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Intravenous ferric derisomaltose in iron-deficient patients undergoing transcatheter aortic valve implantation due to severe aortic stenosis: study protocol of the randomised controlled IIISAS trial

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ABSTRACT

Introduction Iron deficiency is a prevalent comorbidity in patients with severe aortic stenosis and may be associated with procedural and clinical outcomes after transcatheter aortic valve implantation (TAVI). In the *I*ntravenous *I*ron Supplement for *I*ron Deficiency in Patients with *S*evere *A*ortic *S*tenosis (IIISAS) trial, we aim to examine whether a single administration of ferric derisomaltose can improve physical capacity after TAVI.

Methods and analysis This randomised, double-blind, placebo-controlled trial aims to enrol 150 patients with iron deficiency who are scheduled for TAVI due to severe aortic stenosis. The study drug and matching placebo are administered approximately 3 months prior to TAVI, and the patients are followed for 3 months after TAVI. Inclusion criteria are iron deficiency, defined as serum ferritin<100 µg/L or ferritin between 100 and 300 µg/L in combination with a transferrin saturation<20% and written informed consent. Exclusion criteria include haemoglobin<10 g/dL, red blood cell disorders, end-stage kidney failure, intolerance to ferric derisomaltose, and ongoing infections. The primary endpoint is the baseline-adjusted distance walked on a 6 min walk test (6MWT) 3 months after TAVI. Secondary end points include quality of life, New York Heart Association functional class (NYHA functional class), and skeletal muscle strength.

Ethics and dissemination Ethical approval was obtained from the Regional Committee for Medical and Health Research of South-Eastern Norway and The Norwegian Medicines Agency. Enrolment has begun, and results are expected in 2022. The results of the IIISAS trial will be disseminated by presentations at international and national conferences and by publications in peer-reviewed journals.

Trial registration number NCT04206228

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first clinical trial to study the safety and effect of intravenous iron on physical capacity in patients undergoing transcatheter aortic valve implantation due to severe aortic stenosis.
⇒ Iron deficiency is highly prevalent in patients with severe aortic stenosis and may contribute to a lack of improvement in physical function despite successful valve implantation.
⇒ This study will be performed at a single centre in Norway which may limit the generalisability of the results.
⇒ The results of this study will be considered as a proof of concept, and positive results will need to be confirmed in larger multicentre trials.

INTRODUCTION

Calcific aortic stenosis is the most prevalent valvular heart disease in Europe and North America.[1] The prevalence increases with age, and it is estimated that approximately 10% of adults older than 80 years have severe aortic stenosis.[2] The only available therapy is aortic valve replacement. With the advent of transcatheter aortic valve implantation (TAVI), patients previously considered inoperable due to frailty and comorbidity are now offered intervention.[3]

Patients scheduled for TAVI are often elderly and have multiple comorbidities that may affect clinical outcomes despite successful valve implantation. One of the most prevalent comorbidities is iron deficiency (ID). ID is associated with poor exercise capacity, lethargy and reduced quality of life (QoL).[4] In patients with systolic heart failure, clinical trials have shown that treatment with intravenous iron improves exercise capacity, symptom severity and QoL, and reduces the number of hospitalisations for heart failure.[5 6] We have previously found that 53% of patients with severe aortic stenosis

have ID.[7] Observational studies suggest that correction of ID with intravenous iron is feasible in patients with severe aortic stenosis.[8 9] Clinical trials must be performed to evaluate whether the beneficial effects of iron supplementation seen in patients with heart failure also apply to patients with severe aortic stenosis who undergo TAVI.

The *I*ntravenous *I*ron Supplement for *I*ron Deficiency in Patients with *S*evere *A*ortic *S*tenosis (IIISAS) trial is a randomised, controlled, double-blind trial designed to examine whether a single dose of intravenous ferric derisomaltose (formerly known as iron isomaltoside) can improve exercise capacity in iron-deficient patients with severe aortic stenosis who undergo TAVI. To our knowledge, this will be the first trial to investigate the clinical impact of iron treatment in these patients.

