Sodium–glucose cotransporter 2 inhibitors, weight loss therapies, and ferric carboxymaltose: new light shed on innovative ways to reduce cardiovascular risk

Filippo Crea
Centre of Excellence of Cardiovascular Sciences, Gemelli Isola Hospital, Rome, Italy

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This Focus Issue on heart failure and cardiomyopathies contains the State of the Art Review article ‘Mechanisms of enhanced renal and hepatic erythropoietin synthesis by sodium–glucose cotransporter 2 inhibitors’, by Milton Packer from the Baylor Heart and Vascular Institute in Dallas, TX, USA. Packer indicates that sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of major heart failure events. This action is statistically linked to enhanced erythropoiesis, suggesting that stimulation of erythropoietin and cardioprotection might be related to a shared mechanism. Four hypotheses have been proposed to explain how these drugs increase erythropoietin production: (i) renal cortical reoxygenation with rejuvenation of erythropoietin-producing cells; (ii) counter-regulatory distal sodium reabsorption leading to increased tubular workload and oxygen consumption, and thus to localized hypoxia; (iii) increased iron mobilization as a stimulus of hypoxia-inducible factor-2α (HIF-2α)-mediated erythropoietin synthesis; and (iv) direct HIF-2α activation and enhanced erythropoietin gene transcription due to increased sirtuin-1 (SIRT1) signalling. Since SIRT1 up-regulation exerts direct cytoprotective effects on the heart and stimulates erythropoietin, it is well positioned to represent the shared mechanism that links erythropoiesis to cardioprotection during SGLT2 inhibition.

The prevalence of overweight and obesity has reached pandemic proportions. In a second State of the Art Review article entitled ‘The cardiovascular effects of novel weight loss therapies’, Muhammad Sharif Usman from the UT Southwestern Medical Center in Dallas, TX, USA, and colleagues remind us that obesity is known to increase the risk for type 2 diabetes and hypertension, as well as the risk for overt cardiovascular (CV) disease, including myocardial infarction, heart failure, and stroke. The rising prevalence of obesity may counteract the recent advances in primary and secondary prevention of CV disease. Overweight and obesity are common in patients with CV disease; however, cardiologists face several challenges in managing body weight in this population. Many may not consider obesity as a therapeutic target, probably because there were no previous highly effective and safe pharmacological interventions available. In addition, they may not have the expertise or resources to implement lifestyle interventions and may have limited familiarity with obesity pharmacotherapy. Moreover, the long-term CV effects of obesity pharmacotherapy remain uncertain due to limited CV outcome data with weight loss as the primary intervention. Although current CV guidelines recognize the importance of weight loss, they primarily focus on lifestyle modifications, with fewer details on strategies to utilize obesity pharmacotherapy and surgery. This review appraises the current evidence regarding the CV effects of weight loss interventions. Considering this evidence, practical guidance is provided to assist cardiologists in developing and implementing treatment plans, which may allow optimal weight management while maximizing CV benefits and minimizing side effects to improve the overall well-being of people with CV disease.

Atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFP EF) are intimately associated disorders; HFP EF may be overlooked in AF when symptoms are simply attributed to dysrhythmia, and incident AF may identify patients at risk for developing diastolic dysfunction (DD). In a Fast Track Clinical Research article entitled ‘Prevalence and incidence of diastolic dysfunction in atrial fibrillation: clinical implications’, Jwan Naser from the Mayo Clinic College of Medicine in Rochester, MN, USA, and colleagues investigate the prevalence and incidence of DD in patients with new-onset AF compared with sinus rhythm (SR). Adults with new-onset AF (n = 1747) or SR (n = 29 623) and no structural heart disease were identified. Propensity score matching was performed (1:3 ratio) between AF and SR based on age, sex, body mass index, and comorbidities. Severe DD (SDD) was defined by ≥3 of four abnormal parameters (medial e’, medial E/e’, tricuspid regurgitation velocity, and left atrial volume index) and ≥ moderate DD (≥ MDD) by ≥2 of four. New-onset AF was independently associated with SDD (8% vs. 3%) and MDD (25% vs. 16%). Over a median follow-up of 3.2 years, DD progressed two- to four-fold more rapidly in those with new-onset AF (P < .001 for all). The risk for incident DD was increased in new-onset AF [hazard ratio (HR) 2.69 for SDD and 1.73 for ≥ MDD].

