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Outcomes in diabetic patients treated with SGLT2-Inhibitors with acute myocardial infarction undergoing PCI: The SGLT2-I AMI PROTECT Registry

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A R T I C L E I N F O

Keywords:
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A B S T R A C T

Aims: To investigate in-hospital and long-term prognosis in T2DM patients presenting with acute myocardial infarction (AMI) treated with SGLT2-I versus other oral anti-diabetic agents (non-SGLT2-I users).
Methods: In this multicenter international registry all consecutive diabetic AMI patients undergoing percutaneous coronary intervention between 2018 and 2021 were enrolled and, based on the admission anti-diabetic therapy, divided into SGLT-I users versus non-SGLT2-I users. The primary endpoint was defined as a composite of cardiovascular death, recurrent AMI, and hospitalization for HF (MACE). Secondary outcomes included i) in-hospital cardiovascular death, recurrent AMI, occurrence of arrhythmias, and contrast-induced acute kidney injury (CI-AKI); ii) long-term cardiovascular mortality, recurrent AMI, heart failure (HF) hospitalization.
Results: The study population consisted of 646 AMI patients (with or without ST-segment elevation): 111 SGLT2-I users and 535 non-SGLT-I users. The use of SGLT2-I was associated with a significantly lower in-hospital

Abbreviations: AMI, acute myocardial infarction; SGLT2-I, Sodium-glucose cotransporter 2 inhibitors; OAD, oral antidiabetic; T2DM, type 2 diabetes mellitus; HF, heart failure; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; RWMA, regional wall motion abnormalities.

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cardiovascular death, arrhythmic burden, and occurrence of CI-AKI (all $p < 0.05$). During a median follow-up of 24 ± 13 months, the primary composite endpoint, as well as cardiovascular mortality and HF hospitalization were lower for SGLT2-I users compared to non-SGLT2-I patients ($p < 0.04$ for all). After adjusting for confounding factors, the use of SGLT2-I was identified as independent predictor of reduced MACE occurrence (HR=0.57; 95%CI:0.33–0.99; p = 0.039) and HF hospitalization (HR=0.46; 95%CI:0.21–0.98; p = 0.041).
Conclusions: In T2DM AMI patients, the use of SGLT2-I was associated with a lower risk of adverse cardiovascular outcomes during index hospitalization and long-term follow-up. Our findings provide new insights into the cardioprotective effects of SGLT2-I in the setting of AMI.
Registration: Data are part of the observational international registry: SGLT2-I AMI PROTECT. ClinicalTrials.gov Identifier: NCT05261867.

1. Introduction

Sodium-glucose cotransporter 2 inhibitors (SGLT2-I) are oral antidiabetic (OAD) agents that exert beneficial effects on glycemic control in type 2 diabetes mellitus (T2DM). In large, randomized trials, SGLT2-I significantly improved cardiovascular and renal outcomes in diabetic patients, extending benefits to non-diabetic patients with heart failure (HF) [1–5]. Pre-clinical studies have also shown that SGLT2-I mitigates acute myocardial I/R injury, attenuating cardiac infarct size, increasing left ventricular function, and reducing arrhythmias [6,7]. There are some ongoing trials, compounded by the first published results of the EMMY Trial, which did not find any difference in acute troponin values between the SGLT2-I treated and untreated cohorts [8,9]. However, the EMMY trial included only a minority of diabetic patients, and all patients were randomized to the treatment at the time of the AMI admission. Thus, the actual efficacy and safety of SGLT2-I chronic therapy in diabetic patients with AMI remain an under-studied topic. On the clinical ground, we recently demonstrated that T2DM patients hospitalized

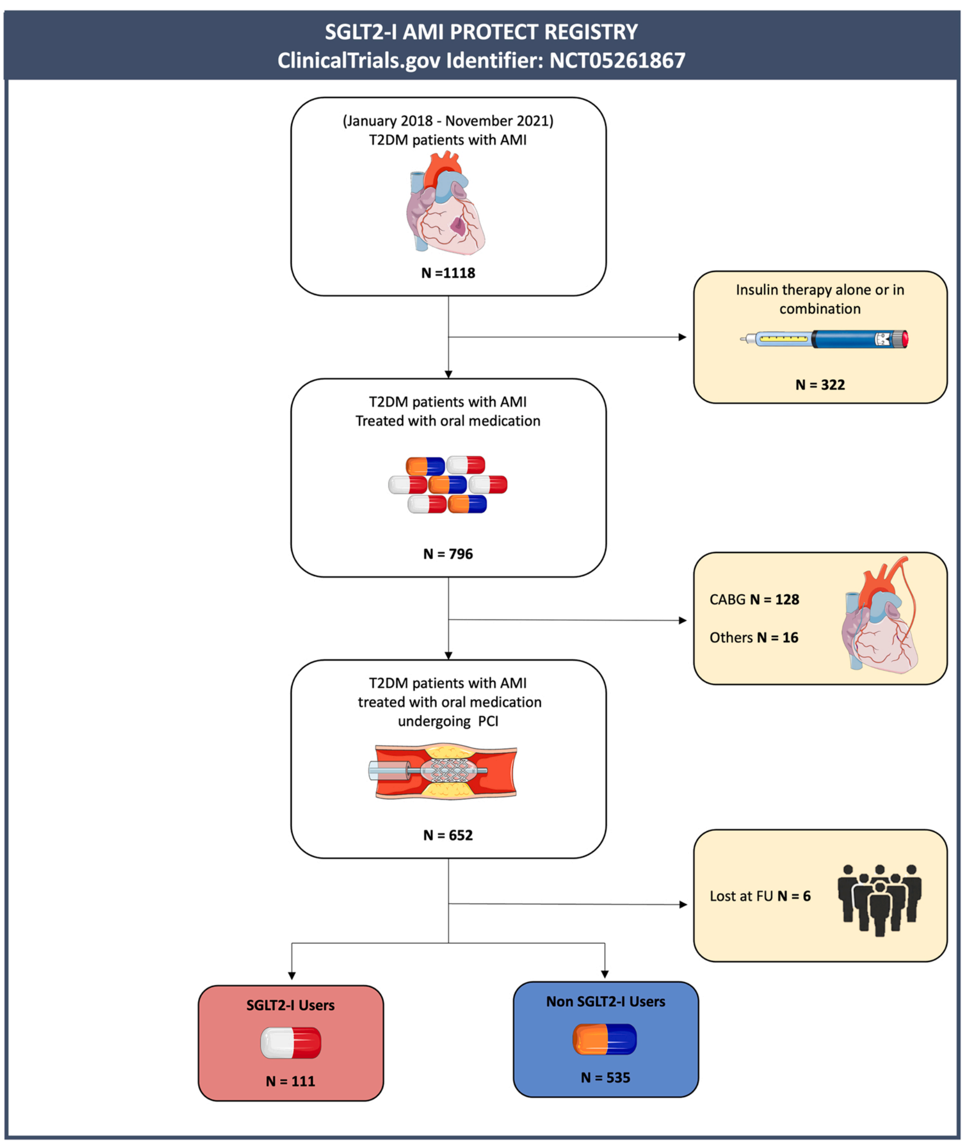

Fig. 1. Study flow chart. Abbreviations: T2DM = type 2 diabetes mellitus; AMI = acute myocardial infarction; CABG = coronary artery bypass graft; PCI = Percutaneous coronary intervention; SGLT2-I = Sodium-glucose co-transporter 2 inhibitors.

for AMI and receiving SGLT2-I exhibited a significantly reduced inflammatory and arrhythmic burden and infarct size compared to non-SGLT2-I users, independently of glucose-metabolic control [10,11].