ID and myocardial dysfunction

Iron is fundamental to oxygen transportation, DNA synthesis and electron transfer.[10] ID decreases the efficacy of the respiratory chain and leads to impaired mitochondrial production of ATP which is required for cardiac contraction and relaxation. Myocardial dysfunction caused by ID might be reversed with iron supplementation.[11]

Definition of ID in cardiovascular disease

The most common definition of ID in cardiovascular medicine is serum ferritin<100 µg/L (absolute ID) or ferritin between 100 and 300 µg/L in combination with a transferrin saturation (TSAT)<20% (functional ID).[5 6] Ferritin is an acute phase reactant, the plasma concentration of which increases with inflammation.[12] Inflammation is an important mechanism associated with several chronic cardiovascular diseases including heart failure and aortic stenosis.[13] This explains why the cut-off for ferritin in patients with cardiovascular disease has been set higher than in the healthy population, in whom ID has been defined by the WHO as ferritin<15 µg/L. Clinical trials have shown that a serum ferritin threshold of 100 µg/L and TSAT of<20% has clinical relevance in patients with heart failure.[5 14] Beverborg *et al* have shown that patients with ID on bone marrow examination have a TSAT<20%, thereby supporting the TSAT cut-off of<20%.[15]

Like heart failure, aortic stenosis is a chronic disease with systemic inflammation. Therefore, we find it reasonable to apply the same definition for ID in aortic stenosis as in heart failure.

Iron therapy in heart failure and non-valvular interventions in the TAVI population

This will be the first trial to investigate whether intravenous iron in patients with severe aortic stenosis administered before TAVI has an impact on physical capacity. Similar trials have been performed in patients with heart failure with both reduced and preserved ejection fraction. The AFFIRM-AHF (A Randomised, Double-blind Placebo Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalisations and Mortality in Iron Deficient Subjects Admitted for Acute Heart Failure) trial assessed the effect of ferric carboxymaltose in iron-deficient patients with acute heart failure and reduced ejection fraction. While the trial narrowly missed its primary endpoint, a composite of all-cause death and the number of hospitalisations for heart failure, the time-to-event analysis favoured the ferric carboxymaltose arm. Patients who received intravenous iron reported significant improvements in health status.[16] In the FAIR-HF (Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure) trial, patients with chronic heart failure and ID were randomised to receive either ferric carboxymaltose or placebo to investigate whether symptoms, QoL and functional capacity are independent of anaemia.[17] Intravenous iron was associated with a significant improvement of the self-reported patient global assessment and NYHA functional class 6 months after infusion, independently of the presence of anaemia. In the CONFIRM-HF (Ferric CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure) trial, ferric carboxymaltose was associated with an improvement in symptoms (both self-reported and NYHA functional class), functional capacity and QoL.[6] In the EFFECT-HF (Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Iron Deficiency and Chronic Heart Failure) trial, patients with HFrEF and ID were randomised in a 1:1 ratio to receive intravenous iron, and the primary end point was exercise intolerance measured by peak VO_2. The trial concluded with improvement of iron stores and a possible effect on peak VO_2 was observed.[18] However, the EFFECT-HF trial has an important limitation regarding the statistical approach. If the deaths were not imputed, the effect of ferric carboxymaltose on peak VO_2 would not be statistically significant.

The results from the PARTNER (placement of AoRTic TraNscathetER Valve Trial Edwards SAPIEN Transcatheter Heart Valve) trial suggest that TAVI is associated with clinically important improvements in the 6 min walk distance.[19] Goetzman *et al* demonstrated in a prospective study that transcatheter valve implantation resulted in increased walk distance.[20] On the other hand, few studies have shown that pharmacological therapy can improve functional capacity in patients with severe aortic stenosis. Helske-Shuiko *et al* investigated whether blockade of the renin–angiotensin system could improve left ventricular dysfunction and survival. Patients were randomised to receive candesartan or placebo, and the conclusion was that treatment with candesartan did not improve symptoms, 6 min walk distance, or left ventricular function.[21]

ID in patients with aortic stenosis

The few studies that exist on the subject suggest that ID is highly prevalent in patients with aortic stenosis. In a study by Rheude *et al*, ID was present in 91 of 115 (79%) patients with anaemia and aortic stenosis referred for TAVI. Patients with anaemia had increased risk of adverse events such as death, rehospitalisation, or worsening

heart failure the first year after TAVI. Patients with anaemia due to ID had the same clinical outcomes as patients with anaemia without ID.[22] A study conducted by our research group showed that ID was present in 53% of patients with severe aortic stenosis, while 20% had anaemia. Among the patients with anaemia, 79% had ID. ID was associated with an adverse clinical profile but not with mortality.[7] The high prevalence of ID in patients with severe aortic stenosis was substantiated by a study which showed that 54% of patients undergoing TAVI had ID. Furthermore, ID was associated with adverse outcomes, suggesting that iron supplement might be beneficial in patients with aortic stenosis undergoing TAVI.[8] The only randomised controlled trial that exists on the subject failed to demonstrate a reduction in red blood cell transfusions when erythropoietin (EPO) and a small amount of iron was administered prior to TAVI. However, in this study, the iron dose was insufficient to replete iron stores, and the lack of effect by EPO administration might thus be explained by persistent ID.[23]

