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FAIR-HF2 Trial: Ferric Carboxymaltose Assessment of Morbidity and Mortality in Patients with Iron Deficiency and Chronic Heart Failure

Dr. Anker:
Hello, everybody. My name is Stefan Anker. I'm here at the American College of Cardiology in Chicago at the 2025 meetings. We just were at the late-breaker session, and I'm here with Dr. Mahir Karakas from Hamburg in Germany, who actually, together with me, we had the chance to lead this trial and investigate the initiated trial.

Hello, welcome.

Dr. Karakas:
Welcome.

Dr. Anker:
So, tell us a little bit, Mahir, what about the design features? What's the reason we did this trial, and the patient population studied, maybe?

Dr. Karakas:
So, FAIR-HF2 is, as you said, an investigator-initiated trial. A total of 1,105 patients were randomized to receive either intravenous iron or placebo saline. These patients were recruited at around 70 sites in Europe, mainly in Germany, but also in five other European countries, and patients were eligible if they had a documented chronic heart failure of at least 3 months of duration with an ejection fraction of 45% or less. We also asked the patients who have of course, a concomitant iron deficiency, which was defined as a ferritin level below 100 nanograms per milliliter, or up to 299 nanograms per milliliter if there isn't transferrin saturation below 20%.

Further main inclusion criteria was mild to moderate anemia, the ferritin level being between 9.5 and 14 grams per deciliter, and these patients were randomized 1-to-1 to ferric carboxymaltose, our choice of iron here in this trial, or placebo, as I said, saline. The placebo-controlled treatment phase with intravenous iron was split into a maintenance phase and a correction phase. The correction phase was set at the start of the trial, so took up to 4 weeks to supplement up to 2,000 milligrams of intravenous iron, by which it was then followed by a pretty aggressive dosing regimen of 500 milligrams of intravenous iron each and every 4 months, unless stop criteria were met. And this stop criteria were a ferritin beyond 800 nanograms per milliliter or a hemoglobin beyond 16 grams per deciliter.

But between the two and us, and we can hear a way, so-to-speak.

Dr. Anker:
This didn't happen very often, right?

Dr. Karakas:
Didn't happen very often, right? Correct. It was very, very rare incident that we had to give placebo instead of instead of iron.

Dr. Anker:

How long was the follow-up of the trial?

Dr. Karakas:
Well, we expected a median follow-up of 2 years to evaluate three main hypothesis. I think you should show this in the results. And the population studied was a pretty representative heart failure population. So, mean age of around 69 to 70 years. Predominantly male patients, so one to, about 740 were male. And the therapy adherence to guideline recommended regimen was pretty high, with a higher rate of intracardiac devices, a high rate of SGLT2 inhibitors, and these patients were followed up as we asked for, up to 4 weeks.

Dr. Anker:
The treatment was given on top of guideline directed medical therapy?

Dr. Karakas:
Yes.

Dr. Anker:
But importantly, we need to emphasize, placebo-controlled.

Dr. Karakas:
Absolutely.

Dr. Anker:
Well, basically, thank you. This is giving us a good idea about this randomized controlled trial. Now, I would like to summarize the result. We have 3 primary endpoints, cardiovascular death and heart failure hospitalization as a time-to-first-event, 21% reduced. P-value of 0.038. Then, we had the recurrent heart failure hospitalization because we know that the burden of disease really is not only affecting first, but also second and third hospitalization, 20% reduced. P-value of 0.1.

And then, interestingly, we had a third primary endpoint where we investigated how this subgroup of patients with a transferrin saturation of less than 20%, which is simply an easier definition worked. Uh Also there, a 21% reduction. Now, in conclusion, we can say that in phase of two, we show event reductions that are in line with the previous trials. We confirm that the quality of life results highly statistically significant, are positive. And we also say something about the definition. I mean, there is a guideline recommended definition that you quoted about ferritin and TSAT using together. But actually, if you use the TSAT less than 20 definition, you also get good results for the study, but not necessarily better results. So, either kind of definition can be used.

Now, what else can you tell us, the audience here about maybe the meta-analysis and other things?

Dr. Karakas:
Yeah. Well maybe, well, let's just start with the note that we have to acknowledge that intravenous iron was a guideline recommended therapy even before FAIR-HF2, right? It was clear evidence that intravenous iron improves functional capacity symptoms and clinical cardiovascular outcomes. And I have three take-home messages, three main messages out of this trial. First, we have a striking consistency with regard to the previous trials, landmark trials. And you mentioned the meta-analysis which you led, which was also published right today. Six large landmark trials, iron outcome trials, and we see striking 20% reduction across these trials for the primary heart failure outcomes.

Second, it’s important to say that there seems to somehow be a differential effect between men and women with regard to heart prognostic outcomes. This is something we didn't expect, but which we need to keep an eye on it.

Dr. Anker:
Do you have an idea mechanistically already, or is this something that still needs to be –

Dr. Karakas:
That’s definitely something that needs a lot of research on, but it might be with somehow connected to estrogen levels and especially decreasing estrogen levels in postmenopausal state. But this is something we asked to keep an eye on.

And thirdly, we again see also, across the meta-analysis, not just in FAIR-HF2, that iron not given is iron not effective. So, there is a strong implication of need for therapy adherence. We have to train physicians and patients that although we know that intravenous therapy in general is somehow challenging sometimes in clinical practice, this is crucial in terms of heart outcome reduction. As the meta-analysis showed, if we stick to year 1 and 2, where the dosages and therapy adherence were pretty high, we have risk reduction for heart outcomes of around 30%.

Dr. Anker:
But how do we give this now in the future, in the long term? I mean, it's inconvenient sometimes of course, in the patient/physician interaction that the spending all the time. Is there easier ways of arranging this maybe in clinics?

Dr. Karakas:
Yeah. What might be a solution, what is nowadays upcoming, the Drip Clinics. So, Drip Clinics might coordinate with physicians, with GP, with GPs and cardiologists, to cover routine IV iron administrations. That might be some way to get over this barrier.

Yeah. Thank you so much.

Well, for the audience, we have here the FAIR-HF2 trial that basically today, came out in JAMA. You can see this online. The meta-analysis of 7,175 patients summarized eloquently also coming out today in Nature Medicine. We basically now, show that this treatment can be used, it should be used as the guideline described. With the previous trials maybe putting some doubts in all of this. If you take, for instance, the HEART FIT trial, this is not justified. It's really a treatment that works for quality of life, for symptoms, for events. We basically, here, had the chance to present this investigator-initiated trial together. And look at the studies, they're showing good results. This is something for the future.

Well, thank you so much for your attention. We are here at the ACC 2025. Stefan Anker says bye-bye, and Mahir Karakas, I guess, as well. Thank you very much. Bye-bye.