Reviews in Cardiovascular Medicine

Rev. Cardiovasc. Med. **2023**; 24(2): 32
https://doi.org/10.31083/j.rcm2402032

Review

SGLT2 Inhibition in Acute Myocardial Infarction—A Comprehensive Review

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Academic Editors: Robert J. Chilton and Badr Harfouch
Submitted: 1 September 2022 Revised: 11 November 2022 Accepted: 21 November 2022 Published: 31 January 2023

Abstract

In heart failure as well as in chronic kidney disease sodium-glucose cotransporter 2 (SGLT2) inhibitors have changed the landscape of medical therapy. Originally developed for use in diabetes, an unforeseen cardiovascular benefit extended SGLT2 inhibitor use from antihyperglycemic agents to cardiovascular and renal risk modifying agents. As their benefit in cardiovascular disease is independent from the diabetic state as well as the left ventricular ejection fraction it is the only class of therapy recommended throughout the spectrum of heart failure. Until very recently, the remaining gap in evidence has been data on the safety and efficacy of SGLT2 inhibitors in patients with acute myocardial infarction (MI) as former trials of SGLT2 inhibitors to date have excluded patients with recent ischemic events. As the first out of three trials conducted in post MI SGLT2 inhibitors therapy the EMMY trial was published. EMMY randomized 476 patients shortly after percutaneous intervention for recent large MI to either 10 mg of empagliflozin daily or placebo. The primary endpoint of changes in N-terminal pro brain natriuretic peptide (NT-proBNP) over 26 weeks as well as the functional and structural secondary endpoints were met. This provides first evidence of SGLT2 inhibitors-mediated beneficial results in this group of patients. We here discuss these results in the light of the two upcoming outcome trials (DAPA-MI and EMPACT-MI) with regard to the future role of this class of drugs early after MI.

Keywords: SGLT2; myocardial infarction; metabolism; inflammation

1. Development of Post-MI Therapy

The pathophysiology of myocardial infarction is a complex mechanism. It includes acute myocardial ischemia driven by energy depletion followed by early reperfusion injury developing during the first minutes/hours of reperfusion, and the subsequent remodeling phase during the first days/weeks after myocardial infarction (MI) resulting in an irreversible necrotic damage of the concerning area. Also, the neurohumoral system is involved with initiation of the renin-angiotensin-aldosterone system and upregulation of the sympathetic nervous system. These mechanisms lead to structural deterioration in the myocardium, called remodelling, affecting functional processes in ischemic and non-ischemic areas. However, effective clinical therapy against reperfusion injury is still missing, despite numerous therapies being effective in preclinical models [1–3]. In this review we report on the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors's to combat the remodeling phase of myocardial infarction.

In the past, therapeutic options have been established for the acute treatment of post-myocardial infarction aiming to reduce myocardial damage in the acute setting as well as to reduce further functional and structural changes. Early initiation of these substances after myocardial infarction has shown beneficial effects on mortality and major adverse cardiovascular events (MACE). First, the SAVE-trial with captopril showed a relative risk reduction of 19% for mortality in patients after myocardial infarction and left ventricular dysfunction compared to placebo. In addition, the trial showed a decrease in the incidence of both fatal and nonfatal major cardiovascular events with a relative risk reduction of 21% for death from cardiovascular causes, 37% for the development of severe heart failure and 25% for recurrent myocardial infarction [4]. Similarly, trandolapril (TRACE-trial) and ramipril (AIRE-trial) improved outcome if initiated early after acute myocardial infarction [5,6]. A comprehensive meta-analysis of large, randomized placebo-controlled trials including ~100,000 patients highlighted beneficial effects of angiotensin converting enzyme (ACE)-inhibitors on long-term survival with 85% of the effect within the first seven days after myocardial infarction [7]. In line, two large clinical trials were showing similar results for the angiotensin-receptor blocker valsartan in the VALIANT trail [8] and losartan in the OPTIMAAL trial [9]. Comparable beneficial results were also reported for betablockers. Metoprolol reduced the all-cause mortality, cardiovascular mortality, ventricular fibrillation, and non-fatal myocardial infarction in patient post myocardial infarction and left ventricular systolic dysfunction compared to placebo [10,11]. However, it has to be acknowledged

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that this therapy can also increase the risk of developing cardiogenic shock because of its negative chronotropic and inotropic effects [11] and therefore should be avoided in hypotonic or bradycardic patients.

