Spotlight on

Iron deficiency in heart failure

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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 therefore ID can have a negative impact on health. 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 haemoglobin within them, which results in reduced, and possibly insufficient, oxygen in the blood.[4 5]

ID worsens HF clinical outcomes and contributes to the burden of HF on people and healthcare systems. It can negatively affect the independence 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. Iron levels are not consistently measured as part of HF care, and symptoms of ID are sometimes mistaken for deteriorating HF.[8-10] Diagnostic criteria for ID differ between people living with HF and the general population.[2] Exacerbation of HF affects the reliability of ID biomarkers,[11] 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 is a gap in ID treatment recommendations in HF guidelines as they focus solely on HF with reduced ejection fraction (HFrEF).[2 12] This leaves healthcare professionals unsupported when it comes to management of ID in other types of HF and during exacerbation.

Even in situations where clinical guidelines are available, management of ID is often suboptimal. For example, ID treatment is not always provided to people with symptomatic HFrEF and ID.[10] In addition, guidelines recommend intravenous iron for treatment of ID in HF,[2 12] but many people are still treated with oral iron[9 13] despite evidence of limited efficacy, increased risk of side effects and potential issues with treatment adherence.[2 14 15] Limited professional awareness of guidelines has been noted as a factor in the poor management of ID in HF.[9 13]

Access to optimal treatment for ID in HF varies across Europe. This may be due to a lack of national or regional guidelines,[16] issues with reimbursement[17 18] and organisational barriers.[10] For example, long waiting times for inpatient admission following arrival at hospital, out-of-pocket expenses and high costs for the healthcare system may limit provision of intravenous iron in people living with HF.

There are clear needs to properly address ID in HF. Taking action in these areas will reduce the burden of ID on HF, and consequently that of HF on each person, the healthcare system and society in general.

Key actions to improve diagnosis and management of ID in HF

1. Raise awareness and improve diagnosis of ID in HF	It is essential that healthcare professionals working in HF are alert for the causes, signs and symptoms of ID in people living with HF.
2. Encourage management of ID as a core component of HF care	There is a need for comprehensive training of professionals involved in providing intravenous iron treatment. Uptake of guideline recommendations should be promoted, for example by incorporating ID-related criteria into performance assessment systems for HF care.
3. Invest in management of ID in outpatient clinics	Outpatient clinics are effective settings to treat ID without the need for hospital admission. They can support management of ID not only in HF but several long-term conditions, benefiting different patient groups and hospital departments.
4. Support clinical research to improve understanding and treatment of ID across the whole spectrum of HF	The development and role of ID is not fully understood in acute HF and types of HF beyond HFrEF. The resulting lack of treatment options for ID in these situations limits effective management of the condition; research is needed to develop an evidence base.
5. Develop guidance for management of ID across HF types	Evidence gathered in ongoing and future research, particularly in HF types other than HFrEF, should be translated into new guidance to support management of ID across all types of HF. National and regional healthcare systems should formally adopt available European guidelines or develop their own recommendations and care pathways to ensure access to ID treatment for people with HF.

1 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 12] potentially contributing to poorer clinical outcomes.[19] 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.[12 20] 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, healthcare systems and society as a whole

HF affects up to 2% of people living in Europe.[21] 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.[22 23] Quality of life and survival rates in HF remain poor.[24] The burden of HF is expected to rise in the coming years due to an ageing population and improved survival rates for other diseases, posing a challenge to the sustainability of healthcare systems across the world.[25]

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),[12] which is the proportion of oxygenated blood pumped out by the left ventricle to the rest of the body with each heartbeat.[26] 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%.[27] HF with mid-range ejection fraction (HFmrEF) refers to an LVEF between 40% and 49% inclusive. HFrEF is better understood than other types of HF, both in terms of its development and treatment options.[27]

Iron is an essential element to 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,[28] a protein in red blood cells responsible for transporting oxygen from the lungs to the rest of the body.[29] 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.[28] 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.[30] 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.[28] 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), and both can occur simultaneously.[2 6 30] Absolute ID is typically caused by low iron consumption, increased iron use and/or blood loss.[31] 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[12 32] – 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 system[33] and cognitive function,[34] and can lead to anaemia,[2 28] 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.[34]

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[19 32] and during episodes of exacerbation; 69–75% of people with acute HF have ID.[13]