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The authors conclude that patients with new-onset AF display high-risk features for HFpEF at diagnosis, emphasizing the importance of evaluating for HFpEF among symptomatic patients with AF. They also have accelerated progression in DD over time, which may identify patients with pre-clinical HFpEF, where preventive therapies may be tested. The contribution is accompanied by an Editorial by Ricardo Inciardi from the University of Brescia in Italy and Scott Solomon from the Brigham and Women’s Hospital and Harvard Medical School in Boston, MA, USA. Inciardi and Solomon observe that although the current study cannot prove causation, there are also cause end-stage HF (ESHF) and malignant ventricular arrhythmia effects and atrial arrhythmias are common to both, but underlying HFpEF or a propensity for development of HFpEF in the future. Hence, among otherwise healthy patients with normal EF and exertional dyspnœa, the presence of AF should raise suspicion of underlying myopathy involving both atria and ventricles, with either underlying HFpEF or a propensity for development of HFpEF in the future. This would argue for a more comprehensive approach to management of AF, by incorporating early HF management alongside control of the arrhythmic substrate.

Emery–Dreifuss muscular dystrophy (EDMD) is caused by variants in EMD (EDMD1) and LMNA (EDMD2) genes. Cardiac conduction defects and atrial arrhythmias are common to both, but LMNA variants also cause end-stage HF (ESHF) and malignant ventricular arrhythmia (MVA). In a Fast Track Clinical Research article entitled ‘Emery–Dreifuss muscular dystrophy 1 is associated with a high risk of malignant ventricular arrhythmias and end-stage heart failure’, Douglas E. Cannie from the University College London in the UK, and colleagues aimed to better characterize the cardiac complications of EMD variants. Consecutively referred EMD variant carriers were retrospectively recruited from 12 international cardiomyopathy units. MVA and ESHF incidences in male and female variant carriers were determined. Male EMD variant carriers with a cardiac phenotype at baseline (EMDCARDIAC) were compared with consecutively recruited male LMNA variant carriers with a cardiac phenotype at baseline (LMNACARDIAC). Longitudinal follow-up data were available for 38 male and 21 female EMD variant carriers (mean ages 33 and 43 years, respectively). Nine (24%) males developed MVA and five (13%) developed ESHF during a median follow-up of 65 months. No female EMD variant carrier developed MVA or ESHF, but nine (43%) developed a cardiac phenotype at a median age of 59 years. In males, incidence rates for MVA were similar for EMDCARDIAC and LMNACARDIAC (4.8 and 6.6 per 100 person-years, respectively). Incidence rates for ESHF were 2.4 and 5.9 per 100 person-years for EMDCARDIAC and LMNACARDIAC, respectively.

Cannie et al. conclude that male EMD variant carriers have a risk of progressive HF and ventricular arrhythmias similar to that of male LMNA variant carriers. Early implantable cardioverter defibrillator implantation and HF drug therapy should be considered in male EMD variant carriers with cardiac disease. This manuscript is accompanied by an Editorial by Daria Kramarenko and Roddy Walsh from the University of Amsterdam in the Netherlands. The authors emphasize that the study by Cannie et al. offers crucial insights into the management of EDMD, particularly in relation to EMD variant carriers. It challenges established guidelines by revealing that males with EMD variants face a similar risk of MVA to those with LMNA variants. The study also sheds light on the cardiac complications in female EMD variant carriers, emphasizing the need for ongoing clinical monitoring in this demographic as well. Furthermore, the study highlights the indispensable role of multi-centre studies and registries in enhancing our understanding and treatment of rare diseases.