Benefits and potential risk of intravenous iron

The first-line treatment for ID is oral iron supplementation. However, in the elderly, intravenous iron is considered more effective.[24] Furthermore, in patients with heart failure, oral iron has been shown to be insufficient to replenish iron stores.[25] Discontinuation of medication due to side effects, lack of compliance, and impaired absorption of iron from the gastrointestinal tract due to increased hepcidin concentration as a result of systemic inflammation, may explain why oral iron fails to replenish iron stores in older individuals with cardiovascular disease.[4] Intravenous iron may therefore be a better alternative. Several formulations of intravenous iron are available. Ferric derisomaltose has been shown to be well tolerated and allows for administration of a high dose of iron in a single infusion, thereby minimising the number of clinical contacts.[4 26]

Potential risks

Experimental studies suggest that parenteral iron administration in elderly patients is safe and effective, and associated with minimal risk of serious adverse events.[27 28] Infusion reactions may occur, but the risk of anaphylaxis is extremely rare and was higher with older intravenous iron preparations than with ferric derisomaltose.[29] A systematic review of 97 randomised trials across various parenteral formulations showed that parenteral iron was not associated with an increased risk of serious adverse events (relative risk 1.04, 95% CI 0.93 to 1.17). The rate of serious infusion reactions was low.[29] Minor infusion reactions include transient nausea, hypotension and myalgia.[24] There is a risk of skin staining if extravasation occurs. Iron may enhance oxidative stress and promote inflammation, underscoring the importance of using a strict definition of true ID based on clinical randomised trials before intravenous iron supplementation is administered broadly.[30] Hypophosphataemia has been reported in patients treated with ferric carboxymaltose, but is rare with ferric derisomaltose.[31] Participants who experience characteristic infusion-related side effects may become effectively unblinded. However, the low expected number of adverse drug reactions and the robustness of the primary endpoint limit this problem.

Potential benefits

In patients with systolic heart failure, repletion of iron stores improves physical capacity and QoL. In the FAIR-HF and CONFIRM-HF trials, patients with heart failure and ID were randomised to receive either intravenous iron or placebo.[5 6] They were followed up for 6 and 12 months, respectively, and the results showed improvements in 6 min walk distance, NYHA functional class, QoL, and reduced the risk of hospital admission. In the observational study by Rheude *et al.* from 2019, ferritin, TSAT, and symptoms at 30-days improved in iron-deficient patients with severe aortic stenosis undergoing TAVI who were treated with intravenous iron.[8]

The benefit of intravenous iron in patients with ID and severe aortic stenosis has not been investigated in a randomised controlled setting. Whether the association between ID and adverse outcomes is just a reflection of comorbidity or frailty, or whether ID represents a therapeutic target in these patients is unclear. Based on the results seen in heart failure, and in the aforementioned observational study in aortic stenosis, it is worth investigating whether patients with severe aortic stenosis and ID may benefit from intravenous iron supplementation.

METHODS AND ANALYSIS

Design

The IIISAS trial is an investigator initiated, phase II, randomised, double-blind, placebo-controlled trial conducted at Oslo University Hospital, Oslo, Norway. The WHO Trial Registration Data Set is presented in online supplemental appendix 1. Oslo University Hospital Rikshospitalet performs approximately 500 TAVI procedures each year. Eligible patients are randomised in a 1:1 fashion to receive either a single dose of intravenous ferric derisomaltose or matching placebo. The trial is designed to demonstrate superiority regarding the primary endpoint in patients assigned to active treatment (intravenous iron) versus placebo.

