Iron Deficiency in Patients with Left Ventricular Assist Devices

William Herrik Nielsen [1] and Finn Gustafsson [1,2]

1. Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark;
2. Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Abstract

Iron deficiency is a common and independent predictor of adverse outcomes in patients with heart failure. The implications of iron deficiency in patients implanted with a left ventricular assist device (LVAD) are less established. This review recaps data on the prevalence, characteristics and impact of Iron deficiency in the LVAD population. A systematic search yielded eight studies involving 517 LVAD patients, with iron deficiency prevalence ranging from 40% to 82%. IV iron repletion was not associated with adverse events and effectively resolved iron deficiency in most patients. However, the effects of iron deficiency and iron repletion on post-implant survival and exercise capacity remain unknown. Although iron deficiency is highly prevalent in LVAD patients, its true prevalence and adverse effects may be misestimated due to inexact diagnostic criteria. Future randomised controlled trials on IV iron treatment in LVAD patients are warranted to clarify the significance of this common comorbidity.

Keywords

Iron deficiency, left ventricular assist device (LVAD), transferrin saturation (TSAT), ferritin, iron supplementation

Received: 22 December 2023 **Accepted:** 18 April 2024 **Citation:** *Cardiac Failure Review* 2024;10:e08. **DOI:** https://doi.org/10.15420/cfr.2023.26

Disclosure: FG has received consulting fees from Abbott, FineHeart, AdjuCor, Pharmacosmos, Bayer, Pfizer, Astra-Zeneca, CorHeart6, Ionis and Alnylam; has received speaker's fees from Novartis and Orion; is a board member of the Heart Failure Association of the European Society of Cardiology and is a section editor on the *Cardiac Failure Review* editorial board; this did not influence peer review.

Funding: This study was funded by a grant from the Novo Nordisk Foundation (20OC0060561; to WHN).

Correspondence: William Herrik Nielsen, Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. E: william.herrik.nielsen@regionh.dk

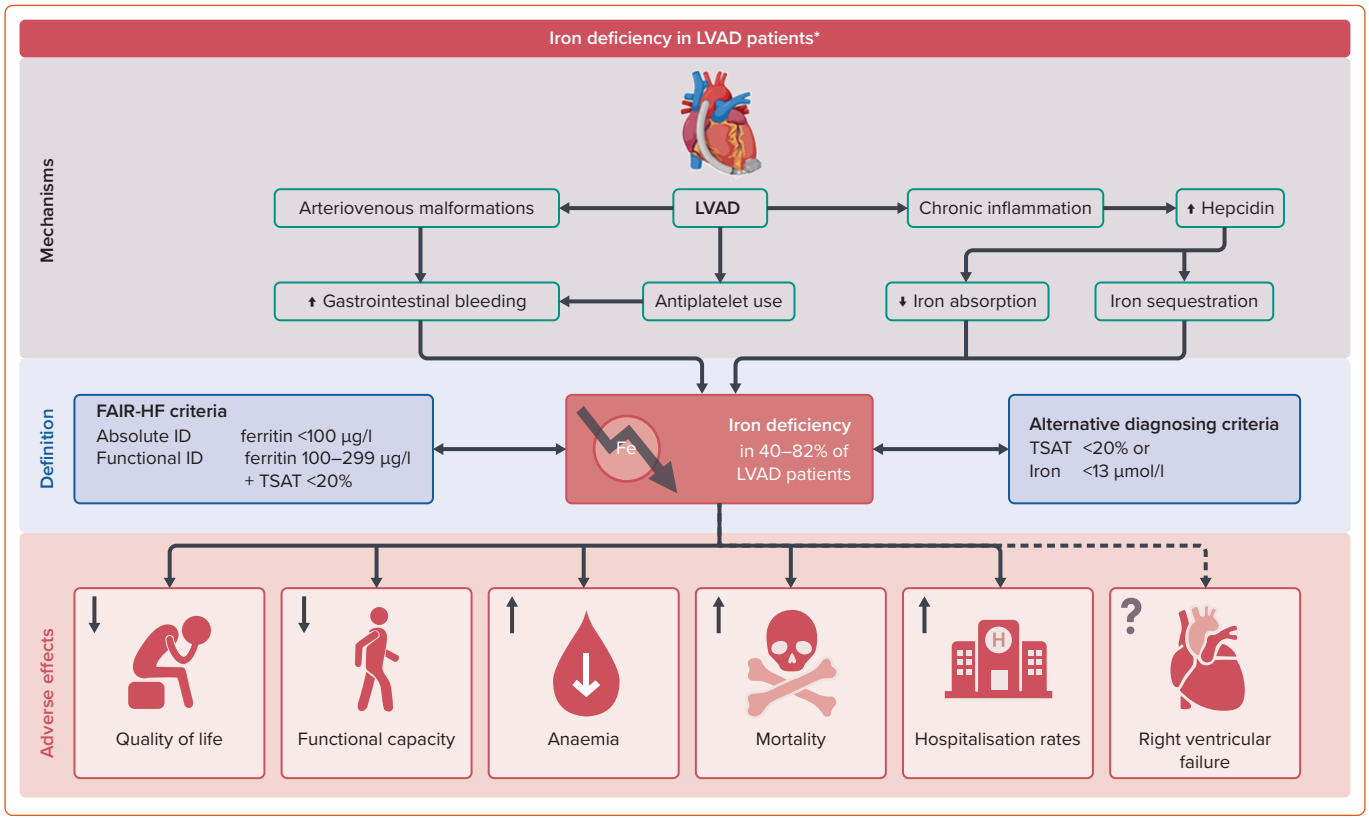
Iron deficiency (ID) is a common comorbidity in patients with heart failure (HF), in which iron stores are insufficient to meet the demands of the body for critical physiological functions, including oxygen storage and transportation (haemo- and myoglobin), mitochondrial oxidative metabolic processes and the metabolism of macronutrients as well as nucleic acids.[1] ID in HF patients is associated with worsening symptoms, impaired functional capacity, reduced quality of life (QoL) and higher risks of mortality and hospitalisation, independent of anaemia.[2–6]

In patients with HF, ID is usually defined according to the FAIR-HF trial criteria as either absolute (ferritin <100 µg/l) or functional (ferritin 100–299 µg/l and transferrin saturation [TSAT] <20%).[7] Using this definition, the prevalence of ID in HF patients is approximately 50%.[2] The underlying pathophysiology of ID in the context of HF is multifactorial and not fully understood; it involves impaired intestinal function and hepcidin dysregulation due to the inflammatory state in HF. For the same reasons, oral iron supplementation is usually ineffective.[8] IV iron repletion is a safe and viable treatment of ID in patients with HF, improving symptoms, QoL and exercise capacity.[9] The effects of IV iron repletion on mortality and HF hospitalisations are less clear. A recent meta-analysis concluded that, compared with placebo, treatment with IV iron significantly reduced the composite outcome of recurrent HF hospitalisations and cardiovascular death (RR 0.77; 95% CI [0.66–0.90]; p<0.001).[2] However, a recent large randomised trial, not included in the meta-analysis, did not find similar clinical benefit of IV iron in HF patients with ID.[10]