Whereas a beneficial effect of i.v. ferric carboxymaltose (FCM) on symptoms and exercise capacity among patients with iron deficiency (ID) and HF with reduced ejection fraction (HFrEF) has been consistently demonstrated, the effects of treatment on clinical events remain the subject of research. In a Fast Track Clinical Research article entitled ‘Efficacy of ferric carboxymaltose in heart failure with iron deficiency: an individual patient data meta-analysis’, Piotr Ponikowski from the Wroclaw Medical University in Poland, and colleagues aimed to characterize the effects of FCM therapy on hospitalizations and mortality. Patient-level data from randomized, placebo-controlled FCM trials including adults with HF and ID with hospitalizations and mortality. The co-primary efficacy endpoints were (1) a composite of total/recurrent CV hospitalizations and CV death and (2) a composite of total HF hospitalizations (HHFs) and CV death, through 52 weeks. Treatment-emergent adverse events were also examined. Three FCM trials with a total of 4501 patients were included. FCM was associated with a significantly reduced risk of co-primary endpoint 1 [rate ratio (RR) .86; P = .029], with a trend towards a reduction of co-primary endpoint 2 (RR.87; P = .076). Treatment effects appeared to result from reduced hospitalization rates, not improved survival. Treatment appeared to have a good safety profile and was well tolerated.

Ponikowski et al. conclude that in ID with HFrEF, i.v. FCM is associated with significantly reduced risk of HHFs and CV death. The contribution is accompanied by an Editorial by Darlington Obinnaya Okonko from Imperial College London in the UK. The authors note that whether the proximate mechanisms that deplete iron levels in HF are amenable to safe therapeutic intervention is unknown. Future research should address this, in addition to tackling how best to define and durably correct ID in HF. Future studies should also unravel how i.v. iron confers benefits in HF as the findings could be used to identify those who will gain the most from i.v. iron. The meta-analysis conducted by Ponikowski et al. lends support to the use of i.v. iron to reduce symptoms, exercise intolerance, and hospitalizations in HF patients. After all, hospitalizations are costly to healthcare budgets and, for most patients, freedom from dyspnœa, debility, and hospital admissions is more important than increasing longevity.

Endocarditis is a challenging clinical condition. In the Partial Oral Treatment of Endocarditis (POET) trial, stabilized patients with left-sided infective endocarditis (IE) were randomized to oral (p.o.) step-down antibiotic therapy or conventional continued i.v antibiotic treatment, showing non-inferiority after 6 months. In a Clinical Research article entitled ‘Clinical implementation of partial oral treatment in infective endocarditis: the Danish POETry study’, Mia Marie Pries-Heje from the Copenhagen University Hospital in Denmark, and colleagues examined the first guideline-driven clinical implementation of the oral step-down POET regimen.

Patients with IE, caused by Staphylococcus aureus, Enterococcus faecalis, Streptococcus spp., or coagulase-negative staphylococci diagnosed between May 2019 and December 2020 were possible candidates for initiation of oral step-down antibiotic therapy, at the discretion of the treating physician. The composite primary outcome consisted of embolic events, unplanned cardiac surgery, relapse of bacteraemia, and all-cause mortality within 6 months. A total of 562 patients (median age 74 years, 70% males) with IE were enrolled. More patients in the i.v. group had IE caused by S. aureus, or had an intracardiac abscess, or a pacemaker, and more were treated surgically. The primary outcome occurred in 30 (13%) patients in the p.o. group.
consider oral step-down antibiotic therapy. Patients in the i.v. group had a shorter median length of stay (p.o. 24 days vs. i.v. 43 days, \(P < 0.001\)). Patients treated p.o. had a higher mortality rate (20 (8%) patients died vs. 46 (14%) patients in the IV group (\(P = 0.024\)). Patients considered possible candidates for POET-treatment and outcomes at 6-month follow-up (right). AB, antibiotic; BMI, body mass index; CRP, C-reactive protein; IE, infective endocarditis; IQR, interquartile range; PO, oral step-down antibiotic therapy; IV, intravenous antibiotic treatment; POET, Partial Oral Treatment of Endocarditis; T, temperature; TEE, transoesophageal echocardiography.24

and in 59 (18%) patients in the i.v. group (\(P = 0.051\)); in the p.o. group, 20 (8%) patients died vs. 46 (14%) patients in the IV group (\(P = 0.024\)). Patients treated p.o. had a shorter median length of stay (p.o. 24 days vs. i.v. 43 days, \(P < 0.001\)) (Figure 1).

