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Treating Iron Deficiency in Patients with HFrEF: A Review of the Recent Data for IV Iron Replacement Therapy

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Dr. Butler:
Symptoms from iron deficiency can greatly affect the overall quality of life of our patients with heart failure. Today, we are exploring the clinical evidence for the use of IV iron replacement in these patients. The most recent study results are from the IRONMAN trial.

This is CME from ReachMD, and I'm Dr. Javed Butler. So welcome to the program.

Dr. Anker:
Thank you so much. I'm very happy to be here. I'm Stefan Anker from Berlin.

Dr. Ponikowski:
Well, I'm also very happy to be here. I am Piotr Ponikowski from Poland – Wroclaw, Poland.

Dr. Mentz:
Thanks for the opportunity. I'm Rob Mentz from Duke University.

Dr. Butler:
Well, great to have all of you here. So let's begin the discussion. So we'll try to focus our discussion today on the new trial that was presented here at IRONMAN trial, but before we go to the IRONMAN trial, maybe, Stefan, I can start with you. There have been several trials with IV iron in patients with heart failure showing consistent benefit in terms of quality of life, functional capacity, emerging data for hospitalizations for heart failure. Can you tell us a little bit about the background of the IRONMAN Trial? What was the question that was being studied, trial design issues?

Dr. Anker:
Yeah, thank you so much. I mean, the history of all of this is going back, you might say, almost 20 years. Don Silverberg first studied combining, actually, erythropoietin with iron and showing some benefits in patients with renal disease and heart failure. There was one arm of development of erythropoietin, another arm was intravenous iron coming out of this. And after several smaller studies, in 2009 we had the chance to publish then, for the first time, in the FAIR-HF1 trial the results of using ferric carboxymaltose versus placebo to actually improve symptoms, quality of life, and really the patient-reported outcomes of patients. Now this developed then further into a second study we did with Piotr together, the CONFIRM-AHF trial to show 6-minute walk test improvements. And so I think you're right. It now can be said there are several trials that achieved kind of these not heart outcome improvements. So AFFIRM-HF, Piotr led this trial. We published a few years back. Then in a population with more acute heart failure or hospitalized for heart failure, and almost like a good-bye shot, plus additional therapies showing also improvements there with reductions in hospitalization.

And now the background is simply, is this something that is specific to one type of an intravenous iron, or is this actually something that maybe also works with other intravenous irons? And so IRONMAN investigated the benefits in chronic heart failure. Some of them, also hospitalized for heart failure, and even recruited in the hospital for the study. But checking whether this also works with another intravenous iron called derisomaltose.

Dr. Butler:
So let me just ask a few clarifying questions for the study design. So it included both ischemic and nonischemic etiology?

Dr. Anker:
Yes, that's true.

Dr. Butler:
And the patients were all heart failure with reduced ejection fraction [HFrEF]? What was the EF [ejection fraction] cutoff in the trial?

Dr. Ponikowski:
45%.

Dr. Butler:
45%. And then the last question is that the endpoint of the trial was – what was the trial designed to look at?

Dr. Anker:
A combination of cardiovascular mortality and recurrent hospitalizations for heart failure, as an analysis of recurrent events.

Dr. Butler:
Got it. Okay, so Piotr, coming to you. What did the trial show?

Dr. Ponikowski:
Well, as Stefan said, the trial was pretty similar in the concept to AFFIRM-AHF. To follow what we actually found, that in AFFIRM-AHF, in the population – different population, the population hospitalized for heart failure, being treated before discharge and for 1 year with ferric carboxymaltose, the design was similar, but the population was, as Stefan already alluded to, different one, mainly ambulatory patients. Two-thirds of these patients were recruited on ambulatory basis. So around, if I remember correctly, 15%-16% were randomized once they were in hospital, and around 20% were randomized based on their previous heart failure hospitalization. So heart failure with reduced ejection fraction, with iron deficiency defined in a little bit different way. So similarities, but tiny differences: transferrin saturation [TSAT] below 20%, or ferritin level below 100.

So tiny differences, and we can discuss this later. A little bit more than 1,100 patients treated with ferric derisomaltose for several years. Median follow-up, 2.7 years, much longer than we did, so we, as Stefan said, we did treatment for 1 year. Here the treatment was much longer. The maximum follow-up person was a little bit more than 5 years, so pretty long follow-up. And the results are very simple. Those – and even also quite important difference – there was not double-blind, placebo-controlled trial. It was the patients who were randomized either to active treatment versus usual care. So there was not placebo arm, so usual care.

