



Spotlight on Iron deficiency in heart failure

Revised edition | June 2022



The Heart Failure Policy Network is an independent, multidisciplinary platform made possible with financial support from Vifor Pharma, AstraZeneca, Bayer AG and Boehringer Ingelheim. The content produced by the Network is not biased towards any specific treatment or therapy. All outputs are guided and endorsed by the Network's members, who have full editorial control. All members provide their time for free.

Authorship and acknowledgements

This report was originally written in 2020 by Sara C Marques, Marissa Mes, Ed Harding and Madeleine Murphy, and was updated in 2022 by Faith Everett, Catherine Hodge, Kirsten Budig and Joe Farrington-Douglas, members of the Secretariat of the Heart Failure Policy Network (HFPN).

Considerable thanks and acknowledgement are due to all members of the Project Advisory Group for their continued input throughout the development of the original report:

- **Josep Comín-Colet**, Cardiologist, Bellvitge University Hospital, Spain
- **Joseph Gallagher**, General Practitioner and Irish College of General Practitioners Clinical Lead in Cardiovascular Disease, Ireland
- **Steven Macari**, Founder and President, Association Vie Et Cœur (AVEC), France
- **Sandra Mulrennan**, Heart Failure Specialist Nurse, St Bartholomew's Hospital Heart Failure Service, Barts Health NHS London, UK
- **Anne-Catherine Pouleur**, Cardiologist, Université Catholique de Louvain and Cliniques Universitaires Saint Luc, Belgium
- **Patricia Vlasman**, Founder and President, Let the Beat Go On, the Netherlands

The HFPN would also like to thank the following experts for sharing their knowledge in interviews:

- **Carys Barton**, Heart Failure Nurse Consultant, Imperial College Healthcare NHS Trust, UK
- **Cândida Fonseca**, Senior Cardiologist and Internist, Head of Heart Failure Clinic of Hospital de São Francisco Xavier, Centro Hospitalar Lisboa Ocidental; Professor of Medicine, NOVA Medical School, Faculdade de Ciências Médicas, Universidade NOVA de Lisboa, Portugal
- **Ewa Anita Jankowska**, Professor and Head of Laboratory of Applied Research on Cardiovascular System, and Head of Department of Structural Heart Diseases, Wroclaw Medical University, Poland; co-author of 2016 European Society of Cardiology/Heart Failure Association heart failure guidelines
- **Giuseppe Rosano**, President-Elect, Heart Failure Association of the European Society of Cardiology; co-author of 2021 European Society of Cardiology/Heart Failure Association heart failure guidelines

Contents

Executive summary	4
1. What are iron deficiency and heart failure?	6
2. Interaction of iron deficiency with heart failure	8
3. Diagnosis of iron deficiency in heart failure: facts and challenges	10
4. Challenges in the management of iron deficiency in heart failure	12
5. Best practice in the management of iron deficiency in heart failure	14
6. The way forward	18
References	20

Executive summary

Iron deficiency (ID) is often overlooked in heart failure (HF) care and policy, despite its high prevalence across all types of HF.^{1 2} Iron has several crucial roles in the human body, and ID can have a negative impact on health and quality of life.

ID worsens HF clinical outcomes and contributes to the burden of HF on people and health systems. Its symptoms include fatigue, reduced exercise capacity and breathlessness.³ ID may lead to anaemia, a condition in which the body has low levels of red blood cells or of haemoglobin, which results in reduced (and possibly insufficient) oxygen in the blood.^{4 5} It can negatively affect the quality of life of people living with HF and interfere with some forms of HF treatment.^{2 6} ID increases the risk and duration of hospitalisation,¹ and is linked to an increased risk of mortality in people living with HF.⁷

Despite its impact, ID often goes unrecognised in people with HF. Guidelines recommend intravenous iron for the treatment of ID in some forms of HF,^{2 8 9} but this treatment is not always provided.¹⁰ Many people are still treated with oral iron^{11 12} despite evidence of limited efficacy, increased risk of side effects with some oral preparations, and potential issues with treatment adherence.^{2 9 13 14}

Recent guidelines have expanded advice on managing ID in HF, which raises the bar for screening and diagnosis. The latest European clinical guidelines, published in 2021, recommend periodic screening for ID in all people with HF. In practice, however, iron levels are not consistently measured as part of HF care, and symptoms of ID are sometimes mistaken for deteriorating HF, contributing to underdiagnosis.^{9-11 15}

Limited professional awareness of guidelines has been noted as a factor in the poor management of ID in HF.^{11 12} Diagnostic criteria for ID differ between people living with HF and the general population.² Exacerbation of HF affects the reliability of ID biomarkers,¹⁶ making diagnosis of ID in acute HF more difficult. Lack of awareness of these factors among healthcare professionals managing HF may act as a barrier to adequate diagnosis of ID.

There remains a gap in ID treatment recommendations in HF guidelines, as they focus only on two types of HF.^{2 8 9} This leaves healthcare professionals unsupported when it comes to management of ID in HF with preserved ejection fraction (HFpEF) and during exacerbation.

People with HF across Europe face barriers to accessing optimal treatment for ID. These include: lack of, or inconsistent, national guidelines for managing HF;¹⁷ issues with reimbursement;^{18 19} and logistical and regulatory barriers.^{10 20} Long waiting times for hospital admission, high costs for payers and out-of-pocket charges may all limit access to intravenous iron for people living with HF.