Pries-Heje and colleagues conclude that after clinical implementation of the POET regimen, almost half of the possible candidates with IE receive oral step-down antibiotic therapy. Patients in the i.v. group have more serious risk factors for negative outcomes. At 6-month follow-up, there is a numerically, but not statistically, significant difference towards a lower incidence of the primary outcome, a lower incidence of all-cause mortality, and a reduced length of stay in the p.o. group. Due to the observational design of the study, the lower mortality may to some extent reflect selection bias and unmeasured confounding. Clinical implementation of p.o. regimens seems feasible and safe. The manuscript is accompanied by an Editorial by Nuria Fernández-Hidalgo and Ignacio Ferreira-González from the Hospital Universitari Vall d’Hebron in Barcelona, Spain, and colleagues.25 They conclude that although much work still needs to be done, the example of determination of the Danish authors as well as the incorporation of patient-related outcomes and patient-related experiences into further studies will help to improve the prognosis and quality of life of IE patients.

In a Clinical Research article entitled ‘Fulminant myocarditis proven by early biopsy and outcomes’, Florent Huang from the Foch Hospital in Suresnes, France and colleagues note that while endomyocardial biopsy (EMB) is recommended in adult patients with fulminant myocarditis, the clinical impact of its timing is still unclear.26 Data were collected from 419 adult patients with clinically suspected fulminant myocarditis admitted to intensive care units across 36 tertiary centres in 15 countries worldwide. The diagnosis of myocarditis was histologically proven in 210 (50%) patients, either by EMB (n = 183, 44%) or by autopsy/explanted heart examination (n = 27, 6%), and clinically suspected myocarditis was confirmed by cardiac magnetic resonance imaging in 96 (23%) patients. The primary outcome of survival free of heart transplantation (HTx) or LV assist device (LVAD) at 1 year was specifically compared between patients with early EMB (within 2 days after intensive care unit admission, n = 103) and delayed EMB (n = 80). A propensity score-weighted analysis was done to control for confounders. Median age on admission was 40 years, and 77% of patients received temporary mechanical circulatory support. A total of 273 (65%) patients survived without HTx/LVAD. The primary outcome was significantly different between patients with early or delayed EMB (70% vs. 49%, \(P = 0.004\)). After propensity score weighting, the early EMB group still significantly differed from the delayed EMB group.
in terms of survival free of HTx/LVAD (63% vs. 40%, \(P = .021\)). Moreover, early EMB was independently associated with a lower rate of death or HTx/LVAD at 1 year (odds ratio of 0.44, \(P = .016\)).

The authors conclude that endomyocardial biopsy should be broadly and promptly used in patients admitted to the intensive care unit for clinically suspected fulminant myocarditis. The contribution is accompanied by an Editorial by Heinz-Peter Schultheiss from the Institute of Cardiac Diagnostics and Therapy in Berlin and Felicitas Escher from the Deutsches Herzcentrum der Charité in Berlin, Germany.\(^{27}\) Schultheiss and Escher note that comprehensive, advanced, and standardized diagnostic differentiation of EMBs seems to be the key approach for both an updated differential diagnosis and a meaningful selection of candidate drugs for effective specific therapeutic regimens. For this reason, timely prediction of the likely course of disease is essential for personalized therapy in fulminant myocarditis. An urgent need for randomized trials or prospective registries testing the effectiveness of precision medicine approaches in the context of fulminant forms is evident. In particular, different immunosuppressive regimens must be evaluated, and prospectively monitored in the acute setting.

