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Use of Sodium-Glucose Co-transporter-2 Inhibitors after Acute Myocardial Infarction

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Abstract

Whether sodium-glucose co-transporters-2 (SGLT2) inhibitors have beneficial effects on cardiovascular (CV) events and mortality if given within few days from acute myocardial infarction (AMI) is unknown. The DAPA-MI trial (n= 4,107) is the only available study designed to evaluate the impact of administration of dapagliflozin on CV outcomes and mortality if started within 10 days from occurrence of an AMI. Using the win-ratio approach, the primary outcome of the DAPA-MI trial was the hierarchical composite of death, hospitalization for heart failure (HFF), nonfatal myocardial infraction (MI), atrial fibrillation/flutter, incident type 2 diabetes, New York Heart Association Functional Class (NYHAFC) at the last visit, and weight decrease of 5% or greater. After a median duration of follow-up of 11.6 months, the win ratio was in favor of dapagliflozin being 1.34 (95% CI, 1.20 to 1.50, P< 0.001). This improvement in win ratio was mainly attributed to weight reduction (-1.65 kg versus placebo), 47% lower rates of incident type 2 diabetes [hazard ratio (HR) 0.53, 95% CI, 0.36 to 0.77)], and mild amelioration in NYHAFC. However, there was tendency toward increase in all-cause death (HR 1.22, 95% CI, 0.77 to 1.92), CV death (HR 1.15, 95% CI, 0.66 to 2.01), all-cause hospitalization (HR 1.12, 95% CI, 0.98 to 1.29), and non-fatal MI (HR 1.11, 95% CI, 0.72 to 1.71) with dapagliflozin. In the EMMY trial, empagliflozin when initiated within 3 days of percutaneous coronary intervention (PCI) in patients with AMI decreased serum levels of N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP) by 15% and marginally improved left ventricular ejection fraction (LVEF) by 1.5% compared with placebo. The ongoing EMPACT-MI trial should clarify the effects of empagliflozin on hard CV outcomes and mortality in patients with recent AMI. In conclusion, current data suggests that early use of SGLT2 inhibitors within days after acute MI may reduce incidence of type 2 diabetes and body weight, but it was associated with a trend toward increased all-cause death, CV death, and MI. Further studies are needed before recommending the early initiation of SGLT2 inhibitors following AMI.

Keywords: Acute myocardial infarction, Dapagliflozin, Empagliflozin, DAPA-MI, EMPACT-MI, Mortality

Introduction

The use of SGLT2 inhibitors was associated with significant reduction in CV outcomes in patients with and without diabetes who had pre-existing CV disease or CV risk factors [1,2]. In addition, SGLT2 inhibitors exert reno-protective effects in patients with broad spectrum of underlying kidney disease and renal function at baseline [3]. However, one large category of patients in whom SGLT2 inhibitors were not adequately studied was in the setting of AMI. Unfortunately, subjects with recent MI within 6 months were excluded from trials of SGLT2 inhibitors [4,5]. In fact, despite marked progress that was achieved in management of AMI, there was still unmet need to find an effective and safe therapy for prevention of its complications, including mortality [5]. Recently published, the DAPA-MI was the first trial to examine the effects of the SGLT2 inhibitor, dapagliflozin, on CV events and mortality if initiated shortly after AMI [6]. The main purpose of this article is to review available data regarding the effects of early use (within days) of SGLT2 inhibitors on CV outcomes in patients with AMI.

The DAPA-MI trial

The DAPA-MI was a randomized, double-blind, placebo-controlled trial conducted in Sweden and UK [6]. Patients presenting with AMI were randomized to dapagliflozin 10

mg/d (n=2019) or matching placebo (n=1998) on top of standard care within a median time of 3 days from hospital admission [6]. Patients' mean age was 63 years, only 20% were women, and mean body mass index was 28.3 kg/m^2. All patients should have evidence of impaired left ventricular systolic function (LVSF) either by imaging or by presence of Q wave MI on an electrocardiogram [6]. Most patients (73%) had LVEF < 50% on admission and 72% had ST-elevation MI [6]. The DAPA-MI had 2 important exclusions: patients with type 2 diabetes and those with history of chronic heart failure requiring hospitalization within the last year associated with LVEF of 40% or less [6]. Using the win ratio analysis approach, the primary outcome was the hierarchical composite of the following 7 outcomes: death, HHF, nonfatal MI, atrial fibrillation/flutter, type 2 diabetes, NYHAFC at the last visit, and reduction in body weight of ≥ 5% [6]. The key secondary outcome was the same as the primary outcome after exclusion of the body weight component [6].