There is a clear need to properly address ID in HF, in research, policymaking and clinical practice. Taking action in these areas will reduce the burden of ID in HF, and consequently that of HF on each person, the health system and society in general.

Key actions to improve diagnosis and management of ID in HF

<p>1. Translate European guidance into national policy and practice</p>	<p>National and regional health systems should formally adopt the latest European guidelines or develop their own recommendations and care pathways to ensure access to ID treatment for people with HF and to incorporate ID into quality systems for HF care.</p>
<p>2. Raise awareness and improve diagnosis of ID in HF</p>	<p>Healthcare professionals working in HF should be trained in and alert to the causes, signs and symptoms of ID in people living with HF. Decision-makers, including regulators and payers, also need to be aware of the need for optimal ID treatment for people with HF.</p>
<p>3. Shift provision of intravenous iron to appropriately resourced outpatient settings</p>	<p>Outpatient clinics can be effective settings to treat ID without the need for hospital admission, benefiting different patient groups and hospital departments, and potentially reducing the cost of provision.</p>
<p>4. Support clinical research to improve understanding and treatment of ID across the whole spectrum of HF</p>	<p>The development and role of ID is not fully understood in acute HF or in HF with preserved ejection fraction (HFpEF). Research is needed to develop an evidence base.</p>

What are iron deficiency and heart failure?

Iron deficiency is a common comorbidity of heart failure

Iron deficiency (ID) is a condition that affects many people with heart failure (HF),^{2 8 9} potentially contributing to poorer clinical outcomes.²¹ It is important for healthcare professionals to recognise ID and understand how it can interact with HF.

HF occurs when the heart is unable to pump enough blood

HF is a complex clinical syndrome in which the heart becomes too weak or stiff to meet the body's needs.^{8 9 22} Signs and symptoms include breathlessness, extreme fatigue, reduced exercise capacity, and fluid retention resulting in weight gain and/or swelling. HF is designated chronic when symptoms appear slowly and worsen gradually, or acute when there is a sudden and rapid onset or exacerbation of symptoms, requiring immediate medical attention.

HF places a high burden on people, health systems and society as a whole

HF affects up to 2% of people living in Europe.²³ It is associated with substantial healthcare costs – it is the most common cause of hospitalisation among people over the age of 65, and the leading cause of unplanned hospital readmissions.^{24 25} Quality of life and survival rates in HF remain poor.²⁶ The burden of HF is expected to rise in the coming years owing to an ageing population and improved survival rates for other diseases, posing a challenge to the sustainability of health systems across the world.²⁷

European guidelines distinguish three types of HF

The European Society of Cardiology (ESC) HF guidelines define the types of HF based on the left ventricular ejection fraction (LVEF),^{8 9} which is the proportion of oxygenated blood pumped out by the left ventricle to the rest of the body with each heartbeat.²⁸ In HF with reduced ejection fraction (HFrEF), the LVEF is below 40%, while in HF with preserved ejection fraction (HFpEF), it is at least 50%.²⁹ HF with mildly reduced ejection fraction (HFmrEF) refers to an LVEF between 40% and 49% inclusive. HFrEF is better understood than other types of HF, in terms of both its development and treatment options.²⁹

Iron is an essential element for the normal functioning of the body

Iron has several roles in the human body, one of the most important being its involvement in the production of haemoglobin,³⁰ a protein in red blood cells responsible for transporting oxygen from the lungs to the rest of the body.³¹ Iron also has a key role in each cell's ability to generate energy and repair itself, processes that are crucial for the normal function of muscles and tissues, such as those in the heart.³⁰ The body fulfils its need for iron through dietary intake, and iron is then found in cells (mostly red blood cells), circulating in the blood or kept in iron stores, for example in the liver and spleen.³² The body can recycle iron in old or damaged red blood cells, and when more iron is needed, such as during pregnancy or after blood loss, iron absorption increases and stored iron is mobilised.³⁰ In some people, however, these processes are impaired and ID occurs.

There are two different types of ID with several potential causes

ID can be absolute (when the body's iron stores are depleted) or functional (when the mobilisation of iron from stores into the circulation is impaired), or both can occur simultaneously.^{2 6 32} Absolute ID is typically caused by low iron consumption, increased iron use and/or blood loss.³³ Functional ID is often the result of chronic inflammation, as this can disrupt how the body absorbs and regulates iron.

ID can have a negative impact on health

Symptoms of ID are unspecific and similar to those of HF^{8 34} – they may include fatigue, reduced exercise capacity and breathlessness, depending on the degree of deficiency.³ ID can have a negative impact on a person's immune system³⁵ and cognitive function,³⁶ and can lead to anaemia,^{2 30} which is when the body has insufficient levels of circulating oxygen due to low levels of haemoglobin or red blood cells.⁴ While ID and anaemia may be linked, they are separate clinical entities – ID does not always lead to anaemia, and anaemia may result from causes other than ID.³⁶

2

Interaction of iron deficiency with heart failure

ID is common in people living with HF

ID affects 40–70% of people living with chronic HF,² and its prevalence seems to be similar across HF types.¹ ID becomes more common in people living with advanced HF^{21 34} and during episodes of exacerbation; 69–75% of people with acute HF have ID.¹²

HF and its treatments may lead to, or worsen, ID

Inflammation is common in people with HF, contributing to a high prevalence of ID.³³ The symptoms of HF and its common treatments can also be a factor in the development or worsening of ID. For example, people living with HF may have less appetite and consequently low consumption of iron through their diet.^{2 37} ID may also arise as a result of anticoagulant or antiplatelet medication, such as those recommended to prevent strokes or heart attacks in people living with HF.³⁸ These medicines increase the risk of bleeding, which may lead to ID. However, such risks can be safely and effectively managed by the treating physician and should not prevent people living with HF from taking these vital medicines.