Based on these observations, we hypothesized that SGLT2-I might have acute and long-term cardioprotective effects with favorable prognostic impact, on top of their anti-hyperglycemic properties [12]. To test this hypothesis, we investigated the in-hospital and long-term prognosis in T2DM patients with AMI receiving SGLT2-I compared to other OAD agents (non-SGLT-I users).

2. Methods

2.1. Study population

In this multicenter international observational registry (SGLT2-I AMI PROTECT, ClinicalTrials.gov Identifier: NCT05261867), we included consecutive diabetic patients admitted with AMI, both ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), undergoing percutaneous coronary intervention (PCI), between January 2018 and November 2021 (Fig. 1). The definition of STEMI and NSTEMI and patient management followed current guidelines [13,14]. Based on admission antidiabetic therapy, patients were divided into SGLT2-I users, if they were admitted on chronic SGLT2-I therapy (started at least 3 months before hospitalization), and non-SGLT2-I users, if they received other OAD strategies. Patients on insulin therapy or with incomplete information on medical therapy were excluded. Further exclusion criteria were coronary artery bypass graft surgery (CABG) as revascularization treatment, severe valvular heart disease, prosthetic heart valves, severe anemia, history of bleeding, pulmonary embolism, glomerular filtration rate < 30 ml/min/1.73 m^2, malignancies, and follow-up data shorter than 3 months. Patients with more than 20 % of missing values in the collected data were excluded due to potential bias. The present study was conducted according to the principles of the Declaration of Helsinki; all patients were informed about their participation in the registry and provided informed consent for the anonymous publication of scientific data.

2.2. Clinical endpoints and follow-up

Patients were followed over time with outpatient visits and telephone contacts using a standard questionnaire. Clinical outcomes were defined according to the current standards [15]. The primary endpoint of our study was defined as a composite of cardiovascular death, recurrent AMI, and hospitalization for HF (MACE). Secondary in-hospital outcomes included length of hospital stay, in-hospital cardiovascular death, recurrent AMI, the occurrence of major arrhythmias, and contrast-induced acute kidney injury. Secondary long-term outcomes were cardiovascular mortality, recurrent AMI, any coronary revascularization, and hospitalization for HF. The definition of clinical endpoints is reported in the Supplementary File.

2.3. Statistical analysis

Normal distribution of continuous variables was assessed by histograms and q-plot; the Shapiro-Wilk test was used when required. Continuous variables with normal distribution were expressed as the mean ± standard deviation and non-normally distributed variables as median and interquartile range. Normal ranges were presented as the 5th and 95th percentiles. Categorical variables were expressed as counts and percentages. Differences between groups were analyzed using the t-test or the Mann–Whitney U-test for continuous variables and the chi-square test or the Fisher's exact test for categorical variables, as appropriate. To compare paired data a Wilcoxon signed-test or a Paired sample T-test were performed as appropriate. Univariate analysis was performed to identify variables associated with cardiovascular death, hospitalization, and MACE. Significant variables were then entered into a multivariable analysis using the Cox regression model to determine the independent association of each risk factor with outcomes occurrence. The hazard ratio (HR) and the associated 95 % confidence interval (CI) for each variable were determined. The final list of covariates was also determined by removing variables that caused high collinearity, as accessed by variance inflation factors. Kaplan-Meier analysis and Log-rank test were used to compare the cumulative incidence of clinical events between groups. In addition, linear and polynomial regression models were fit to evaluate the relationship between continuous variables. P-values < 0.05 is considered statistically significant. All analyses were performed using R statistical software version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria), Statistical Package for Social Sciences, version 25.0 (SPSS, PC version, Chicago, IL, USA) and GraphPad Prism (GraphPad Software, Inc., CA, US).

3. Results

3.1. Study population

Out of 1118 diabetic patients with AMI screened, 322 were excluded due to insulin therapy, 128 because they underwent CABG, 16 for all the other exclusion criteria. and 6 due to a clinical follow-up either unavailable or shorter than 3 months. The final study population consisted of 646 diabetic patients with AMI treated with PCI, divided into SGLT2-I (n = 111) or non-SGLT2-I users (n = 535) (Fig. 1).

3.2. Baseline and procedure characteristics

Baseline characteristics, cardiovascular risk factors, and comorbidities are reported in Table 1**.** The mean age of the overall study population was 70 [61–79] years, and more than 77% were males. The mean T2DM duration was similar for both groups (6.9±2.9 years for SGLT2-I users and 7.1±1.5 years for non-SGLT2-I users, p = 0.123). SGLT2-I patients were younger and with better renal function at admission compared to non-SGLT2-I users. The mean time of SGLT2-I therapy duration was 7.3 ± 3 months. At variance, gender, body mass index/surface area, main cardiovascular risk factors, glucose-metabolic control, and comorbidities were similar in the two groups. Regarding admission medical therapy, no differences were found, except for a lower intake of sulfonylureas in SGLT2-I users (Table 2).

The two study groups exhibited similar admission characteristics, including Killip Class, the occurrence of angina, AF, and VT/VF presentation (Table 1). The rate of STEMI was similar between the two study groups and the median times from symptoms to diagnostic coronary angiography did not differ between groups for both STEMI and NSTEMI (Table 1). The main angiographic characteristics were also similar between the two study groups (Supplementary Table 1), except for the higher number of stents implanted in the SGLT2-I group (p = 0.041). Vascular access and contrast dosage did not differ between the 2 cohorts. Finally, a similar rate of complete revascularization, staged procedure and complex PCI was observed between the study groups. On admission and after 24 h, non-SGLT2-I users exhibited a higher inflammatory burden compared to the SGLT2-I group. Stress hyperglycemia was significantly lower in SGLT2-I patients compared to the non-SGLT2-I group (p = 0.007), even though HbA1c did not differ between groups (Supplementary Table 2). Discharge medical therapy, as well as in-hospital glucose-lowering strategies, are provided in Table 2**.** Due to the lower stress admission hyperglycemia, insulin therapy (both s.c. and i.v.) and hypoglycemic episodes were significantly lower in SGLT2-I users (p < 0.01 for all). In the latter cohort, no patient had to discontinue SGLT2-I for hypoglycemic episodes that occurred during hospitalization.

Table 1
Study population baseline characteristics and clinical presentation.

