

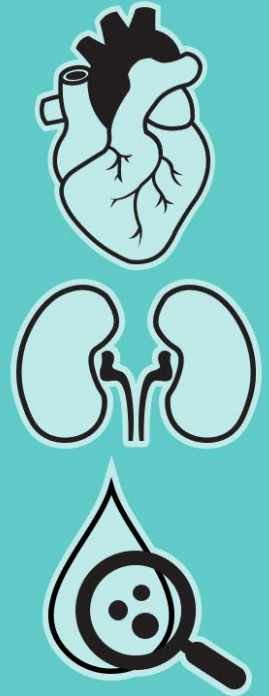


Optimizing Therapeutic Strategies in the Management of Cardiorenal Anemia Syndrome

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



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



Bibliography & Suggested Reading

Agarwal AK. Iron metabolism and management: focus on chronic kidney disease. *Kidney Int Suppl* (2011). 2021;11(1):46-58.

Anand IS, Gupta P. Anemia and Iron Deficiency in Heart Failure: Current Concepts and Emerging Therapies. *Circulation*. 2018;138(1):80-98.

Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med*. 2009;361(25):2436-2448.

Anker SD, Khan MS, Butler J, et al. Effect of intravenous iron replacement on recurrent heart failure hospitalizations and cardiovascular mortality in patients with heart failure and iron deficiency: A Bayesian meta-analysis. *Eur J Heart Fail*. 2023;25(7):1080-1090.



Anker SD, Kirwan BA, van Veldhuisen DJ, et al. Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. *Eur J Heart Fail.* 2018;20(1):125-133.

Auerbach M, Gafter-Gvili A, Macdougall IC. Intravenous iron: a framework for changing the management of iron deficiency. *Lancet Haematol.* 2020;7(4):e342-e350.

Avni T, Bieber A, Grossman A, et al. The safety of intravenous iron preparations: systematic review and meta-analysis. *Mayo Clin Proc.* 2015;90:12-23.

Babitt JL, Eisenga MF, Haase VH, et al. Controversies in optimal anemia management: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. *Kidney Int.* 2021;99(6):1280-1295.

Beavers CJ, Ambrosy AP, Butler J, et al. Iron Deficiency in Heart Failure: A Scientific Statement from the Heart Failure Society of America. *J Card Fail.* 2023;29(7):1059-1077.

Ben-Assa E, Shacham Y, Shashar M, et al. Target Hemoglobin May Be Achieved with Intravenous Iron Alone in Anemic Patients with Cardiorenal Syndrome: An Observational Study. *Cardiorenal Med.* 2015;5(4):246-253.

Bhandari S, Kalra PA, Berkowitz M, Belo D, Thomsen LL, Wolf M. Safety and efficacy of iron isomaltoside 1000/ferric derisomaltose versus iron sucrose in patients with chronic kidney disease: the FERWON-NEPHRO randomized, open-label, comparative trial. *Nephrol Dial Transplant.* 2021;36(1):111-120.

Bock JS, Gottlieb SS. Cardiorenal syndrome: new perspectives. *Circulation.* 2010;121(23):2592-2600.

Buliga-Finis ON, Ouatu A, Tanase DM, et al. Managing Anemia: Point of Convergence for Heart Failure and Chronic Kidney Disease?. *Life (Basel).* 2023;13(6):1311.

Butler J, Khan MS, Friede T, et al. Health status improvement with ferric carboxymaltose in heart failure with reduced ejection fraction and iron deficiency [published correction appears in *Eur J Heart Fail.* 2023 Mar;25(3):443]. *Eur J Heart Fail.* 2022;24(5):821-832.

Caimmi S, Crisafulli G, Franceschini F, et al. Hypersensitivity to Intravenous Iron Preparations. *Children (Basel).* 2022;9(10):1473.

Camaschella C. Iron deficiency [published correction appears in *Blood.* 2023 Feb 9;141(6):682]. *Blood.* 2019;133(1):30-39.

Cozzolino M, Mangano M, Stucchi A, Ciceri P, Conte F, Galassi A. Cardiovascular disease in dialysis patients. *Nephrol Dial Transplant.* 2018;33(suppl_3):iii28-iii34.

DeLoughery TG. Iron deficiency anemia. *Med Clin North Am.* 2017;101:319-332.

DeLoughery TG. Safety of oral and intravenous iron. *Acta Haematol* 2019;142:8-12.



Drugs@FDA: FDA-Approved Drugs. Ferric carboxymaltose. May 31, 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/203565s020lbl.pdf. Accessed September 2023.

Drugs@FDA: FDA-Approved Drugs. Ferric derisomaltose. August 4, 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208171Orig1s002lbl.pdf. Accessed September 2023.

Drugs@FDA: FDA-Approved Drugs. Ferumoxytol. June 16, 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022180s025lbl.pdf. Accessed September 2023.

