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### Don't Be Fooled: It's Not Just Anemia, It's Iron Deficiency

Announcer:

Welcome to CME on ReachMD. This activity, entitled "Don't Be Fooled: It's Not Just Anemia, It's Iron Deficiency" is provided by Medtelligence and is supported by an independent educational grant from Vifor Pharma.

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Dr. Mentz:

Iron deficiency is a common comorbidity in heart failure, affecting up to 50% of patients. It affects exercise capacity, quality of life and patient outcomes. But, when should clinicians be thinking about iron deficiency, and how is it diagnosed and treated?

I'm Dr. Robert Mentz, and joining me today to discuss iron deficiency in heart failure is Dr. Piotr Ponikowski. Dr. Ponikowski, welcome to the program.

Dr. Ponikowski:

Well, thank you very much for the invitation. It's a great subject, so I am very happy to join you.

Dr. Mentz:

I can think of no one better to go through this, so thank you for joining us. Let's begin our discussion with when should we be thinking about iron deficiency in patients with heart failure. Should we only be focusing on those patients with anemia?

Dr. Ponikowski:

We sort of intuitively link iron with hematopoiesis, which is correct, because iron takes a place, a crucial role in the bone marrow and it's very much involved in efficient hematopoiesis. This is why we immediately link iron deficiency with low hemoglobin and with anemia. However, over the last 15–20 years, we sort of changed this mindset, and we now know that iron deficiency can be present and in parallel can be a comorbidity which complicates the natural course of heart failure regardless of hemoglobin level.

There is very interesting data we published together with colleagues from the Netherlands in which we evaluated iron deficiency in patients with heart failure and reduced ejection fraction. We use a definition, to which I would refer in a second—just remember it was a chronic setting of heart failure, more than 1,500 patients, and what we discovered was that iron deficiency was present in around 60% of anemics but also complicated heart failure in around 45% of patients who did not have anemia. So, as I said, regardless of hemoglobin and regardless of anemia status, iron deficiency was very common. Importantly, iron deficiency was present in all the heart classes, I would say, again, regardless of heart failure severity.

Later on, I'm sure we will be discussing different types of iron deficiency, but I can only say that iron deficiency was present in around 30–40%, even with mild heart failure and then complicated heart failure in around 60%, even to 70% of patients with advanced NYHA Class B-IV. Additional studies also were done in patients who were admitted to the hospital due to heart failure decompensation with acute heart failure with virtually the same results. Over 50% of patients who presented to the hospital with heart failure decompensation tended to have iron deficiency, again regardless of ejection fracture, regardless of etiology and regardless of hemoglobin level.

Dr. Mentz:

Thank you so much, Dr. Ponikowski, really highlighting some of the most important considerations that iron deficiency is very common in heart failure, as you noted, regardless of EF, regardless of anemia status and even regardless of severity of heart failure disease, so really important key take-home pearls for our group today. Maybe moving on a little bit—and you started to begin to mention this, really—how do we diagnose iron deficiency in patients with heart failure?

Dr. Ponikowski:

We focused on 2 biomarkers, ferritin and transferrin saturation. Ferritin in the peripheral blood reflects the iron storage, whereas transferrin saturation reflects the level of iron being utilized in the periphery. So, in brief, we tended to build up the definition on the basis of 2, on low ferritin level, and in heart failure, we use this catch level of 100 mcg/liter. So we say iron deficiency when serum ferritin is below 100 mcg/deciliter, or in the case when we have ferritin in this gray zone, in this borderline zone, between 100–300 mcg/liter, then we add to this a second criterium, which is transferrin saturation with a catch level of 20%, so we say transferrin saturation should be below 20%.

To be quite honest with you, some people are using only transferrin saturation and saying perhaps transferrin saturation below 20% would be enough. However, I think that according to the European and also American guidelines, ferritin and transferrin saturation should be performed simultaneously and evaluated together in order to diagnose iron deficiency. But we also need to remember that iron deficiency and anemia, as we said, often coexist, and in the process of iron deficiency diagnosis, we always need to take this into consideration because underlying causes of anemia should be also looked at, and we always take into account the possibility of coexisting malignancy.

Dr. Mentz:

Moving on a little bit then, when should we test for iron deficiency in clinical practice? What do the guidelines tell us here in this space?

Dr. Ponikowski:

Again, we are testing virtually everyone. That is what we wrote in 2016. I am sure that some guidelines from different parts of the world may take a little bit different view but what was our recommendation based on, as we discussed, studies pointing out really high prevalence. An additional argument was that iron deficiency is an important element affecting quality of life and exercise tolerance, and the third one was association between iron deficiency and poor outcome. This is why we said iron deficiency should be looked at and should be diagnosed in all new cases of patients who are coming in with a preliminary diagnosis of heart failure. I think that is the bottom line of the guideline recommendation.

We may also consider a little bit different scenario, what about patients who already have heart failure diagnosed? So, it's not the beginning when, as I said, we need to actively look for iron deficiency. What about those who already have heart failure diagnosed? In which cases we need to think of potential iron deficiency perhaps as a cause of underlying exercise intolerance or deterioration.

