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Addressing Issues of CV Mortality in Clinical Trials with IV Iron: Are We Still Getting a Medical Benefit?

Announcer:
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Dr. Anker:
Hello, everybody. Today we are addressing here cardiovascular mortality, hospitalization events, and other interesting discussion points of clinical trials of intravenous iron in patients with heart failure with iron deficiency. Are we actually still getting the medical benefit we are looking for, or are we falling short of the benefit we are seeking in these studies?

This is CME on ReachMD, and I am Dr. Stefan Anker. And with me are Professor Ponikowski and Professor Cleland. Glad to have you here.

Dr. Cleland:
Glad to be here.

Dr. Ponikowski:
Glad to be here, Stephan, with you.

Dr. Anker:
Now, in terms of the design of the many clinical trials we are doing, and here now, of course, with the focus on intravenous iron, the key endpoints that we are assessing for these patients, hard endpoints, many times called. Are we really, when assessing them, asking the right question?

Piotr, what do you think?

Dr. Ponikowski:
Well, I think that we are indeed, because we all know, a long time ago once we started, we were focusing mainly on exercise capacity, we were focusing on quality of life, which are a very important part of their normal life for patients with heart failure. We wanted them to live better. But after providing enough evidence that, indeed, we are able to improve quality of life, exercise tolerance, functional capacity with IV iron in patients with heart failure and iron deficiency, we obviously moved our bar higher and ask the next question, as you already asked, are we also able to change their outcomes? Are we able by repleting iron deficiency, giving them IV iron, to change mortality and morbidity. So now we are in a little bit more mature phase, better developed, so I think that we are now asking good questions. Yes.

Dr. Anker:
So, John, what would you comment on this? Are we doing it the right way? Having problems? How do we see all of this?

Dr. Cleland:

No, I think it's natural progression, and, as Piotr has said, first batch of trials was looking to see whether patients felt better in the short term with intravenous iron. Now what we wanted to show was whether this was both safe and effective in terms of improving longer-term outcomes. And those longer-term outcomes, yes, we're still interested in how the patient feels, but also did that have an impact on hospitalization? Did that have an impact on mortality?

Dr. Anker:
Yeah. And then of course, with this, we then can also establish whether the treatment in the long term is cost-effective also for society. I guess this is also an important part here.

Now, John, there are sometimes in trials external events. How do they, in your experience and maybe also with a particular focus on intravenous iron trials, how have they actually influenced some of the things you've done?

Dr. Cleland
Well, I think they've had a major impact on all of the larger landmark clinical outcome trials of intravenous iron. It's true of AFFIRM-AHF, it was true of IRONMAN, and it's also true for HEART-FID. The COVID pandemic affected all 3 of these trials and also the Ukraine conflict affected HEART-FID. The big problem with these studies was that when COVID came along, actually bringing patients back for research visits to get further intravenous iron became very difficult. And that meant that patients probably didn't receive the full intended dose of intravenous iron in many of these studies. So I think that they have certainly – the impact of these have diluted the benefit. We're trying to compensate for that in some way by the COVID sensitivity analysis. The COVID sensitivity analysis suggests much stronger results than the full analysis.

Dr. Anker:
And, Piotr, didn't you also experience that patients were actually kept out of hospital not only for the visits but for the actual hospitalization? You might say they were managed at home in some ways?

Dr. Ponikowski:
Well, indeed, not only my country, across Europe and also in the United States, we have clear evidence that what you're saying is right. Many people didn't want to even consider going to the hospital. They were kept out of the hospital. And also, in our everyday life, as John already said, we had a little problem to convince people even to come for regular ambulatory visit. But we also tried to avoid this for many different reasons.

So from the clinical trial perspective, it was sort of a – kind of a 10 disaster, make it this way, not to follow them accurately, not to convince them to come, et cetera, et cetera. But as John is saying, we tried to overcome this in this sensitivity analysis, which made even the results stronger, showing us that the iron in this iron trial, but also in other trials, worked very, very well, so that would be my comment.

Dr. Anker:
So maybe you can then also now, having described the overall problem, say what are the results overall, what are the results of the COVID sensitivity analysis in AFFIRM, and maybe then you in IRONMAN?