Main results of DAPA-MI

After a median duration of follow-up of 11.6 months, there were 32.9% wins for dapagliflozin versus 24.6% wins for placebo yielding a win ratio of 1.34 (95% CI, 1.20 to 1.50, P< 0.001) [6]. The amelioration in the primary outcome was primarily driven by the benefits achieved in weight loss, incident type 2 diabetes, and to a lesser extent by NYHA functional status [6]. Thus, compared with placebo, in the dapagliflozin arm, weight loss was -1.65 kg (95% CI, -2.12 to -1.18) and reduction of incident type 2 diabetes was 47% (HR 0.53, 95% CI, 0.36 to 0.77) [6]. In addition, there was trend towards decrease frequency of adjudicated HHF (HR 0.83, 95% CI, 0.50 to 1.39), stroke HR 0.61 (95% CI, 0.28 to 1.34), and atrial fibrillation/flutter (HR 0.88, 95% CI 0.36-0.77) with dapagliflozin [6]. However, in the dapagliflozin group, there was a trend toward increased all-cause death (HR 1.22, 95% CI, 0.77 to 1.92), CV death (HR 1.15, 95% CI, 0.66 to 2.01), all-cause hospitalization (HR 1.12, 95% CI, 0.98 to 1.29), and non-fatal MI (HR 1.11, 95% CI, 0.72 to 1.71) [6]. Regarding the key secondary outcome, after excluding the outcome of weight loss, the win ratio in favor of dapagliflozin was attenuated but still statistically significant at 1.20 (95% CI, 1.04 to 1.40; P =0.015) [6]. The above results remained unchanged in various patients' subgroups classified by age, gender, weight, baseline LVEF and troponin levels, ST-elevation versus non-ST-elevation MI, and other possible pertinent factors (e.g. type of background therapy) [6].

Interpretation of results of DAPA-MI

No doubt, the tendency toward increases in all-cause and CV death, and non-fatal MI with dapagliflozin is concerning [6]. Moreover, while the reduction in frequency of HHF by approximately 25-30% is a consistent benefit observed with all SGLT2 inhibitors, the average reduction of 17% in adjudicated HHF in the DAPA-MI trial was less than expected [6]. There are multiple possible explanations for the above findings. First, patients with AMI may represent a distinct population with specific pathology that does not respond favorably to dapagliflozin. Second, subjects included in the DAPA-MI trial were overall low-risk as reflected by exclusion of type 2 diabetes, lack of history of symptomatic heart failure, relatively preserved LVEF, and well-preserved kidney function [(estimated glomerular filtration rate (eGFR) at baseline was 83.5 ml/min/1.73 m^2)] [6]. Thus, the total number of events was insufficient to unravel differences in outcomes between the dapagliflozin and placebo arms. Third, the duration of follow-up was short [6]. It should be emphasized that patients enrolled in the DAPA-MI represent ethnicities in Sweden and UK with 94% Whites, and minimal representation of minority groups (for instance less than 1% subjects were Blacks). Therefore, results of DAPA-MI should not be generalized to non-Whites.

Safety of dapagliflozin in acute heart failure

Dapagliflozin was overall fairly tolerated. The proportion of patients who discontinued dapagliflozin was slightly higher than placebo, 2.6% and 1.8%, respectively [6]. No increase in cases of ketosis, hypovolemia, hypotension, amputation, or genital infections was reported in association with dapagliflozin [6].

