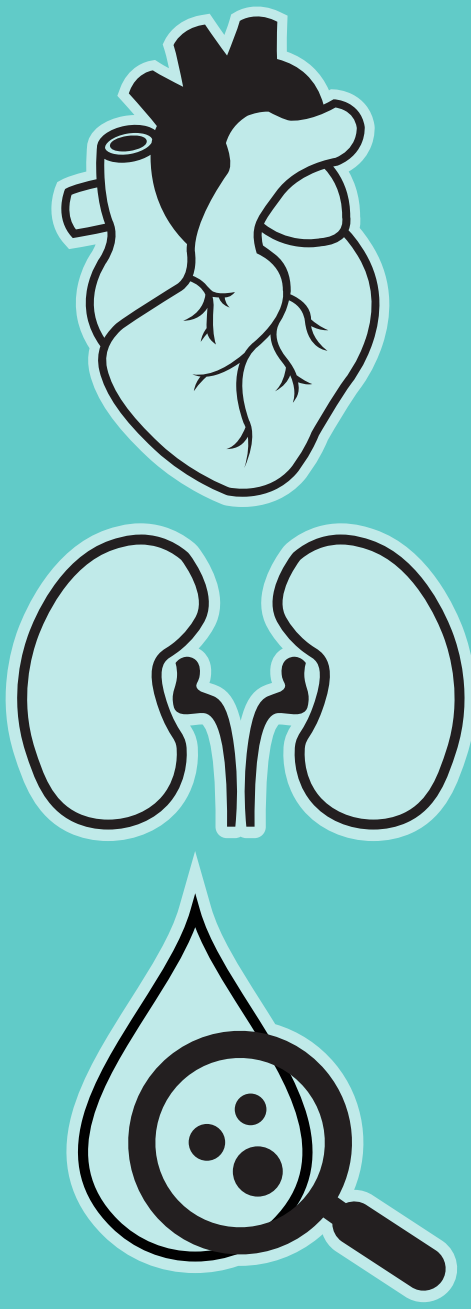
Optimizing Therapeutic Strategies in the Management of Cardiorenal Anemia Syndrome

A Whiteboard-Animated Guide to Disrupting the Pathologic Triad with Intravenous Iron



Cornerstone Medical Education

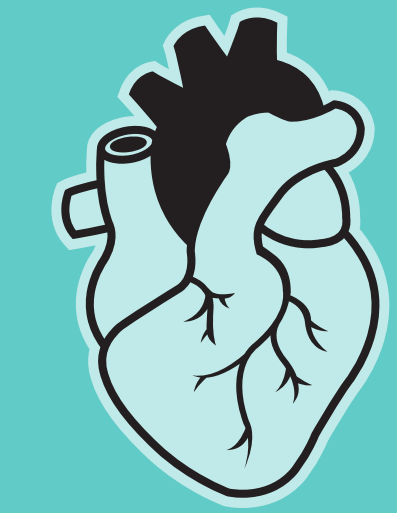
AACME® AMERICAN ACADEMY OF CME, INC.

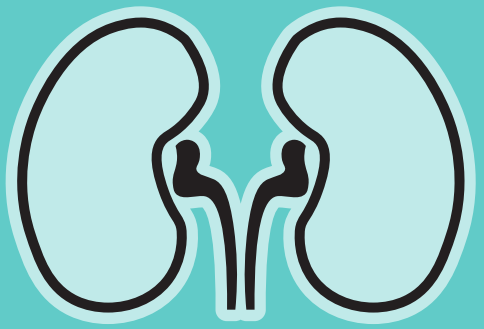
Presented by Cornerstone Medical Education, LLC
Supported by an independent educational grant from American Regent.

Webinar 1

Characterizing the Pathologic Triad of Cardiorenal Anemia Syndrome

A Review of the Complex Interconnectivity of Heart Failure, Chronic Kidney Disease, and Anemia





Cornerstone Medical Education

AACME® AMERICAN ACADEMY OF CME, INC.

Presented by Cornerstone Medical Education, LLC
Supported through an independent educational grant from American Regent.

Presented by

Cornerstone Medical Education

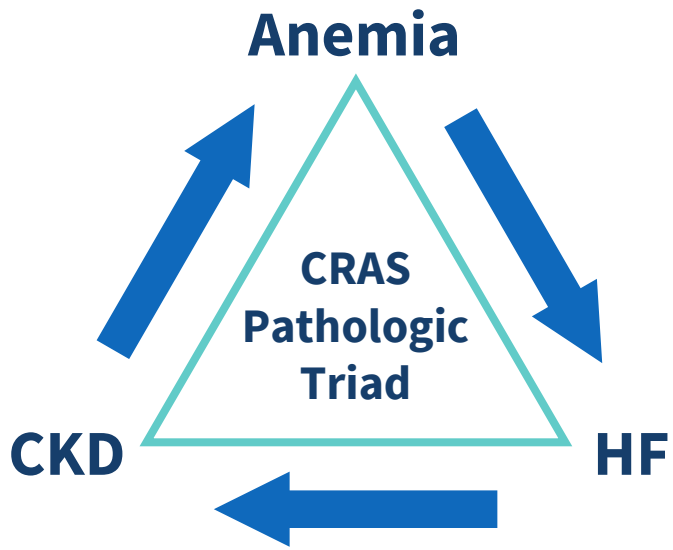
AAACME®
AMERICAN ACADEMY OF CME, INC.

Supported by an independent educational grant from American Regent.

Cardiorenal Anemia Syndrome (CRAS)
An Empiric Characterization of Disease

- **At the core of CRAS is CRS – the 'cardiorenal syndrome'**
  - Complex pathophysiologic interlacing of HF and CKD
  - Loss of function in one organ → reduced function in the other organ
  - Categorized into 5 disease subtypes
- **CRS + comorbid anemia = CRAS**
  - **Anemia:** Hb <13 g/dL in men, <12 g/dL in women
    - Comorbid anemia makes both HF and CKD more progressive and difficult to manage
  - Much like in CRS, anemia can ***both cause and be caused*** by both HF and CKD

Concomitant anemia fundamentally catalyzes the vicious cycle of CRAS



HF, heart failure; CKD, chronic kidney disease; Hb, hemoglobin

McCullough P. *Kidney Int Suppl*. 2021; Rangaswami J, et al. *Circulation*. 2019; Ronco C, et al. *Blood Purif*. 2009; WHO. Hemoglobin concentrations for the diagnosis of anemia and assessment of severity. 2011.

Cardiorenal Anemia Syndrome (CRAS)
Epidemiologic Interconnectivity

- **CRAS prevalence in HF patients ranges as high as ~44%**
- Comorbid CVD (including HF) prevalence in CKD = **as high as ~47%**
  - CVD is leading cause of morbidity and mortality in CKD
- Comorbid CKD prevalence in HF = **as high as ~50%**
  - Concomitant CKD (any stage) increases overall HF mortality risk by 56%, with late-stage CKD increasing risk by 131%

- **Both HF and CKD increase the risk for anemia – individually and cumulatively**
  - **Comorbid anemia prevalence in CRS = 39-45%**
  - Anemia prevalence increases linearly with advancing CKD stage and HF NYHA class
- Reciprocally, **anemia is an independent risk factor for both CVD and CKD**

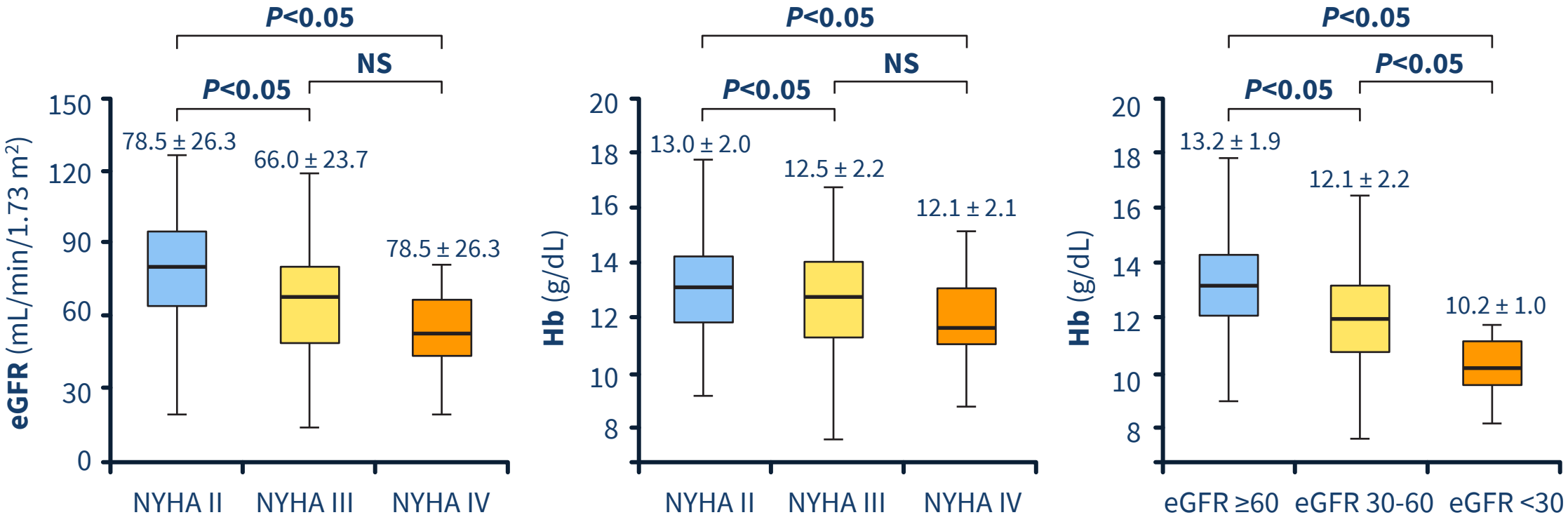
eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease

McCullough P. *Kidney Int Suppl*. 2021; Kim CJ, et al. *Cardiorenal Med*. 2016; Lu KJ, et al. *Am J Cardiol*. 2013; Scrutinio D, et al. *Eur J Heart Fail*. 2011; Cozzolino M, et al. *Am J Kidney Dis*. 2019; Yuan J, et al. *BMC Nephrol*. 2017; Go AS, et al. *N Engl J Med*. 2004; Parikh NI, et al. *Arch Intern Med*. 2006; Kim-Matsuyama S, et al. *Hypertens Res*. 2019; Silverberg DS, et al. *J Am Coll Cardiol*. 2000.

Cardiorenal Anemia Syndrome (CRAS)

Epidemiologic Interconnectivity

Interplay Between Renal Function and Anemia in Patients with HF

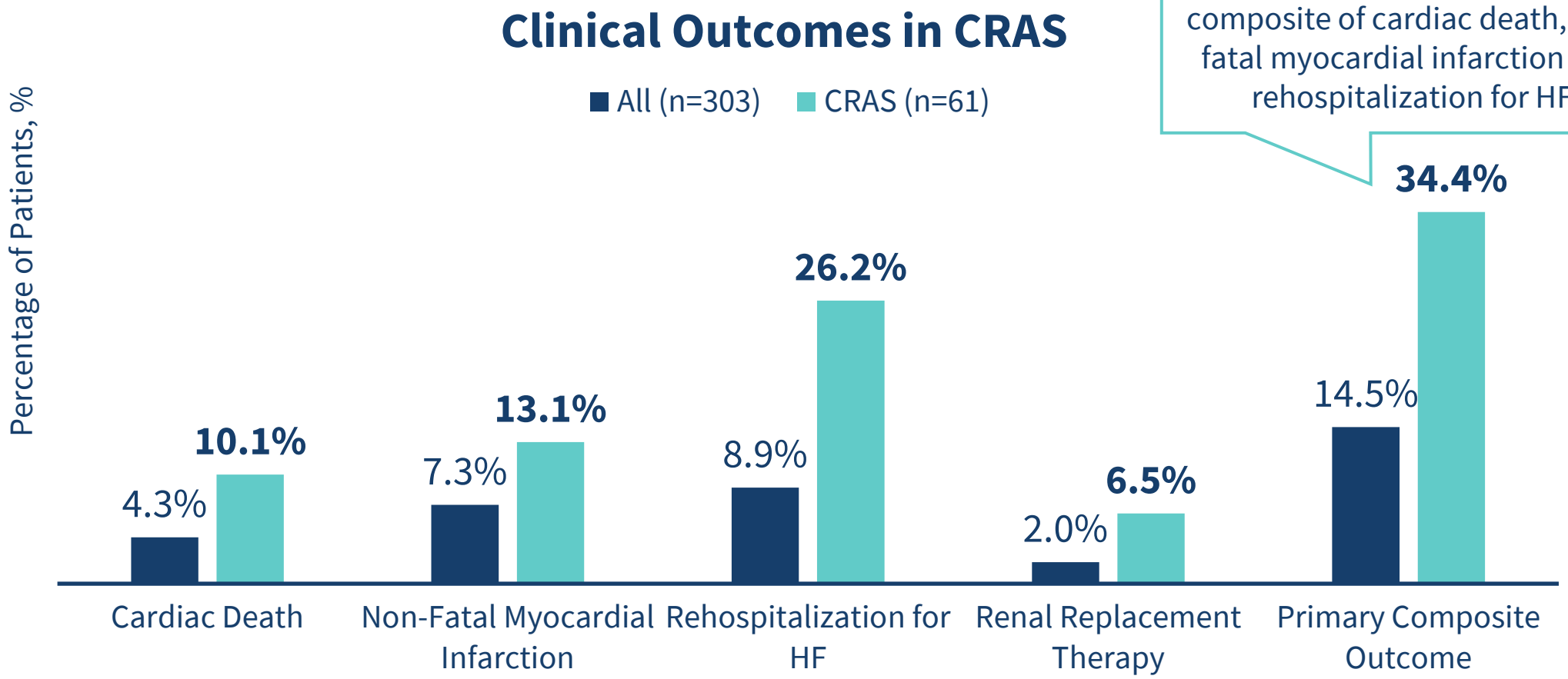


Kim CJ, et al. *Cardiorenal Med*. 2016.

Cardiorenal Anemia Syndrome (CRAS)

Epidemiologic Interconnectivity

Primary Composite Outcome: composite of cardiac death, non-fatal myocardial infarction and rehospitalization for HF



Kim CJ, et al. *Cardiorenal Med*. 2016.

Cardiorenal Anemia Syndrome (CRAS)
Appraising Clinical Gravity & Patient Burden

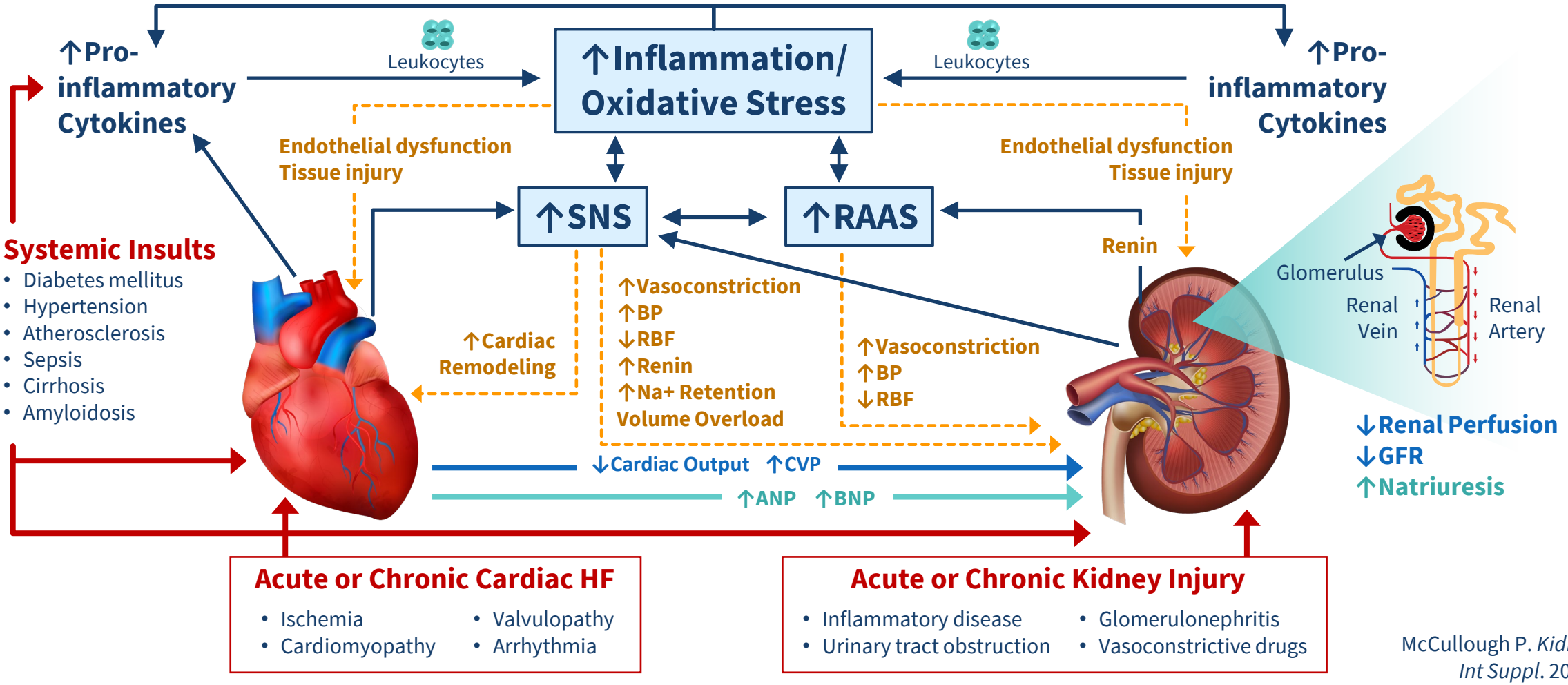
- The clinical ramifications of CRAS are substantial and multifaceted
  - **Diminished HRQoL**
  - **Increased risk of hospitalization and overall morbidity**
  - **Elevated risk of mortality**
- Even in patients with existing HF, CRAS development dramatically worsens prognosis
  - Increased all-cause mortality rate ($P<0.001$)
  - Increased composite of death, nonfatal MI, and HF rehospitalization ($P<0.001$)
  - For patients with CVD at risk for HF, comorbid CKD and anemia increase risk of MACE ($P<0.001$)
- Associated with depression, anxiety, and diminished vitality scores
- ***Correction of anemia is essential to breaking the vicious cycle*** and improving clinical trajectory

HRQoL, health-related quality of life; MACE, major adverse cardiovascular events

McCullough P. *Kidney Int Suppl*. 2021; Rangaswami J, et al. *Circulation*. 2019; Kim CJ, et al. *Cardiorenal Med*. 2016; Kosiborod M, et al. *Am J Med*. 2003; Silverberg DS, et al. *Clin Exp Nephrol*. 2009; Kim-Matsuyama S, et al. *Hypertens Res*. 2019; Lu KJ, et al. *Am J Cardiol*. 2013; Minamisawa M, et al. *AHA.* 2017. Abstract 14876.

The Pathophysiology of the Pathologic Triad

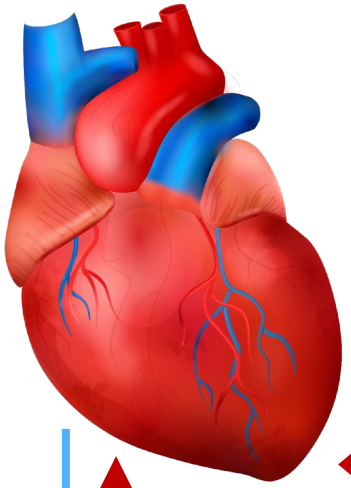
The HF-CKD Confluence (CRS)



McCullough P. *Kidney Int Suppl*. 2021.