	Tota (N = 646)	SGLT2-I users (N = 111)	Non-SGLT2-I users (N = 535)	P-value
Baseline characteristics				
Age, years	70 [61–79]	66 [59–73]	72 [62–80]	<0.001
Male Sex, n (%)	498 (77.1)	90 (81.1)	405 (75.7)	0.222
BMI, kg/m^2	27.7 [25 – 31.3]	27.1 [24.6–30]	27.7 [25 – 31.4]	0.245
BSA, m^2	1.94 [1.8 – 2.1]	1.96 [1.8 – 2.03]	1.93 [1.78 – 2.1]	0.261
Smoking, n (%)	370 (57.3)	67 (60.4)	303 (56.6)	0.470
Hypertension, n (%)	541 (83.7)	98 (88.3)	443 (82.8)	0.154
Dyslipidemia, n (%)	508 (78.6)	90 (81.1)	418 (78.1)	0.490
PAD, n (%)	82 (12.7)	16 (14.4)	66 (12.3)	0.550
COPD, n (%)	90 (13.9)	15 (13.5)	75 (14)	0.889
CKD, n (%)	58 (9)	10 (9)	47 (8.8)	0.886
Previous TIA/CVA, n (%)	52 (8)	10 (9)	42 (7.9)	0.683
Previous AMI, n (%)	169 (26.2)	30 (27)	136 (25.4)	0.724
Previous PCI, n (%)	183 (28.3)	35 (31.5)	144 (26.9)	0.322
Clinical presentation				
STEMI, n (%)	309 (47.8)	52 (46.8)	257 [48]	0.819
Time symptoms–balloon (STEMI), hours	3 [2–5]	3 [2–6]	3 [2–5]	0.648
Time symptoms–balloon < 24 h (NSTEMI)	207 (61.4)	39 (66.1)	175 (62.9)	0.647
SBP, mmHg	140 [125–160]	140 [125–155]	140 [125–160]	0.639
DBP, mmHg	80 [70–90]	83 [70–90]	80 [70–90]	0.551
HR, bpm	81 [70–94]	75 [68–86]	83 [72–95]	<0.001
Angina, n (%)	466 (72.1)	80 (72.1)	386 (72.1)	0.987
NYHA> 2, n (%)	113 (17.5)	16 (14.4)	101 (18.9)	0.266
Killip Class ≥ 2, n (%)	135 (20.9)	18 (16.2)	117 (21.9)	0.183
VT/VF, n (%)	21 (3.3)	2 (1.8)	19 (3.6)	0.344
AF, n (%)	58 (9)	9 (8.1)	49 (9.2)	0.725

Continuous variables are presented as mean±SD or as median [IQR]; while categorical variables as number (%). Abbreviations: BMI=Body Mass Index; BSA=Body Surface Area; CKD=chronic kidney disease with 30 <GFR< 60 ml/min; PCI=Percutaneous Coronary Intervention; AF=atrial fibrillation; ACEI=Angiotensin-converting enzyme; ARB=Angiotensin II Receptor Blockers; CCB=Calcium Channel Blockers; BB=B-blockers; GFR=Glomerular Filtration Rate. STEMI=ST-segment Elevation Myocardial Infarction; NSTEMI=non-ST segment Elevation Myocardial Infarction; SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=heart rate; NYHA=New York Heart Association; VT=Ventricular Tachycardia; VF=Ventricular Fibrillation; AF=Atrial Fibrillation.

3.3. Impact of SGLT2-I on left ventricular function

Troponin values were significantly lower in SGLT2-I users than in non-SGLT2-I patients ($p \leq 0.003$ for all, Table 3). Consistently, ST-segment resolution post-PCI was more frequently observed in the SGLT2-I group ($p = 0.001$). On admission, left ventricular volume, ejection fraction (LVEF) and regional wall motion abnormalities (RWMA) were similar between the two study groups. In both study cohorts, the LVEF increased significantly after the revascularization, between admission and discharge ($p < 0.001$ in both cohorts). However, the increase was significantly higher in the SGLT2-I users compared to non-SGLT2-I users ($p < 0.001$, Table 3 and Fig. 2). In addition, at discharge, RWMA were significantly reduced in the SGLT2-I users (81.1 % versus 62.2 %, $p = 0.003$), but not in the non-SGLT2-I cohort (83.6 % versus 79.8 %, $p = 0.133$). As a result, a lower rate of discharge moderate-to-severe mitral regurgitation was detected in SGLT2-I users than in the non-SGLT2-I cohort, compared to hospital admission (Table 3 and Fig. 2).

3.4. Impact of SGLT2-I on in-hospital endpoints

Overall, 19 patients died during hospitalization due to cardiovascular causes. The in-hospital mortality was significantly higher in non-SGLT2-I users (3.6 % vs 0 %, $p = 0.041$). SGLT2-I users patients exhibited a lower arrhythmic burden during hospitalization - ventricular arrhythmias and atrial fibrillation - compared to non-SGLT2-I patients ($p = 0.010$, Table 4). No significant differences were noticed for mechanical circulatory support with an intra-aortic balloon pump, re-AMI, and days of hospital stay between the 2 study groups (Table 4). Interestingly, SGLT2-I users experienced a lower occurrence of contrast-induced acute kidney injury ($p = 0.022$).

3.5. Impact of SGLT2-I on endpoints at the follow-up

The median follow-up duration after discharge was 24 ± 13 months. Over this period, 76 (12.2 %) deaths were recorded, 8.6 % related to cardiovascular causes. Thirty-nine (6.2 %) patients had re-AMI, 53 (8.5 %) any revascularization, 104 patients (16.6 %) were hospitalized for HF, while 160 (25.6 %) experienced the composite endpoint. Kaplan-Meier estimates along with 3 years are shown in Fig. 3. The composite endpoint (MACE) was higher for the non-SGLT2-I patients compared to SGLT2-I users ($p < 0.001$, Table 4 and Fig. 3), without any gender difference in both cohorts (11.1 % vs 19.4%, $p = 0.753$ % and 28.4% vs 23.8 % $p = 0.368$). Among SGLT2-I users, cardiovascular mortality and HF hospitalization occurred less frequently than in no-SGLT2-I patients ($p < 0.04$ for both, Table 4 and Fig. 3). During the follow-up, the 2 study groups exhibited a similar rate of re-AMI, any coronary revascularization, and implantable-cardioverter-defibrillator (ICD) implantation. In the multivariable Cox regression model, after adjusting for all confounding factors, the use of SGLT2-I was identified as an independent predictor of reduced MACE occurrence (HR=0.57; 95 %CI 0.33–0.99; $p = 0.039$), together with complete revascularization, lower discharge moderate-to-severe mitral regurgitation, and lower creatine values. Similarly, SGLT2-I therapy appeared to be an independent predictor of reduced HF hospitalization (HR=0.46; 95 %CI 0.21–0.98; $p = 0.041$), together with complete revascularization (Table 5).

4. Discussion

Our study is the first report investigating the in-hospital and long-term outcomes in a cohort of T2DM patients admitted with AMI, comparing chronic SGLT2-I therapy versus non-SGLT2-I users. The main findings include: i) a mitigated negative LV remodeling was detected in patients receiving SGLT2-I compared to non-SGLT2-I ones; ii) the use of SGLT2-I was associated with a lower in-hospital cardiovascular death,

Table 2
Admission, in-hospital and discharge medical therapy.

