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Practical Strategies for Optimizing Outcomes in Patients with Iron Deficiency and Heart Failure

Announcer:
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Dr. Mentz:
Despite clinical practice guidelines, healthcare providers face challenges in the management of iron deficiency in patients with heart failure. Will new evidence improve best practices?

Join us as we review iron deficiency diagnosis, evaluate guideline-based management, interpret clinical trial data, and thus, discuss how to implement patient centered treatment approaches. This is CME on ReachMD, and I’m Dr. Robert Mentz.

Dr. Ponikowski:
And I'm Dr. Piotr Ponikowski.

Dr. Mentz:
So, Dr. Ponikowski, welcome. Let's begin with the review of how to diagnose heart failure in iron deficiency. Piotr, what are the best practices around diagnosis?

Dr. Ponikowski:
So, first of all, awareness, recognition. Yes, my patient may have iron deficiency. Number one. Then, what kind of assessment? Very straightforward, just serum ferritin level and transferrin saturation and hemoglobin. We don't want to get into the details, but intuitively, many physicians link iron deficiency with anemia, which is not quite correct. Several of us, as we all know. And we, again, kept saying this, not very many people recognize this. So, many patients tend to have a normal hemoglobin level and still iron deficiency. So, number two.

Number three. Ferritin level below 100 or transferrin saturation below 20%. There is some debate, discussion, which one would be more important, less important. But if we consider what we applied for many years in clinical trials, if you have serum ferritin level below 100 micrograms per liter, if you have transferrin saturation below 20%, consider your patient iron deficient. And then, the first next step would be how to intervene, if necessary. I would add on the top of it, if you have also anemia, you follow-up your patients for secondary diagnosis of anemia because it may be simply malignancy, chronic inflammatory diseases. And I'm sure that we will be discussing how now to implement this diagnosis into clinical practice regarding treatment.

Dr. Mentz:
Really nice summary. So, as we think through it, we need to first, have iron deficiency top of mind in patients with heart failure regardless of anemia status. And then, it’s ferritin less than 100, or 100 to 300 with a TSAT less than 20.

Now, Piotr, could you talk through, a little bit, about the timing of diagnosis? So, as we think, do we need to wait and make sure they're on optimal doses of GDMT? What are the considerations around timing of diagnosis and treatment?

Dr. Ponikowski:
Well, great question. We also take for granted that if the patient is optimally treated with four pillars, enough. No. The sooner you diagnose, the sooner you think that my patient who is symptomatic may also have iron deficiency, the better. The sooner you establish the diagnosis, the better. The sooner you initiate the therapy, the better. So, there are two different pathways not interfering. So, think of diagnosis and treatment as soon as you have your patient either in your ambulatory circumstances, or in the hospital.

Dr. Mentz:
So, really underscoring, let's not wait. We need to look for iron deficiency and treat early.

Dr. Ponikowski:
Robert, can you, once we already have this diagnosis kept in mind, what about the current guideline recommendations for the management of iron deficiency?

Dr. Mentz:
So, let's summarize some of the key guideline recommendations from the ACC, AHA and HFSA first, to start.

We've got a Class 1 recommendation in patients with heart failure to check for iron deficiency. We send the ferritin, the TSAT. We need to look for iron deficiency.

And then, in terms of the ACC/AHA/HFSA recommendations around management in patients with heart failure and iron deficiency, we have a class one recommendation to use intravenous iron to improve functional status and quality of life. So, really key considerations around a recommendation for IV iron in heart failure.

In the ESC guidelines, we have several important recommendations as well. We have a Class 1 recommendation, as noted, around functional status and quality of life, and then the ESC also give a Class 2A recommendation for heart failure hospitalization reduction in HFrEF and mildly reduced ejection fraction. So, that is that Class 2A recommendation in the ESC guidelines around heart failure hospitalization reduction.

Dr. Ponikowski:
So, very high recommendation from both ESC and American Heart Association.

Dr. Mentz:
That's right, yes.

Dr. Ponikowski:
Just to make sure, is this applied into clinical practice? In Europe, I'm sorry to say, it's not that widely recognized and implemented. What about America?

Dr. Mentz:
I think there are still certain areas where there's an underappreciation of how common it is to have iron deficiency. We're seeing increasingly that in the hospital, clinicians will check for iron deficiency, but there's still a huge gap around providing IV iron in the hospital. And then on the outpatient setting, even checking iron indices. And I think highlighting that we need to follow their renal function and potassium, we need to get labs while they're on RAS inhibitors. Let’s add iron indices as well.