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

Inflammation is very common in people with HF, contributing to a high prevalence of ID.[31] 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 35] 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.[36] These medicines increase the risk of bleeding, which may lead to ID. However, such risks can be safely and effectively managed by the HF care team 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 19 37] This not only adds to the strain on people with HF and their families/carers, 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.[37] It is also linked to the need for cardiac surgery (including heart transplantation) and for blood transfusions in people awaiting such interventions.[38 39] ID increases the risk of mortality in people with HF by 40–60%.[7]

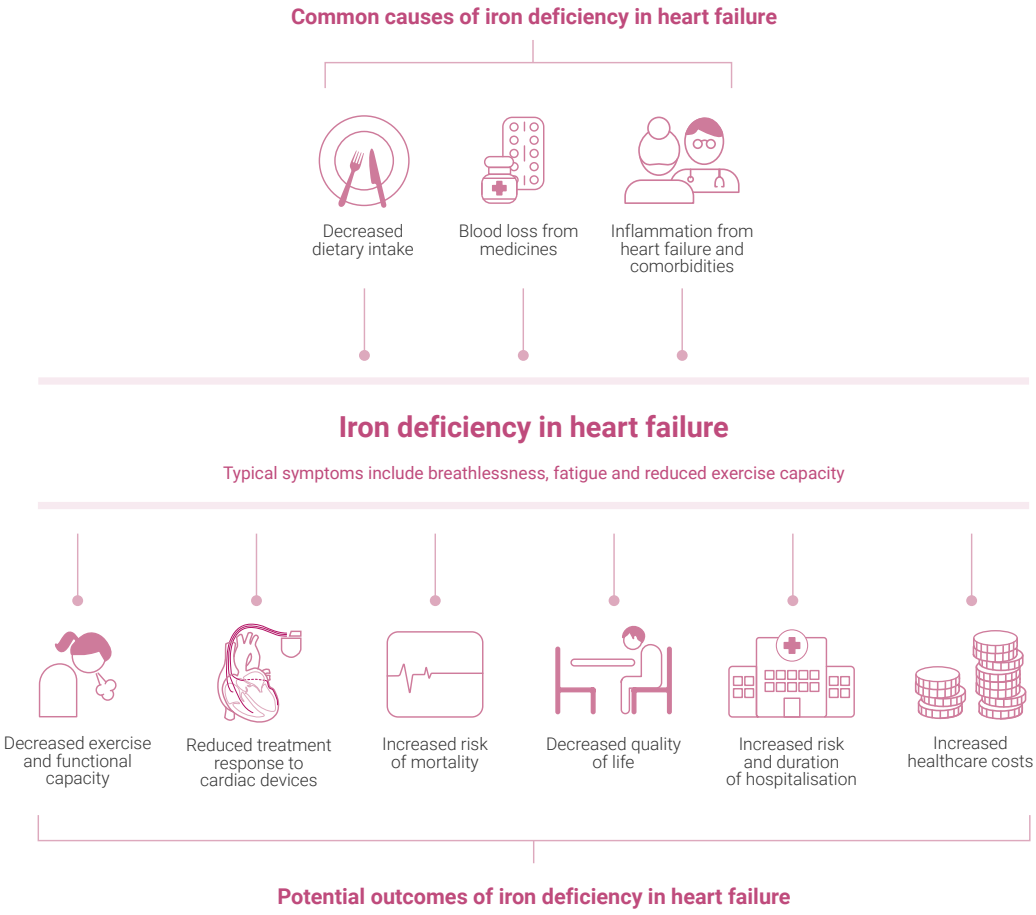
ID adds to the devastating impact of HF on independence and quality of life

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, housekeeping and climbing stairs more difficult.[40] 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.[41 42]

'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

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.[9] 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 with those of HF may have a role in the poor diagnosis rates of ID – healthcare professionals may mistake ID for deteriorating HF.[8] 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.[43]

Diagnosis of ID relies on indirect measures

A bone marrow biopsy is the accepted gold standard for diagnosing ID.[3 32] However, this procedure is costly, invasive and complex, making it inappropriate for routine monitoring of iron levels. Instead, diagnosis of ID usually relies on two biomarkers, ferritin and transferrin[2 12] – their levels are slightly less accurate but accepted in clinical practice. Ferritin is a protein that stores iron, and transferrin is a protein that transports iron in the blood. For the purpose of diagnosing ID, ferritin levels can be measured directly, while the proportion of transferrin bound to iron should be determined – transferrin saturation (TSAT).[31] Guidelines recommend determining ferritin levels and TSAT rather than the serum iron concentration (in the bloodstream) as this may change every hour.[2 12 30] 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.[31]

