Scientific letters

Potential role of empagliflozin in myocardial iron repletion following ferric carboxymaltose for heart failure

Uso potencial de empagliflozina en la repleción miocárdica de hierro tras carboximaltosa férrica en pacientes con insuficiencia cardiaca

To the Editor,

In patients with heart failure (HF) and left ventricular systolic dysfunction, treatment with intravenous ferric carboxymaltose (FCM) and sodium-glucose co-transporter-*2* inhibitors (SGLT2i) is associated with substantial clinical benefits.[1] However, the mechanisms behind such benefits remain incompletely understood. Some preliminary findings suggest that SGLT2i may increase cell-iron availability.[2] In the Myocardial-IRON trial, we found that in patients with HF and iron deficiency, FCM was associated with cardiac magnetic resonance (CMR) changes indicative of myocardial iron repletion (decrease in the T_2^* and T_1 mapping sequences).[3] The current analysis evaluated the association between treatment with FCM with early short-term changes in T_2^* and T_1-mapping CMR sequences across baseline treatment with SGLT2i.

This is a posthoc analysis of a randomized, double-blind, placebo-controlled Myocardial-IRON trial. Inclusion and exclusion

Table 1
Baseline characteristics by treatment arm

Variables	Placebo-no empagliflozin (n = 23)	Placebo-empagliflozin (n = 3)	FCM- no empagliflozin (n = 25)	FCM- empagliflozin (n = 2)	*P*
Demographics and medical history					
Age, y	71 [67-79]	67 [59-77]	73.5 [64-77]	72 [65.5-79]	.886
Male sex	16 (69.6)	3 (100)	19 (76)	2 (100)	.821
Hypertension	16 (69.6)	3 (100)	20 (80)	2 (100)	.745
Dyslipidemia	13 (56.5)	3 (100)	16 (64)	2 (100)	.435
Diabetes mellitus	11 (47.8)	3 (100)	13 (52)	2 (100)	.260
Former smoker	3 (13)	1 (33.3)	3 (12)	0	.635
Coronary artery disease	9 (39.1)	1 (33.3)	11 (44)	2 (100)	.472
Admission for AHF in last year	15 (65.2)	1 (33.3)	15 (60)	1 (50)	.763
COPD	4 (17.4)	2 (66.7)	7 (28)	0	.263
NYHA functional class					.435
II	23 (100)	3 (100)	22 (88)	2 (100)	
III	0	0	3 (12)	0	
KCCQ, points	68 [54-90]	91 [31-94]	74 [63-92]	80 [75-84]	.858
Vital signs					
Heart rate, bpm	68 [65-77]	64 [58-108]	74 [70-82]	68.5 [67-70]	.522
SBP, mmHg	126 [113-148]	122 [118-146]	116 [109-130]	139.5 [125-154]	.224
Electrocardiogram					
Atrial fibrillation	11 (47.8)	3 (100)	9 (36)	1 (50)	.200
LBBB	5 (21.7)	1 (33.3)	6 (24)	0	1.000
CMR parameters					
LVEF, %	36 [30-46]	33 [31-38]	44 [38-49]	41 [32-49]	.384
T_1 mapping at baseline, ms	1068 [1030-1116]	1101 [1082-1152]	1082 [1062-1106]	1108.5 [1037-1180]	.196
T_2^* mapping at baseline, ms	38 [30-42]	34 [33-77]	40 [36-45]	37 [34-40]	.527
Laboratory					
Hemoglobin, g/dL	13.4 [12.1-14.4]	14.6 [13.1-14.8]	13.0 [11.9-13.3]	13.3 [13.1-13.4]	.204
Transferrin saturation, %	14.9 [9.6-19.0]	21.9 [9.6-22.0]	15.0 [12.0-19.2]	16.0 [15.7-16.2]	.863
Ferritin, ng/mL	47.1 [23.0-131.0]	48.4 [30.0-65.0]	77.0 [56.0-126.0]	60.0 [58.0-62.0]	.292
eGFR, mL/min/1.73 m^2	64.3 [48.9-80.0]	49.7 [46.8-9.2]	59.4 [50.0-71.2]	72.7 [50.4-95.0]	.867
NT-proBNP, pg/mL	1180 [1010-2849]	1990 [601-2527]	1990 [976-2830]	2255 [1728-2781]	.871
Seric sodium, mmol/L	141 [140-142]	137 [135-144]	140 [140-142]	141 [140-142]	.633
Seric potassium, mmol/L	4.6 [4.4-4.9]	4.6 [3.9-4.7]	4.7 [4.2-5.0]	4.4 [4.3-4.5]	.627