Dr. Ponikowski:
So, it is essential as well to interpret correctly all the data from the clinical trials highlighting the efficacy, highlighting the safety of, as you correctly said, intravenous iron for correction of iron deficiency in heart failure. Could you give me the insight from new publications?

Dr. Mentz:

So, to remind our listeners, we have the earlier trials, FAIR-HF, CONFIRM-HF, clearly showing that IV iron improves functional status, quality of life for our patients. And now, we've had multiple larger clinical outcomes trials with AFFIRM-AHF in the in-hospital setting, IV iron showing – while missing that statistical significance – showing us that there's a clinical benefit around heart failure hospitalization reduction in a trial impacted by COVID, that you and colleagues nicely led. And a follow-up study with a different intravenous iron compound, the IRONMAN trial, that was looking at ferric derisomaltose, looking at a repletion strategy compared to usual care, showed a similar point estimate in terms of reduction in cardiovascular death and total heart failure hospitalization.

And then more recently, we had presented the HEART-FID trial that we worked on together, showing that while we narrowly missed statistical significance, there was what we think is a clinically relevant reduction in clinical events and a modest improvement in that setting in terms of 6-minute walk distance.

And we'll have exciting data presented at this very meeting from the FAIR-HF2 trial, looking at a follow up study, not just at an iron repletion, but actually, a supplementation strategy in these patients, in an important meta-analysis that was pre specified. If you want to, share a little bit of some of the insights that you and colleagues found in that work.

Dr. Ponikowski:
Well, indeed. As you remember, two years ago we published the meta-analysis based on individual patient's data from major clinical trials, highlighting very clearly that the benefit is there. And now we have the meta-analysis Stefan Anker will be discussing tomorrow, but to make a long story short, everything we found in the previous meta-analysis is confirmed in this one. There is a benefit. There is a benefit regarding reduction of cardiovascular hospitalization once we are treating our patients with iron deficiency with IV iron. We have this heart failure hospitalization, recurrent heart failure hospitalization reduction.

Very importantly, there is no signal regarding all-cause mortality in a bad direction. We even have a tendency for reduction.

Maybe here I mentioned, very important analysis from IRONMAN which was just recently published by John Cleland group in *European Journal of Heart Failure,* showing that the safety issues some people raise about potential infection, increased risk of infection in patients being treated with IV iron, is no longer there. IRONMAN study showed very clearly that there was even a reduction in the risk of hospitalization related to infection.

So, totality of the data, with thousands of patients now telling us, based on this meta-analysis of FAIR-HF2 trial, that yes, this is a beneficial therapy regarding heart cardiovascular hospital admission once we give IV iron to our patients.

Dr. Mentz:
So, now we have this meta-analysis with more than 7,000 patients, multiple different IV iron formulations, really clear around safety. The ease of use as we gain clinical experience with this, and now we know we can help our patients feel and function better and that, as we look at the totality of evidence, there's a reduction in heart failure hospitalizations and a suggestion of a benefit around cardiovascular death, as we look at all of these together.

Dr. Ponikowski:
Yeah.

Dr. Mentz:
Piotr, can you give us a summary of the data being presented here, maybe a little bit of a deeper dive into FAIR-HF2? How was the trial set up? How does it build upon this earlier experience? And maybe now the hindsight as you look at some of the endpoint considerations.

Dr. Ponikowski:
At ACC this year, there will be a FAIR-HF2 trial presented in summary. The same approach for diagnosis, as we discussed. Patients with heart failure and mildly reduced ejection fraction, so ejection fraction below 50%. And the concept which was a little bit different. So, replete iron with up to 2 grams at the first instance, and then keep repeating it. Keep giving IV iron 500 milligrams every 4 months during the follow-up. Only if patients tended to have hemoglobin above 16 and ferritin above 800 micrograms per liter, they were disqualified of this repeating dosing.

So, to make a long story short, 1,100 patients, half/half placebo and ferric carboxymaltose. Thirty percent, one-third, women, NYHA Class 2 and 3, predominantly NYHA Class 2. Typical comorbidity, so very typical population.

The bottom line is, the trial's neutral, but let me comment on this very briefly. The primary endpoint is composed of three elements. The first one is time-to-first-event, time-to-first cardiovascular death or heart failure hospitalization. [*P*-value 0.038], reduction by 21%. Somebody says great, you go.