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.[8] 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.[11 44]

Limited professional knowledge of ID in HF may hinder diagnosis

There is a need to educate the HF care team about diagnosis of ID.[17] Some healthcare professionals may not realise that iron levels should be tested in all people living with HF.[9] 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.[11 44] Equally, many professionals may misinterpret ID symptoms for those typical of HF deterioration.[8] Although European HF guidelines introduced specific diagnostic criteria for ID in 2016,[12] practical guidance – for example, clinical case studies – was initially lacking.[7] This may continue to affect professional understanding and uptake of guideline recommendations for diagnosis of ID in HF.

> ***'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

Guidelines for treatment of ID focus solely on HFrEF

HF guidelines recommend intravenous iron to treat ID in people with symptomatic HFrEF.[2 12] One particular formulation has been well evidenced to improve exercise capacity and quality of life, and to reduce the risk of hospitalisation for worsening HF.[45 46] However, guidelines do not make treatment recommendations for ID either in acute HF or in HF types beyond HFrEF,[2] as the safety and efficacy of intravenous iron in these situations is still under study.[47 48] This poses a significant challenge in clinical management, especially considering the high prevalence of ID during exacerbation of HF.[1 36]

> ***'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

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] potentially due to impaired iron absorption[36] and increased risk of gastrointestinal side effects.[14] In addition, people with HF often take several medicines, and adding another oral treatment may make adherence more challenging.[14] Despite this, oral iron is often prescribed as first-line treatment for ID in people with HF.[13] Intravenous iron, despite being recommended in people with ID and symptomatic HFrEF,[12] is often only provided to people with anaemia or severe HF symptoms.[9] A specialist HF service in the UK found that none of its patients with symptomatic HFrEF and diagnosed ID were treated with intravenous iron.[10]

> ***'Previous intravenous formulations of iron could result in serious allergic reactions, which was why they had to be administered only in hospitals. Nowadays, we have different formulations and the risk of allergic reactions is very low, but some healthcare professionals still think of this and are wary of administering intravenous iron in outpatient settings.'***
>
> Professor Ewa Anita Jankowska, Poland

Access to and reimbursement of intravenous iron varies between countries

Across Europe, access to treatment of ID in HFrEF is not equitable, despite European guideline recommendations.[2 12] For example, the National Institute for Health and Care Excellence (NICE) in England and Wales has not developed its own guidelines for treatment of ID in HF, which poses a barrier to the prescription of intravenous iron for people with HF in those countries.[16] As a result, these individuals 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 for ID treatment with intravenous iron.[17 18]

Organisational barriers can hinder treatment of ID

Even when intravenous iron is commissioned, 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 infection[2] – but often has to be provided in hospital settings due 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.[16 49] 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 HF clinics are needed for ID treatment, but some countries, like Portugal, don't have enough of them.'***
>
> Professor Cândida Fonseca, Portugal

5

Best practice in management of iron deficiency in heart failure

Clinical management of HF should include regular screening for ID

ESC guidelines recommend measuring iron levels in people with newly diagnosed HF, and routinely monitoring levels once or twice a year in all people with HF.[2 12] 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.[36] 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.[19 32 36]

> ***'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

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] Iron levels in people with chronic HF should be re-evaluated three months after treatment to determine whether further sessions are required.

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

ID is best managed in an outpatient setting through short and accessible appointments, which eliminates the need for hospital admission and reduces the cost of treatment.[10] However, it is essential that outpatient settings have the tools and skilled personnel needed to manage complications, for example allergic reactions.[2 7] 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 care[50]

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 ID[10]

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 cause for this – notably, admission was shown to take a median of seven hours, whereas the actual medical administration time was only 15–30 minutes.

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.

6 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,[30 44] and increases hospitalisations and mortality.[1 7] However, awareness of ID among healthcare professionals involved in HF care is limited, diagnosis is delayed and treatment is suboptimal, which results in poor clinical outcomes and a significant burden on people with HF, the healthcare system and society.[6 7 37]

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

1. 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.

2. Encourage management of ID as a core component of HF care

Professionals involved in providing intravenous iron treatments should be trained on dosage calculations and management of allergic reactions among people living with HF. Uptake of guideline recommendations should be promoted, for example by incorporating ID-related criteria into performance assessment systems for HF care, such as the routine monitoring of iron levels and their correction if needed.