	Total (N = 646)	SGLT2-I users (N = 111)	Non-SGLT2-I users (N = 535)	P value
Admission medical therapy				
Antiplatelets, n (%)	321 (49.7)	60 (54.1)	261 (48.8)	0.312
Anticoagulation, n (%)	55 (8.5)	6 (5.4)	49 (9.2)	0.197
RAAS inhibitor, n (%)	378 (58.5)	69 (62.2)	309 (57.8)	0.391
Diuretics, n (%)	196 (30.3)	31 (27.9)	165 (30.8)	0.543
Β-blockers, n (%)	296 (45.8)	55 (49.5)	241 (45)	0.386
CCB, n (%)	197 (30.5)	35 (31.5)	162 (30.3)	0.794
Statins, n (%)	329 (50.9)	61 [55]	268 (50.1)	0.351
Low/moderate intensity	238 (72.3)	39 (63.9)	199 (74.3)	0.104
High intensity	91 (27.7)	22 (36.1)	69 (25.7)	
Ezetimibe, n (%)	78 (12.1)	15 (13.5)	63 (11.8)	0.609
Admission glucose-lowering agents				
Metformin, n (%)	467 (72.3)	80 (72.1)	387 (72.3)	0.955
Sulfonylureas, n (%)	166 (25.7)	13 (11.7)	153 (28.6)	0.001
DPP-4 Inhibitors, n (%)	54 (8.4)	8 (7.2)	46 (8.6)	0.630
GLP-1 Agonist, n (%)	19 (2.9)	5 (4.5)	14 (2.6)	0.284
In-hospital glucose-lowering strategy				
Insulin sc., n (%)	430 (66.6)	57 (51.4)	394 (73.6)	<0.001
Insulin iv., n (%)	65 (10.1)	17 (15.3)	144 (26.9)	0.010
Discharge medical therapy (*)				
Antiplatelets, n (%)	621 (99.4)	110 (99.1)	511 (99.4)	0.704
DAPT, n (%)	609 (97.4)	109 (98.4)	500 (97.3)	0.577
Anticoagulation, n (%)	81 (12.5)	10 (9)	71 (13.3)	0.217
SRAA, n (%)	416 (66.6)	89 (80.2)	409 (79.6)	0.885
Diuretics, n (%)	271 (43.4)	38 (34.2)	233 (45.3)	0.032
Β-blockers, n (%)	545 (87.2)	98 (88.3)	445 (86.6)	0.315
CCB, n (%)	147 (23.5)	34 (30.6)	113 (22)	0.053
Statins, n (%)	587 (93.9)	109 (98.2)	495 (96.3)	0.315
Ezetimibe, n (%)	118 (18.9)	44 (39.6)	210 (40.9)	0.812
Discharge glucose-lowering agents (*)				
Metformin, n (%)	404 (64.6)	83 (74.8)	321 (62.5)	0.014
Sulfonylureas, n (%)	137 (21.9)	9 (8.1)	128 (24.9)	<0.001
DPP-4 Inhibitors, n (%)	83 (13.3)	13 (11.7)	70 (13.6)	0.591
GLP-1 Agonist, n (%)	26 (4.2)	8 (7.2)	18 (3.5)	0.081
Insulin sc., n (%)	96 (15.4)	8 (7.2)	78 (15.2)	0.027

RAAS = Renin-angiotensin-aldosterone system; CCB = Calcium channel blockers; DPP-4 = Dipeptidyl peptidase-4; GLP-1 = Glucagon-like peptide-1; sc. = subcutaneous; iv. = intravenous; DAPT = Dual Antiplatelet Therapy.
* Percentages calculated on the number of patients discharged alive.

arrhythmic burden and occurrence of contrast-induced acute kidney injury; iii) in SGLT2-I users the composite endpoint (MACE), as well as, cardiovascular mortality and HF-hospitalization were significantly lower compared to no-SGLT2-I patients; iv) after adjusting for all confounding factors, the use of SGLT2-I was identified as an independent predictor of reduced MACE occurrence and HF-hospitalization.

In the last years, SGLT2-I gained an intense interest in searching for the mechanisms responsible for their beneficial effects in patients with and without DM [3,16,17]. More recently, SGLT2-I revealed cardioprotective effects in HF patients, independently of their diabetic status [2,5]. Since the expression of SGLT2 in human cardiomyocytes is still doubtful, it is intriguing how SGLT2-I might display beneficial off-target effects on the cardiovascular system [18]. SGLT2-I might reduce ischemia/reperfusion injury and affect cell ionic homeostasis, resulting in mitigation of the infarct size, LV remodeling, and arrhythmic burden. The attenuated myocardial necrosis and arrhythmic burden point out a novel mechanism underlying the significant reduction of cardiovascular mortality found in our study [4,19]. In addition, a reduction of myocardial necrosis might improve both the AMI-related in-hospital and long-term outcomes and reduce the progression to HF. SGLT2-I also directly affect the arrhythmic burden, particularly acting on sodium and calcium homeostasis. Taken together, these cardioprotective properties might favorably impact the in-hospital and long-term outcomes in AMI T2DM patients treated with SGLT2-I.

4.1. Impact of SGLT2-I on left ventricle remodeling

Infarct size and left ventricular remodeling following AMI increase the risk for HF and significantly decrease survival [20,21]. Earlier treatment strategies sought to reverse mechanical changes after AMI, reducing pre, after, and volume load. Current therapeutic strategies mostly improve cardiovascular mortality but occasionally fail to prevent the progression toward HF [22,23]. This aspect suggests that current therapeutic approaches miss further key pathophysiological mechanisms like inflammation, cardiac energy metabolism, and myocardial fibrosis, which also contribute to the extent of infarct size and adverse LV remodeling. Interestingly, many of the proposed actions of SGLT2-I coincide with known mechanisms recognized to mitigate infarct size extension and LV remodeling after AMI [3,24]. Clinical and in vitro data demonstrated that SGLT2-I exhibit favorable properties against inflammation, ischemia/reperfusion injury, and generation of reactive oxygen species, thereby improving cardiac energy metabolism and metabolic flexibility, myocardial hypertrophy and fibrosis, myocardial regeneration and proliferation, as well as neurohormonal activation and cardio-renal interplay [3,25,26]. The SGLT2-I-related lower inflammatory burden might be pivotal in explaining infarct size attenuation [10, 27]. Inflammation is an essential contributor of infarct size severity, and pro-inflammatory biomarkers correlate with the prognosis of AMI [28–30]. In our recent study, inflammatory indices on admission and after 24 h were significantly higher in non-SGLT2-I users, with a significant increase in neutrophil levels at 24 h observed in non-SGLT2-I patients but not in the SGLT2-I group [10]. The in vitro evidence that

Table 3
LV remodeling in SGLT2-I users versus non-SGLT2-users.