The epidemiology of peripartum cardiomyopathy (PPCM) in Europe is poorly understood and data on long-term outcomes are lacking. In a Clinical Research contribution entitled ‘A 20-year population study of peripartum cardiomyopathy’, Alice Jackson from the University of Glasgow and colleagues conducted a retrospective, observational, population-level study of validated cases of PPCM in Scotland from 1998 to 2017.\(^{28}\) Women hospitalized with presumed de novo LV systolic dysfunction around the time of pregnancy and no clear alternative cause were included. Each case was matched to 10 controls. Incidence and risk factors were identified. Morbidity and mortality were examined in mothers and children. Among 225 women with PPCM, obesity, gestational hypertensive disorders, and multi-gestation were found to be associated with having the condition. Over a median follow-up of 8.3 years, 8% of women with PPCM died and 75% were hospitalized for any cause at least once. Mortality and rehospitalization rates in women with PPCM were \(\sim 2\) and \(\sim 3\) times that of controls, respectively. The composite of all-cause death, mechanical circulatory support, or HTx occurred in 14%. LV recovery occurred in 76% and, of those who recovered, 13% went on to have a decline in LV systolic function despite initial recovery. The mortality rate for children born to women with PPCM was \(\sim 5\) times that of children born to controls and they had an \(\sim 3\) times greater incidence of CV disease over a median of 8.8 years (Figure 2).

The authors conclude by noting that PPCM affects \(1\) in \(4950\) women around the time of pregnancy. The condition is associated with considerable morbidity and mortality for the mother and child. There should be a low threshold for investigating at-risk women. Long-term follow-up, despite apparent recovery, should be considered. The contribution is accompanied by an Editorial by Charle Viljoen, Karen Siwa, and Julian Hoevelmann from the University of Cape Town in South Africa. The authors note that the identification of better predictors of LV recovery will be crucial for optimizing patient management. Additional research focusing on neonatal outcomes in PPCM-affected pregnancies is vital to ensure the well-being of both mother and child. Moreover, assessing the safety of discontinuing drug therapy in women with LV recovery and developing targeted drug therapies specifically for PPCM are critical areas that still demand rigorous investigation. Addressing these unmet research...
needs will advance our understanding of PPCM and enhance patient care and outcomes of mother and child.29

Hypertrophic cardiomyopathy (HCM) is characterized by phenotypic heterogeneity that is partly explained by the diversity of genetic variants contributing to disease. In a Translational Research contribution entitled ‘Ethnicity, consanguinity, and genetic architecture of hypertrophic cardiomyopathy’, Mona Allouba from the Aswan Heart Centre in Egypt, and colleagues remind us that accurate interpretation of these variants constitutes a major challenge for diagnosis and implementing precision medicine, especially in understudied populations.30 The aim of the study was to define the genetic architecture of HCM in North African cohorts with high consanguinity using ancestry-matched cases and controls. Prospective Egyptian patients (n = 514) and controls (n = 400) underwent clinical phenotyping and genetic testing. Rare variants in 13 validated HCM genes were classified according to standard clinical guidelines and compared with a prospective HCM cohort of majority European ancestry (n = 684). A higher prevalence of homozygous variants was observed in Egyptian patients (4.1% vs. 0.1%, P = 2 × 10−5), with variants in the minor HCM genes MYL2, MYL3, and CSR3 more likely to present in homozygosity than the major genes, suggesting that these variants are less penetrant in heterozygosity. Biallelic variants in the recessive HCM gene TRIM63 were detected in 2.1% of patients (five-fold greater than European patients), highlighting the importance of recessive inheritance in consanguineous populations. Finally, rare variants in Egyptian HCM patients were less likely to be classified as (likely) pathogenic compared with Europeans (40.8% vs. 61.6%, P = 1.6 × 10−5) due to the under-representation of Middle Eastern populations in current reference resources. This proportion increased to 53.3% after incorporating methods that leverage new ancestry-matched controls presented here.