Dr. Ponikowski:
Yes, as John said, overall, we just narrowly missed the clinical or statistical significance for the combined endpoint of heart failure hospitalization or heart failure hospitalization and cardiovascular death. However, reanalyzing everything using, well, in this COVID sensitivity, the statistical significance appears. So I think that just to reassure us it works well, and also, if you ask me what about the complement of this primary endpoint of discussion we have today, so what about hospitalization? Both cardiovascular and heart failure hospitalization, not only first, but all hospitalization, recurrent hospitalization, the risk is significantly reduced in patients being treated in our study with ferric carboxymaltose with apparent no effects on cardiovascular mortality. This is the brief summary of the trial.

Dr. Anker:
How was it in IRONMAN?

Dr. Cleland:
So slightly different. The first thing I'd like to say is we looked at all unplanned hospitalizations for cardiovascular and non-cardiovascular reasons. They were both reduced with intravenous iron, and if you actually look at all cause of hospitalization, not heart failure or cardiovascular, that's reduced significantly, and you don't even need a COVID sensitivity analysis to show that impact. So that's very interesting that it's having that impact on the non-cardiovascular. Most of those were things like chest infections, et cetera. The way I interpret that is that the intravenous iron is making the patient less frail, and if the patient is more resilient, then when they get a chest infection, instead of the heart failure decompensating and coming into hospital, they could just be treated at home with antibiotics and recover. So I think that's what we were seeing there. The headline result on the primary analysis was like AFFIRM-HF. It narrowly

missed the primary endpoint. When we did a prespecified COVID sensitivity analysis it was statistically significant. The reviewers for *The Lancet*, and I understand one or more of them might be standing next to me, asked us to do further analysis at the COVID lockdown and so on. Then it became stronger and stronger to the extent that we saw really quite not yet statistically significant, but a strong signal for reduction in cardiovascular mortality.

Dr. Anker:
Particularly when you shorten the follow-up time observed.

Dr. Cleland:
Shorten the follow-up when the patients were actually getting the iron.

Dr. Anker:
Yeah. That's important.

Dr. Cleland:
The latter part of the study was problematic because the patients could no longer come up and get further intravenous iron. So you're quite right that, you know, one of the reasons for the loss of that cardiovascular mortality signal, and this is hypothesis, you know, we're not suggesting it's proven, but it certainly didn't go the wrong way and an interesting signal. And I think, you know, we need to put that together with the rest of the data. I think we need to look at slightly different cuts of the data because I'm not sure that we got the definition of iron deficiency right, as you know, and maybe that's a topic for discussion today. I don't know.

Dr. Anker:
Hello. For those just tuning in, you're listening to CME on ReachMD. I am Dr. Stefan Anker, and here with me today are Drs. Piotr Ponikowski and John Cleland, and we are discussing the changing landscape of clinical trials with intravenous iron in heart failure.

Let's focus on one little part of the non-cardiovascular events you mentioned, the infection. And maybe for the audience we should say that there is a historic fear that when you give iron that you may have more infections, but now first time we saw in the PIVOTAL trial of more iron versus less intravenous iron, that there was actually with more iron less infection. And now you're saying in IRONMAN, similar. So this is reassuring in many ways.

Dr. Cleland:
And even more than that, a highly significant reduction in COVID-related serious adverse events.

Dr. Ponikowski:
So, well, I don't think we want to suggest at this moment treatment of COVID with intravenous iron, but if you're iron deficient, there is an indication to treat actually any patient with iron deficiency.

Dr. Cleland:
Well, I would say, you know, older patients, what was the factor that drove their poor outcome? It may well be that iron deficiency was one of the factors why we have such a high morbidity and mortality of the older population.

Dr. Anker:
Just to follow what John is saying, we are strongly considering IV iron in frail elderly patients in order to make them not only protected in the context of heart failure or cardiovascular – I mean, non-cardiovascular hospital admissions in this population and then being resilient, as John is saying, is more important. So this is very, very interesting concept. Yes.

Dr. Cleland:
We've just done a population study of Glasgow and anemia, which is mainly iron deficiency-related anemia. Very strong marker of mortality in the general population. Have 2- to 3-fold increase in risk once you're 2 g below the WHO [World Health Organization] definition. So anemia is a marker of some really quite bad things going on. And this idea that it's not an important disease, I think we need to stir things up a little bit and get people to think that perhaps anemia, we need to look at what's the cause and we need to treat it.

Dr. Anker:
Yeah. And maybe coming back, then, to the subgroups, and, Piotr, you just recently completed the meta-analysis on all of this. When you take the subgroups, well, one obvious one is the definition of iron deficiency, make it a little more narrow or maybe slightly different than what we are –

Dr. Cleland:
Clearer.

