Challenges and Advances in Diagnosis and Treatment of Iron Deficiency in HF:
The Role of Clinical Decision Support Tools

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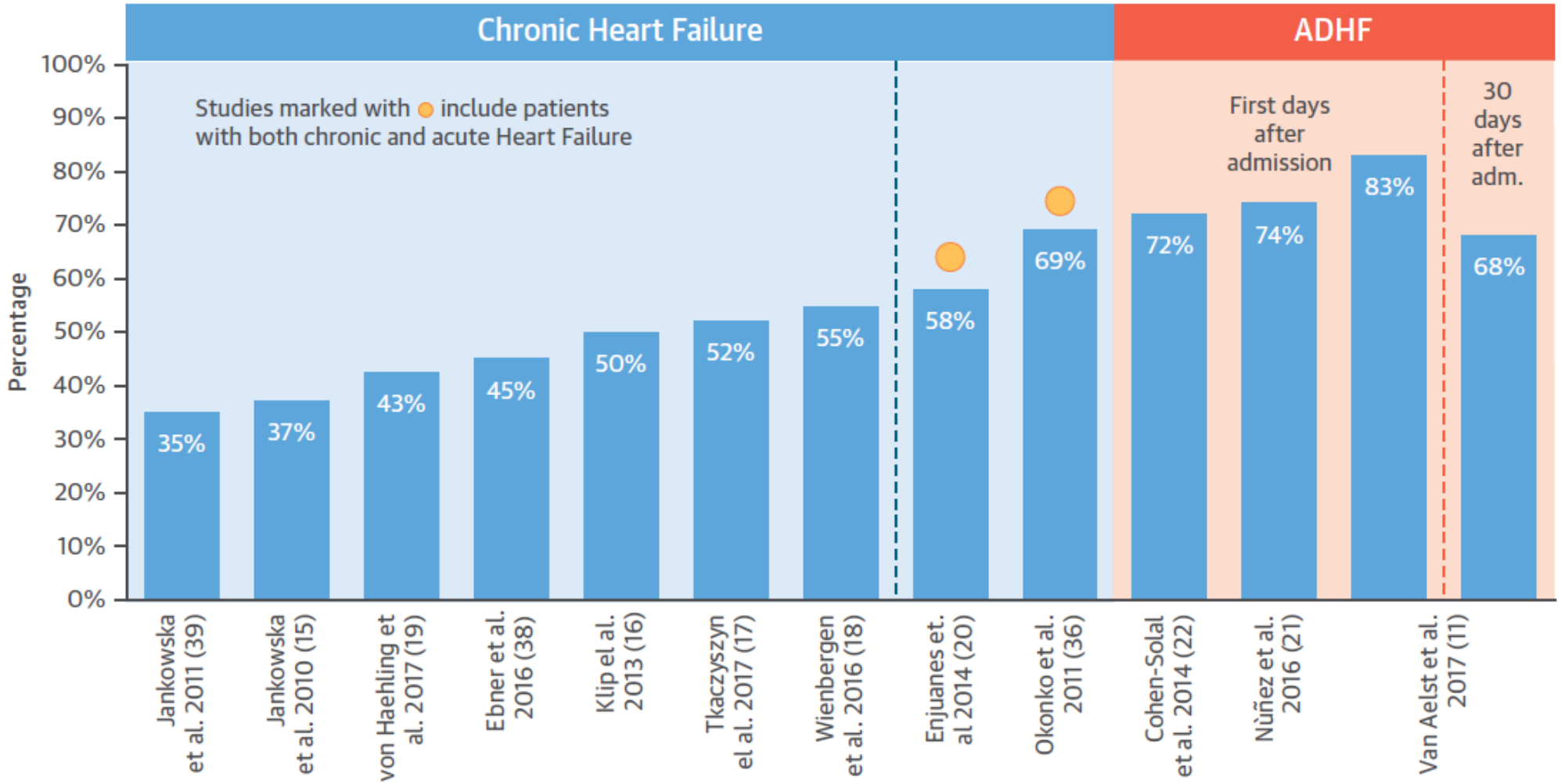
Prevalence of iron deficiency in heart failure



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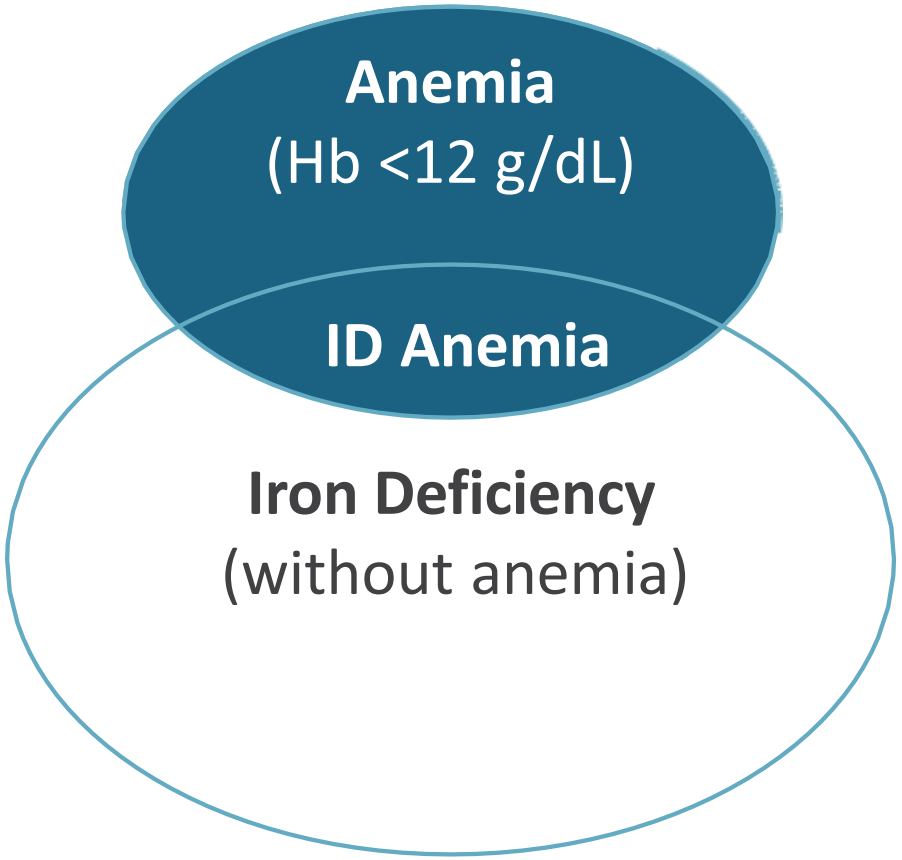
Rocha BML, et al. J Am Coll Cardiol. 2018;71:782-93.

