transfusions administered during TAVI substantially affected the iron parameters measured 3 months after TAVI.^{21,22}

Whether the definition of iron deficiency applied in patients with heart failure is valid in patients with severe aortic stenosis has not been investigated. A TSAT <20% is useful to define low plasma iron availability to tissues in iron deficiency.²³ Little evidence is available from high-quality studies to justify specific thresholds for serum ferritin. However, clinical trials have proved that the cut-points used in heart failure are clinically useful in this condition, and consequently, they are now largely accepted.^{4,17} Further investigation is warranted to determine optimal cut-off values for iron deficiency in patients with severe aortic stenosis.

Table 3 Adverse events during follow-up including procedural findings and outcomes related to transcatheter aortic valve implantation

	Ferric derisomaltose (n = 73)	Placebo (n = 75)
Adverse events	53	66
Serious adverse events	37	49
Infections		
Intravenous treatment	5	6
Per oral treatment	2	1
Deaths	2	5
Infusion reactions		
Mild	3	2
Hypersensitivity reaction	1	0
Skin discoloration	0	0
Procedural findings and outcomes during/after TAVI	n = 63	n = 61
Femoral access	63	61
Balloon-expandable prosthesis	48	47
Self-expanding valve	14	12
Death within 3 months after TAVI	0	2
Periprocedural ischaemic stroke, mild (NIHSS 0–5)/moderate (NIHSS 6–14)/severe (NIHSS ≥15)	3 / 1 / 0	1 / 1 / 0
Vascular complications		
Aortic dissection	1	0
Access-related	4	3
Periprocedural myocardial infarction	0	0
Tamponade after TAVI	2	2
Unsuccessful TAVI due to occlusion of the coronary arteries	0	1
Unsuccessful TAVI due to perforation of the left ventricle with subsequent open-heart surgery	0	1
Unsuccessful implantation due to calcification in the aorta and difficult access	1	0
Periprocedural blood cell transfusion	7	4
New left bundle branch block the day after TAVI	8	14
Permanent pacemaker after TAVI	10	10
Echocardiographic data at 3-month follow-up after TAVI	n = 51	n = 53
Patient–prosthesis mismatch	0	1
Paravalvular/valvular leak (small/moderate/severe)	34/1/0	32/1/0
Aortic peak velocity, m/s	2.2 ± 0.4	2.3 ± 0.5
Aortic mean gradient, mmHg	12.0 ± 4.1	12.1 ± 5.4
Aortic valve area, cm ²	1.7 ± 0.4	1.7 ± 0.4

NIHSS, National Institutes of Health Stroke Scale; TAVI, transcatheter aortic valve implantation.

In our trial, however, there were no signals towards a benefit of treatment in the prespecified subgroups with either ferritin <30 µg/L or in the patients with TSAT <20%.

Across the treatment arms, the TAVI procedure improved quality of life, NYHA class, and 6-min walk distance 3 months after TAVI. However, the results of our proof of concept trial do not provide support for routinely administration of intravenous iron to improve these outcome measures in patients with severe aortic stenosis and iron deficiency scheduled for TAVI. Except for one hypersensitivity reaction, the administration of intravenous ferric derisomaltose was safe.

Limitations

The IISAS trial was a single-centre trial, performed at a high-volume centre. The sample size was calculated to ensure sufficient power for the primary endpoint. The number of

participants may have been too small to evaluate effect on secondary endpoints and the effects in the subgroups of patients. Only one 6MWT was performed at each visit, although two measurements have been proposed to account for the learning effect.²⁴ We chose a pragmatic study design where we included the patients while they were being evaluated for aortic valve intervention, but before the final decision was made by the heart team regarding valvular intervention. This resulted in a higher drop-out rate than expected. On the other hand, if we were to have waited for the final decision, this would imply an additional study visit for the patients. This could have resulted in a more selected patient population where we only included those patients who could endure an extra visit to the hospital. Due to the COVID-19 pandemic, inclusions took longer than expected and some patients did not wish to attend the 3-month follow-up visit for fear of contracting COVID-19.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Funding

This was an investigator-initiated trial. Pharmacosmos© has provided the study medication and a grant. The funding source had no role in the study design, collection, analyses or the decision to publish. Pharmacosmos was given the opportunity to review the manuscript.

Due to the sensitive nature of the data collected for this study, the material will not be made publicly available. Excerpts of de-identified data relevant to the study are available from the corresponding author upon reasonable request.

Conflict of interest: L.G. has received lecture fees from AstraZeneca, Boehringer Ingelheim, Novartis and Amgen and has sat on advisory boards for AstraZeneca and Boehringer Ingelheim. K.B. has received lecture fees from Pharmacosmos, AstraZeneca, Boehringer Ingelheim, Pfizer, Orion Pharma, and Vifor Pharma and has sat on advisory boards for Pfizer and AstraZeneca. All other authors have nothing to disclose.