The Pathophysiology of the Pathologic Triad

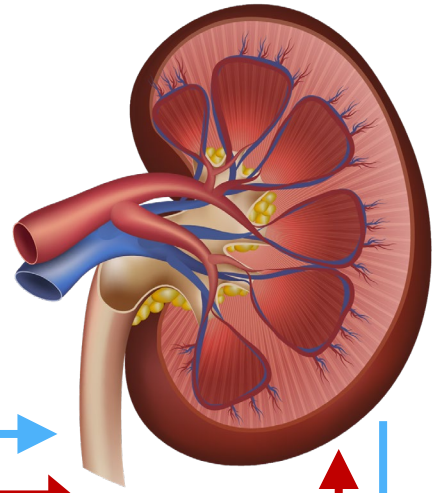
The HF-CKD-Anemia Confluence (CRAS)



↑Inflammation/
Oxidative Stress

CRS

↑SNS ↑RAAS



Hemodynamic Changes (↓cardiac output ↑central venous pressure)

Systemic Insults
- Diabetes mellitus
- Hypertension
- Atherosclerosis
- Sepsis
- Cirrhosis
- Amyloidosis

Acute or Chronic Cardiac HF
- Ischemia
- Cardiomyopathy
- Valvulopathy
- Arrhythmia

Acute or Chronic Kidney Injury
- Inflammatory disease
- Urinary tract obstruction
- Glomerulonephritis
- Vasoconstrictive drugs

Anemia

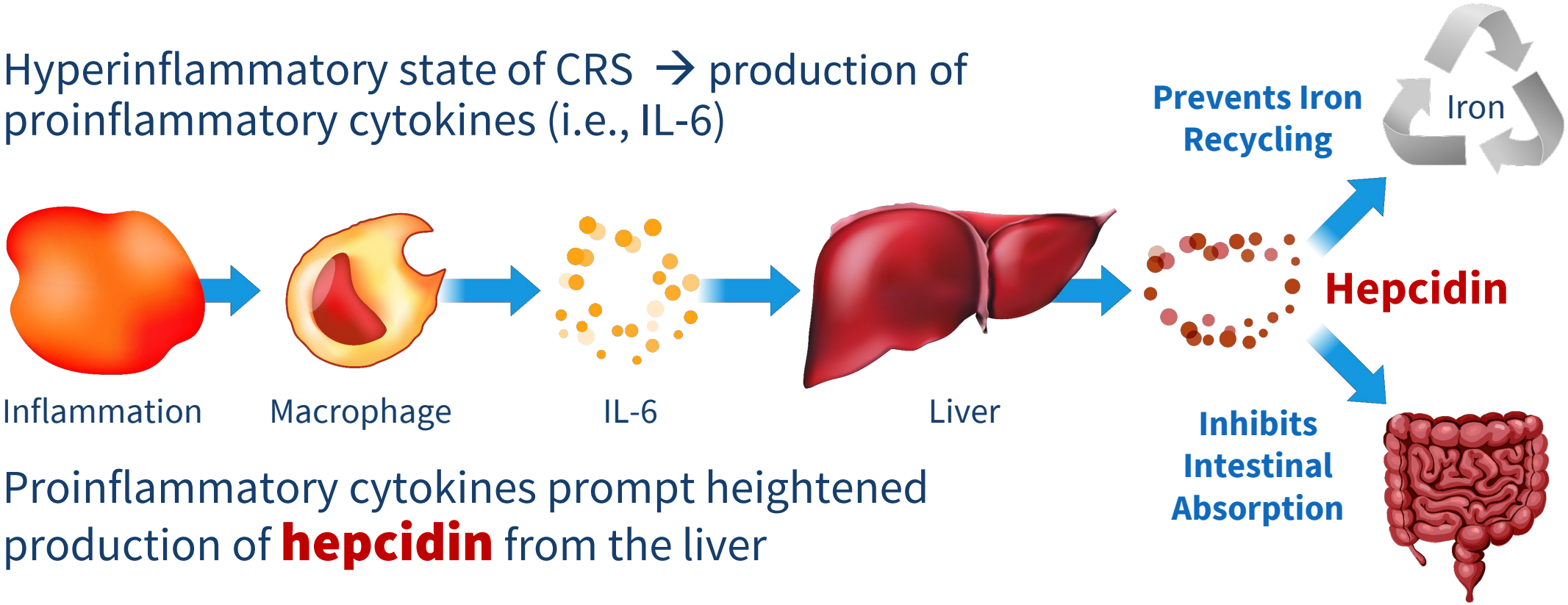
HF, heart failure; CKD, chronic kidney disease

McCullough P. *Kidney Int Suppl*. 2021.

The Pathophysiology of the Pathologic Triad

The Pivotal Influence of Hepcidin

- Hyperinflammatory state of CRS → production of proinflammatory cytokines (i.e., IL-6)



- Proinflammatory cytokines prompt heightened production of **hepcidin** from the liver

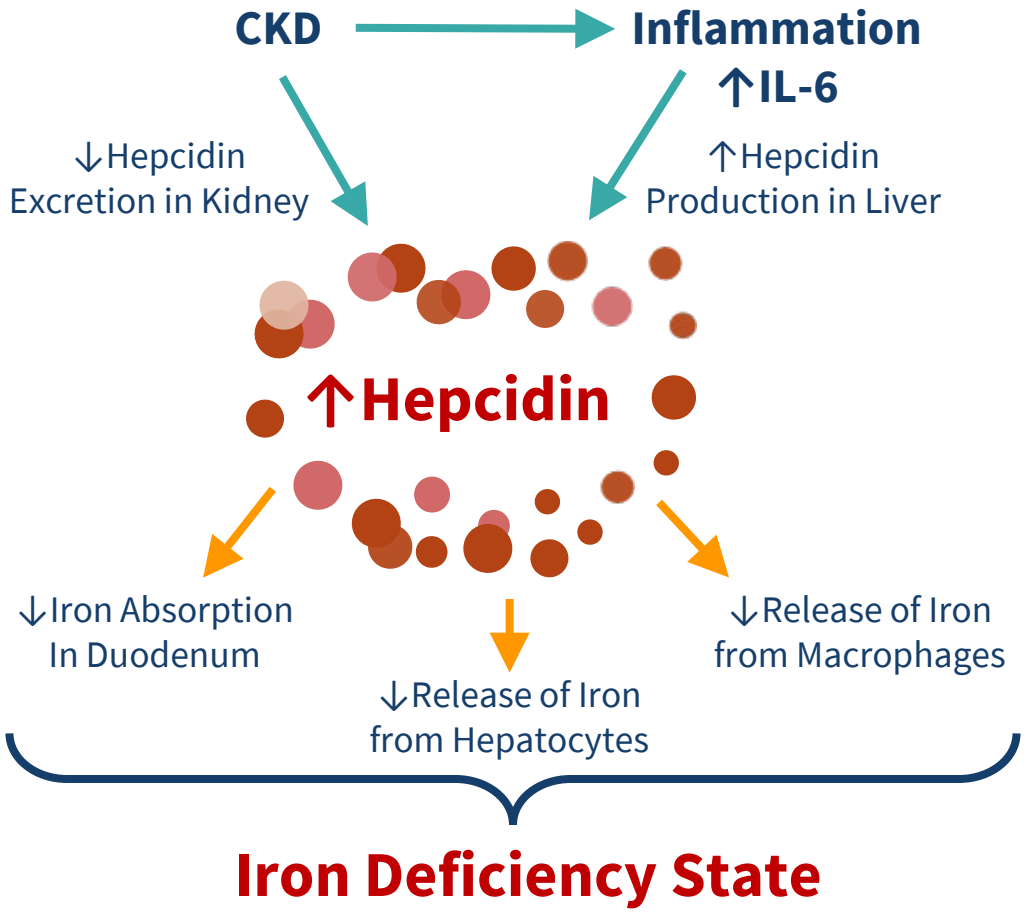
Hb, hemoglobin; TSAT, transferrin saturation

McCullough P. *Kidney Int Suppl*. 2021; Agarwal A. *Kidney Int Suppl*. 2021; Anand IS, et al. *Circulation*. 2018; Pagani A, et al. *Front Physiol*. 2019.

The Pathophysiology of the Pathologic Triad

The Pivotal Influence of Hepcidin

- Critically, hepcidin causes **functional iron deficiency (FID)** via a fundamental multi-mechanism
  - *Reduced intestinal absorption of iron*
  - *Pathologic sequestration of iron in reticuloendothelial macrophages and hepatocytes*
- FID = sufficient storage iron pool (serum ferritin >100 ng/mL) but deficient functional iron pool (TSAT <20%)
- FID **impedes Hb synthesis** and leads to **iron-restricted erythropoiesis**, thereby causing **anemia**



Hb, hemoglobin; TSAT, transferrin saturation

McCullough P. *Kidney Int Suppl*. 2021; Agarwal A. *Kidney Int Suppl*. 2021; Anand IS, et al. *Circulation*. 2018; Pagani A, et al. *Front Physiol*. 2019.

Summarizing CRAS

An Overview of Foundational Principles

ANIMATED WHITEBOARD VIDEO

McCullough P. *Kidney Int Suppl*. 2021; Rangaswami J, et al. *Circulation*. 2019; Agarwal A. *Kidney Int Suppl*. 2021; Anand IS, et al. *Circulation*. 2018; Pagani A, et al. *Front Physiol*. 2019; Buliga-Finis ON, et al. *Life*. 2023.

Iron Deficiency in CRAS

A Closer Look

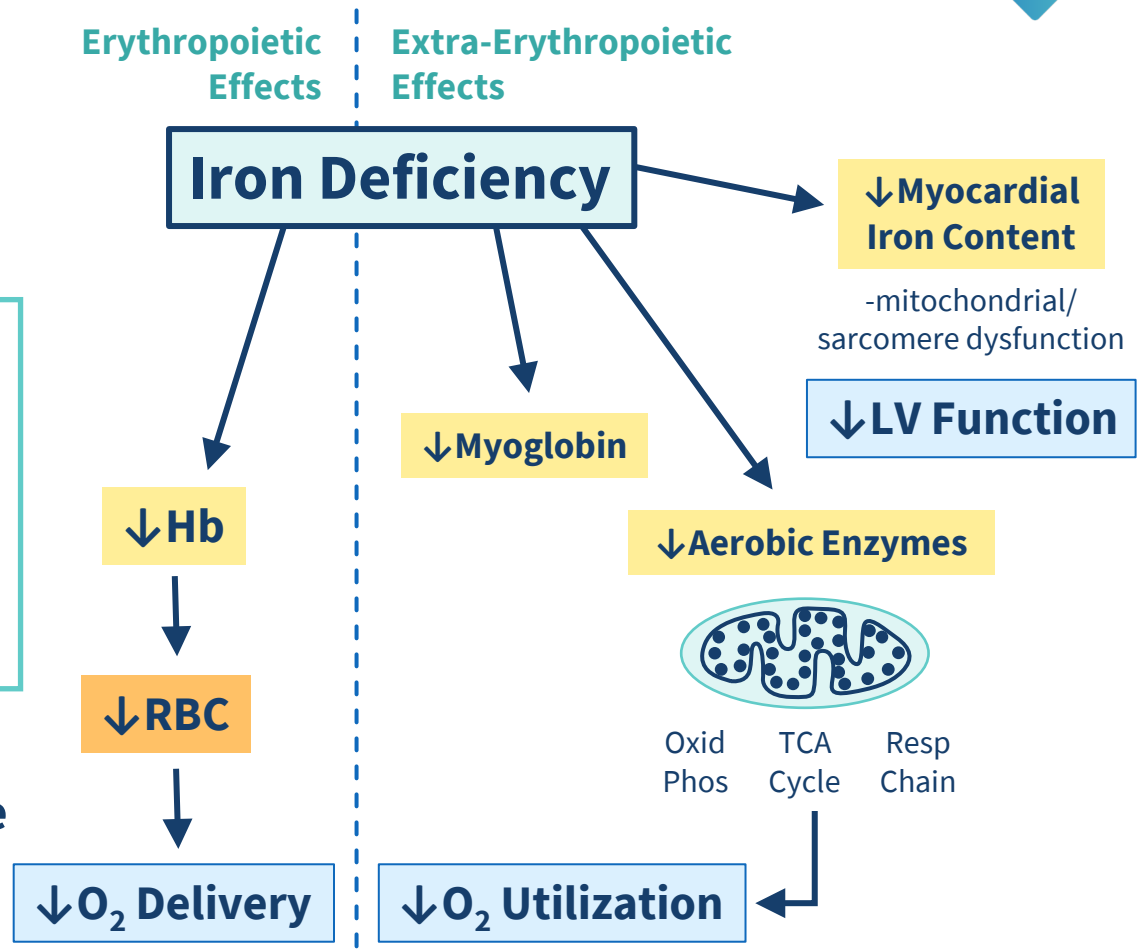
- ID prevalence = **~50% in HF**, including ~25-40% of patients who have ID *without concomitant anemia*

- ID is generally defined by serum ferritin and TSAT:
  - Serum ferritin <100 ng/mL = **absolute ID**
  - Serum ferritin 100-299 ng/mL + TSAT <20% = **functional ID**

Note: evolving evidence suggests these thresholds may shift, *particularly TSAT*

- Iron-restricted erythropoiesis → ***late-stage*** ID manifestation → **early ID treatment improves care**

- **ID *empirically undergirds* the pathophysiology of CRAS**

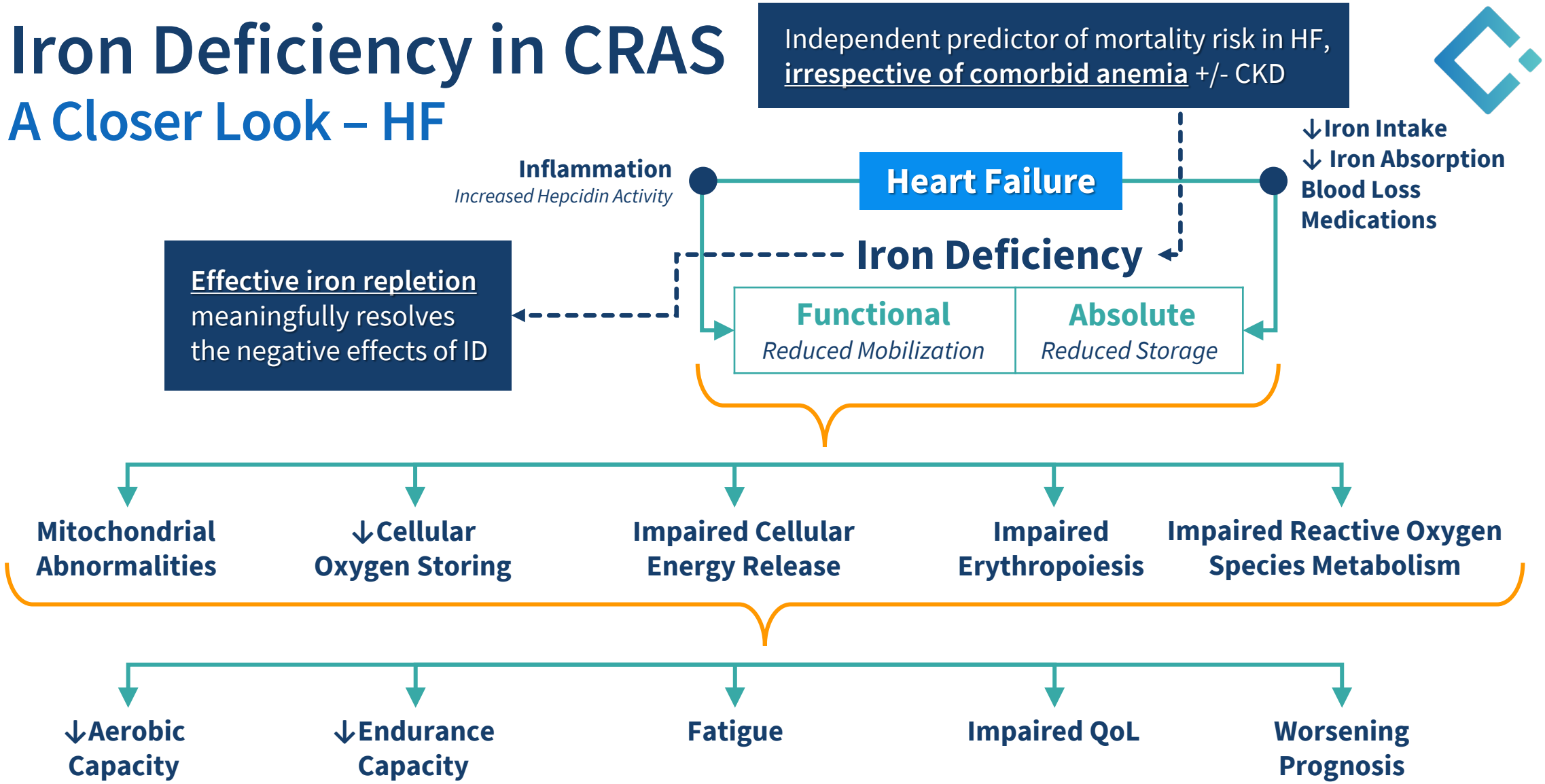


ID, iron deficiency; EPO, erythropoietin

Beavers C, et al. *J Card Fail*. 2023; MacDougall IC, et al. *Eur Heart J*. 2012; Klip I, et al. *Eur Heart J*. 2014; Rizzo C, et al. *Front Cardiovasc Med*. 2021; Kovesdy C, et al. *Clin Kidney J*. 2022; Hain D, et al. *Kidney Med*. 2023; Heidenreich P, et al. *Circulation*. 2022; McDonagh T, et al. *Eur Heart J*. 2021.

