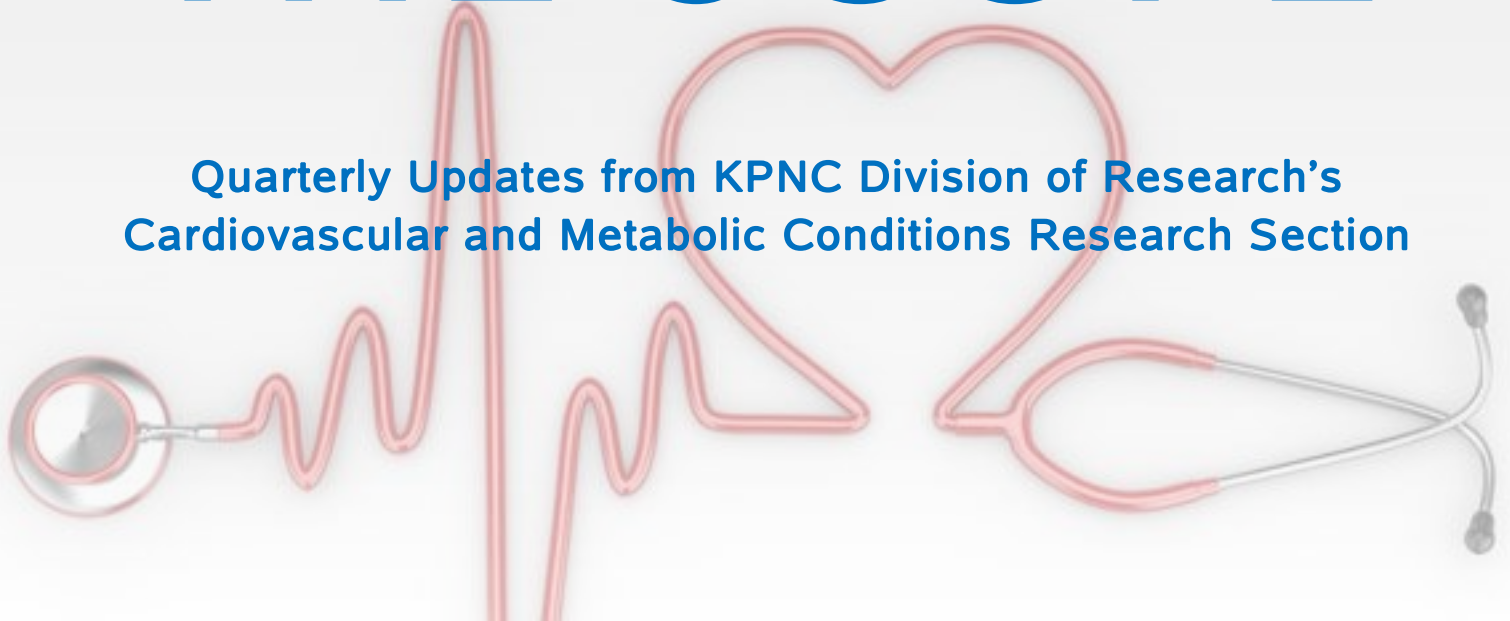


THE SCOPE

Quarterly Updates from KPNC Division of Research's
Cardiovascular and Metabolic Conditions Research Section



Celebrating Cardiovascular & Metabolism Research in KPNC

In this newsletter and through upcoming events, we continue to celebrate the wide range and depth of high-impact cardiovascular & metabolism research being done within KPNC!

Toward that end, we are excited to announce the **4th Annual Regional Cardiovascular Research Symposium** happening on **Thursday, May 1, 2020** that is co-sponsored by DOR and the TPMG Cardiac Service Line. More details are on Page 7, including a link to register for the event.

In addition, through the TPMG Physician Researcher Program, Matt Solomon is working with DOR to expand our recognition of cardiovascular research being done in KP (see Page 7) and to facilitate new, productive research collaborations.

Alan Go, Ed McNulty, and Matt Solomon

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Brief Update on Iron Deficiency in Heart Failure

BY ANDREW P. AMBROSY, M.D.

