Title: HFA 23: IRONMAN: Anemia, Iron Deficiency and Quality of Life
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Dr Paul Kalra

"Hello. My name is Paul Kalra. I'm consultant cardiologist and heart failure specialist at Portsmouth Hospital's University NH Trust in the United Kingdom. And I was chief investigator for IRONMAN, which was atrial that was funded by the British Heart Foundation.

Please briefly outline the IRONMAN Trial.

So, IRONMAN was a randomized trial of intravenous ferric derisomaltose and usual care versus usual care alone in patients with heart failure, a reduced ejection fraction and an iron deficiency. We presented this and published this in 2022and the main trial showed that intravenous ferric derisomaltose reduced the risk of the primary endpoint which was a combination of cardiovascular death and recurrent heart failure hospitalization by 18%. The p value was 0.07. But our trial was markedly impacted by COVID and when we did a prespecified COVID sensitivity analysis we had a rate ratio of 0.75 and the p value of less than 0.05. The main benefit appeared to be on a reduction in heart failure hospitalization.

What were the substudies you presented at HFA 23?

So, we now have several secondary analyses from IRONMAN. Firstly, we have been interested in looking at the impact of ferric derisomaltose on infections and the reason for this is that previous trials of intravenous iron in other disease areas have questioned as to whether it might be associated with a higher risk of infection. But they've had major limitations because this wasn't a prespecified analysis and as such, subject to potential reporting bias in IRONMAN, all deaths and hospitalizations were blindly adjudicated, and this was a prespecified endpoint and we found that there was no excess risk of infections as a cause of hospitalization or death. And in fact, when you look to time to first event there was a 21% reduction with ferric derisomaltose that approached

statistical significance of p-value of 0.055. What we did find looking at COVID adverse events was there was a 60% statistical reduction in COVID-related events with intravenous iron.

What are the main findings?

So, I think that the benefits of these data are when we are speaking to our patients discussing the risk benefit of a drug like intravenous iron, we now have increasing data about the safety profile, if you like, for intravenous iron and the fact that there's no excess risk with infections is good news. We've also had other presentations having a deeper dive into quality of life at four months and consistent with previous studies with the different intravenous iron, ferric carboxymaltose, that have shown benefits on quality of life, we found very similar findings at four months with the Minnesota living with heart Failure questionnaire. That was primarily driven by improvements in the physical domain. And what we've seen is as patients had lower TSATs then their quality of life was worse at baseline, but they appeared to have more to gain from intravenous iron. And similarly, the patients with moderate anaemia as opposed to mild anaemia or normal haemoglobin again had impaired quality of life at baseline and they appeared to have more to gain from intravenous iron in terms of benefits on quality of life. So, again, that's good news. We can tell our patients seems to benefit on the reducing the risk of heart failure hospitalization, but also an improvement in quality of life. And finally, we've looked across the ages, age of patients, that is, we had a quarter of our patients were 79 or older. And again, what is important here, because these are people that we're seeing in real life, day to day clinical pathways, the benefits seem to be maintained in that older age group.

What are your take-home messages for clinicians?

So, I think the important thing is if you've got a patient with heart failure and any degree of reduced ejection fraction, please screen them for iron deficiency. If you don't look for it, you're not going to find it. And when present, then correction with high dose intravenous iron is a good way to help patients feel better and reduce the risk of heart failure hospitalization, and there's a low risk of adverse events with intravenous iron.

What further study is required?

So, there are a few things we still need to establish. One is, is there a better marker for iron deficiency and the potential response to intravenous iron than we're using now? These have been arbitrary definitions and I think the data that we're seeing from IRONMAN and pooled analysis with other studies is that a transferring saturation of less than 20% is particularly important here. I think we need to understand more about the potential benefits in patients with heart failure and preserved ejection fraction. We haven't got data on that group now and hopefully we'll see some later this year. And then finally, whilst there were numerically fewer cardiovascular deaths in IRONMAN, it didn't reach statistical significance. There's another trial called Heart Fit that we'll present later this year and I think looking at a pooled analysis of trials will be very interesting in that respect.