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What Are We Missing? Iron Deficiency in Heart Failure

Announcer:

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Dr. Mentz:

Iron deficiency is common in patients with heart failure. However, it remains underdiagnosed and undertreated. Iron deficiency is commonly overlooked in our nonanemic patients. Let me say that again, this is so important. It's overlooked in our nonanemic patients, and this can have a significant impact on outcomes and quality of life, especially for patients who also have diabetes. So how can we better recognize and treat iron deficiency in our patients 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.

Dr. Mentz:

So Peter, let's discuss a patient case that we unfortunately see quite often, and I'll be relying on your expertise as part of a cardiology consult. I have a 73-year-old woman, with a history of heart failure with reduced ejection fraction, or HFrEF, and diabetes. She was recently discharged from the hospital, after an NYHA class IV acute decompensation. She required inotropic support during this. She was decongested, and there was up-titration for pharmacotherapies including ACE [angiotensin-converting enzyme] inhibitors and beta-blockers. But this was limited, because of symptomatic hypotension, and after initial improvement to NYHA class II symptoms, unfortunately her symptoms deteriorated to class III, and she was readmitted. During this evaluation, test results revealed a hemoglobin of 13.5 g/dL, serum ferritin of 150 µg/L, a TSAT of 11%, and negative fecal occult blood tests.

What do you think are some of the likely causes of this patient's heart failure? And maybe you could comment a little bit on the comorbidity burden?

Dr. van der Meer:

Well, Rob, that's a very challenging case. Especially like the recent decompensation and again very symptomatic with functional class of class III. 73-year-old lady, so if we talk about the comorbidities, she has diabetes, of course, which is a risk factor really leading to higher morbidity and mortality, and also like you mentioned, she has iron deficiency. Although she's non-anemic – her hemoglobin level is 13.5, you said, but clearly her transferrin saturation is too low, so even though she does not have anemia, she does have iron deficiency, and these comorbidities probably also have led to her symptoms and perhaps her readmission again.

Dr. Mentz:

Could you maybe talk a little bit about your approach, then. You're now seeing her back in clinic. You're noting the iron deficiency. What are the things you're thinking about in terms of evaluating for iron deficiency? How do we do that in patients with heart failure?

Dr. van der Meer:

So it's a good point. Because heart failure is a chronic, inflammatory disease, so the markers you're using for defining iron deficiency are 2. So you need ferritin, but also the transferrin saturation. So which part of the transferrin – the transferrin which transports the iron throughout the body – which of that proportion of transferrin is saturated with iron? And because ferritin is an acute phase protein, so ferritin goes up in inflammatory conditions. Since heart failure is a chronic inflammatory condition, your ferritin are falsely elevated, so it could mask the presence of iron deficiency. So that's why the definition has actually 2 parts. So if your ferritin, in a patient with heart failure, is below 100, you're done. Patient does have iron deficiency. But if your ferritin is between 100 and 300, you need additional evidence, because it could be falsely elevated due to the heart failure condition. So then you add the transferrin saturation, and when the transferrin saturation is below 20, also then the patient does have iron deficiency. I think that's exactly what we see in your case. The ferritin is 150. The transferrin saturation is too low; it's below 20.

Dr. Mentz:

Maybe share with us a little bit, help us better understand, how common is iron deficiency in heart failure? And, you know, as we're thinking of helping take care of our patients, how does it impact their quality of life and clinical outcomes?

Dr. van der Meer:

Excellent question. So iron deficiency, it depends a bit on what kind of patient population you're studying.

So if you're studying stable patients, I think in HFrEF more or less 50% of the patients do have iron deficiency. But if you go into the sicker population, for example, this patient with acute decompensated heart failure, it goes up to two-thirds to three-quarters of the patients being iron deficient. Females are more often iron deficient than males. Also reduced iron intake is a risk factor. Decompensation is a risk factor. Perhaps bowel edema leads to a reduced uptake of iron. So a lot of factors play a role in the etiology of iron deficiency in patients with heart failure. And the patients who do have iron deficiency, they have a clearly higher morbidity and mortality rate, so they are more often rehospitalized for heart failure – same as your patient – and also mortality is substantially higher in these patients, and quality of life is lower.