Fortunately, or unfortunately, the investigators decided to go for the composed primary endpoint with three different elements. One was this one. The second one was total heart failure hospitalization, also favorably reduced by around 20%. The third one was the primary endpoint, so time-to-first-event in patients with TSAT below 20%. Here again, borderline significance. But they applied statistical procedure, called Hochberg approach, and having all these three, they needed to have a certain level of *P*-value, which we didn't reach. So, once you see the results, you say time-to-first-event is reduced, significant importance. But based on the statistical approach, it is not so.

The conclusion in *JAMA* is the trial is neutral, but the trend is the reduction in, as I said, time-to-first-event, reduction in total heart failure hospitalization and also, causative effects in patients with TSAT below 20%. That would be my short summary.

Dr. Mentz:
So, now it's not that we just have one trial. Right? We've got four large outcomes trials with the totality of evidence, when we prespecify that we're going to pool this that there's a clinically relevant reduction in hospitalization events and even this suggestion around CV death, so.

Dr. Ponikowski:
Yes, indeed.

Dr. Mentz:
So, how do you incorporate these data into practice as you think of your patients with heart failure and iron deficiency?

Dr. Ponikowski:
We're having a lot of patients in whom we infusion with, you go for infusion with IV iron. I would even tell you that in HFpEF patients, although we do not have clear evidence for, where we have only 1 trial. We also believe that it is an important indication. Symptomatically, they are doing OK.

Dr. Mentz:
Yeah, nicely stated. I think, to really take a deep dive then, into the quality of life data. As you're talking to your patients and they're bringing in their symptom burden in HFrEF. They're on great quad therapy and they say, doc, is there anything else you can do to help me feel and function better? How do you talk through this with your patient?

Dr. Ponikowski:
Well, as we all know, patient-centered outcomes is mainly about feeling better, better quality of life – that's what we already discussed – and also, being less often in the hospital. That's extremely important.

And we have convincing data from the trials you mentioned that repleting iron deficiency with IV iron in our patients with heart failure is able to really significantly reduce the risk of hospital admission and also recurrent heart failure hospitalization, which all of them make a real pattern in the context of that patient feeling better. What patients really want.

And we're also talking to them, saying that oral iron does not work. We have the evidence and this is one shot and we keep repeating this, say, every 4 to 6 months, and that's a straightforward approach.

And now, I think that the final question is, we're discussing about strategy, and what about the dosing?

Dr. Mentz:
So, we have now lots of experience from these clinical trials. We do have a label with ferric carboxymaltose for heart failure with iron

deficiency. And what we need to look at is the iron indices, the hemoglobin and the weight. And we incorporate those data and we give doses separated by a several day period. And then, one of the most common questions that comes up is not just the dose, but when do we need to recheck? And from trials like HEART-FIT, we know that at a 3 to 6 month cadence when patients are coming back into clinic, we checked their iron indices, you'll get those data back within a day or so, and then you can schedule the follow-up infusions if they are still iron deficient at these follow-up periods.

So, before we wrap up, let's each offer a final take-home message. Piotr, what do you hope our listeners will leave with today?

Dr. Ponikowski:
Well, I would like to make our listeners to remember that iron deficiency is common in heart failure. We have very simple tools to diagnose iron deficiency, so please only remember to measure to assess serum transferrin saturation and serum ferritin. Also, consider hemoglobin. Please remember that we have convincing evidence that in patients with heart failure and that reducing mildly reduced ejection fraction, repleting iron deficiency with IV iron tends not only to improve quality of life, exercise capacity, but also reduces the risk of rehospitalization.

Dr. Mentz:
I would probably reiterate pretty similar comments. So it's, in patients with heart failure, we've got to think about iron deficiency. Check the labs, whether it's in the hospital or the outpatient setting. If they're on oral iron, you can stop it. They're not getting a clear benefit from it. We can think about deprescribing. And then, we use IV iron and we use these high-dose formulations. Very safe and clear data around functional status benefits and likely a reduction in clinical events.

And that's all the time we have today. So, I want to thank our audience for listening in, and thank you, Dr. Ponikowski, for joining me and for sharing all of your valuable insights and expertise. It was great speaking with you today.

Dr. Ponikowski:
Well, thank you very much and goodbye.

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