Drugs@FDA: FDA-Approved Drugs. Iron dextran. April 20, 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/017441s179lbl.pdf. Accessed September 2023.

Drugs@FDA: FDA-Approved Drugs. Iron sucrose. January 20, 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021135Orig1s037lbl.pdf. Accessed September 2023.

Drugs@FDA: FDA-Approved Drugs. Sodium ferric gluconate. February 28, 2012. Accessed September 2023.

Filippatos G, Ponikowski P, Farmakis D, et al. Association Between Hemoglobin Levels and Efficacy of Intravenous Ferric Carboxymaltose in Patients With Acute Heart Failure and Iron Deficiency: An AFFIRM-AHF Subgroup Analysis. *Circulation*. 2023;147(22):1640-1653.

Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization [published correction appears in *N Engl J Med*. 2008;18(4):4]. *N Engl J Med*. 2004;351(13):1296-1305.

Graham FJ, Masini G, Pellicori P, et al. Natural history and prognostic significance of iron deficiency and anaemia in ambulatory patients with chronic heart failure. *Eur J Heart Fail*. 2022;24(5):807-817.

Graham FJ, Pellicori P, Kalra PR, Ford I, Bruzzese D, Cleland JGF. Intravenous iron in patients with heart failure and iron deficiency: an updated meta-analysis. *Eur J Heart Fail*. 2023;25(4):528-537.

Greene SJ, Bauersachs J, Brughts JJ, et al. Management of Worsening Heart Failure With Reduced Ejection Fraction: JACC Focus Seminar 3/3. *J Am Coll Cardiol*. 2023;82(6):559-571.

Greenwood SA, Oliveira BA, Asgari E, et al. A Randomized Trial of Intravenous Iron Supplementation and Exercise on Exercise Capacity in Iron-Deficient Nonanemic Patients With CKD. *Kidney Int Rep*. 2023;8(8):1496-1505.



Guedes M, Muenz DG, Zee J, et al. Serum Biomarkers of Iron Stores Are Associated with Increased Risk of All-Cause Mortality and Cardiovascular Events in Nondialysis CKD Patients, with or without Anemia. *J Am Soc Nephrol*. 2021;32(8):2020-2030.

Hain D, Bednarski D, Cahill M, et al. Iron-Deficiency Anemia in CKD: A Narrative Review for the Kidney Care Team. *Kidney Med*. 2023;5(8):100677.

Harrington J, Mentz RJ, Rockhold FW, et al. Baseline characteristics of patients in the randomized study to investigate the efficacy and safety of ferric carboxymaltose as treatment for heart failure with iron deficiency: HEART-FID trial [published online ahead of print, 2023 Aug 19]. *Am Heart J*. 2023;266:25-31.

Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. *Nat Rev Cardiol*. 2017;14(1):30-38.

Heidenreich PA, Bozkurt B, Aguilar D, et al. 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 correction appears in *Circulation*. 2022 May 3;145(18):e1033] [published correction appears in *Circulation*. 2022 Sep 27;146(13):e185] [published correction appears in *Circulation*. 2023 Apr 4;147(14):e674]. *Circulation*. 2022;145(18):e895-e1032.

Heidenreich PA, Bozkurt B, Aguilar D, et al. 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 correction appears in *J Am Coll Cardiol*. 2023 Apr 18;81(15):1551]. *J Am Coll Cardiol*. 2022;79(17):e263-e421.

Jimenez K, Kulnigg-Dabsch S, Gasche C. Management of Iron Deficiency Anemia. *Gastroenterol Hepatol (N Y)*. 2015;11(4):241-250.

Johnson-Wimbley TD, Graham DY. Diagnosis and management of iron deficiency anemia in the 21st century. *Therap Adv Gastroenterol*. 2011;4(3):177-184.

Kalra PR, Cleland JGF, Petrie MC, et al. Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. *Lancet*. 2022;400(10369):2199-2209.

Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. *Blood*. 2014;123(5):615-624.

Khan H, May P, Kuo E, et al. Safety and efficacy of a single total dose infusion (1020 mg) of ferumoxytol. *Ther Adv Hematol*. 2021;12:20406207211006022.

Kidney Disease Improving Global Outcomes (KDIGO). KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. August 2, 2012. Available at: <https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-Anemia-Guideline-English.pdf>. Accessed September 2023.