Use of Empagliflozin in Acute Myocardial Infarction

No data are available so far with respect to the effects of empagliflozin on CV outcomes in AMI. The EMMY trial was a randomized double-blind trial that examined the effects of empagliflozin on intermediate outcomes of AMI, namely serum levels of NT-proBNP (primary outcome), a predictor of subsequent CV events, and LVEF (one of the secondary outcomes) [8]. In EMMY trial, empaglifozin 10 mg/d was started within 3 days after percutaneous coronary intervention (PCI) in all patients (n=476, mean age 57 years-old, 82% men) [8]. After 26 weeks, mean NT-proBNP levels were 15% lower in the empagliflozin group compared with the placebo group (95% CI, 4.4 to 23.6, P=0.026) [8]. LVEF was minimally increased with empagliflozin versus placebo, with an absolute difference of 1.5% (95% CI, 0.2 to 2.9%; P=0.014) [8]. The EMMY study was too short to examine CV events [8]. Meanwhile, hospital stay was similar in the empagliflozin and placebo groups [8]. Somewhat concerning was the finding that the 3 deaths reported in the EMMY trial occurred in the empagliflozin arm, 2 of them happened within 5 days of enrolment due to large MI, and the third death after 149 days due to lung cancer [8]. Currently, empagliflozin is being evaluated in a dedicated trial, the EMPACT-MI, to assess its effects on CV events in patients with AMI [9]. The EMPACT trial is still ongoing, but its design and patients' characteristics were published [9]. The primary end point of EMPACT-MI is time to first HHF or all-cause death. There are some important differences in patients' characteristics between EMPACT-MI and DAPA-MI trials. Thus, the EMPACT-MI trial is larger than DAPA-MI (n=6,522 versus

4,017) [6,9]. In addition, patients in EMPACT-MI are at higher CV risk at baseline: 31.7% of patients had type 2 diabetes and 25% have LVEF < 35% [9].

Conclusions and Current Needs

Available data suggests that dapagliflozin if initiated within median time of 3 days after AMI had no statistically significant effects on all-cause death, CV death, or non-fatal MI. In fact, there was a concerning trend towards an increase in such events with dapagliflozin. On the other hand, dapagliflozin significantly decreased incident diabetes by 47%, and mean weight by 1.6 kg compared with placebo. The ongoing EMPACT-MI trial should clarify the therapeutic role of empagliflozin in the setting of AMI and help define the best candidates for such therapy as well as the optimum timing to start the SGLT2 inhibitor following AMI. Until further information becomes available, the current data does not support the early use of the SGLT2 inhibitors after AMI.

Conflict of Interest

The author does not have any conflict of care to report.

References

1. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28.

2. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet. 2020;396(10254):819-29.

3. EMPA-KIDNEY Collaborative Group. Impact of primary kidney disease on the effects of empagliflozin in patients with chronic kidney disease: secondary analyses of the EMPA-KIDNEY trial. Lancet Diabetes Endocrinol. 2024;12(1):51-60.

4. Furtado RHM, Bonaca MP, Raz I, Zelniker TA, Mosenzon O, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus and Previous Myocardial Infarction. Circulation. 2019 May 28;139(22):2516-27.

5. Udell JA, Jones WS, Petrie MC, Harrington J, Anker SD, Bhatt DL, et al. Sodium Glucose Cotransporter-2 Inhibition for Acute Myocardial Infarction: JACC Review Topic of the Week. J Am Coll Cardiol. 2022;79(20):2058-68.

6. James S, Erlinge D, Storey RF, McGuire DK, de Belder M, Eriksson N, et al. Dapagliflozin in Myocardial Infarction without Diabetes or Heart Failure. NEJM Evid. 2024;3(2):EVIDoa2300286.

7. Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. Lancet. 2022;400(10354):757-67.

8. von Lewinski D, Kolesnik E, Tripolt NJ, Pferschy PN, Benedikt M, Wallner M, et al. Empagliflozin in acute myocardial infarction: the EMMY trial. Eur Heart J. 2022;43(41):4421-32.

9. Harrington J, Udell JA, Jones WS, Anker SD, Bhatt DL, Petrie MC, et al. Baseline characteristics of patients enrolled in the EMPACT-MI trial. Eur J Heart Fail. 2023;25(9):1708-15.