Iron Deficiency in CRAS

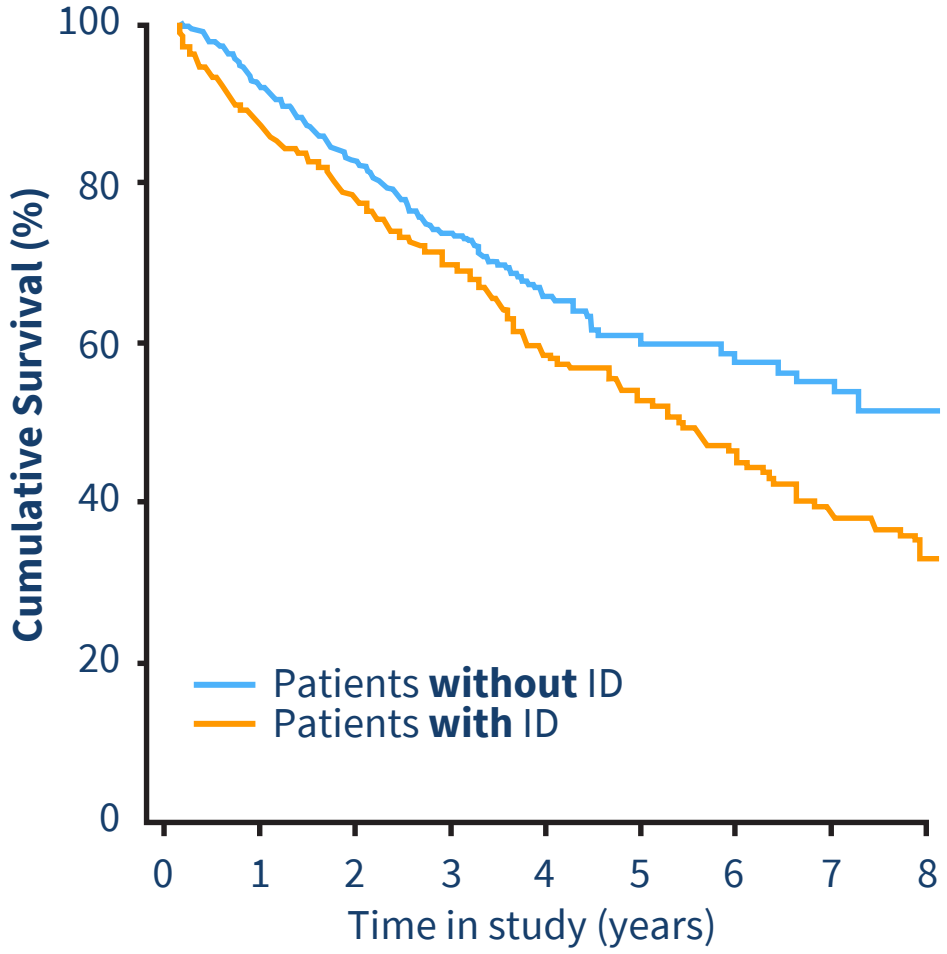
A Closer Look – HF

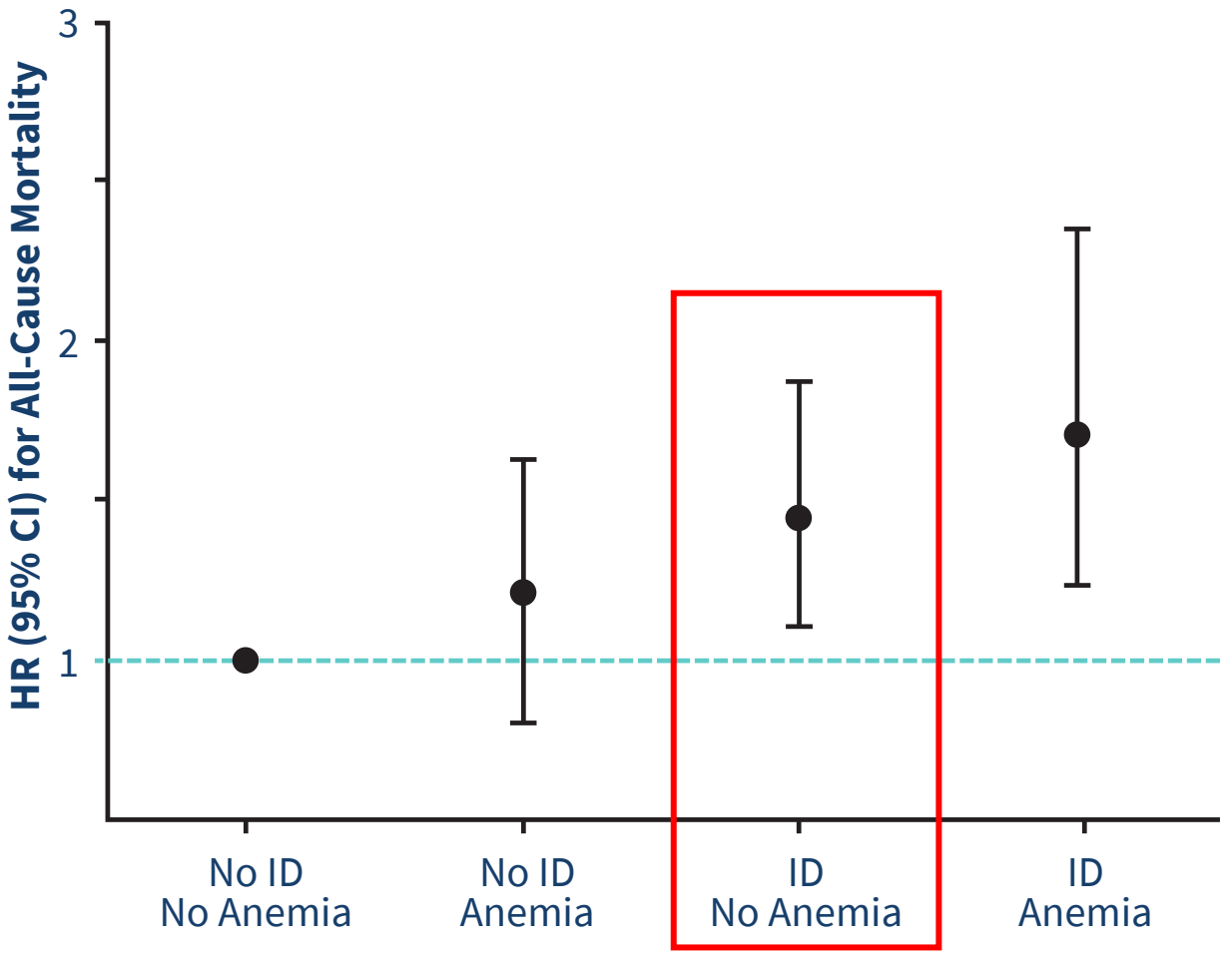


Rizzo C, et al. *Front Cardiovasc Med*. 2021; Klip I, et al. *Am Heart J*. 2013; Graham FJ, et al. *Eur J Heart Failure*. 2022.

Iron Deficiency in CRAS

A Closer Look – HF





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.

Iron Deficiency in CRAS

A Closer Look – NDD-CKD

METHODS

Study

International Cohort Study
N=5145 NDD-CKD Patients
Locations: Brazil (6%), France (43%), Germany (41%), US (10%)

Exposure

TSAT <15%
(vs 25-35%)

Outcomes

1.Mortality
2.MACE

Mediator of Interest

Hemoglobin (Hgb)

OUTCOMES

Patients

Age: 69 years
eGFR: 28 mL/min
HF: 15%
Follow-up: 3 years

Hgb: 12 g/dL
TSAT: 24%
TSAT<15%: 18%
Ferritin: 196 ng/mL

Results

			Adjusted HR (95% CI)
TSAT <15%	→	**Mortality***	**1.59** (1.15-2.20)
TSAT <15%	→	**MACE**	**1.96** (1.26-3.06)

*No interaction by Hgb, *P*=0.67

NDD-CKD, non-dialysis-dependent chronic kidney disease

Guedes M, et al. *J Am Soc Nephrol*. 2021.

Iron Deficiency in CRAS

A Closer Look – NDD-CKD

METHODS

Study

International Cohort Study
N=5145 NDD-CKD Patients
Locations: Brazil (6%), France (43%), Germany (41%), US (10%)

Exposure

TSAT <15%
(vs 25-35%)

Outcomes

1.Mortality
2.MACE

Mediator of Interest

Hemoglobin (Hgb)

OUTCOMES

Patients

Age: 69 years
eGFR: 28 mL/min
HF: 15%
Follow-up: 3 years

Hgb: 12 g/dL
TSAT: 24%
TSAT<15%: 18%
Ferritin: 196 ng/mL

Results

			Adjusted HR (95% CI)
TSAT <15%	→	**Mortality***	**1.59** (1.15-2.20)
TSAT <15%	→	**MACE**	**1.96** (1.26-3.06)

*No interaction by Hgb, *P*=0.67

In NDD-CKD, low TSAT is associated with increased all-cause mortality and MACE risk, *irrespective of the presence or absence of anemia*

NDD-CKD, non-dialysis-dependent chronic kidney disease

Guedes M, et al. *J Am Soc Nephrol*. 2021.

Managing CRAS
Gaps in Care & the Therapeutic Promise of IV Iron

- Historical – and ongoing – paucity of expert consensus guidance for the diagnosis, evaluation, and treatment of CRAS
- Instead, ***current approaches rely on guidelines from individual CRAS disease states***
  - **HF**: 2022 ACC/AHA/HFSA, 2023 ESC
  - **CKD**: 2012 KDIGO (update in development)
- Therapeutic optimization strategies largely **hinge on managing comorbid anemia**
  - Mitigate and manage anemia → impede the vicious cycle of disease → slow HF and CKD disease progression and improve responsiveness to available therapeutics
- Evolving understanding of anemia in HF and CKD = **increased recognition of pivotal role of ID**
  - *Iron supplementation as keystone treatment strategy for uncoupling the pathologic triad*

Webinar 2 Focus: IV vs. oral iron considerations, established and emerging clinical trial evidence, GDMT

GDMT, guideline-directed medical therapy

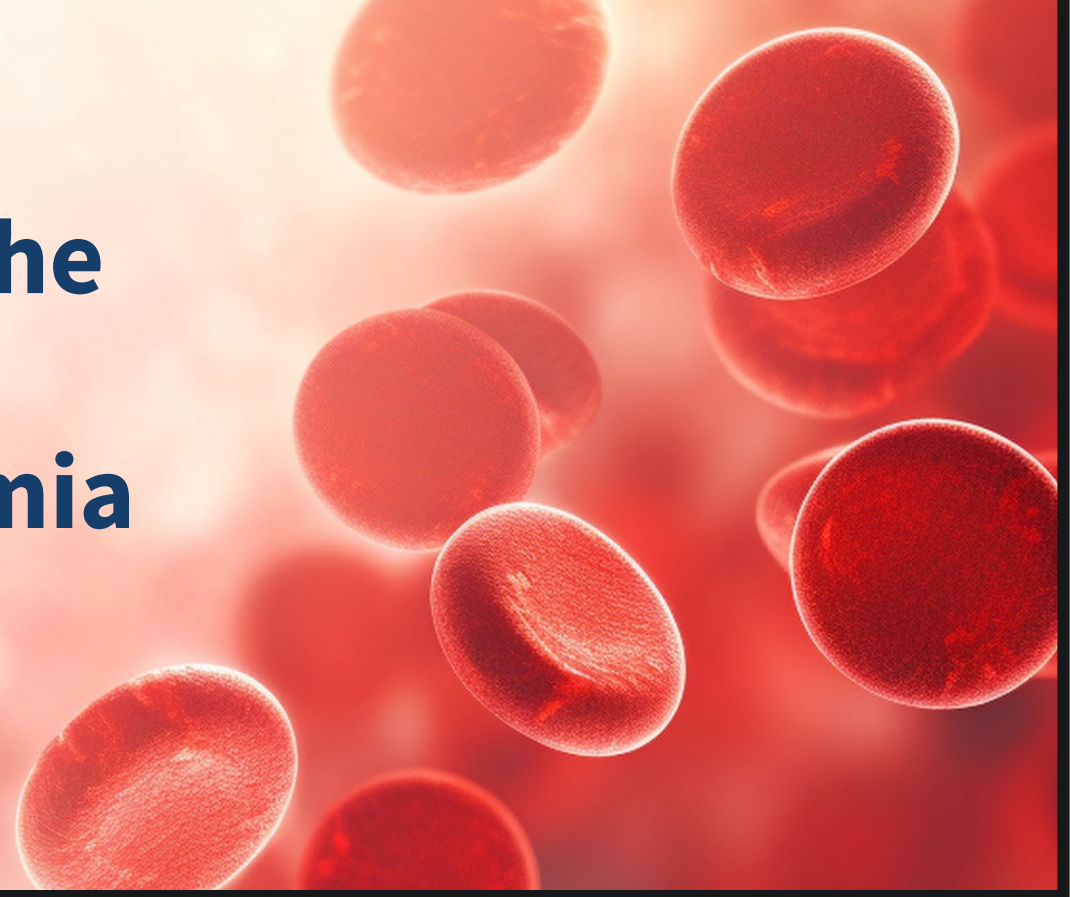
McCullough P. *Kidney Int Suppl*. 2021; Rangaswami J, et al. *Circulation*. 2019; Beavers C, et al. *J Card Fail*. 2023; Heidenreich P, et al. *Circulation*. 2022; McDonagh T, et al. *Eur Heart J.* 2021; KDIGO Clinical Practice Guidelines for Anemia in CKD. *Kidney Int Suppl*. 2012.

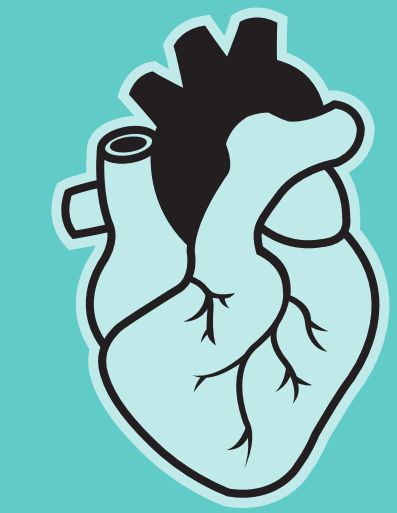
Summary of Key Teaching Points
The Foundational Fundaments of CRAS

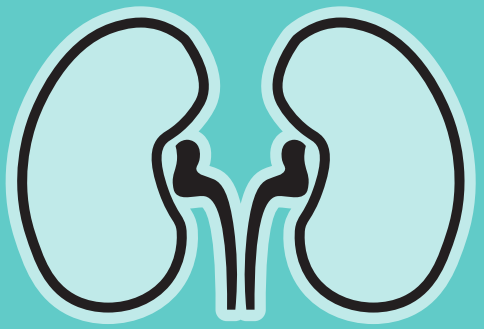
- CRAS is a complex condition of interrelated and interdependent disease states
  - The pathologic **triad of HF, CKD, and anemia**
  - Each of the three can either cause or be caused by the others
- **Anemia functions as a catalyst for the CRAS vicious cycle**
  - Makes HF and CKD more progressive and treatment-refractory
- The hyperinflammatory nature of HF and CKD (and thus, CRS) leads to:
  - Elevated hepcidin levels via increased production in the liver
  - Reduced intestinal absorption and increased sequestration of iron into macrophages and hepatocytes, thereby leading to **functional iron deficiency**
- **ID is a principal etiology** for **anemia development** in both **HF and CKD**
  - Impaired Hb synthesis and iron-restricted erythropoiesis
  - Independent predictor of poor prognosis in both HF and CKD, ***irrespective of concomitant anemia***
- Iron supplementation represents an important – and evolving – treatment option in CRAS

Webinar 2

Deconstructing the Vicious Cycle of Cardiorenal Anemia Syndrome and Improving Care







The Emerging Promise of Next-Generation IV Iron Products for CRAS Management

Cornerstone Medical Education

AACME® AMERICAN ACADEMY OF CME, INC.

Presented by Cornerstone Medical Education, LLC
Supported through an independent educational grant from American Regent.

Presented by

Cornerstone Medical Education

AAACME®
AMERICAN ACADEMY OF CME, INC.

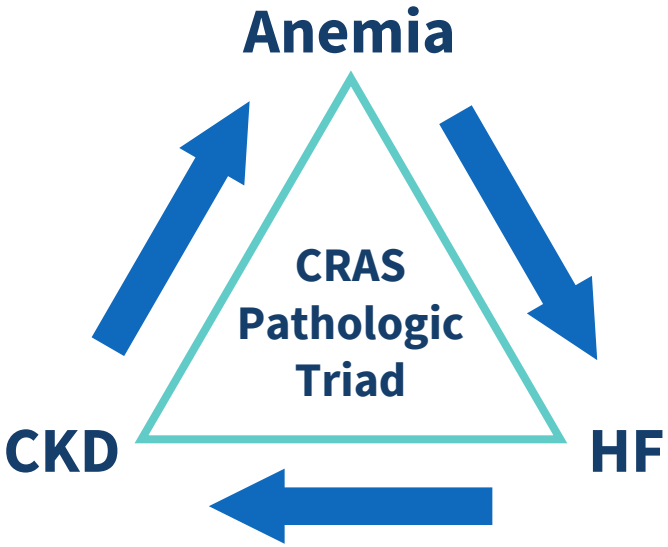
Supported by an independent educational grant from American Regent.

Iron Supplementation Strategies in CRAS

IV vs. Oral

- HF and CKD are intrinsically hyperinflammatory conditions
  - Characterized by proinflammatory cytokine cascades
  - Consequent **elevations in *hepcidin***
- **Hepcidin is the master regulator of iron homeostasis**, and when elevated, causes FID via a multi-mechanism:
  - **Reduced intestinal absorption** of iron
  - **Increased sequestration into/decreased export from** reticuloendothelial macrophages and hepatocytes

Concomitant anemia fundamentally catalyzes the vicious cycle of CRAS



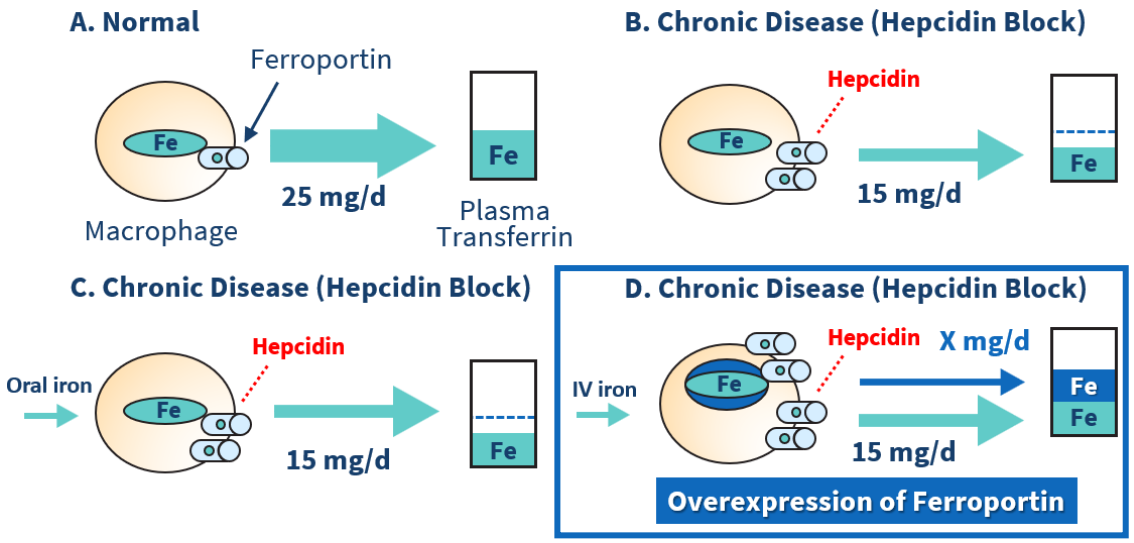
HF, heart failure; CKD, chronic kidney disease; FID, functional iron deficiency

McCullough P. *Kidney Int Suppl*. 2021; Rangaswami J, et al. *Circulation*. 2019; Pagani A, et al. *Front Physiol*. 2019; McDonagh T, et al. *Eur J Heart Failure*. 2015.

Iron Supplementation Strategies in CRAS

IV vs. Oral

- **IV iron** possesses the unique capacity to ***overcome*** hepcidin-induced functional iron blockade via:
  - *Circumvention of reduced intestinal absorption*
  - *Overwhelming restricted ferroportin activity*
- In IRONOUT-HF, high-dose oral iron did not improve exercise capacity vs. placebo (*P*=0.46)
- Therefore, **IV iron has *preferred clinical utility* vs. oral iron for the management of ID and IDA comorbid to HF and CKD**



HF, heart failure; CKD, chronic kidney disease; FCM, ferric carboxymaltose; FID, functional iron deficiency

McCullough P. *Kidney Int Suppl*. 2021; Rangaswami J, et al. *Circulation*. 2019; Pagani A, et al. *Front Physiol*. 2019; McDonagh T, et al. *Eur J Heart Failure*. 2015; Lewis GD, et al. *JAMA*. 2017.

Iron Supplementation Strategies in CRAS

Illustrating the Unique Ability of IV Iron to Overcome Hepcidin-Induced Functional Iron Blockade

ANIMATED WHITEBOARD VIDEO

McCullough P. *Kidney Int Suppl*. 2021; Pagani A, et al. *Front Physiol*. 2019; McDonagh T, et al. *Eur J Heart Failure*. 2015; Lewis GD, et al. *JAMA*. 2017.