Dr. Anker:

Well, I make a suggestion. Transferrin saturation [TSAT] less than 20%, that's it. Acceptable?

Dr. Cleland:
I think that would be a major step forward. I think that we can maybe do even better than that. Piotr would go with soluble transferrin receptors. I would go very simply, and I think serum iron is – actually might be the best of them all.

Dr. Ponikowski:
Unfortunately, in this meta-analysis we do not have the data on serum iron. I agree with John: now it's time to sit and challenge the definition of iron deficiency so there is no question about it. Your suggestion about low transferrin saturation is a very intriguing one, and I think at that moment we can say perhaps if you have a high TSAT, say about 22%-24%, at least this is the result we have. There may be no benefit at all, so why not to dilute the effect. I'm not saying harm, but I'm saying no benefit at all, so why not sit and try to reconsider the definition? But also, not only in the context of iron deficiency definition and just entering the patients or starting the therapy, but also redosing. In other words, it's not only 1 IV iron shot, but also redosing during the follow-up. What would be the ideal biomarker portfolio? Maybe a simple one. To give iron after 4, 6 months, just to repeat the dose. Perhaps that very strict criteria we use are no longer valid. We will need to get back to the data and see.

Dr. Anker:
Now there's one last point about the clinical trial signs that has an impact possibly on the results, and that is the timing when you do the trials in the sense of which data did you use. Now, you have the AFFIRM trial reported in 2021; IRONMAN 2022, I think; CONFIRM was 2015; FAIR-HF 1 was 2009. So can we take the results of all trials and still apply them today? What are the problems in this context?

Dr. Cleland:
I think most of the trials have, apart from SGLT2 inhibitors, have been studied with contemporary therapy, and I think SGLT2 inhibitor, there's potentially an interaction with iron. Personally, I think it might be synergistic and we might see additive or synergistic benefits with intravenous iron. There are some people who think the opposite, so I think it's an area of interest and for study. The vast majority of patients that we come across, even for FAIR-HF, I don't think that those patients are that far removed from contemporary therapy in 2023.

Dr. Anker:
Yeah. I think the biggest difference in FAIR-HF 1 was it was a 6-month study and the patients really got treated throughout the whole 6 months. And so what we saw in terms of exercise capacity, symptoms, and quality of life change, was a reflection of the immediacy of the treatment, and you might say if you calculated per month of therapy, relatively high dose compared to the average doses.

Dr. Ponikowski:
It was a different design, different concept. In AFFIRM, and the same in IRONMAN and HEART-FID, we wanted to make this trial very pragmatic, easy, but the FAIR-HF 1 was a different design. But I agree with you entirely. Can't agree more with John, that perhaps even in this SGLT2 inhibitor's time there would be even kind of a very beneficial combination of these two. We will see. But it's not that far. Ten years is not that far.

Dr. Anker:
So I understand you right, the year when these trials were reported and done is not so much important, very similar.

Well, guys, this has been a very enlightening discussion. Very informative. Maybe one take-home point each of you wants to give the audience?

Dr. Ponikowski:
Professor Cleland starts.

Dr. Cleland:
So, well, I very much agree with you on the TSAT issue. I think we have a great opportunity here to make it clearer who needs treatment. I actually also think that patients who have got the most to gain in terms of symptoms and other things are the patients who have anemia. So anemia with a TSAT less than 20%, I think those are the patients who get the really big benefit from intravenous iron.

Dr. Ponikowski:
I can only say that it's good that for the last 15 years we're still interested in discussing this. Not everything is sorted out. With this big meta-analysis with individual patients' data and sensitivity analysis for which we included IRONMAN, I think we need to be reassured that the real clinical benefit is there with IV iron in patients with iron deficiency. We just need to identify those who would benefit mostly, and that's what John is saying.

Dr. Anker:

Well, and if I may also add one point, I mean, we focused here on clinical hard endpoints today. Let's not forget quality of life symptoms and exercise capacity are also beneficially affected by intravenous iron. It's even a class 1 recommendation in the most recent European guidelines. Let's see what the next US guidelines will say about this. So here's our prediction for the audience. We can compare notes in the near future. Really, thank you so much for having been with us, with me on this discussion here.

Unfortunately, that's all the time we have today, so I want to thank our audience for listening, and I particularly would like to thank Drs. Piotr Ponikowski and John Cleland for joining me here on ReachMD and for sharing all their valuable insights. It was great to speak with you today. Thank you.

Dr. Ponikowski:
Thank you.

Dr. Cleland:
Thank you.

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