Iron deficiency is present in ~50% of patients with heart failure (HF) and has been strongly linked to a worse prognosis. Iron acts as a cofactor for many cellular proteins and enzymes in the body and plays a pivotal role in both oxygen delivery (i.e., erythropoiesis) and utilization (i.e., energy metabolism) (**Figure 1**). The cause of iron deficiency in HF is likely multifactorial. Notably, HF is a pro-inflammatory condition associated with elevated levels of cytokines and leukotrienes. Inflammation increases the expression of

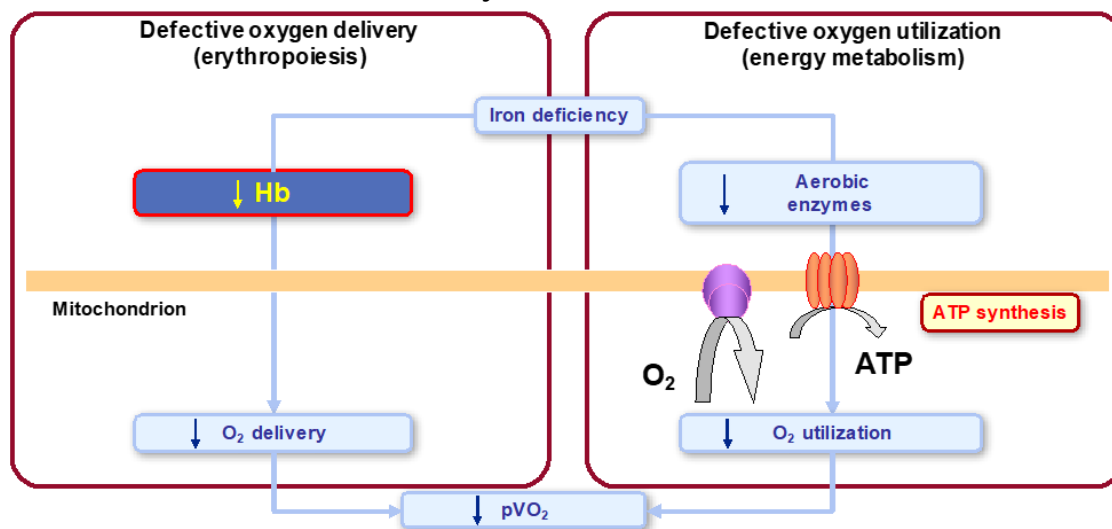


Figure 1. The dual effects of iron deficiency in heart failure on defective oxygen delivery and utilization.

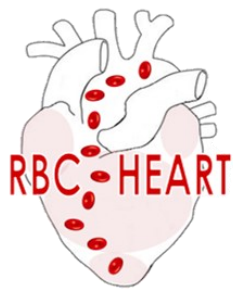
hepcidin, a regulatory protein, which causes an absolute decrease in oral absorption of iron and a relative reduction in circulating levels of iron in the body.

This fact has important implications for the diagnosis of iron deficiency in the

setting of HF. Iron stores status is generally assessed by measuring levels of plasma proteins that complex with iron (i.e., which exists in solution in the form of a toxic free radical) to facilitate its safe intracellular storage (i.e., ferritin) and/or extracellular transport (i.e., transferrin). Hence, a presumptive diagnosis of iron deficiency is classically made based on an isolated low ferritin level or a low ferritin level in combination with a reduced TSAT. However, ferritin and transferrin are acute phase reactants and are increased and decreased, respectively, in patients with HF. As a result, the cutoffs used to define iron deficiency in HF remain controversial and the current ACC/AHA/HFSA guidelines recommend a ferritin <100 ng/mL or a ferritin 100-300 ng/mL and a TSAT <20%.

A recently completed NIH-funded study found that high-dose oral iron supplementation, compared to matching placebo, did not improve iron indices and had no impact on exercise capacity. In contrast, several early phase clinical trials of IV iron have shown that with 1-2 doses it is possible to fully replenish total body iron stores and improve signs and symptoms of HF, quality of life, and functional status. In addition, pooled meta-analyses of existing randomized trials suggest IV iron may even improve survival in HF. Within KPNC, KPSC and KPNW, observational data suggest that iron deficiency may not routinely be assessed in patients with HF and anemia but reduced iron stores are frequently identified as part of a comprehensive work-up. As described in the next section, a novel pilot study is currently underway to test the feasibility of implementing a pragmatic clinical trial leveraging the electronic health record in order to evaluate a strategy of screening for and treating iron deficiency anemia in older adults with HF compared to usual care.





Research Highlight: The RBC HEART Pragmatic Clinic Trial Pilot

BY ALAN S. GO, M.D. and ANDREW P. AMBROSY, M.D.

The RBC HEART pragmatic clinical trial pilot was

launched in 2019 within KPNC. This effort involves a collaboration between the TPMG Division of Research, Duke Clinical Research Institute, and KP Oakland and San Francisco Medical Centers. This quality improvement initiative aims to investigate the systematic evaluation and treatment of reduced iron stores, and its impact in the short-term clinical outcomes of older patients with HF and anemia.

