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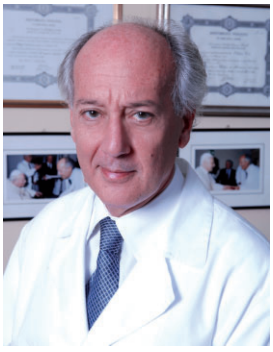
Sodium–glucose co-transporter inhibitors, iron therapy, and checkpoint inhibitors: new clinical and translational pieces of the heart failure puzzle



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This Focus Issue on heart failure and cardiomyopathies contains a Viewpoint article entitled '**Sodium–glucose co-transporter inhibitors and heart failure outcomes across different patient populations**' by Javed Butler from the University of Mississippi Medical Center in Jackson, MS, USA, and colleagues.[1] The authors note that hospitalization for heart failure (HF) marks a fundamental change in the natural history of the disease and portends a poor prognosis for the patients. Butler *et al.* assess recent trials and conclude that the success in reducing the risk of a HF events by sodium–glucose co-transporter (SGLT) inhibitors across patient populations to a clinically important and remarkably consistent degree is not only a moment for celebration, but also an opportunity for humility, recognizing the serendipity as these strikingly effective drugs were originally and primarily developed to lower blood glucose.[2–5]

Hyperkalaemia is a common complication of type 2 diabetes mellitus (T2DM) and limits the optimal use of agents that block the renin–angiotensin–aldosterone system, particularly in patients with chronic kidney disease (CKD).[6–9] In patients with CKD, SGLT2 inhibitors provide cardiorenal protection, but whether they affect the risk of hyperkalaemia remains uncertain. In a Fast Track Clinical Research article entitled '**Effects of canagliflozin on serum potassium in people with diabetes and chronic kidney disease: the CREDENCE trial**', Brendon Neuen from UNSW Sydney in Australia, and colleagues look into this issue further.[10] The CREDENCE trial randomized 4401 participants with T2DM and CKD to the SGLT2 inhibitor canagliflozin or matching placebo. In this post-hoc analysis using an intention-to-treat approach, the authors assessed the effect of canagliflozin on a composite outcome of time to either investigator-reported hyperkalaemia or the initiation of potassium binders. They also analysed effects on central laboratory-determined hyper- and hypokalaemia (serum potassium ≥6.0 and <3.5 mmol/L, respectively) and change in serum potassium. The incidence of investigator-reported hyperkalaemia or initiation of potassium binders was lower with canagliflozin than with placebo [hazard ratio (HR) 0.78, $P = 0.014$]. Canagliflozin similarly reduced the incidence of laboratory-determined hyperkalaemia (HR 0.77, $P = 0.031$), with no effect on the risk of hypokalaemia (HR 0.92, $P = 0.53$).

Neuen and colleagues conclude that among patients treated with renin–angiotensin–aldosterone system inhibitors, SGLT2 inhibition with canagliflozin may reduce the risk of hyperkalaemia in people with T2DM and CKD without increasing the risk of hypokalaemia. The article is accompanied by an interesting **Editorial** by Ileana Piña from the Central Michigan University College of Medicine, MI, USA.[4] Piña notes that the overall results reported are impressive, in that canagliflozin reduced the risk of investigator-reported hyperkalaemia or the initiation of potassium binders compared with placebo and extend the findings of other SGLT2 inhibitor studies in patients without CKD at entry. In addition, Neuen and colleagues have constructed a 'U'-shaped curve for kidney and cardiovascular outcomes that mirror those of registries and clinical trials, supporting the maintenance of potassium within normal limits and avoiding both extremes. Finally, the implications of this study for clinicians caring for patients with diabetes mellitus and CKD should increase confidence in the use of SGLT2 inhibitors not just to prevent hyperkalaemia, but also to allow the maintenance of renally protective drugs, now with a new one on the shelf.