Overall, ACE-inhibitors/angiotensin-receptor blocker as well as betablockers should be early initiated in the acute setting of acute myocardial infarction [12–14].

The additional treatment with the mineralocorticoid receptor antagonist eplerenone resulted in reductions in mortality and the rate of death from cardiovascular causes or hospitalization for cardiovascular events in the acute setting of myocardial infarction complicated by left ventricular dysfunction and heart failure in the EPHESUS-trial. In addition, there was also a reduction in cardiovascular mortality and the rate of death from any cause or any hospitalization in the eplerenone group compared to placebo [15]. For spironolactone similar results were observed for the STEMI-subgroup, but no beneficial effects were noted for the early initiation in the NSTEMI-subgroup compared to placebo in the ALBATROSS-trial [16].

In contrast, the angiotensin-neprilysin inhibitor sacubitril/valsartan has been reported to show a significant reduction of cardiovascular death and hospitalization for heart failure in heart failure with reduced ejection fraction (HFrEF) compared to enalapril in the PARADIGM-trial [17] and led to a greater reduction in the N-terminal pro brain natriuretic peptide (NT-proBNP) concentration than enalapril in acute decompensated heart failure in the PIONEER-trial [18]. However, patients with acute myocardial infarction and reduced left ventricular ejection fraction in the PARADISE-MI trial did not show significantly lower incidence of death from cardiovascular causes or incident heart failure compared to ramipril [19]. Interestingly, the very large subgroup of patients treated with percutaeous coronary intervention (PCI) as recommended in the guidelines and accounting for 88% of the total trial population did have a significantly better outcome.

With respect to SGLT2 inhibition there is no clinical data available on outcome after acute myocardial infarction yet. The small EMBODY trial reported effects of empagliflozin initiated shortly after the acute phase focusing on sympathomimetic activity [20].

Two ongoing outcome trials are testing the effects of dapagliflozin vs. placebo (DAPA-MI) on the composite endpoint cardiovascular death and hospitalization for heart failure and of empagliflozin vs. placebo (EMPACT-MI) on the composite endpoint time to first heart failure hospitalisation or all-cause mortality. Longitudinal data on functional and structural parameters after SGLT2 inhibitor use is scarce and no data available in post MI patients. The recently published EMMY-trial [21] now filled that gap being the first trial showing a significant reduction in the primary endpoint NT-proBNP as well as functional and structural echo parameters using the SGLT2-inhibitor empagliflozin compared to placebo and thus represents a new treatment option in patients with acute myocardial infarction.

2. The Role of SGLT2 Inhibitors in Myocardial Infarction

The SGLT2-receptor is mainly expressed in the proximal tube of human nephrons and intestinal cells and thus play an important role in renal glucose excretion and lowering blood glucose levels [22] but could not be detected in human myocardium so far [23]. Thus, there is no receptor-mediated effect of SGLT2-inhibitors on the human myocardium, but various indirect pathways seem to play an important role in the anti-remodeling effects [24]. A key role of the SGLT2 pathway is an increased myocardial uptake of ketone bodies resulting in an improved myocardial energy supply and thus impacts the energetic state of the myocardial cells leading to a decrease in cardiac necrosis and cardiac dysfunction [24]. Moreover, various experimental studies showed potential beneficial myocardial effects of SGLT2-inhibition through upregulation of cardioprotective proteins. Asensio *et al.* [25] published an increased uptake of the GTP enzyme cyclohydrolase-1 for empagliflozin independent of diabetic status affecting the cGCH1-BH4/NO-pathway and resulting in a reduction of cardiac dysfunction by its anti-remodeling effect. Next, SGLT2-inhibitors demonstrates positive cardiac effects in decreasing cytoplasmatic sodium through inhibition of the Na+/H+ exchanger sodium-hydrogen antiporter 1 (NHE1) with alternations in cellular calcium hemostasis by intracellular calcium overload in rats and rabbits [26] as well as in mice [27], although the effects on the NHE1 were independent of the SGLT-receptor [26,27]. SGLT2-inhibitors ameliorates left ventricular remodeling in heart failure by the adenosine monophosphate-activated protein kinase (AMPK)-pathway with reduction in myocardial necrosis and cardiac inflammatory processes [28] through enhancing myocardial energetics [29] and attenuating ischemia and reperfusion injury [30]. A further mechanism of SGLT2-inhibition is the reduction of oxidate stress levels mediating anti-inflammatory effects by the BCL2- as well as Signal transducer and activator of transcription 3/janus kinase 2 (STAT3/JAK2)-pathway and thus, decreasing myocardial necrosis and cardiac dysfunction [31–33]. All these preclinical molecular effects ameliorates inflammatory response and necrosis of cardiomyocytes resulting in smaller infarct size, less reperfusion injury and anti-remodeling effects.