AHF, acute decompensated heart failure; CMR, cardiac magnetic resonance; COPD, chronic pulmonary obstructive disease; eGFR, estimated glomerular filtration rate assessed by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; KCCQ, Kansas City Cardiomyopathy Questionnaire; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal propeptide brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.
Values are expressed as No. (%) or [percentile 25% to percentile 75%].

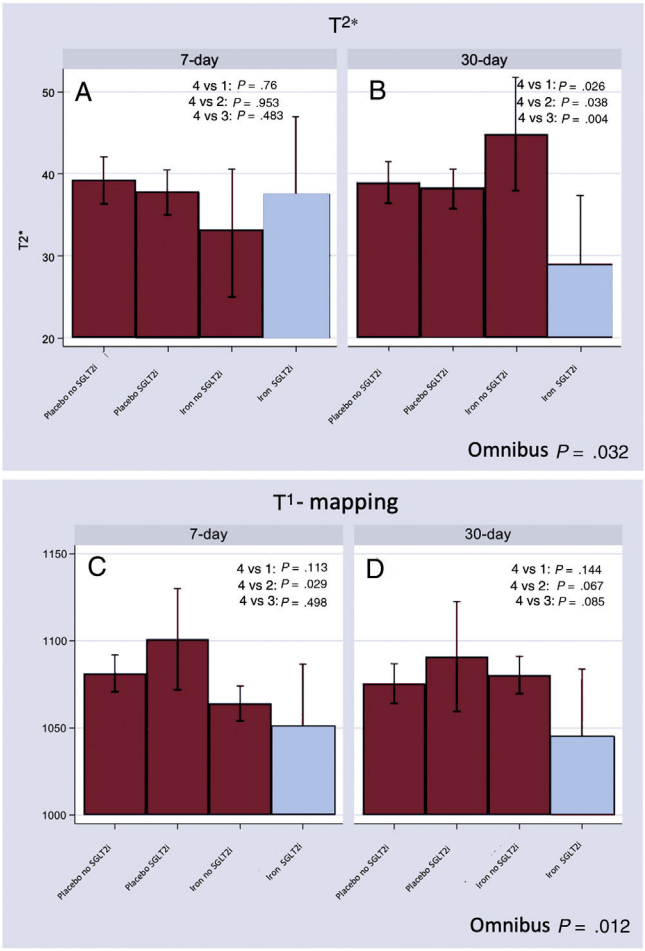

Figure 1. T_2^* and T_1 mapping CMR changes across treatment groups. A: T_2^* CMR changes at 7 days.. B: T_2^* CMR changes at 30 days. C: T_1 mapping CMR changes at 7 days. D: T_1 mapping CMR changes at 30 days. Group 1: placebo without empagliflozin; Group 2: FCM without empagliflozin; Group 3: placebo with empagliflozin; Group 4: FCM with empagliflozin.
CMR, cardiac magnetic resonance; FCM, ferric carboximaltose.