In this pilot trial, KP members with HF and confirmed anemia who were not previously evaluated for reduced iron stores were randomly assigned into an intervention arm or control arm of the study. The Intervention arm consists of a one-time evaluation of iron stores (serum ferritin, iron, TIBC, TSAT) to evaluate for iron deficiency. If present, patients are recommended to receive a one-time treatment of IV ferric carboxymaltose


(750 mg) or 90-day oral iron

supplements if the patient refused IV iron therapy. In the usual care control group, patients are passively monitored through the electronic health records. The main outcomes include a feasibility assessment for integration of the intervention into infusion centers and research facilities, changes in hemoglobin level, and short-term health care utilization.

The pilot has also launched in KP Southern California and is launching soon in KP Northwest, with ongoing efforts to secure funding for the definitive trial through the National Institute on Aging.




Figure 2. The RBC HEART Pilot Team at the launch of KP Southern California.



RBC HEART: Quality Improvement Initiative


What is RBC HEART?

- In adults with heart failure, anemia (i.e. low hemoglobin level) is a common occurrence and can contribute to worse clinical outcomes
- RBC HEART is evaluating the use of iron treatment to treat low iron levels in patients with heart failure.




Why am I being asked to participate in RBC HEART?

- Your recent blood test shows you have low iron levels
- You have diagnosed heart failure
- You are at least 65 years old




What will happen if I partake in RBC HEART?

1. A RBC HEART Nurse will call you in the next week to answer your questions and order a single IV iron shot (or a 90-day supply of oral iron pills) at no cost to you
2. You will visit the clinic and our staff will administer the IV iron over ~10 minutes with a 30 minute monitoring period after that
3. Three months after you receive the iron therapy you will complete a lab test to check your anemia status at no cost to you and your participation will then be complete



What is IV iron and why should I take it?

- IV iron is in liquid form and delivered into a vein as a single shot.
- IV iron is approved by the FDA and used to treat reduced iron stores.
- It is highly effective in restoring low iron levels and is absorbed by the body more rapidly than oral iron.




 **KAISER PERMANENTE** For more information call 1-833-892-8265.

Figure 1. Informational flyer for patients recruited for the RBC HEART Pragmatic Clinical Trial Pilot

New & Notable: Honors, Publications, & Collaborations

Congratulations to **Steve Sidney** for being invited to give an Oral Presentation at the 2020 AHA Epi/Lifestyle meeting based on their recent JAMA Cardiology paper, *Association Between Aging of the US Population and Heart Disease Mortality from 2011 to 2017* (JAMA Cardiol. 2019 Oct 30. doi: 10.1001/jamacardio.2019.4187). The paper received nationwide attention, including an article in the Wall Street Journal. KP co-authors included **Alan Go, Marc Jaffe, Matthew Solomon, Andrew Ambrosy, and Jamal Rana**.

We also wanted to recognize **Erica Gunderson** on reaching her 20-year anniversary with KPNC. She has a broad research portfolio related to metabolic and cardiovascular risk in women, with particular interests in gestational diabetes and subsequent maternal and child risks of diabetes mellitus, pre- and peri-partum hypertensive disorders and clinical complications, metabolomics, and the influence of pregnancy itself on long-term cardiovascular disease risk, among others. We are proud of her accomplishments during her tenure at DOR!



Congratulations to **Matthew Solomon** and DOR collaborators for winning the 2019 AHA Scientific Sessions' Early Career Investigator Award for his poster abstract, *Using Natural Language Processing to Accurately Identify Aortic Stenosis in a Large, Integrated Healthcare Delivery System*. The abstract was one of two to have received the highest score among the abstracts accepted as a poster presentation under the Population Science focus submitted by an Early Career investigator.

Kudos to **Yariv Gerber** for winning The American Heart Association's Paul Dudley White International Scholar Award. Their abstract, *Nonalcoholic Fatty Liver Disease and Cognitive Function in Middle-aged Adults: The CARDIA Study*, was the Highest Ranked Abstract from Israel at the 2020 AHA Epi/Lifestyle meeting. KP co-authors included **Jamal Rana** and **Steve Sidney**.

We would also like to recognize the following selected grant recipients:

- **Andrew Ambrosy** - Site PI for an U01 from NHLBI for a multi-institutional project titled, "*TRANSFORM-HF (ToRsemide comparison with furosemide FOR Management of Heart Failure) Study*."
- **Carlos Iribarren** - Site PI for a grant from Genentech for his project on "*Community-based, longitudinal cohort of patients with interstitial lung disease in the Kaiser Permanente Northern California health system*," and a grant from Abbott Laboratories to measure a selected panel of cardiac, metabolic, and cancer biomarkers in blood samples already collected by the MultilethNic study of brEast aRterial calcium gradation and cardioVAscular disease (MINERVA) Study.
- **Erica Gunderson** - Site PI and CARDIA study representative for a R21 from NHLBI for a project on "*Shared antecedents to pre-term birth and cardiovascular disease in women*."
- **Steve Sidney** - Site PI for a R01 from NHLBI for his ancillary CARDIA study on "*Leveraging multi-omics approaches to examine metabolic challenges of obesity in relation to cardiovascular diseases*."
- **Alan Go** - Multiple PI for R01 from NHLBI on "*Atrial Fibrillation in Chronic Kidney Disease: ATRIA-CKD*."