Dr. Mentz:

You've walked us through how we diagnose this, the impact on quality of life and outcomes.

Now let's talk how do we treat it? Can we use oral iron? And help us understand the IV iron data that we have from trials.

Dr. van der Meer:

Yeah, so it's a good point. So there are 2 options. So there is intravenous iron and there is oral iron. Chronologically, the IV iron trials were first in heart failure. So there were 3 trials – the FAIR-HF, the CONFIRM, and the EFFECT-HF – and all 3 trials looked at soft endpoints, and they all used intravenous iron. And what they found is that when patients with iron deficiency and HFrEF, when iron deficiency was treated, quality of life was higher, the exercise capacity increased, and there were less symptoms. So and that's also why, for example, the 2016 guidelines from the ESC already mention the use of IV iron to improve quality of life and to improve exercise tolerance. And at the same time, when these 3 trials had been done, the question was, can we also use a relatively simple approach, just a pill? Can we give oral iron?

And that was the IRONOUT trial. And the IRONOUT trial, they tested oral iron versus placebo, and they had as a primary outcome, peak VO_2 . And also at the same time, the EFFECT-HF study was done with IV iron, and they also had peak VO_2 as their endpoint. The EFFECT-HF study – so the IV iron study – they showed that if you give IV iron you can prevent a decrease in your peak VO_2 over time, so IV iron was effective in – there was a significant difference between patients getting IV iron versus not getting IV iron. They had higher peak VO_2 . So the same study, at the same time, was executed in the US, the IRONOUT study, where they studied oral iron. Same outcome, peak VO_2 primary outcome. And what they saw is that oral iron only marginally increased ferritin and TSAT, and there was no effect on peak VO_2 . So that led to the conclusion, I think, that oral iron often has side effects, not well tolerated, but also it did not really increase your iron parameters.

Dr. Mentz:

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 challenges we see with iron deficiency in patients with HFrEF and diabetes, plus screening and evidence-based approaches to care.

Maybe walk us through, now, the AFFIRM-AHF trial results, how that has really impacted your practice, and then maybe the recent guideline update.

Dr. van der Meer:

So with the AFFIRM, we wanted to study what are the effects of IV iron on hard endpoints. So heart failure rehospitalization and cardiovascular mortality. So 1,100 patients were recruited, all patients who were admitted with acute heart failure. And when they were recompensated, just before they were being sent home, they were randomized to receive either the IV iron or placebo. The follow-up was exactly 1 year. And in the AFFIRM, we found that giving IV iron reduced rehospitalization for heart failure. There was no effect on cardiovascular mortality, but there was a clear signal in lower rehospitalization rates in the patients treated with IV iron. And also, in further studies, quality of life was higher in the patients who were treated with IV iron, but that's, of course, confirmatory because that's what we already knew, also, from the other 3 studies, who looked more at also at the softer endpoints.

So the AFFIRM really changed how to look at iron deficiency. It's not only that you improve quality of life and exercise capacity, but you also do something on harder endpoints, like rehospitalization. So I think that's a very important study, and it also made changes in the guidelines. It's of course, one study, so it got a 2A recommendation, level of evidence B, that IV iron in patients who have been hospitalized for acute heart failure, that the administration of IV iron reduces the rate of rehospitalization.

Dr. Mentz:

Wonderful summary of the data, the guidelines. Now let's take it back to our patient. So we've diagnosed this patient's iron deficiency. We've identified this as an important contributing factor, likely, to their exacerbation. So what are your recommendations for treatment and management for our patient?