ID worsens clinical outcomes for HF

ID has a drastic impact on morbidity and mortality in HF. It increases the risk and duration of hospitalisation and readmission in people with HF.^{1 21 39} This not only adds to the strain on people with HF and their loved ones, but also contributes to significant healthcare costs. For example, in England, ID increases the cost of HF hospitalisations by an average of £138 per hospital admission.³⁹ It is also linked to the need for cardiac surgery (including heart transplantation) and for blood transfusions in people awaiting such interventions.^{40 41} ID increases the risk of mortality in people with HF by 40–60%.⁷

ID adds to the devastating impact of HF on independence and quality of life

ID decreases functional capacity (the ability to perform daily activities requiring physical exertion) and exercise capacity in people with HF,^{1 2 6} making daily tasks such as leaving the house, gardening and climbing stairs more difficult.⁴² People living with both HF and ID may experience greater fatigue, breathlessness and loss of appetite than those with HF alone. ID can also interfere with HF treatment; for example, it may reduce symptomatic improvement from devices used to treat irregular heart rhythms, such as cardiac resynchronisation therapy.^{43 44}

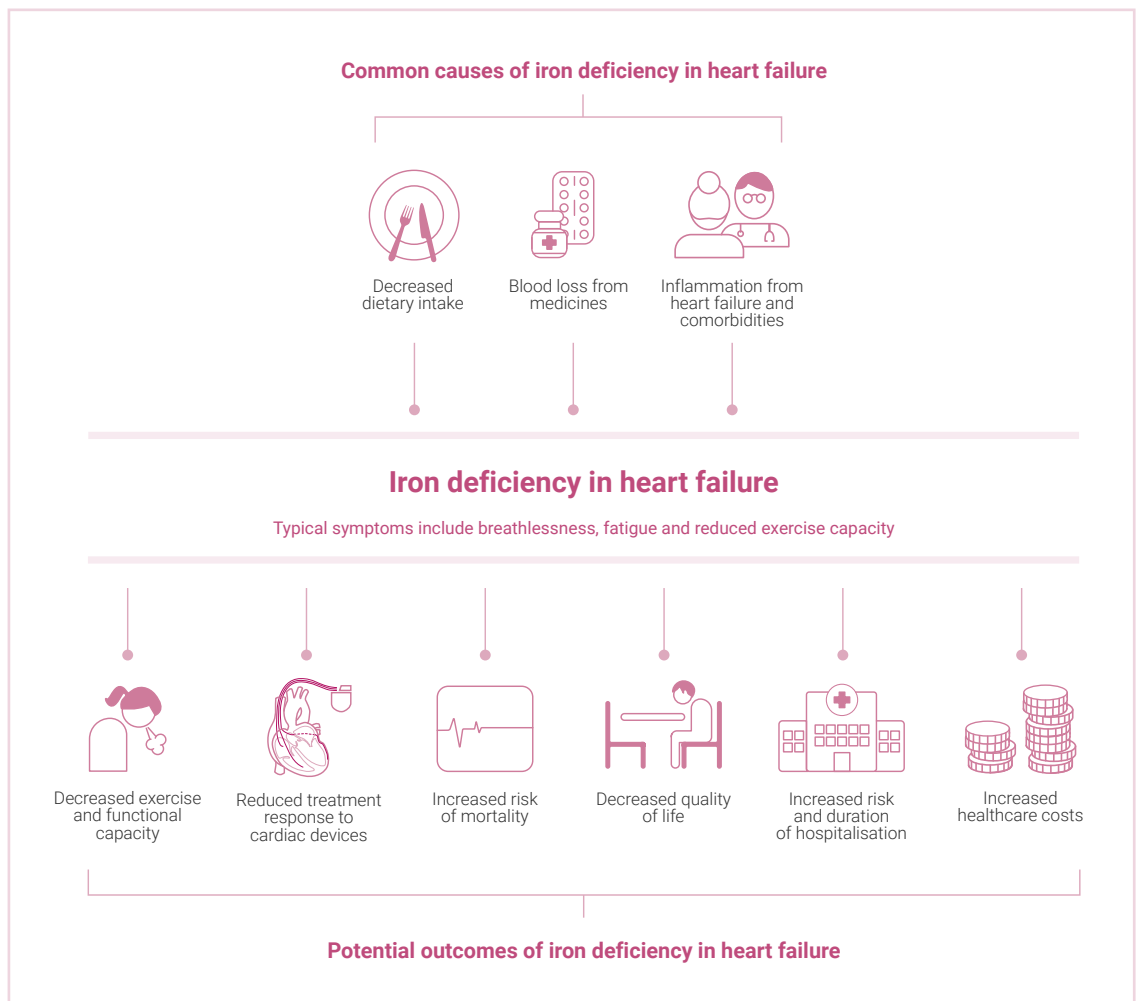
'Iron deficiency has a negative impact on all people, and in particular people living with heart failure as they already have reduced quality of life and functional capacity. Iron deficiency exacerbates these issues.'

