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Applying Evidence to Practice: What Can We Learn from Recent Clinical Trials of IV Iron Use in HF?

Announcer:
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Dr. Ponikowski:
Iron deficiency is common in heart failure and is associated with an increased risk for heart failure hospitalization and cardiovascular mortality, reduced functional status, poor exercise performance. Several trials have demonstrated a positive impact on safety on intravenous iron in patients with heart failure with reduced ejection fraction, but some questions still remain.

Today, we are looking for answers and exploring the long-term effect of IV iron treatment on morbidity and mortality in these patients, and how IV iron therapy addresses poor exercise performance.

This is CME on ReachMD, and I am Dr. Piotr Ponikowski.

Dr. Mentz:
Hi. I'm Rob Mentz, a Heart Failure Cardiologist at Duke, and it's a pleasure to be with you today.

Dr. Ponikowski:
Pleasure is all mine. So, Rob let's talk first about new clinical trials in IV iron – with IV iron heart failure, and how do recent trials differ from the past trials, and what would be the clinical impact on everyday practice?

Dr. Mentz:
Really great question. So, as you know well, the earlier clinical trials were smaller in size, but looked at really important measures of quality of life and functional status, with the utilization of IV iron in patients with heart failure and iron deficiency. And now, with your elegant study AFFIRM-AHF in patients with EF less than 50% with iron deficiency in the hospital with heart failure, giving IV iron and then looking at long-term clinical outcomes. So, really important data there – out to 52 weeks. Now, we're excited in upcoming months we'll be able to share the HEART-FID data that we worked on together with other colleagues. Now, over 3,000 patients with heart failure ejection fraction that's reduced with iron deficiency but looking in the outpatient setting. So, this is patients that are stabilized, giving IV FCM at 6-month intervals and looking at the long-term clinical outcomes with a primary end point. Looking at mortality and heart failure hospitalizations at 12 months, and then 6-months 6-minute walk distances, as well as other important clinical outcomes, as you know.

Dr. Ponikowski:
So, Rob, tell me please how your trial, HEART-FID trial, in this population you just mentioned – how it differs from the other trials? What about the population? What about the dosing? Maybe definition and what the clinical outcome – impact for the clinical practice, please?

Dr. Mentz:
Great. Thanks, Piotr. So, going through it, so HEART-FID will look at over 3,000 patients heart failure with reduced ejection fraction. So, this is already one difference. Our EF cutoff is 40% or less. Some of the recent programs, including AFFIRM, it was less than 50. Ours

is an outpatient population; so, stabilized, on optimal medical therapies. And that differs, right? So, AFFIRM was in the hospital, right, prior to discharge.

Some other important considerations; we did have some enrichment criteria; so, patients either had heart failure hospitalization within the past year, or an elevated NT-proBNP.

Dr. Ponikowski:
What about the endpoint? If I remember, you have very nice endpoint. So, could you please explain us how it works in clinical practice, this endpoint, we are using in HEART-FID?

Dr. Mentz:
Great question. So, as you know well, the earlier programs intended to look at cardiovascular death in total heart failure hospitalizations; so, recurrent event analysis out – in AFFIRM-AHF, out to 52 weeks at that point. What HEART-FID is looking at is a primary endpoint that's hierarchical. And what that means, that we start with all–cause death and we compare patients in the two arms based on that. Then, if there were no deaths, then we look at heart failure hospitalizations. So, that's total heart failure hospitalizations out through 12 months. And then, if those patients were not hospitalized, then we look at 6-month 6-minute walk. So, some of the strengths of this are that it includes ability for all patients to contribute to the endpoint and looking at this hierarchy based on the impact for our patients beginning with death, the morbidity of heart failure hospitalizations, and then a functional endpoint.

Dr. Ponikowski:
So, it's a great, great idea. I really believe in this win ratio story combining different elements of natural history of heart failure, as you said. That hospital admission, then quality of life, exercise intolerance. So, thank you very much.

For those just tuning in, you are listening to CME on ReachMD. I am Dr. Piotr Ponikowski and here with me today is Dr. Rob Mentz. We are discussing recent clinical trials in IV iron therapy and how to apply what we have learned from these new trials to our heart failure patients with iron deficiency.