Dr. van der Meer:

Of course, we should never forget that the foundational 4 – ACE inhibitor, or sacubitril/valsartan, of course; the beta-blocker; the MRA; and the SGLT2 inhibitors. They are all class 1A recommendations for patients with HFrEF. So clearly, that's foundational therapy. But then it's very important to check for the comorbidities, and for example, the iron deficiency is important here because she has a lot of symptoms. She has clearly iron deficiency, so these are patients who would benefit, if we look at the trials, from treating the comorbidity. So I would stick also to the trials which we have done. So this is a decompensated patient, admitted to the hospital. I would just check before she goes home, does she have iron deficiency? Well, she does have iron deficiency, and I would give 1 g of IV iron.

Dr. Mentz:

Wonderful. So, Peter, we've discussed how to approach the care of this patient in the inpatient setting. We've talked through some about this transition to the outpatient care as well, but let's maybe finish with some of your recommendations on how we would follow this patient. How would we maintain continuity of care? What would their trajectory look like from here?

Dr. van der Meer:

Yeah, so I think it depends on how you set it up in your hospital, but if we stick to the trial data, then all patients in the AFFIRM, they were getting a second shot of IV iron 6 weeks after their first dose irrespective of their iron levels, because I think it's very important that – do not measure ferritin and transferrin saturation too early after you've administrated IV iron. Because these levels might be very high and sometimes it leads to a lot of noise, like, oh, shoot, is it iron overload? It's not. But just don't check early after administration. So after 6 weeks in the trial, the majority of the patients got a second shot of IV iron, and then they were followed at 12 and 24 weeks, and another time at 52 weeks.

So you need to recheck iron deficiency, and I think in your case I fully agree to do a fecal occult blood test to see whether there are other etiologies, especially if the patient is also anemic. Like, if it's a severe anemia and iron deficiency, always think, could there be a gastrointestinal problem why the patient is iron deficient. So really think about it, and I think that's very nice that you did that in your patient. And then, well, check them regularly, also, for the comorbidities.

Dr. Mentz:

Wonderful. Well, this has certainly been just an excellent conversation, and before we wrap up, Peter, so maybe you could summarize for us some of your key take-home messages for our audience.

Dr. van der Meer:

Well, I think, if you don't look for comorbidities, you don't find them. So I think it's important that, especially in the patient you presented, with a lot of symptoms and a recent decompensation, a hospitalization, check for the comorbidities. So if you don't measure the iron or the transferrin saturation, the ferritin, you do not find the iron deficiency. So I think that would be one important take-home message. And two is, don't stop with the hemoglobin. Hemoglobin level is normal, oh, then there is no iron deficiency. That is not true. So if we look at, let's say, 50% of the patients in a stable condition were iron deficient. Only one-third of this half have anemia. So the large proportion of the patients with iron deficiency are non-anemic, so don't be satisfied with only a hemoglobin. You need to do the iron checkup – ferritin, transferrin saturation. And when you find it, well, treatment really improves quality of life, improves exercise tolerance, and reduces the rate of rehospitalization. So these would be my 3 take-home messages, Rob.

Dr. Mentz:

Wonderful. So I think, really, a nice summary as we walk through how common iron deficiency is. We've got to disconnect this from anemia. It's so common, even in those patients who are not anemic. We described the impact on quality of life and the rehospitalizations we see in these patients who are iron deficient. We know that oral iron is going to be insufficient. We have to use IV iron. We have guideline updates to describe, now, this important benefit around clinical outcomes and quality of life. And we need to follow our patients and understand whether they need repeat infusions of IV iron and look at the total burden of our patients. And especially in our case, as we talked about, diabetes as well, that this is very common in patients with 1 comorbidity, that you see 2, 3, and 4 as well.

So this has just been a phenomenal discussion. Thank you all for joining us today. Appreciate you tuning in. You're listening to CME on ReachMD, and I'm Dr. Robert Mentz, and here with me today is Dr. Peter van der Meer. We're discussing the challenges we see with iron deficiency in patients with HFrEF and diabetes, plus screening and evidence-based approaches to care. Thanks for joining.

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