In patients with end-stage advanced HF, treatment options include heart transplantation and implantation of left ventricular assist devices (LVADs). Worsening shortages in donor organ availability severely limit heart transplantation, making LVADs an increasingly important alternative.[11] Survival after LVAD implantation has improved in recent years, with 5-year overall survival at 58% with contemporary devices (HeartMate 3), as reported by the MOMENTUM 3 trial, and 2-year survival equivalent to that of heart transplantation recipients.[12,13] Although LVAD therapy ameliorates HF symptoms and end-organ dysfunction and is associated with improvements in the 6-minute walk distance (6MWD) and QoL, exercise capacity (peak oxygen uptake; $pV\dot{O}_2$) remains significantly reduced after implantation.[14,15] Furthermore, readmission rates are significant, at 1.3–2.6 per patient-year, attributable to episodes of infections, bleeding and HF-related events.[15,16] It may be hypothesised that ID is an important mediator of these adverse events. In the recent updates of the European Society of Cardiology (ESC) guidelines on managing HF, treating ID with IV iron to improve QoL and functional capacity has been given a Class I recommendation.[17] However, the guidelines do not address HF patients treated with LVAD. As such, there is uncertainty in the clinical community about how to manage ID in LVAD patients.

In this narrative review, we present an overview of the existing research on the prevalence, characteristics and effects of ID in the LVAD population, shedding light on potential implications for patient management and identifying areas for further investigation.

Figure 1: Iron Deficiency in Left Ventricular Assist Device Patients



The adverse effects of ID are extrapolated from the general heart failure population, where no data on LVAD patients exist. The described mechanisms leading to ID in LVAD patients were simplified to guide readability and based on the scope of this review. The adverse effects of ID include findings from the general heart failure population, where no studies in LVAD exist. Based on the relationship, they are marked by either an upward (↑) or downward (↓) pointing arrow. The effect on right ventricular failure is marked with a question mark because the association is currently hypothetical due to the lack of studies. ID = iron deficiency; LVAD = left ventricular assist device; TSAT = transferrin saturation. Source: Created with BioRender.com.

Methods

Search Strategy

A systematic literature search was conducted through the PubMed and Embase databases up to 26 September 2023 to identify ID studies in adult patients implanted with an LVAD (search terms are provided in *Supplementary Table 1*). Only original articles on ID in adult LVAD patients were included. After removing duplicates, screening was performed by title, abstract and full-text (*Supplementary Figure 1*). Ultimately, we searched ClinicalTrials.gov for ongoing trials, although we could only identify a single terminated study (NCT03774615).

Data Collection and Analysis

Study characteristics (e.g. centre, population size, inclusion/exclusion criteria) and patient baseline criteria (e.g. age, sex, LVAD type) were extracted from the published articles. Laboratory results were harmonised to SI units (e.g. creatinine in µg/dl to µmol/l) and durations of LVAD support were converted to months to facilitate comparisons. Continuous variables are presented as the mean with 95% CI or median with interquartile range (IQR), depending on the source material. Two-tailed p≤0.05 was considered statistically significant. *Figure 1* was drawn using BioRender.com, whereas all statistical analyses and other visualisations were conducted in R.

Results and Discussion

Our literature search identified eight studies of ID in LVAD patients, published between 2017 and 2023, with a combined population of 517 patients (*Table 1*). Seven studies were retrospective (one cross-sectional); all were single-centre studies and generally had small sample sizes. All studies used the FAIR-HF definition of ID, and iron supplementation was addressed in six studies.[19,20,22,23,47,48] The study populations were similar in age, sex and HF aetiology, but differed in LVAD characteristics and the research area in focus (*Supplementary Table 2*). Across studies, the most common device was HeartMate 3 (49%), followed by HeartMate II (34%) and the HeartWare Ventricular Assist Device (14%), with the type of device unreported in 3% of patients. Key findings and concepts from our review are summarised in *Figure 1*.

How Common is Iron Deficiency in LVAD Patients?

Prevalence data were reported in six studies and are presented in *Figure 2*, with prevalence ranging between 40% and 82%.[18,19,21,23,47,48] Peters et al. identified ID in 213 of a total of 528 LVAD patients, making the prevalence of 40% notably lower than in the other studies.[48] The authors of that study did not state whether all 528 patients were screened, which may explain the lower prevalence of ID. Absolute ID (ferritin <100 µg/l) was the most frequent subtype (~75%), and most patients had concurrent anaemia (67–87%).[18–22]

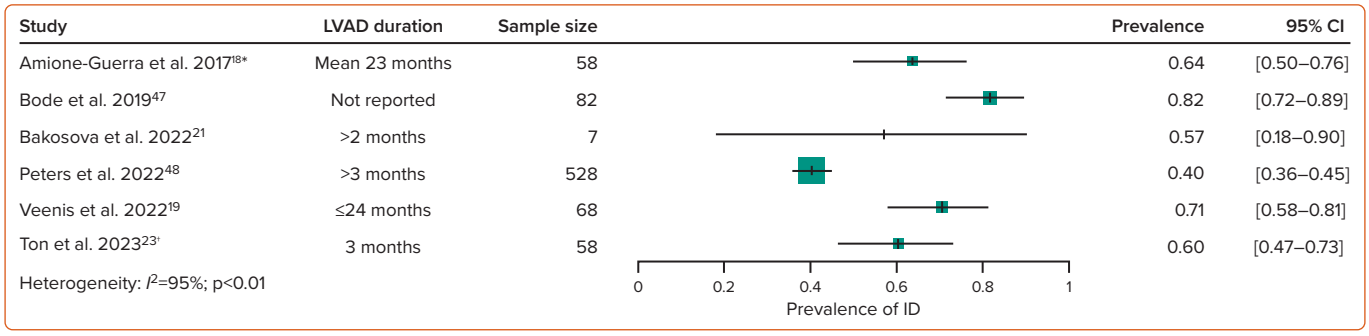
The prevalence of ID at different times (*Figure 3*) was reported in two studies, with a pre-implant (i.e. prior to LVAD implantation) prevalence of 53% and 51%, similar to the general HF population.[2,19,23] The prevalence of ID decreased in the early post-implant period (0–3 months), but increased above baseline from 3 months onward, which may be explained by the peri- and postoperative blood transfusions related to LVAD implantation.[24] Ton et al. reported that 79% of patients were transfused with a median of 3 units (IQR 2–6 units) of packed red blood cells <14 days after implantation.[23] At subsequent follow-ups, the prevalence of ID increased even though haemoglobin levels increased.[23] Transfusion rates were not reported by Veenis et al.[19]