Finally, kudos to the following authors on their recent publications between November 2019 to February 2020:

- **Go AS, Ambrosy AP, Kheder K, Fan D, Sung SH, Inveiss AI, Romo-LeTourneau V, Thomas SM, Koren A, Lo JC**; Kaiser Permanente Cholesterol-Lowering Therapy in High-Risk Adults: Management and Patient Risks (KP CHAMP) Study. [Statin Therapy and Risk of Incident Diabetes Mellitus in Adults With Cardiovascular Risk Factors](#). *Am*



- Freeman JV, **Tabada GH**, Reynolds K, **Sung SH**, Singer DE, Wang PJ, **Liu TI**, Gupta N, Hlatky MA, **Go AS**. Comparison of Long-Term Adverse Outcomes in Patients With Atrial Fibrillation Having Ablation Versus Antiarrhythmic Medications. *Am J Cardiol.* 2020 Feb 15;125(4):553-561. doi: 10.1016/j.amjcard.2019.11.004. PMID: 31843233
- **Rana JS**, **Liu JY**, **Moffet HH**, **Karter AJ**, Nasir K, **Solomon MD**, **Jaffe MG**, **Ambrosy AP**, **Go AS**, **Sidney S**. Risk of atherosclerotic cardiovascular disease by cardiovascular health metric categories in approximately 1 million patients. *Eur J Prev Cardiol.* 2020 Feb 10:2047487320905025 [Epub ahead of print].
- **Izano MA**, **Lo JC**, **Ettinger B**, Ott SM, Li BH, Niu F, Hui RL, **Neugebauer R**, **Adams AL**. Determinants of Oral Bisphosphonate Use Beyond 5 Years. *J Manag Care Spec Pharm.* 2020 Feb;26(2):197-202. doi: 10.18553/jmcp.2020.26.2.197. PMID: 32011964
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- Yano Y, Reis JP, Lewis CE, **Sidney S**, et al. Association of Blood Pressure Patterns in Young Adulthood With Cardiovascular Disease and Mortality in Middle Age. *JAMA Cardiol.* 2020 Jan 22. doi: 10.1001/jamacardio.2019.5682. PMID: 31968050 [Epub ahead of print]
- **Masson R**, **Ambrosy AP**, **Kheder K**, et al. A Novel In-hospital Congestion Score to Risk Stratify Patients Admitted for Worsening Heart Failure (from ASCEND-HF). *J Cardiovasc Transl Res.* 2020 Jan 13. doi: 10.1007/s12265-020-09954-x. PMID: 31933144 [Epub ahead of print]
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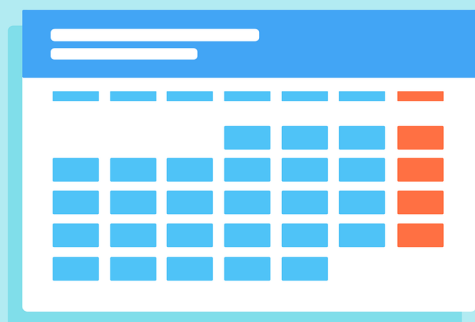
Additional KP Cardiovascular Research Information

BY MATTHEW SOLOMON, MD, PHD

In 2019, the TPMG Cardiac Service Line (CSL) in collaboration with DOR and the Delivery Science and Applied Research ([DARE](#)) and Physician Researcher Programs (PRP) launched the first TPMG CSL research survey and newsletter, the first regional CSL research webinar, and is developing a [cardiovascular research specialty network](#), with the goal of making research collaboration and resources more streamlined for interested clinicians. More to come!

Upcoming Events

A last reminder that the **4th Annual KPNC Regional Cardiovascular Research Symposium** will take place on **Friday, May 1, 2020** at 1950 Franklin St in Oakland! Please use this link: <https://na.eventscloud.com/ehome/516169> to get more details and to register for the event. We look forward to seeing you there!



Get Ready! The 4th KPNC Regional Cardiovascular Research Symposium will be on May 1, 2020!

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Questions? Email Alan Go, MD at Alan.S.Go@kp.org