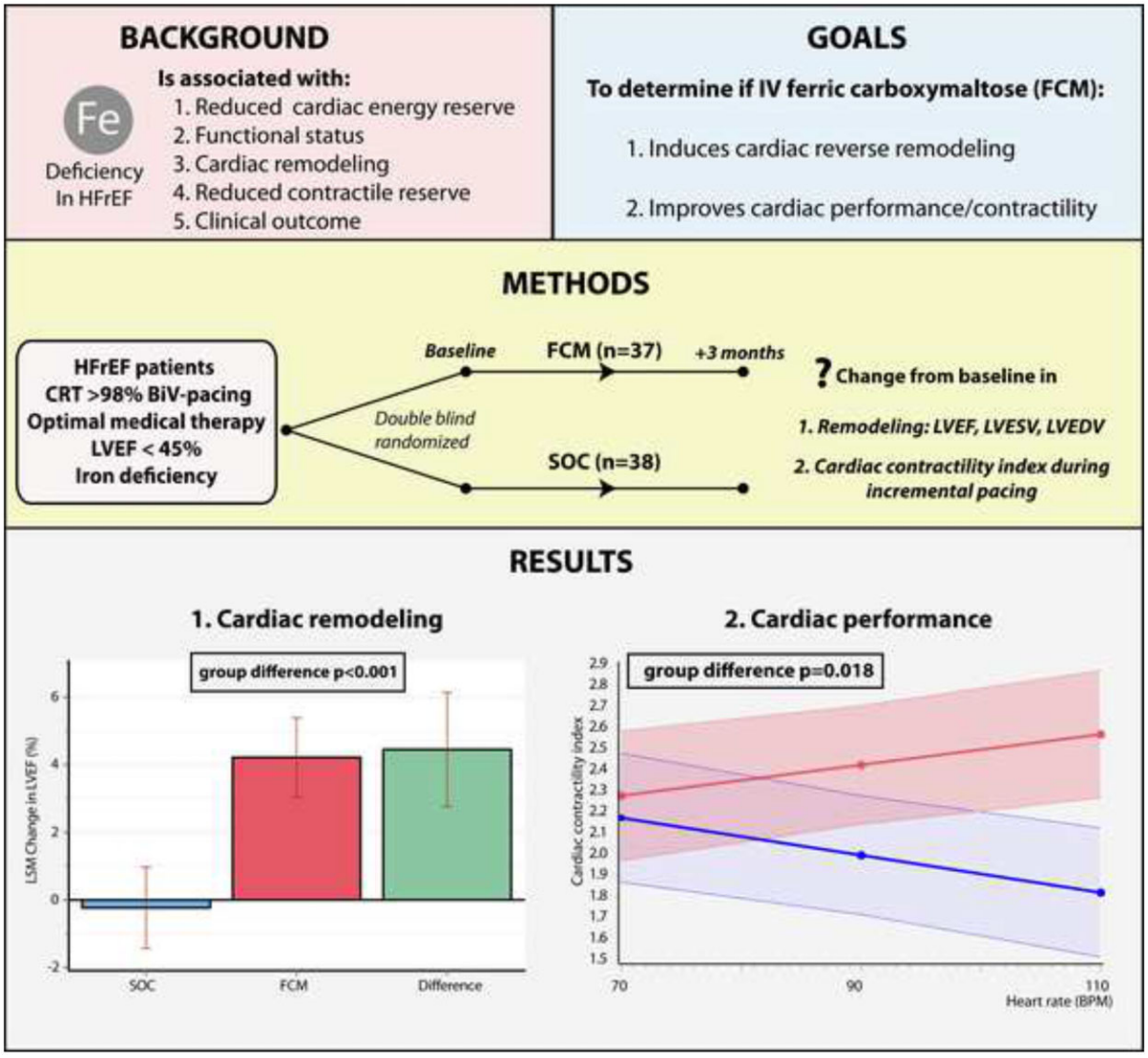

Figure 1 Overview of study design and main findings (from Martens P, Dupont M, Dauw J, Nijst P, Herbots L, Dendale P, Vandervoort P, Bruckers L, Tang WHW, Mullens W. The effect of intravenous ferric carboxymaltose on cardiac reverse remodelling following cardiac resynchronization therapy: the IRON-CRT trial. See pages 4905–4914).

