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RESEARCH ARTICLE

Empagliflozin improves high-sensitive cardiac troponin-I and high-density lipoprotein cholesterol in patients with type 2 diabetes mellitus and coronary artery disease: a post-hoc analysis of EMPA-CARD Trial

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Abstract

Background Empagliflozin is a sodium glucose cotransporter-2 (SGLT2) inhibitor that has been suggested to improve cardiac function and vascular recovery. The risk of coronary artery diseases is much higher in diabetic patients and is associated with greater morbidity and mortality. High-sensitivity cardiac troponin-I (hs-cTnI) is an important prognostic biomarker in cardiac diseases. Therefore, this study aimed to investigate the effect of empagliflozin compared to placebo on changes in hs-cTnI and lipid profile after 26 weeks of treatment.

Methods This was an ancillary study in a randomized trial of patients with concomitant type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD) (The EMPA-CARD study). Patients who were already on standard anti-diabetic/anti-ischemic medications were randomized to receive either placebo or empagliflozin 10 mg/daily. Serum hs-cTnI and lipid profile were measured at baseline and after 26 weeks.

Results Of the 95 randomized patients, hs-cTnI and lipid profile were measured for a total of 77 patients. No significant difference was observed regarding the baseline characteristics between the two arms. Compared to placebo, empagliflozin significantly reduced hs-cTnI after 26 weeks (mean difference (MD) of -13.242, 95%CI: -14.151 to -12.333, $p < 0.001$). In the empagliflozin group, non-significant reductions in total cholesterol, LDL-C, and triglyceride have resulted; however, there was an increase in HDL-C level (MD = 2.40,95%CI:0.16–4.60, $p < 0.04$).

Conclusion Empagliflozin compared to placebo was superior in reducing circulating hs-cTnI that may indicate improvements in cardiomyocytes function in patients with T2DM and CAD. Moreover, empagliflozin had a modest impact on the serum lipid profile biomarkers.

Trial registration The original EMPA-CARD study has been registered in Iranian Registry of Clinical Trials. www.IRCT.ir, Identifier: IRCT20190412043247N2. Registration Date: 6/13/2020. Registration timing: prospective.

Keywords SGLT2 inhibitor · Empagliflozin · Troponin · Lipid profile · Randomized controlled trial

Introduction

Patients with type 2 diabetes mellitus (T2DM) are substantially at higher risk for coronary artery disease (CAD). High-sensitivity cardiac troponin-I (hs-cTnI) is considered a cardiomyocyte contractile component with powerful prognostic significance [1]. Hs-cTnI represents that myocardial cell damage and is essential in the diagnosis of acute myocardial infarction (MI) [2]. The approved antihyperglycemic class of sodium-glucose cotransporter 2 (SGLT2) inhibitors carry beneficial impacts on vascular resistance and arterial stiffness [3] and therefore have shown an absolute benefit in attenuating atherosclerotic diseases and reducing the incidence of MI [4]. Empagliflozin is a selective SGLT2 inhibitor that was associated with lower rates of cardiovascular outcomes in T2DM patients [5].

The unfavorable shifts in lipid balance particularly the increases in low-density lipoproteins (LDL) cholesterol are

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commonly reported to be one of the side effects of SGLT2 inhibitors. However, the evaluations on the changes in lipid profiles have been highly diverse [6, 7]. It has not been elucidated yet whether these agents are lipid-neutral or lipid-friendly and whether the changes in lipid metabolism are clinically relevant [8].

In this post hoc study of the EMPA-CARD trial, concerning the cardioprotective potential of empagliflozin, we have investigated the changes in hs-cTnI levels. Additionally, we have examined the effect of empagliflozin on the level of lipid parameters.