Absolute vs. functional iron deficiency



- **Absolute iron deficiency** (reduction in iron stores)
  - **Causes:** chronic blood loss (aspirin), malnutrition, malabsorption
  - **Diagnosis: low serum ferritin level <100 µg/L**
- **Functional iron deficiency** (disturbed iron metabolism in bone marrow and systemic iron utilization; iron stores normal or elevated)
  - **Causes:** chronic inflammation (elevated hepcidin) and kidney dysfunction
  - **Diagnosis: serum ferritin 100–299 µg/L and TSAT <20%**

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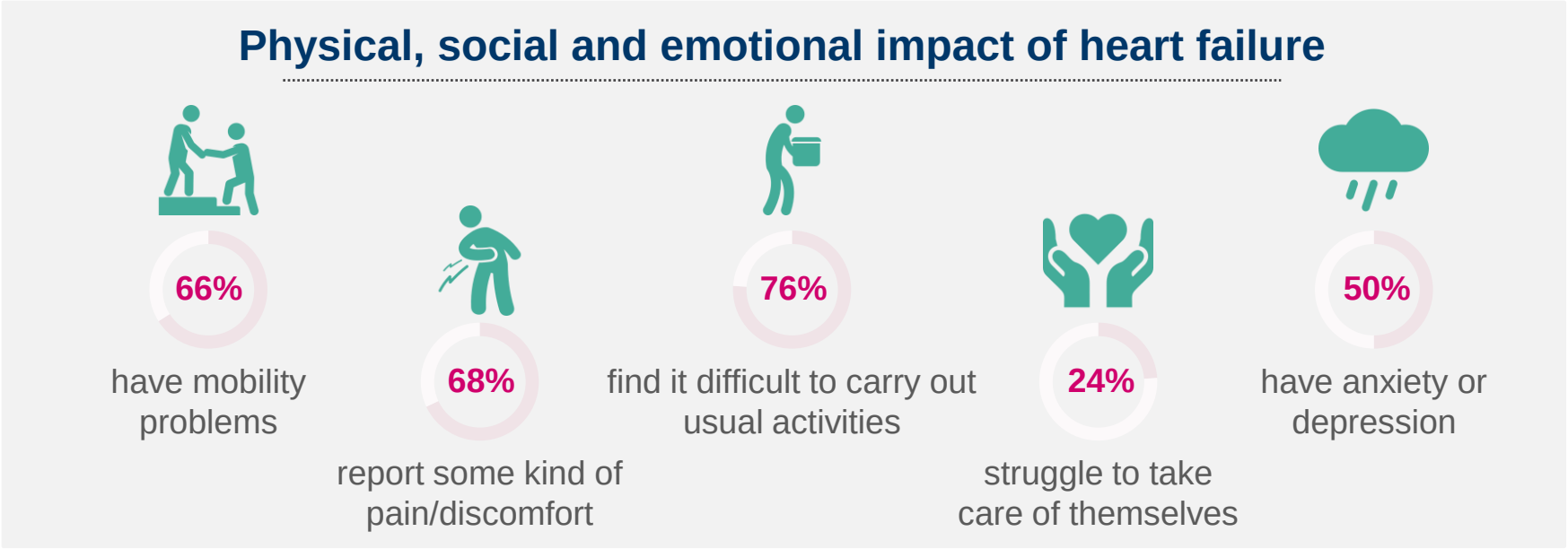
Wish JB. Clin J Am Soc Nephrol. 2006; 1 Suppl 1:S4-8; Muñoz M, et al. World J Gastroenterol. 2009.15:4666-74.

Unmet medical need in patients with heart failure



Improving symptoms and quality of life, such as physical activity, continues to be an unmet medical need in patients with heart failure

In addition to impacting cardiovascular outcomes (death and hospitalization), heart failure also leads to a substantial reduction in quality of life and a high symptom burden