Iron deficiency is common in HF with reduced ejection fraction (HFrEF) and negatively affects cardiac function and structure. In another Fast Track Clinical Research article, entitled '**The effect of intravenous ferric carboxymaltose on cardiac reverse remodelling following cardiac resynchronization therapy: the IRON-CRT trial**', Pieter Martens from the Ziekenhuis Oost-Limburg hospital in Genk, Belgium, and colleagues study the effect of ferric carboxymaltose (FCM) on cardiac reverse remodelling and contractile status in HFrEF.[11] Symptomatic HFrEF patients with iron deficiency and a persistently reduced left ventricular ejection fraction (LVEF <45%) at least 6 months after cardiac resynchronization therapy (CRT) implant were prospectively randomized to FCM or standard of care (SOC) in a double-blind manner. The primary endpoint was the change in LVEF from baseline to 3 month follow-up assessed by three-dimensional echocardiography. Secondary endpoints included the change in left ventricular end-systolic volume (LVESV) and end-diastolic volume (LVEDV) from baseline to 3 month follow-up. Cardiac performance was evaluated by the force–frequency relationship as assessed by the slope change of the cardiac contractility index (CCI = systolic blood pressure/LVESV index) at 70, 90, and 110 beats of biventricular pacing. A total of 75 patients were randomized to FCM ($n = 37$) or SOC ($n = 38$). After 3 months, the change in LVEF was significantly higher in the FMC group (4.22%) than in the SOC group (-0.23; $P < 0.001$). Similarly, LVESV (-9.72 mL vs. -1.83 mL; $P = 0.001$), but not LVEDV ($P = 0.748$), improved in the FCM vs. the SOC group. In addition, FCM resulted in an improvement in the CCI slope during incremental biventricular pacing, with a positive force–frequency relationship at 3 months (*Figure* 1). Finally,