	Total (N = 646)	SGLT2-I users (N = 111)	Non-SGLT2-I users (N = 535)	P-value
Hospital Admission				
Q wave, n (%)	160 (24.8)	24 (21.6)	136 (25.4)	0.399
LV-EDV, ml	108 ± 33	107 ± 35	108 ± 33	0.627
LV-EF, %	47 ± 11	48 ± 10	47 ± 11	0.183
RWMA, n (%)	537 (83.1)	90 (81.1)	447 (83.6)	0.527
Mitral regurgitation, n (%)				0.014
Moderate	52 (8.7)	8 (7.2)	44 (9.1)	
Severe	11 (1.8)	0 (0)	11 (2.3)	
I hs-TnI, ng/L	233 [47–1450]	158 [35–730]	245 [53 – 1959]	0.003
II hs-TnI, ng/L	1397 [341–9224]	652 [170–1998]	1740 [373 – 9223]	<0.001
III hs-TnI, ng/L	1328 [420–9224]	485 [155–1308]	2316 [576 – 9223]	<0.001
hs-TnI peak, ng/L	2368 [625–9224]	903 [278–2438]	3155 [731 – 9223]	<0.001
Hospital Discharge				
ST resolution, n (%)	206 (66.7)	44 (84.6)	162 (63)	0.003
LV-EDV, ml	109 ± 36	103 ± 29	110 ± 38	0.267
LV-EF, %	49 ± 10	53 ± 9	48 ± 10	<0.001
RWMA, n (%)	496 (76.8)	69 (62.2)	427 (79.8)	0.001
Mitral regurgitation, n (%)				<0.001
Moderate	40 (6.4)	3 (2.7)	37 (7.2)	
Severe	12 (1.9)	0 (0)	2 (2.3)	

Continuous variables are presented as mean±SD or as median [IQR]; while categorical variables as number (%).
Abbreviations: LV-EDV=Left Ventricular End Diastolic Volume; LVEF=left ventricular ejection fraction; RWMA=regional wall motion abnormalities; Hs-TnI=high sensitivity Troponin I.

SGLT2-I might inhibit the nucleotide-binding domain-like receptor protein-3 (NLRP3) inflammasome, thus reducing the secretion of inflammatory markers, further strengthens our hypothesis [31]. Alternative explanations for the smaller infarct size in diabetic patients receiving SGLT2-I include improving cardiomyocyte energy metabolism and metabolic flexibility with a shift towards ketone bodies as the metabolic substrate for the cardiomyocytes, with a larger cardiac ATP production [3,32,33]. Finally, stress admission hyperglycemia was more frequently observed in non-SGLT2-I users than in those receiving SGLT2-I, confirming the effect of ameliorating glycemic parameters when used alone or in combination in T2DM patients [34].

In pre-clinical studies, SGLT2-I provided evidence for a reduction in acute myocardial I/R injury, infarct size, and arrhythmias, decreasing myofibroblast infiltration and myocardial fibrosis, both key pathophysiological mechanisms related to LV remodeling, with a parallel increase in the left ventricular function, independent of diabetic status [6,7,35–39]. On the clinical ground, in line with these studies, our results showed significantly lower troponin values, with a concomitant higher rate of post-PCI ST-resolution, a higher increase of LVEF with a lower rate of RWMA after the revascularization in patients treated with SGLT2-I. As a result, a lower rate of discharge moderate-to-severe mitral regurgitation was detected in SGLT2-I users than in the non-SGLT2-I cohort, compared to hospital admission. The latter finding becomes even more important considering that ischemic MR, as a consequence of LV remodeling, has been recognized as an important predictor of an adverse prognosis after AMI and is known to worsen patients' prognoses even if its degree is moderate [40]. Interestingly, lower troponin peak levels were documented as an independent predictor of improvement in ischemic MR after primary PCI in the chronic phase, further emphasizing the lower troponin values found in SGLT2-I users in our study [41]. Although troponin values, LVEF, and RWMAs do not represent the current gold standard for assessing infarct size, our results provide new insights into the possible cardioprotective properties of chronic SGLT2-I therapy in type 2 diabetic patients hospitalized for AMI, exhibiting a significantly mitigated LV adverse remodeling with reduced moderate-to-severe MR, compared to non-SGLT2-I users.

Remarkably, most of these effects discussed previously could be related to persistent molecular and metabolic changes since all patients

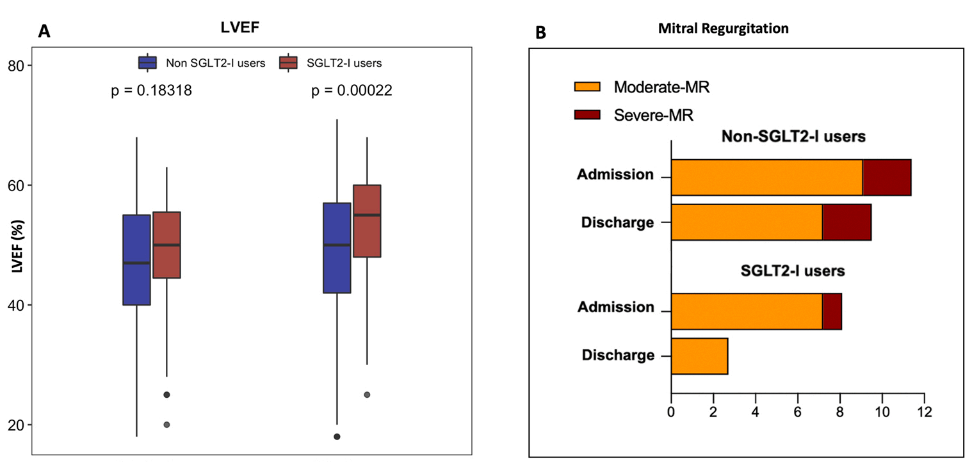

Fig. 2. Comparison of the LVEF values (*panel A*) and mitral regurgitation degree (*panel B*) in SGLT2-I users versus non-SGLT2-I users at hospital admission versus hospital discharge. Abbreviations: LVEF = left ventricular ejection fraction; MR = mitral regurgitation; SGLT2-I = Sodium-glucose co-transporter 2 inhibitors.

Table 4
Outcomes of SGLT2-I users versus non-SGLT2-users.

	Total (N = 646)	SGLT2-I users (N = 111)	Non-SGLT2-I users (N = 535)	P-value
In-hospital outcomes				
Cardiovascular-death, n (%)	19 (2.9)	0 (0)	19 (3.6)	0.041
Arrhythmia, n (%)	91 (14.1)	7 (6.3)	84 (15.7)	0.010
New-onset AF, n (%)	56 (8.7)	5 (4.5)	51 (9.5)	
VT/VF, n (%)	35 (5.4)	2 (1.8)	33 (6.2)	
Re-AMI, n (%)	7 (1.1)	1 (0.9)	6 (1.1)	0.838
Re-PCI, n (%)	13 (2.0)	4 (3.6)	9 (1.7)	0.190
IABP, n (%)	23 (3.6)	4 (3.6)	19 (3.6)	0.978
CI-AKI, n (%)	68 (10.5)	6 (5.4)	70 (13.1)	0.022
Hospital stay, days	5 [4–8]	5 [4–8]	5 [4–8]	0.526
Long-term outcomes (*)				
All-cause deaths, n (%)	76 (12.2)	7 (6.3)	69 (13.4)	0.037
Cardiovascular-death, n (%)	54 (8.6)	4 (3.6)	50 (9.7)	0.036
Re-AMI, n (%)	39 (6.2)	6 (5.4)	33 (6.4)	0.759
Re-PCI, n (%)	53 (8.5)	11 (9.9)	42 (8.2)	0.551
HF Hospitalization, n (%)	104 (16.6)	7 (6.3)	97 (18.9)	0.001
MACE, n (%)	160 (25.6)	14 (12.6)	146 (28.4)	<0.001
ICD, n (%)	44 (6.8)	7 (1.1)	37 (5.7)	0.817