Methods and materials

Study design and population

The detailed design of the EMPA-CARD study has been described elsewhere [9]. Briefly, EMPA-CARD was a multicenter double-blind randomized placebo-controlled trial (RCT) that evaluated the effects of empagliflozin 10 mg/day versus placebo in patients with both T2DM and evidence of CAD involving 4 clinical centers including Mousavi hospital (coronary angiography registry), Vali-e-Asr hospital, and two cardiology clinics of Zanjan University of Medical Sciences in Zanjan, Iran between the years 2020 and 2021. Ethical approval was acquired from the ethics committee of Zanjan University of Medical Sciences (ID: IR.ZUMS.REC.A-12–594-29). This trial has also been prospectively registered at the Iranian Registry of Clinical Trials (www.IRCT.ir; Identifier: IRCT20190412043247N2). At the pre-recruitment phase, the records of 8000 patients were garnered. Eligible patients went through interviews and randomization process. Prior to the recruitment, the investigators handed the written informed consent to all the participants.

Key inclusion criteria included: patients with T2DM and documented history of CAD, who aged between 40 to 75 years, serum HBA_{1c} of 6.5 to 9.5%, and under standard oral anti-diabetic/anti-ischemic therapy for at least 3 months prior to the recruitment. CAD must have been proven with a documented coronary angiography. Any participant that reported allergic reactions to SGLT2-inhibitors or had a history of these medications; body mass index (BMI) higher than 40 kg/m^2; history of acute coronary syndrome (ACS), coronary artery bypass graft (CABG) surgery, transient ischemic attack (TIA) or cerebrovascular accident (CVA), and percutaneous coronary intervention (PCI) during the past 3 months; use of alcohol during the past 3 months, liver enzymes more than 3 folds of normal range in addition to pregnant patients were all excluded.

A block stratified randomization procedure used to randomize eligible, consenting patients to treatment or control group. Patients were stratified by gender (male and female), age (45–54, 55–64, and 65–75 years old), and HbA1c (6.5–7.9% and 8–9.5%) and assigned into one of the two arms of the study. The randomization sequence was created using Winpepi software (version 11.6). To ensure that the allocation sequence was concealed from study participants, a sealed envelopes mechanism was used. During this process, researchers, healthcare providers and patients themselves were all blinded to the assigned treatment.

Study interventions

Baseline characteristics and laboratory data of all eligible patients were collected through interviews and blood sampling, respectively. Patients were randomized into two groups to receive either empagliflozin tablet 10 mg/daily (Dr. Abidi Co, Iran) or placebo for 6 months in addition to their previously prescribed antidiabetic drugs. Prior to the interventions, fasting blood samples were obtained to measure hematological indices. All tests were performed in a single laboratory in one of the hospitals. Blood samples were taken at the end of 26 weeks to reassess serum biomarkers. Due to the onset of COVID-19 pandemic, in order to facilitate the patients' referral and prevent their presence in the crowded environment of the hospital, the second round of sample collection was performed in a laboratory outside the hospital and then samples were transferred to our hospital for final analyses. Hs-cTnI was measured by quantitative luminescence method (Abbott Architect i2000, USA), and other biochemical tests were measured enzymatically (Prestige 50i, Japan) using Bionic kits in our hospital.

Outcomes

The outcomes for this ancillary study entailed 1) Changes in serum hs-cTnI levels in the treatment arm compared to the placebo after 26 weeks of treatment. 2) Changes in the levels of lipid profile (total cholesterol, LDL-C, high-density lipoprotein-cholesterol (HDL-C), and triglyceride (TG)) compared to placebo after 26 weeks of treatment.

Statistical analysis

Data were presented as mean ± standard deviation (SD) and frequency (percentage) for quantitative and categorical variables, respectively. The per-protocol method was implemented for the analysis of data. As the study population in each arm included more than 30 patients, based on the central limit theorem, the means (SD) were used for the analysis of the non-normally disturbed continuous data [10]. Consequently, the analysis of covariance (ANCOVA) was used in examining the differences in the mean values of the assessed parameters that were related to the effect of the empagliflozin. P values of ≤ 0.05 were considered

statistically significant. The statistical analyses were performed via IBM SPSS statistics version 21.0 for Windows (IBM, Armonk, New York).

Results

In the original study, 95 patients underwent 1:1 randomization at baseline and after 26 weeks 82 patients returned for reevaluation. The data of 77 patients (42 in the empagliflozin and 35 in the placebo arm) were available for this study and underwent statistical analysis. As summarized in Table 1, the empagliflozin and placebo groups were well balanced in baseline characteristics of gender, age, underlying comorbidities (hypertension and hyperlipidemia), oral medications, and baseline laboratory indices including cardiac enzyme and lipid profiles.