Well, so, very intriguing questions and it's an entirely different clinical population from those who are ready to go home before hospital discharge with iron deficiency, that's what we did AFFIRM. So, great complementation for what we have done.

So, given these changes, how do you think the current clinical trial design of HEART-FID may impact the clinical practice in the near future?

Dr. Mentz:
Great point. So, I would underscore that we really need to have iron deficiency top of mind. So, when we're seeing patients with heart failure, we need to test for iron deficiency and remembering that now we'll have consistent definitions using multiple trials, where the diagnosis it's ferritin less than 100, or ferritin of 100 to 300 with a TSAT less than 20. So, underscoring that as in AFFIRM, now in HEART-FID, and when we see iron deficiency, then we need to replete it with IV iron. We know that oral iron is insufficient, the guidelines give us recommendations around testing for iron deficiency and then using IV iron to help improve functional status, quality of life, and now with your data, and soon to have data from HEART-FID, it'll add to that broad evidence base around clinical outcomes.

Dr. Ponikowski:
Well, what about the definition – you think that the definition we're using is an optimal one, good one? You expecting something to be changed based on our trials or you think that in the clinical practice we'll be using this kind of definition still because it works well?

Dr. Mentz:
Good question. I would underscore a recent scientific statement from the HFSA that looked through each of these different definitions and how they have differed in some studies; everything from looking at bone marrow levels of iron, to different measures, even novel biomarkers in the blood. But I think the real strength of it is now the consistency of this definition, but importantly keeping in mind that subgroup analyses and others will help inform how we can best identify responders in individuals most likely to benefit.

Dr. Ponikowski:
Entirely agree. Thank you very much. So, Rob, let's put this into the context for our audience, can you please take me through a patient case that highlights how is that key clinical trial impact the use of IV iron in patients with – HF, rEF, for our colleagues?

Dr. Mentz:
Great question. So, I would say, if we have a patient; 75-year-old woman coming into the hospital, worsening signs and symptoms of heart failure, volume overload, reduced ejection fraction, long-standing history, she's been managed on excellent medical therapy, but she is still having worsening. She is now in the hospital and in addition to those routine labs we're checking, we need to check for iron deficiency. So, her EF is less than 35%, her ferritin is less than 100, we confirm that there's no other bleeding source and she's not

having signs of anemia on top of all this, and we optimize her oral therapies and think about IV iron in the hospital just as you did in the AFFIRM-AHF program, indicating that this is going to help improve, likely not only her quality of life, but clinical outcomes as well to help keep her out of the hospital.

Dr. Ponikowski:
Well, great comment and I entirely agree that having patients with, in the hospital before discharge, we need to think of it, but also in those who are coming to us with some deterioration, we are now calling it worsening heart failure, as you know well. Maybe in this particular situation, we also need to consider underlying iron deficiency as a potential target for this intervention, but also cause for underlying cause of symptoms and deterioration, to be easily repleted with ferric carboxymaltose. I think that's it.

So, it is fascinating conversation but, before we wrap up, Rob, can you share one of your critical take-home message with us?

Dr. Mentz:
I would say the key thing is, when patients are in the hospital or the outpatient setting, if they have underlying heart failure, we need to test for iron deficiency and then we need to treat it. And we need to treat with IV iron to best help our patients.

Dr. Ponikowski:
Well, that's it. I can only say that I have nothing actually to add, but what really matters is please remember that iron deficiency is one of the most common comorbidities affecting between 50 – 70% of our patients regardless of hemoglobin level, although we intuitively tend to link anemia with iron deficiency, it's not that simple. Please remember that oral iron, at least with the formulation we have, doesn't work. And please remember what Rob, says we have a way to replete iron with IV iron for these patients. So thank you Rob.

Unfortunately, that's all the time we have today, so I want to thank our audience for listening and thank you, Rob, for joining me and sharing of your all valuable input and, also, we're all looking forward to HEART-FID data soon I hope in the best journal we can predict.

Dr. Mentz:
Wonderful. Thanks so much for the opportunity and until we get to discuss again.

Dr. Ponikowski:
Yeah, thank you very much.

Announcer:
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