Professor Cândida Fonseca, Portugal

Clinical research has identified effective treatment for ID in people with HF

Evidence on ID in HF has evolved significantly over the past decade. In 2009, a foundational study in ID and HF demonstrated promising results in iron therapy treatment for people living with chronic HF and ID.⁴⁵ In 2015, a Europe-wide study concluded that treatment of symptomatic ID in HF with intravenous iron was successful in improving symptoms and quality of life.⁴⁶ Following this, the ESC 2016 guidelines were published, featuring ID in HF for the first time.⁸ Recognition of ID in HF has been imperative for driving research and improving care. Treatment with intravenous iron for people living with ID and HF has been found to be a tolerable and effective way of reducing the risk of future hospital admissions.⁴⁷ The most recent ESC guidelines, released in 2021, feature three recommendations for the management of ID in HF.⁹

Figure 1. Causes and consequences of iron deficiency in heart failure



3

Diagnosis of iron deficiency in heart failure: facts and challenges

'It's important to raise awareness of iron deficiency in heart failure and make the distinction between iron deficiency and anaemia. About half of all people with heart failure and normal haemoglobin levels have iron deficiency – this must be tested for.'

Professor Ewa Anita Jankowska, Poland

ID often goes unrecognised in people with HF

Iron levels are not routinely measured as part of HF care. A study across specialist HF centres in Germany and Switzerland found that only 62% of people being treated for HFrEF had their iron levels measured.¹¹ Similarly, a centre in the UK found that only half of the patients who attended the HF clinic in February 2015 had been tested for ID in the previous six months.¹⁰

The similarity of symptoms between ID and HF may contribute to underdiagnosis of ID

The close resemblance of ID symptoms to those of HF may have a role in the poor diagnosis rates of ID; healthcare professionals may mistake ID for deteriorating HF.¹⁵ As a result, healthcare professionals may increase the dose of HF medicines instead of treating the mineral deficiency, which may increase the risk of side effects, medicines waste and healthcare costs while not improving outcomes for the person.⁴⁸

Diagnosis of ID relies on indirect measures

Guidelines recommend screening for ID in people living with HF by measuring full blood count, serum ferritin concentration and transferrin saturation (TSAT; see *Box 1*).^{2 8 9 32} Reduced ferritin levels are the basis for a diagnosis of absolute ID, whereas normal ferritin levels and reduced TSAT are the basis for a diagnosis of functional ID.^{33 49} A bone marrow biopsy is the accepted gold standard for diagnosing ID, but it is a costly, invasive and complex procedure, so is not appropriate for routine monitoring of iron levels. Measuring ferritin and TSAT levels is generally accepted by clinicians due to its greater feasibility in practice.

Box 1. Ferritin concentration and transferrin saturation

Ferritin and transferrin are two biomarkers used in the diagnosis of ID.² Ferritin is a protein that stores iron; transferrin is a protein that transports iron in the blood. Serum ferritin concentration refers to the concentration of ferritin in the bloodstream. Transferrin saturation refers to the proportion of transferrin in the bloodstream that is bound to iron.³³

ID diagnosis is complicated by the need for special diagnostic criteria for people with HF

Chronic inflammation commonly seen in people living with HF typically raises blood levels of ferritin.¹⁵ Therefore, cut-off values for the diagnosis of ID in HF are higher than in the general population. Instead of the normal upper threshold of 30µg/L for serum ferritin levels, diagnostic criteria for ID in HF use the higher limit of 100µg/L, or 100–299µg/L with TSAT lower than 20%.² However, ferritin levels and TSAT often fluctuate during exacerbation of HF, making them unreliable markers of ID in acute HF – they should only be used for ID diagnosis when HF is stable again.^{16 50}

Limited knowledge of ID in HF may hinder diagnosis

There is a lack of educational programmes and professional training on diagnosis and management of ID in HF.^{17 18} As a result, some healthcare professionals may not recognise that iron levels should be tested in all people living with HF.^{11 18} They may also be unaware of factors that can complicate diagnosis, such as the need for HF-specific diagnostic criteria and the fluctuation of biomarker levels in acute HF.^{16 50} Equally, healthcare professionals may misinterpret ID symptoms for those typical of HF deterioration.¹⁵ Although European HF guidelines introduced specific diagnostic criteria for ID in 2016,⁸ practical guidance – for example, clinical case studies – was initially lacking.⁷ The 2021 guidelines include more detailed guidance on diagnosing ID in people with different types of HF.⁹

‘While healthcare professionals are becoming increasingly aware of the prevalence of iron deficiency in people living with heart failure, screening is still not systematic and is mostly carried out at the request of informed patients.’

Mr Steven Macari, France



4

Challenges in the management of iron deficiency in heart failure

Use of guideline-based treatment for ID in HF remains suboptimal

Established HF guidelines point to limited effectiveness of oral iron in people with HF,^{2,9} potentially due to impaired iron absorption³⁸ and increased risk of gastrointestinal side effects with some oral iron preparations.¹³ In addition, people with HF often take several medicines, and adding another oral treatment may make adherence more challenging.¹³ Despite this, oral iron is often prescribed as first-line treatment for ID in people with HF.¹² Intravenous iron, despite being recommended in people with ID and symptomatic HFrEF,⁹ is often only provided to people with anaemia or severe HF symptoms.¹¹ A review of HF services across the UK, for example, found that some have no provision to treat people with ID.⁵²

'Nowadays, we have different formulations for intravenous iron and the risk of allergic reactions is lower than in the past, but some healthcare professionals are not aware of this and are therefore wary of administering intravenous iron in outpatient settings.'