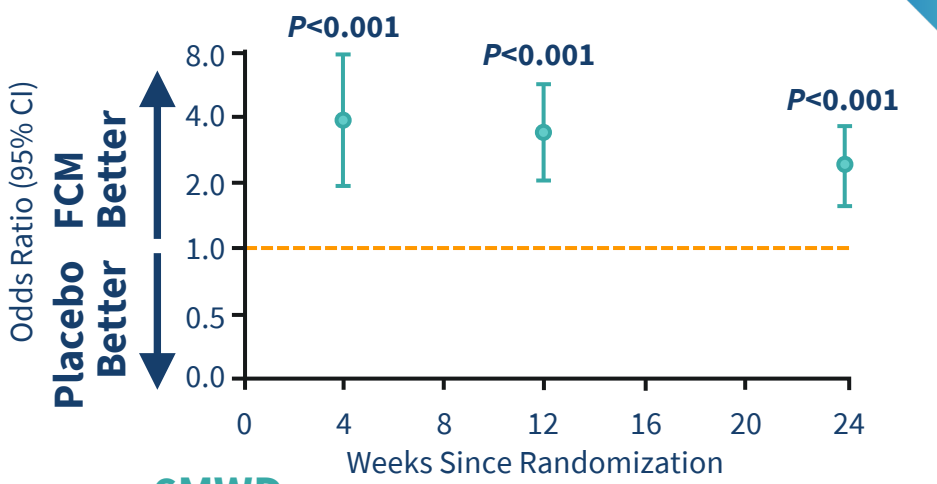
IV Iron in CRAS

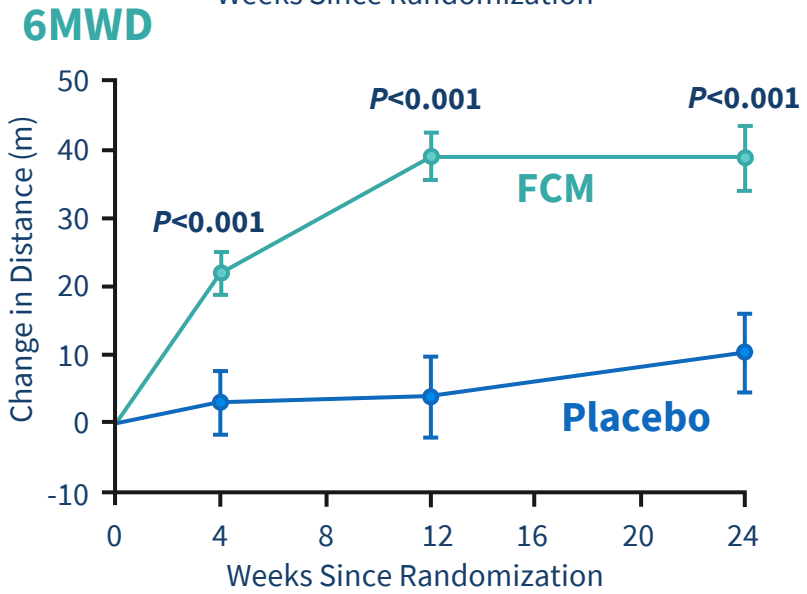
Examining the Evidence in *Heart Failure*

IV Iron Evidentiary Base in HF

FAIR-HF

- 459 patients with NYHA class II or III HFrEF and ID randomized to IV FCM vs. placebo
- ID inclusion criteria
  - Serum ferritin < 100 ng/mL OR 100-299 ng/mL with TSAT < 20%
- IV FCM achieved improvements in:
  - **Symptom burden**
  - **Functional/exercise capacity**
  - **NYHA functional class**
  - **Quality of life**
- Substantive clinical benefits with IV FCM were observed for ID in HFrEF ***irrespective of the presence or absence of anemia***





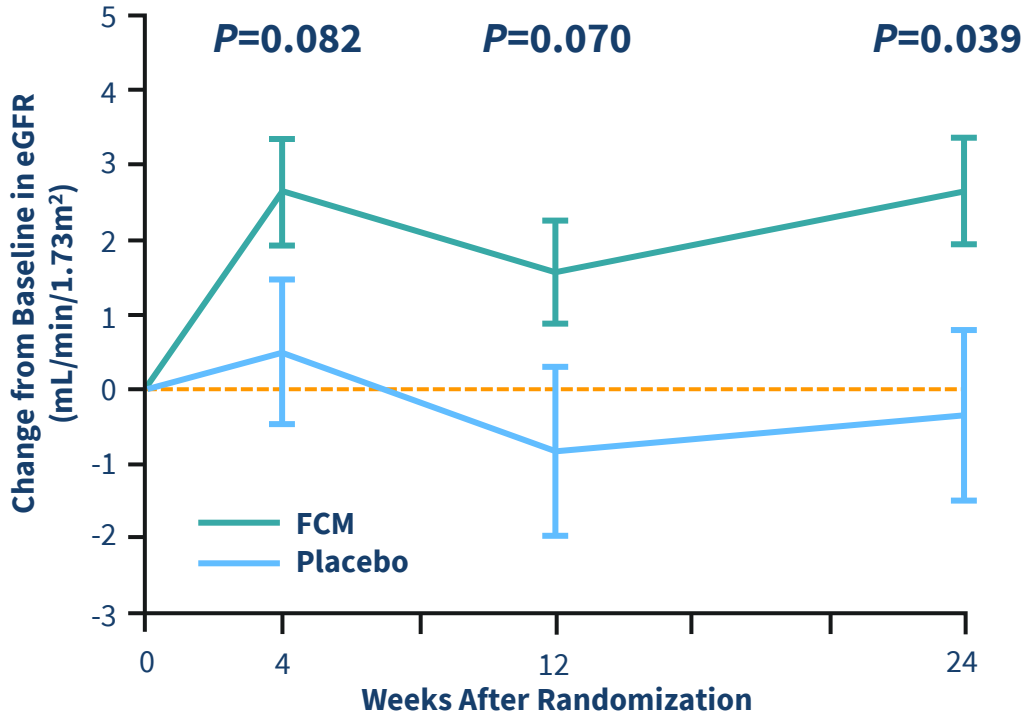
HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association

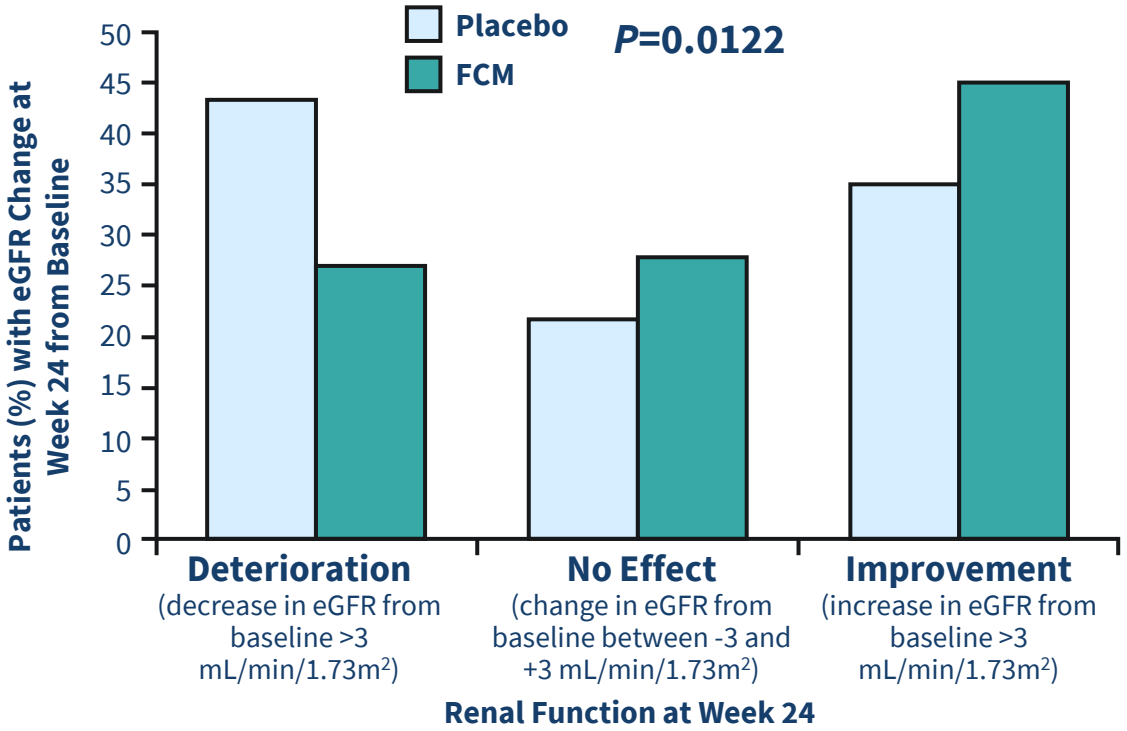
Anker SD, et al. *N Engl J Med*. 2009.

IV Iron Evidentiary Base in HF

FAIR-HF Subanalysis

- IV FCM not only safe and effective for ID management in HFrEF patients with renal impairment, *but* ***significantly improved renal function***



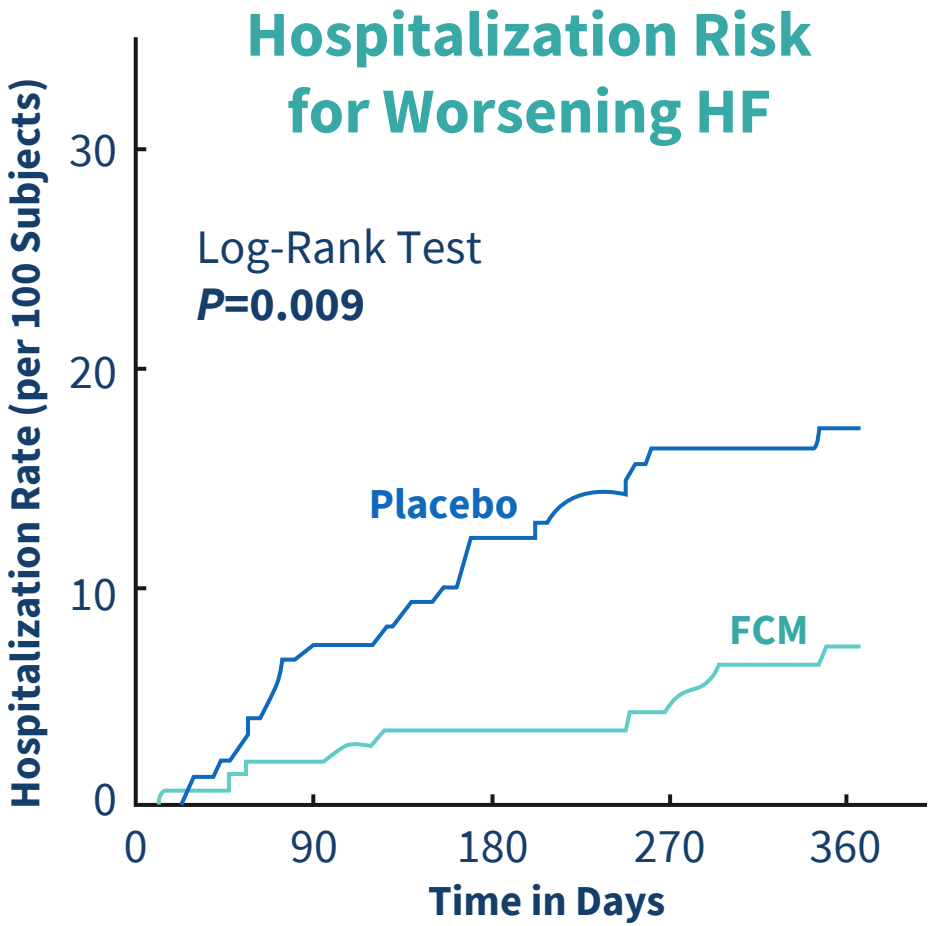


Ponikowski P, et al. *Eur J Heart Failure*. 2015.

IV Iron Evidentiary Base in HF

CONFIRM-HF

- 304 ambulatory patients with symptomatic HFrEF (LVEF ≤45%) and ID randomized to **IV FCM vs. placebo**
- IV FCM achieved primary endpoint – improved 6MWT distance at week 24 (*P*=0.002)
  - NYHA class, symptom burden, HRQoL, and fatigue scores were also meaningfully improved with IV FCM
- Clinical benefits sustained through week 52 across all IV FCM treatment subgroups
- An important secondary endpoint – ***hospitalization risk for worsening HF*** – was **significantly reduced** with **IV FCM**



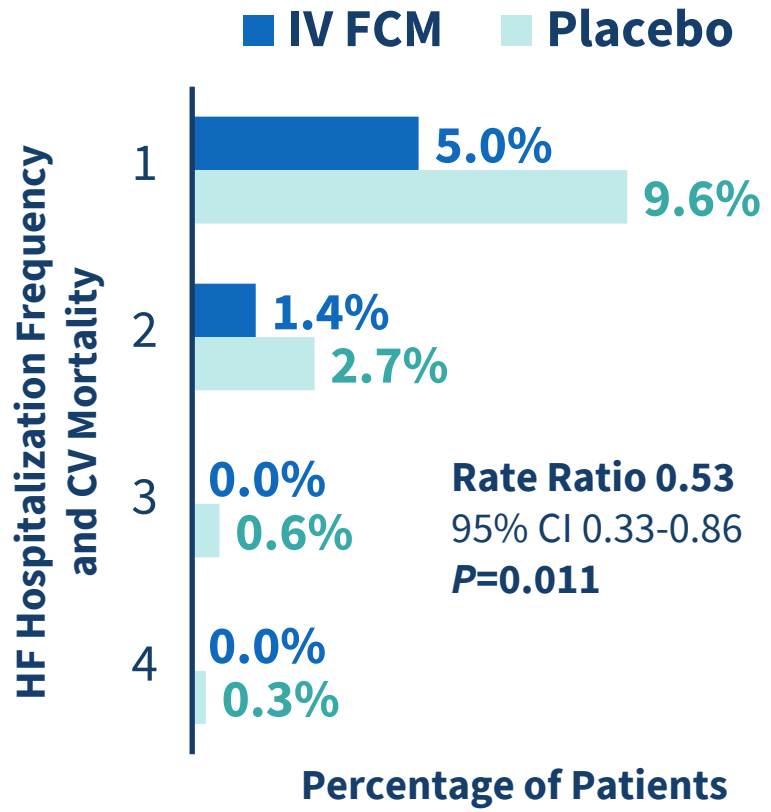
LVEF, left ventricular ejection fraction; 6MWT, 6-minute walk test

Ponikowski P, et al. *Eur Heart J*. 2015.

IV Iron Evidentiary Base in HF

Meta-Analyses

- FAIR-HF, CONFIRM-HF, and multiple meta-analyses have convincingly demonstrated the benefits of IV FCM for ambulatory patients with HFrEF and ID
  - Increased exercise/functional capacity
  - Enhanced quality of life and reduced symptomatic burden
  - Improvements in NYHA functional class
- Meta-analysis encompassing FAIR-HF and CONFIRM-HF evidenced association of IV FCM with reductions in recurrent HF hospitalizations and CV-related mortality in patients with ID and HFrEF
- Benefits were consistently **durable and sustained**
- **Outstanding questions:**
  - Can IV iron significantly reduce hard clinical endpoints (i.e., HF hospitalizations and CV-related death) in large RCTs?
  - What about for patients recently hospitalized for an acute heart failure event?



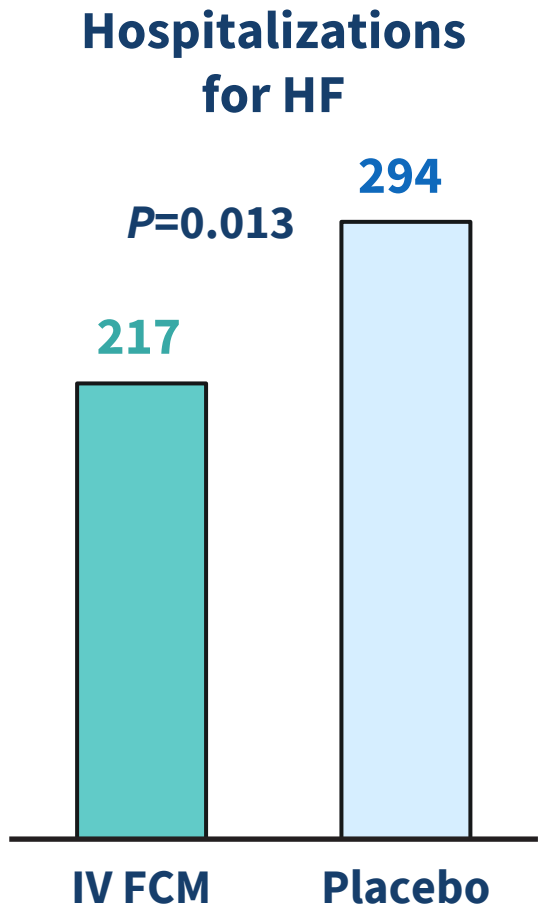
LVEF, left ventricular ejection fraction; 6MWT, 6-minute walk test; RCTs, randomized controlled trials

Anker SD, et al. *N Engl J Med*. 2009; Ponikowski P, et al. *Eur Heart J*. 2015; Anker SD, et al. *Eur J Heart Failure*. 2018; Butler J, et al. *Eur J Heart Failure*. 2022.

IV Iron Evidentiary Base in HF

AFFIRM-AHF

- 1,132 patients with HFrEF (LVEF <50%) and ID hospitalized for acute heart failure randomized to IV FCM vs. placebo for up to 24 weeks
- **Primary endpoint:** composite of total HF hospitalizations or CV-related deaths up to 1-year post-randomization
- **Results:**
  - 293 primary events occurred with FCM vs. 372 with placebo (*P*=0.059)
  - No difference in CV-related death was observed between the treatment arms
  - **The benefit of IV FCM was driven predominantly by reductions in HF hospitalizations**
  - Safety profiles were comparable for IV FCM vs. placebo



Ponikowski P, et al. *Lancet*. 2020; Filippatos G, et al. *Circulation*. 2023.

IV Iron Evidentiary Base in HF

AFFIRM-AHF – Pandemic Effect on Primary Endpoint?

Modified Intention-to-Treat Analysis	HR (95% CI)	P-value
Total heart failure hospitalization and CV death	**0.79 (0.62–1.01)**	**0.059**
Total CV hospitalization and CV death	0.80 (0.64–1.00)	0.050

COVID-19 Sensitivity Analysis*	HR (95% CI)	P-value
Total heart failure hospitalization and CV death	**0.75 (0.59–0.96)**	**0.024**
Total CV hospitalization and CV death	0.77 (0.62–0.97)	0.024

*Patients were censored in each country on the date when the first patient with COVID-19 was reported in the respective country.

Ponikowski P, et al. *Lancet*. 2020.

IV Iron Evidentiary Base in HF

AFFIRM-AHF Subanalyses

- Baseline Hb level
  - **No interaction** between baseline Hb strata (<12 g/dL vs. ≥12 g/dL) and IV FCM treatment effect was observed
  - **Benefits of IV FCM** – including sustained increases in key iron parameters – **were consistently demonstrated over time** ***irrespective of baseline Hb level***
- Diabetes status
  - **No interaction** between diabetes status and IV FCM treatment effect was observed
  - Clinical and patient-reported benefits of IV FCM are **independent of diabetes status**
- Impaired kidney function
  - Though event rates were found to be higher in lower eGFR groups, ***the treatment effect and therapeutic benefit of IV FCM was consistent across the eGFR spectrum***

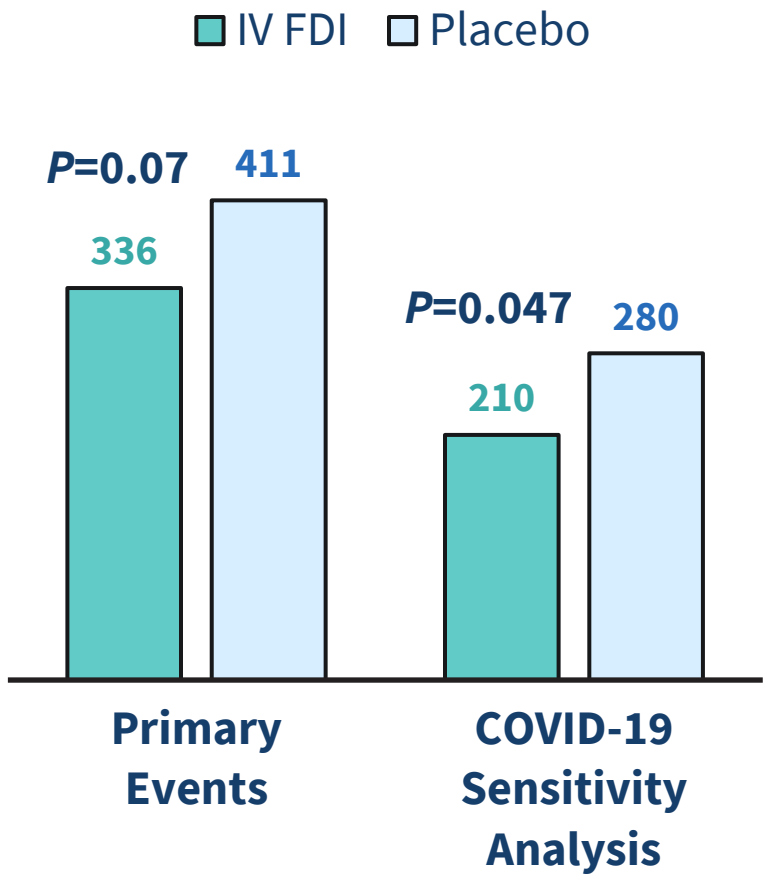
eGFR, estimated glomerular filtration rate

Filippatos G, et al. *Circulation*. 2023; Rosano G, et al. *Cardiovasc Diabetol*. 2023; MacDougall IC, et al. *Clin J Am Soc Nephrol*. 2023.