The changes in laboratory biomarkers from the 26th week compared to the baseline following study interventions are shown in Table 2. Changes in the levels of hs-cTnI in the empagliflozin arm compared to placebo had significant higher decreases (mean difference of -13.242, 95%CI: -14.151 to -12.333, $p < 0.001$). The changes in the level of lipid parameters of total cholesterol, LDL-C and TG between the two groups had no significant difference; however, compared to placebo, there was a significant increase from baseline in HDL-C in the empagliflozin group (Fig. 1).

Discussion

This post-hoc study had two main findings for the comparison of 10 mg daily empagliflozin to placebo: 1) significant reduced level of plasma hs-cTnI and 2) improved HDL-C level in the treatment group, however, there were no concomitant changes in total cholesterol, LDL-C, and TG.

Hs-cTnI

Current evidence supports the cardioprotective effects of SGLT2 inhibitors and has examined several potential mechanisms for the cardiovascular benefits of such drugs. Hs-cTnI has emerged to be a prognostic predictor in cardiovascular diseases as well as a robust discriminating indicator in patients with chronic heart failure [11, 12].

Our results are in line with the study of Januzzi et al. where canagliflozin for over 2 years was associated with delayed increment in plasma hs-cTnT [13]. Moreover, among T2DM patients with AMI who were users of SGLT2 inhibitors, individual and peak hs-TnT values as well as the infarct size were significantly lower [14]. Packer et al. observed a stepwise relationship between the hs-cTnT concentration and the severity and instability of heart failure among patients with reduced ejection fraction who were on empagliflozin [15]. However, they have only measured hs-cTnT at baseline and the drug-induced changes following empagliflozin were not observed. In contrast, SUGAR-DM-HF and Empire HF trials, empagliflozin was not associated with significant changes in hs-TnI levels [16, 17]. Current studies are not consistent on whether SGLT2 inhibitors are associated with greater cardiac benefits in cases with higher or lower baseline cardiac biomarker [15, 18, 19]. Plus, there are still concerns regarding the challenges in the interpretation of hs-cTnT assays in patients with chronic kidney disease and T2DM in whom basal levels are more likely elevated.

During post-ischemic reperfusion, the heart is susceptible to oxidative stress, and eventually the formation of free radicals leads to apoptosis and necrosis through mitochondrial pathways. Additionally, diabetes-associated cardiac remodeling involves increased deposition of extracellular matrix and cardiomyocyte hypertrophy [20]. Following MI, pro-inflammation cytokine responses along with the impaired cardiac structural and metabolism in the context of DM contribute to inducing infiltrative and myocardial apoptosis processes. On the other hand, the release of hs-cTnI is deemed to be promoted by such processes [21]. In view of this, empagliflozin through modulating the increases in hs-cTnI may improve adverse cardiovascular events in T2DM patients.

Lipid profile

Total cholesterol, TG and LDL-C in our study had no significant changes in the empagliflozin group compared to placebo. Accordingly, in the study of Fadini et al. and Pujante et al. dapagliflozin for 12 weeks [22] and SGLT2 inhibitors for 4 months in diabetic patients have shown the same results [23]. The addition of 10 and 25 mg empagliflozin has been evaluated by Ozcelik et al. and both groups demonstrated neutral effects on LDL levels [24]. In contrast, several studies reported an increase in LDL-C levels [25–28]. Empagliflozin may switch energy metabolism to lipid utilization and lead to a moderate increase in LDL-C concentrations [29]. Despite the association of empagliflozin with an increase in serum LDL in most of the studies, the drug confers angioprotective properties [30]. Our study showed significantly improved HDL-C levels in patients treated with empagliflozin. Similarly, Kovacs et al. demonstrated that empagliflozin increased serum HDL-C, yet no significant reductions in total cholesterol, LDL-C, and TG were observed [31]. Similar to this study, dapagliflozin 10mg/day for 24-week in diabetic patients revealed no significant changes in plasma TG [32]. Our results are consistent with rodent model studies as well [33, 34]. Furthermore, SGLT 2 inhibitors were not associated with higher risk of dyslipidemia, according