Professor Ewa Anita Jankowska, Poland

Access to and reimbursement of intravenous iron varies

Across Europe, access to treatment of ID in HFrEF is not equitable, despite European guideline recommendations.^{2,8,9} For example, the National Institute for Health and Care Excellence (NICE) in England and Wales has still not developed its own guidelines for treatment of ID in HF. This poses a barrier to the funding and provision of intravenous iron for people with HF in those countries.^{10,17} People with ID may have to be treated with oral iron, or may have to rely on the care pathways of comorbidities to grant them access to intravenous iron, such as renal services if they also live with chronic kidney disease. In Poland, intravenous iron administered in any outpatient setting is not reimbursed, meaning that people with HF receiving treatment in outpatient clinics often have to pay out of pocket.^{18,19}

Organisational barriers can hinder treatment of ID

Even when intravenous iron is prescribed, there are difficulties surrounding its delivery to people with HF. For example, intravenous iron should only be given to people in a stable condition – their HF should be under control and they should not have an acute or chronic infection² – but often has to be provided in hospital settings owing to its route of administration (directly into a vein). Therefore, people with HF who need ID treatment should receive it close to hospital discharge or in outpatient clinics.^{17,52} If these clinics are not available, the person will need to return to hospital for management of ID – this means that a hospital bed has to be available, which may involve long waiting times and high treatment costs.¹⁰

'The organisation of healthcare is not adequately prepared to support treatment of iron deficiency in heart failure. The recommended treatment is intravenous iron, which has to be administered in hospital settings but can only be given to stable patients, who are cared for in outpatient settings. This means that outpatient heart failure clinics are needed for iron deficiency treatment, but some countries, like Portugal, don't have enough of them.'

Professor Cândida Fonseca, Portugal

Guidelines for treatment of ID focus on HFrEF and HFmrEF

HF guidelines recommend intravenous iron to treat ID in people with symptomatic HFrEF. One particular formulation has been well evidenced to improve exercise capacity and quality of life, and the potential to reduce the risk of hospitalisation for worsening HF.⁹ However, guidelines do not make treatment recommendations for ID either in acute HF or for HFpEF,² as the safety and efficacy of intravenous iron in these situations is still under investigation. Further research is needed to understand the mechanisms behind ID in acute HF and HFpEF, to identify treatment options that have a positive impact on clinical endpoints. The deficit of research carries a high cost, given the high prevalence of ID in acute HF and HFpEF and the role of ID in driving poorer outcomes, including increased risk of hospitalisation and readmission.^{1 21 38} This poses a significant challenge in clinical management, especially considering the high prevalence of ID during exacerbation of HF.

'Heart failure specialist nurse teams are often commissioned to manage only people with HFrEF. Therefore, it is a challenge to manage iron deficiency in people with other types of heart failure.'

Ms Carys Barton, UK



5

Best practice in the management of iron deficiency in heart failure

Clinical management of HF should include regular screening for ID

As of 2021, ESC guidelines recommend measuring iron levels in people with newly diagnosed HF, and periodically monitoring iron levels in all people with HF.^{2 8 9} Hospitalisation for HF and persistence of symptoms despite optimal treatment should also trigger the investigation of iron levels.² This is particularly important for people with HF who have reduced appetite or are on antiplatelet or anticoagulant medication, as they may be at increased risk of ID.³⁸ In acute care, iron levels should be assessed close to discharge, when HF treatment has been optimised and HF is stable, to avoid unreliable test results and effectively assist in clinical decision-making.^{21 34 38}

'We need to start measuring iron levels consistently. Ferritin and transferrin saturation should be given the same level of importance during consultations as other parameters, like cholesterol or diabetes markers.'

Professor Ewa Anita Jankowska, Poland

Intravenous iron can be used to treat ID in some types of HF

Following diagnosis of ID, guidelines recommend the consideration of treatment with intravenous iron depending on the type of HF.⁹ People living with HFrEF and some of those living with HFmrEF should be given intravenous iron to alleviate symptoms and improve quality of life. In the case of HFrEF, intravenous iron could be administered regardless of whether or not the person has been admitted to hospital.

Correction of iron levels in HF should be monitored closely

Administration of intravenous iron may require close monitoring to identify and manage any potential allergic reaction.^{2 53} Iron levels in people with chronic HF should be re-evaluated three months after treatment to determine whether further sessions are required.⁵⁴



Provision of ID treatment in outpatient settings can benefit people with HF and the health system

Managing ID in an outpatient setting through short and accessible appointments may eliminate the need for hospital admission and reduce the cost of treatment, as well as improving convenience for people with HF.¹⁰ However, it is essential that outpatient settings have the tools and skilled personnel needed to manage complications, such as allergic reactions.^{2 7 53} A range of healthcare professionals can administer intravenous iron, including general practitioners (GPs) and nurses, depending on local prescribing regulations and resources.² Training for healthcare professionals responsible for the administration of intravenous iron should include all technical aspects related to ID treatment.

'The existence of heart failure clinics with different levels of competence and an adequate referral system involving primary care settings would support all elements of heart failure management – including diagnosis and treatment of iron deficiency.'