Patients

Patients>18 years who are admitted for evaluation for transfemoral TAVI are screened for participation. Eligible patients must have severe aortic stenosis as defined in the current guidelines, and a V_{max}>3.5 m/s. They must also have ID defined as serum ferritin<100 µg/L or ferritin between 100 and 300 µg/L in combination with a TSAT<20%. Main exclusion criteria include contraindication to the investigational medicinal product, failure to obtain written informed consent, and inability to walk at least 100 m on the 6 min walk test (6MWT). Patients

Table 1 Inclusion and exclusion criteria

Inclusion criteria	► Patients with aortic stenosis with peak flow velocity(> 3.5 m/s) scheduled for aortic valve replacement with TAVI ► Iron deficiency defined as serum ferritin<100 µg/L or ferritin between 100 and 300 µg/L in combination with a transferrin saturation<20% ► Age>18 years ► Signed informed consent and expected compliance with protocol
Exclusion criteria	► Anaemia (haemoglobin<10 g/dL) ► Haemochromatosis ► Haemosiderosis ► Porphyria cutanea tarda ► Blood dyscrasias or any disorders causing haemolysis or unstable red blood cells ► Decompensated liver disease (Child-Pugh score 7 or higher) ► End-stage renal failure, that is, estimated glomerular filtration rate (eGFR) <15 mL/min or on renal replacement therapy ► Planned major surgery within 6 months ► Unresolved cancer predisposing to chronic bleeding or associated with life expectancy<2 years ► On erythropoietin analogues ► Known sensitivity or intolerance to ferric derisomaltose or other parenteral iron preparations ► Intravenous iron supplement within 6 months prior to inclusion ► A clear indication for intravenous iron supplement ► On oral iron substitution (unless the subject agrees to stop treatment prior to randomisation) ► Alcohol or drug abuse within 3 months of informed consent that would interfere with trial participation or any ongoing condition leading to decreased compliance with study procedures or study drug intake ► Intake of an investigational drug in another trial within 30 days prior to intake of study medication in this trial or participating in another trial involving an investigational drug and/or follow-up ► Failure to obtain written informed consent ► Inability to walk at least 100 m over 6 min ► Women of childbearing potential

TAVI, transcatheter aortic valve implantation.

who are too frail or have short life expectancy are not included. A full list of inclusion and exclusion criteria is shown in table 1.

Study procedures and visit schedule

The overall study design is presented in figure 1. Study participants are recruited among patients who are admitted to the Department of Cardiology, Rikshospitalet, Oslo, Norway, for evaluation of severe aortic stenosis. The rationale for administration of intravenous iron during evaluation for valve replacement is that the restoration of iron stores takes time, and one potential benefit of iron replenishment is to increase patient robustness prior to the TAVI procedure. Before randomisation and administration of the study drug, the patients undergo study

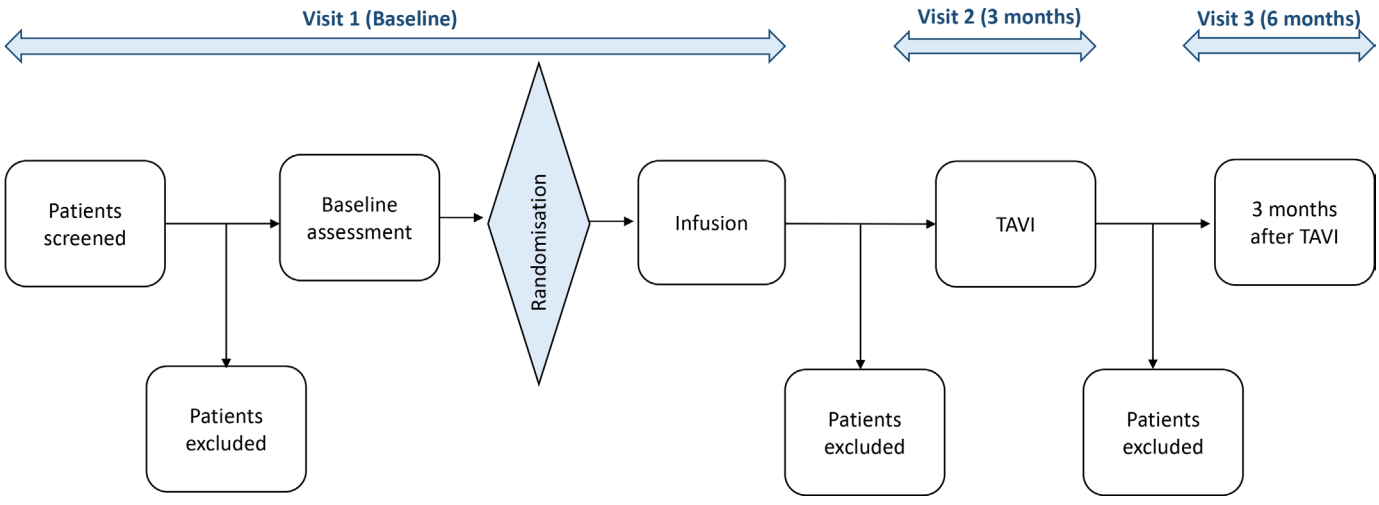

Figure 1 Overall study design. TAVI, transcatheter aortic valve implantation.