IV Iron Evidentiary Base in HF

IRONMAN

- 1,137 patients with HFrEF (LVEF <45%) and ID randomized to **IV ferric derisomaltose (FDI) vs. usual care**
  - Median follow-up = **2.7 years**
  - ***Pre-specified*** COVID-19 sensitivity analysis in September 2020
- **Primary endpoint:** recurrent hospital admissions for HF and CV-related death
- **Results:**
  - 336 primary events occurred with FDI vs. 411 with usual care (*P*=0.070)
  - In **COVID-19 sensitivity analysis**, however, primary events were 210 with FDI vs. 280 in usual care **(*P*=0.047)**
  - Safety profiles were comparable for IV FDI vs. usual care
  - Considered a positive trial that ***further reinforces the clinical benefit of IV iron repletion for ID in HFrEF***



Kalra PR, et al. *Lancet*. 2022.

IV Iron Evidentiary Base in HF

Meta-Analysis – AFFIRM-AHF & IRONMAN

Study or Subgroup	Drug	Treatment N	Control N	Weight	*Rate Ratio (95% CI)
AFFIRM-AHF	IV FCM	558	550	44.1%	0.79 (0.62-1.01)
IRONMAN	IV FDI	569	568	55.9%	0.82 (0.66-1.02)
Total		**1127**	**1118**	**100.0%**	**0.81 (0.69-0.95)**

*Primary endpoint = composite of recurrent HHF and CV-related death

Conclusion: IV FCM/FDI safe and effective at ↓composite outcome of recurrent HF hospitalization and CV-related death; impact on CV-related death alone is indeterminate

NNT = 7

NNT, number needed to treat; HHF, hospitalization for heart failure

Vukadinovic D, et al. *Clin Res Cardiol*. 2023.

IV Iron Evidentiary Base in HF

Other Recent Meta-Analyses

Salah H, et al.

- 10 RCTs, comprising 3,438 patients with HF and ID
- **Significant Reductions:**
  - **Composite of CV mortality and first HHF**
  - **First HHF**
  - **Total HHF**
- No significant reduction in all-cause mortality or CV mortality

Graham F, et al.

- 10 RCTs, comprising 3,373 patients with HF and ID (1,759 randomized to receive IV iron)
- **Significant Reductions:**
  - **Composite of recurrent HHF and CV mortality**
  - **First HHF or CV mortality**
- Inconclusive: Effect on all-cause mortality or CV mortality

Anker S, et al.

- FAIR-HF, CONFIRM-HF, AFFIRM-AHF, and IRONMAN
- **Significant Reductions:**
  - **Composite of recurrent HHF and CV mortality (FCM and FDI both achieved)**
- Benefits consistent across sex, age, ***eGFR, Hb, serum ferritin/TSAT***, and NYHA class

RCT, randomized controlled trial

Salah H, et al. *ESC Heart Failure*. 2023; Graham F, et al. *Eur J Heart Failure*. 2023; Anker S, et al. *Eur J Heart Failure*. 2023.

IV Iron Evidentiary Base in HF

FDA Approval

May 31, 2023

- The FDA approves ferric carboxymaltose (FCM) for an indication of *"iron deficiency in adult patients with heart failure and NYHA class II/III to improve exercise capacity."*
- This is the **first-ever approval of an IV iron product for a HF indication.**

FDA Prescribing Information.

IV Iron Evidentiary Base in HF

HEART-FID

- Enrolled >3,000 ambulatory patients with symptomatic HFrEF and ID (**largest trial to-date**) at ~300 sites
  - Randomized to IV FCM vs. placebo
  - Follow-up = 12 months
- Key inclusion criteria: NYHA class II-IV (stable), LVEF ≤40%, ID standard definition, prior HHF or ↑NT-proBNP
- Similar patient enrollment to other HFrEF trials, **but larger and more racially diverse**

Primary Objective

Hierarchical Composite:

- Death at 12 months, and if not
- Hospitalization for HF at 12 months, and if not
- Change from baseline in 6MWD at 6 months

Secondary Objectives

- Time to CV death or hospitalization for HF
- Time to CV death or CV hospitalization
- Time to CV death
- Time to CV death or intervention for worsening HF
  - ✓ Hospitalization for HF
  - ✓ Urgent HF visits
- Change in 6MWD at 12 months

6MWD, 6-minute walk distance

ClinicalTrials.gov; Mentz RJ, et al. *Circ Heart Fail*. 2021; Harrington J, et al. *Am Heart J*. 2023.

IV Iron Evidentiary Base in HF

HEART-FID

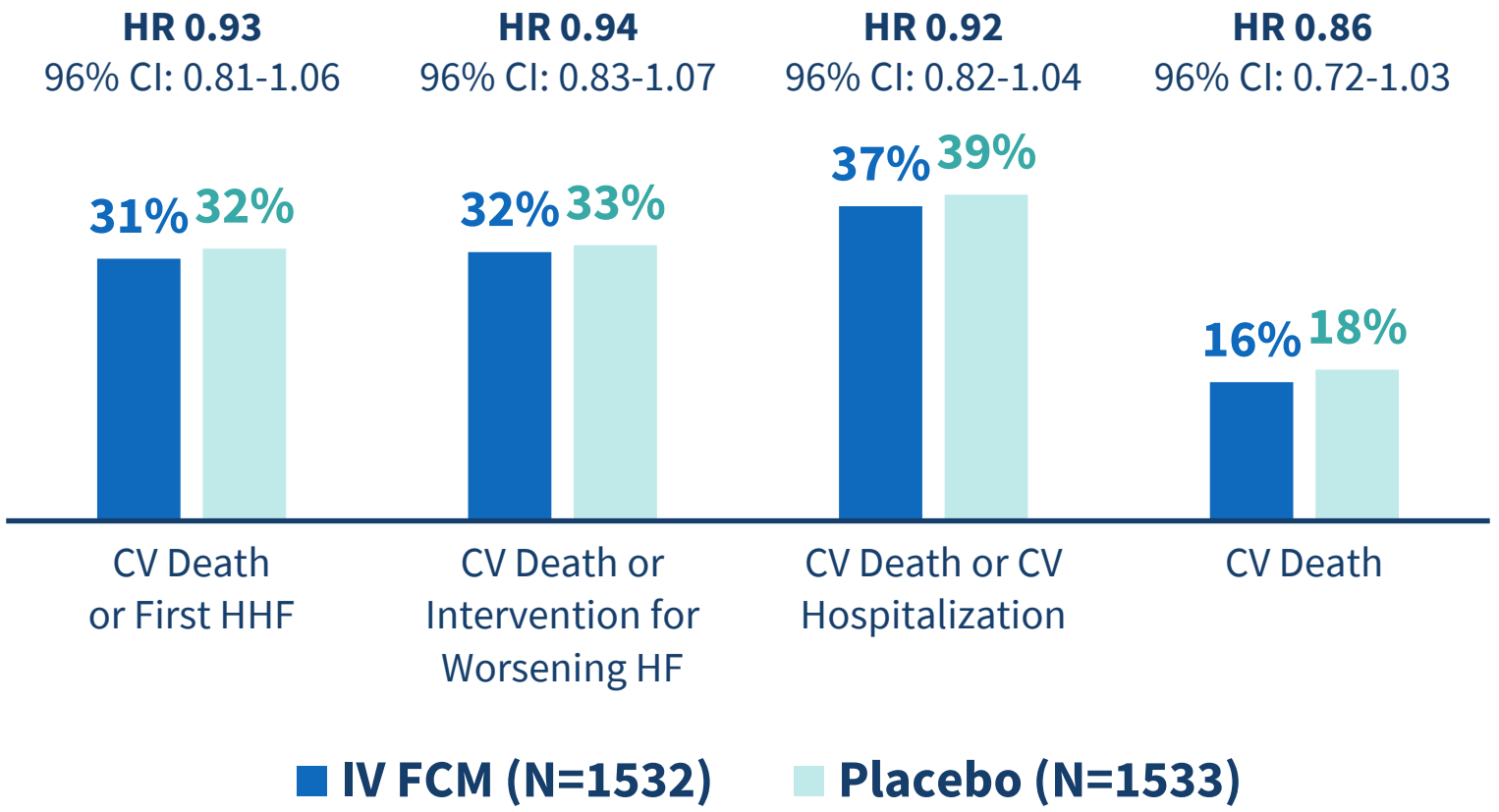
Primary Outcome

Overall Unmatched Win Ratio*: **1.10**

99% CI: 0.99-1.23

*Calculated by adding all the wins (as defined by hierarchical composite primary endpoint) in the ferric carboxymaltose group and dividing the sum by all the wins in the placebo group. *P*=0.02 for the comparison of the ferric carboxymaltose group with the placebo group.

Secondary Outcomes



Mentz RJ, et al. *N Engl J Med*. 2023; Martens P, et al. *N Engl J Med*. 2023.

IV Iron Evidentiary Base in HF

HEART-FID Discussion

- No apparent difference between FCM vs. placebo with respect to hierarchical composite primary endpoint
- Enrolled a ***generally lower-risk population*** relative to AFFIRM-AHF and IRONMAN
- **Higher TSAT at baseline relative to prior trials**
  - Suggests TSAT may be more important than ferritin in defining ID in HF
- ***IV iron generally not effective in patients with TSAT >20%***
- Long-term safety of FCM was confirmed – *no long-term hypophosphatemia-related ADRs were identified*
- Unspecified effects of COVID-19 during enrollment

Mean Lab Values at Baseline	IV FCM	Placebo
Hb, g/dL	12.6	12.5
SF, µg/L	56.0	57.3
TSAT, %	**23.9**	**23.0**

ADR, adverse drug reaction

Mentz RJ, et al. *N Engl J Med*. 2023; Martens P, et al. *N Engl J Med*. 2023.

IV Iron Evidentiary Base in HF

FCM in HF – Individual Patient Data Meta-Analysis

- **Pooled data from 3 RCTs of IV FCM**: CONFIRM-HF, AFFIRM-AHF, and HEART-FID
  - 4,501 adult patients with HF and ID
  - Follow-up: 52 weeks

Primary Objectives

Composite of Total CV Hospitalizations and CV Death
RR 0.86, 95% CI 0.75-0.98, ***P*=0.029**

Composite of Total HF Hospitalizations and CV Death
RR 0.87, 95% CI 0.75-1.01, *P*=0.076

Secondary Objectives

Total CV Hospitalizations
RR 0.83, 95% CI 0.73-0.96, ***P*=0.009**

Total HF Hospitalizations
RR 0.84, 95% CI 0.71-0.98, ***P*=0.025**

CV Death
No Difference in IV FCM vs PBO

Conclusion

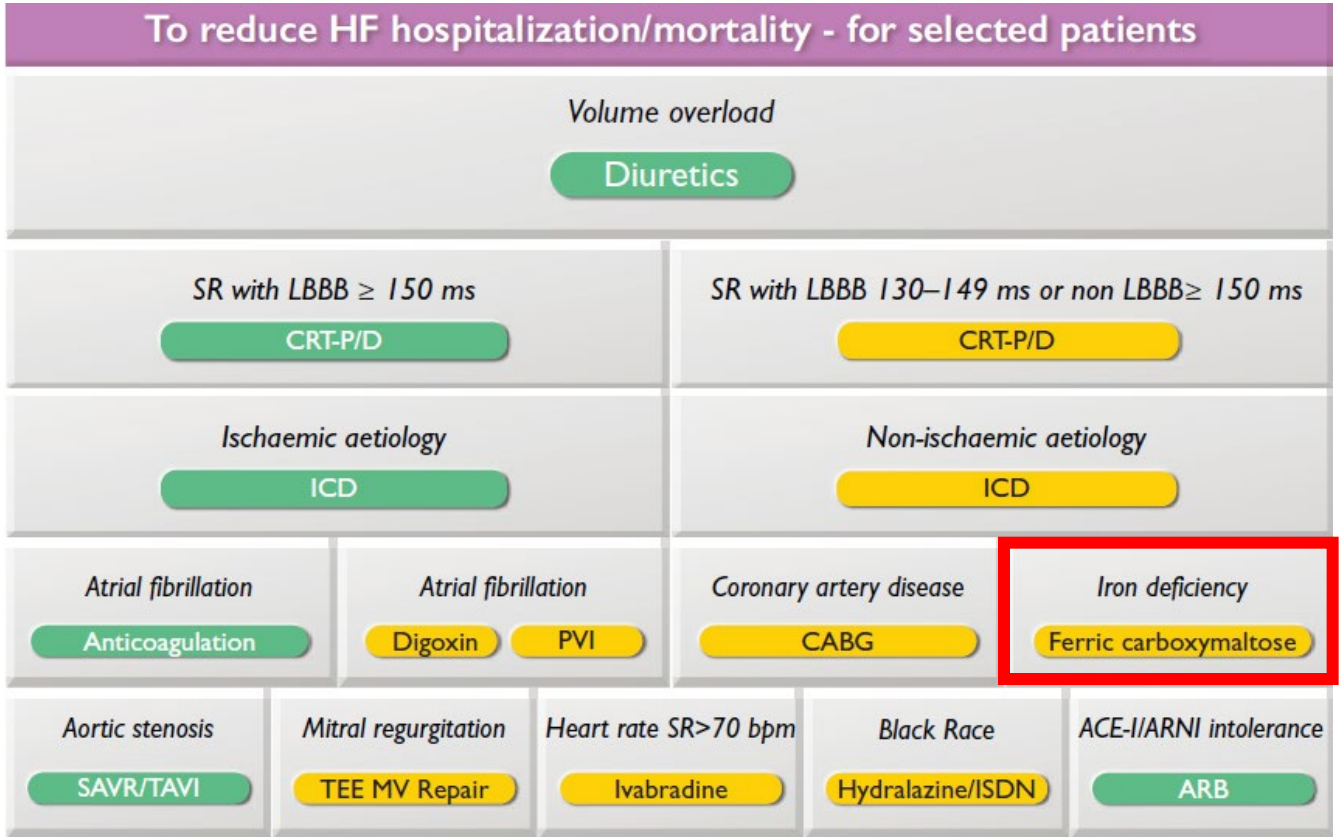
IV FCM should be considered in iron-deficient patients with HF and reduced or mildly reduced LVEF to **reduce the risk of hospitalization due to HF and CV causes**.

Ponikowski P, et al. *Eur Heart J*. 2023.

IV Iron Evidentiary Base in HF

2021 ESC Guidelines – Endorse IV FCM in HFrEF

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 HF

2023 Focused Update of the 2021 ESC HF Guidelines

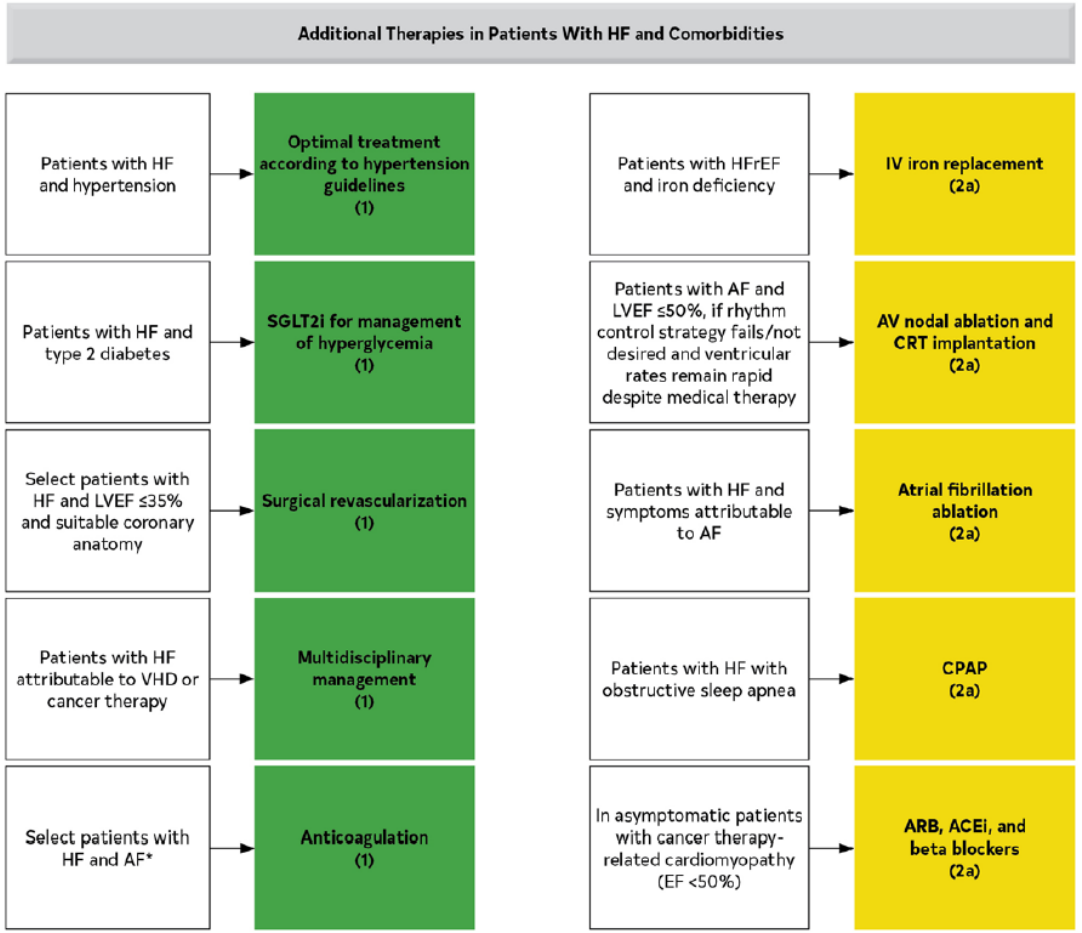
- Integrated new clinical trial evidence up to March 31, 2023
  - With respect to IV iron in HF, **guidelines now incorporate data from the recently-reported IRONMAN trial**
  - With HEART-FID data reporting out at ESC 2023, *further guideline updates may be warranted*
- All new recommendations are additive to the 2021 Guidelines, while all updated recommendations are substitutional

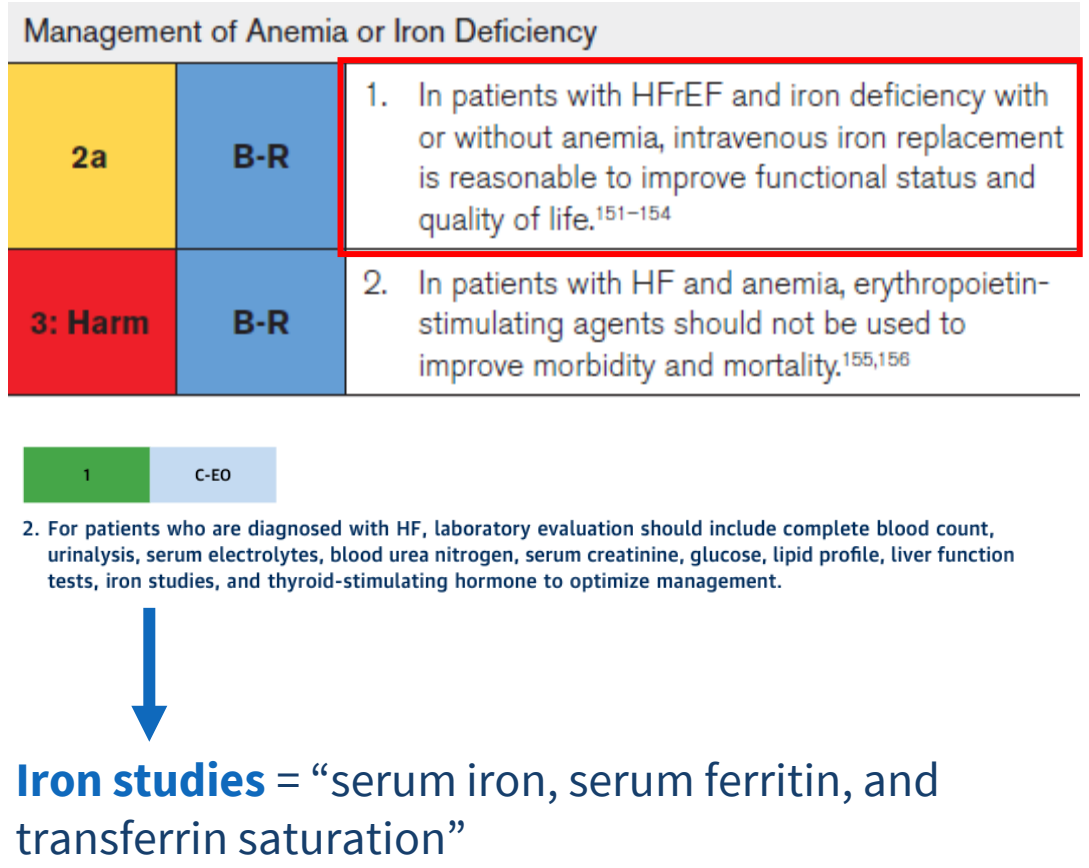
Recommendations	Class[a]	Level[b]
Intravenous iron supplementation is recommended in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to alleviate HF symptoms and improve quality of life.[c] [12,41,47–49]	I	A
Intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose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

McDonagh T, et al. *Eur Heart J*. 2023.