Table 1: Summary of Included Studies

Study	No. Patients*	Patients	Major Exclusion Criteria	Focus	Comparator	Iron Preparations
Amione-Guerra et al. 2017[18]	58†	LVAD ≥6 months Anaemia (Hb <12 g/dl)	GI bleed/transfusion ≤3 months Conditions influencing anaemia‡	Anaemia aetiology	ID versus non-ID anaemia	Oral ferrous sulphate
Bode et al. 2019[47]	31	LVAD + ID	Transfusion ≤3 months Signs of PT (LDH >3 × normal) Active bleeding/infection	Resolution of ID	IV versus oral iron§	IV ferric gluconate IV ferumoxytol Oral ferrous sulphate
Bakosova et al. 2022[21]	7	Enlisted for HTx (LVAD arm)	Conditions limiting prognosis‖	Prevalence of ID	LVAD versus non-LVAD	N/A
Peters et al. 2022[48]	205	LVAD+ID	N/A	Efficacy and safety of IV iron	IV iron versus no IV iron	IV iron sucrose
Veenis et al. 2022[19]	84	LVAD ≥3 months follow-up	N/A	Prevalence of ID and iron supplementation	LVAD versus non-LVAD	Not reported
Vesper et al. 2024[22]	33	HM3 + ID	Transfusion ≤6 months IV iron outside index submission Dialysis requirement at index discharge	Efficacy of early IV iron	IV iron versus no IV iron	IV ferric gluconate
Bernier et al. 2023[20]	12	LVAD Treated ≤30 days after implant	Transfusion ≤90 days after IV iron	Efficacy of IV iron	LVAD versus non-LVAD	Not reported
Ton et al. 2023[23]	87	LVAD ≥3 plasma samples (2 weeks before, 1, 3 or 6 months after implant)	N/A	Hepcidin dysregulation	N/A	Not reported

**Number of patients implanted with an LVAD (may be a subgroup). †The retrospective analysis was excluded because it did not address ID. ‡Myelodysplastic syndrome, chemotherapy or haemochromatosis. §Selection to IV versus oral treatment was decided by the treating physician, accounting for patient factors (i.e. cost, logistics). ‖Infections, malignancies, severe kidney, liver, or lung dysfunction. GI = gastrointestinal; Hb = haemoglobin; HM3 = HeartMate 3; ID = iron deficiency (all studies defined ID by FAIR-HF criteria); LDH = lactate dehydrogenase; LVAD = left ventricular assist device; PT = pump thrombosis.*

Figure 2: Prevalence of Iron Deficiency in Patients with Left Ventricular Assist Device across Studies



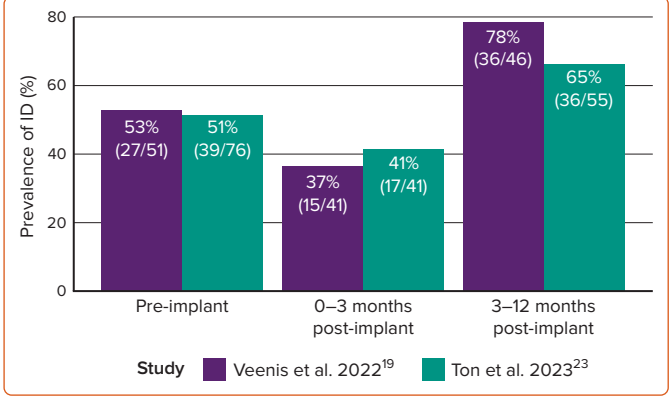
*Two studies (Vesper et al. 2024[22] and Bernier et al. 2023[20]) were not included in the figure because they used ID as an inclusion criterion (i.e. 100% of patients) and did not state the proportion of ID in the total number of LVAD patients at risk. *The whole sample size had anaemia; thus, the reported prevalence was specifically for ID anaemia. No data on non-anaemic ID was available. †A single time point was selected for the comparison; see Figure 3 for the remaining data. ID = iron deficiency; LVAD = left ventricular assist device.*

Although all studies used the same definition of ID, the timing of iron measurements (relative to the time of implant) varied considerably across studies (e.g. both before index discharge and 2 years after implant). Criteria for when to test for ID (iron indices) were generally undisclosed by the studies. It is probable that adverse events, including bleeding and haemolysis, triggered blood testing, as in the study by Veenis et al., introducing a significant risk of sampling bias in the results.[19] Interestingly, Veenis et al. reported that the number of patients screened for ID prior to LVAD implant increased significantly after the publication of the 2016 ESC HF guidelines (from 36% to 79% of patients screened; p<0.001), which may have influenced other studies as well.[19,25] Although these numbers were not adjusted for blood transfusions or iron supplementation and were subject to further sampling bias due to the independent nature of the sampling, the results suggest that LVAD therapy does not alleviate ID. Protocolised testing for ID is necessary to estimate the true prevalence of ID in the LVAD population.

Defining and Diagnosing Iron Deficiency

The FAIR-HF trial definition of ID is widely used in HF research and was adopted by both American and European HF guidelines, but the accuracy of the criteria has been questioned. Ferritin is closely correlated to iron stores in healthy subjects, but acts as an acute phase protein, and thus levels increase during infections and other inflammatory conditions.[25–27] Furthermore, chronic inflammation induces the hepatic hormone hepcidin,

Figure 3: Prevalence of Iron Deficiency Through Left Ventricular Assist Device Therapy



Data presented from the study by Ton et al. 2023[23] are specifically at 1 and 6 months after implant; the prevalence of ID at 3 months after implant (not shown) was 35/58 (60%). Numbers were not adjusted for blood transfusions or iron supplementation. Data should be interpreted as unpaired samples, because the sampled patients may have varied between time points. ID = iron deficiency.

which inhibits iron absorption in the gut while increasing the release of ferritin from cells, in turn clouding the relationship between serum ferritin and iron stores *in vivo*.[28] Taking this into account, the conventional definition used higher limits of ferritin to account for the chronic inflammation of HF, inspired by data on ID in patients with chronic kidney disease.[28] Although the chosen cut-off values are empirical, they have successfully identified patients who benefitted from treatment with IV iron in several studies.[9] TSAT, the quotient of serum iron divided by serum transferrin (or total iron-binding capacity), is a more direct marker of available iron in the bloodstream and is less sensitive to inflammation.[29]