Table 2 Overview of the study procedures

	Baseline		At hospitalisation for TAVI	3 months after TAVI	12 months after TAVI (telephone interview)
Time	0		3 months	6 months	15 months
Informed consent	x				
Clinical examination	x		x	x	
ECG	x		x	x	
NYHA functional class	x		x	x	x
Echocardiography	x			x	
Safety samples	x		x	x	
Randomisation	x				
Biobank samples	x		x	x	
6 min walk test	x		x	x	
Hand grip strength	x		x	x	
Body mass composition	x		x	x	
Cognitive function	x		x	x	
Quality of life	x		x	x	
EFT	x		x	x	
Hospitalisation	x		x	x	x
Adverse events	<-x->				

Study drug infusion

ECG, Electrocardiogram; EFT, Essential Frailty Toolset[42] ; NYHA, New York Heart Association.

procedures that include measurements of physical function (6MWT and handgrip strength), cognitive function and self-assessed QoL. Table 2 shows the study procedures performed in the IIISAS trial. The study procedures are performed three times: prior to drug infusion (baseline), approximately 3 months after randomisation (the day before TAVI) and 3 months after TAVI. At each visit, the patients undergo standard physical examination, and any medical or adverse event will be followed up and recorded in accordance with the study protocol.

Randomisation and study treatment

The Research Support Unit at Oslo University Hospital generated a balanced, permuted, variable block size randomisation list (in a 1:1 ratio for the two study arms). Cards marked 'ferric derisomaltose 20 mg/kg' or 'placebo' were placed in sealed and numbered envelopes by a third-party nurse not otherwise involved in the study. The envelopes are kept in a locked cupboard. Once the informed consent has been signed and the patient has been assigned a trial number, a third-party nurse opens the corresponding envelope and prepares the ferric derisomaltose or matching placebo according to information on the card. The active drug, ferric derisomaltose, is administered as a single, intravenous infusion of 20 mg/kg body weight (rounded off to the nearest 100 mg; the maximal dose is set at 2000 mg) dissolved in 100 mL NaCl 0.9%. Patients allocated to placebo receive an intravenous infusion of 100 mL NaCl 0.9%. Because ferric derisomaltose is a dark-brown solution that is easily distinguishable from the saline placebo, preparation and administration of the study drug are performed by third-party, trained and unblinded personnel. To maintain double blinding, the infusion stand, intravenous lines, syringes, and injection site are covered, and the patients are blindfolded. The infusion is administered over 30 min, and the patients are observed for adverse effects for a minimum of 2 hours following the infusion. All study investigators and study participants (patients) are blinded and do not participate in treatment allocation or administration of the study drug.

Study outcomes

Study outcomes are listed in table 3. The primary endpoint of the IIISAS trial is the baseline-adjusted distance walked on the 6MWT 3 months after TAVI (approximately 6 months after the trial intervention). Secondary endpoints are the effects of the treatment on QoL, NYHA functional class and muscle strength. Safety and tolerability of the study drug, and complications during the TAVI procedure are also included among the secondary endpoints. Restoration of iron stores is an important explanatory endpoint regarding the effect or lack of effect of the intervention on the clinically relevant endpoints.

Rationale for the primary study endpoint

ID is highly prevalent in patients with aortic stenosis.[7] Symptoms of ID, such as fatigue, reduced exercise capacity, dyspnoea and cognitive dysfunction, are similar to those seen in symptomatic aortic stenosis. Improved exercise capacity after TAVI is associated with procedural

Table 3 Study outcomes

Primary endpoint	► The baseline-adjusted distance walked on a 6 min walk test performed 3 months after TAVI
Secondary endpoints	► Quality of life as assessed by the KCCQ, SF-36v2, EQ-5D 3L, and EQ-VAS questionnaires ► NYHA functional class ► Muscle strength as measured by the Kern MAP hand-held dynamometer
Exploratory endpoints	► Myocardial structure and function ► Cognitive function as assessed by the CANTAB battery ► N-terminal pro-B-type natriuretic peptide (NT-proBNP) ► Cardiac troponin T (TnT) ► C-reactive protein (CRP) ► Inflammatory and vasoactive peptides
Explanatory endpoints	► Iron stores
Safety endpoints	► Complications during TAVI procedures ► Safety and tolerability

CANTAB, Cambridge Neuropsychological Test Automated Battery; EQ-5D, EuroQol 5-dimension; EQ-VAS, EuroQol Visual Analogue Scale; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; SF-36v2, Short Form Healthy Survey 36 version 2; TAVI, transcatheter aortic valve implantation.

success. However, despite successful valve implantation, symptoms may persist and only two in three patients experience improvement in exercise capacity following TAVI.[32] We postulate that some of these symptoms are due to ID and hypothesise that intravenous iron supplement will improve the distance walked on the 6MWT, health-related QoL, and muscle strength in patients with severe aortic stenosis and ID who undergo TAVI.