Table 1 Baseline demographic and laboratory variables randomized in 2 arms

Variables	Empagliflozin ($n=42$)	Placebo ($n=35$)	P value
Demographic			
Age	62.07 ± 7.34	60.58 ± 7.54	0.734
Gender			0.258
Male	21 (50.0)	13 (37.1)	
Female	21 (50.0)	22 (62.9)	
Comorbidity (yes)			
HTN	39 (92.9)	31 (88.6)	0.695
HLP	34 (81.0)	25 (71.4)	0.203
Drug history (yes)			
Metformin	42 (100.0)	33 (94.3)	0.116
Sulfonylurea	15 (35.7)	9 (25.7)	0.346
DPP4-i	8 (19.0)	4 (11.4)	0.530
Insulin	2 (4.8)	3 (8.6)	0.654
BB	37 (88.1)	32 (91.4)	0.721
ACEi/ARB	36 (85.7)	31 (88.6)	0.748
CCB	16 (38.1)	12 (34.3)	0.729
Diuretic	18 (42.9)	14 (40)	0.800
Statins	41 (97.6)	32 (91.4)	0.325
Laboratory			
FBS (mg/dL)	161.86 ± 40.45	168.94 ± 54.13	0.525
HbA_{1c} (%)	7.99 ± 0.96	7.83 ± 0.99	0.463
Cr (mg/dL)	0.98 ± 0.19	1.01 ± 0.24	0.541
ALT (U/L)	21.58 ± 11.72	24.52 ± 14.58	0.353
AST (U/L)	16.85 ± 6.65	20.27 ± 11.45	0.135
Hs-cTnI (ng/L)	22.85 ± 1.7	22.39 ± 1.94	0.898
Total cholesterol (mg/dL)	141.73 ± 18.32	141.17 ± 17.52	0.889
HDL-C (mg/dL)	39.25 ± 5.68	38.24 ± 5.36	0.756
LDL-C (mg/dL)	78.84 ± 16.91	79.29 ± 16.01	0.689
TG (mg/dL)	144.28 ± 22.16	144.17 ± 20.98	0.898
IPAQ			
Physical Activity (MET min/week)	977.52 ± 632.39	881.50 ± 533.96	0.483
FFQ			
TEI (Kcal/day)	2160.95 ± 284.65	2085.96 ± 346.33	0.314
Total Fat (g/day)	70.92 ± 20.96	65.03 ± 17.88	0.216
Total Cholesterol (mg/day)	208.92 ± 69.93	227.65 ± 143.41	0.482
Saturated Fat (g/day)	22.28 ± 7.06	19.81 ± 7.61	0.174
MUFA (g/day)	22.05 ± 8.17	21.30 ± 5.81	0.660
PUFA (g/day)	14.63 ± 6.25	15.33 ± 3.93	0.593
Trans-Fat (g/day)	> 0.01	> 0.01	0.324

Data are presented as mean ± SD or frequency (%)

HTN Hypertension, *HLP* Hyperlipidemia, *DPP4-i* Inhibitors of dipeptidyl peptidase-4 inhibitor, *BB* Beta blocker, *ACEi* Angiotensin convertase enzyme inhibitor, *ARB* Angiotensin receptor blocker, *CCB* Calcium channel blocker, *FBS* Fasting blood sugar, HbA_{1c} Glycated hemoglobin, *Cr* Creatinine, *AST* Aspartate aminotransferase, *ALT* Alanine aminotransferase, *Hs-cTnI* High sensitivity cardiac troponin-I, *HDL-C* High density lipoprotein cholesterol, *LDL-C* Low density lipoprotein cholesterol, *TG* Triglyceride, *IPAQ* International physical activity questionnaire, *FFQ* Food frequency questionnaire, *TEI* Total energy intake, *MUFA* Monounsaturated fatty acids, *PUFA* Polyunsaturated fatty acids

to a meta-analysis [35]. However, there are numerous established data on TG lowering characteristics of SGLT2 inhibitors that are associated with endothelial function recovery [36]. Therefore, reduced levels of TG may have ameliorating effects on atherosclerosis progression. The postulated mechanisms may be the enhanced lipoprotein clearance