First trial to show the effects of SGLT2-inhibitors in acute myocardial infarction was by Paolisso *et al.* [34] reporting a significant decrease in initial inflammatory parameters (white-blood-cell count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), neutrophil-to-platelet ratio (NPR), and C-reactive protein) as well as infarct size (echocardiographic parameters and peak troponin levels) in diabetic patients already treated with an SGLT2-inhibitor before myocardial infarc-

tion compared to other oral anti-diabetic agents independently of glucose-metabolic control. Based on this trial, it can be speculated that potential anti-inflammatory effects of SGLT2-inhibitors after acute myocardial infarction mediate beneficial cardiovascular outcome such as reducing infarct size and anti-remodeling effects. In addition, a diuretic effect with impact on hemodynamics via lowering the blood pressure as well as an increase in hematocrit have been described in the EMPA-REG OUTCOME trial [35–37]. The antiarrhythmic properties of SGLT2-inhibitors in patients with structural and functional cardiac diseases is still unclear. First trial to show strong evidence with beneficial effects was the DAPA-HF demonstrating in a post-hoc analysis a significant lower number of serious ventricular arrythmias, resuscitated cardiac arrest and sudden death in patients with HFrEF with a relative risk reduction of 21% in dapagliflozin compared to placebo [38]. Regarding atrial fibrillation a post hoc analysis of the DELACRE-TIMI 58 trial attenuates the incidence of atrial fibrillation with a relative risk reduction of 19% in dapagliflozin compared to placebo in patients with type 2 diabetes mellitus (T2DM) [39]. Further, two recent metanalysis including large clinical trials show a significant reduction in the incidence of atrial fibrillation in patients treated with an SGLT2-inhibitors [40,41]. Based on these finding, further trials need to be initiated to observe potential effects of SGLT2-inhibitors on arrhythmic events. A recent ongoing study, the ERASe-trial, is a placebo-controlled randomized investigator initiated phase 3b trial in Austria proving potential beneficial effect of the SGLT2-inhibitor ertugliflozin on ventricular arrhythmias in patients with internal cardioverter defibrillator (ICD) $\pm$ cardiac resynchronisation therapy (CRT) [42]. Indirect data on SGLT2 inhibitors with respect to acute myocardial infarction was derived from a meta-analysis of the EMPA-REG OUTCOME-, CANVAS and DECLARE TIMI-58 trials depicting a reduction of 11% in major adverse cardiovascular events defined as MI, stroke, and cardiovascular death (hazard ratio (HR) 0.89 [95% cofidence interval (CI) 0.83 to 0.96], p = 0.0014). Benefits observed in patients with manifest coronary artery disease tended to be even larger with a reduction of 15% (HR 0.86 [0.80–0.93] p for interaction = 0.0501) for SGLT2-inhibitors vs. placebo [43]. A recent meta-analysis of 238 clinical randomized trials showed a reduction of cardiovascular mortality in patients with SGLT-2 inhibitors compared to placebo with an odds ratio of 0.84 (95% CI 0.76 to 0.92) and a reduction in non-fatal myocardial infarction with an odds ratio 0.87 (95% CI 0.79 to 0.97) [44].

