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Released: 10/26/2021

Valid until: 10/26/2022

Time needed to complete: 15 minutes

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### Making the Case for Iron Replacement Therapy in HFrEF: Clinical and Pharmacoeconomic Impact

Announcer:

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Dr. Kosiborod:

Patients with heart failure are at high residual risk despite advancement in care, but there is so much that can be done to improve their outcomes, with the main goals of making patients live longer, stay out of the hospital, and also improve their quality of life, which means making patients be able to feel better and do more. Of course, one target for us to consider more closely in this patient population is iron deficiency. While we know that this is quite common in our patient population with heart failure, it remains underdiagnosed, underappreciated, and undertreated in a large proportion of patients. So can addressing iron deficiency in our patients with heart failure really improve their lives?

This is CME on ReachMD, and I'm Dr. Mikhail Kosiborod from Saint Luke's Mid America Heart Institute in Kansas City, and it's my pleasure today to be joined by my colleagues, Dr. Jankowska and Dr. McEwan. Welcome.

Dr. Jankowska:

Hello. Good to see you.

Dr. McEwan:

Thank you, Mikhail.

Dr. Kosiborod:

Terrific. So, Ewa, let's start by addressing the current challenges being faced in clinical practice. Why is addressing iron deficiency important in heart failure? Why is it clinically significant? And what are some of the bigger challenges that you see in clinical management? So perhaps we will start with, specifically, about the effects of correcting iron deficiency in patients with heart failure and what we learned, especially from AFFIRM-AHF trial, in terms of effect and clinical outcomes and also patient symptoms and quality of life.

Dr. Jankowska:

Yes, indeed. Iron deficiency is extremely common comorbidity seen in patients with heart failure. I would even say this is the most common non-cardiovascular comorbidity seen across the whole spectrum of patients with heart failure. Another issue is that this problem is not just common, but this problem translates into several clinical consequences for our patients. First of all, patients with heart failure who are iron deficient, they have poor quality of life. They have exaggerated heart failure symptoms. They have higher risk of recurrent heart failure hospitalization. And unfortunately, very high risk of death.

So we see that the problem is very common, and the problem is really clinically significant. We are quite lucky that at the moment, we

can easily, cheaply diagnose iron deficiency in everyday clinical practice using 2 very cheap parameters: ferritin and TSAT. These parameters have been used for decades by hematologists, but also by cardiologists. And using 2 simple measures, we can very easily immediately pick up patients who can benefit from the treatment. We define iron deficiency as ferritin below 100, or ferritin between 100 and 299 with TSAT below 20%. And I think it's very important to emphasize that this definition differs from definition for iron deficiency used for general population. And using this definition, we can identify patients who have been shown in several already trials that these patients can benefit from intravenous ferric carboxymaltose therapy.

Dr. Kosiborod:

So, Ewa, you just very eloquently outlined how we can appropriately diagnose iron deficiency in our patients with heart failure. But, of course, the clinically relevant question that's most important is, once diagnosed, what do we do about it? Is there a way for us to correct iron deficiency, and does correcting iron deficiency actually translate to better patient outcomes, including hospitalizations, but also symptoms, function, quality of life?

Dr. Jankowska:

Indeed. Using very simple parameters, we can identify patients who are iron deficient, and these patients are suitable for intravenous iron supplementation. Importantly, please remember that we already have evidence that oral iron therapy does not work in patients with heart failure, so the only option to effectively supplement iron is intravenous therapy. This treatment is provided in a very simple, pragmatic way. Usually, patients can receive 1 or 2 doses of intravenous ferric carboxymaltose, and thanks to this treatment – and it has been shown already in some clinical trials – we can immediately, within a few weeks, improve quality of life of our patients, but also we can cause that they have better exercise capacity, and the symptoms of heart failure significantly alleviate. The effects are really important from a clinical point of view, but something that we also observed in our patients, and it has been confirmed, demonstrated in our recent AFFIRM-AHF trial, is that when we supplement intravenous ferric carboxymaltose in patients with heart failure, most of them have experienced heart failure hospitalization, we reduced the risk of recurrent heart failure hospitalization.

Dr. Kosiborod:

So that's a critical point, right? That you don't necessarily need to be anemic or have iron deficiency anemia. If you have iron deficiency period, supplementation with intravenous iron appears to significantly reduce the risk of heart failure hospitalizations and, in the relatively short term, shows improvements in symptoms, function, quality of life as measured by Kansas City Cardiomyopathy Questionnaire (KCCQ).

Well, for those just tuning in, you're listening to CME on ReachMD. I'm Dr. Mikhail Kosiborod, and here with me today are Dr. Ewa Jankowska and Dr. Phil McEwen. We're discussing the impact of iron deficiency on patients with heart failure, and key considerations for the use of IV iron in clinical practice.

So let's shift gears just a little bit. And, Phil, I'm going to ask you to really give us some additional information that given this clear evidence for iron repletion therapy as being efficacious and those important endpoints, what is the perspective from pharmacoeconomic standpoint? Is it actually a cost-effective strategy to improve symptoms in this patient population?

