The Lancet

Possible confounding factors in the IRONMAN trial

--Manuscript Draft--

Manuscript Number:	THELANCET-D-22-07400
Article Type:	Correspondence
Keywords:	Heart failure; iron deficiency; intravenous iron; ferric derisomaltose; blood transfusion
Corresponding Author:	Tomohiko Sato, M.D., Ph.D. Jikei University Hospital: Tokyo Jikeikai Ika Daigaku Fuzoku Byoin Honin Minato, Tokyo JAPAN
First Author:	Tomohiko Sato, M.D., Ph.D.
Order of Authors:	Tomohiko Sato, M.D., Ph.D.
	Ayumi Nojiri, M.D., Ph.D.
Manuscript Region of Origin:	JAPAN
Additional Information:	
Question	**Response**
Are you are writing in response to published content in The Lancet?	Yes
Please type the full reference to that content here (for example: Cuzick J et al. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. Lancet 2020; 394: 117-22). as follow-up to "Are you are writing in response to published content in The Lancet?"	Kalra PR et al. Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. Lancet 2022; 400: 2199–209.
Author Comments:	This is a correspondence letter to the Lancet article entitled "Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial" by Kalra PR et al (Lancet 2022; 400: 2199–209).

Powered by Editorial Manager® and ProduXion Manager® from Aries Systems Corporation

Manuscript Click here to view linked References

Title

Possible confounding factors in the IRONMAN trial

Text

Considering the equal efficacy and better safety profile of intravenous ferric derisomaltose (FDI) compared to ferric carboxymaltose (FCM),[1,2] and the recent European Society of Cardiology guidelines that strongly recommend FCM administration for treating iron deficiency in patients with systolic heart failure,[3] the IRONMAN trial results seemed disappointing. Our related concerns are as follows.

First, permitting oral iron therapy in the usual-care group might have had a substantial effect on relieving heart failure patients with iron deficiency, given the increasing trend of haemoglobin levels (Figure S5). Subdividing the usual-care group by oral iron therapy will enable to compare the effects between intravenous and oral iron, enhancing the value of the trial. Additionally, hepcidin levels can be helpful as these are associated with responsiveness to oral iron therapy, including changes in ferritin, TSAT, and sTfR.[4]

Second, as both groups had a sizable dropout due to cardiac/non-cardiac death, the resultant population shifts could have obscured the between-group differences; the remaining FDI-treated group consisted of patients requiring and not requiring FDI for their survival, while the remaining usual care group consisted of those not requiring FDI. Furthermore, even with FDI treatment, 4% had blood transfusions at the discretion of attending physicians (Table S4), suggesting the suitability of a liberal transfusion strategy for iron-deficient elderly patients with symptomatic heart failure.

Third, anaemia-prone subpopulation should be considered separately, such as patients treated with angiotensin-converting enzyme inhibitor[5] and those with low estimated GFR, since the related symptoms are indistinguishable from those with iron deficiency and/or heart failure.

References

1 Zoller H, Wolf M, Blumenstein I, *et al*. Hypophosphataemia following ferric derisomaltose and ferric carboxymaltose in patients with iron deficiency anaemia due to inflammatory bowel disease (PHOSPHARE-IBD): a randomised clinical trial. *Gut* 2022; **0**: 1–10.

2 Pollock RF, Biggar P. Indirect methods of comparison of the safety of ferric derisomaltose, iron sucrose and ferric carboxymaltose in the treatment of iron deficiency anemia. *Expert Rev Hematol* 2020; **13**: 187–95.

3 McDonagh TA, Metra M, Adamo M, *et al*. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021; **42**: 3599–3726.

4 Bregman DB, Morris D, Koch TA, He A, Goodnough LT. Hepcidin levels predict nonresponsiveness to oral iron therapy in patients with iron deficiency anemia. *Am J Hematol*

2013; **88**: 97–101.

5 Ishani A, Weinhandl E, Zhao Z, *et al*. Angiotensin-converting enzyme inhibitor as a risk factor for the development of anemia, and the impact of incident anemia on mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2005; **45**: 391–9.

Keywords

Heart failure; iron deficiency; intravenous iron; ferric derisomaltose; blood transfusion

Authors

Tomohiko Sato, M.D., Ph.D.
Associate Professor
Division of Transfusion Medicine and Cell Therapy
The Jikei University Hospital
Tokyo, Japan
tomosatou@jikei.ac.jp

Ayumi Nojiri, M.D., Ph.D.
Lecturer
Department of Laboratory Medicine
The Jikei University School of Medicine
Tokyo, Japan
ayunoji@jikei.ac.jp

All authors declare no competing interests.

Link to the published version of this manuscript:
10.1016/S0140-6736(23)00449-X