Professor Cândida Fonseca, Portugal

Case study

Including treatment and monitoring of ID in multidisciplinary and integrated HF care⁵⁵

The Germans Trias Hospital in Spain tested a STOP-HF-Clinic service to support people living with HF following hospital discharge, which included screening for and management of ID. Older and/or frail people hospitalised for HF in the internal medicine or geriatric departments were eligible for the service, which included:

- a follow-up appointment within seven days of discharge with an HF nurse, GP, cardiologist, internist or geriatrician. In this appointment, people were examined for known risk factors of HF exacerbation, including ID, fluid retention and high levels of natriuretic peptides (hormones produced by the heart)
- a face-to-face educational session with an HF nurse, whom patients could contact thereafter by telephone
- a minimum of three visits for optimisation of medication, including the administration of intravenous iron when needed.

After 30 days, patients were transitioned from the STOP-HF-Clinic service to standard care led by their GP or relevant specialist.

An evaluation of the STOP-HF-Clinic service found that around 17% of people were treated with intravenous iron, and that the programme significantly reduced hospital readmissions compared with standard care, which may in part be due to the identification and treatment of ID in people living with HF.

Case study

Educating healthcare professionals to improve the treatment of ID¹⁰

The Royal Brompton Hospital, a heart and lung specialist centre in the UK, developed an awareness campaign targeted at the HF care team to improve management of ID in HF.

The campaign was launched after it was discovered that people with symptomatic HFrEF managed in the hospital were not being systematically screened and treated for ID. It included the use of reminders during multidisciplinary team meetings, email notifications and stickers on clinic notes. These interventions succeeded in increasing the number of people with HF tested for ID from 50% to 100%, but this effect was not sustained over time. Treatment rates did not increase, and organisational barriers were identified as a potential reason for this – notably, admission was shown to take a median of seven hours, whereas the actual medical administration time was only 15–30 minutes. Hospital costs were also not fully reimbursed under the NHS tariff.

As part of this study, the HF care team assessed the feasibility of treating ID in an outpatient setting, based on a single patient. The visit lasted 75 minutes (including treatment administration and monitoring) and was found to be cost-saving.



The way forward

ID is a treatable condition that increases the burden of HF

ID decreases functional and exercise capacity in people with HF,^{2 6} may reduce benefit from HF treatment,^{32 50} and increases hospitalisations and mortality.^{1 7} However, awareness of ID among healthcare professionals involved in HF care is limited, screening and diagnosis are inconsistent, and treatment is suboptimal. These issues result in poor clinical outcomes and a significant burden on people with HF, the health system and society.^{6 7 39}

Concerted action is required to improve the diagnosis and management of ID in people living with HF

1. Translate European guidance into national policy and practice

Available European clinical guidance, such as that for universal ID screening and for intravenous iron treatment for people with symptomatic HFrEF, is not always translated into national guidelines. This directly affects access to treatment in many countries. It is essential that national and regional health systems formally adopt European guidelines or develop their own clinical recommendations and care pathways to support access to and delivery of care. Uptake of guideline recommendations should be promoted, for example by incorporating ID-related criteria into performance assessment systems for HF care. Clinical leaders and patient advocates should be empowered by the evidence and the unmet needs of people with HF to demand changes in their national health systems.

2. Raise awareness and improve diagnosis of ID in HF

Healthcare professionals working in HF should understand the potential causes of ID in people living with HF, and be ready to recognise signs and symptoms of ID to improve diagnosis rates. Efforts to train the healthcare workforce on ID should start during formal education and should target both specialist and relevant non-specialist professionals who may interact with people living with both HF and ID. There is also a need to raise awareness of ID guidelines among health system decision-makers including regulators, payers and providers, so that the structural barriers can be removed to allow healthcare professionals to deliver guideline-based care.

3. Shift the provision of intravenous iron to appropriately resourced outpatient settings

Hospitalisations are costly for the health system and burdensome for people living with HF.^{10 38 39} Outpatient provision could be a more convenient and cost-effective model than using a hospital bed. Professional bodies and specialist societies should develop guidance for outpatient provision of intravenous iron that addresses concerns about clinical risk. Policymakers, healthcare commissioners and providers should invest in outpatient clinics to deliver intravenous iron treatment without the need for hospital admission. This could benefit several patient groups and hospital departments, as treating ID supports management of not just HF but other long-term conditions, such as chronic kidney disease.⁵⁶

4. Support clinical research to improve understanding and treatment of ID across the whole spectrum of HF

Further research is needed to understand the mechanisms behind ID in acute HF and HFpEF, to identify treatment options that have a positive impact on clinical endpoints. The deficit of research carries a high cost, given the high prevalence of ID in acute HF and HFpEF and the role of ID in driving poorer outcomes, including increased risk of hospitalisation and readmission.^{1 21 38}

The time has come to recognise and manage ID in people with HF

The scientific consensus on best practice for the diagnosis and management of ID in HF has progressed in the past decade, but policy and practice have not kept pace. There must now be concerted action from clinicians, researchers, policymakers and patient advocates to ensure that ID is researched, recognised and treated effectively.

We hope this report and the actions proposed may lead to positive changes in policy, diagnosis and management of ID in HF – ultimately improving the lives of the millions of people living with HF across Europe.