Long term outcomes (*): total numbers of patients discharge alive (N = 625): SGLT2-I users (N = 111) and non-SGLT2-I users (N = 514). Abbreviations: AF=Atrial Fibrillation; VT=Ventricular Tachycardia; VF=Ventricular Fibrillation; AMI=Acute Myocardial Infarction, PCI=Primary Percutaneous Coronary Intervention; IABP=Intra-Aortic Balloon Pump; CI-AKI=Contrast-Induced Acute Kidney Injury; HF=Heart Failure; MACE=major adverse cardiovascular events; ICD=Implantable-Cardioverter-Defibrillator.

had been treated with SGLT2-I for at least 3 months before the AMI. Indeed, the recently published EMMY trial did not find any difference in acute troponin values between the SGLT2-I treated and untreated cohorts [9]. However, the EMMY trial included only a minority of diabetic patients, and all patients were randomized to the treatment at the time of the AMI admission, for only 3 days, rather than receiving SGLT2-I some months earlier as in our study.

4.2. Impact of SGLT2-I on the arrhythmic burden

Our study demonstrated that in diabetic AMI patients, SGLT2-I significantly reduced the AF and ventricular arrhythmias episodes that occur in the acute phase of AMI. The anti-arrhythmic effects of SGLT2-I remain to be better explored. It might be partly related to the reduction in inflammatory burden, admission stress hyperglycemia, and LV infarct size. Previous reports hypothesized that SGLT2-I might induce changes in calcium ion currents, reducing calcium-related arrhythmogenesis. [42–44]. Another beneficial effect of SGLT2-I is the protection against hyperglycemia-induced sympathetic overstimulation slowing the action potential duration [45]. Accordingly, our patients treated with SGLT2-I exhibited a lower heart rate and admission blood glucose level than patients treated with other OAD agents. Moreover, the lower number of hypoglycemic episodes associated with reduced insulin therapy (both s.c. and i.v.), resulting from minor stress admission hyperglycemia, further corroborates the reduced in-hospital occurrence of arrhythmias in SGLT2-I users [46].

4.3. Study limitations

Our results should be interpreted considering some limitations. First, the sample size was powered to evaluate only a "class effect" but not the "doses effect." However, a recent analysis of a nationwide real-world dataset suggested that the risk of cardiovascular events including HF, MI, stroke, and AF would be comparable between individual SGLT2 inhibitors, supporting our hypothesis of "class effects"[47]. Second, the observational study design represents a methodological limitation

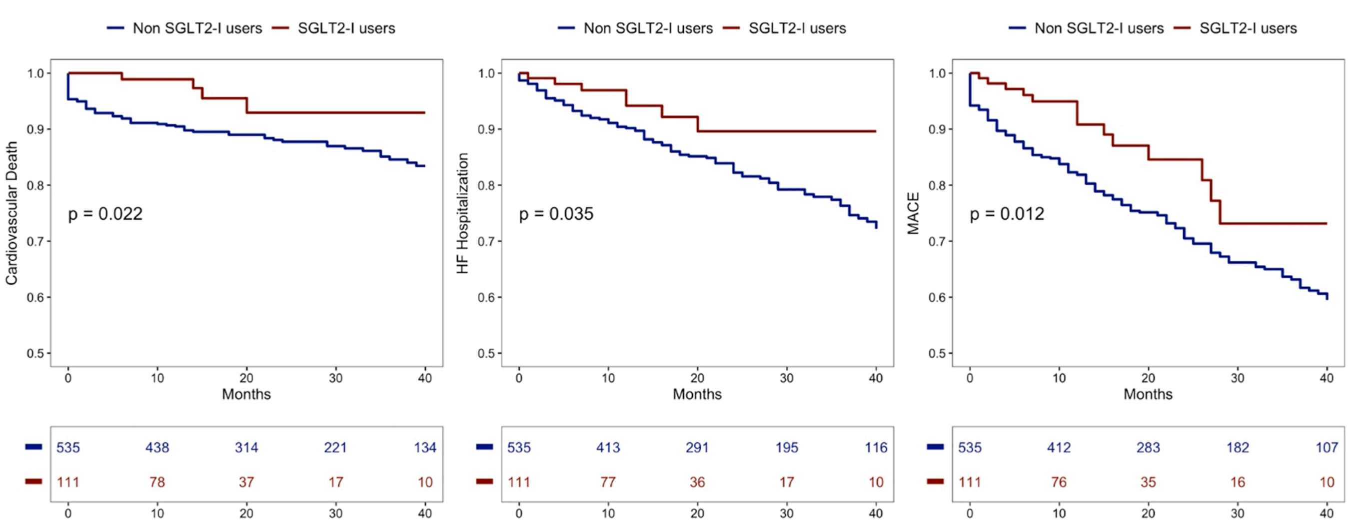

Fig. 3. Kaplan-Meier survival curves in SGLT2-I users (red curve) versus non-SGLT2-I users (blue curve). *Panel A*: cardiovascular mortality. *Panel B*: heart failure hospitalization. *Panel C*: MACE. Abbreviations: SGLT2-I = Sodium-glucose co-transporter 2 inhibitors; MACE = major adverse cardiovascular events.

Table 5
Univariate and multivariable analysis. Predictors of cardiovascular death, HF hospitalization, and MACE.