IV Iron Evidentiary Base in HF

2022 ACC/AHA/HFSA Guidelines – Endorse IV Iron in HFrEF



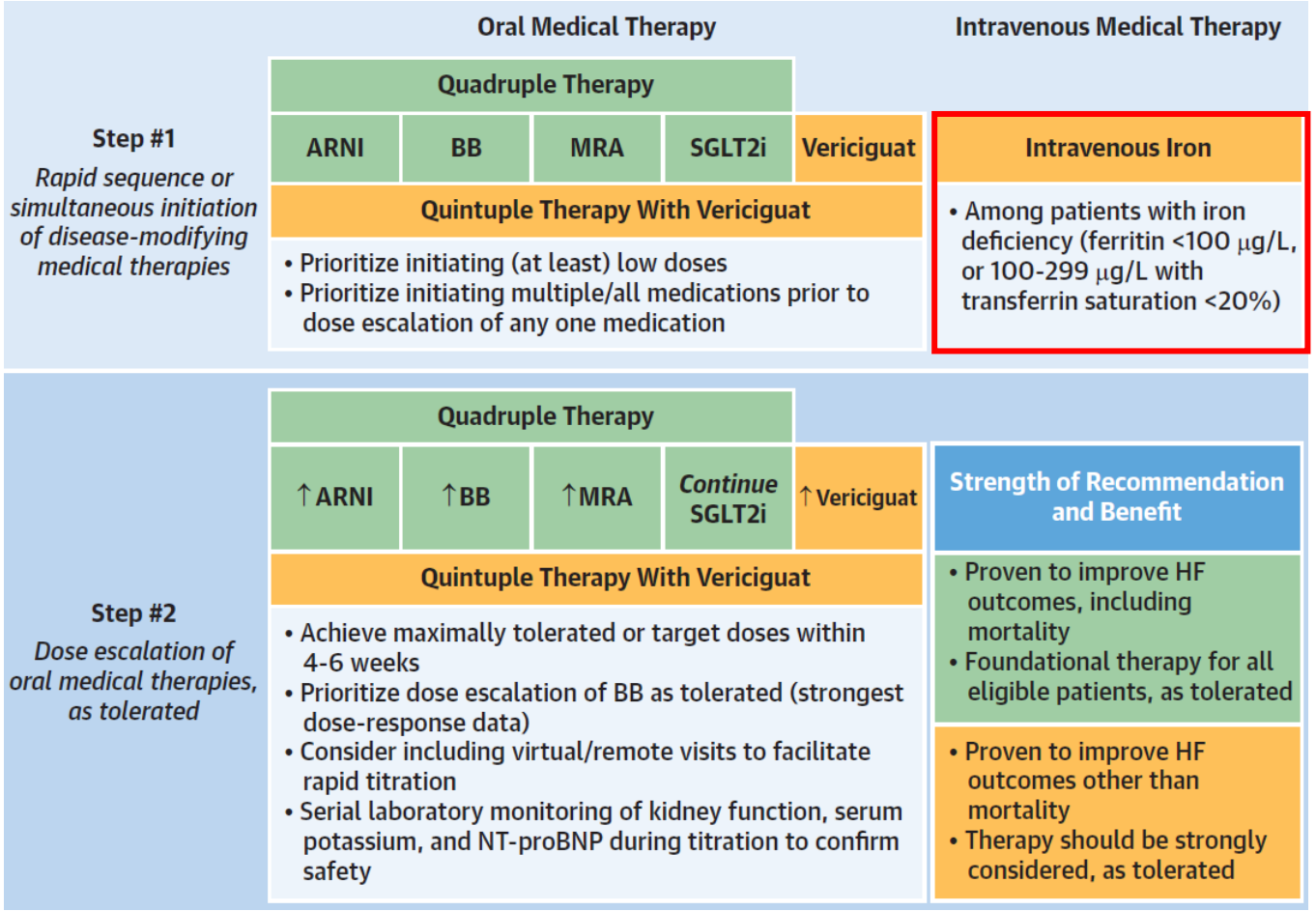


Iron studies = "serum iron, serum ferritin, and transferrin saturation"

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

IV Iron Evidentiary Base in HF

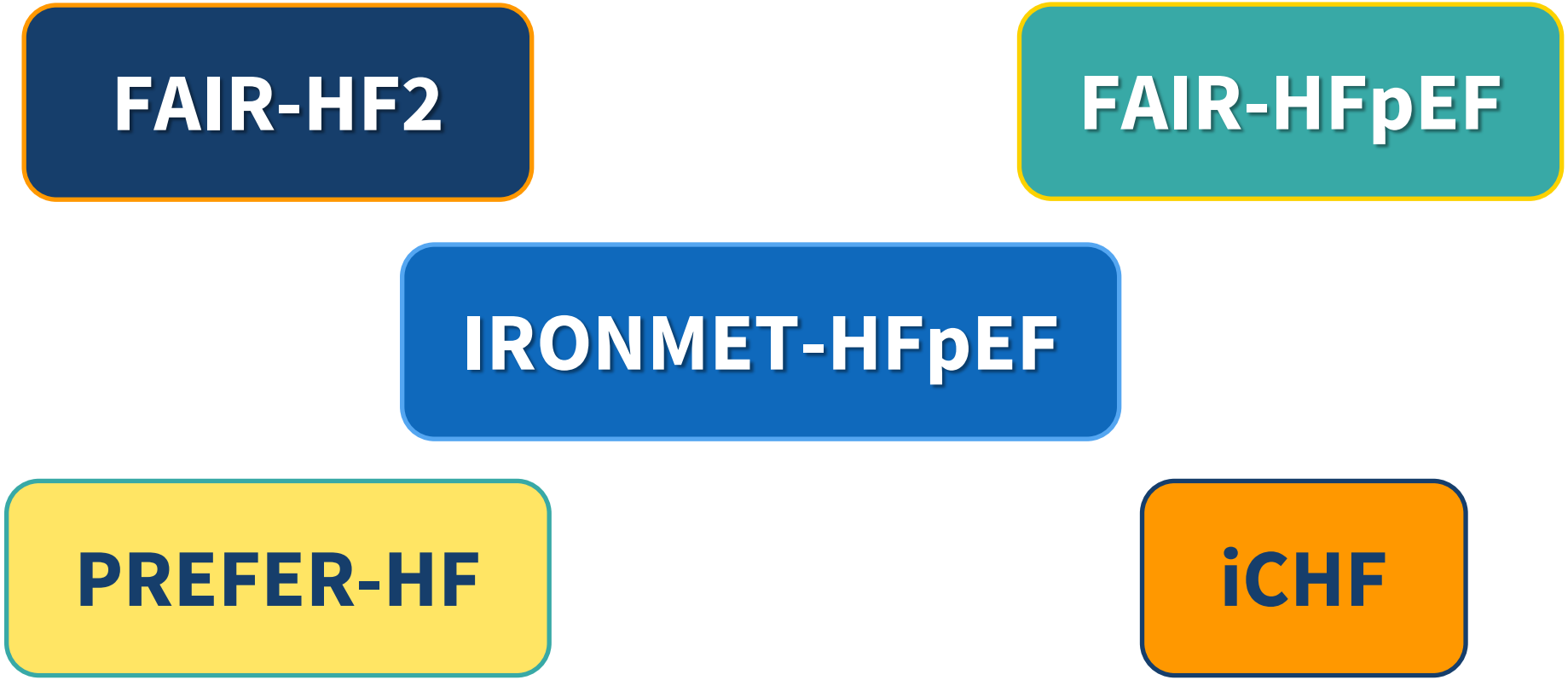
2023 JACC Focus Seminar – Worsening HFrEF



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

IV Iron Evidentiary Base in HF

Ongoing Studies



ClinicalTrials.gov; Beavers C, et al. *J Card Fail*. 2023.

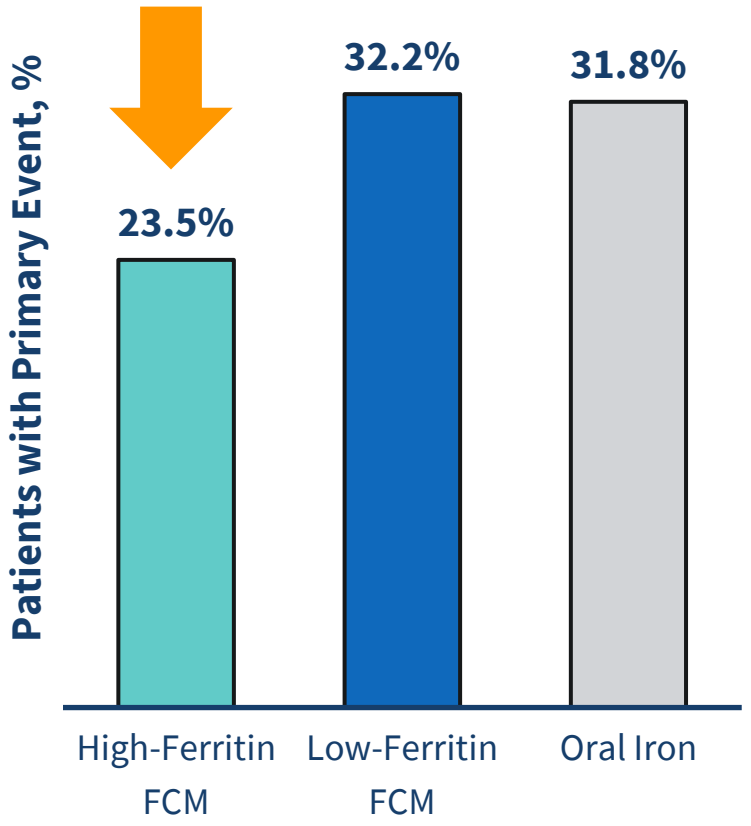
IV Iron in CRAS

Examining the Evidence in *Chronic Kidney Disease*

IV Iron Evidentiary Base in CKD

FIND-CKD

- 56-week open-label RCT, randomizing 626 patients with NDD-CKD, anemia, and ID not receiving ESAs to 2 arms of IV FCM or oral iron (1:1:2)
  - High-target IV FCM arm: targeting serum ferritin = 400-600 ng/mL
  - Low-target IV FCM arm: targeting serum ferritin = 100-200 ng/mL
- **Primary endpoint:** time to initiation of other anemia management or two consecutive Hb <10 g/dL during study weeks 8-52
- **Results:**
  - **High-ferritin IV FCM outperformed oral iron (*P*=0.014)**
  - Safety profiles were similar between the treatment arms, with no renal toxicity observed with any treatment



NDD-CKD, non-dialysis-dependent chronic kidney disease; ESA, erythropoiesis-stimulating agent

MacDougall IC, et al. *Nephrol Dial Transplant*. 2014.

IV Iron Evidentiary Base in CKD

FERWON-NEPHRO

- Open-label RCT randomizing 1,538 patient with NDD-CKD and IDA randomized to single-dose IV FDI (1,000 mg) vs. IV iron sucrose (IIS) 200 mg given up to 5 times over 2 weeks
- **Primary endpoint:** serious or severe hypersensitivity reactions and Hb change from baseline to week 8
- **Results:**
  - No significant difference in hypersensitivity reactions between FDI and IIS
  - **Composite CV-related adverse events were lower with FDI vs. IIS (*P*=0.025)**
  - **FDI achieved a greater Hb response** than IIS at week 4 (*P*<0.021)
  - Change in Hb at week 8 was *noninferior* with FDI (single-dose) vs. up to 5 doses of IIS

Bhandari S, et al. *Nephrol Dial Transplant*. 2021.

IV Iron Evidentiary Base in CKD

IV Iron Effects on Exercise Capacity for ID in NDD-CKD (without anemia)

- Prospective trial randomizing 75 patients with NDD-CKD and ID (without anemia) to IV iron vs. placebo
- **Primary endpoint:** difference in 6MWD at week 4
- **Results:**
  - **Significant increases in serum ferritin and TSAT** were achieved for IV iron vs. placebo at weeks 4 and 12 **(*P*<0.02)**
  - **Significant increases in Hb levels** for IV iron vs. placebo at week 12 **(*P*=0.009)**
  - However, no significant difference was observed for the primary endpoint of 6MWD at week 4
  - *Given the small sample size for this study, larger trial are needed to confirm results*

Greenwood SA, et al. *Kidney Int Reports*. 2023.

IV Iron Evidentiary Base in CKD

KDIGO Guideline for Managing Anemia in CKD

TREATMENT WITH IRON AGENTS

2.1.1: When prescribing iron therapy, balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risks of harm in individual patients (e.g., anaphylactoid and other acute reactions, unknown long-term risks). (*Not Graded*)

2.1.2: For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (*2C*):

- an increase in Hb concentration without starting ESA treatment is desired* and
- TSAT is ≤30% and ferritin is ≤500 ng/ml (≤500 µg/l)

2.1.3: For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (*2C*):

- an increase in Hb concentration** or a decrease in ESA dose is desired*** and
- TSAT is ≤30% and ferritin is ≤500 ng/ml (≤500 µg/l)

2.1.4: For CKD ND patients who require iron supplementation, select the route of iron administration based on the severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, patient compliance, and cost. (*Not Graded*)

2.1.5: Guide subsequent iron administration in CKD patients based on Hb responses to recent iron therapy, as well as ongoing blood losses, iron status tests (TSAT and ferritin), Hb concentration, ESA responsiveness and ESA dose in ESA treated patients, trends in each parameter, and the patient's clinical status. (*Not Graded*)

2.1.6: For all pediatric CKD patients with anemia not on iron or ESA therapy, we recommend oral iron (or IV iron in CKD HD patients) administration when TSAT is ≤20% and ferritin is ≤100 ng/ml (≤100 µg/l). (*1D*)

2.1.7: For all pediatric CKD patients on ESA therapy who are not receiving iron supplementation, we recommend oral iron (or IV iron in CKD HD patients) administration to maintain TSAT >20% and ferritin >100 ng/ml (>100 µg/l). (*1D*)

KDIGO. Clinical Practice Guideline for Managing Anemia in CKD. 2012.

IV Iron Evidentiary Base in CKD

KDIGO Guideline for Managing Anemia in CKD

IRON STATUS EVALUATION

2.2.1: Evaluate iron status (TSAT and ferritin) at least every 3 months during ESA therapy, including the decision to start or continue iron therapy. (*Not Graded*)

2.2.2: Test iron status (TSAT and ferritin) more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron, and in other circumstances where iron stores may become depleted. (*Not Graded*)

CAUTIONS REGARDING IRON THERAPY

2.3: When the initial dose of IV iron dextran is administered, we recommend (*1B*) and when the initial dose of IV non-dextran iron is administered, we suggest (*2C*) that patients be monitored for 60 minutes after the infusion, and that resuscitative facilities (including medications) and personnel trained to evaluate and treat serious adverse reactions be available.

Iron during infection

2.4: Avoid administering IV iron to patients with active systemic infections. (*Not Graded*)

KDIGO. Clinical Practice Guideline for Managing Anemia in CKD. 2012.

IV Iron Evidentiary Base in CKD

KDIGO Controversies in Optimal Anemia Management

- Overarching theme – ***data is limited and ongoing trials are needed***, *especially those evaluating the specific utility of IV iron to reduce cardiovascular events in patients with NDD-CKD*
- More robust safety data in this patient population is also warranted

Table 2 | Evidence for clinical benefits of iron administration

	Patients with CKD not on dialysis	Patients on dialysis
Reduction of congestive heart failure	Limited[60,61]	Yes[62]
Reduced occurrence of myocardial infarction	Limited[63]	Yes[62]
Improved quality of life	Not studied	Limited[64]
Reduced occurrence of fatigue	Not studied	Limited[64]
Improved cognitive function	Not studied	Limited[64]
ESA dose reduction	Yes[65]	Yes[65]
Reduced blood transfusions	Not studied	Yes[62]

Table 3 | Evidence for increased risk of clinical harm with iron administration

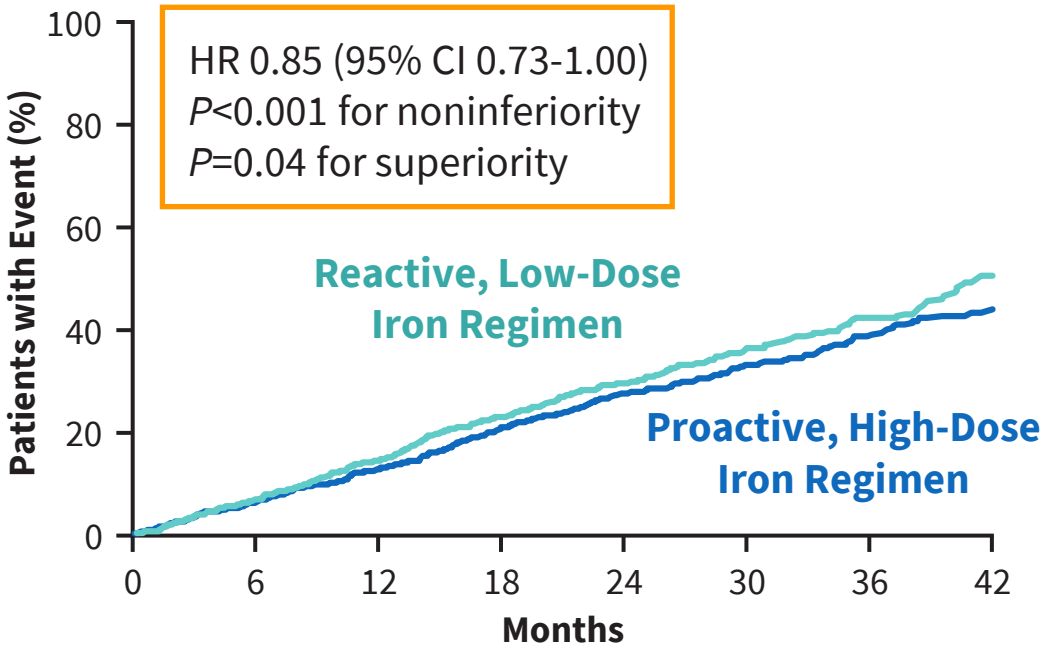
	Patients with CKD not on dialysis	Patients on dialysis
Infections	Limited[78,79]	No[80,81]
Cardiovascular events	Limited[78,79,82]	No[62]
Diabetes	Limited[83]	Limited[83]
CKD progression	Limited[78,79]	Not applicable
Anaphylaxis	Minimal[84]	Minimal[84]

Babitt JL, et al. *Kidney Int*. 2021.