We will use the 6MWT to evaluate the effect of iron repletion on exercise capacity. Peak oxygen capacity is considered the gold standard for evaluating exercise capacity. However, measurement of peak oxygen capacity is often not feasible in elderly and multimorbid patients. The 6MWT has been the principal measure of exercise capacity in trials that have assessed the effect of intravenous iron on exercise capacity in patients with heart failure and ID.[33 34] The 6MWT has also been used to assess exercise capacity in patients with severe aortic stenosis following TAVI.[35]

The effect of iron may be diluted by the effect of the TAVI itself. However, aortic valve replacement is a firmly established, life-saving treatment in symptomatic, severe aortic stenosis. It would therefore be unethical to defer TAVI in these patients to assess the effect of intravenous iron. At present, the clinical question is whether intravenous iron might improve functional capacity in iron deficient patients with symptomatic severe artic stenosis *beyond* TAVI.

Assessment of study endpoints

6 min walk test

The 6 min walk distance is measured as the number of metres that the subject is able to walk over 6 min. The patients walk back and forth on a 30-metre marked walking course in a hospital corridor. Turnaround points are marked with orange cones. Standardised encouragement is provided. Heart rate, blood pressure and oxygen saturation are measured before and after the 6MWT. NYHA functional status is recorded at the end of the test, and Borg scale is used to evaluate the participants' effort, breathlessness and overall fatigue.

Quality of life

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a well-established and validated questionnaire used to measure outcomes of heart failure over time.[36] It comprises seven domains (symptom frequency; symptom burden; symptom stability; physical limitations; social limitations; QoL; and self-efficacy) and measures symptoms, physical and social limitations, and QoL. Combination of different domains create different scores including a symptom score and an overall summary score. The overall summary score from the KCCQ, scaled from 0 to 100, is the principal measure of QoL in the IIISAS trial. For in-depth analyses of the impact of intravenous iron on QoL in this population, we also measure QoL assessed by the Short Form Healthy Survey 36 version 2 (SF36v2), EuroQol 5-dimension (EQ-5D), and the EuroQol Visual Analogue Scale (EQ-VAS). The SF36v2 consists of eight scales, and components from these scales compound two distinct dimensions: a physical dimension (physical component summary) and a mental dimension (mental component summary).[37] The EQ-5D consists of five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression and each domain has three different response alternatives. In the EQ-VAS scale, the respondents are asked to rate their overall health state on a scale from 0 to 100.[38]

Hand grip strength

We will use the Kern MAP hand-held dynamometer to measure hand grip strength. Among older adults, hand grip strength is considered an indicator of overall body strength.[39] Hand grip strength is an objective component of frailty and associated with cardiovascular mortality.[40] By measuring hand grip strength at baseline, before TAVI

and 3 months after TAVI, we can detect changes in muscle strength.

Laboratory analyses

Blood samples are taken to determine haemoglobin, white blood cell count, platelet count, serum electrolytes, kidney function, glucose, glycated haemoglobin, liver function, albumin, C-reactive protein, N-terminal pro-B-type natriuretic peptide, total cholesterol, ferritin, transferrin, serum iron, and total iron binding capacity. Blood will also be drawn for storage in a biobank and subsequent analysis of biomarkers.

Body composition

Body composition is assessed with the InBody 770 bioelectrical impedance analyser. Weight, total water, total fat, percent fat, the ratio of extracellular water to intracellular water (measuring oedema), and visceral fat are measured.

Cognitive function

The Cambridge Neuropsychological Test Automated Battery will be used to assess cognitive function.[41] In addition, the Mini-Cog test is used to detect cognitive impairment and frailty in elderly.[42] The Mini-Cog test is a quick screening test for cognitive impairment in older adults. It consists of two components, a 3-item recall test and a clock draw test.