Dr. McEwan:

Yeah, it's a great question, and as we've heard, the significant burden associated with heart failure and iron deficiency, it really manifests itself in increased risk of hospitalization and a decrease in quality of life. And of course, a key consideration, given that healthcare budgets aren't infinite, is the acquisition costs associated with therapies that bring about improvements like this. Do they represent good value for money? And that's exactly what we undertook. We undertook a cost-effectiveness analysis that was designed to ascertain whether the acquisition cost of the ferric carboxymaltose delivered good value for money. And in order to do that, we developed a lifetime cost-effectiveness model aligned to the patient-level data of the AFFIRM-AHF trial in order to predict both the frequency of heart failure hospitalizations, the expected levels of mortality over a lifetime, as well as changes in quality of life as measured by the KCCQ linked to the EQ5D [EuroQoL-5D]. What was particularly interesting about the study we did was that the cost savings associated with the reduction in hospitalizations for heart failure episodes that was seen in the clinical trial more than compensated for the acquisition cost associated with ferric carboxymaltose, resulting in a situation of cost saving, or expected cost saving. We explored this over a number of predefined subgroups and came up with the similar conclusions. That, taken into consideration alongside the improvements in quality-adjusted life years associated with both those reductions in hospitalizations as well as improved functional status as measured by KCCQ, resulted in a term that we use, which is dominant, which means that the therapy is expected to be both cost saving and associated with improved quality-adjusted life years.

Dr. Kosiborod:

And that's – and correct me if I'm wrong, Phil – but that's not a very common situation in the heart failure world or the world of cardiovascular disease that we live in, when we do clinical trials and find efficacious therapies, that not only you would have clinical

effectiveness, which clearly was shown in the AFFIRM-AHF trial, but there is also not just cost-effectiveness, but in fact, cost savings. So essentially, and correct me if I'm misinterpreting what you are saying, but essentially, you do the right thing for the patient, and this also results in cost savings, at least from the economic standpoints that you did the study with.

Dr. McEwan:

That's exactly the case, and I think it's even more interesting, or even more rare, in the sense that often with chronic conditions, you tend to see an additional up-front increase in expenditure associated with pharmacotherapy, bringing about cost savings in the longer term. But what we saw here was cost savings within years. So essentially, even when we did a within-trial analysis, we still saw a reduction in costs, and that result was robust across all key subgroups that we looked at. And the gains in quality-adjusted life years, given that these were a fairly advanced cohort of patients with heart failure, the gains in quality-adjusted life years was of similar order of magnitude and has been seen and predicted in studies like PARADIGM and DAPA-HF.

Dr. Kosiborod:

Got it. So I think pretty straightforward and consistent data across a variety of economic conditions, which is really important.

So, Ewa, let me maybe pose another question to you, because I think it's really critically important. We had a highly symptomatically impaired patient population in AFFIRM-AHF that had a high risk of repeat hospitalizations, and of course those are the kinds of patients that you would expect to have high risk of hospitalization and death. We see clinical events benefit, we see quality of life benefits, it's economically dominant, but the problem is that most patients are at risk of not potentially benefiting from the therapy, because frankly, most patients aren't being tested for iron deficiency. Do you have any thoughts about how we can change that and make sure that our colleagues that are taking care of these patients are aware of this very important data?

Dr. Jankowska:

I think extremely important is to increase awareness about this problem among us as cardiologists, among GPs, among nurses, but also among patients themselves, because it also can be the patient which comes to the physician and is asking for screening for iron deficiency. Something which I think is extremely important also to emphasize, the screening for iron deficiency is extremely cheap, and also the treatment of iron using intravenous ferric carboxymaltose can be also applied in outpatient settings. Extremely important that we do not need to hospitalize patients to supplement intravenous iron. And also, there have been some hesitations among physicians, among nurses, that there may be some side effects like allergic reactions due to intravenous iron treatment, but we need to remember that this reaction was seen with old formulas of intravenous iron. The modern therapy with intravenous ferric carboxymaltose is extremely safe. It's much safer to use intravenous iron than, for example, using intravenous antibiotics, which we are using in everyday clinical practice in our patient clinic.

Dr. Kosiborod:

So again, really important point, and I think, overall, this certainly has been a fascinating conversation. But before we wrap up, Dr. Jankowska and Dr. McEwan, can you each share your one take-home message with our audience, who of course, majority of which are going to be clinicians? So, Ewa, I'm going to ask you first. What would you say is the key take-home message for those that are going to be watching this?

Dr. Jankowska:

I think that with the example of iron deficiency and its correction in patients with heart failure, we are observing such phenomenon that correcting non-cardiovascular morbidity, we can change the natural history of heart disease. This is something unique.

Dr. Kosiborod:

And Phil? What about you, from your standpoint?

Dr. McEwan:

Yeah, thanks. I mean I think from the substantial burden that heart failure places on both healthcare systems and patients, to have a new therapeutic option that results in both a cost saving and gains in quality-adjusted life years is really quite remarkable.

Dr. Kosiborod:

So there you have it, folks. Essentially, here is a take-home point from my standpoint. Iron deficiency is very common in patients with heart failure. Correcting iron deficiency with intravenous iron has now been demonstrated to reduce the risk of clinical events such as heart failure hospitalizations, improve the quality of life within a relatively short term. It's economically dominant, meaning that it actually saves money, and this is something that we as cardiologists, given how common it is, really need to keep in mind in the patients that we see. And given such a high residual risk in this patient population, it's a really critically important learning point, I think, for all of us. So with that, thank you all for watching.

Dr. Jankowska:

Thank you very much.

Dr. McEwan:

Thank you.

Announcer:

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