To validate the FAIR-HF definition, Grote Beverborg et al. referenced serum iron indices to bone marrow iron staining, the gold standard for diagnosing ID.[30] The FAIR-HF criteria had a sensitivity of 82% and specificity of 72% in diagnosing ID, and were surpassed by both TSAT ≤19.8% and serum iron ≤13 µmol/l (94% sensitivity for both and 84% and 88% specificity, respectively; p<0.05 versus the standard criteria).[30] These alternative criteria have significantly outperformed the conventional definition in retrospectively identifying patients who benefitted from iron repletion across several HF cohorts.[30–34]

In a cohort of 387 HF patients, both TSAT and serum iron were significantly associated with mortality, whereas isolated hypoferritinaemia (ferritin <100 µg/l) did not predict mortality.[30] When applying the results to a meta-analysis by Anker et al., patients with TSAT ≤19.8% had significantly improved outcomes (in terms of cardiovascular hospitalisation and cardiovascular death), whereas patients with TSAT >19.8% did not benefit from treatment with IV ferric carboxymaltose.[30,31] Similarly, subgroup analysis in the iron-CRT trial showed a significantly greater effect of ferric carboxymaltose in patients with TSAT <20% (versus TSAT ≥20%).[35] TSAT <20% predicted all-cause mortality in patients with HF with preserved ejection fraction and higher all-cause 5-year mortality, but FAIR-HF criteria did not.[33,34] Curiously, Masini et al. found a trend towards lower 5-year mortality in patients with ferritin <100 µg/l (absolute ID; HR 0.91; 95% CI [0.81–1.01]; p=0.09). The AFFIRM-AHF trial did not find a treatment interaction with low versus high TSAT.[34,36] Dhaliwal and Kalogeropoulos argued that the optimal definition depends on the outcome of interest. TSAT seems to be the superior predictor of mortality, whereas ferritin is a stronger predictor of functional capacity and QoL.[37] Soluble transferrin receptor and hepcidin have been suggested as alternative and possibly more robust biomarkers of ID, but these are less readily available for routine testing.[38]

In the study by Ton et al., median ferritin levels initially increased from 188 µg/l (IQR 111–417 µg/l) before implantation to 320 µg/l (IQR 134–503 µg/l) at 1 month before decreasing to 91 µg/l (IQR 40–179 µg/l) 6 months after implantation (p=0.0001).[23] Although rates of ID increased above baseline after 3 months, the median hepcidin/TSAT ratio decreased quantitatively from 103 ng/ml/% before implantation to 56 ng/ml/% 6 months after implantation (p=0.1), remaining above the 50 ng/ml/% limit of responsiveness to oral iron repletion established by the IRONOUT HF trial.[23,39] The hepcidin/TSAT ratios were higher in patients with functional versus absolute ID and were not correlated with infections or bleeding episodes.[23] It has been argued that LVAD therapy accentuates the inflammation associated with HF, at least initially, due to the shear stress and foreign body surfaces introduced by the device.[40,41] Furthermore, driveline and other LVAD-related infections are common adverse events during LVAD therapy, which has been linked to a systemic inflammatory response, including interactions with the bone marrow, often undetectable by changes in serum concentrations of white blood cells or C-reactive protein.[12,42,43] Fluctuations in the proinflammatory cytokine interleukin-6, a well-known inducer of hepcidin, are of interest, but reported changes during LVAD therapy have been conflicting.[41,44] To the best of our knowledge, no studies have examined correlations between inflammatory and ID markers in LVAD patients.

Based on the reviewed studies of LVAD patients, ID is most often of the absolute type, characterised by depleted iron stores, usually ascribed to malnutrition, impaired gut absorption and chronic blood loss, but not inflammation.[45] Gastrointestinal (GI) bleeding is a common adverse event of LVAD therapy: 5-year outcome data from the MOMENTUM 3 trial revealed that bleeding events have become less frequent in patients with contemporary HeartMate 3 devices, but remain substantial at 0.43 events per patient-year.[46] Haemolysis events were minor at 0.0005 per patient-year.[12] To adjust for this, several of the included studies excluded patients with recent GI bleeding (*Table 1*), but may have missed those with occult bleeding. The intricate and inverse effects of persistent blood loss and chronic inflammation on ferritin levels may further diminish the validity of the FAIR-HF criteria in LVAD patients. The optimal diagnostic criteria for ID in patients with LVAD remain uncertain; future studies validating the various definitions through bone marrow staining in LVAD patients would be beneficial.

Efficacy and Safety of Iron Supplementation

In total, 130 (25%) patients were treated with a single infusion of IV iron (iron sucrose, ferric gluconate, ferumoxytol or unreported), 131 (25%) were treated with oral iron (ferrous sulfate or unreported) and 36 (7%) were treated with both IV and oral iron. The decision to treat patients with iron supplementation was not randomised, and the studies generally did not disclose the indication criteria, exposing them to considerable risk of selection bias.

Both oral and IV iron treatment led to significant and comparable improvements in haemoglobin levels, ranging between +0.74 and 1.37 mmol/l at follow-up.[18,20,47,48] The clinical importance of these small increments in haemoglobin levels is questionable. However, one study reported that IV iron resolved anaemia in 62.5% of patients (versus 20% of patients not treated with IV iron; p=0.051).[22] Improvements in ferritin levels were significantly greater in patients treated with IV versus oral iron (+165.2 µg/l versus +8.65 µg/l, respectively; p=0.0006), whereas no

difference in the change in TSAT was found.[47] Vesper et al. reported increases in ferritin of 91.5 µg/l and TSAT of 14.5% after treatment with IV iron (not compared to control).[22] IV iron effectively resolved ID, with resolution in 85% of patients (versus 20% not treated with IV iron; p=0.001) and 40% of patients (versus 0% in patients treated with oral iron; p=0.008).[22,47] The relative ineffectiveness of oral iron in resolving ID may be attributed to elevated hepcidin levels.[23] Furthermore, oral iron may induce oxidative stress in the intestinal mucosa, possibly exposing LVAD patients to an increased risk of GI bleeding, further challenging the justification for the treatment.[49] A single study reported greater odds for improvement in New York Heart Association functional class (OR 2.84; 95% CI [1.42–5.68]) after IV iron compared with oral iron, whereas another study did not find a significant difference between treatment groups.[47,48] Compared with oral iron, IV iron did not improve 6MWD (+240 ± 220 versus +110 ± 226 m, respectively; p=0.208) at follow-up (within 180 days after implant).[22] Because the study was conducted immediately after implantation, the positive effects of IV iron on functional capacity may have been masked by the expected improvement in 6MWD attributable to the LVAD therapy itself.[50]

Treatment with IV iron was not associated with significant improvements in QoL measures. In the study by Bode et al., five patients had paired Kansas City Cardiomyopathy Questionnaire (KCCQ-12) data, with a median change in the KCCQ-12 score of +9.38 (p=0.075 from baseline), and Vesper et al. reported no difference in the mean change in Minnesota Living With Heart Failure Questionnaire scores between groups.[22,47] The sample sizes in these studies were small, and the studies were probably not powered to detect any significant effects of IV iron, making the results inconclusive.