- Kim CJ, Choi IJ, Park HJ, et al. Impact of Cardiorenal Anemia Syndrome on Short- and Long-Term Clinical Outcomes in Patients Hospitalized with Heart Failure. *Cardiorenal Med.* 2016;6(4):269-278.
- Kim-Mitsuyama S, Soejima H, Yasuda O, et al. Anemia is an independent risk factor for cardiovascular and renal events in hypertensive outpatients with well-controlled blood pressure: a subgroup analysis of the ATTEMPT-CVD randomized trial. *Hypertens Res.* 2019;42(6):883-891.
- Klip IT, Comin-Colet J, Voors AA, et al. Iron deficiency in chronic heart failure: an international pooled analysis. *Am Heart J.* 2013;165(4):575-582.e3.
- Klip IT, Jankowska EA, Enjuanes C, et al. The additive burden of iron deficiency in the cardiorenal-anaemia axis: scope of a problem and its consequences. *Eur J Heart Fail.* 2014;16(6):655-662.
- Kosiborod M, Smith GL, Radford MJ, Foody JM, Krumholz HM. The prognostic importance of anemia in patients with heart failure. *Am J Med.* 2003;114(2):112-119.
- Kovesdy CP, Davis JR, Duling I, Little DJ. Prevalence of anaemia in adults with chronic kidney disease in a representative sample of the United States population: analysis of the 1999-2018 National Health and Nutrition Examination Survey. *Clin Kidney J.* 2022;16(2):303-311.
- Lewis GD, Malhotra R, Hernandez AF, et al. Effect of Oral Iron Repletion on Exercise Capacity in Patients With Heart Failure With Reduced Ejection Fraction and Iron Deficiency: The IRONOUT HF Randomized Clinical Trial [published correction appears in JAMA. 2017 Jun 20;317(23):2453]. *JAMA.* 2017;317(19):1958-1966.
- Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. *Lancet.* 2016;387(10021):907-916.
- Lu KJ, Kearney LG, Hare DL, et al. Cardiorenal anemia syndrome as a prognosticator for death in heart failure. *Am J Cardiol.* 2013;111(8):1187-1191.
- Macdougall IC, Bock AH, Carrera F, et al. FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia. *Nephrol Dial Transplant.* 2014;29(11):2075-2084.
- Macdougall IC, Canaud B, de Francisco AL, et al. Beyond the cardiorenal anaemia syndrome: recognizing the role of iron deficiency. *Eur J Heart Fail.* 2012;14(8):882-886.
- Macdougall IC, Ponikowski P, Stack AG, et al. Ferric Carboxymaltose in Iron-Deficient Patients with Hospitalized Heart Failure and Reduced Kidney Function [published online ahead of print, 2023 Jun 29]. *Clin J Am Soc Nephrol.* 2023;10.2215/CJN.0000000000000223.
- Macdougall IC, Vernon K. Complement Activation-Related Pseudo-Allergy: A Fresh Look at Hypersensitivity Reactions to Intravenous Iron. *Am J Nephrol.* 2017;45(1):60-62.



Macdougall IC, White C, Anker SD, et al. Intravenous Iron in Patients Undergoing Maintenance Hemodialysis [published correction appears in *N Engl J Med*. 2019 Jan 14;:]. *N Engl J Med*. 2019;380(5):447-458.

Martens P, Mullens W. Treating Iron Deficiency in Heart Failure [published online ahead of print, 2023 Aug 26]. *N Engl J Med*. 2023;10.1056/NEJMe2308305.

McCullough PA. Anemia of cardiorenal syndrome. *Kidney Int Suppl (2011)*. 2021;11(1):35-45.

McDonagh T, Macdougall IC. Iron therapy for the treatment of iron deficiency in chronic heart failure: intravenous or oral?. *Eur J Heart Fail*. 2015;17(3):248-262.

McDonagh T, Metra M, Adamo M, et al. 2023 Focused update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2023;(00):1-13.

McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [published correction appears in *Eur Heart J*. 2021 Oct 14;:]. *Eur Heart J*. 2021;42(36):3599-3726.

Mehmood T, Swe K, Das G, et al. Safety and efficacy of total dose infusion of low molecular weight (LMW) iron dextran in a large population of anemic patients across a broad spectrum of diagnoses associated with iron lack. *Blood*. 2014;124(21):4028.

Mentz RJ, Ambrosy AP, Ezekowitz JA, et al. Randomized Placebo-Controlled Trial of Ferric Carboxymaltose in Heart Failure With Iron Deficiency: Rationale and Design. *Circ Heart Fail*. 2021;14(5):e008100.

Mentz RJ, Garg J, Rockhold FW, et al. Ferric Carboxymaltose in Heart Failure with Iron Deficiency [published online ahead of print, 2023 Aug 26]. *N Engl J Med*. 2023;10.1056/NEJMoa2304968.

Miller JL. Iron deficiency anemia: a common and curable disease. *Cold Spring Harb Perspect Med*. 2013;3(7):a011866.

Minamisawa M, Miura T, Motoki H, et al. Prognostic impact of cardiorenal anemia syndrome in patients at-risk for heart failure. Presented at 2017 AHA Scientific Sessions; Chicago, IL. Abstract 14876.

