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A Clinical Guide to the Role of Iron in HF Pathophysiology

Announcer:
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Dr. Mentz:
It is well known that about half of patients with heart failure are iron deficient, and iron deficiency is associated with poor exercise capacity, poor quality of life, and increased morbidity and mortality. And additionally, hospitalized patients with acute heart failure often have iron deficiency independent of anemia. So with that in mind, should we be focusing on treating iron deficiency in our patients who are hospitalized with heart failure?

This is CME on ReachMD, and I'm Dr. Robert Mentz.

Dr. van der Meer:
And I'm Dr. Peter van der Meer from the Netherlands.

Dr. Mentz:
Great, so let's get right to it, Peter. How does iron deficiency relate to heart failure, and how does it impact patient outcomes?

Dr. van der Meer:
Well, Rob, thanks for the introduction. I think you phrased it quite well. We see iron deficiency very commonly in patients with heart failure. So if we look into patients with chronic heart failure, around 50% of the patients are diagnosed with iron deficiency. If we move to the sicker patients who just have been hospitalized for acute heart failure, rates go up to 60% to 70% of the patients. So it's very common. And we know from several studies that it's not only very common, but also associated with poor exercise tolerance. So lower 6-minute walk test, lower peak VO_2, and that's independent of anemia. I think that's very important to stress out that iron deficiency can be present even if anemia is absent. So iron deficiency is common. It's associated with a poor exercise tolerance, but iron deficiency is also associated with a poor outcome. Patients with iron deficiency are more often hospitalized, have a higher mortality rate, so yes, it's common and a severe condition.

Dr. Mentz:
Really an excellent summary. I think you've nicely pulled out the key points around iron deficiency being so common, both in the acute and the chronic settings. That it's independent of anemia, really important point. And then this association with worse quality of life, worse functional capacity, and worse outcomes. Maybe for our listeners, if you could quickly summarize how do we diagnose iron deficiency as well.

Dr. van der Meer:
Yeah, that's a good point. I think there are many definitions. But if we stick to the definitions which have been used in the clinical trials, and I think that's important to stress out, the definition has two parameters which you need to measure. So you need to measure ferritin

and you need to measure transferrin saturation [TSAT]. So transferrin saturation is the percentage of transferrin which is saturated with iron. So you can talk about iron deficiency when ferritin is below 100.

But because ferritin is also an acute phase protein, it might be elevated in inflammatory conditions like heart failure. So even when ferritin levels are above 100, so between 100 and 300, iron deficiency can be present, but you need an additional marker, and your transferrin saturation needs to be below 20%.

So two ways: either your ferritin is below 100, yes, you're iron deficient, or if your ferritin is between 100 and 300 and your TSAT is less than 20%, they are also patients who are also considered iron deficient. And these are the definitions which have been used in the majority of the trials.

Announcer:
Iron is crucial to the transport of oxygen by hemoglobin. Iron is also essential for mitochondrial energy production and cellular oxygen storage. With iron deficiency, hemoglobin levels can be normal or diminish causing anemia and loss of oxygen delivery. It is hypothesized that iron deficiency also causes declines in energy production in cells with high energy demands, such as cardiac and skeletal myocytes. Both iron deficiency and iron deficiency anemia can contribute to reductions in heart function and exercise capacity.

Dr. Mentz:
So, Peter, maybe a specific question related to the underlying mechanisms and pathophysiology. For our listeners, could you share some of your perspectives on why do we need to even be thinking about iron deficiency? And how does this translate on a mechanistic level for our patients?

Dr. van der Meer:
That's an excellent question and also a quite difficult question. So traditionally, it has been thought that the effects of iron are the effects on the hematopoiesis. But I think we learned from many of the intervention trials that IV iron was as effective in patients who were anemic versus nonanemic patients. So also in nonanemic patients, IV iron was highly effective. So the effects of iron should go beyond the hematopoietic effects.

And it makes sense because iron is needed in many of the complexes which build up an H+ gradient in order to create ATP. And from a smaller in vitro study, we have been shown that if cardiomyocytes are being made iron deficient, their mitochondrial function goes down and their contractile function also decreases. And when we gave iron back to these cells, mitochondrial function was restored and contractility improved. So it clearly goes beyond a hematopoietic effect. And there are direct effects of iron on mitochondrial function. And perhaps there are more which we still don't know.

Dr. Mentz:
Really a beautiful summary. Thanks so much for going through that.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Robert Mentz, and here with me today is Dr. Peter van der Meer. We're discussing the impact of iron deficiency and heart failure with reduced ejection fraction and the evidence for treatment with IV iron repletion therapy.

So maybe let's transition a little bit now. So, Peter, it seems that iron deficiency has really moved from just being known as a marker of disease outcome into a treatment target. And now maybe you could go through what really is the clinical evidence for iron repletion therapy in patients with heart failure who are iron deficient.

Dr. van der Meer:
Yeah, excellent question, Rob. So if we go back 10, 12 years, the first trial with IV iron in patients with iron deficiency and heart failure was the FAIR-HF study. It was a study with soft endpoints, so patient global assessment, so how was the patient feeling. And also one of the endpoints was the functional class and New York Heart Association functional class. And in this first study on soft endpoints, we saw that patients who were treated with IV iron felt better, and also their functional class went down.

This first trial, the FAIR-HF, was followed by the CONFIRM-HF, which had 6-minute walk test as a primary outcome. And in that trial, it was observed that patients who were randomized to IV iron had a better exercise capacity so could walk more meters in 6 minutes.