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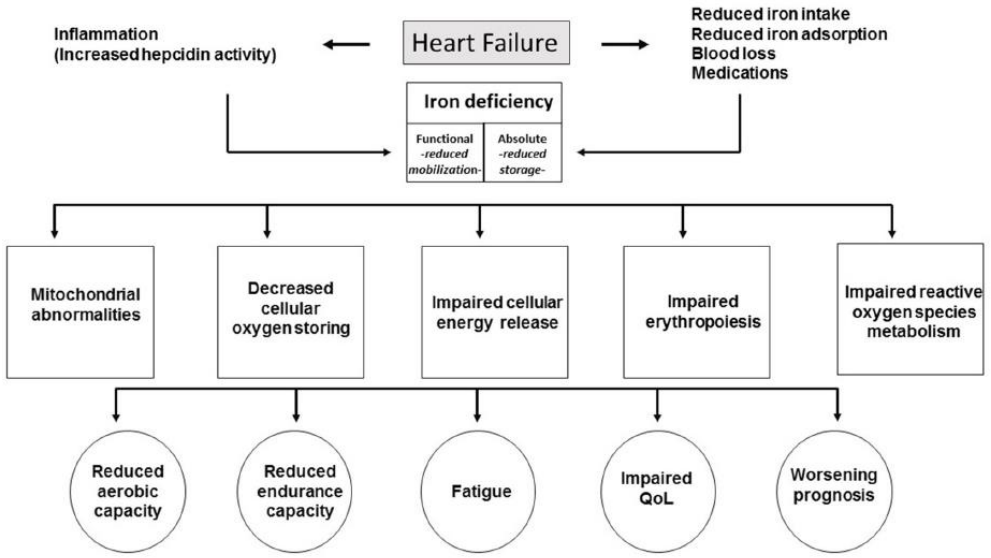
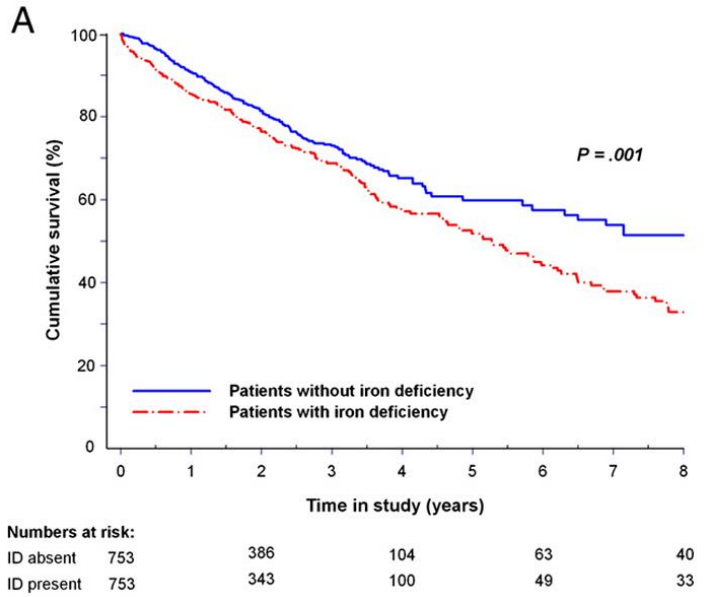
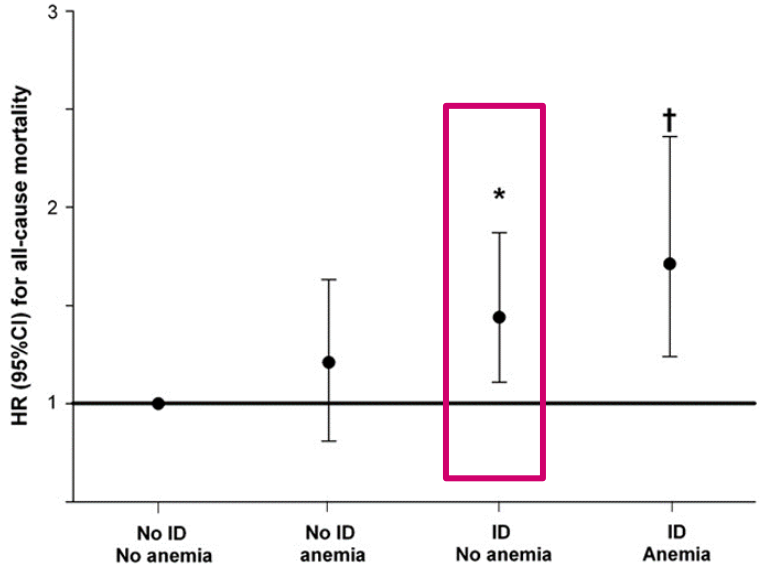
Calvert MJ et al. Eur J Heart Fail 2005;7:243

Impact of iron deficiency on clinical outcomes

- Iron deficiency is an **independent predictor of mortality risk in heart failure**, irrespective of comorbid anemia +/- CKD
- The deleterious prognostic impact is not only independent of anemia, but stronger than anemia
- Effective iron repletion meaningfully resolves the negative effects of iron deficiency, **including mortality risk**







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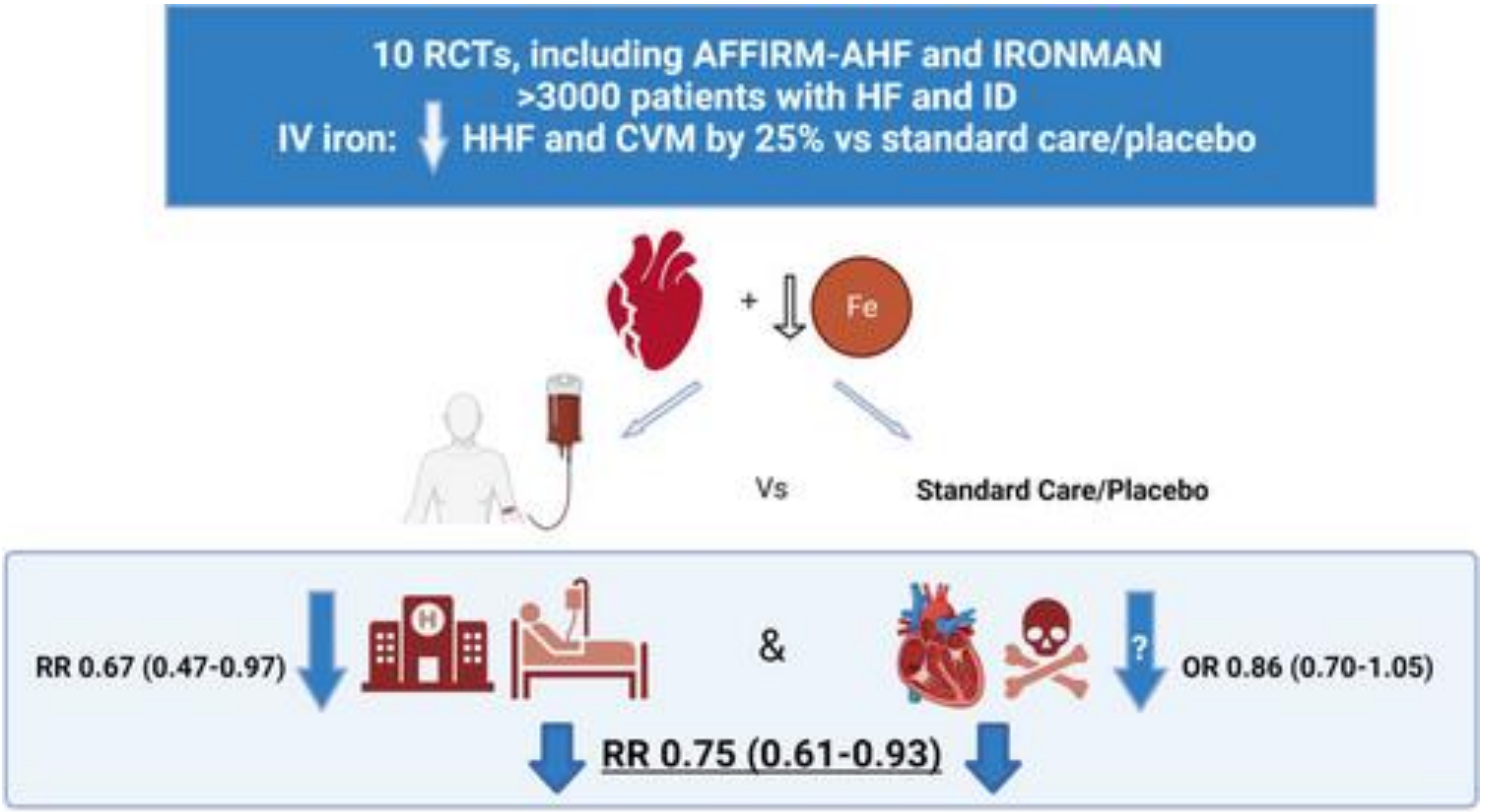
Rizzo C, et al. Front Cardiovasc Med. 2021; Klip I, et al. Am Heart J. 2013; Graham FJ, et al. Eur J Heart Failure. 2022.