Regarding the safety of IV iron, previous studies have linked IV iron treatment to an increased risk of infection in patients with ID and chronic kidney disease.[51] This has led to concerns regarding the treatment of LVAD patients, because device-associated and bloodstream infections are associated with poor outcomes, including increased mortality.[42,52,53] Three studies reported safety endpoints after treatment with IV iron, and none reported increased rates of any adverse events, including infection rates, concluding that the treatment is safe in this population.[22,47,48] Although sample sizes were small, the results are consistent with the findings in studies of non-LVAD HF patients with ID.[2]

Importance of Iron Deficiency on Clinical Outcomes

In HF in general, ID is correlated with poorer QoL and worse functional capacity, impairing long-term outcomes.[54] However, none of the studies involving LVAD patients reported associations between ID and outcomes in terms of mortality, right ventricle (RV) failure, hospitalisation rates or exercise capacity. Studies are clearly required to address these important topics. Due to the lack of data, we propose two possible mechanisms through which ID may affect adverse outcomes.

First, exercise capacity remains severely impaired following LVAD implantation, affecting mortality, QoL and functional capacity.[55–58] In the non-LVAD HF population, ID has been associated with reduced pVO_2, whereas IV iron repletion has been shown to improve exercise capacity in patients with ID.[38,59,60] In LVAD patients, pVO_2 is associated with haemoglobin levels.[61,62] ID is a common cause of anaemia, and treatment with IV iron significantly improved haemoglobin levels while resolving anaemia in most patients.[18,22] This may suggest a possible link between exercise intolerance and ID. However, the direct interactions between ID, iron repletion and pVO_2 have not been studied in LVAD patients.

Second, preserved RV function is crucial during LVAD therapy, because the pump relies on continuous LV filling driven by the RV.[15] Early haemodynamic and inflammatory stress often leads to RV dysfunction, and RV failure, which develops in up to 40% of LVAD patients after implant, is a significant mediator of morbidity and mortality during support.[63,64] RV failure accounted for 10% of deaths in patients implanted with centrifugal flow LVADs in an analysis of the International Society for Heart and Lung Transplantation Mechanical Assisted Circulatory Support (IMACS) Registry and may have contributed to other causes of death (e.g. multisystem organ failure).[65] Several studies in non-LVAD HF patients have linked RV dysfunction to ID; one study found an association between ID and RV dysfunction in patients hospitalised with acute HF, whereas treatment with IV iron has been associated with improved RV function, structure and contractile reserve in non-LVAD HF patients.[32,66,67] In LVAD patients, several studies have reported that pre-implantation anaemia and blood transfusions are associated with RV failure.[24,68,69] A recent study based on Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Registry data (n=19,509 LVAD patients), although not statistically significant, found a similar trend between the severity of pre-implant anaemia and rates of postimplant RV failure, and a likely explanation for the association between multitransfusion and RV failure may very well be increased RV afterload rather than reduced contractile force of the RV.[62] Please note that, due to the lack of data, the suggested association is extrapolated from studies of non-LVAD HF patients without direct evidence to confirm ID as a causal factor for RV failure in the LVAD population. Still, we believe that this hypothesis warrants further investigation.

Although most of the discussed studies were based on anaemia specifically, ID is a significant cause of anaemia in LVAD patients.[18] Furthermore, treating anaemic LVAD patients with blood transfusions leads to unfavourable sensitisation in bridged heart transplantation candidates.[70] Previous attempts at improving haemoglobin levels in LVAD patients using erythropoiesis-stimulating agents were deemed unsafe due to higher rates of mortality and suspected pump thromboses.[71] Although it is difficult to ascertain the respective influences of anaemia and ID on LVAD patient outcomes based on the available data, haemoglobin levels increase after treatment with IV iron, and thus may limit transfusions in LVAD patients.[72]

Limitations

Our review of ID in LVAD patients has several inherent limitations. First, it is based on a limited number of studies, exhibiting significant heterogeneity in methodology, research focus and LVAD characteristics. Most of these studies were retrospective and performed at single centres, with small sample sizes (range 7–205 patients). This could potentially limit the generalisability of our findings. Furthermore, there were inconsistencies in the data reported across these studies. Important data points, such as the type of LVAD device, duration of LVAD support and markers of ID, were not uniformly tested and reported. In addition, the iron preparation used was inconsistently reported, which could influence the interpretation of results. The studies were also subject to several biases, including sampling bias due to undisclosed criteria for when ID screening was to be performed and selection bias from non-randomised decisions to treat patients with iron supplementation.

Conclusion

The reported prevalence of ID in HF patients supported with an LVAD ranges from 40 to 82%. Although criteria for diagnosing ID in LVAD patients have not been validated, all studies followed FAIR-HF criteria.

TSAT <20% as a lone criterion may increase both the sensitivity and specificity of the screening. Due to the unique inflammatory and circulatory conditions in LVAD patients, oral iron supplementations appear to be ineffective and possibly counterproductive in treating ID. IV iron treatment significantly resolved ID in most patients, leading to increased haemoglobin, ferritin and TSAT levels without being associated with any adverse events.

However, the impact of ID and subsequent iron repletion on survival and exercise capacity after LVAD implantation remains unknown. Although ID has been linked to RV dysfunction, studies of cardiac structure and function in relation to ID have not been conducted in LVAD patients. Because no guideline on diagnosing and treating ID in LVAD patients currently exists, and optimal diagnosing criteria remain unproven, the true prevalence and adverse effects of ID may be severely misestimated. Although no randomised controlled trials of IV iron treatment of ID in patients with LVAD have been conducted, effects similar to those found in the wider HF population may exist.

