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Clinical Implications of the Evidence from IV Iron Trials in Heart Failure

Announcer:
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Dr. Anker:
Hello, everybody. Did you know that iron deficiency is an independent predictor of decreased functional capacity and reduced survival of your patients? Do you know that in your outpatient clinic, when you see heart failure patients, at least 30% to 50% will have iron deficiency? And even greater numbers of patents will have iron deficiency in acute heart failure, and this is regardless of ejection fraction or presence of anemia. Well, today we are exploring these issues and the clinical implications from the evidence of intravenous iron trials in patients with heart failure and iron deficiency.

This is CME on ReachMD, and I am Dr. Stefan Anker.

Dr. Mentz:
And I'm Dr. Robert Mentz.

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

Dr. Anker:
So, Robert, good to see you again. Can you tell our audience what we've learned from the initial trials in IV iron treatment in patients with heart failure so far?

Dr. Mentz:
Great. Thanks so much. So it's really an exciting history as we look at the earlier studies of IV iron in patients with heart failure. So realizing that this is independent of anemia status. Looking at patients where we've diagnosed based on ferritin levels and TSAT [transferrin saturation]. We know that oral iron doesn't help these patients, but by giving IV iron we're able to improve exercise capacity, quality of life, and symptom burden. And again, disconnecting that from anemia status. So these are benefits around these function and feel endpoints for our patients with heart failure with iron deficiency.

Dr. Anker:
Piotr, you want to comment, as well?

Dr. Ponikowski:
Well, indeed, you remember our first publication in *New England* with FAIR-HF. And we truly believe that the major strength at that time, it was more than 10 years ago – actually 13 years ago now when we provided the evidence that IV iron with ferric carboxymaltose works very well in anemic and non-anemic iron-deficient patients.

So as Robert is saying, regardless of anemia status, although we all intuitively linked iron deficiency with anemia, we also have proven

safety, which was a clinically very relevant issue.

Dr. Anker:
Well, and then, Piotr, turning really a little bit more in the history and getting to understand how everything kind of worked out. You'd started the CONFIRM-HF trial; you started the AFFIRM-AHF trial. How did the first knowledge make you design these trials?

Dr. Ponikowski:
Well, first of all, as you remember very well, we tended to accumulate the evidence that, as Robert already mentioned, IV iron – ferric carboxymaltose – being given to iron-deficient patients with heart failure is able to improve quality of life, functional capacity, but the size of the study were not that big. We wanted to have a reassurance; this is why we did CONFIRM. And then, having everything in mind, having all this meta-analysis in mind, which you were first author, where we combined earlier studies, where we put together all the evidence, where we put together individual patient's data, the message came up that maybe we also are able to improve the outcomes. So all the totality of evidence formed a very strong background. Maybe this is not only better life, better quality of life, better exercise tolerance, functional capacity, but perhaps this is also to strongly consider in the future trials to prove the benefits of IV iron in iron-deficient patient for mortality and morbidity.

Dr. Anker:
And that's why you then started the AFFIRM-AHF trial focusing really on patients that just were finishing a hospitalization, and we sometimes use it as a good-bye shot. Can you explain that concept?

Dr. Ponikowski:
Yes, indeed. The initial concept was indeed to focus on these patients with a very high risk of deterioration in the early post-discharge phase to make sure that they are able to protect them somehow. We didn't know how. However, we strongly believed that, indeed, giving them iron – you remember originally we planned this as a 1 IV iron shot, as you were saying, but then we changed the design and we, with our better understanding, we continued this during this post-discharge. Now we know how to do it better anyway. So but to make long story short, yes, this was the background to extend this not only to quality of life, exercise tolerance, but also to initiate the discussion whether we can improve the outcomes.

Dr. Anker:
Yeah. Thank you so much. Robert, back to you. Now with all of this, and AFFIRM was presented 2 years ago, what really is now going on? What is, in the last 2 years, happening? What is still happening? What is coming out, yeah, near everybody's kind of desk to read?

Dr. Mentz:
Yeah. Great. So I think building on the really rich data from AFFIRM, where we know that it's safe and effective to start this therapy in the hospital to help patients improve their outcomes, and now we need additional data. So the HEART-FID trial will provide an additional piece of this. So it's now looking in chronic HFrEF [heart failure with reduced ejection fraction] with iron deficiency based on the similar definitions that you all did in the earlier studies, and now looking in HEART-FID, it's a hierarchical endpoint. So it's looking at 12-month all-cause mortality, total number of heart failure hospitalizations, and then 6-minute walk distance. So this will give us important data about infusions every 6 months. We'll understand the changes in iron indices over time, the long-term safety and efficacy. And then important other studies including FAIR-HF2 that will complement these data.

Dr. Anker:
So what are basically, first of all, Piotr, the summary outcomes of all these trials? What is really the totality of evidence at this stage? And then, Robert, after that, what are really the fine details of the differences in the dosing schemes? What should really the listeners, the learners, what should they know about all of this?

Dr. Ponikowski:
I think the one sentence, or to make long story short and to summarize, is that today we know that patients with heart failure and concomitant iron deficiency, they need to have IV iron repletion with ferric carboxymaltose in order not only to improve quality of life, functional capacity, but also to improve the outcomes, mainly heart failure and cardiovascular hospitalization. That would be, I believe, a fair summary, and I'm sure that Rob would tell us more.

Dr. Mentz:
Yeah, that's exactly right. So we know about the safety and efficacy, whether in hospital, out of hospital; HEART-FID will complement that. And it's high-dose IV iron, and in some patients, they may need repeat infusions to make sure they're iron replete.