Barriers and gaps in identification and treatment

- Despite its high prevalence and implication on clinical outcomes, iron deficiency is often overlooked in patients with heart failure.

- Barriers and gaps leading to underdiagnosis and management include:
  - Similarity of symptoms
  - Special diagnostic criteria due to chronic inflammation
  - Suboptimal awareness among health care professionals
  - Access and reimbursement
  - System fragmentation

Insights from meta-analyses



- Use of ferric carboxymaltose and ferric derisomaltose were safe
- IV iron repletion with FCM or FDI compared to placebo reduced the risk of recurrent HF hospitalization and CV death [composite endpoint] compared to placebo in patients with HF and iron deficiency
- **Mainly driven by a reduction in HF hospitalization**

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Anker S, et al. Eur J Heart Failure. 2023.

Currently available IV iron formulations

NEXT-GEN FORMULATIONS

Iron product	Dosing and administration	Approved indications	Common adverse drug events	Warnings	Evaluated in patients with heart failure
Ferric carboxymaltose (FCM)*	• For patients weighing ≥50 kg, may give 15 mg/kg up to 1,000 mg (*single-dose TDI*) or 750 mg infusion • If 750 mg is given, may be repeated in 7 days, for a total dosage per course of 1,500 mg • For patients weighing <50 kg, give 15 mg/kg in 2 doses, separated by at least 7 days	IDA in patients 1 yo and older who have intolerance or unsatisfactory response to oral iron, and in adults who have *non–dialysis-dependent CKD (NDD-CKD)* ***ID in adult patients with heart failure and NYHA class II/III to improve exercise capacity***	Nausea, hypertension, hypophosphatemia, flushing	Hypersensitivity reactions, symptomatic hypophosphatemia, hypertension	**Yes, in large randomized controlled trials**
Ferric derisomaltose (FDI)*	• For patient weighing ≥ 50 kg, give 1,000 mg (*single dose TDI*) • For patients weighing <50 kg, give 20 mg/kg in a single dose	IDA in adult patients who have intolerance or unsatisfactory response to oral iron, or who have *non–hemodialysis-dependent CKD*	Nausea, injection site reactions, rash, hypotension	Hypersensitivity reactions, iron overload	**Yes, in large randomized controlled trials**

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FDA Prescribing Information.

Recognizing, mitigating, and managing hypersensitivity

- Life-threatening anaphylaxis/severe hypersensitivity is *very rare* with next-gen IV iron products

Product	Anaphylaxis/ Anaphylactoid-reactions
Ferric carboxymaltose	0.1%
Ferumoxytol	0.2%
Ferric derisomaltose	0.3%

- **Essential to clinically differentiate minor acute reactions to IV iron from true anaphylaxis**

- Most common acute infusion reactions to IV iron are Fishbane and complement activation-related pseudo-allergy (CARPA) reactions
  - Clinical manifestations: facial flushing, chest tightness, arthralgia/myalgia, itching, mild dyspnea
- Though these reactions may seem to mimic onset of anaphylaxis, they are *NOT* anaphylaxis
  - Often self-resolving and typically do not recur
  - Can re-initiate of same IV iron product at slower rate (~50% reduction)

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Avni T, et al. Mayo Clin Proc. 2015; DeLoughery TG. Acta Haematol. 2019; Rampton D, et al. Haematologica. 2014; MacDougall IC, et al. Am J Nephrol. 2017; Steveling-Klein EH, et al. J Allergy Clin Immunol Pract. 2021; Caimmi S, et al. Children (Basel). 2022.

Intravenous approach to iron repletion

Median iron repletion dose in patients with heart failure is **1000 mg**

Daily dose of up to 1000 mg* with 100% **IV** bioavailability

*Newer formulations of IV iron products offer this higher dosing; ferric carboxymaltose (FCM), for instance, can be given as a 2-injection course, separated by 7 days, at a total iron dose of 1,500 mg.

