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Breaking Down the Criteria for Iron Deficiency in Heart Failure

Dr. Butler:
You're listening to *Heart Matters* on ReachMD. I am Dr. Javed Butler. And joining me today to discuss the criteria for iron deficiency in heart failure are Drs. John Cleland and Fraser Graham. Dr. Cleland is a professor at the Institute of Health and Wellbeing and Director of the Robertson Centre for Biostatistics at the University of Glasgow.

John, welcome to the program.

Dr. Cleland:
Thank you.

Dr. Butler:
And Dr. Graham is an honorary clinical lecturer at the Institute of Health and Wellbeing with Dr. Cleland, who works alongside with him in the Robertson Centre for Biostatistics. Dr. Graham, glad to have you with us as well.

Dr. Graham:
Glad to be here. Thank you.

Dr. Butler:
So, John, can you start us off in terms of just the basic epidemiology prevalence of iron deficiency in patients with heart failure?

Dr. Cleland:
It's an interesting question. Of course, what we need is a gold standard test and that proves a bit problematic. Clearly, the gold standard is looking at bone marrow aspiration, how much iron is in the bone marrow, but that's quite a big undertaking both for us and our patients, so what we're looking for are blood markers. The simplest blood marker, of course, is hemoglobin, and it's said that there's a lot of iron deficiency and anemia. Well, they're close allies, but many patients have iron deficiency, even if they don't have anemia. I think that is a little bit superficial. If you look at the studies that we've done of intravenous iron, they've all excluded people with really normal hemoglobins, so we have included only patients who are anemic or who have a low normal hemoglobin.

We must remember that the World Health Organization definition of anemia is really quite extreme. You have to have a very low hemoglobin, below 13 for a man, below 12 for a woman, before they count that as abnormal, but a truly normal hemoglobin is 1 or 2 grams above the WHO definition. So it may be that anemia itself is quite a useful marker of iron deficiency. The problem with serum ferritin is in the heart failure patients, it's more a marker of inflammation than of iron deficiency, and that same inflammation is also leading to impaired iron absorption. So serum ferritin really is moving in 2 directions. One is going up with the inflammation. The other one is going down with the iron deficiency. And basically, it's very difficult to interpret serum ferritin in heart failure. I think serum iron and TSAT may be better markers.

Dr. Butler:
That's very interesting the way you talked about anemia. Let me come back to you about the definitions in a minute. But, Dr. Graham, let me come to you. Can you tell us what's the issue with iron deficiency in patients with heart failure? Is it outcomes? Is it symptoms?

Dr. Graham:
So what we know is that iron deficiency in heart failure is important because it's so common. At least half the patients with chronic heart failure have evidence of iron deficiency on blood tests, but it's also been shown to be associated with worsening symptoms, worsening exercise capacity, and quality of life in patients with heart failure. And what we know is that the majority of research probably shows iron deficiency is associated with worse outcomes, but again, that's really dependent upon how we define iron deficiency. With respect to anemia, most of the associations with iron deficiency tend to be irrespective of your hemoglobin concentration, but outcomes and symptoms are probably worse if you're also anemic, which reflects a more severe iron deficiency most likely.

Dr. Butler:
For those just joining us, you're listening to *Heart Matters* on ReachMD. I am Dr. Javed Butler, and I'm speaking with Drs. John Cleland and Fraser Graham about the criteria for iron deficiency in heart failure.

So, John, let me get back to you. So you have raised some concerns about both the level of hemoglobin for the diagnosis of anemia and that how ferritin is sort of going up and going down, and there are these sort of bidirectional poles in a proinflammatory disease like heart failure. So what has been the traditional definition for iron deficiency in heart failure? And how do you think we should be thinking about defining iron deficiency?

Dr. Cleland:
Okay. So for iron deficiency, the classical one is taken from the intravenous trials of ferric carboxymaltose, which have generally used a serum ferritin less than 100 or if the serum ferritin is between 1 and 300, a TSAT less than 20%. That actually is not strongly related to patient outcomes. And of course you might say, "Well, that's irrelevant. What we're looking for is the correct set of criteria for iron deficiency that identify patient benefit from giving iron supplements," because ultimately, that's what we want to use iron markers not as a prognostic tool but rather to identify management decisions—do I give this patient intravenous iron or not, and I think the jury is out on that.