criteria are reported elsewhere but included patients with stable HF, left ventricular ejection fraction < 50%, and iron deficiency.[3] A total of 53 patients were randomized 1:1 to receive either FCM 1000 mg (n = 27) or placebo (n = 26). CMR studies were performed by 2 experienced operators on a 1.5 Tesla magnetic resonance scanner using the spine and phased array 6-channel surface coils. A region of interest was chosen for T_1 and T_2^* analysis in the mid-left ventricular septum. Detailed information on technical issues is published elsewhere.[3] The endpoints were changes in myocardial iron content as measured by T_2^* and T_1 mapping CMR sequences 7 and 30 days after FCM or placebo administration across treatment with empagliflozin. All patients gave written informed consent. The study conforms to the principles outlined in the Declaration of Helsinki and Good Clinical Practice of the International Conference on Harmonization. The study protocol was approved by the *Agencia Española del Medicamento y Productos Sanitarios* and by the *Comité Etico de Investigación Cínica* of *Hospital Clínico Universitario de Valencia*. All statistical comparisons were performed under the intention-to-treat principle. Linear mixed effect models were used to evaluate the endpoints. All analyses were adjusted for the baseline value of the regressed outcome, type 2 diabetes mellitus, and the interaction term treatment*visit (7- and 30-day). No adjustment was made for multiple comparisons. The linear mixed effect models are presented as least square means with their respective 95% confidence intervals and *P* values. All analyses were performed using STATA 15.1. A 2-sided *P* value of .05 was considered significant.

The median age was 73 years [interquartile range: 65 to 78], 40 (75.5%) were men, 29 (54.7%) were diabetic, 5 (9.4%) were on stable treatment with empagliflozin 10 mg/d, and most of the patients (94.3%) were in New York Heart Association class II. At baseline, the median left ventricular ejerction fraction and NT-proBNP were 39% [33-47], and 1690 pg/mL [1010-2828], respectively. All patients exhibited iron deficiency. No significant differences in baseline characteristics were found across the treatment groups, including T_2^* and T_1-mapping (table 1).

At follow-up, T_2^* differed across treatment groups (omnibus *P* value = .032). At 7 days, no differences were found (figure 1A). At 30 days, those receiving FCM on treatment with empagliflozin showed significantly lower 30-day T_2^* [Δ-15.8 ms (−26.5 to −5.1; *P* = .004)] compared with the FCM-no empagliflozin group (figure 1B). At this same time frame, T_2^* values remained lower when compared with the other treatment categories (figure 1B).

Likewise, T_1-mapping significantly differed across treatment groups (omnibus *P* value = .012). At 7 days, patients in the FCM-empagliflozin group exhibited lower T_1-mapping; however, the difference was only significant compared with those who received placebo and were on treatment with empagliflozin (figure 1C). At 30 days, compared with the FCM-no empagliflozin group, patients in the FCM-empagliflozin group exhibited a statistical trend to lower T_1-mapping values (figure 1D).

In this posthoc analysis, we found that in patients with stable HF with left ventricular ejerction fraction < 50% and iron deficiency, myocardial iron repletion following FCM was greater in patients on baseline treatment with empagliflozin. Recently, in a subanalysis of the EMPATROPISM trial Santos-Gallego et al., [4] suggested that treatment with empagliflozin may increase myocardial iron repletion. Specifically, they found a decrease in T_2^* evaluated by CMR after 6 months of treatment with SGLT2i compared with placebo and without iron supplementation. Ferritin levels were equally significantly reduced, and soluble transferrin receptor was increased in the empagliflozin arm.[4]

Prior and current data reinforce the hypothesis that SGLT2i seems to increase the myocardial availability of iron. Although there is no definitive explanation for this phenomenon, a study by Ghanim H et al.[5] reported that dapagliflozin causes hepcidin suppression, one of the main proteins involved in iron homeostasis, which avoids iron release from storage sites and which is increased in proinflammatory states, such as HF. In the same study, dapagliflozin also increased plasma concentrations of transferrin and the expression of transferrin receptors 1 and 2, responsible for the entry of iron into the cardiomyocyte.[5]

The current report has some limitations. First, it is a nonprespecified subgroup analysis of a small clinical trial. Second, the number of patients on treatment with empagliflozin was low, and all of them had type 2 diabetes, which may provide considerable uncertainty about the current findings. Further studies are warranted.