Rapid** repletion

Oftentimes in just **1–2 infusions

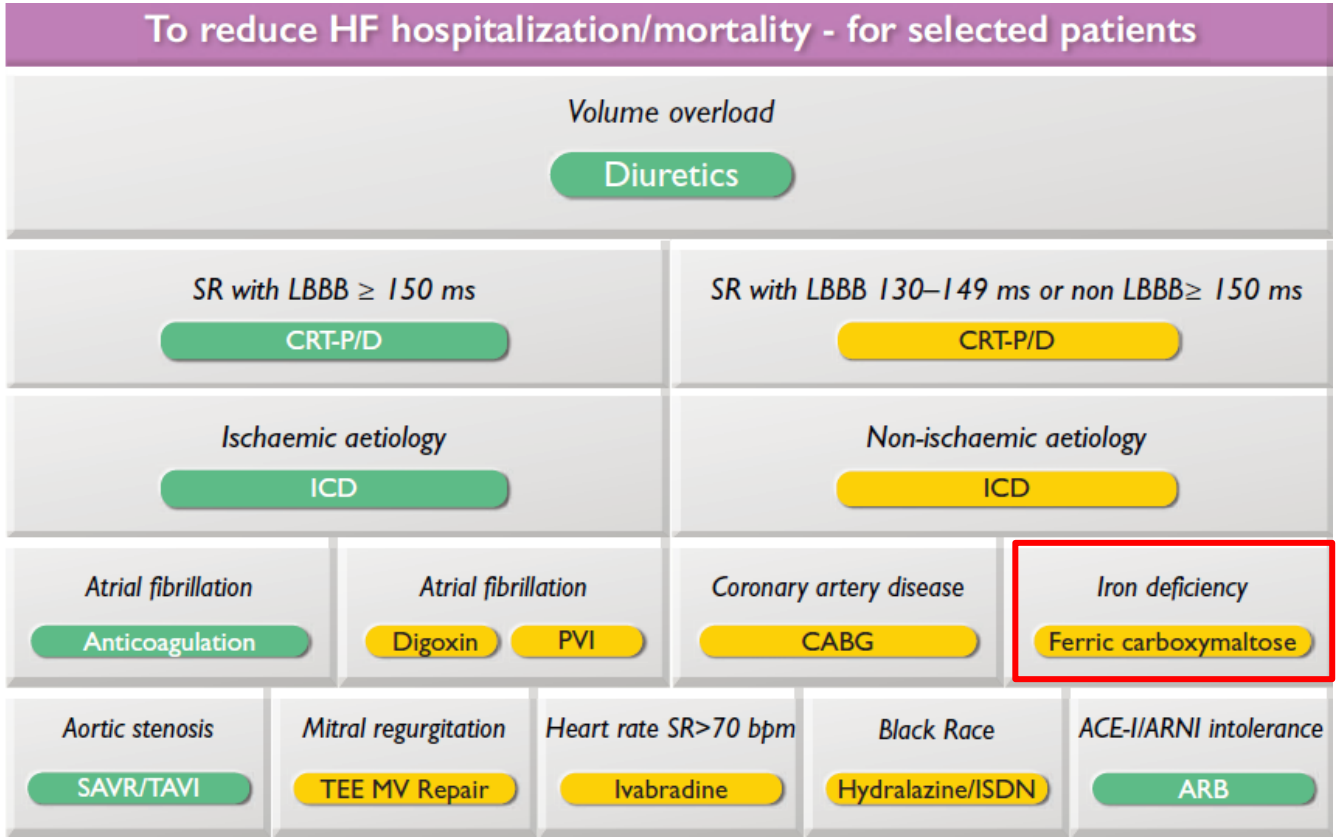
KNOW ID in HF

McDonagh T, MacDougall IC. Eur J Heart Fail. 2015;17:248-62. FDA Prescribing Information.

IV iron evidentiary base in heart failure

2021 ESC GUIDELINES

Recommendations	Class[a]	Level[b]
It is recommended that all patients with HF be periodically screened for anaemia and iron deficiency with a full blood count, serum ferritin concentration, and TSAT.	I	C
Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic patients with LVEF <45% and iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with TSAT <20%, to alleviate HF symptoms, improve exercise capacity and QOL.[720,722,724]	IIa	A
Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic HF patients recently hospitalized for HF and with LVEF <50% and iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with TSAT <20%, to reduce the risk of HF hospitalization.[512]	IIa	B



McDonagh T, et al. Eur Heart Journal. 2021.

IV iron evidentiary base in heart failure

2023 FOCUSED UPDATE OF THE 2021 ESC HF GUIDELINES

Recommendations	Class[a]	Level[b]
Intravenous iron supplementation is recommended in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to alleviate HF symptoms and improve quality of life.[c] 12,41,47–49	I	A
Intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose should be considered in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to reduce the risk of HF hospitalization.[c] 12,41,43–46	IIa	A

- Integrated new clinical trial evidence up to March 31, 2023 including recently-reported IRONMAN trial