The earlier studies of the FAIR-HF studies suggested that TSAT was a much better marker of the response to intravenous iron than serum ferritin. On the other hand, the more recent AFFIRM-AHF trial, it's a bit harder to see a difference between the ferritin and TSAT as a marker, so I think the jury is out on which marker is the best marker of response to intravenous iron. But when it comes to prognosis, I think there's no doubt about what's going on. All the studies show that the higher your serum ferritin, the worse your outcome, so actually a low serum ferritin is associated with a good outcome, so that would be a bit weird if we think that iron deficiency is a bad thing. Serum ferritin really doesn't help you. On the other hand, if we're just thinking about mortality, the TSAT is strongly linearly and vastly related to prognosis. The lower your TSAT the worse your outcome. So serum iron itself might be the best marker of iron deficiency in heart failure. It's just that we haven't used this marker in the clinical trials to find out whether it really indicates a population who gets special benefit from intravenous iron.

Dr. Butler:
Would you define a threshold?

Dr. Graham:
So that leads us kind of nicely to discuss about our study, which we used a threshold of serum iron of less than or equal to 13 µmol/L, and that was really informed from a well-performed bone marrow study correlating serum markers with bone marrow iron staining in patients with heart failure with reduced ejection fraction. So we took this threshold forward and sought to validate it prognostically in our group of patients.

Dr. Butler:
So this treatment of iron deficiency makes a difference. Are there any data to suggest that if you were to replete patients with iron that their outcomes or symptoms get better?

Dr. Graham:
There's obviously one large outcome trial, the AFFIRM-AHF trial, in hospitalized patients with heart failure with an LV ejection fraction of less than 30%. And while they just missed their combined endpoint of recurrent hospitalizations for heart failure or cardiovascular mortality, there was a very strong signal that intravenous iron did reduce hospitalizations for heart failure—and actually, the COVID-19 sensitivity analysis because recruitment in the trial and the trial running was [occurring during the first wave of the pandemic, and they found that if they excluded those patients and recruited after the pandemic began, then intravenous iron did successfully reduce hospitalizations for heart failure and cardiovascular mortality.

Dr. Cleland:
Yeah, I think the trial was pretty neutral on cardiovascular mortality, so I think it's important to make that distinction. In a sense, the heart failure hospitalizations are another aspect of the symptomatic wellbeing of the patient and stability, but so far we're not seeing that pushing through to a reduction in mortality

But the important thing is if we're not getting the definition of iron deficiency right and we are including people who are already iron replete in these studies, then it may dilute the benefit, so this is I think why we do need to prospectively look at the way we're going to analyze these studies just in case the results are uncertain. And if we have prospectively defined iron deficiency and we have prespecified analysis that would give far more weight to any subgroup of patients who have a particular benefit from intravenous iron.

Dr. Butler:
John, you made a very sort of cogent argument about the issue of definition. So can you leave our listeners with some practical management tips today that if they were to treat their heart failure patients with iron deficiency—since all the trials were done using the traditional definition, but there is good reason to think about it differently—what should the clinicians do today?

Dr. Cleland:
Trying to minimize confusion, I would abandon serum ferritin. I think it's just not helpful. I would go for TSAT. I think a TSAT less than 20% is pretty useful. The bottom line is that I think maybe in 5 years' time we'll be using serum iron itself as the marker for iron deficiency. The serum ferritin is terribly confounded, TSAT is slightly confounded, and serum iron seems to be the truth.

Dr. Butler:
I very much appreciate all your insights on iron deficiency in our heart failure patients, lots of epidemiologic, biologic, and clinical insights. But that's about all the time we have today, so we will have to bring it to a close. I want to thank my guests for joining me today to share their expertise on this important topic. Dr. Cleland, it was a pleasure.

Dr. Cleland:
My pleasure too.

Dr. Butler:
And, Dr. Graham, same to you.

Dr. Graham:
Yes, thank you very much for the invitation. It was great speaking to you.

Dr. Butler:
For ReachMD, I am Dr. Javed Butler. To access this and other episodes in our series, visit ReachMD.com/HeartMatters, where you can Be Part of the Knowledge. Thanks for listening.