Next Steps

Several key research topics are relevant to establish the clinical implications of ID in LVAD patients. The relationships between ID and RV dysfunction, mortality, HF hospitalisations, QoL and exercise intolerance should be explored. In addition, mechanistic studies and validation of diagnostic criteria specific to the LVAD population are warranted. Finally, the interaction between anaemia and ID on adverse outcomes should be investigated. Drawing from the insights of this review, we suggest a randomised double-blind placebo-controlled trial examining the effects of IV iron repletion on QoL and $pV\dot{O}_2$, similar to the unblinded FERRIC-HF trial.[60] These endpoints are increasingly important, with still improving survival in the LVAD population. ❑

Clinical Perspective

- Iron deficiency remains highly prevalent in HF patients after left ventricular assist device (LVAD) implantation, with prevalence estimates ranging from 40% to 82%.
- The FAIR-HF diagnostic criteria (ferritin <100 µg/l or ferritin 100–299 µg/l and transferrin saturation <20%) are commonly used to diagnose ID; however, transferrin saturation <20% alone may be more accurate in LVAD recipients.
- IV iron repletion improves haemoglobin levels and resolves iron deficiency in most patients; however, effects of iron repletion on mortality, hospitalisation rates, quality of life and functional capacity in LVAD patients require further investigation.
- Future studies are needed to consider the true effects of iron deficiency in the LVAD population.

1. Shamsi A, Cannata A, Piper S, et al. Treatment of iron deficiency in heart failure. *Curr Cardiol Rep* 2023;25:649–61. https://doi.org/10.1007/s11886-023-01889-4; PMID: 37329419.
2. Vukadinović D, Abdin A, Emrich I, et al. Efficacy and safety of intravenous iron repletion in patients with heart failure: a systematic review and meta-analysis. *Clin Res Cardiol* 2023;112:954–66. https://doi.org/10.1007/s00392-023-02207-2; PMID: 37074386.
3. Bekfani T, Pellicori P, Morris D, et al. Iron deficiency in patients with heart failure with preserved ejection fraction and its association with reduced exercise capacity, muscle strength and quality of life. *Clin Res Cardiol* 2019;108:203–11. https://doi.org/10.1007/s00392-018-1344-x; PMID: 30051186.
4. Okonko DO, Mandal AKJ, Missouris CG, Poole-Wilson PA. Disordered iron homeostasis in chronic heart failure: prevalence, predictors, and relation to anemia, exercise capacity, and survival. *J Am Coll Cardiol* 2011;58:1241–51. https://doi.org/10.1016/j.jacc.2011.04.040; PMID: 21903058.
5. Jankowska EA, Rozentryt P, Witkowska A, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. *Eur Heart J* 2010;31:1872–80. https://doi.org/10.1093/eurheartj/ehq158; PMID: 20570952.
6. Wienbergen H, Pfister O, Hochadel M, et al. Long-term effects of iron deficiency in patients with heart failure with or without anemia: the RAID-HF follow-up study. *Clin Res Cardiol* 2019;108:93–100. https://doi.org/10.1007/s00392-018-1327-y; PMID: 30003365.
7. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009;361:2436–48. https://doi.org/10.1056/NEJMoa0908355; PMID: 19920054.
8. Alnuwaysir RIS, Hoes MF, Van Veldhuisen DJ, et al. Iron deficiency in heart failure: mechanisms and pathophysiology. *J Clin Med* 2021;11:125. https://doi.org/10.3390/jcm11010125; PMID: 35011874.
9. Mei Z, Chen J, Luo S, et al. Comparative efficacy of intravenous and oral iron supplements for the treatment of iron deficiency in patients with heart failure: a network meta-analysis of randomized controlled trials. *Pharmacol Res* 2022;182:106345. https://doi.org/10.1016/j.phrs.2022.106345; PMID: 35810949.
10. Mentz RJ, Garg J, Rockhold FW, et al. Ferric carboxymaltose in heart failure with iron deficiency. *N Engl J Med* 2023;389:NEJMoa2304968. https://doi.org/10.1056/NEJMoa2304968; PMID: 37632463.
11. Khush KK. Donor selection in the modern era. *Ann Cardiothorac Surg* 2018;7:126–34. https://doi.org/10.21037/acs.2017.09.09; PMID: 29492390.
12. Mehra MR, Goldstein DJ, Cleveland JC, et al. Five-year outcomes in patients with fully magnetically levitated vs axial-flow left ventricular assist devices in the MOMENTUM 3 randomized trial. *JAMA* 2022;328:1233–42. https://doi.org/10.1001/jama.2022.16197; PMID: 36074476.
13. Varshney AS, DeFilippis EM, Cowger JA, et al. Trends and outcomes of left ventricular assist device therapy: JACC focus seminar. *J Am Coll Cardiol* 2022;79:1092–107. https://doi.org/10.1016/j.jacc.2022.01.017; PMID: 35300822.
14. Bhimaraj A, Uribe C, Suarez EE. Physiological impact of continuous flow on end-organ function: clinical implications in the current era of left ventricular assist devices. *Methodist deBakey Cardiovasc J* 2015;11:12–7. https://doi.org/10.14797/mdcj-11-1-12; PMID: 25793024.
15. Gustafsson F, Rogers JG. Left ventricular assist device therapy in advanced heart failure: patient selection and outcomes. *Eur J Heart Fail* 2017;19:595–602. https://doi.org/10.1002/ejhf.779; PMID: 28198133.
16. Vidula H, Takeda K, Estep JD, et al. Hospitalization patterns and impact of a magnetically-levitated left ventricular assist device in the MOMENTUM 3 trial. *JACC Heart Fail* 2022;10:470–81. https://doi.org/10.1016/j.jchf.2022.03.007; PMID: 35772857.
17. McDonagh TA, Metra M, Adamo M, et al. 2023 Focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2023;44:ehad195. https://doi.org/10.1093/eurheartj/ehad195; PMID: 37622666.
18. Amione-Guerra J, Cruz-Solbes AS, Bhimaraj A, et al. Anemia after continuous-flow left ventricular assist device implantation: characteristics and implications. *Int J Artif Organs* 2017;40:481–8. https://doi.org/10.5301/ijao.5000607; PMID: 28623639.
19. Veenis JF, Radhoe SP, Roest S, et al. Prevalence of iron deficiency and iron administration in left ventricular assist device and heart transplantation patients. *ASAIO J* 2022;68:899–906. https://DOI.ORG/10.1097/MAT.0000000000001585; PMID: 34643575.
20. Bernier TD, Stern G, Buckley LF, et al. Intravenous iron repletion in patients with continuous-flow left ventricular assist devices. *ASAIO J* 2023;69:e115–7. https://DOI.ORG/10.1097/MAT.0000000000001800; PMID: 36228660.
21. Bakosova M, Krejci J, Godava J, et al. Iron deficiency in patients with advanced heart failure. *Medicina (Kaunas)* 2022;58. https://doi.org/10.3390/medicina58111569; PMID: 36363528.
22. Vesper RM, Kemp L, Iyer P, et al. Safety and efficacy of early post-operative intravenous iron replacement in patients with HeartMate III left ventricular assist device. *J Pharm Pract* 2024;37:100–3. https://doi.org/10.1177/08971900221127500; PMID: 36113089.
23. Ton VK, Drezek K, Boerboom S, et al. Persistent iron deficiency and dysregulated hepcidin levels after durable left ventricular assist device therapy. *ASAIO J* 2023;69:e152–4. https://DOI.ORG/10.1097/MAT.0000000000001811; PMID: 36084293.
24. Shore S, Hanff TC, Mazurek JA, et al. The effect of transfusion of blood products on ventricular assist device support outcomes. *ESC Heart Fail* 2020;7:3573–81. https://doi.org/10.1002/ehf2.12780; PMID: 33263224.
25. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129–200. https://doi.org/10.1093/eurheartj/ehw128; PMID: 27206819.
26. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation* 2022;145:e895-e1032. https://DOI.ORG/10.1161/CIR.0000000000001063; PMID: 35363499.
27. Daru J, Colman K, Stanworth SJ, et al. Serum ferritin as an indicator of iron status: what do we need to know? *Am J Clin Nutr* 2017;106(Suppl 6):1634S–9S. https://doi.org/10.3945/ajcn.117.155960; PMID: 29070560.
28. Savarese G, von Haehling S, Butler J, et al. Iron deficiency and cardiovascular disease. *Eur Heart J* 2023;44:14–27. https://doi.org/10.1093/eurheartj/ehac569; PMID: 36282723.
29. Rohr M, Brandenburg V, Brunner-La Rocca HP. How to diagnose iron deficiency in chronic disease: a review of current methods and potential marker for the outcome. *Eur J Med Res* 2023;28:15. https://doi.org/10.1186/s40001-022-00922-6; PMID: 36617559.
30. Grote Beverborg N, Klip IT, Meijers WC, 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. https://DOI.ORG/10.1161/CIRCHEARTFAILURE.117.004519; PMID: 29382661.
31. Anker SD, Kirwan BA, van Veldhuisen DJ, 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. https://doi.org/10.1002/ejhf.823; PMID: 28436136.
32. Martens P, Dupont M, Dauw J, 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. https://doi.org/10.1002/ejhf.2489; PMID: 35303390.
33. Fitzsimons S, Poppe KK, Choi Y, et al. Relationship between soluble transferrin receptor and clinical outcomes in patients with heart failure according to ejection fraction phenotype: the New Zealand PEOPLE study. *J Card Fail*