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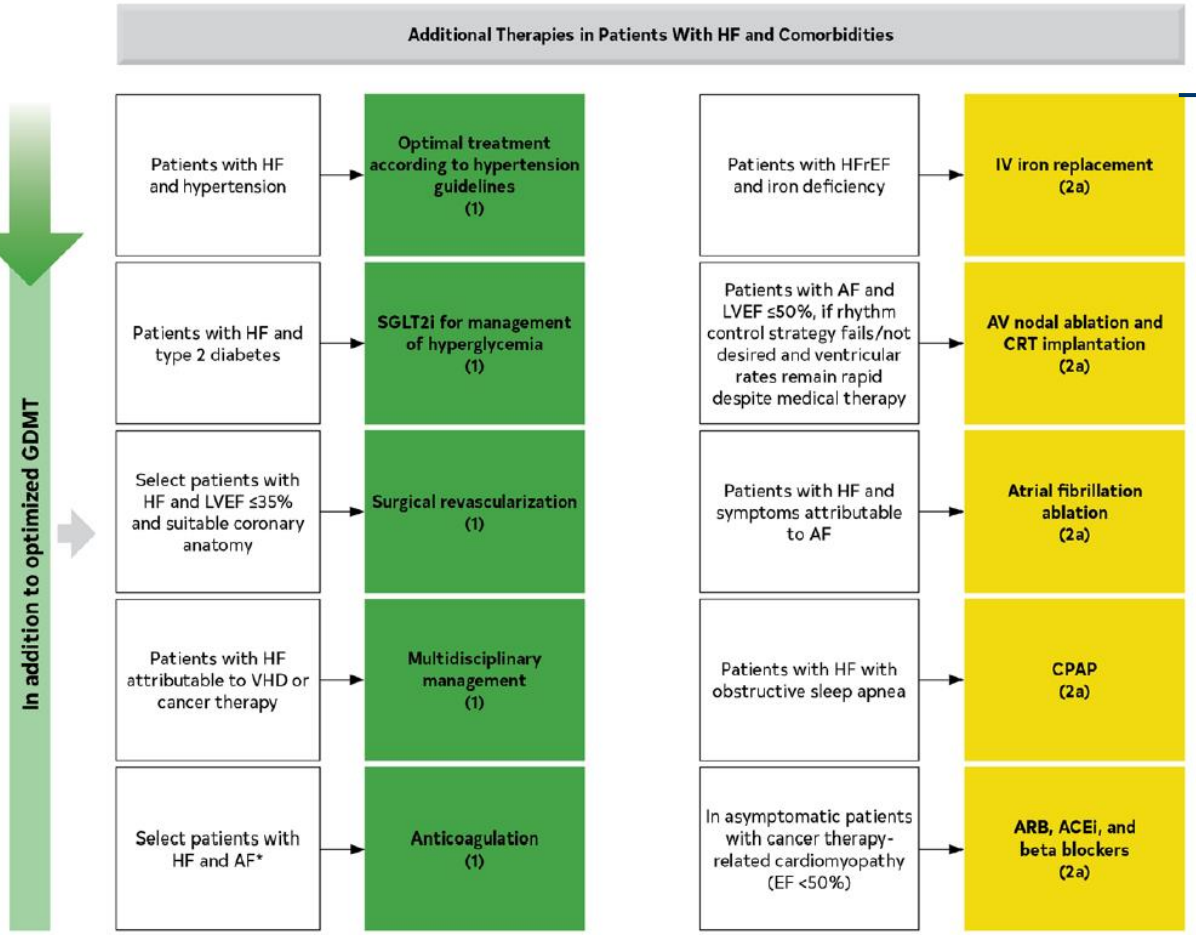
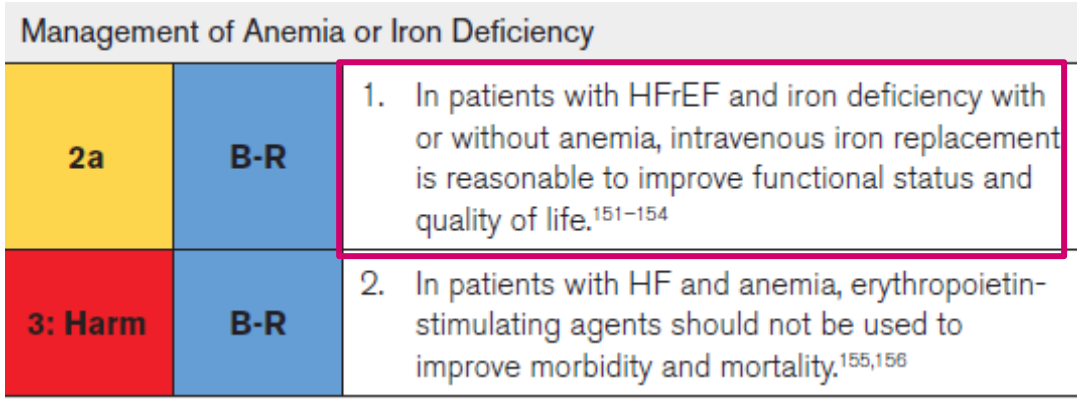
McDonagh T, et al. Eur Heart Journal. 2023.

IV iron evidentiary base in heart failure

2022 ACC/AHA/HFSA GUIDELINES





1 C-EO

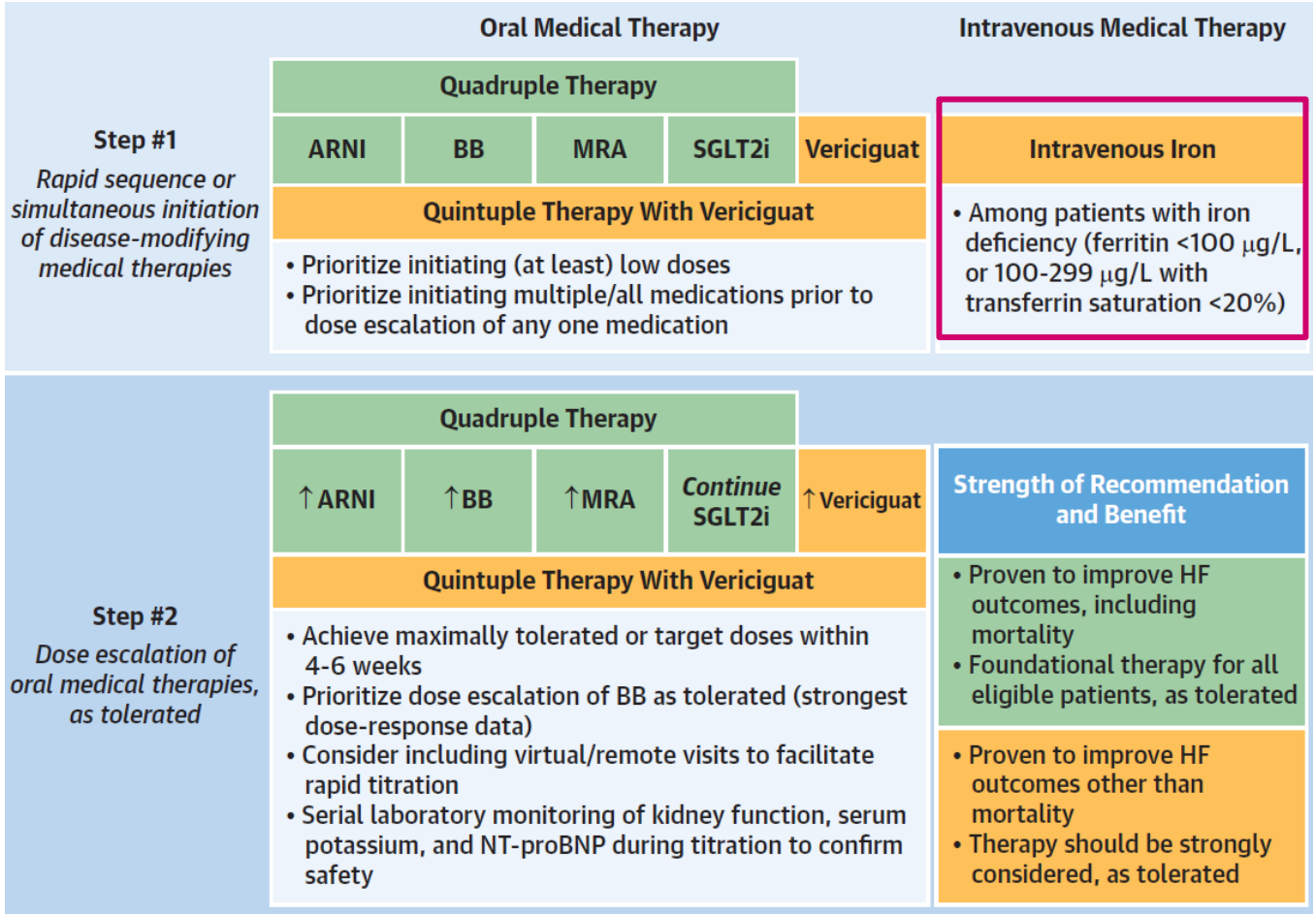
2. For patients who are diagnosed with HF, laboratory evaluation should include complete blood count, urinalysis, serum electrolytes, blood urea nitrogen, serum creatinine, glucose, lipid profile, liver function tests, iron studies, and thyroid-stimulating hormone to optimize management.