We can also discuss how this kind of a design can affect the results. So to make long story short, very similar effect – results what we observed in AFFIRM. Treatment with ferric derisomaltose resulted in a nonsignificant – so a reduction of numerically lower events with a ratio of 0.82, just narrowly missing statistical significance. In the AFFIRM, we had 0.79, so very close, very similar. Again, as we already had recurrent heart failure hospitalization plus cardiovascular death, prespecified COVID-19 sensitivity analysis reveals significant effect of ratio less than 80 – 0.78 if I remember correctly – so significant, as we had in the AFFIRM. So pretty consistent results. To make long story short: safe, well tolerated, they focus on the infection relating, safety endpoints – no difference whatsoever. No signal regarding a safety issue, well tolerated, as I said.

So I see this as a next step in the further development of the concept data repletion IV iron to replete iron deficiency in patients with heart failure and reduced ejection fraction across the whole natural history – in hospital, in ambulatory basis – results in significant improvement in outcomes. And also, importantly, in quality of life, but there are some differences in this trial, which we can discuss later.

Dr. Butler:
So you specifically mentioned that this is not a double-blind, randomized trial, but an open-label. So was there IV iron used in the control arm?

Dr. Ponikowski:
That's a great question, Javed. Yes, it was. If I remember correctly, 17% of patients – 17% tended to receive IV iron in the usual care

arm. Several percentage were oral iron, but perhaps we should take this with a grain of salt, because we may not believe that oral iron works, but definitely this information, that at least 1 IV iron infusion in the usual control was received by, as I am saying, 17% of patients may well be really important issues.

Dr. Butler:
So I mean the trial design is what it is, and obviously we should analyze its intention-to-treat analysis and whatever the prespecified – the statistical analytic plan was. But clinical interpretation, would it be a fair thing to say that, if anything, the benefits that were seen in this trial were attenuated because of the open-label – almost 20%, 1 in 5, used in the control arm?

Dr. Ponikowski:
It may well be. It may well be also, some other issues related to the differences in the design of the trial. Maybe ethnicity, maybe – please remember that AFFIRM was across all over the world. Here, is only 1-country trial. I think that endpoints were blindly adjudicated, although this was an open-label study. So differences, but as I am saying, I see these 2 trials as a very – the results as very consistent, showing that IV iron, whichever compound we use, in iron-depleted, iron-deficient patients with HFrEF helps and improves mortality and morbidity. That would be my interpretation. I am sure that Bob will tell us some more about his trial because maybe it will be the final piece of evidence, but I will leave you to, as the moderator, to carry this discussion further.

Dr. Butler:
Yeah, so I have a few more questions about the results, but before we go there,maybe, Rob, I can turn over to you. So what's the clinical interpretation? How does this trial impact your practice now?

Dr. Mentz:
Sure, so I think as my colleagues have nicely highlighted, it's another piece of the puzzle. We're getting additional perspectives, a different compound, slightly different trial design, right, so you have this longer-term follow-up, and you have repeat dosing every 4 months, so now a median follow-up of more than 2 and a half years. So we get to see the long-term implications. And there are a couple other important nuances here. It did include those de novo patients, so we'll take a deeper dive there as we better understand. There's some suggestion, as we look at IV iron, that potentially the de novo, nonischemic, is there evidence of a differential – or maybe even not as strong a benefit. Importantly, as we look at IRONMAN, the prespecified subgroups, nothing meeting statistical significance for differences there. So I think as my colleagues nicely highlighted, this is another piece of the puzzle, showing – fairly consistent, we see in the 20%-25% reduction in events really driven by heart failure hospitalization. I commend the investigators for this effectiveness study.

So I think it really, with the pragmatic elements, we're getting more of an effectiveness study, where you do have open-label use; you do have challenges with COVID. But they should be commended for answering this question and, I think, demonstrating this nominal reduction in hospitalizations. So as I take this now into clinical practice, I think, in truth, we know that there's going to be formulary considerations at different institutions, so this gives us additional data around the utility of IV iron, and I would actually take a little bit of a step back and say, we've talked about the evidence generation piece here, but the steps are we have to think about iron deficiency in our clinical practice, right? Knowing how common iron deficiency is, if you don't think about it, you're not going to check iron indices, so it's: think, check, and then treat. And as my colleagues have nicely noted, it's not oral iron. That's ineffective. It needs to be IV iron, and we have now data with multiple compounds demonstrating improvements of quality of life, functional status, albeit with some nuance that we may want to get into it with the different trials around 6-minute walk distance. But this reduction in hospitalization, that matters for our patients and our systems.