References

1. Martens P, Nijst P, Verbrugge FH, *et al.* 2018. Impact of iron deficiency on exercise capacity and outcome in heart failure with reduced, mid-range and preserved ejection fraction. *Acta Cardiol* 73(2): 115-23
2. McDonagh T, Damy T, Doehner W, *et al.* 2018. Screening, diagnosis and treatment of iron deficiency in chronic heart failure: putting the 2016 European Society of Cardiology heart failure guidelines into clinical practice. *Eur J Heart Fail* 20(12): 1664-72
3. Cohen-Solal A, Leclercq C, Deray G, *et al.* 2014. Iron deficiency: an emerging therapeutic target in heart failure. *Heart* 100(18): 1414-20
4. World Health Organization. 2015. *The global prevalence of anaemia in 2011*. Geneva, Switzerland: WHO
5. NHS. Iron deficiency anaemia. [Updated 29/01/21]. Available from: <https://www.nhs.uk/conditions/iron-deficiency-anaemia/> [Accessed 04/04/22]
6. von Haehling S, Gremmler U, Krumm M, *et al.* 2017. Prevalence and clinical impact of iron deficiency and anaemia among outpatients with chronic heart failure: The PrEP Registry. *Clin Res Cardiol* 106(6): 436-43
7. Lam CSP, Doehner W, Comín-Colet J, *et al.* 2018. Iron deficiency in chronic heart failure: case-based practical guidance. *ESC Heart Fail* 5(5): 764-71
8. Ponikowski P, Voors AA, Anker SD, *et al.* 2016. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur J Heart Fail* 18(8): 891-975
9. McDonagh TA, Metra M, Adamo M, *et al.* 2021. 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 Heart J* 42(36): 3599-726
10. Hayward C, Patel H, Allen C, *et al.* 2016. Improving the management of iron deficiency in ambulatory heart failure patients. *BMJ Qual Improv Rep* 5(1): 10.1136/bmjquality.u209822.w4076
11. Wienbergen H, Pfister O, Hochadel M, *et al.* 2016. Usefulness of iron deficiency correction in management of patients with heart failure [from the Registry Analysis of Iron Deficiency-Heart Failure (RAID-HF) Registry]. *Am J Cardiol* 118(12): 1875-80
12. Cohen-Solal A, Damy T, Terbah M, *et al.* 2014. High prevalence of iron deficiency in patients with acute decompensated heart failure. *Eur J Heart Fail* 16(9): 984-91
13. McDonagh T, Macdougall IC. 2015. Iron therapy for the treatment of iron deficiency in chronic heart failure: intravenous or oral? *Eur J Heart Fail* 17(3): 248-62
14. Lewis GD, Malhotra R, Hernandez AF, *et al.* 2017. 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* 317(19): 1958-66
15. Dignass A, Farrag K, Stein J. 2018. Limitations of serum ferritin in diagnosing iron deficiency in inflammatory conditions. *Int J Chronic Dis* 2018: 10.1155/2018/9394060
16. Van Aelst LNL, Abraham M, Sadoune M, *et al.* 2017. Iron status and inflammatory biomarkers in patients with acutely decompensated heart failure: early in-hospital phase and 30-day follow-up. *Eur J Heart Fail* 19(8): 1075-76
17. Barton C. 2020. Interview with Marissa Mes at The Health Policy Partnership [telephone]. 06/01/20
18. Jankowska EA. 2020. Interview with Marissa Mes at The Health Policy Partnership [telephone]. 06/01/20
19. Jahnz-Rózyk K, Kawalec P, Malinowski K, *et al.* 2017. Drug policy in Poland. *Value Health Reg Issues* 13(C): 23-26