Iron studies = “serum iron, serum ferritin, and transferrin saturation”

Heidenreich P, et al. Circulation. 2022; Heidenreich P, et al. J Am Coll Cardiol. 2022.

IV iron evidentiary base in heart failure

2023 JACC FOCUS SEMINAR WORSENING HF WITH REDUCED EF



"There is a clear rationale for routine use of IV iron supplementation as part of an aggressive upfront treatment approach for patients with worsening HFrEF to maximally reduce clinical risk. ***Moreover, as a matter of practicality, patients hospitalized with worsening HFrEF*** *or receiving outpatient IV diuretic agents already have IV access, which may further facilitate implementation of IV iron for worsening HFrEF in clinical practice."*

Greene SJ, et al. J Am Coll Cardiol. 2023.

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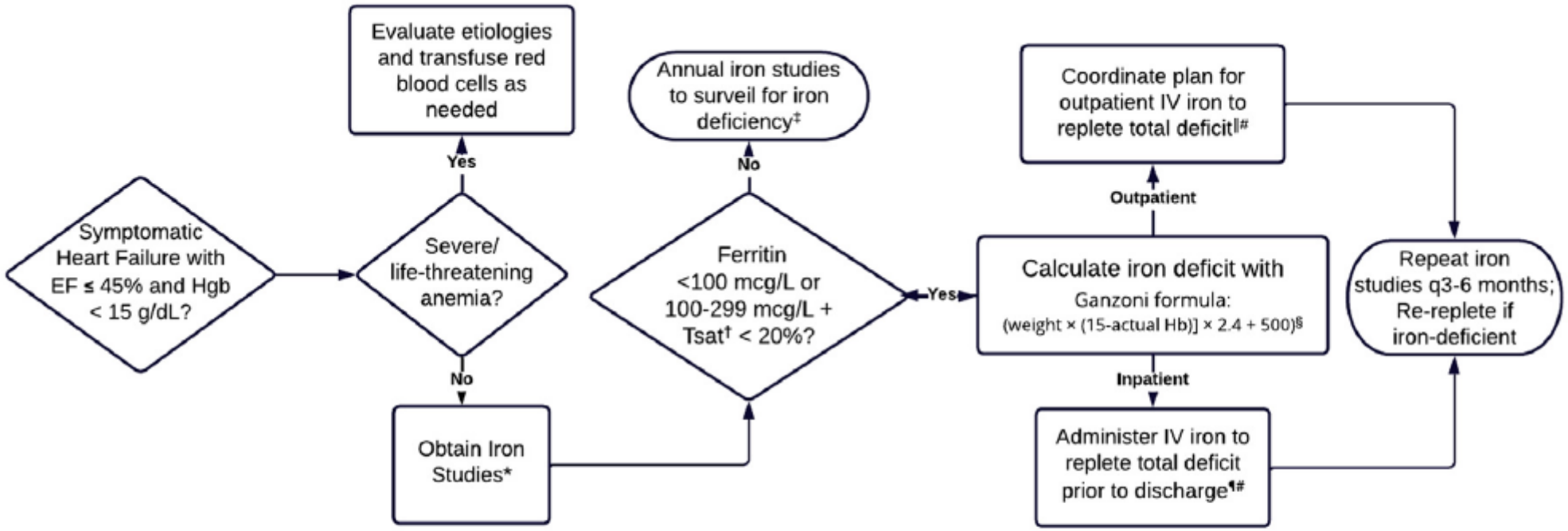
IV iron evidentiary base in heart failure

HFSA SCIENTIFIC STATEMENT



*Iron studies consist of iron, total iron binding capacity (TIBC) and ferritin and can be measured from the same green-top tube used for a basic metabolic panel at a cost of ~$10.
†Tsat, transferrin saturation, derived from iron/TIBC
‡If a patient newly develops anemia, mycrocytosis (MCV < 80 fL) or RDW >14.5%, implement earlier re-screening of iron studies.
§Substitute ideal body weight for actual body weigh in obese indivuduals.
‖Agent used based on coverage, patient preference, and facilitation or administration schedule
¶Agent used based on institutional formulary
#Number of doses depends on formulation used (Table 1). To correct and maintain iron parameters above the thresholds for iron deficiency the mean and median dose of IV iron over 1-yer enrollment of CONFIRM-HF was 1500 mg per subject delivered in 2 infusions.