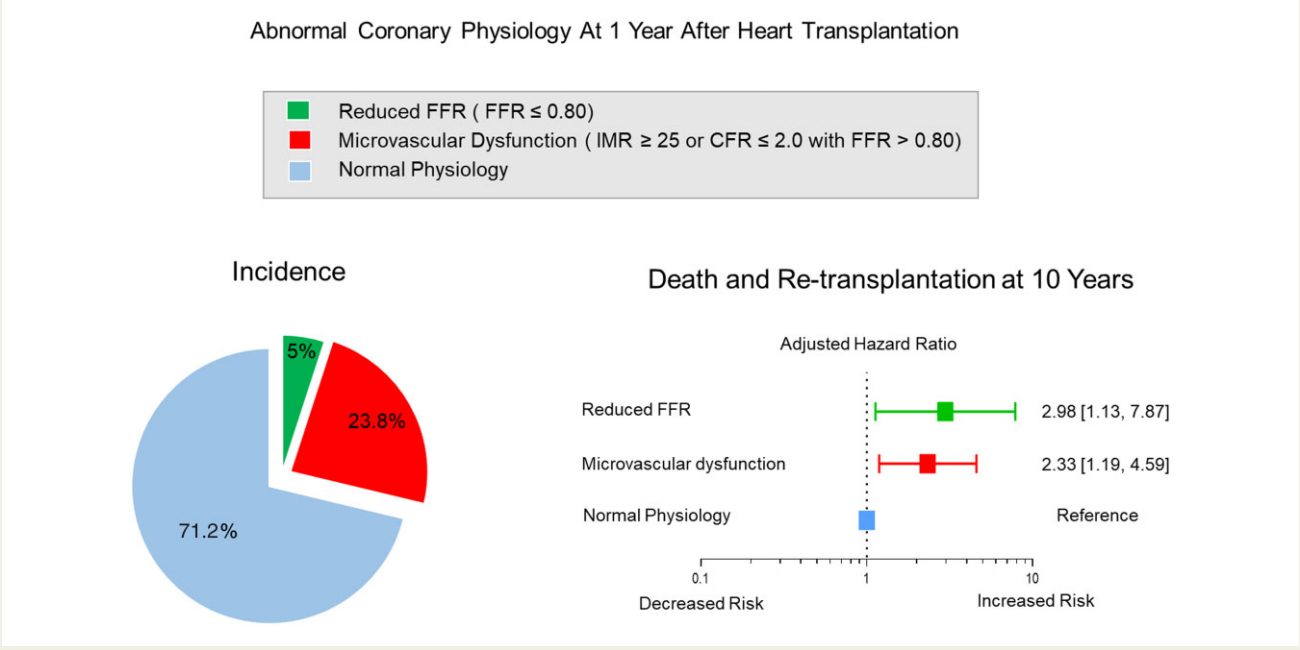

Figure 2 Graphical Abstract (from Ahn JM, Zimmermann FM, Arora S, Solberg OG, Angerås O, Rolid K, Rafique M, Aaberge L, Karason K, Okada K, Luikart H, Khush KK, Honda Y, Pijls NHJ, Lee SE, Kim JJ, Park SJ, Gullestad L, Fearon WF. Prognostic value of comprehensive intracoronary physiology assessment early after heart transplantation. See pages 4918–4929).

functional status and exercise capacity, as measured by the Kansas City Cardiomyopathy Questionnaire and peak oxygen consumption, were improved by FCM.

Martens *et al.* conclude that treatment with FCM in HFrEF patients with iron deficiency and persistently reduced LVEF after CRT results in an improvement of cardiac function measured by LVEF, LVESV, and cardiac force–frequency relationship. The manuscript is accompanied by an **Editorial** by Ewa Jankowska and Piotr Ponikowski from the Wroclaw Medical Institute, and University Hospital in Wroclaw in Poland.[12] The authors conclude that we are currently witnessing a growing interest in iron deficiency as a therapeutic target in the cardiology world, with the emphasis on HF. Taking into consideration the critical role of iron in cellular metabolism (in particular in cellular energy metabolism) and close links with inflammatory pathways, one may expect the contribution of abnormal iron status also to other cardiovascular diseases and conditions.

In a third Fast Track Clinical Research article entitled '**Prognostic value of comprehensive intracoronary physiology assessment early after heart transplantation**', Jung-Min Ahn from the University of Ulsan College of Medicine in Seoul, Korea, and colleagues evaluated the long-term prognostic value of invasively assessing coronary physiology after heart transplantation in a large multicentre registry.[13] Comprehensive intracoronary physiology assessment measuring fractional flow reserve (FFR), the index of microcirculatory resistance (IMR), and coronary flow reserve (CFR) was performed in 254 patients at baseline (a median of 7.2 weeks) and in 240 patients at 1 year after transplantation (199 patients had both baseline and 1 year measurement). Patients were classified into those with normal physiology, reduced FFR (FFR ≤0.80), and microvascular dysfunction (either IMR ≥25 or CFR ≤2.0 with FFR >0.80). The primary outcome was the composite of death or re-transplantation at 10 years. At baseline, 5.5% had reduced FFR and 37% had microvascular dysfunction. Baseline reduced FFR [adjusted HR (aHR) 2.33; $P = 0.088$] and microvascular dysfunction (aHR 0.88; $P = 0.73$) were not predictors of death and re-transplantation at 10 years. At 1 year, 5.0% had reduced FFR and 24% had microvascular dysfunction. One-year reduced FFR (aHR 2.98; $P = 0.028$) and microvascular dysfunction (aHR 2.33; $P = 0.015$) were associated with significantly increased risk of death or re-transplantation at 10 years (*Figure* 2). Invasive measures of coronary physiology improved the prognostic performance of clinical variables (χ^2 improvement: 7.41, $P = 0.006$).