	Cardiovascular Death						HF Hospitalization						MACE					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
Variables	HR	95 %CI	p-value	HR	95 %CI	p-value	HR	95 %CI	p-value	HR	95 % CI	p-value	HR	95 %CI	p-value	HR	95 % CI	p-value
Age, years	1.03	1.01–1.05	0.004	1.02	0.99 – 1.05	0.085	1.01	0.98–1.02	0.863	–	–	–	1.02	0.99–1.03	0.053	–	–	–
Gender, male	1.42	0.86–2.34	0.167	–	–	–	0.80	0.49–1.29	0.357	–	–	–	1.13	0.81–1.59	0.467	–	–	–
Admission BGL	1.01	1.01–1.02	0.009	1.01	0.99 – 1.01	0.776	1.01	0.99–1.01	0.623	–	–	–	1.01	0.99–1.02	0.098	–	–	–
Admission CRP	1.01	0.99–1.01	0.292	–	–	–	0.99	0.97–1.02	0.606	–	–	–	1.01	0.99–1.02	0.094	–	–	–
Peak Hs-TnI, ng/L	1.01	1.01–1.03	<0.001	1.01	1.01 – 1.03	0.018	1.01	1.01–1.03	0.023	1.01	1.01–1.03	0.068	1.01	1.01–1.02	0.026	1.01	0.99–1.00	0.238
NSTEMI	0.63	0.40–1.02	0.054	–	–	–	0.86	0.59–1.26	0.441	–	–	–	0.90	0.67–1.21	0.482	–	–	–
Complex PCI	1.15	0.65–2.04	0.620	–	–	–	1.35	0.85–2.15	0.200	–	–	–	1.34	0.94–1.91	0.101	–	–	–
Complete Rev.	0.32	0.20–0.51	<0.001	0.51	0.30 – 0.89	0.017	0.39	0.26–0.58	<0.001	0.38	0.25 – 0.57	<0.001	0.30	0.22–0.40	<0.001	0.37	0.26–0.51	0.001
Discharge moderate-to-severe MR	2.07	1.55–2.77	<0.001	1.48	1.05 – 2.09	0.025	1.28	1.06–1.69	0.040	1.17	0.89 – 1.55	0.251	1.48	1.21–1.82	<0.001	1.29	1.04–1.59	0.018
Discharge crea.	1.24	1.14–1.35	<0.001	1.33	1.17 – 1.52	<0.001	1.11	0.99–1.26	0.061	–	–	–	1.22	1.14–1.30	<0.001	1.13	1.04–1.22	0.003
SGLT2-I	0.33	0.12–0.90	0.031	0.53	0.19 – 1.52	0.237	0.45	0.21–0.97	0.038	0.46	0.21 – 0.98	0.041	0.51	0.29–0.87	0.014	0.57	0.33–0.99	0.039

Abbreviations: BGL=blood glucose level; CRP=C-reactive Protein; Hs-TnI=high sensitivity Troponin I; NSTEMI=non-ST segment Elevation Myocardial Infarction; PCI=Primary Percutaneous Coronary Intervention; Complete Rev.=complete revascularization. MR=mitral regurgitation; HF=Heart Failure; MACE=major adverse cardiovascular events.

concerning the applicability of the study results that should be considered as hypothesis-generating. Third, our results could not be extended to patients revascularized with CABG strategy, on insulin therapy, with GFR < 30 ml/min and severe VHD.

5. Conclusions

In T2DM patients with AMI, the use of SGLT2 inhibitors was associated with a lower risk of adverse cardiovascular outcomes during index hospitalization and long-term follow-up. Our findings are hypothesis-generating and provide new insights into the cardioprotective role of SGLT2-I in the setting of CAD pointing out the potential clinical impact of these drugs in improving cardiovascular outcomes after AMI.

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Ethics approval and consent to participate

Data were collected as part of an approved international multicenter observational study. The present study was conducted according to the principles of the Declaration of Helsinki; all patients were informed about their participation in the registry and provided informed consent for the anonymous publication of scientific data.

Statement of guarantor

C.P. and E.B. are the guarantors of the research and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Author contributions

PP and LB contributed conception and design of the study; **PP, LB, AC, NM, FG, MA, AS, AS, GE** and **AI** organized the database and collected data; **LB** and **EG** performed the statistical analysis; **PP** and **LB** wrote the first draft of the manuscript; **FG** and **AC** wrote sections of the manuscript. **GS, CS, AF, GC, CM, RM, NM, JAO, DV, PC, EB** and **CP** revised the article and approved the final version of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

Competing interests

The authors declare that they have no competing interests.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2022.106597.

References

[1] J.A. Udell, W.S. Jones, M.C. Petrie, et al., Sodium glucose cotransporter-2 inhibition for acute myocardial infarction: JACC review topic of the week, J. Am. Coll. Cardiol. 79 (2022) 2058–2068.

[2] S.D. Anker, J. Butler, G. Filippatos, et al., Empagliflozin in heart failure with a preserved ejection fraction, N. Engl. J. Med. 385 (2021) 1451–1461.

[3] F. Varzideh, U. Kansakar, G. Santulli, SGLT2 inhibitors in cardiovascular medicine, Eur. Heart J. Cardiovasc. Pharmacother. 7 (2021) e67–e68.

[4] B. Zinman, C. Wanner, J.M. Lachin, et al., Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes, N. Engl. J. Med. 373 (2015) 2117–2128.

[5] J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, et al., Dapagliflozin in patients with heart failure and reduced ejection fraction, N. Engl. J. Med. 381 (2019) 1995–2008.

[6] I. Andreadou, R.M. Bell, H.E. Bøtker, C.J. Zuurbier, SGLT2 inhibitors reduce infarct size in reperfused ischemic heart and improve cardiac function during ischemic episodes in preclinical models, Biochim Biophys. Acta Mol. Basis Dis. 1866 (2020), 165770.

[7] S. Lahnwong, S. Palee, N. Apaijai, et al., Acute dapagliflozin administration exerts cardioprotective effects in rats with cardiac ischemia/reperfusion injury, Cardiovasc Diabetol. 19 (2020) 91.

[8] J. Harrington, J.A. Udell, W.S. Jones, et al., Empagliflozin in patients post myocardial infarction rationale and design of the EMPACT-MI trial, Am. Heart J. 253 (2022) 86–98.

[9] D. von Lewinski, E. Kolesnik, N.J. Tripolt, et al., Empagliflozin in acute Myocardial Infarction: the EMMY trial, Eur. Heart J. (2022).

[10] P. Paolisso, L. Bergamaschi, G. Santulli, et al., Infarct size, inflammatory burden, and admission hyperglycemia in diabetic patients with acute myocardial infarction treated with SGLT2-inhibitors: a multicenter international registry, Cardiovasc Diabetol. 21 (2022) 77.

[11] A. Cesaro, F. Gragnano, P. Paolisso, et al., In-hospital arrhythmic burden reduction in diabetic patients with acute myocardial infarction treated with SGLT2-inhibitors: insights from the SGLT2-I AMI PROTECT study, Front. Cardiovasc. Med. 9 (2022) 1012220.

[12] R. Marfella, N. D'Onofrio, M.C. Trotta, et al., Sodium/glucose cotransporter 2 (SGLT2) inhibitors improve cardiac function by reducing JunD expression in human diabetic hearts, Metabolism 127 (2022), 154936.

[13] J.P. Collet, H. Thiele, E. Barbato, et al., ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation, Eur. Heart J. 2021 (42) (2020) 1289–1367.

[14] B. Ibanez, S. James, S. Agewall, et al., ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC), Eur. Heart J. 2018 (39) (2017) 119–177.

[15] K.A. Hicks, K.W. Mahaffey, R. Mehran, et al., Cardiovascular and stroke endpoint definitions for clinical trials, Circulation 2018 (137) (2017) 961–972.

[16] A. Mascolo, C. Scavone, L. Scisciola, P. Chiodini, A. Capuano, G. Paolisso, SGLT-2 inhibitors reduce the risk of cerebrovascular/cardiovascular outcomes and mortality: a systematic review and meta-analysis of retrospective cohort studies, Pharmacol. Res. 172 (2021), 105836.

[17] S. Ciardullo, R. Trevisan, G. Perseghin, Sodium-glucose transporter 2 inhibitors for renal and cardiovascular protection in US adults with type 2 diabetes: impact of the 2020 KDIGO clinical practice guidelines, Pharmacol. Res. 166 (2021), 105530.