Transthoracic echocardiography

The severity of the aortic stenosis is assessed by continuous wave Doppler in multiple acoustic windows to obtain the maximal jet velocity. The mean pressure gradient across the aortic valve is measured using the time velocity integral, and the aortic valve area is estimated using the continuity equation. We assess myocardial structure and function after TAVI. The principal measure of myocardial function in the IIISAS trial is peak left ventricular global longitudinal strain.

Hospitalisations and adverse events

The potential associations between treatment with intravenous iron and in-hospital complications, including death, myocardial infarction, bleeding, pacemaker implantation, renal insufficiency and days in hospitals will be examined. Patients are followed-up for the first year after the TAVI procedure for safety.

Sample size calculations

This trial is designed to assess the effect of treatment with intravenous iron on the baseline-adjusted 6 min walk distance. We consider an increase of 30 m to represent a clinically meaningful improvement.[6] We expected a repeat-measurement SD of 50 m. With a power of 80% and an α of 5%, we would need at least 44 patients in each group. To ensure adequate power, we performed a per-protocol, interim, blinded analysis of the SD of the repeat measurement 6 min walk distance after 50 patients had completed the last study visit (visit 3). The measured SD was 53 m. By the revised sample size calculations, we need 49 patients in each group. Due to a higher number of patient dropouts than expected, we aim to include 150 patients to ensure sufficient power.

Statistical analysis

All statistics will be performed using a two-sided 5% level of significance. The baseline demographics will be presented by columns for each treatment (Placebo, Intravenous ferric derisomaltose). All analyses will be performed on an intention-to-treat basis. All continuous variables will be summarised using the following descriptive statistics: mean±SD deviation; median (IQR). The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures.

For the primary endpoint, only patients who receive TAVI and perform an adequate 6MWT at baseline and follow-up can be analysed (modified intention-to-treat population). The primary endpoint will be assessed as the baseline-adjusted between-group difference in the 6 min walk distance by analysis of covariance (ANCOVA); the statistical null-hypothesis being that the baseline-adjusted 6 min walk distance does not differ between the two treatment arms. All secondary continuous endpoints will be analysed with ANCOVA, in the same manner as for the primary endpoint. All dichotomous endpoints will be analysed with the Newcombe hybrid score interval and the Fisher mid-P test. All categorical endpoints with more than two categories (ie, NYHA) will be analysed with the Wilcoxon-Mann-Whitney test. Possible subgroup effects for continuous endpoints will be analysed by adding an interaction term between the variable defining the subgroup and the treatment variable in the linear regression. Secondary endpoints will be analysed in a non-hierarchical manner and without formal adjustment for multiple testing, but with due consideration to the fact that multiple testing increases the risk of chance findings, and that the results regarding secondary endpoints in a proof-of-concept trial must be regarded as hypothesis-generating only.

To determine the robustness of the analysis of the primary endpoint, we will perform sensitivity analyses with imputations for missing data. While we do not expect the trial intervention to affect dropouts, it is unreasonable to assume that dropouts will occur completely at random, and dropouts may therefore bias the final results. We therefore aim to do best-case, worst-case, no-change scenario imputations for missing data.

Safety analyses will include tabulation of type and frequency of all adverse events. Any serious adverse events will be reported with comprehensive narratives. Safety laboratory parameters outside normal ranges will be identified. Statistical analyses will be performed in IBM SPSS Statistics V.21 or later.

Patient and public involvement

Neither patients nor members of the public were involved in the design of this clinical trial. The patients receive

Table 4 Baseline data of the first 100 included patients in the IIISAS trial, n=100

