Unanswered questions from the IRONMAN trial – Authors' reply

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We thank Pierre Ambrosi and Gilbert Habib, and Tomohiko Sato and Ayumi Nojiri for their Correspondences. Ambrosi and Habib cast doubt on the morbidity and mortality benefits of intravenous iron in heart failure and commented on the potential risks of hypophosphataemia, allergic reaction, and infection. Although there is no current evidence that intravenous iron reduces the risk of death, there is good evidence that it reduces heart failure hospitalisation risk.[1, 2, 3] We agree that any proposed treatment should be discussed with patients as part of shared decision making. Although hypophosphataemia can be seen after intravenous iron infusion, it is substantially less common with ferric derisomaltose than with ferric carboxymaltose.[4] The risk of serious hypersensitivity reaction varies according to the formulation of intravenous iron.[5] Among 35 737 iron infusions, serious reactions were exceedingly rare with only two documented epinephrine administrations—both in patients receiving iron dextran. We did not find any excess risk of infection or serious hypersensitivity with intravenous ferric derisomaltose in the IRONMAN trial.[2]

Sato and Nojiri expressed disappointment in the results of IRONMAN and commented on both oral iron use in the usual-care group and the importance of measuring hepcidin concentrations. Additionally, they mentioned dropouts due to cardiac and non-cardiac deaths, blood transfusions, and the importance of subgroups based on anaemia and estimated glomerular filtration rate (eGFR). The primary endpoint in the IRONMAN trial included cardiovascular death (the majority of deaths), which included all cardiac and some non-cardiac deaths. There was no evidence of an increase in all-cause mortality. Hence, we do not understand the relevance of their comments on the effect of cardiac and non-cardiac deaths as dropouts. The IRONMAN trial was greatly affected by COVID-19, resulting in underutilisation of intravenous iron in the ferric derisomaltose group. In these circumstances we did not find the results disappointing. We intend to publish analyses to explore the effect of oral iron use in the usual-care group. We have a biobank of blood samples and will be measuring markers involved in iron metabolism, including hepcidin. The decisions to give some patients blood transfusions are likely to have been influenced by multiple factors (eg, haemoglobin concentration and evidence of acute blood loss) and, as such, we do not think it is possible to comment on whether this constitutes a liberal

transfusion strategy. Finally, we have already analysed data according to anaemia status and eGFR; these data can be found in the appendix of our IRONMAN study (pp 12–13).[2]

Disclosures:

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References:

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3 Graham FJ, Pellicori P, Ford I, Petrie MC, Kalra PR, Cleland JGF. Intravenous iron for heart failure with evidence of iron deficiency: a meta-analysis of randomised trials. Clin Res Cardiol 2021; 110: 1299–307.

4 Wolf M, Rubin J, Achebe M, et al. Effects of iron isomaltoside vs ferric carboxymaltose on hypophosphatemia in iron-deficiency anemia: two randomized clinical trials. JAMA 2020; 323: 432–43.

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