Dr. Butler:
So I really want to ask you a question about the trial that you are leading, but before we go there, do we know the quality of life results in IRONMAN, and what were the differences and nuances?

Dr. Ponikowski:
Yeah, and in the previous studies, we convincingly demonstrated that IV iron with ferric carboxymaltose tends to improve significantly quality of life, including also in ambulatory patients 6-minute walking test distance. It was a confirmed study, which we published several years ago. Here, in this population, again, in as Dr. Mentz alluded to, in a little bit different study design, the quality of life measured with Minnesota Living with Heart Failure Questionnaire was improved; with some other questionnaire, it was not. And also 6-minute walking test did not significantly change in those being treated with IV iron. This is a piece of puzzle we need to digest and explain, which for me is a little bit surprising, because we take for granted with all our studies that this is certain, that correcting iron deficiency will end up with improvement in exercise capacity, including the 6-minute walking test distance. But perhaps as you said, maybe those treated with usual care, they were treated with also IV iron; maybe there are some other differences, as well. Maybe something we cannot simply explain by first interpretation. So overall, it does not surprise me, but this 6-minute walking test is a little bit kind of a puzzle for me.

Dr. Anker:
Yeah, I would like to add to this that besides the point that it's 17% kind of open treatment in the control group with intravenous iron, there is also second issue, and it's the dose given in the trial is maybe a little bit on the low side overall. It was a little under 1,000 mg on average per patient, and in our trials, we usually have 1,500 mg in the first half year, and then 500 to 1,000 mg in the second half year. So you would have expected, at least I would say, 2,000 mg in the trials that we are currently doing – I don't know how it is in HEART-FID. Certainly, that's the amount we are doing in FAIR-HF2. That's the amount we previously gave in the other trials. So there may also be a hint towards a dose response issue, that you need to give a little more to get an even more convincing quality of life and symptom benefit and exercise capacity.

Dr. Mentz:
Yeah, and I would also just highlight that in the context of the COVID lockdowns, a number of patients actually didn't get the follow-up dosing. So the prespecified COVID analyses as well as some additional post hoc COVID analyses really do demonstrate that there is this reduction in hospitalizations, and in truth, if there was more complete dosing without crossovers that certainly did happen, I think, really, the totality of evidence demonstrating the efficacy of this medication.

Dr. Butler:
Yeah, so this trial, I mean, really recently just came out, so we all need to digest a little bit of data. I was also intrigued by the fact that the quality of life scores did not improve early, but then improved later, so it just sort of raises all these questions, not only – so one obvious question people will ask is that is there a differential effect based on the iron preparation? So that's the lowest hanging question. Then the issue of those that Stefan mentioned, but also I don't know this for a fact, but one assumption would be that the 17% open-label use was all up front, but over time, with COVID or whatever, the standard of care arm did not get recurrent injections, but as the per-protocol injections were given more frequently. So there's a lot of explanation that we need to understand here.

So, Rob, you're leading the HEART-FID study. Can you tell us quickly a little bit about the HEART-FID study and what you hope that that will add to already AFFIRM-HF and IRONMAN?

Dr. Mentz:
Wonderful. So HEART-FID is a large trial now looking at FCM, so the compound distinct from IRONMAN. And it's over 3,000 patients, heart failure with reduced ejection fraction, chronic heart failure, so outpatient setting, and now getting dosing every 6 months. Long-term follow-up, and importantly, the primary endpoint is a hierarchical one, so it's all-cause mortality. The total burden of heart failure hospitalizations and then 6-month 6-minute walk distance, with the first 2 components at 12 months. Importantly, it's powered based on a key secondary endpoint: cardiovascular death and heart failure hospitalization.

So in 2023, we'll be excited to report out these data and hopefully provide an important and potentially kind of final piece around the HFrEF elements here, and then my colleagues are working on additional complementary studies that'll help us better understand in different populations, a little bit of difference in HFrEF and HFpEF [heart failure with preserved EF]. So I think it's an exciting time as we think of – certainly there's evolution of guideline-directed medical therapy in terms of medication pills, but this idea of polypharmacy's an issue, and if we're able to effectively use IV iron to help our patients feel, function, and have better clinical outcomes and implement this in an effective way, that could really save many lives.

Dr. Butler:
It looks like we need to get together again soon to have the discussion on HEART-FID like this.

But Stefan, you're leading FAIR-HF2. What is that about, and what about HFpEF?