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AUTHORS' CONTRIBUTIONS

M. Lorenzo and R. de la Espriella contributed equally.

M. Lorenzo and R. de la Espriella were responsible for drafting the manuscript as well as preparing the tables and figures. I. Cardells was responsible for monitoring the patients during the study and for data collection. J.L. Górriz and A. Bayés-Genís have critically reviewed the manuscript and contributed to the correction of errors and suggestions from the reviewers. J. Núñez is responsible for devising the working hypothesis, statistical analysis and review of the different versions of the manuscript.

CONFLICTS OF INTEREST

J. Núñez has received board speaker fees and travel expenses from Novartis, Roche Diagnostics, Abbott, Rovi, Vifor Pharma, Novo Nordisk, Boehringer Ingelheim, and AstraZeneca (modest). A. Bayés-Genís has received board membership fees and travel expenses from Novartis, Roche Diagnostics, Vifor Pharma, and Critical Diagnostics (modest). The remaining authors have no disclosures to report.

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Comparison of two cardiac magnetic resonance imaging postprocessing software tools in a pig model of myocardial infarction

Comparación de dos programas de posprocesamiento de imágenes de cardiorresonancia magnética en un modelo porcino de infarto de miocardio

To the Editor,

Cardiovascular magnetic resonance (CMR) imaging has been increasingly used for testing of translational and clinical trial surrogate endpoints in cardioprotective therapies. While the JACC Scientific Expert Panel provides imaging technique recommendations and standardization[1], postprocessing and analysis methods vary institutionally. Moreover, most previous CMR postprocessing comparison and software testing data stem from human hearts. Pig hearts largely resemble their human counterparts. However, pigs have cone-shaped chests and higher resting heart rates than humans. Medis Suite (QMass MR v.3.2.60.4, The Netherlands) and CVI[42] (v.5.11, Circle Cardiovascular Imaging, Canada) are among the most widely used scanner-independent CMR postprocessing software programs. However, their interchangeability to assess anatomical and functional parameters in preclinical models has not been tested. We aimed to compare Medis Suite and CVI[42] readouts in a pig model of experimentally induced closed-chest acute myocardial infarction (MI). All procedures were authorized by the Animal Experimental Committee (#5601) of the local government.[2] We assessed anatomical and functional parameters in randomly selected 28 Landracex-Large white female pig datasets, which included baseline (before MI), early- (3 days post-MI), and late- (42 days post-MI) remodeling phase scans.[2] In addition, 25 of 28 scans included a dobutamine stress study (5-10-20-30 μg/kg/min of i.v. dobutamine at 3-minute intervals to elevate heart rate by 30-50%) using the volumetric module. To exclude interobserver- and experience-related variabilities, all images were blindly assessed by a Level 3 accredited operator. Due to animals' cardiac orientation, the quality of semi- and fully-automated ventricular contour segmentation was suboptimal in both products; thus, manual contouring was chosen.

The following were recorded: left ventricular (LV) end-diastolic volume, LV end-systolic volume, LV stroke volume, LV ejection fraction (LVEF), LV mass, right ventricular (RV) end-diastolic volume, RV end-systolic volume, RV stroke volume, and RV ejection fraction. Edema, microvascular obstruction (MVO), and necrosis mass were assessed on T_2 short-tau inversion recovery and T_1 inversion recovery sequences at early (1 minute) and late (10 minutes) gadolinium phases, respectively. On Medis Suite, we used visual assessment-defined manual planimetry on the volumetry module to draw the region(s) of interest (the late gadolinium enhancement [LGE] volume was multiplied by the myocardial density of 1.055 g/mL), and the full-width half-max (FWHM) technique, using the tissue characterization module with semiautomatic pixel value segmentation. Of note, MVO measurement on Medis Suite FWHM is planimetry-based, as the region of interest is user-defined without semiautomatic segmentation. On CVI,[42] as planimetry was unavailable for tissue characterization,