The authors conclude that abnormal coronary physiology 1 year after heart transplantation was common and was a significant predictor of death or re-transplantation at 10 years. This manuscript is accompanied by an **Editorial** by Fernando Alfonso from the Universidad Autónoma de Madrid, and colleagues.[14] The authors conclude that this is the largest study looking at the prognostic value of invasive physiological assessment in heart transplantation recipients. Characterization of the physiological phenotype in these patients provides unique prognostic insights and may pave the way for additional mechanistic and clinical studies in heart transplantation. Despite the pathophysiological appeal of intracoronary imaging and physiological assessment, these techniques, like endomyocardial biopsy, remain invasive strategies. It is tempting to envisage that, one day, non-invasive assessment of coronary anatomy and physiology might replace their invasive counterparts to inform clinical decisions in these challenging patients.

Since 1968, heart transplantation has become the definitive treatment for patients with end-stage HF. In a Clinical Research article entitled '**The Stanford experience of heart transplantation**

over five decades', Yuanjia Zhu from the Stanford University School of Medicine in CA, USA, and colleagues aimed to summarize their experience in heart transplantation at Stanford University since the first transplantation performed >50 years ago.[15] From 6 January 1968 to 30 November 2020, a total of 2671 patients presented to Stanford University for heart transplantation, of which 1958 were adult heart transplantations. Stabilized inverse probability weighting was applied to compare patients in 1996–2006 ($n = 356$) vs. 2007–2019 ($n = 515$). The primary endpoint was all-cause mortality. After the application of stabilized inverse probability weighting, the distance the organ travelled increased from 84 miles to 159 miles from 1996–2006 to 2007–2019. Total allograft ischaemia time also increased over time (200 vs. 225 min). Patients in 2007–2019 showed superior survival to those in 1996–2006, with a median survival of 12.1 vs. 11.1 years.

The authors conclude that in this half-century retrospective descriptive study from one of the largest heart transplant programmes in the USA, long-term survival after heart transplantation has improved over time despite increased recipient and donor age, worsening comorbidities, increased technical complexity, and prolonged total allograft ischaemia time. The contribution is accompanied by an **Editorial** by Donna Mancini from the Icahn School of Medicine at Mount Sinai in NY, USA, and colleagues.[16] The authors conclude by pointing out that the field of cardiac transplantation continues to evolve, including more complex recipients and donors, yet advances in medical and surgical management have so far outstripped the challenges with sustained improved survival. Focused detailed statistical analysis of outcomes such as this Stanford report is needed to monitor when and if these challenges outbalance the risks.

Recent clinical trials indicate that SGLT2 inhibitors improve cardiovascular outcomes in HF patients, but the underlying mechanisms remain unknown. In a Translational Research article entitled '**Effects of canagliflozin on human myocardial redox signalling: clinical implications**', Hidekazu Kondo from the University of Oxford in the UK, and colleagues explored the direct effects of canagliflozin, an SGLT2 inhibitor with mild SGLT1 inhibitory effects, on myocardial redox signalling in humans.[17] Study 1 included 364 patients undergoing cardiac surgery. Right atrial appendage biopsies were harvested to quantify superoxide sources and the expression of inflammation, fibrosis, and myocardial stretch genes. In Study 2, atrial tissue from 51 patients was used *ex vivo* to study the direct effects of canagliflozin on NADPH oxidase activity and nitric oxide synthase (NOS) uncoupling. Differentiated H9C2 and primary human cardiomyocytes (hCMs) were used to further characterize the underlying mechanisms (Study 3). SGLT1 was abundantly expressed in human atrial tissue and hCMs, in contrast to SGLT2. Myocardial SGLT1 expression was positively associated with superoxide production and profibrotic, proinflammatory, and wall stretch gene expression. Canagliflozin reduced NADPH oxidase activity via AMP kinase (AMPK)/Rac1 signalling and improved NOS coupling via increased tetrahydrobiopterin bioavailability *ex vivo* and *in vitro*. These were attenuated by knocking down SGLT1 in hCMs. Canagliflozin had striking *ex vivo* transcriptomic effects on myocardial redox signalling, suppressing apoptotic and inflammatory pathways in hCM.