Dr. Mentz:

Great. Thank you, Dr. Ponikowski. And just to highlight one area that has caused some confusion in the US guidelines—I think some of this is how the document is set up—but the discussion around iron deficiency occurs in a section entitled Anemia, so I think that has led some to have a harder time differentiating or distinguishing when iron deficiency can occur even if it is not in the setting of anemia. I think you've summarized this nicely, that we need to be thinking about iron deficiency at the time of diagnosis as well as, importantly, during the follow-up period, so really across the disease spectrum.

For those just joining us, this is CME on ReachMD. I'm Dr. Robert Mentz, and I'm speaking with Dr. Piotr Ponikowski about iron deficiency in heart failure.

We'll move on to the next section here. Dr. Ponikowski, what do the guidelines say about how to treat iron deficiency in heart failure with reduced ejection fraction?

Dr. Ponikowski:

We have CONFIRM-HF and FAIR-HF in which, in patients with heart failure and reduced ejection fraction, we corrected iron deficiency with IV iron, so intravenous iron, and we observed in both studies the same results—double-blind, placebo-controlled, randomized trials, patients with heart failure and reduced ejection fraction in the Heart Class II and III, and we had a very clear message. Correction of iron deficiency improves exercise capacity, improves duration of exercise test, improves quality of life, is safe. And we have also, based on meta-analysis of the data, individual patients put together, we have the evidence that perhaps there will also be a beneficial effect on mortality and morbidity. However, now we are testing this in randomized clinical trials.

I am sure that you'll ask me the next question: Why not to treat iron deficiency with oral iron? This study called IRONOUT was meant to prove that repleting iron deficiency with oral iron would give the same results as intravenous iron. Unfortunately, giving oral iron for 3

consecutive months in this pretty big trial, also double-blind, placebo-controlled study, nothing happened. There was nothing in terms of improvement in exercise capacity. Even more importantly, there was no improvement in biomarkers reflecting iron deficiency. I'm sorry to say oral iron does not work in patients with heart failure.

Dr. Mentz:

So really, IV iron for iron deficiency has been shown to be safe and efficacious with respect to some of these important surrogate measures, and we await some of those larger clinical outcome trials.

Now that we've discussed which patients should be treated and how, let's consider a patient case, Dr. Ponikowski.

Dr. Ponikowski:

Let me discuss with you a case referred to us quite a few weeks ago. It was a 76-year-old woman with pretty advanced symptoms and had stage III. She has got dyslipidemia, hypertension, myocardial infarction several years ago. Heart failure was diagnosed only 4 years ago. It was pretty stable but gradually deteriorating. The last echo showed ejection fraction of around 35%. Now she experiences deterioration and shortness of breath from moderate exertion. She was pretty active, but now she's only able to walk 330 meters during her 6-minute walking test. She denies angina. She's pretty well treated, receiving spironolactone 50 mg once daily, sacubitril/valsartan, and her maximum dose is 97/103 mg twice daily, carvedilol 25 mg twice daily, and her volume status is well-controlled with furosemide. On physical exam her heart rate was 75, blood pressure around 115, 120, respiratory rate 23 breaths per minute, and there was no peripheral edema and no congestion. She's not happy with the current status, and she is referred to us for some sort of help and changes in her management. So, how would you respond? Please comment.

Dr. Mentz:

, so this is a good example of a patient who is still symptomatic, and we need to be considering iron deficiency. I would approach this by checking a CBC in this patient, checking those iron indices that you went through, and then based on those data and an additional discussion making sure that there isn't some other etiology for potential underlying anemia, if we do discover that she does have iron deficiency, we need to think about IV iron in this patient, and that is something that really could help in terms of her functional status, her symptoms, and potentially even improve her clinical outcomes as we await some of those additional data.

Is there anything you'd like to add, Dr. Ponikowski? Really, a remarkable case.

Dr. Ponikowski:

I entirely share your view. That's exactly what we did. She has got clear evidence of iron deficiency with pretty low ferritin of around 65, 70, with transferrin saturation far below 20%. As you correctly pointed out, at her age we performed a pretty broad diagnostic checkup related to any potential malignancy, fortunately nothing there, and we just initiated IV iron in this case, and we see what is going on, and we really keep our fingers crossed that we improve her exercise capacity and hopefully her outcome as well. Thanks that we are on the same side.

Dr. Mentz:

Great. Thank you so much. These are really very important points for our colleagues in clinical practice to remember. We need to be more proactive in screening patients with heart failure for iron deficiency and then treating those patients who are symptomatic with IV iron.

I'd like to thank Dr. Piotr Ponikowski for helping us better understand this important topic. Dr. Ponikowski, it was great speaking with you today.

Dr. Ponikowski:

Thank you very much. It was my pleasure. Thank you very much for the invitation. I hope that we at least introduced this important topic and gave some hints on how to diagnosis and treat.

Announcer:

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