

## Invited Editorial / Davetli Editöryal Yorum

### Anemia and heart failure: Is there still a role for erythropoiesis-stimulating agents?

#### Anemi ve kalp yetersizliği: Eritropoezi uyaran ajanların hâlâ bir rolü var mı?

Massimo Volpe, M.D., Vittoria Mastromariona, M.D.

Department of Cardiology, Clinical and Molecular Medicine, Sapienza University of Rome at Sant'Andrea Hospital, Rome, Italy

After early reports of erythropoiesis-stimulating agents (ESAs) having success correcting anemia in heart failure (HF), the Reduction of Events by Darbepoetin Alfa in Heart Failure (RED-HF) study, a large phase III trial, demonstrated that darbepoetin alfa was not able to improve clinical outcomes in patients with HF who had reduced ejection fraction and mild to moderate anemia, and indeed, it led to an excess of thromboembolic events.<sup>[1]</sup> In view of those results, recent guidelines do not recommend ESAs for the treatment of anemia in HF patients.<sup>[2]</sup>

Concerns regarding the safety of ESA therapy had been already raised for patients with chronic kidney disease (CKD).<sup>[3,4]</sup> In fact, in 2011, the US Food and Drug Administration issued a boxed warning for the label of ESAs for patients with CKD recommending initiation of ESA treatment when hemoglobin level was less than 10 g/dL (previously, 10-12 g/dL). Individualized dosing and using the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions were also recommended.<sup>[5]</sup> This has been addressed extensively in earlier review articles.<sup>[6-8]</sup>

At present, it remains unclear whether it is the dose of ESA administered, the level of hemoglobin achieved, or a hyporesponsiveness to therapy that explain these adverse outcomes.

It is well known that anemia is common in HF and is associated with an increased mortality risk.<sup>[9]</sup> The pathogenesis of anemia in HF is multifactorial,

and includes renal dysfunction, chronic inflammation, iron deficiency, and erythropoietin (EPO) deficiency.<sup>[9,10]</sup> Patients with HF actually have markedly elevated plasma EPO level, which is related to the severity of HF and which is a prognostic marker for impaired survival, independent of hemoglobin levels.<sup>[11-13]</sup> Impaired renal perfusion, fluid retention, and general hypoxia are all factors that can contribute to increase in serum EPO.<sup>[14,15]</sup> Moreover, the presence of EPO resistance in the bone marrow, due to a state of inflammation, or of iron, vitamin B12, or folate deficiency, may explain why, although increased in absolute terms, plasma EPO levels are still relatively low and inadequate to stimulate hematopoiesis in the bone marrow.<sup>[10,16]</sup> Based on these data, it was postulated that ESAs could be a useful tool in the treatment of anemia in HF patients. A better understanding of the etiology of anemia, the optimal hemoglobin target, and of the comorbidities in which use of ESAs should be avoided, would likely permit one to identify the potential beneficial effect of ESAs that still might have a rationale in the treatment of HF. It might also be interesting to investigate the effect of ESA therapy in patients with HF with preserved ejection fraction, as it has pathophysiological and clinical expression that is substantially different from HF with reduced ejection fraction. This may imply different impact on treatments.<sup>[17]</sup>

**Conflict-of-interest issues regarding the authorship or article: None declared.**

Received: December 08, 2016 Accepted: December 08, 2016

Correspondence: Dr. Massimo Volpe. Via Di Grottarossa, 1035-39 00189 Rome, Italy.

Tel: +390633775979 e-mail: massimo.volpe@uniroma1.it

© 2017 Turkish Society of Cardiology



## REFERENCES

1. Swedberg K, Young JB, Anand IS, Cheng S, Desai AS, Diaz R, et al. Treatment of anemia with darbepoetin alfa in systolic heart failure. *N Engl J Med* 2013;368:1210–9. [CrossRef]
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129–200. [CrossRef]
3. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;355:2085–98. [CrossRef]
4. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009;361:2019–32. [CrossRef]
5. <http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm>. Accessed April 10, 2017.
6. Mastromarino V, Volpe M, Musumeci MB, Autore C, Conti E. Erythropoietin and the heart: facts and perspectives. *Clin Sci (Lond)* 2011;120:51–63. [CrossRef]
7. Mastromarino V, Musumeci MB, Conti E, Tocci G, Volpe M. Erythropoietin in cardiac disease: effective or harmful? *J Cardiovasc Med (Hagerstown)* 2013;14:870–8. [CrossRef]
8. Volpe M, Santolamazza C, Mastromarino V. Erythropoiesis-stimulating agents in heart failure: leave it or re-take it? *Eur J Heart Fail* 2015;17:1089–90. [CrossRef]
9. Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, van Veldhuisen DJ, et al. Anemia and mortality in heart failure patients a systematic review and meta-analysis. *J Am Coll Cardiol* 2008;52:818–27. [CrossRef]
10. van der Meer P, van Veldhuisen DJ. Anaemia and renal dysfunction in chronic heart failure. *Heart* 2009;95:1808–12.
11. Volpe M, Tritto C, Testa U, Rao MA, Martucci R, Mirante A, et al. Blood levels of erythropoietin in congestive heart failure and correlation with clinical, hemodynamic, and hormonal profiles. *Am J Cardiol* 1994;74:468–73. [CrossRef]
12. van der Meer P, Voors AA, Lipsic E, Smilde TD, van Gilst WH, van Veldhuisen DJ. Prognostic value of plasma erythropoietin on mortality in patients with chronic heart failure. *J Am Coll Cardiol* 2004;44:63–7. [CrossRef]
13. Nagai T, Nishimura K, Honma T, Higashiyama A, Sugano Y, Nakai M, et al. Prognostic significance of endogenous erythropoietin in long-term outcome of patients with acute decompensated heart failure. *Eur J Heart Fail* 2016;18:803–13.
14. Belonje AM, Voors AA, van der Meer P, van Gilst WH, Jaarsma T, van Veldhuisen DJ. Endogenous erythropoietin and outcome in heart failure. *Circulation* 2010;121:245–51. [CrossRef]
15. Westenbrink BD, Visser FW, Voors AA, Smilde TD, Lipsic E, Navis G, et al. Anaemia in chronic heart failure is not only related to impaired renal perfusion and blunted erythropoietin production, but to fluid retention as well. *Eur Heart J* 2007;28:166–71. [CrossRef]
16. Westenbrink BD, Voors AA, de Boer RA, Schuringa JJ, Klinkenberg T, van der Harst P, et al. Bone marrow dysfunction in chronic heart failure patients. *Eur J Heart Fail* 2010;12:676–84. [CrossRef]
17. Coats AJS, Shewan LG. The management of heart failure with preserved ejection fraction (HFpEF). *Int. Cardiovasc. Forum J* 2014;1:108–12.