The authors conclude that these findings reveal a novel mechanism contributing to the beneficial cardiac effects of canagliflozin. The manuscript is accompanied by an **Editorial** by Gabriele Schiattarella and David Bode from the Charité–Universitätsmedizin Berlin in Germany.[18] Schiattarella and Bode conclude that Kondo *et al.* provided evidence in support of canagliflozin improving NOS coupling and NADPH oxidase activity through SGLT1/AMPK/Rac1–GTP signalling in the heart. The authors should be congratulated for their work which suggests a novel role for SGLT1 inhibitors in regulating myocardial redox signalling and puts SGLT1 in the spotlight of SGLT(s) research.

The risk and incidence of cardiovascular (CV) immune-related adverse events (irAEs) associated with immune checkpoint inhibitors (ICIs) is a matter of growing interest.[19–25] In a meta-analysis entitled '**Cardiovascular immunotoxicities associated with immune checkpoint inhibitors: a safety meta-analysis**', Charles Dolladille from Normandie University in Caen, France, and colleagues systematically reviewed all randomized clinical trials (RCTs) including at least one ICI-containing arm and available CV adverse event (CVAE) data in cancer patients in the ClinicalTrials.gov registry, Medline, and the Cochrane CENTRAL Register of Controlled Trials, up to 31 August 2020 (CRD42020165672).[26] The primary outcome was the summary risk of 16 different CVAEs associated with ICI exposure vs. controls (placebo and non-placebo) in RCTs. ICI use was associated with an increased risk of six CV irAEs, namely myocarditis, pericardial diseases, HF, dyslipidaemia, myocardial infarction, and cerebral arterial ischaemia. with higher risks for myocarditis [odds ratio (OR) 4.42, $P < 0.01$)] and dyslipidaemia (OR 3.68, $P < 0.01$). The incidence of these CVAEs ranged from 3.2 to 19 per 1000 patients in studies with a median follow-up ranging from 3.2 to 33 months.

The authors conclude that in RCTs, ICI use is associated with six CV irAEs, not confined to myocarditis and pericarditis. The manuscript is accompanied by an **Editorial** by Tomas Neilan from the Massachusetts General Hospital in Boston, MA, USA and Lavanya Kondapalli from the University of Colorado in Aurora, CO, USA.[27] The two conclude that the study of Dolladille *et al.* elegantly approaches the difficult question of determining the incidence of cardiac irAES in oncology trials. In addition to the well-known irAEs myocarditis and pericarditis, they report that ICIs increase the risk of HF, dyslipidaemia, myocardial infarction, and cerebral arterial ischaemia. Specifically, the finding that ICIs potentiates atherosclerosis is an important one and an opportunity for cardiologists and oncologists to expand collaborations with the combined goal of mitigating cardiotoxicity. Additionally, these therapies also provide, in an accelerated fashion, a remarkable insight into the key role of the immune system in cardiovascular biology.

The issue is also complemented by two Discussion Forum contributions. In a commentary entitled '**Percutaneous intervention in patients with cancer: can we offer an improvement in safety?**', Iñigo Lozano from the Hospital de Cabueñes in Gijón, Spain, and colleagues comment on the recent publication '**Percutaneous coronary intervention in patients with cancer and readmissions within 90 days for acute myocardial infarction and bleeding in the USA**' by Mamas Andreas Mamas from Keele University in the UK.[28,29] Mamas responds in a separate comment.[30]

The editors hope that readers of this issue of the *European Heart Journal* will find it of interest.

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