[18] R. Marfella, L. Scisciola, N. D'Onofrio, et al., Sodium-glucose cotransporter-2 (SGLT2) expression in diabetic and non-diabetic failing human cardiomyocytes, Pharmacol. Res. 184 (2022), 106448.

[19] B. Neal, V. Perkovic, K.W. Mahaffey, et al., Canagliflozin and cardiovascular and renal events in type 2 diabetes, N. Engl. J. Med. 377 (2017) 644–657.

[20] A. Torabi, J.G. Cleland, N.K. Khan, et al., The timing of development and subsequent clinical course of heart failure after a myocardial infarction, Eur. Heart J. 29 (2008) 859–870.

[21] G.W. Stone, H.P. Selker, H. Thiele, et al., Relationship between infarct size and outcomes following primary PCI: patient-level analysis from 10 randomized trials, J. Am. Coll. Cardiol. 67 (2016) 1674–1683.

[22] G.M. Fröhlich, P. Meier, S.K. White, D.M. Yellon, D.J. Hausenloy, Myocardial reperfusion injury: looking beyond primary PCI, Eur. Heart J. 34 (2013) 1714–1722.

[23] A. Jelani, B.I. Jugdutt, STEMI and heart failure in the elderly: role of adverse remodeling, Heart Fail. Rev. 15 (2010) 513–521.

[24] P. Theofilis, A.S. Antonopoulos, T. Katsimichas, et al., The impact of SGLT2 inhibition on imaging markers of cardiac function: a systematic review and meta-analysis, Pharmacol. Res. 180 (2022), 106243.

[25] S. Frantz, M.J. Hundertmark, J. Schulz-Menger, F.M. Bengel, J. Bauersachs, Left ventricular remodelling post-myocardial infarction: pathophysiology, imaging, and novel therapies, Eur. Heart J. (2022).

[26] Mone P., Varzideh F., Jankauskas S.S. et al., SGLT2 inhibition via empagliflozin Improves endothelial function and reduces mitochondrial oxidative stress: insights from frail hypertensive and diabetic patients, Hypertension 2022.

[27] C.N. Koyani, I. Plastira, H. Sourij, et al., Empagliflozin protects heart from inflammation and energy depletion via AMPK activation, Pharmacol. Res. 158 (2020), 104870.

[28] P. Paolisso, A. Foà, L. Bergamaschi, et al., Impact of admission hyperglycemia on short and long-term prognosis in acute myocardial infarction: MINOCA versus MIOCA, Cardiovasc Diabetol. 20 (2021) 192.

[29] P. Paolisso, A. Foà, L. Bergamaschi, et al., Hyperglycemia, inflammatory response and infarct size in obstructive acute myocardial infarction and MINOCA, Cardiovasc. Diabetol. 20 (2021) 33.

[30] Y. Zhong, X. Yu, X. Li, H. Zhou, Y. Wang, Augmented early aged neutrophil infiltration contributes to late remodeling post myocardial infarction, Microvasc. Res. 139 (2022), 104268.

[31] S.R. Kim, S.G. Lee, S.H. Kim, et al., SGLT2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease, Nat. Commun. 11 (2020) 2127.

[32] E. Ferrannini, S. Baldi, S. Frascerra, et al., Shift to fatty substrate utilization in response to sodium-glucose cotransporter 2 inhibition in subjects without diabetes and patients with type 2, Diabetes Diabetes 65 (2016) 1190–1195.

[33] T.A. Zelniker, E. Braunwald, Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors: JACC state-of-the-art review, J. Am. Coll. Cardiol. 75 (2020) 422–434.

[34] J.B. Buse, D.J. Wexler, A. Tsapas, et al., Update to: management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), Diabetologia 2020 (63) (2019) 221–228.

[35] P. Tanajak, P. Sa-Nguanmoo, S. Sivasinprasasn, et al., Cardioprotection of dapagliflozin and vildagliptin in rats with cardiac ischemia-reperfusion injury, J. Endocrinol. 236 (2018) 69–84.

[36] A.A. Sayour, C. Celeng, A. Oláh, M. Ruppert, B. Merkely, T. Radovits, Sodium-glucose cotransporter 2 inhibitors reduce myocardial infarct size in preclinical animal models of myocardial ischaemia-reperfusion injury: a meta-analysis, Diabetologia 64 (2021) 737–748.

[37] T.M. Lee, N.C. Chang, S.Z. Lin, Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts, Free Radic. Biol. Med. 104 (2017) 298–310.

[38] V.G. Lim, R.M. Bell, S. Arjun, M. Kolatsi-Joannou, D.A. Long, D.M. Yellon, SGLT2 inhibitor, canagliflozin, attenuates myocardial infarction in the diabetic and nondiabetic heart, JACC Basic Transl. Sci. 4 (2019) 15–26.

[39] C.G. Santos-Gallego, J.A. Requena-Ibanez, R. San Antonio, et al., Empagliflozin ameliorates adverse left ventricular remodeling in nondiabetic heart failure by enhancing myocardial energetics, J. Am. Coll. Cardiol. 73 (2019) 1931–1944.

[40] F. Grigioni, M. Enriquez-Sarano, K.J. Zehr, K.R. Bailey, A.J. Tajik, Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment, Circulation 103 (2001) 1759–1764.

[41] S. Nishino, N. Watanabe, T. Kimura, et al., The course of ischemic mitral regurgitation in acute myocardial infarction after primary percutaneous coronary intervention: from emergency room to long-term follow-up, Circ. Cardiovasc Imaging 9 (2016), e004841.

[42] A.A. Manolis, T.A. Manolis, H. Melita, A.S. Manolis, Sodium-glucose cotransporter type 2 inhibitors and cardiac arrhythmias, Trends Cardiovasc. Med. (2022).

[43] T. Attachaipanich, S.C. Chattipakorn, N. Chattipakorn, Potential roles of sodium-glucose co-transporter 2 inhibitors in attenuating cardiac arrhythmias in diabetes and heart failure, J. Cell Physiol. 237 (2022) 2404–2419.

[44] K. Philippaert, S. Kalyaanamoorthy, M. Fatehi, et al., Cardiac late sodium channel current is a molecular target for the sodium/glucose cotransporter 2 inhibitor empagliflozin, Circulation 143 (2021) 2188–2204.

[45] W. Shimizu, Y. Kubota, Y. Hoshika, et al., Effects of empagliflozin versus placebo on cardiac sympathetic activity in acute myocardial infarction patients with type 2 diabetes mellitus: the EMBODY trial, Cardiovasc. Diabetol. 19 (2020) 148.

[46] A. Andersen, P.G. Jørgensen, F.K. Knop, T. Vilsbøll, Hypoglycaemia and cardiac arrhythmias in diabetes, Ther. Adv. Endocrinol. Metab. 11 (2020), 2042018820911803.

[47] Y. Suzuki, H. Kaneko, A. Okada, et al., Comparison of cardiovascular outcomes between SGLT2 inhibitors in diabetes mellitus, Cardiovasc. Diabetol. 21 (2022) 67.