IV Iron Evidentiary Base in CKD

What about Dialysis-Dependent CKD?

- The PIVOTAL study randomized 2,141 patients on maintenance hemodialysis to either high-dose *proactive* IV iron sucrose or low-dose *reactive* IV iron sucrose
- **Primary endpoint:** composite of nonfatal MI, nonfatal stroke, HHF, or death
  - Key secondary endpoint: **effect on ESA dosage requirements**
- High-dose proactive IV iron was both noninferior ($P<0.001$) and superior ($P=0.04$) to low-dose reactive IV iron for the primary endpoint
  - Reduced first and total HHF and MI
  - Also achieved **substantial reduction in ESA dosage requirements**, with consequent CV safety implications
  - No increased risk of infections or access thrombosis



MacDougall IC, et al. *N Engl J Med*. 2019.

IV Iron in CRAS

Examining the Evidence in ***Heart Failure***
+ Chronic Kidney Disease

IV Iron Evidentiary Base in CRAS

IV Iron Monotherapy in HF + CKD

- 40 patients with anemia, ID, CKD, and HFrEF (LVEF ≤35%) were randomized (1:1) to receive **IV iron sucrose 200 mg weekly x 5 weeks** or **placebo**
- **Primary endpoint:** NT-proBNP and CRP levels, as well as changes in clinical and functional parameters throughout the study period

Results at 6-month follow-up

- Benefits were observed with the IV iron treatment arm across study endpoints
  - Improved CrCl (***P*<0.01**)
  - Reduced CRP (***P*<0.01**)
  - Reduced NT-proBNP (***P*<0.01**)
  - LVEF, HRQoL, and 6MWT (***P*<0.01**)
  - Reduced all-cause hospitalizations (***P*<0.01**)

Mean Lab Values	Baseline		After 6 Months	
	PBO	IV Iron	PBO	IV Iron
Hb, g/dL	10.2	10.3	9.8	**11.8***
SF, µg/L	70.6	73.0	78.9	**240.4***
TSAT, %	20	20	20	**25***
NT-proBNP, pg/mL	267.5	255.9	450.9	**117.5***
CRP, mg/L	6.6	6.1	6.5	**2.3***
CrCl, mL/min	37.7	39.8	31.7	**44.9***
6MWD, m	190.7	192.3	184.5	**240.1***
Hospitalizations	-	-	5	**0**

***P*<0.01 vs placebo**

CRP, c-reactive protein; CrCl, creatinine clearance; PBO, placebo

Toblli JE, et al. *J Am Coll Cardiol*. 2007.

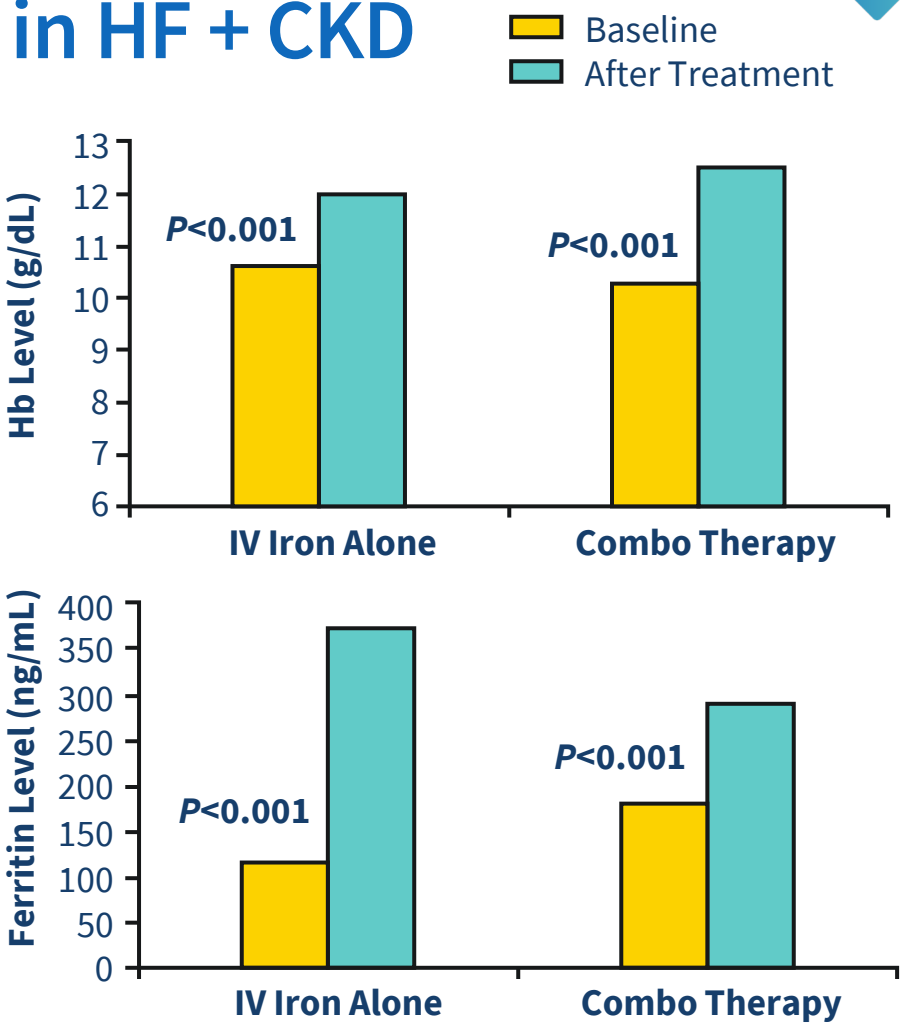
IV Iron Evidentiary Base in CRAS

IV Iron Monotherapy vs. IV Iron + ESA in HF + CKD

- **Observational study:** 81 patients with CRS + anemia (CRAS)
- All patients given **IV iron for 6 weeks**
  - IV iron monotherapy vs. IV iron + ESA combo therapy
- **Primary endpoint**: improvement in Hb and serum ferritin levels from baseline to week 8

Results

- Hb levels increased with significance (P<0.001) in both the IV iron monotherapy and ESA combo arms, but more greatly with combo
  - No difference between arms in percent of patients reaching Hb target of 11 g/dL (non-inferiority)
- Importantly, *IV iron monotherapy arm led to decreased platelet counts, while the ESA combo arm did not*



Ben-Assa E, et al. *Cardiorenal Med*. 2015.

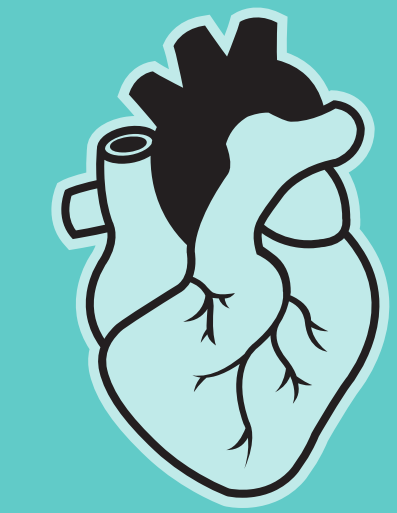
Summary of Key Teaching Points
IV Iron in CRAS

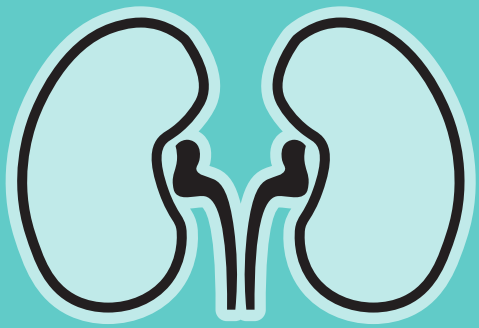
- IV iron has ***preferential clinical utility in hyperinflammatory conditions*** (such as CRAS)
  - Ability to **overcome hepcidin-induced functional iron blockade**
- IV iron has been – and continues to be – **studied extensively in HF**
  - **FCM first IV iron to garner an approved HF indication** in May 2023
  - FAIR-HF, CONFIRM-HF, AFFIRM-AHF, IRONMAN, HEART-FID, myriad meta-analyses
  - Numerous ongoing trials, included dedicated HFpEF studies
  - Consensus guidelines from ACC/AHA/HFSA and ESC
- IV iron has **established utility for CKD anemia**, but *limited data for non-anemic ID* in NDD-CKD
- Paucity of dedicated trials or expert guidance for IV iron specific to CRAS patients
- Recent regulatory approvals and ongoing data emergence are driving expanded role for IV iron in HF, CKD, and CRAS

Webinar 3

An Infusion of Change in the Cardiorenal Anemia Syndrome Treatment Paradigm

Practical Pearls for Optimizing Patient Outcomes with Intravenous Iron





Cornerstone Medical Education

AACME® AMERICAN ACADEMY OF CME, INC.

Presented by Cornerstone Medical Education, LLC
Supported through an independent educational grant from American Regent.

Presented by

Cornerstone Medical Education

AAACME®
AMERICAN ACADEMY OF CME, INC.

Supported by an independent educational grant from American Regent.

Implementing IV Iron in CRAS

Currently-Available Products

Iron Product	Dosing and Administration	Approved Indications	Common Adverse Drug Effects	Warnings
Low-Molecular-Weight Iron Dextran	• 100 mg daily via IV push over at least 2 minutes • Total dose is calculated based on iron deficit • May repeat daily	Iron deficiency (ID) in adult and pediatric patients 4 months of age and older for whom oral therapy is unsatisfactory or intolerable	Pruritis, abdominal pain, nausea, vomiting, diarrhea	**Black box**: fatal and serious hypersensitivity reactions, including anaphylaxis
Ferumoxytol	• 510 mg via IV infusion over at least 15 minutes • 2nd (510 mg) dose 3–8 days later	Iron deficiency anemia (IDA) in adult patients who have intolerance or unsatisfactory response to oral iron, or who have a diagnosis of *CKD*	Dizziness, hypotension, constipation, nausea	**Black box**: fatal and serious hypersensitivity reactions, including anaphylaxis
Sodium Ferric Gluconate	• 125 mg (adults) via IV infusion over 1 hour, per dialysis • 1.5 mg/kg in peds • Repeated weekly for up to 8 weeks	IDA in patients 6 years old and older who are receiving hemodialysis and supplemental EPO therapy for *CKD*	Chest pain, leg cramps, dizziness, dyspnea, nausea, vomiting, diarrhea	Hypersensitivity reactions, hypotension, iron overload, benzyl alcohol toxicity

FDA Prescribing Information.

Implementing IV Iron in CRAS

Currently-Available Products

Iron Product	Dosing and Administration	Approved Indications	Common Adverse Drug Effects	Warnings
Iron Sucrose	• 100–400 mg, by setting • Doses may be repeated based on clinical response and iron indices	IDA in adult and pediatric patients (2 years of age and older) with ***CKD***	Diarrhea, nausea, vomiting, headache, hypotension, pruritus	Hypersensitivity reactions, hypotension, iron overload
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
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

FCM, ferric carboxymaltose; FDI, ferric derisomaltose

FDA Prescribing Information.

Implementing IV Iron in CRAS

Practical Pearls & Product-Specific Considerations

Iron Product	Concentration of Elemental Iron (mg/mL)	Total Dose Infusion (TDI) Capacity On-Label	Test Dose Required?	Infusion Time
Iron Sucrose	20	No	No	≥15 minutes
Sodium Ferric Gluconate	12.5	No	No	1 hour
Low–Molecular-Weight Iron Dextran	50	No	**Yes**	1 hour (not to exceed 50 mg/min)
Ferumoxytol	30	No	No	≥15 minutes
FCM	50	**Yes**	No	≥15 minutes
FDI	100	**Yes**	No	≥20 minutes

Auerbach M, et al. *Lancet Haematol*. 2020; FDA Prescribing Information.

Implementing IV Iron in CRAS

Total Dose Infusion (TDI) Capacity by IV Iron Product

Iron Product	TDI *on the Label*	TDI *in the Clinic*
Low-Molecular-Weight Iron Dextran	• No • Label: max of 100 mg (2 mL) daily via IV push over at least 2 minutes	• Yes • Routinely given in practice as up to 1,000 mg administered over 1 hour
Ferumoxytol	• No • Label: 510 mg via IV infusion over at least 15 minutes; repeat in 3–8 days	• Yes • Trial data support 1,020 mg TDI
FCM	• **Yes** • For patients weighing ≥50 kg, may give either 1,000 mg TDI over at least 15 minutes or 750 mg x 2 doses, at least 7 days apart	• Yes • **Per label**
FDI	• **Yes** • For patients weighing ≥50 kg, 1,000 mg given over at least 20 minutes; <50 kg, 20 mg/kg	• Yes • **Per label**

FDA Prescribing Information; Mehmood T, et al. *Blood*. 2014; Khan H, et al. *Ther Adv Hematol*. 2021; ClinicalTrials.gov.

Implementing IV Iron in CRAS

Recognizing, Mitigating, and Managing Hypersensitivity

- Life-threatening anaphylaxis/severe hypersensitivity is *very rare* with *next-gen IV iron products
  - <1 event per 200,000 doses administered
- Essential to clinically differentiate minor acute reactions to IV iron vs true anaphylaxis → lack of differentiation = major source of ***erroneous stigma***
- Most common acute infusion reactions to IV iron: *Fishbane* and *complement activation-related pseudo-allergy (CARPA)* reactions
  - **Clinical manifestations**: facial flushing, chest tightness, arthralgia/myalgia, itching, mild dyspnea

*'Next-gen' primarily refers to FCM and FDI

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.

Implementing IV Iron in CRAS

Recognizing, Mitigating, and Managing Hypersensitivity

- Acute infusion reactions to IV iron may seem to mimic onset of anaphylaxis, they are ***NOT* anaphylaxis**
- Often **self-resolving**
- **Typically don't recur** – thus, allow for **re-initiation of same IV iron product**, albeit at slower rate (~50% reduction)
  - **NOT a contraindication to future IV iron use with same product**
- "Wait and watch" approach, requiring at least a 15–30-minute infusion pause

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.

Implementing IV Iron in CRAS

IV Iron Mechanism, Safety, and Nanocolloidal Design

ANIMATED WHITEBOARD VIDEO

Nikravesh N, et al. *Nanomedicine*. 2020; Avni T, et al. *Mayo Clin Proc*. 2015; DeLoughery TG. *Acta Haematol*. 2019; FDA Prescribing Information.

Optimizing CRAS Outcomes

Patient Case - Roger

Meet Roger

- 71-yo male
- **Stage 3b CKD** (most recent eGFR = 43 mL/min/1.73 m^2)
- **HFrEF** (LVEF = 39%; NYHA class II)
- **T2D**

Optimizing CRAS Outcomes

Patient Case - Roger

- **Physical Exam and Lab Studies**
  - Weight = 93 kg
  - BP = 136/85 mmHg
  - Serum creatinine = 1.9 mg/dL
  - Hb = 9.8 g/dL
  - Serum ferritin = 274 ng/mL
  - TSAT = 15%
- **Current Medications**
  - Metoprolol succinate 200 mg QD
  - Spironolactone 25 mg QD
  - Sacubitril/valsartan 49/51 mg BID
  - Metformin 500 mg ER QD
  - Empagliflozin 10 mg QD
  - Ferrous sulfate 325 mg BID (started 2 months ago)

Optimizing CRAS Outcomes

Diagnosing Roger

- Roger has previously been diagnosed with both CKD and HFrEF and today's labs reveal concomitant anemia
  - Roger's **Hb = 9.8 g/dL**
  - WHO anemia threshold for men = Hb <13 g/dL
- Therefore, by definition, **Roger has CRAS**
- Additionally, Roger's iron indices suggest functional iron deficiency (FID)
  - Roger's **serum ferritin = 274 ng/mL**; **TSAT = 15%**
  - Generally accepted definition of FID = ferritin 100-299 ng/mL and TSAT <20%
- Thus, we can determine based on medical history and lab values that ***Roger has CRAS-associated FID***

McCullough P. *Kidney Int Suppl*. 2021; Rangaswami J, et al. *Circulation*. 2019; WHO. Hemoglobin concentrations for the diagnosis of anemia and assessment of severity. 2011; Beavers C, et al. *J Card Fail*. 2023.

Optimizing CRAS Outcomes

Evaluating Roger

- Upon patient-centric discussion, Roger reveals that he has recently been dyspneic, particularly upon exertion, and it has progressively worsened over the past 3-4 months
  - States “difficulty walking the dog and getting the mail”
- PCP started **oral ferrous sulfate 325 mg PO BID ~2 months ago**
- Roger reports ***poor compliance*** to the oral iron regimen (~50% compliance), citing “stomach trouble”
- Roger’s medical records show that his serum ferritin, TSAT, and Hb have ***improved only modestly*** since starting oral iron
  - Hb increase from 9.1 to 9.8 g/dL
  - Serum ferritin increase from 255 to 274 ng/mL
  - TSAT increase from 13 to 15%

Optimizing CRAS Outcomes

Treating Roger

- Roger is experiencing intolerance – and consequent inefficacy – with oral iron, leading to persistent anemia and FID
  - Note – the **hyperinflammatory nature of Roger's HFrEF and CKD also render oral iron less effective** by causing elevations in ***hepcidin***, which reduces intestinal iron absorption and diminishes iron export from storage
- **IV iron has been extensively studied in HF**, demonstrating meaningful therapeutic benefits for exercise capacity, quality of life, symptomatic burden, and HF hospitalization risk
- IV iron has also demonstrated safety and efficacy in dedicated CKD trials
- Current expert consensus guidelines endorse IV iron for managing ID +/- anemia in HF and anemia in CKD

Beavers C, et al. *J Card Fail*. 2023; Pagani A, et al. *Front Physiol*. 2019; McDonagh T, et al. *Eur J Heart Failure*. 2015; Heidenreich P, et al. *Circulation*. 2022; McDonagh T, et al. *Eur Heart Journal*. 2021; Greene SJ, et al. *J Am Coll Cardiol*. 2023; KDIGO. Clinical Practice Guideline for Managing Anemia in CKD. 2012; ClinicalTrials.gov.