The authors conclude that studying consanguineous populations reveals novel insights with relevance to genetic testing and our understanding of the genetic architecture of HCM. The contribution is accompanied by an Editorial by Jodie Ingles and Daniel MacArthur from the Garvan Institute of Medical Research in Sydney, Australia.31 The authors note that there is a clear need to actively expand genomic research in previously understudied and ancestrally diverse populations on both moral and practical grounds. This will ensure that we do not continue to widen health disparity gaps, while also providing a more complete picture of the underlying genetic architecture of disease. Inequitable representation is not a problem that can be solved by any one community alone. Empowering local research teams, as well as increasing diversity of existing specialized research centres, is a critical step in increasing representation within HCM research. Patients and communities must be seen as necessary and valuable partners, rather than passive participants, in these efforts, and genuine engagement with these groups needs to be recognized and incentivized by funders. Diverse teams, partnering closely with diverse communities, will be required to fully understand the underlying genetic basis of diseases such as HCM, and to move as swiftly as possible towards new treatments.

In a Rapid Communications contribution entitled ‘Prognostic value of intravascular ultrasound early after heart transplantation’, Satish Arora from the Oslo University Hospital in Norway, and colleagues enrolled 243 de novo adult HTx recipients aged 18–70 years from four transplant centres.32 Serial intravascular ultrasound (IVUS) examination of the left anterior descending artery was performed at baseline (within 12 weeks post-HTx) and at year 1. Percent atheroma volume (PAV) was calculated based on IVUS. Increases in PAV ≥7.0%, diabetes mellitus, and mycophenolate mofetil (MMF) therapy at baseline were found to be independent predictors of all-cause mortality (all P < 0.1). The authors conclude that this is the first multicentre study to date evaluating the prognostic value of volumetric IVUS early after HTx. They find that early cardiac allograft vasculopathy (CAV) development, as defined by a PAV increase ≥7.0% at year 1, is an independent predictor of subsequent all-cause mortality and major adverse cardiovascular events (MACE).

In another Rapid Communications contribution ‘Ertugliflozin and hospitalization for heart failure across the spectrum of pre-trial ejection fraction: post-hoc analyses of the VERTIS CV trial’, Ambarish Pandey from the University of Texas Southwestern Medical Center in Dallas, TX, USA and colleagues note that SGLT2 inhibitors consistently reduce the risk of HHF in HFpEF and HFrEF.33 However, less is known regarding the treatment efficacy at or above the normal EF range (>60%). Of 8246 participants in VERTIS CV, 1187 (14.4%) had EF >60%. Among participants with known EF, those with EF >60% vs. EF ≤45% were more likely to be women, had a lower burden of coronary artery disease (80.0% vs. 95.6%), had a higher burden of cerebrovascular disease (22.5% vs. 11.4%), and had lower use of diuretics (43.1% vs. 58.5%) and beta-blocking agents (70.3% vs. 87.3%) at baseline. In the overall cohort, ertugliflozin (vs. placebo) significantly reduced the risk of the first HHF (HR.70). In the subgroup analysis by pre-trial EF, the interaction between treatment and EF did not reach significance for the first HHF. Indeed, the treatment effect of ertugliflozin for the first HHF among participants with EF >60% (HR.72) was comparable with that observed in the overall cohort. The authors conclude that study findings should be interpreted in the context of recent observations from the pooled phase III trials of other SGLT2 inhibitors in patients with HF across the spectrum of EF. The pooled analysis of the DAPA-HF and DELIVER trials demonstrated that dapagliflozin is associated with a consistent reduction in the risk of first and total HHF across the EF spectrum, including those with EF >60%. In contrast, prior observation from the EMPEROR-Preserved trial demonstrated a greater treatment effect of empagliflozin in reducing the risk of first and total HHF among individuals with EF <60% vs. those with EF >60%.

The editors hope that this issue of the European Heart Journal will be of interest to its readers.

Dr. Crea reports speaker fees from Abbott, Amgen, Astra Zeneca, BMS, Chiesi, Daiichi Sankyo, Menarini outside the submitted work.

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References