3. EMMY as the First SGLT2-Inhibitor Trial in Post MI Treatment

SGLT2-inihibtors have shown various beneficial effects in patients with chronic heart failure, diabetes as well as chronic kidney disease, but data in the setting of an acute myocardial infarction is scarce.

The EMMY-trial is the first multicenter, randomized, double-blind, placebo-controlled trial assessing the impact of empagliflozin on biomarkers of heart failure as well as cardiac function and structure in patients with acute myocardial infarction. It is the first clinical trial to show beneficial effects of SGLT2-inhibitors in patients with an acute myocardial infarction compared to placebo [45] and was recently published in the European Heart Journal [21].

From 11th May 2017 until 3rd May 2022, eleven Austrian centers enrolled 476 patients with large acute myocardial infarction (defined as creatinin kinase (CK) $>$800 and troponin $>10\times$ upper limit of normal (ULN)) receiving 10 mg empagliflozin once daily vs. placebo in addition to guideline directed medical therapy within 72 hours after percutaneous coronary intervention.

Participants had a median age (IQR) of 57 (52–64) years, an average BMI of 27.6 (25.1–30.3) kg/m^2 with 18% of patients were female and 13% of study participants had established type 2 diabetes. Median baseline CK (IQR) for measuring infarct size was 1673 U/l (1202–2456), the median (IQR) NT-proBNP at baseline was 1294 pg/mL (757–2246) and the median systolic pressure was 125 mmHg (117–131). More than 96% of the patients received state-of-the-art post-MI medical therapy consisting of ACEI/Angiotensin receptor blocker (ARB)/angiotensin receptor-neprilysin inhibitor (ARNI), betablocker, and Statin. 40% of all patients received an mineral corticoid antagonist (MRA).

The primary outcome, being the change in NT-proBNP levels, was 15% (95% CI –4.4 to –23.6%) lower with empagliflozin at week 26 compared to placebo (p = 0.026). This larger decline could already be observed after 12 weeks (–13.3%, 95% CI –3.0 to –22.5%) of treatment (p = 0.021).

Secondary outcomes included changes in echocardiographic parameters, HbA1c, body weight, and ketone bodies. The circulating ketone bodies concentrations (β-hydroxybutyric acid) was 0.123 $\pm$ 0.021 and 0.0917 $\pm$ 0.01 mmol/L in the empagliflozin group and the placebo group at baseline, respectively. It showed a significant increase in the empagliflozin group (Δ = 41.9%; 95% CI 21.8 to 63.8%, $p < 0.0001$) compared to the place group (Δ = 23.4%; 95% CI 5.9–42.4%, p = 0.0066).

The trial showed a significantly larger increase of left ventricular function (by absolute 1.5%; 95% CI 0.15 to 2.88%; p = 0.029) in the empagliflozin as compared to the placebo group and a significantly better development of diastolic function in the empagliflozin group with an E/e' at week 26 being 6.8% (95% CI 1.3% to 11.3%; p = 0.015) lower than placebo. Structural parameters were also significantly improved with left ventricular endsystolic and end-diastolic volumes being significantly lower in the empagliflozin group (see Table 1).

Table 1. Primary and secondary echocardiography outcome parameters.

	Empagliflozin				Placebo				
	Baseline	Week 26	Absolute change	Percent change	Baseline	Week 26	Absolute change	Percent change	Difference at week 26
LV-EF (%)	48 (43–53)	53 (47–58)	4.7 (3.6; 5.8)	11.1 (8.6; 13.6)	49 (43–54)	52 (47–57)	2.8 (1.8; 3.9)	7.6 (5.2; 9.9)	1.5% (95% CI 0.2% to 2.9%; $p = 0.029$)
E/e'	8 (7–11)	8 (7–9)	–1.3 (–1.6; –0.9)	–9.7 (–13.1; –6.4)	9 (8–11)	8 (7–10)	–0.7 (–1.1; –0.4)	–3.5 (–7.4; 0.4)	–6.8% (95% CI –11.3% to –1.3%; $p = 0.015$)
LVESV (mL)	61 (48–76)	60 (46–73)	–3.6 (–6.3; –1.0)	–2.2 (–6.4; 2.0)	60 (46–73)	59 (46–81)	4.30 (1.2; 7.4)	12.1 (6.4; 17.7)	–7.5 mL (95% CI –11.5 to –3.4; $p = 0.0003$)
LVEDV (mL)	119 (93–139)	122 (101–145)	3.4 (–0.7; 7.4)	5.9 (1.8; 10.1)	114 (92–134)	120 (100–154)	13.5 (8.7; 18.3)	14.8 (10.2; 19.4)	–9.7 mL (95% CI –15.7 to –3.7; $p = 0.001$)