IV Iron Evidentiary Base in CKD

KDIGO Guideline for Managing Anemia in CKD

TREATMENT WITH IRON AGENTS

2.1.1: When prescribing iron therapy, balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risks of harm in individual patients (e.g., anaphylactoid and other acute reactions, unknown long-term risks). (*Not Graded*)

2.1.2: For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (*2C*):

- an increase in Hb concentration without starting ESA treatment is desired* and
- TSAT is ≤30% and ferritin is ≤500 ng/ml (≤500 µg/l)

2.1.3: For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (*2C*):

- an increase in Hb concentration** or a decrease in ESA dose is desired*** and
- TSAT is ≤30% and ferritin is ≤500 ng/ml (≤500 µg/l)

2.1.4: For CKD ND patients who require iron supplementation, select the route of iron administration based on the severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, patient compliance, and cost. (*Not Graded*)

2.1.5: Guide subsequent iron administration in CKD patients based on Hb responses to recent iron therapy, as well as ongoing blood losses, iron status tests (TSAT and ferritin), Hb concentration, ESA responsiveness and ESA dose in ESA treated patients, trends in each parameter, and the patient's clinical status. (*Not Graded*)

2.1.6: For all pediatric CKD patients with anemia not on iron or ESA therapy, we recommend oral iron (or IV iron in CKD HD patients) administration when TSAT is ≤20% and ferritin is ≤100 ng/ml (≤100 µg/l). (*1D*)

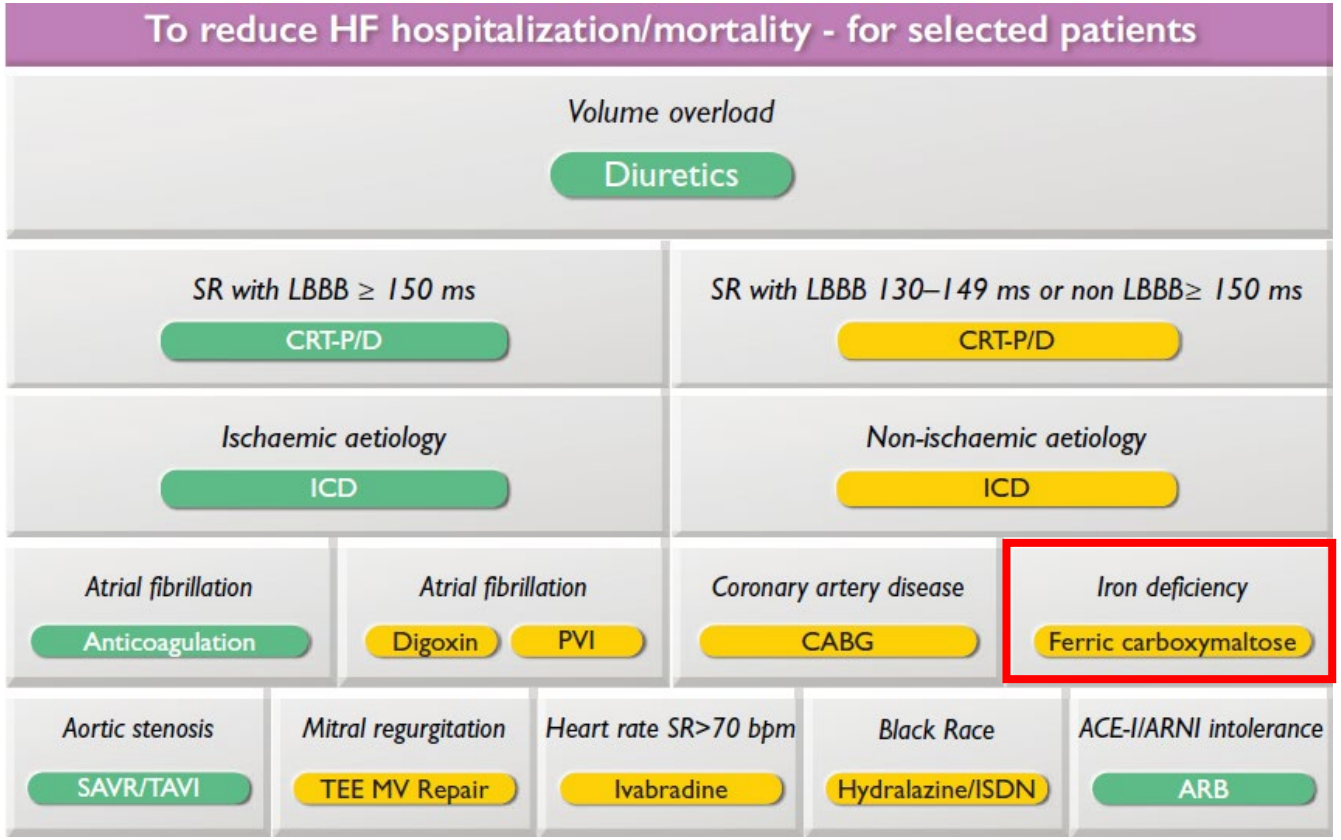
2.1.7: For all pediatric CKD patients on ESA therapy who are not receiving iron supplementation, we recommend oral iron (or IV iron in CKD HD patients) administration to maintain TSAT >20% and ferritin >100 ng/ml (>100 µg/l). (*1D*)

KDIGO. Clinical Practice Guideline for Managing Anemia in CKD. 2012.

IV Iron Evidentiary Base in HF

2021 ESC Guidelines – Endorse IV FCM in HFrEF

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 HF

2023 Focused Update of the 2021 ESC HF Guidelines

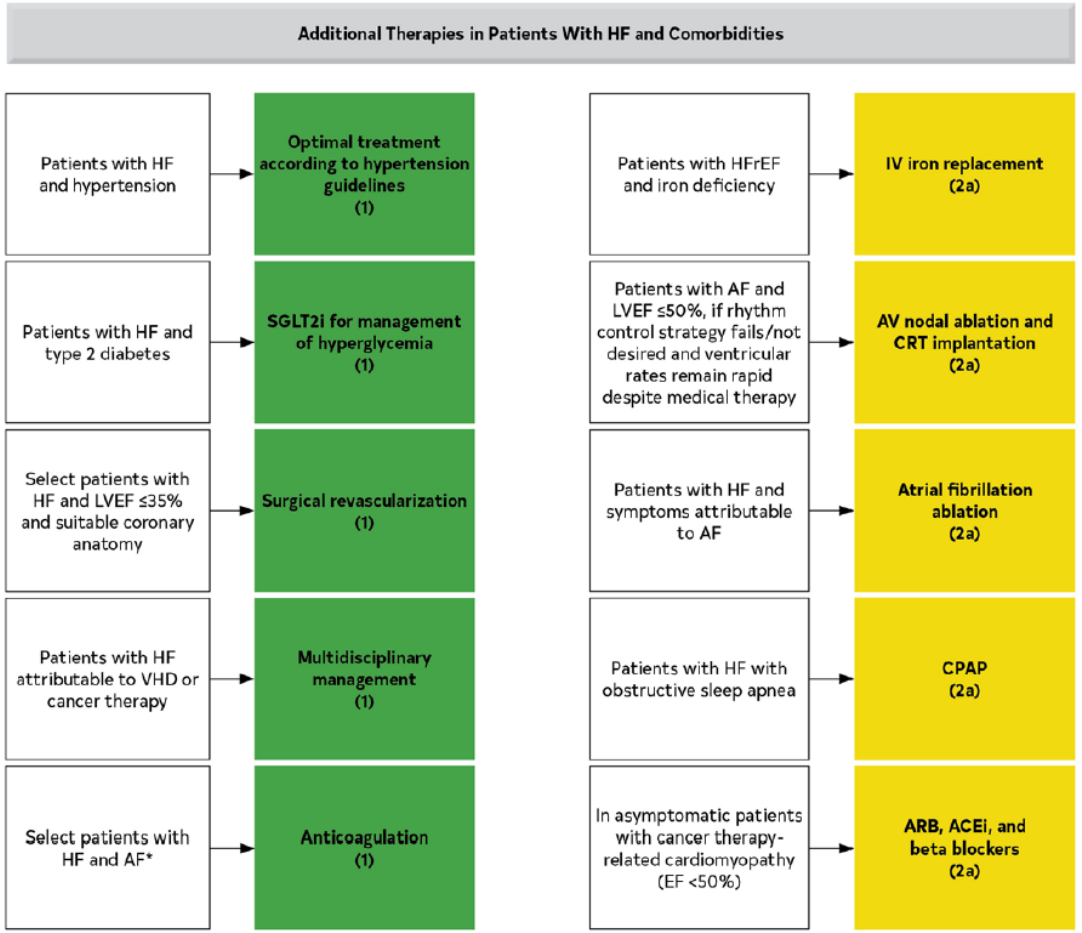
- Integrated new clinical trial evidence up to March 31, 2023
  - With respect to IV iron in HF, **guidelines now incorporate data from the recently-reported IRONMAN trial**
  - With HEART-FID data reporting out at ESC 2023, *further guideline updates may be warranted*
- All new recommendations are additive to the 2021 Guidelines, while all updated recommendations are substitutional

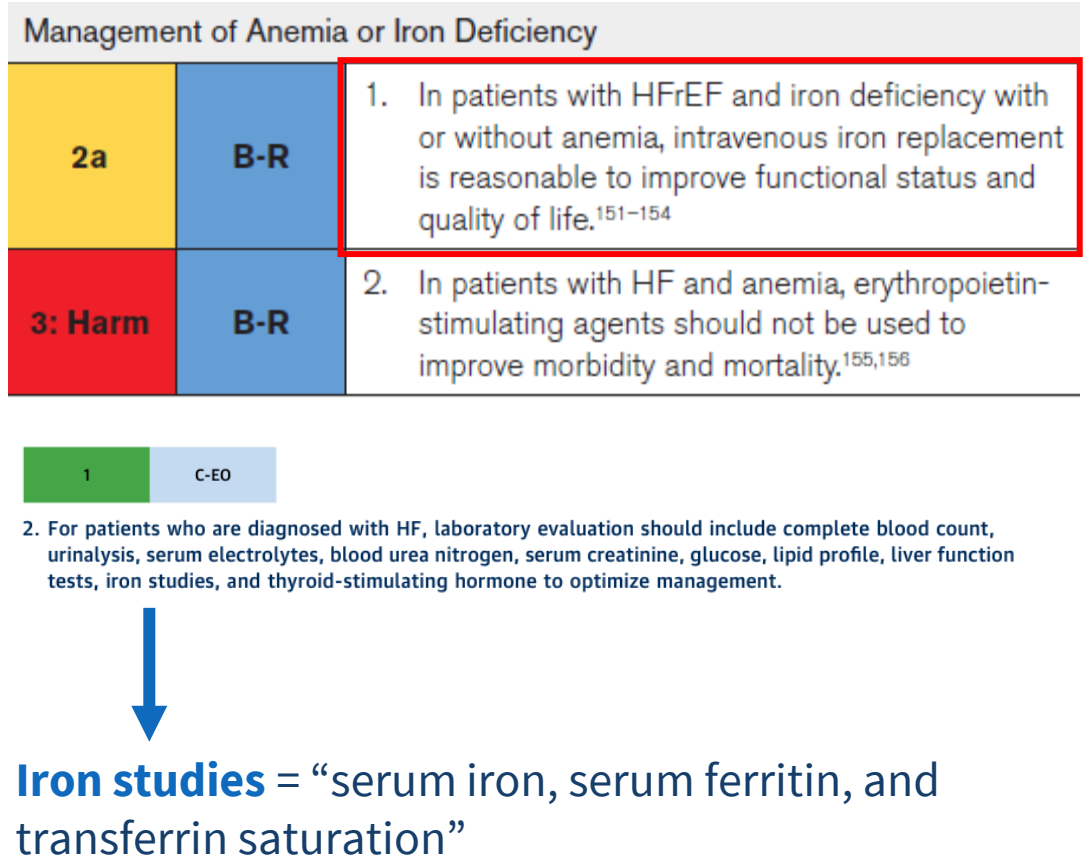
Recommendations	Class[a]	Level[b]
Intravenous iron supplementation is recommended in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to alleviate HF symptoms and improve quality of life.[c] [12,41,47–49]	I	A
Intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose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

McDonagh T, et al. *Eur Heart J*. 2023.

IV Iron Evidentiary Base in HF

2022 ACC/AHA/HFSA Guidelines – Endorse IV Iron in HFrEF



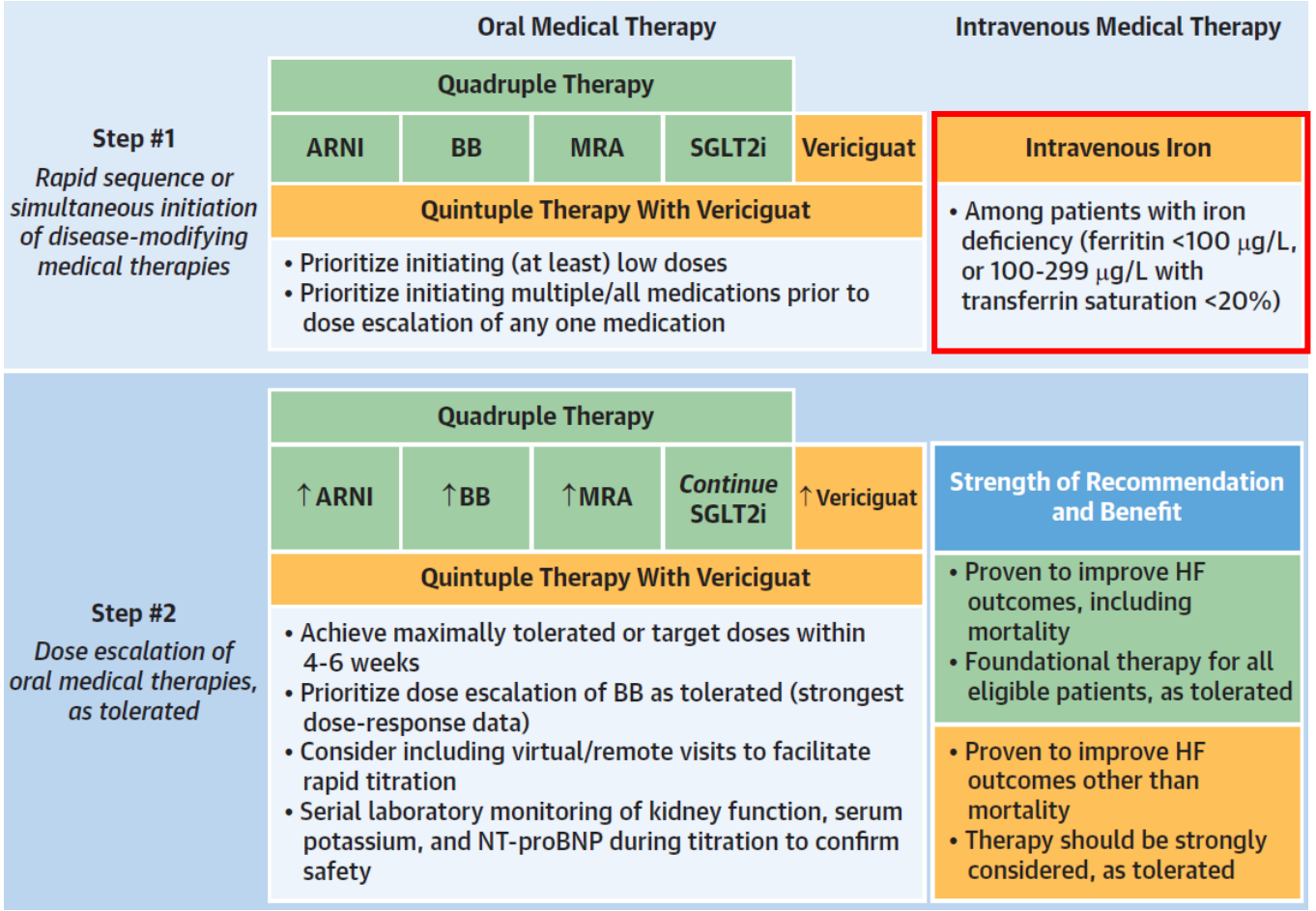


Iron studies = "serum iron, serum ferritin, and transferrin saturation"

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

IV Iron Evidentiary Base in HF

2023 JACC Focus Seminar – Worsening HFrEF



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

IV Iron Evidentiary Base in HF

FDA Approval

May 31, 2023

- The FDA approves ferric carboxymaltose (FCM) for an indication of *"iron deficiency in adult patients with heart failure and NYHA class II/III to improve exercise capacity."*
- This is the **first-ever approval of an IV iron product for a HF indication.**

FDA Prescribing Information.

Optimizing CRAS Outcomes

Patient Case Revisited - Roger

You have now diagnosed Roger with CRAS-associated FID and upon further evaluation, have identified significant symptomatic burden of disease, including substantive reductions in exercise capacity and quality of life.

- **Physical Exam and Lab Studies**
  - Weight = 93 kg
  - BP = 136/85 mmHg
  - Serum creatinine = 1.9 mg/dL
  - **Hb = 9.8 g/dL**
  - **Serum ferritin = 274 ng/mL**
  - **TSAT = 15%**
- **Current Medications**
  - Metoprolol succinate 200 mg QD
  - Spironolactone 25 mg QD
  - Sacubitril/valsartan 49/51 mg BID
  - Metformin 500 mg ER QD
  - Empagliflozin 10 mg QD
  - **Ferrous sulfate 325 mg BID** (started 2 months ago)

Optimizing CRAS Outcomes

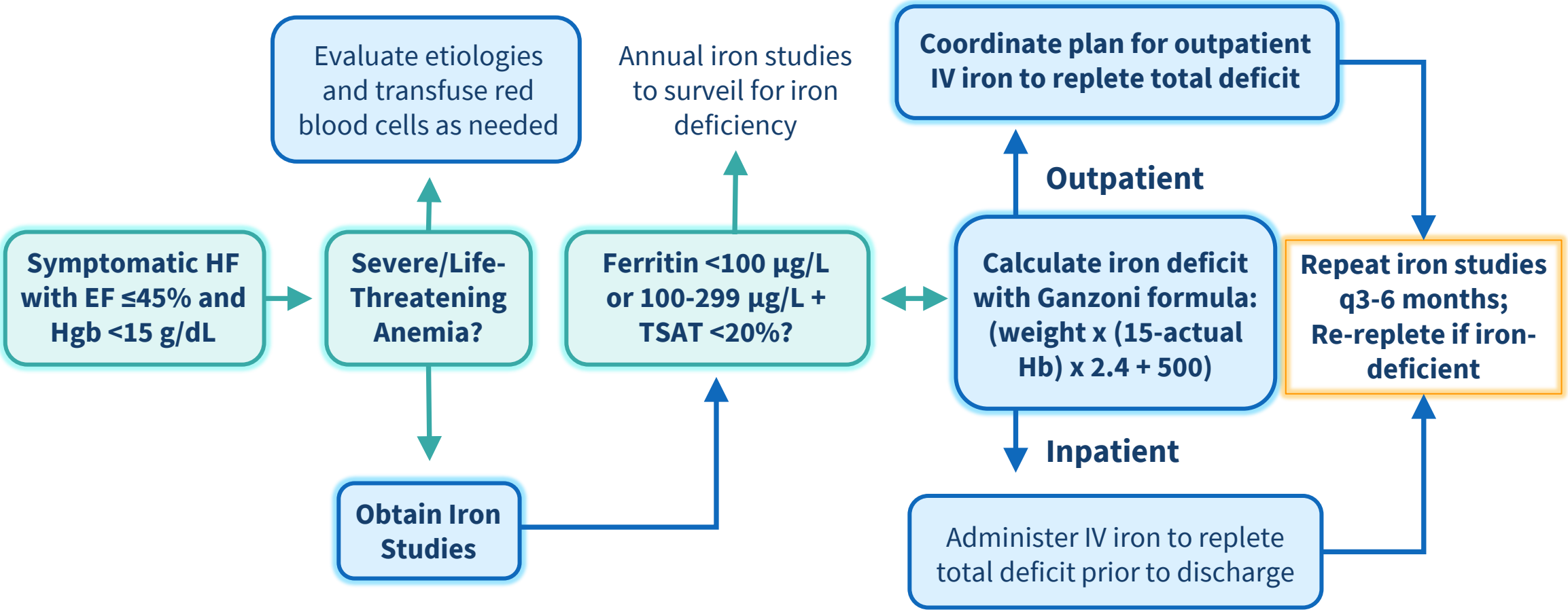
Patient Case Revisited - Roger

Decision Point:

As a member of the CRAS multidisciplinary and interprofessional treatment team, and based on available evidence, ***what treatment plan do you recommend for managing Roger's CRAS-associated FID?***

Optimizing CRAS Outcomes

Evidence-based Integration of IV Iron into Practice



FDA Prescribing Information; Beavers C, et al. *J Card Fail*. 2023.

Optimizing CRAS Outcomes

Patient Case Revisited - Roger

Treatment Plan:

- Based on the totality of trial data, expert guidelines, and regulatory approvals, you decide to **stop oral iron** and **initiate IV FCM 1,000 mg TDI**, administered today

- You will **repeat iron studies at his next appointment in 3 months** and will re-administer another IV FCM TDI at that time, if clinically warranted

Summary of Key Teaching Points
IV Iron in CRAS

- There are currently **6 FDA-approved IV iron products**
  - TDI capacity on-label: only FCM and FDI
- Imperative to differentiate Fishbane and CARPA reactions from true anaphylaxis
  - Often self-resolve and are a leading cause of misplaced IV iron safety stigma
- Next-gen IV iron products have ***dramatically improved safety profiles*** vs. older agents
- IV iron has evidence-driven and guideline-supported therapeutic utility in both HF and CKD
  - **HF:** FAIR-HF, CONFIRM-HF, AFFIRM-AHF, IRONMAN, HEART-FID; 2022 ACC/AHA/HFSA, 2023 ESC
  - **CKD:** FIND-CKD, FERWON-NEPHRO, KDIGO
  - **FCM first IV iron to garner an approved HF indication** in May 2023
  - FCM, FDI, ferumoxytol, and iron sucrose **all have indications for NDD-CKD**
- Recent regulatory approvals and ongoing data emergence are driving expanded role for IV iron across the CRAS continuum