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Beavers CJ et al J Card Fail. 2023.

What the evidence tells us

- **From the patient perspective, IV iron can:**
  - Reduce burden of symptoms
  - Improve quality of life
  - Improve functional status and exercise capacity
  - Reduce risk of recurrent hospitalizations for heart failure

- **From the health system perspective, IV iron can:**
  - Reduce health care resource utilization
  - Reduce costs
  - Improve quality metrics (?)
    - 30-day readmission rate
    - Excess days in acute care
    - Avoidable admissions for chronic disease

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What our practice tells us

- “Of the 10,381 total admissions with a component of HF, **only 158 individual patients had adequate iron studies performed**.” – Mistry et al J Am Coll Cardiol. 2019 (Philadelphia, PA)
- “Only 22 of the 150 had iron studies performed during admission … **only 1 of the 15 patients was initiated on IVIR**. Additionally, 22 of the 150 total patients were on oral iron replacement.” – Ruiz et al. Circulation. 2021 (Phoenix, AZ)
- “Overall, 411 men and 421 women were evaluated … **only 35 (8.5%) men and 39 (9.3%) women received iron supplementation** at the time of admission.” – Cohen-Solal et al. J Am Coll Cardiol. 2014 (Paris, France)
- “Out of 557 HF patients, **only 61.6% (343)** were screened with the complete blood count, ferritin, and TSAT.” – Alaryani et al. J Card Fail. 2023 (Abu Dhabi, United Arab Emirates)
- “Post-QI, physician-ordered ferritin, iron panel, and IV iron treatments increased from 22.6 to 27%, 20.5 to 24.5%, and 9.4 to 12.5% … **routine inpatient ID screening and treatment remain low**.” – Garza et al. J Card Fail. 2023 (Galveston, TX)

Multidisciplinary strategies for practice integration

- All multidisciplinary team members can promote implementation of evidence-based diagnosis, evaluation, and treatment of iron deficiency

Nurses, APPs, Pharmacists

- Identify appropriate patients with HF for screening and/or treatment with IV iron therapy

APPs, pharmacists

- Dose or prescribe IV iron therapy per collaborative agreement

Nurses, pharmacists

- Ensure medication access and mitigate financial toxicity

Nurses

- Provide patient and caregiver education to improve adherence

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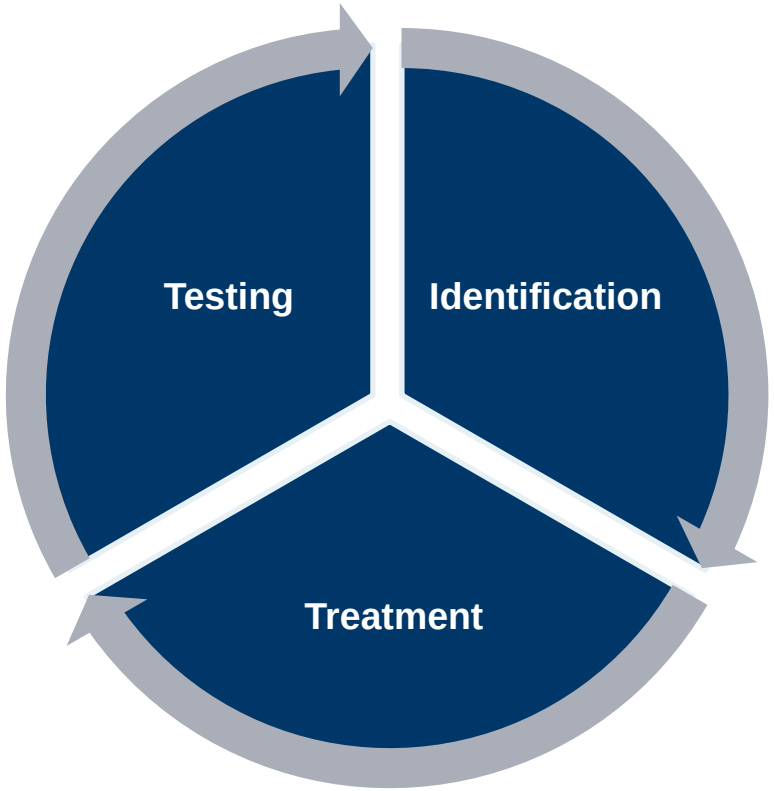
Role of screening and clinical decision support

- Clinical decision support (CDS) provides timely information, usually at the point of care, to help inform decisions about a patient's care
- CDS tools and systems help clinical teams by taking over some routine tasks, warning of potential problems, or providing suggestions for the clinical team and patient to consider
- These tools can be embedded within the electronic health record (EHR) and designed, organized, and implemented among at-risk persons with heart failure and iron deficiency
  - Stratum 1: Population health (at-risk)
  - Stratum 2: Recently discharged
  - Stratum 3: Currently hospitalized

Levering the electronic health record

- Examples of EHR screening and CDS tools
  - Registry reports
  - Automated best practice alerts
  - Order sets
  - E-consults
  - Medication onboarding notes

Structured ambulatory and inpatient pathways



Inadequate iron indices (ferritin levels <100 µg/L or <300 µg/L if TSAT is <20%)

IV FCM or FDM as evidence-based IV iron formulation

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Best practices for iron deficiency in heart failure

- **IV iron is the rule, PO iron is the exception**

- Follow-up iron status (serum ferritin and Tsat) should be routinely assessed to ensure adequacy of repletion and need for subsequent dosing as part of a treat-to-target strategy

- IV iron has strong potential to improve patient-reported symptoms, functional/exercise capacity, and prevent HF hospitalizations in HFrEF (stay tuned for HFpEF)

- Multidisciplinary team-based care may facilitate prompt diagnosis, necessary follow-up, and longitudinal patient access to therapies

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