LV-EF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVEDV, left ventricular end diastolic volume; CI, Confidence interval.

Table 2. Current trials with SGLT2 inhibitor treatment post myocardial infarction.

	EMMY (Phase III)	EMPACT-MI (Phase III)	DAPA-MI (Phase III)
Drug	Empagliflozin vs. placebo	Empagliflozin vs. placebo	Dapagliflozin vs. placebo
Trial design	RCT	RCT	Registry-based RCT
Number of patients	476 patients	6500 patients	6400 patients
Primary endpoint	Change of NT-proBNP	Composite of time to first HHF or all-cause mortality	Composite of time to first occurrence of HHF or CV death
Randomization	Within 3 days after MI	Within 14 days after MI	Within 10 days after MI
Age	18–80 years of age	$\geq$18 years of age	$\geq$18 years of age
Kidney function	eGFR $>$45 mL/min/1.73 m^2	eGFR $>$20 mL/min/1.73 m^2	eGFR $>$20 mL/min/1.73 m^2
Follow-up period	26 weeks	26 months	Up to approximately 3 years
Centres	11 centres	465 centres	113 centres
Start date	May 11, 2017	December 16, 2020	December 22, 2020
Status	Completed	Ongoing	Ongoing
Inclusion criteria	- Large MI (STEMI & NSTEMI) with CK $>$800 U/L - BP $>$110/70 mmHg	- MI (STEMI & NSTEMI) - High risk of HF, defined as EITHER - Symptoms or signs of congestion that require treatment OR - Newly developed LVEF $<$45% AND - At least one further CV risk factor	- MI (STEMI & NSTEMI) - Either impaired LV systolic function or evidence of Q wave MI - Hemodynamically stable
Exclusion criteria	- Any other form of diabetes mellitus than type 2 diabetes mellitus, history of diabetic ketoacidosis	- Type I diabetes mellitus	- Known T1DM or T2DM history of ketoacidosis
	- Blood pH $<$7.32	- Diagnosis of chronic HF	- Chronic symptomatic HF with a prior HHF within the last year and known reduced ejection fraction (LVEF $\leq$40%)
	- Known allergy to SGLT-2 inhibitors	- Systolic blood pressure $<$90 mmHg	- Severe hepatic impairment (Child-Pugh class C)
	- Hemodynamic instability	- Cardiogenic shock or use of i.v. inotropes in last 24 hours before randomisation	- Active malignancy requiring treatment
	- $>$1 episode of severe hypoglycemia within the last 6 months	- Coronary Artery Bypass Grafting planned	
	- Females of childbearing potential	- Current diagnosis of Takotsubo cardiomyopathy	
	- Acute symptomatic UTI or genital infection	- Any current severe valvular heart disease	

Abbreviations: RCT, randomized controlled trial; NT-proBNP, N-terminal pro brain natriuretic peptide; HHF, hospitalisation for heart failure; CV, cardio-vascular; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; STEMI, ST elevation myocardial infraction; NSTEMI, non-ST elevation myocardial infraction; CK, creatinin kinase; BP, blood pressure; LV, left ventricular; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; LVEF, left ventricular ejection fraction; HF, heart failure; UTI, urinary tract infection; EMMY, Empagliflozin in acute myocardial infarction; EMPACT-MI, A Streamlined, Multicentre, Randomised, Parallel Group, Double-blind Placebo-controlled Superiority Trial to Evaluate the Effect of EMPAgliflozin on Hospitalisation for Heart Failure and Mortality in Patients With aCuTe Myocardial Infarction; DAPA-MI, Dapagliflozin Effects on Cardiovascular Events in Patients With an Acute Heart Attack; SGLT-2, sodium glucose co-transporter type 2.