References

- Kvaslerud AB, Hussain AI, Auensen A, Ueland T, Michelsen AE, Pettersen KI, et al. Prevalence and prognostic implication of iron deficiency and anaemia in patients with severe aortic stenosis. *Open Heart*. 2019;5:e000901.
- Rheude T, Pellegrini C, Lessmann L, Wiebe J, Mayr NP, Michel J, et al. Prevalence and clinical impact of iron deficiency in patients with severe aortic stenosis referred for transcatheter aortic valve implantation. *Am J Cardiol*. 2019;124:1442–8.
- Hoes MF, Grote Beverborg N, Kijlstra JD, Kuipers J, Swinkels DW, Giepmans BNG, et al. Iron deficiency impairs contractility of human cardiomyocytes through decreased mitochondrial function. *Eur J Heart Fail*. 2018;20:910–9.
- Cappellini MD, Comin-Colet J, de Francisco A, Dignass A, Doehner W, Lam CS, et al.; IRON CORE Group. Iron deficiency across chronic inflammatory conditions: international expert opinion on definition, diagnosis, and management. *Am J Hematol*. 2017;92:1068–78.
- Abdul-Jawad Altisent O, Puri R, Regueiro A, Chamandi C, Rodriguez-Gabella T, del Trigo M, et al. Predictors and association with clinical outcomes of the changes in exercise capacity after transcatheter aortic valve replacement. *Circulation*. 2017;136:632–43.
- De Larochelière H, Puri R, Eikelboom JW, Rodés-Cabau J. Blood disorders in patients undergoing transcatheter aortic valve replacement: a review. *JACC Cardiovasc Interv*. 2019;12:1–11.
- Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, et al.; CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J*. 2015;36:657–68.
- Anker SD, Comin-Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al.; FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med*. 2009;361:2436–48.
- Anker SD, Kirwan BA, van Veldhuisen DJ, Filippatos G, Comin-Colet J, Ruschitzka F, et al. Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. *Eur J Heart Fail*. 2018;20:125–33.
- Jankowska EA, Kirwan BA, Kosiborod M, Butler J, Anker SD, McDonagh T, et al. The effect of intravenous ferric carboxymaltose on health-related quality of life in iron-deficient patients with acute heart failure: the results of the AFFIRM-AHF study. *Eur Heart J*. 2021;42:3011–20.
- Martens P, Dupont M, Dauw J, Nijst P, Herbots L, Dendale P, et al. The effect of intravenous ferric carboxymaltose on cardiac reverse remodelling following cardiac resynchronization therapy – the IRON-CRT trial. *Eur Heart J*. 2021;42:4905–14.
- Martens P, Dupont M, Dauw J, Nijst P, Bertrand PB, Tang WHW, et al. The effect of intravenous ferric carboxymaltose on right ventricular function – insights from the IRON-CRT trial. *Eur J Heart Fail*. 2022;24:1106–13.
- Zimmermann MB, Hurrell RF. Nutritional iron deficiency. *Lancet*. 2017;370:511–20.
- Pasricha SR, Tye-Din J, Muckenthaler MU, Swinkels DW. Iron deficiency. *Lancet*. 2021;397:233–48.
- Afilalo J, Lauck S, Kim DH, Lefèvre T, Piazza N, Lachapelle K, et al. Frailty in older adults undergoing aortic valve replacement: the FRAILTY-AVR study. *J Am Coll Cardiol*. 2017;70:689–700.
- Burström K, Sun S, Gerdtham UG, Henriksson M, Johannesson M, Levin LÅ, et al. Swedish experience-based value sets for EQ-5D health states. *Qual Life Res*. 2014;23:431–42.
- McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2022;24:4–131.
- Cammalleri V, Muscoli S, Versaci F, Romeo F. Periprocedural anemia management in severe aortic stenosis patients undergoing transcatheter aortic valve implantation. *J Cardiol*. 2020;75:117–23.
- Jankowska EA, Ponikowski P. Anaemia (and iron deficiency?) in aortic stenosis – a bystander or a potential therapeutic target? *Eur J Heart Fail*. 2015;17:994–6.
- Rheude T, Pellegrini C, Michel J, Trenkwalder T, Mayr NP, Kessler T, et al. Prognostic impact of anemia and iron-deficiency anemia in a contemporary cohort of patients undergoing transcatheter aortic valve implantation. *Int J Cardiol*. 2017;244:93–9.
- Froissart A, Rossi B, Ranque B, Jarrin I, Bergmann JF, Beaune S, et al.; SiFMI Group. Effect of a red blood cell transfusion on biological markers used to determine the cause of anemia: a prospective study. *Am J Med*. 2018;131:319–22.
- Ho CH. The effects of blood transfusion on serum ferritin, folic acid, and cobalamin levels. *Transfusion*. 1992;32:764–5.
- Grote Beverborg N, Klip IT, Meijers WC, Voors AA, Vegter EL, van der Wal HH, et al. Definition of iron deficiency based on the gold standard of bone marrow iron staining in heart failure patients. *Circ Heart Fail*. 2018;11:e004519.
- Adsett J, Mullins R, Hwang R, Hogden A, Gibson E, Houlihan K, et al. Repeat six-minute walk tests in patients with chronic heart failure: are they clinically necessary? *Eur J Cardiovasc Prev Rehabil*. 2011;18:601–6.