2022;28:1255–63. https://doi.org/10.1016/j.cardfail.2021.12.018; PMID: 35051624.
34. Masini G, Graham FJ, Pellicori P, et al. Criteria for iron deficiency in patients with heart failure. *J Am Coll Cardiol* 2022;79:341–51. https://doi.org/10.1016/j.jacc.2021.11.039; PMID: 35086656.
35. Martens P, Dupont M, Dauw J, 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. https://doi.org/10.1093/eurheartj/ehab411; PMID: 34185066.
36. Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet* 2020;396:1895–904. https://doi.org/10.1016/S0140-6736(20)32339-4; PMID: 33197395.
37. Dhaliwal S, Kalogeropoulos AP. Markers of iron metabolism and outcomes in patients with heart failure: a systematic review. *Int J Mol Sci* 2023;24:5645. https://doi.org/10.3390/ijms24065645; PMID: 36982717.
38. Papadopoulou C, Reinhold J, Grüner-Hegge N, et al. Prognostic value of three iron deficiency definitions in patients with advanced heart failure. *Eur J Heart Fail* 2023;25:2067–74. https://doi.org/10.1002/ejhf.2949; PMID: 37635412.
39. Lewis GD, Malhotra R, Hernandez AF, et al. Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency the IRONOUT HF randomized clinical trial. *JAMA* 2017;317:1958–66. https://doi.org/10.1001/jama.2017.5427; PMID: 28510680.
40. Grosman-Rimon L, McDonald MA, Jacobs I, et al. Markers of inflammation in recipients of continuous-flow left ventricular assist devices. *ASAIO J* 2014;60:657–63. https://DOI.ORG/10.1097/MAT.0000000000000129; PMID: 25232767.
41. Radley G, Pieper IL, Ali S, et al. The inflammatory response to ventricular assist devices. *Front Immunol* 2018;9:2651. https://doi.org/10.3389/fimmu.2018.02651; PMID: 30498496.
42. Rahal A, Ruch Y, Meyer N, et al. Left ventricular assist device-associated infections: incidence and risk factors. *J Thorac Dis* 2020;12:2654–62. https://doi.org/10.21037/jtd.2020.03.26; PMID: 32642173.
43. Hupe J, Worthmann H, Ravenberg KK, et al. Interplay between driveline infection, vessel wall inflammation, cerebrovascular events and mortality in patients with left ventricular assist device. *Sci Rep* 2023;13:18552. https://doi.org/10.1038/s41598-023-45110-6; PMID: 37899422.
44. Sangkhae V, Nemeth E. Regulation of the iron homeostatic hormone hepcidin. *Adv Nutr* 2017;8:126–36. https://doi.org/10.3945/an.116.013961; PMID: 28096133.
45. Singer CE, Vasile CM, Popescu M, et al. Role of iron deficiency in heart failure – clinical and treatment approach: an overview. *Diagnostics (Basel)* 2023;13:304. https://doi.org/10.3390/diagnostics13020304; PMID: 36673114.
46. Draper KV, Huang RJ, Gerson LB. GI bleeding in patients with continuous-flow left ventricular assist devices: a systematic review and meta-analysis. *Gastrointest Endosc* 2014;80:435–446.e1. https://doi.org/10.1016/j.gie.2014.03.040; PMID: 24975405.
47. Bode LE, Wesner S, Katz JN, et al. Intravenous versus oral iron replacement in patients with a continuous-flow left ventricular assist device. *ASAIO J* 2019;65:e90–1. https://DOI.ORG/10.1097/MAT.0000000000000904; PMID: 30312210.
48. Peters CJ, Hanff TC, Genuardi MV, et al. Safety and effectiveness of intravenous iron therapy in patients supported by durable left ventricular assist devices. *J Clin Med* 2022;11. https://doi.org/10.3390/jcm11133900; PMID: 35807184.
49. Qi X, Zhang Y, Guo H, et al. Mechanism and intervention measures of iron side effects on the intestine. *Crit Rev Food Sci Nutr* 2020;60:2113–25. https://doi.org/10.1080/10408398.2019.1630599; PMID: 31232087.
50. Gustafsson F, Mirza KK, Pya Y, et al. Predictors of physical capacity 6 months after implantation of a full magnetically levitated left ventricular assist device: an analysis from the ELEVATE registry. *J Card Fail* 2020;26:580–7. https://doi.org/10.1016/j.cardfail.2020.04.004; PMID: 32417377.
51. Del Vecchio L, Longhi S, Locatelli F. Safety concerns about intravenous iron therapy in patients with chronic kidney disease. *Clin Kidney J* 2016;9:260–7. https://doi.org/10.1093/ckj/sfv142; PMID: 26985378.
52. Zinoviev R, Lippincott CK, Keller SC, Gilotra NA. In full flow: left ventricular assist device infections in the modern era. *Open Forum Infect Dis* 2020;7:ofaa124. https://doi.org/10.1093/ofid/ofaa124; PMID: 32405511.
53. Kirklin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: special focus on framing the impact of adverse events. *J Heart Lung Transplant* 2017;36:1080–6. https://doi.org/10.1016/j.healun.2017.07.005; PMID: 28942782.
54. Docherty KF, Welsh P, Verma S, et al. Iron deficiency in heart failure and effect of dapagliflozin: findings from DAPA-HF. *Circulation* 2022;146:980–94. https://DOI.ORG/10.1161/CIRCULATIONAHA.122.060511; PMID: 35971840.