Table 2 Changes in laboratory variables among 2 arms

Variables	Empagliflozin $n=42$		Placebo $n=35$		Mean Diff	*P* value	95% CI
	Baseline	Week 26	Baseline	Week 26			
Cardiac Enzyme							
Hs-cTnI (ng/L)	22.85 ± 1.7	9.77 ± 1.03	22.39 ± 1.94	23.01 ± 2.69	-13.24	< 0.001	-14.15; -12.33
Lipid profile							
Total Cholesterol (mg/dL)	141.73 ± 18.32	133.54 ± 16.42	141.17 ± 17.52	131.69 ± 20.12	1.85	0.669	-6.78; 10.50
TG (mg/dL)	144.28 ± 22.16	140.90 ± 22.5	144.17 ± 20.98	139.38 ± 19.9	1.52	0.761	-11.87; 8.73
LDL-C (mg/dL)	101.38 ± 12.11	97.74 ± 14.48	98.28 ± 12.69	94.43 ± 22.65	3.313	0.467	-5.72;12.35
HDL-C (mg/dL)	39.25 ± 5.68	39.11 ± 5.23	38.24 ± 5.36	36.71 ± 3.64	2.40	0.036	0.16; 4.60

Data are presented as mean ± SD. *Hs-TnI* High sensitivity troponin-I, *HDL-C* High density lipoprotein cholesterol, *LDL-C* Low density lipoprotein cholesterol, *TG* Triglyceride

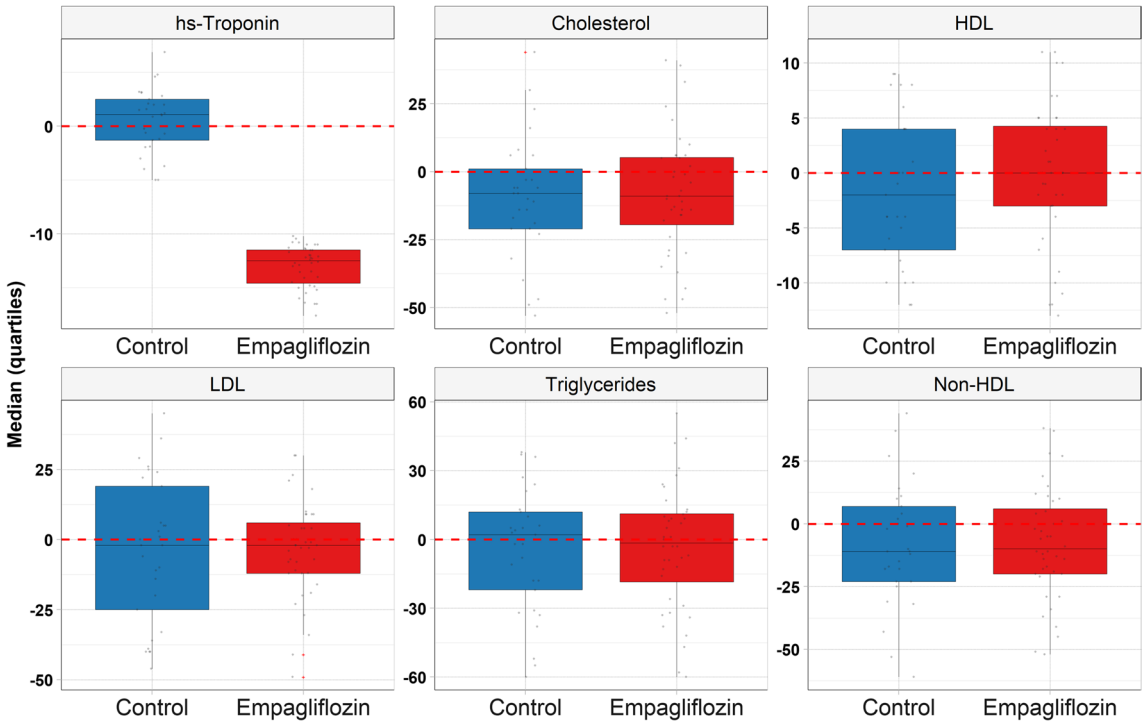

Fig. 1 The serum levels of hs-troponin-I and lipid profile of patients in each arm after 26 weeks of treatment. hs-troponin: High sensitive troponin; HDL: High density lipoprotein cholesterol; LDL: Low density lipoprotein cholesterol