3. Invest in management of ID in outpatient clinics

There is a huge missed opportunity to prevent unnecessary hospitalisation for treatment of ID in HF. Hospitalisations are costly for the healthcare system and burdensome for people living with HF.[10 36 37] Policymakers and healthcare commissioners 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.[51]

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 types of HF beyond HFrEF, 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 19 36]

5. Develop guidance for management of ID across HF types

As a result of gaps in the research, there is a lack of guidance for managing ID in people with acute HF or those with an LVEF higher than 40%, leaving many healthcare professionals unsupported in terms of clinical decision-making. In addition, available European clinical guidance, such as that for ID treatment in people with symptomatic HFrEF, is not always translated into national guidelines, which directly affects access to treatment in many countries. Therefore, it is also essential that national and regional healthcare systems formally adopt European guidelines or develop their own clinical recommendations and care pathways to support access to and delivery of care.

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

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 12/01/18]. Available from: https://www.nhs.uk/conditions/iron-deficiency-anaemia/ [Accessed 22/08/19]

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. 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

9. 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

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. 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

12. 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

13. 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

14. 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

15. 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

16. Barton C. 2020. Interview with Marissa Mes at The Health Policy Partnership [telephone]. 06/01/20

17. Jankowska EA. 2020. Interview with Marissa Mes at The Health Policy Partnership [telephone]. 06/01/2020

18. Jahnz-Różyk K, Kawalec P, Malinowski K, et al. 2017. Drug policy in poland. *Value Health Reg Issues* 13(C): 23-26

19. Núñez J, Comín-Colet J, Minana G, *et al*. 2016. Iron deficiency and risk of early readmission following a hospitalization for acute heart failure. *Eur J Heart Fail* 18(7): 798-802

20. The Heart Failure Policy Network. 2019. *Understanding heart failure guidelines: Diagnosis*. London: HFPN

21. Savarese G, Lund LH. 2017. Global public health burden of heart failure. *Card Fail Rev* 3(1): 7-11

22. 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

23. Gheorghiade M, Vaduganathan M, Fonarow GC, *et al.* 2013. Rehospitalization for heart failure: problems and perspectives. *J Am Coll Cardiol* 61(4): 391-403

24. 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

25. The Heart Failure Policy Network. 2018. *The handbook of multidisciplinary and integrated heart failure care*. London: HFPN

26. 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 23/01/20]

27. The Heart Failure Policy Network. 2020. *Spotlight on HFpEF: heart failure with preserved ejection fraction*. London: HFPN

28. Muckenthaler MU, Rivella S, Hentze MW, *et al*. 2017. A red carpet for iron metabolism. *Cell* 168(3): 344-61

29. NHS. Red blood cell count. [Updated 21/09/18]. Available from: https://www.nhs.uk/conditions/red-blood-count/ [Accessed 10/01/20]

30. Mordi IR, Tee A, Lang CC. 2018. Iron therapy in heart failure: ready for primetime? *Card Fail Rev* 4(1): 28-32

31. 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

32. 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

33. 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

34. Camaschella C. 2017. New insights into iron deficiency and iron deficiency anemia. *Blood Rev* 31(4): 225-33

35. 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

36. 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

37. 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

38. 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

39. 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

40. 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

41. 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

42. 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 23/01/20]

43. 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

44. Cunha GJL, Rocha BML, Menezes Falcão L. 2018. Iron deficiency in chronic and acute heart failure: A contemporary review on intertwined conditions. *Euro J Intern Med* 52(June): 1-7

45. 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

46. 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

47. Ponikowski P, Kirwan B-A, Anker SD, et al. 2019. Rationale and design of the AFFIRM-AHF trial: a randomised, double-blind, placebo-controlled trial comparing the effect of intravenous ferric carboxymaltose on hospitalisations and mortality in iron-deficient patients admitted for acute heart failure. *Eur J Heart Fail* 21(12): 1651-58

48. Von Haehling S, Ebner N. 2017. Effect of IV iron in patients with heart failure with preserved ejection fraction (FAIR-HFpEF). [Updated 25/03/16]. Available from: https://clinicaltrials.gov/ct2/show/NCT03074591 [Accessed 12/11/19]

49. Fonseca C. 2020. Interview with Sara C Marques at The Health Policy Partnership [telephone]. 05/02/20

50. 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

51. Mikhail A, Brown C, Wiliams 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.

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