55. Mirza KK, Szymanski MK, Schmidt T, et al. Prognostic value of peak oxygen uptake in patients supported with left ventricular assist devices (PRO-VAD). *JACC Heart Fail* 2021;9:758–67. https://doi.org/10.1016/j.jchf.2021.05.021; PMID: 34391745.
56. Jung MH, Gustafsson F. Exercise in heart failure patients supported with a left ventricular assist device. *J Heart Lung Transplant* 2015;34:489–96. https://doi.org/10.1016/j.healun.2014.11.001; PMID: 25577562.
57. Mirza KK, Gustafsson F. Determinants of functional capacity and quality of life after implantation of a durable left ventricular assist device. *Card Fail Rev*. Review 2020;6:e29. https://doi.org/10.15420/cfr.2020.15; PMID: 33133643.
58. Mirza KK, Bonne T, Nordsborg NB, et al. Oxygen uptake during activities of daily life in patients treated with a left ventricular assist device. *J Heart Lung Transplant* 2022;41:982–90. https://doi.org/10.1016/j.healun.2022.03.009; PMID: 35400588.
59. Ebner N, Jankowska EA, Ponikowski P, et al. The impact of iron deficiency and anaemia on exercise capacity and outcomes in patients with chronic heart failure. Results from the Studies Investigating Co-morbidities Aggravating Heart Failure. *Int J Cardiol* 2016;205:6–12. https://doi.org/10.1016/j.ijcard.2015.11.178; PMID: 26705670.
60. Okonko DO, Grzeslo A, Witkowski T, et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency. FERRIC-HF: a randomized, controlled, observer-blinded trial. *J Am Coll Cardiol* 2008;51:103–12. https://doi.org/10.1016/j.jacc.2007.09.036; PMID: 18191732.
61. Kondo T, Okumura T, Oishi H, et al. Associations between hemodynamic parameters at rest and exercise capacity in patients with implantable left ventricular assist devices. *Int J Artif Organs* 2021;44:174–80. https://doi.org/10.1177/0391398820949888; PMID: 32783493.
62. Tie H, Li T, Huang B, et al. Presence and impact of anemia in patients supported with left ventricular assist devices. *J Heart Lung Transplant* 2023;42:1261–74. https://doi.org/10.1016/j.healun.2023.04.013; PMID: 37127070.
63. Boulet J, Nayak A, Mehra MR. Hemodynamic aberrancies in left ventricular assist device-associated heart failure syndromes. *J Card Fail* 2022;28:1738–40. https://doi.org/10.1016/j.cardfail.2022.09.007; PMID: 36170947.
64. Bravo CA, Navarro AG, Dhaliwal KK, et al. Right heart failure after left ventricular assist device: from mechanisms to treatments. *Front Cardiovasc Med* 2022;9:1023549. https://doi.org/10.3389/fcvm.2022.1023549; PMID: 36337897.
65. Goldstein DJ, Meyns B, Xie R, et al. Third annual report from the ISHLT mechanically assisted circulatory support registry: a comparison of centrifugal and axial continuous-flow left ventricular assist devices. *J Heart Lung Transplant* 2019;38:352–63. https://doi.org/10.1016/j.healun.2019.02.004; PMID: 30945637.
66. Miñana G, Santas E, De La Espriella R, et al. Right ventricular function and iron deficiency in acute heart failure. *Eur Heart J Acute Cardiovasc Care* 2021;10:406–14. https://doi.org/10.1093/ehjacc/zuaa028; PMID: 33620455.
67. Del Canto I, Santas E, Cardells I, et al. Short-term changes in left and right ventricular cardiac magnetic resonance feature tracking strain following ferric carboxymaltose in patients with heart failure: a substudy of the myocardial-IRON trial. *J Am Heart Assoc* 2022;11:e022214. https://DOI.ORG/10.1161/JAHA.121.022214; PMID: 35301854.
68. Soliman OII, Akin S, Muslem R, et al. Derivation and validation of a novel right-sided heart failure model after implantation of continuous flow left ventricular assist devices: the EUROMACS (European registry for patients with mechanical circulatory support) right-sided heart failure risk score. *Circulation* 2018;137:891–906. https://DOI.ORG/10.1161/CIRCULATIONAHA.117.030543; PMID: 28847897.
69. Shore S, Hanff TC, Mazurek JA, et al. The anemia stress index – anemia, transfusions, and mortality in patients with continuous flow ventricular assist devices. *J Clin Med* 2022;11:4517. https://doi.org/10.3390/jcm11154517; PMID: 35956132.
70. Scornik JC, Meier-Kriesche HU. Blood transfusions in organ transplant patients: mechanisms of sensitization and implications for prevention. *Am J Transplant* 2011;11:1785–91. https://doi.org/10.1111/j.1600-6143.2011.03705.x; PMID: 21883910.
71. Nassif ME, Patel JS, Shuster JE, et al. Clinical outcomes with use of erythropoiesis stimulating agents in patients with the HeartMate II left ventricular assist device. *JACC Heart Fail* 2015;3:146–53. https://doi.org/10.1016/j.jchf.2014.08.005; PMID: 25660839.
72. Mardis A, Straw LB, Robinson A, et al. Intravenous iron replacement in patients with left ventricular assist devices. *J Heart Lung Transplant* 2021;40:S181. https://doi.org/10.1016/j.healun.2021.01.530.