Moreover, with empagliflozin we observed the body weight to be significantly more decreased than in the placebo group and ketone bodies were significantly increased after 26 weeks of treatment. Of note, no difference in HbA1c levels was observed as only a minority (13%) of patients suffered from type 2 diabetes.

According to the adverse events, no amputation, no ketoacidotic events, and no severe hypoglycemia were reported. Only seven patients were hospitalized for heart failure (3 in the placebo group and 4 in the empagliflozin group). Three patients died (all in the empagliflozin group), one due to lung cancer and two of cardiogenic shock due to large myocardial infarction size.

Based on these results, the EMMY trial is the first clinical trial to show beneficial effects of SGLT2-inhibitors on biomarkers and cardiac function and structure in patients with acute myocardial infarction and enables to speculate on beneficial outcomes of the upcoming large outcome trials DAPA-MI and EMPACT-MI.

4. Upcoming Outcome Trials in Post MI Patients

DAPA-MI and EMPACT-MI are investigating the effect of dapagliflozin and empagliflozin, respectively on the incidence of heart failure or cardiovascular (or all-cause in EMPACT-MI) death in patients with acute myocardial infarction, respectively. DAPA-MI is a registry-based RCT whereas EMPACT-MI is a traditional RCT.

Table 2 summarizes sample sizes, inclusion and exclusion criteria as well as outcome measures for these trials in comparison to the EMMY trial. As shown, EMMY focused on heart failure biomarker as well as functional and structural changes in the heart, whereas DAPA-MI and EMPACT-MI use typical heart failure endpoints. Moreover, EMMY on the one side recruited MI patients independent of heart failure signs, symptoms or enrichment factors whereas DAPA-MI and EMPACT-MI require additional heart failure associated factors. Lastly, due to their more than 10-fold larger size DAPA-MI and EMPACT-MI are powered for hard clinical endpoints whereas EMMY was originally designed for changes in NT-proBNP and echocardiography parameters only.

5. New Directions of Medical Therapy after MI

Heart failure is a major complication following severe acute myocardial infarction and develops in about 17% of all patients with acute myocardial infarction (AMI) [46]. Many pharmacological options have shown to have significant beneficial effects in reducing long-term cardiovascular outcome (ACEi, ARBs, ARNI, MRA, Betablocker (BB)). Since publishing the results of the EMPA-REG OUTCOME trial, beneficial effects of SGLT2-inhibitors on hospitalization for heart failure and potentially mortality became obvious in diabetic patients. Almost identical beneficial effects were reported later for patients with heart failure with reduced, mildly reduced and preserved ejection fraction for empagliflozin (EMPEROR-reduced, EMPEROR preserved) as well as dapagliflozin (DAPA-HF, DELIVER) independent of the glycemic state. This led to the implementation in recent guidelines for the treatment of chronic heart failure [14,47]. However, beneficial effects of SGLT2 inhibition after myocardial infarction might reach beyond improving heart failure.

The EMMY trial was positive with respect to its primary endpoint (change in NTproBNP) although this effect was only moderate. NT-proBNP has been shown to be an established parameter for neurohumoral activation and a powerful predictor for cardiovascular prognosis in patients with AMI within 180 days [48–50]. A significant decline in NT-proBNP levels in patients suffering from large AMI was associated with subsequent cardiovascular outcome [49,50]. However, changes in NT-proBNP were only mildly or even non-significantly affected in recent SGLT2 inhibitor trials in heart failure patients [51–53]. In the randomized, double-blind, placebo-controlled multicentre EMPA-RESPONSE-AHF trial the SGLT2-inhibitor empagliflozin had no beneficial effect on dyspnoe score, weight, NTproBNP levels within the observation period of up to day 4 after the index event as well as length of hospital stay but showed a reduced combined endpoint of worsening HF, rehospitalization for HF or death at 60 days and a significant increase in urinary output compared to placebo [54]. Moreover, absolute NT-proBNP concentrations did not significantly differ in EMPEROR-Preserved when analyzed after 52 weeks [55], but a recent analysis depicted significantly lower NT-proBNP concentrations in the empagliflozin group after 52 weeks when adjusted geometric mean NT-proBNP values were used for statistical analysis [56]. Interestingly, this modest NT-proBNP difference was associated with a highly significant improvement in clinical outcome. Similarly, a retrospective analysis of the CANVAS trial attributed only ~10% of the reduction in hospitalization due to heart failure in this trial to the NT-proBNP lowering seen with canagliflozin [51]. This view is supported by recent meta-analyses showing highly significant reductions in hospitalization for heart failure for HFrEF [57] and for HFpEF [58–60] despite only moderate and/or non-significant larger NT-proBNP reductions with SGLT2 inhibitor treatment.