20. Rosano G. 2022. Interview with Catherine Hodge and Kirsten Budig at The Health Policy Partnership [video call]. 26/01/22
21. Núñez J, Domínguez E, Ramón JM, *et al.* 2016. Iron deficiency and functional capacity in patients with advanced heart failure with preserved ejection fraction. *Int J Cardiol* 207: 365-67
22. Heart Failure Policy Network. 2019. *Understanding heart failure guidelines: Diagnosis*. London: HFPN
23. Savarese G, Lund LH. 2017. Global public health burden of heart failure. *Card Fail Rev* 3(1): 7-11
24. Cowie MR, Anker SD, Cleland JGF, *et al.* 2014. Improving care for patients with acute heart failure: before, during and after hospitalization. *ESC Heart Fail* 1(2): 110-45
25. Gheorghiade M, Vaduganathan M, Fonarow GC, *et al.* 2013. Rehospitalization for heart failure: problems and perspectives. *J Am Coll Cardiol* 61(4): 391-403
26. Crespo-Leiro MG, Anker SD, Maggioni AP, *et al.* 2016. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail* 18(6): 613-25
27. Heart Failure Policy Network. 2018. *The handbook of multidisciplinary and integrated heart failure care*. London: HFPN
28. American Heart Association. Ejection fraction heart failure measurement. [Updated 31/05/17]. Available from: <https://www.heart.org/en/health-topics/heart-failure/diagnosing-heart-failure/ejection-fraction-heart-failure-measurement> [Accessed 04/04/22]
29. The Heart Failure Policy Network. 2020. *Spotlight on HFpEF: heart failure with preserved ejection fraction*. London: HFPN
30. Muckenthaler MU, Rivella S, Hentze MW, *et al.* 2017. A red carpet for iron metabolism. *Cell* 168(3): 344-61
31. NHS. Red blood cell count. [Updated 21/09/18]. Available from: <https://www.nhs.uk/conditions/red-blood-count/> [Accessed 04/04/22]
32. Mordi IR, Tee A, Lang CC. 2018. Iron therapy in heart failure: ready for primetime? *Card Fail Rev* 4(1): 28-32
33. Jankowska EA, von Haehling S, Anker SD, *et al.* 2013. Iron deficiency and heart failure: diagnostic dilemmas and therapeutic perspectives. *Eur Heart J* 34(11): 816-29
34. Rocha BML, Cunha GJL, Menezes Falcao LF. 2018. The burden of iron deficiency in heart failure: therapeutic approach. *J Am Coll Cardiol* 71(7): 782-93
35. Nairz M, Haschka D, Demetz E, *et al.* 2014. Iron at the interface of immunity and infection. *Front Pharmacol* 5(152): 10.3389/fphar.2014.00152
36. Camaschella C. 2017. New insights into iron deficiency and iron deficiency anemia. *Blood Rev* 31(4): 225-33
37. Silverberg DS, Wexler D, Schwartz D. 2015. Is correction of iron deficiency a new addition to the treatment of the heart failure? *Int J Mol Sci* 16(6): 14056-74
38. Van Aelst LNL, Mazure D, Cohen-Solal A. 2017. Towards holistic heart failure management - how to tackle the iron deficiency epidemic? *Curr Heart Fail Rep* 14(4): 223-34
39. Beattie JM, Khatib R, Phillips C, *et al.* 2017. 4 Iron deficiency in heart failure patients in England: insights from analysis of hospital episode statistics. *Heart* 103(Suppl 5): A2-A3
40. Jankowska EA, Rozentryt P, Witkowska A, *et al.* 2010. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. *Eur Heart J* 31(15): 1872-80
41. Piednoir P, Allou N, Driss F, *et al.* 2011. Preoperative iron deficiency increases transfusion requirements and fatigue in cardiac surgery patients: a prospective observational study. *Eur J Anaesthesiol* 28(11): 796-801

42. Klip IT, Comín-Colet J, Voors AA, *et al.* 2013. Iron deficiency in chronic heart failure: an international pooled analysis. *Am Heart J* 165(4): 575-82.e3
43. Martens P, Verbrugge F, Nijst P, *et al.* 2017. Impact of iron deficiency on response to and remodeling after cardiac resynchronization therapy. *Am J Cardiol* 119(1): 65-70
44. Heart Failure Association. Heart Failure Matters: cardiac resynchronisation therapy (CRT). Available from: https://www.heartfailurematters.org/en_GB/What-can-your-doctor-do/Cardiac-Resynchronisation-Therapy-CRT [Accessed 04/04/22]
45. Anker SD, Comín-Colet J, Filippatos G, *et al.* 2009. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 361(25): 2436-48
46. Ponikowski P, van Veldhuisen DJ, Comín-Colet J, *et al.* 2015. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J* 36(11): 657-68
47. Ponikowski P, Kirwan B-A, Anker SD, *et al.* 2020. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *The Lancet* 396: 1895-904
48. Comín-Colet J, McDonagh T, Ponikowski P. 2019. Managing iron deficiency in heart failure patients. European Society of Cardiology Webinar; 24/10/19; Paris, France
49. Przybyłowski P, Wasilewski G, Golabek K, *et al.* 2016. Absolute and functional iron deficiency is a common finding in patients with heart failure and after heart transplantation. *Transplant Proc* 48(1): 173-6
50. Cunha GJL, Rocha BML, Menezes Falcão L. 2018. Iron deficiency in chronic and acute heart failure: A contemporary review on intertwined conditions. *Eur J Intern Med* 52(June): 1-7
51. Kwok CS, McDermott S, Bennett S, *et al.* 2021. United Kingdom treatment of iron deficiency in heart failure: are we missing opportunities? *Br J Cardiol*: 10.5837/bjc.2021.s02
52. Fonseca C. 2020. Interview with Sara C. Marques at The Health Policy Partnership [telephone]. 05/02/20
53. Heart Failure Association of the ESC. 2022. Iron deficiency in heart failure: translating guideline recommendations into clinical practice. Available from: <https://esc365.escardio.org/event/329> [Accessed 26/01/22]
54. von Haehling S, Ebner N, Evertz R, *et al.* 2019. Iron deficiency in heart failure an overview. *JACC Heart Fail* 7(1): 36-47
55. Pacho C, Domingo M, Núñez R, *et al.* 2017. Early postdischarge STOP-HF-clinic reduces 30-day readmissions in old and frail patients with heart failure. *Rev Esp Cardiol (Engl Ed)* 70(8): 631-38
56. Mikhail A, Brown C, Williams J, *et al.* 2017. *Clinical practice guideline anemia of chronic kidney disease*. Bristol, UK: The Renal Association

About the Heart Failure Policy Network

The Heart Failure Policy Network is an independent, multidisciplinary group of healthcare professionals, patient advocacy groups, policymakers and other stakeholders from across Europe whose goal is to raise awareness of unmet needs surrounding heart failure and its care. All Network members provide their time for free. All Network content is non-promotional and non-commercial. The Secretariat is provided by The Health Policy Partnership Ltd, an independent health policy consultancy based in London.

Please cite this report as: Heart Failure Policy Network. 2022. *Spotlight on iron deficiency in heart failure*. London: HFPN



The Spotlight series is a set of reports by



**The Heart
Failure Policy
Network**