Then the third study was the EFFECT-HF study, which was a study with peak VO_2 as the primary endpoint. And in patients who were treated with IV iron, peak VO_2 remained stable during a follow-up period of 6 months, whereas in patients randomized to standard of care, peak VO_2 went down. So these 3 trials are the cornerstone of the effect of IV iron on exercise capacity and patient global assessment, so how the patient was actually feeling.

Dr. Mentz:

So really a nice summary through some of the foundational work that led to additional follow-up studies then. So maybe if you could give us some of the more recent exciting data from the AFFIRM-AHF trial.

Dr. van der Meer:
Yeah, sure. So after these 3 trials on soft endpoints, several large trials have been designed, and the results of the AFFIRM study have been recently been published. In that trial the role of IV iron was assessed on hard endpoints, so cardiovascular mortality and repeated heart failure hospitalizations in patients with recompensated heart failure. So patients were ineligible for the AFFIRM study if they were admitted for acute heart failure when they were stabilized, and just at the moment when they were being sent home, they were randomized to either placebo or IV iron.

And this is really the first trial with around 1,100 patients who assessed the effects of IV iron on harder endpoints. And the AFFIRM trial showed that IV iron reduced heart failure hospitalization rates. And we really need to wait for the follow-up, for the further studies like the study you're executing, the HEART-FID, the largest trial in more chronic heart failure setting, and also the IRONMAN trial which is currently executed in the UK.

Dr. Mentz:
Peter, really a nice job taking us through the evolving data and some of the exciting upcoming studies as well. But now patients and family members may often ask, well, what about oral iron? Would that be sufficient? Do I really need to be thinking about IV iron?

Dr. van der Meer:
That's a good question. And the answer is it has been studied in a clinical trial. So at the same time when the EFFECT-HF study was executed in Europe with the primary outcome peak VO_2, the IRONOUT study was executed in the US. And in that trial, patients with iron deficiency and heart failure were randomized to oral iron or placebo, whereas the EFFECT-HF study with IV iron showed stabilization of the peak VO_2 in the IV iron group where there was a decrease in peak VO_2 randomized to the standard of care. So there was a significant difference in peak VO_2 after 6 months. No differences in peak VO_2 were observed in the IRONOUT study. So oral iron did not have an effect on peak VO_2 compared to placebo.

But I think one of the key points from the IRONOUT study is that IV iron parameters like ferritin and TSAT significantly went up in a short period of time, whereas with oral iron, only a marginal increase in TSAT and ferritin has been observed. So that has probably to do with the uptake of oral iron.

Dr. Mentz:
So maybe let's transition a little bit in the last couple moments of our time. So we've gone through the data, we've talked about how prevalent iron deficiency is, that we need to think about it regardless of anemia status in the inpatient as well as the outpatient setting. But now as we see these evolving data, how do we need to approach long-term care for our patients?

Dr. van der Meer:
Yeah, that's a good question. Well, before really talking about long-term care, it starts with the patient you're seeing in your outpatient clinic or in a patient who just has been hospitalized with acute heart failure. Before you think about treating it, the first thing you should do is measure the iron parameter, so measure ferritin, measure the transferrin saturation, and then you can assess whether the patient is iron deficient. And now we have not only data on surrogate endpoints like exercise capacity, quality of life – I think it's also very important to note that quality of life increases when patients with iron deficiency are treated with IV iron. And from the AFFIRM, we know that in patients who have been hospitalized with acute heart failure but recompensated, that they have a lower rehospitalization rate if they have been treated with IV iron. So I think it starts with measuring the iron parameters, treating it, and then – very good point, like, when should you measure again for iron status?

From the trials, patients were followed – in the AFFIRM, patients got 2 shots of IV iron at baseline after 6 weeks. And then after 6 months, iron status was measured again. And if they were persistently iron deficient, they were given another treatment of IV iron, but the majority of the patients were fine with 2 shots of iron at baseline and 6 weeks. And it did not need to be repeated within the first 6 months. So it might be reasonable to measure it again after 6 months or after 1 year after you started treatment, but I think we do not have data yet to support how often it should be measured. But it's a Class 1C recommendation to measure it based on your outpatient clinic and in patients also hospitalized with acute heart failure.

Dr. Mentz:
Great, so a nice summary of the evolving data in this space and how we really integrate this into routine clinical practice. And certainly, as you're noting we'll garner additional insights from the HEART-FID program. So this will be 3,000 patients recruited worldwide and it's placebo controlled, and it's re-dosing every 6 months. So based on iron indices and hemoglobin levels at follow-up, it'll be the cadence of every 6 months getting IV iron or placebo. And then once patients are repleted, they would then cross over in terms of therapy to

placebo. So really a nice strategy that will better understand over time the long-term needs, recurrent needs for infusions in these patients to really optimize clinical outcomes.

Well, this has certainly been a fascinating conversation. But before we wrap up, Dr. van der Meer, could you share just a couple of your take-home messages for our audience?

Dr. van der Meer:
I think the most important point is to understand that iron deficiency is a very common comorbidity—up to 50% to 70% of the patients with heart failure. Two, you need to measure it. Also, in patients who are nonanemic, measure ferritin, measure transferrin saturation. You do need both parameters to make the appropriate conclusion whether a patient is iron deficient or not. And three, we have so much evidence now that the effect of IV iron on exercise capacity, on quality of life, but also on recurrent heart failure hospitalization, I think it's time to start treating patients.

Dr. Mentz:
Really a nice summary that takes us from the earlier data around some of these surrogate measures now to incorporating this into routine practice.

So unfortunately, that's all the time we have for today. So I want to thank our audience for listening in and thank you, Dr. Peter van der Meer, for joining me and for sharing your valuable insights. It was great speaking with you today, and I look forward to seeing you soon.

Dr. van der Meer:
Thank you very much, Rob. I really enjoyed the discussion with you.

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