through downregulation the lipoprotein lipase (LPL) inhibitor; diacylglycerol O-acyltransferase 2 [30]. The elevated activity of LPL leads to greater lipolysis of TG-rich lipoproteins [36]. The discrepancies among studies may be due to the different durations and dosages of treatment protocols along with the differences between populations of each study. Additionally, one might note that visceral adipose fat may interfere with empagliflozin effect on decreasing TG synthesis [37]. Although highly evaluated, the true effect of SGLT 2 inhibitors on lipids hasn't been clarified, thus it has remained a controversial issue and further longitudinal studies are needed.

Limitations

This study was performed as a post hoc exploratory analysis and sample size inconsistency may have affected the results. Plus, since EMPA-CARD was not primarily designed to evaluate serum lipids and troponin changes, though this study may have been underpowered to identify the exact changes as the investigated outcomes were considered exploratory. Moreover, the per-protocol method implementation for the analysis of data may have also influenced the result of the study. Additionally, despite that this was a multi-center study, all the clinical centers were located in a

single city, for more generalizability of our findings, future nationwide and global studies are warranted.

Conclusion

This post hoc study presents the favorable effect of empagliflozin on the risk of CAD in patients with T2DM through reducing hs-cTnI which pronounces the role of this agent in cardiovascular diseases. Additionally, we have observed that treatment with empagliflozin had a beneficial effect on HDL-C. Therefore, our results suggest that the use of 10 mg/daily Empagliflozin can improve lipid profile which is an integral part of preventing cardiovascular complications of diabetes, however, further confirmatory studies are warranted.

Abbreviations *T2DM*: Type 2 diabetes mellitus; *CAD*: Coronary artery disease; *Hs-cTnI*: High-sensitivity cardiac troponin-I; *MI*: Myocardial infarction; *SGLT2 inhibitors*: Sodium-glucose cotransporter-2 inhibitors; *LDL-C*: Low-density lipoproteins cholesterol; *RCT*: Randomized controlled trial; *BMI*: Body mass index; *ACS*: Acute coronary syndrome; *CABG surgery*: Coronary artery bypass graft surgery; *TIA*: Transient ischemic attack; *CVA*: Cerebrovascular accident; *HDL-C*: High-density lipoprotein cholesterol; *TG*: Triglyceride

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Authors' contribution All authors have participated in the work and have reviewed and agree with the content of the article. HT: Conceptualization, main investigator, Outcome assessor. HC: Supervision, critical revision, patient follow up. TR and SEP G: Study design, conceptualization, outcome assessor. AJ: Study design, resource. SAJ: Statistical Analysis, data curation. FIB: Supervision, study design. SAM G, MD and AA: patient follow up. MM: Manuscript draft. AKH: Outcome assessor. HA: Project Administration, supervision, resource, manuscript editing, patient follow up.

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Data availability The data/information supporting this study is available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate All methods were conducted in accordance with relevant guidelines and regulations. This study was approved by the ethics committee of Zanjan university of Medical Sciences (ID: IR.ZUMS.REC.A-12–594-29). Moreover, the study protocol of the original study was prospectively registered on the Iranian Registry of Clinical Trials (www.IRCT.ir, Identifier: IRCT20190412043247N2). All patients were provided with written informed consent prior to the recruitment.

Consent for publication Not applicable.

Role of Dr. Abidi Pharmaceutical Company The company supplied the medication and placebo for the original study. The company had no role in the development of the protocol, process of the study, or preparation of this manuscript.

Competing interest The authors contributing to the study have nothing relevant to disclose.

Conflict of interest None Declared.

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