Dr. Anker:
Yeah, thank you. I mean, basically, FAIR-HF2 is, of course, an extension in the chronic heart failure field of all our experience with ferric carboxymaltose, really focusing as a primary endpoint on recurrent cardiovascular mortality and heart failure hospitalization events. In a population that after we have just recently submitted an amendment, if and when this is implemented, with an ejection fraction up to 55%, so HFrEF and HfmrEF [heart failure with midrange EF], you might say. And in this study, we are on an average observing in the end about 3 to 3 and a half, possibly even on average a little more than that, 4 years of clinical care for patients with intravenous iron. And also, repeat kind of therapy of the patients over time in a double-blind setting, which for sure – and this I can already relate – very much contributes to having much, much less kind of open-label treatment in the whole study at all, because nobody knows the assignment of the patients. And so I think this is an important quality, but also a rather costly kind of element of a study. So we will do this and hopefully then report, maybe 1 year after the HEART-FID trial, this very final and then maybe even definite kind of result, I hope.

Dr. Butler:
So, Piotr, Rob made a suggestion to maybe differential benefit in ischemic versus nonischemic, which automatically raises the question,

what about post-MI [myocardial infarction] population?

Dr. Ponikowski:
Great question, Javed. I think that we quite recently published that analysis from our study showing that ischemics – it works versus nonischemic, which may well not work that well. I think that reading the supplementary materials for IRONMAN, we see that there is also difference favoring those who have ischemic heart failure. Although the authors mentioned that there was no heterogeneity, they mentioned in the discussion, perhaps there may be something. Perhaps if we combine everything together, we will see. So what we are now and we will be discussing with Rob and with you once we finish this nice discussion here, what about prevention of heart failure in those who tended to have a myocardial infarction and have iron deficiency without having heart failure already at baseline? It is a concept quite similar to EMPACT-MI or this study with sacubitril/valsartan, to prevent heart failure event in those at high risk of heart failure, post-MI.

Dr. Butler:
For those just tuning in, you're listening to CME on ReachMD. I am Dr. Javed Butler, and here with me today are Drs. Stefan Anker, Piotr Ponikowski, and Robert Mentz.

So, you know, we talked a little bit about subgroup differences. You know, one question that always comes up is that it's very easy to understand that if you have iron deficiency anemia, and you're short of breath or tired or fatigued or what have you, because you're anemic. But then, iron deficiency also impacts patients who are not anemic, and the benefit with IV iron replacement is seen in both patients with and without anemia. So can you explain to us a little bit about how does IV iron work in patients who are not even anemic?

Dr. Anker:
Yeah, thank you so much, Javed. This really, I think, is possibly for the whole iron deficiency kind of therapeutic field, the contribution of heart failure to the medicine in general, because in all other fields, it was really a restrictive kind of approach, iron deficiency being synonymous to the anemia kind of indication, and only in heart failure we started to actually say, oh, no, we also want to treat patients without anemia having iron deficiency. Why could it work there? Well, simply, we are talking here about making musculature – any musculature, the heart muscle, the respiratory muscle, but also the skeletal muscle – more energy efficient. Energy comes basically out of the work from mitochondria, and they use the respiratory chain to produce ATP. And the respiratory chain reaction needs iron as a catalyst. And it becomes simply more efficient in producing energy when you have sufficient iron supply in the cells, and that is totally independent of the issue of carrying oxygen to the periphery through hemoglobin, using also iron for this. So iron has 2 functions. One is helping in the oxygen transport, but also helping in the oxygen utilization, and the latter seems to be the really important part when it comes to basically improving quality of life and performance, because energy is needed for this performance, and that's why it works also in the non-anemic patients.

Dr. Butler:
So this is really fascinating. What you're basically saying is that iron deficiency obviously complicates things when you develop anemia, but iron deficiency is a disease state in itself regardless of anemia. So that's interesting.

Piotr, so, you know, IRONMAN had a little bit of a different definition of iron deficiency than all other previous trials. Which begs the question: What was wrong, or right, with the previous definition? Why do we need a new definition? Can you tell us a little bit about that controversy related to the diagnosis of iron deficiency?