Nikraves N, Borchard G, Hofmann H, et al. Factors influencing safety and efficacy of intravenous iron-carbohydrate nanomedicines: From production to clinical practice. *Nanomedicine*. 2020;26:102178.

Pagani A, Nai A, Silvestri L, Camaschella C. Hcpidin and Anemia: A Tight Relationship. *Front Physiol*. 2019;10:1294.

Parikh NI, Hwang SJ, Larson MG, Meigs JB, Levy D, Fox CS. Cardiovascular disease risk factors in chronic kidney disease: overall burden and rates of treatment and control. *Arch Intern Med*. 2006;166(17):1884-1891.



Ponikowski P, Filippatos G, Colet JC, et al. The impact of intravenous ferric carboxymaltose on renal function: an analysis of the FAIR-HF study. *Eur J Heart Fail*. 2015;17(3):329-339.

Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial [published correction appears in *Lancet*. 2021 Nov 27;398(10315):1964]. *Lancet*. 2020;396(10266):1895-1904.

Ponikowski P, Mentz RJ, Hernandez A, et al. Efficacy of ferric carboxymaltose in heart failure with iron deficiency: an individual patient data meta-analysis. *Eur Heart J*. 2023. [Epub ahead of print].

Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†. *Eur Heart J*. 2015;36(11):657-668.

Rampton D, Folkersen J, Fishbane S, et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. *Haematologica*. 2014;99(11):1671-1676.

Rangaswami J, Bhalla V, Blair JEA, et al. Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association. *Circulation*. 2019;139(16):e840-e878.

Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and Prevention. *MMWR Recomm Rep*. 1998;47(RR-3):1-29.

Rizzo C, Carbonara R, Ruggieri R, Passantino A, Scrutinio D. Iron Deficiency: A New Target for Patients With Heart Failure. *Front Cardiovasc Med*. 2021;8:709872.

Ronco C, Chionh CY, Haapio M, Anavekar NS, House A, Bellomo R. The cardiorenal syndrome. *Blood Purif*. 2009;27(1):114-126.

Rosano G, Ponikowski P, Vitale C, et al. Intravenous ferric carboxymaltose for iron repletion following acute heart failure in patients with and without diabetes: a subgroup analysis of the randomized AFFIRM-AHF trial. *Cardiovasc Diabetol*. 2023;22(1):215.

Salah HM, Savarese G, Rosano GMC, Ambrosy AP, Mentz RJ, Fudim M. Intravenous iron infusion in patients with heart failure: a systematic review and study-level meta-analysis. *ESC Heart Fail*. 2023;10(2):1473-1480.

Scrutinio D, Passantino A, Santoro D, Catanzaro R. The cardiorenal anaemia syndrome in systolic heart failure: prevalence, clinical correlates, and long-term survival. *Eur J Heart Fail*. 2011;13(1):61-67.

Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol*. 2000;35(7):1737-1744.



Silverberg DS, Wexler D, Iaina A, Schwartz D. The correction of anemia in patients with the combination of chronic kidney disease and congestive heart failure may prevent progression of both conditions. *Clin Exp Nephrol*. 2009;13(2):101-106.

Smith GL, Lichtman JH, Bracken MB, et al. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. *J Am Coll Cardiol*. 2006;47(10):1987-1996.

Steveling-Klein EH, Mateluna CM, Meienberg A, et al. Management of Hypersensitivity Reactions to Nondextran Iron Products: New Insights Into Predisposing Risk Factors. *J Allergy Clin Immunol Pract*. 2021;9(6):2406-2414.e2.

Strauss WE, Auerbach M. Health-related quality of life in patients with iron deficiency anemia: impact of treatment with intravenous iron. *Patient Relat Outcome Meas*. 2018;9:285-298.

Toblli JE, Lombraña A, Duarte P, Di Gennaro F. Intravenous iron reduces NT-pro-brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. *J Am Coll Cardiol*. 2007;50(17):1657-1665.

U.S. National Library of Medicine. ClinicalTrials.gov. Available at: <https://classic.clinicaltrials.gov/>. Accessed September 2023.

Vukadinović D, Abdin A, Emrich I, Schulze PC, von Haehling S, Böhm M. Efficacy and safety of intravenous iron repletion in patients with heart failure: a systematic review and meta-analysis. *Clin Res Cardiol*. 2023;112(7):954-966.

World Health Organization (WHO). Hemoglobin concentrations for the diagnosis of anemia and assessment of severity. 2011. Available at: https://apps.who.int/iris/bitstream/handle/10665/85839/WHO_NM_H_NHD_MNM_11.1_eng.pdf. Accessed September 2023.

Yuan J, Zou XR, Han SP, et al. Prevalence and risk factors for cardiovascular disease among chronic kidney disease patients: results from the Chinese cohort study of chronic kidney disease (C-STRIDE). *BMC Nephrol*. 2017;18(1):23.