Dr Anker:
Well, everybody, for those just tuning in, you're listening to CME on ReachMD. I am Dr. Stefan Anker, and I'm here with Dr. Robert Mentz and Dr. Piotr Ponikowski. We are discussing the clinical implications of the evidence from IV iron trials in heart failure.

So, Robert, Piotr, this is all very interesting evidence from the past, and there's many trials done. Could you, for the audience, maybe contrast a little bit the differences between the trials and the similarities, of course, and how this relates to the results possibly? I'm thinking of a certain subgroup of patients that may benefit more or less so that, really, the audience gets a feeling for the differences and similarities and the lessons to learn.

Dr. Mentz:
Yeah, thanks so much. So I think a couple key points are how do we define iron deficiency? And it was consistent across all the ferric carboxymaltose studies. So ferritin less than 100 or 100 to 300 with a TSAT less than 20%. That's consistent across these. We have different patient populations. So AFFIRM-AHF, an inpatient setting. And then we have HEART-FID, a chronic outpatient setting. So that's helpful because it really gives you the full spectrum. So we can use that higher-risk patient population, giving a dose while they're in the hospital, then we have the HEART-FID data on the outpatient side. Again, remembering that it's regardless of anemia status, another important consistency. And the final piece, I think, to really underscore the history of increasing sample sizes, right? So you have now not only thousands of patients, but longer-term follow-up. So AFFIRM-AHF going out through 52 weeks and then HEART-FID going many years, actually, for some of our patients.

Dr. Ponikowski:
Well, indeed, Robert already alluded to a very important issue, pointing out that definition of iron deficiency, or maybe we should rather say definition of iron deficiency which is the indication to start the therapy. This will evolve, I'm sure. The second issue is obviously the dose. The dose and the redosing regimen, this is also evolving. First of all, what is the initial dose, and even more importantly, during the follow-up, because Robert already mentioned that we will be following this patient for longer period of time, we'll be redosing. So the obvious thing is how to define the optimal redosing strategy, based perhaps on the biomarkers of iron deficiency we used, or maybe reevaluate this or maybe use this only for safety, not for the redosing regimen. So we will learn more and more over the next couple of months.

Dr. Anker:
Yeah, I think it's possible that there will be one conclusion that you use the iron deficiency definition to identify the person who will benefit from chronic treatment with intravenous iron, but then use subsequent biomarker assessment only to stop possibly the treatment for safety reasons, but otherwise continue. Because how can you expect the treatment that you only give for half a year to actually get you benefits at 2 or 3 years. And this is almost like acute heart failure. Three days of treatment and you expect half-a-year benefit. Difficult.

Dr. Ponikowski:
That's indeed the issue we tested in AFFIRM. If only we can reconsider this, we probably would make some changes, but I am sure that Robert tells you more about his concept regarding the longer treatment. I entirely agree with you, but I also strongly believe that – you remember that we have borrowed this definition from the nephrology group, which may well not be that applicable for heart failure population, so in the future with our already existing experience, I am sure that we will be reevaluating the issue, and I think the results will be also better. That's my hope.

Dr. Mentz:
Yeah, I think that's exactly right. So this will really help as we can share these data about the dosing strategy, right? So AFFIRM, it's in the hospital, a month and a half, 3 months, 6 months, whereas HEART-FID, a little bit different. So it's you get the dose at day zero, day 7, so early on, and then 6 months later. So we'll best understand what is the tempo of repletion and how do we best help patients.

Dr. Anker:
And then there is also some data coming out that maybe patients can be identified in an easier way by just using a low transferrin saturation for diagnosis. Do you think there's – because the ferritin sometimes is not available, sometimes it costs money, sometimes it sounds too complicated that you have 2 different cut points. Can we simplify this?

Dr. Mentz:
Ultimately, what matters is the implementation of these therapies. Right? So we have the important trial data, but we need to best translate that for the routine clinician helping take care of these patients.

Dr. Anker:
I mean, if you're sitting in front of a patient, patient has lots of symptoms, you improve symptoms, you've improved quality of life and exercise capacity, I think you also have a good chance of having less hospitalizations. Now the patient asks a simple question, "Doctor, is more therapy better than less therapy?" And of course, I'm thinking here not only heart failure trials but also renal disease trials where we maybe also have some evidence. Is there evidence that more is better than less?

Dr. Mentz:

Well, I think what we certainly know is that we have quad therapy now in HFrEF. We know each of those therapies has incremental benefit regardless of the background therapies. But now from a patient-centered perspective, I'd say this is another tool in our tool kit that is not another pill you have to take every day. Right? It's an easy infusion in clinic or during the hospital stay. Let's help our patients with effective therapies.

Dr. Ponikowski:
Yes. Easy, safe, it works very well, and I think this is a quite reasonable argument for the patient.

Dr. Anker:
So, Robert, Piotr, just as the very last question. What are the key takeaway messages for the audience?

Dr. Mentz:
My rapid-fire answers would be iron deficiency, common in patients with heart failure. You've got to test for it in order to find it. We know that regardless of anemia status, it's common. Oral iron is not effective; IV iron is the way to go. It helps patients feel and function better, and we have important clinical outcome benefits, too.

Dr. Ponikowski:
What else can I add? Only reiterate what Robert is saying. But please remember that it is really a very important and common comorbidity, and please read the guidelines and implement IV iron therapy for iron-deficient patients with heart failure for them to live better, to reduce hospital admissions, and that's it.

Dr. Anker:
Thank you so much. That's straightforward.

Well, gentlemen, thank you so much. For our audience, I would like to emphasize again this has been a fascinating conversation. I hope you learned a lot of good insights, and of course, there's also more to learn in the future, so stay tuned with the CME program and see you soon again.

I'm Stefan Anker here for ReachMD CME program.

Dr. Mentz:
Thank you.

Dr. Ponikowski:
Thank you.

Announcer:
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