Dr. Ponikowski:
Great question, Javed. I think it was nothing wrong, nothing good. We simply used the definition which we have somehow borrowed, or we did borrow from the nephrology group. So we used this nephrology kind of a paradigm, which we implemented in our first study. It worked, and it worked the same way in the following studies. So it was low ferritin, lower than – so 100, make it this way. Or if 100 to 300, additional criterion should be transferrin saturation below 20%. It created some discussion. It worked in our study repeatedly. And there was a story, what about serum biomarkers which are best to diagnose and to reflect iron deficiency? We can talk about this for at least an hour. What would be the ideal parameter? Is this transferrin saturation? Is this ferritin? Is this soluble transferrin receptor, which is a new kind of a biomarker which may well be important? What about biomarkers – blood-borne biomarkers refracting iron deficiency in the bone marrow, it's in – reflecting iron deficiency in the cells, which we still do not understand, because we take for granted that what we measure in the blood reflects iron deficiency at the periphery, in the cells – what Stefan said – which may be entirely wrong. But anyway, we have this definition. Colleagues in the IRONMAN used, in principle, the same approach. Low transferrin saturation or low ferritin level. I would say that I'm not that much difference. As you know well, some people decided also to go for the hepcidin, maybe. Without getting into the details, we want parameters which are simple, which are readily used, are simple in terms of a – also cost-effective. So I think this is simply saying that definition based on TSAT and ferritin works well, so we should continue with this.

Dr. Butler:

Great. So, Rob, we were talking about a lot of theoretical considerations which are really important, but let's talk a little bit about some practical considerations. So in the cardiology community, there's still some fear about, you know, anaphylactic reaction, inpatient, you know, referral to an infusion center, referral to hematology. What about the new preparations? What are the risk profiles? Can you give it in the outpatient setting? Can you just give us a little bit of a practical management tips?

Dr. Mentz:
Yeah, thanks, Javed. So I think you're getting at the really important question here, right? So we've talked through the data. We need to talk through the implementation.

And fortunately, on the inpatient side, we know that we need to think about systematic ways to get this implemented. And what that means is we need order sets. I mean, when you're coming into the hospital, you're checking all these routine labs, iron indices need to be considered, and then they need to be acted on. And, you know, the average length of stay in the US, 5 days, so you check the labs on admission, you've got time to give IV iron and tune this patient up before getting out of the hospital.

So the in-hospital setting, we know it can be easily executed, it's safe, older formulations we worried about anaphylaxis, infection concerns – not an issue. Exceedingly low rates with any concerns around adverse events, so we really have to debunk that. And I think the infection piece, now we have additional data from IRONMAN really showing the safety overall there. You know, many of our training experiences we had thoughts of, oh, you know, they're here with heart failure, but maybe they've got concerns of a pneumonia. Do we need to hold off on IV iron? We really know we can safely give it. And my final comment around the outpatient setting is similarly, right now, at many institutions, it requires sending our patient to an IV infusion clinic. That's just insufficient. The idea that it's going to require additional scheduling, additional time, coordination – we've got to really push our institutions to get this effectively given in the heart failure clinics, in the general cardiology clinics, to best serve our patients.

Dr. Butler:
Well, that makes a lot of sense. You know, there's a lot of concern with the earlier forms of IV iron preparations, and those reactions and adverse effects are really not seen with the newer IV iron preparations as well. And you don't necessarily need to observe the patient in the outpatient setting after you give the injections, and for all those reasons, it's a whole lot more practical than perhaps sometimes we make of it.

Well, that's about all the time we have today. We can literally go on with this discussion for a very long time. Let me ask my colleagues for some closing thoughts and comments. Maybe I'll start it off with the direction. Rob?

Dr. Mentz:
I would just echo my comment. Think about iron deficiency. Check the labs and think IV iron for treatment to help our patients.

Dr. Butler:
Piotr?

Dr. Ponikowski:
Well, I can only fully concur with this, adding that, consider a treatment with IV iron in iron-deficient patients as their cheapest way to reduce heart failure hospitalization.

We have a very, I would say, comprehensive cost-effectiveness analysis that this would be a good way to reduce the cost of heart failure hospital admissions, and that would be my comment.

Dr. Butler:
Stefan, I will give you the last word.

Dr. Anker:
Thank you so much. Well, intravenous iron works. Oral iron, we know, doesn't work. You need to think of it, you need to diagnose it, and hopefully you can then also treat it.

Dr. Butler:
Well, gentlemen, thank you very much for all of your insights and your thoughts and your experience on all the trials that have already occurred and will be declared in the next few years. So we look forward for the discussion. And thank you very much to all our viewers for this program. I hope this information will help you and your patients. Thank you very much.

Dr. Anker:
Thank you.

Dr. Mentz:

Thanks.

Dr. Ponikowski:
Thanks.

Dr. Butler:
So this was a great discussion, and we discussed a broad spectrum of topics related to iron deficiency. I hope that this discussion was of benefit to you and your patients and that you enjoyed listening to this discussion. Thank you very much for listening to us.

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