Berlin, September 2022

Iron defficiency as a treatment target for patients with chronic heart failure.

Professor Stefan D Anker, MD PhD
s.anker@cachexia.de

Department of Cardiology (CVK); and Berlin Institute of Health Center for Regenerative Therapies (BCRT); German Centre for Cardiovascular Research (DZHK) partner site Berlin; Charité Universitätsmedizin Berlin, Germany.

Iron is importantly involved in numerous physiological processes including oxygen transport (via haemoglobin) and oxidative phosphorylation and energy production. Chronic illnesses like heart failure (HF) and kidney disease are characterized by presence of tissue inflammation leading to functional iron deficiency, which occurs in 40-60% of HF patients in Europe, and even more frequently develops in patients in Asia. Iron deficiency can cause anaemia, negatively impact on exercise capacity and symptoms and independently relates to poor prognosis.

Presence of iron deficiency predicts poor quality of life and increased mortality. Hence we can consider it an important biomarker. The current 2021 ESC/HFA Heart Failure Guidelines (McDonagh T et al *Eur Heart J* 2021) recommend its assessment in symptomatic patients in the ambulatory setting but also during hospitalisations and before discharge from hospital (class I recommendation).

Iron deficiency as therapeutic target in chronic HF was investigated in several clinical trials over the past 13 years. Data from the FAIR-HF and CONFIRM-HF studies (Anker SD et al. *N Engl J Med* 2009 & Ponikowski P et al. *Eur Heart J* 2014) demonstrate that treatment with IV ferric carboxymaltose compared to placebo improves symptom status, quality of life and submaximal exercise capacity in patients with chronic HF and functional iron deficiency and systolic heart failure. The diagnosis of iron deficiency was made when ferritin is <100 µg/L or when ferritin is <300 µg/L AND TSAT<20%. Importantly, the benefit of IV iron therapy is equally present in HF patients with or without anaemia, implicating iron deficiency rather than anaemia as a true therapeutic target in patients with HF. AFFIRM-AHF reconfirmed the usefulness of such therapy in the setting of treatment in the peri-discharge period after a hospitalisation for decompensated heart failure. Most importantly, correcting iron deficiency at the time of discharge led to a reduction of rehospitalisation events >20% (Ponikowski P et al. *Lancet* 2020). The most recent addition to the set of trials that is to be considered is the IRONMAN study that investigates the efficacy of ferric derisomaltose in patients with chronic HF to reduce the event of cardiovascular deaths and recurrent hospitalisations for HF. The trial results will be reported at the AHA congress in November 2022.

Several more trials – including the FAIR-HF2 study which is supported by the German Center for Heart Research (DZHK) – are also ongoing and will report in the next 2 years.

Taken all the available data it is suggested that therapy with intravenous iron could play a central role in the management of iron deficiency in patients with chronic HF. The ESC / HFA guidelines for the diagnosis and treatment of acute and chronic HF therefore recommend treatment with IV iron (namely ferric carboxymaltose) in symptomatic patients with iron deficiency (IIa, A).