Demography	
Age, years	79 (75–85)
Male, sex	56 (56)
Smoker, current/previous smoker	33 (33)
Body mass index, kg/m^2	27.8±4.9
Systolic blood pressure, mm Hg	149±23
Diastolic blood pressure, mm Hg	72±11
Heart rate, rpm	73±12
Medical history	
Previous cardiac arrest	1 (1)
Previous or current history of coronary artery disease	47 (47)
Hypertension	43 (43)
Diabetes mellitus	18 (18)
Hypercholesterolaemia	23 (23)
Atrial fibrillation	43 (43)
Previous stroke or transient ischaemic attack (TIA)	8 (8)
Peripheral vascular disease	4 (4)
Chronic obstructive pulmonary disease	10 (10)
Medication	
Angiotensin-converting-enzyme (ACE) inhibitor/Angiotensin II Receptor Blockers (ARB)	52 (52)
Beta-blocker	51 (51)
Acetylsalicylic acid (ASA)	42 (42)
Non-ASA platelet inhibitors	10 (10)
Warfarin (Marevan)	9 (9)
Direct oral anticoagulation	26 (26)
Cholesterol lowering agent	78 (78)
Oral iron supplementation	4 (4)*
Biochemistry	
Haemoglobin, g/dL	13.2±1.1
N-terminal pro-B-type natriuretic peptide (NT-proBNP), ng/L	1015 (451–1797)
Troponin T, ng/L	17 (11–31)
C-reactive protein (CRP), mg/L	1.7 (0.8–4.8)
Creatinine, µmol/L	92±30
Estimated glomerular filtration rate (eGFR), mL/min	65±18
Cholesterol mmol/L	4.1±1.0
LDL cholesterol, mmol/L	21 (15–27)
Ferritin, µg/L	56 (39–87)
Iron, µmol/L	13±5
Transferrin, g/L	2.7±0.4
Transferrin saturation (TSAT) (%)	18 (14–24)
Transferrin receptor, ng/mL	3.6 (2.7–4.1)
Total iron-binding capacity (TIBC), µmol/L	65 (60–73)
Presence of ID, n (%)	
Absolute (ferritin<100 µg/L)	85 (85)
Functional (ferritin 100–300 µg/L and TSAT<20%)	15 (15)
Echocardiographic measures	
Aortic peak velocity, m/s	4.4 (4.1–4.8)
Aortic mean gradient, mm Hg	48 (41–59)
Aortic valve area, cm^2	0.7 (0.6–0.8)
NYHA functional class	
Class I	3 (3)
Class II	55 (55)
Class III	40 (40)
Class IV	2 (2)
Essential Frailty Toolset Score†	
Score 0	39 (39)
Score 1	55 (55)
Score 2	17 (17)
Score 3	3 (3)
Score 4	0 (0)
Score 5	0 (0)
6 min walk distance, metres	368±117

Selected characteristics of the study sample (n=100) Results are reported as median (IQR), number (%) or mean±SD.
*These patients agreed to stop oral iron supplementation prior randomisation.
†Essential Frailty Toolset Score, see reference.[42]

their test results from baseline and follow-up. Once the study is completed, all study participants will receive a written letter with information about which treatment arm they were allocated to and a thorough information about the study results and their implications.

Trial governance and monitoring

The IIISAS trial is an investigator-initiated trial. The manufacturer of the investigational medicinal product, Pharmacosmos, provides the study drugs and matching placebo, and has provided a grant for the conduct of this trial. Pharmacosmos will take no role in the collection, analyses, interpretation of the data, or in the decision to publish. The sponsor, Oslo University Hospital and the investigators take sole responsibility for the integrity of the data and the dissemination of the results.

An independent data monitoring committee is responsible for the regular monitoring of the trial data. Based on the accumulated safety data, the monitor can advise temporary or permanent stop in patient enrolment. The

monitor is independent from sponsor and free from any conflict of interest.

ETHICS AND DISSEMINATION

The IIISAS trial is designed to assess the effect of a therapeutic intervention with the aim to improve outcome in a population with considerable morbidity and mortality. The trial will be conducted according to Good Clinical Practice Guidelines and complies with the declaration of Helsinki. The study was approved by the Regional Committee for Medical and Health Research of South-Eastern Norway (2019/825/REK Sør-Øst C), The Norwegian Medicines Agency, and the Data Protection Officer (Personvernombudet) at Oslo University Hospital.

All patients included in this trial will provide written informed consent before enrolment and randomisation. Consent will be obtained by trained personnel in accordance with routine investigations at Rikshospitalet prior to surgery. The patients are informed that agreeing to participation also means consenting to storage of biological material in the biobank. All information collected in the study will be processed without name and social security number or other personally identifiable information. A code links the patients to the collected information through a list of names. The end date for the data storage is 31 December 2036, and information collected in this project will be deleted after this date. Based on previous trials on intravenous iron administration, we do not expect a substantial number of drug-related serious adverse events.

The IIISAS trial was initiated in January 2020. We expect the trial to be completed and results available by the summer of 2022. Baseline characteristics of the first 100 patients are presented in table 4. The results will be disseminated by presentations at international and national conferences and by publications in peer-reviewed journals.

The IIISAS trial will provide novel insights into whether iron supplementation can improve physical capacity in patients with ID and aortic stenosis undergoing TAVI. If the results suggest that intravenous iron is associated with improved outcomes after TAVI, the findings should be confirmed in larger, multicentre studies.

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