The trial demonstrated a significant increase in ketone bodies after 26 weeks in empagliflozin compared to placebo. Given the fact that circulating ketone bodies are increased after acute myocardial infarction, higher ketone bodies are associated with functional outcome after STEMIs [61]. Upregulation of ketone bodies mediates a higher utilization resulting in increased energy supply with reduction of myocardial necrosis and cardiac dysfunction due to its anti-remodeling effects and, thus suggest a potential role for ketone metabolism in response to myocardial

ischemia [24]. However, increased blood ketones are not always observed with SGLT2 inhibitors's in preclinical [62] and clinical research [63,64] and therefore, measurement of circulating ketone bodies and their trajectories after an index event as well as additional biomarkers will certainly play an important role in further clinical research of cardiac diseases.

Although, the EMMY trial shows significant reduction of NT-proBNP levels in acute myocardial infarction compared to placebo, the trial was not powered for hard clinical endpoints like hospitalization for heart failure or mortality. It has also to be noted that these clinical endpoints were rather infrequent in the EMMY trial. Despite the differences between EMMY and the two upcoming outcome trials with respect to more heart failure enriched populations and longer follow-up periods in the two latter ones, one might anticipate rather low event rates in the large trials, too. This already led to the increases in the enrollment target of the EMPACT-MI trial twice, now planning to recruit 6500 patients instead of the originally planned 3312 participants.

Based on the EMMY endpoints and previous outcome trials [55,65–67] outcome numbers are likely to be mainly based on heart failure events rather than mortality in DAPA-MI and EMPACT-MI as well.

The degree of LVEF recovery after MI is an important prognostic factor and patients showing no recovery in LVEF after MI are at high risk of sudden cardiac arrest events and death [68]. Moreover, LVEF recovery was associated with a substantial decrease in all-cause and cardiovascular mortality [69]. Concerning systolic function, the EMMY-trial shows a greater increase in LV-EF in the empagliflozin group compared to placebo post MI.

Furthermore, the EMMY-trial showed an improvement in diastolic function in line with data on empagliflozin being the first pharmacological treatment option in patients with HFpEF improving long-term clinical outcome [55].

6. Conclusions

With the recently published EMMY-trial, the first randomized and placebo-controlled trial is available showing the efficacy of empagliflozin on cardiac biomarkers as well as cardiac function and structure post MI independent. This is accompanied by a placebo-like safety profile. As the trial was not powered for hard clinical endpoints due to comparably low patient numbers and a rather short follow-up period of 26 weeks, NT-proBNP was selected as surrogate parameter for primary outcome. The lower NT-proBNP levels in the empagliflozin group together with functional (LV-EF, diastolic function) and structural (LVESV, LVEDV) benefits, the EMMY trial provides evidence for a clinical benefit of SGLT2-inhibitors in patients suffering from MI. Based on the finding of large clinical trials and meta-analyses, NT-proBNP represents an effective outcome parameter for SGLT2 inhibition in heart failure, but potential clinical effects of SGLT2-inhibitors seem to be underestimated.

Author Contributions

MB, EK and HS gave substantial contributions to the conception and interpretation of the manuscript and revised it critically and approved the final version to be published; DVL drafted the manuscript, gave substantial contributions to the conception and interpretation of the manuscript and approved the final version to be published.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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