ACC/AHA/HFSA Guideline for the Management of Heart Failure

Iron Deficiency With or Without Anemia

Derived From:

Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, Fang JC, Fedson SE, Fonarow GC, Hayek SS, Hernandez AF, Khazanie P, Kittleson MM, Lee CS, Link MS, Milano CA, Nnacheta LC, Sandhu AT, Stevenson LW, Vardeny O, Vest AR, Yancy CW. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. [published online ahead of print April 1, 2022]. *J Am Coll Cardiol*. doi: 10.1016/j.jacc.2021.12.012

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American College of Cardiology
www.acc.org

The American Heart Association
professional.heart.org

Full-text guidelines available in *Circulation, JACC* and *JCF*.

4. Initial and Serial Evaluation

4.1.1. Initial Laboratory and Electrocardiographic Testing

COR	LOE	Recommendations
1	B-NR	1. For patients presenting with HF, the specific cause of HF should be explored using additional laboratory testing for appropriate management.
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.
1	C-EO	3. For all patients presenting with HF, a 12-lead ECG should be performed at the initial encounter to optimize management.

1. Identifying the specific cause of HF is important, because conditions that cause HF may require disease-specific therapies. Depending on the clinical suspicion, additional diagnostic studies are usually required to diagnose specific causes such as ischemic cardiomyopathy, cardiac amyloidosis, sarcoidosis, hemochromatosis, infectious mechanisms (eg, HIV, COVID-19, Chagas), hypothyroidism, hyperthyroidism, acromegaly, connective tissue disorders, tachycardia-induced cardiomyopathy, Takotsubo, peripartum cardiomyopathy, cardiotoxicity with cancer therapies, or substance abuse would require specific management in addition to or beyond GDMT.

2. Laboratory evaluation with complete blood count, urinalysis, serum electrolytes, blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function tests, iron studies (serum iron, ferritin, transferrin saturation), and thyroid-stimulating hormone levels provides important information regarding patients' comorbidities, suitability for and adverse effects of treatments, potential causes or confounders of HF, severity and prognosis of HF, and is usually performed on initial evaluation. Pertinent laboratory tests are repeated with changes in clinical condition or treatments (e.g., to monitor renal function or electrolytes with diuretics).

3. Electrocardiography is part of the routine evaluation of a patient with HF and provides important information on rhythm, heart rate, QRS morphology and duration, cause, and prognosis of HF. It is repeated when there is a clinical indication, such as a suspicion for arrhythmia, ischemia or myocardial injury, conduction, or other cardiac abnormalities.

10. Comorbidities in Patients With HF

10.1. Management of Comorbidities in Patients With HF

COR	LOE	Recommendations
		Management of Anemia or Iron Deficiency
2a	B-R	1. In patients with HFrEF and iron deficiency with or without anemia, intravenous iron replacement is reasonable to improve functional status and QOL.
3: Harm	B-R	2. In patients with HF and anemia, erythropoietin-stimulating agents should *not* be used to improve morbidity and mortality.

1. Routine baseline assessment of all patients with HF includes an evaluation for anemia. Anemia is independently associated with HF disease severity and mortality, and iron deficiency appears to be uniquely associated with reduced exercise capacity. Iron deficiency is usually defined as ferritin level <100 μg/L or 100 to 300 μg/L, if the transferrin saturation is <20%. Intravenous repletion of iron has been shown to improve exercise capacity and QOL. The FAIR-HF (Ferric Carboxymaltose Assessment in Patients With Iron Deficiency and Chronic Heart Failure) trial showed significant improvement in NYHA classification, the 6-minute walk test, and QOL of 459 outpatients with chronic HF who received weekly intravenous ferric carboxymaltose until iron repletion. The improvement was independent of the presence of anemia. These findings were confirmed in 2 more recent trials. The IRONOUT HF (Iron Repletion Effects on Oxygen Uptake in Heart Failure) trial, however, showed no such improvement with oral iron supplementation. This is attributed to the poor absorption of oral iron and inadequacy of oral iron to replete the iron stores in patients with HF. Therefore, oral iron is not adequate to treat iron deficiency anemia in patients with HF. Although these trials were underpowered to detect reductions in hard clinical endpoints, 2 meta-analyses have suggested intravenous iron is associated with a reduction in cardiovascular death and hospitalizations. Most recently, the AFFIRM-AHF multicenter trial, which included 1132 patients with EF <50% hospitalized for HF, showed a decrease in hospitalization for HF with intravenous ferric carboxymaltose compared to placebo (RR, 0.74; 95% CI, 0.58–0.94) but no reduction in cardiovascular death.

2. Anemia in patients with HF is associated with impaired erythropoietin production, with low levels found to be associated with worse long-term outcomes. Although small studies examining the use of erythropoietin-stimulating agents for the treatment of anemia in patients with HF have suggested a trend toward improvement in functional capacity and reduction in hospitalization, a high-quality randomized trial of darbepoetin alpha in 2278 patients showed no benefit and an increase in thrombotic events, including stroke. A meta-analysis of 13 trials supports these findings. Accordingly, erythropoietin-stimulating agent therapy is not recommended for the treatment of anemia in patients with HF.

CLASS (STRENGTH) OF RECOMMENDATION

CLASS 1 (STRONG) — **Benefit >>> Risk**

Suggested phrases for writing recommendations:

- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS 2a (MODERATE) — **Benefit >> Risk**

Suggested phrases for writing recommendations:

- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS 2b (WEAK) — **Benefit ≥ Risk**

Suggested phrases for writing recommendations:

- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well-established

CLASS 3: No Benefit (MODERATE) — **Benefit = Risk**

(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:

- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS 3: Harm (STRONG) — **Risk > Benefit**

Suggested phrases for writing recommendations:

- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡	
LEVEL A	
■ High-quality evidence‡ from more than 1 RCT ■ Meta-analyses of high-quality RCTs ■ One or more RCTs corroborated by high-quality registry studies	
LEVEL B-R	**(Randomized)**
■ Moderate-quality evidence‡ from 1 or more RCTs ■ Meta-analyses of moderate-quality RCTs	
LEVEL B-NR	**(Nonrandomized)**
■ Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies ■ Meta-analyses of such studies	
LEVEL C-LD	**(Limited Data)**
■ Randomized or nonrandomized observational or registry studies with limitations of design or execution ■ Meta-analyses of such studies ■ Physiological or mechanistic studies in human subjects	
LEVEL C-EO	**(Expert Opinion)**
Consensus of expert opinion based on clinical experience	

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; RCT, randomized controlled trial.

Abbreviations

ECG, electrocardiogram; **HF**, heart failure; **HFrEF**, heart failure with reduced ejection fraction; **NYHA**, New York Heart Association, **QOL**, quality of life; **RCT**, randomized controlled trial; **RR**, relative risk

Source

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Disclaimer

This pocket guide attempts to define principles of practice that should produce high-quality patient care. It is applicable to specialists, primary care, and providers at all levels. This pocket guide should not be considered exclusive of other methods of care reasonably directed at obtaining the same results. The ultimate judgment concerning the propriety of any course of conduct must be made by the clinician after consideration of each individual patient situation. Neither IGC, the medical associations, nor the authors endorse any product or service associated with the distributor of this clinical reference tool.

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