Review Article

EMMY trial: What we know and what we need to know

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Abstract

SGLT-2 inhibitors are a class of antidiabetic drugs with additional cardiovascular benefits. Though initially developed for glycemic control, subsequent studies in the heart failure (HF) population also demonstrated positive outcomes. Currently, they are approved for use in HF with both reduced and preserved ejection fraction. More recently, encouraging data have emerged on acute HF. Following an episode of acute myocardial infarction, patients are also at high risk for developing HF and experiencing recurrent events despite optimal therapy. The PARADISE MI study failed to demonstrate any benefits of ARNI in this scenario. The EMMY trial explored the role of SGLT-2i in >450 odds patients with acute MI. At 26 weeks SGLT-2i (empagliflozin) use led to a higher fall in NT-pro-BNP levels compared to standard treatment. There was additional improvement in left ventricular echocardiographic parameters with empagliflozin too. However, it was a small trial, had a short follow-up and there were no clinical endpoints. But none the least, it attested to the safety of SGLT-2i in the post-MI scenario. Because the primary care physician frequently encounters patients in the post-MI scenario, the manuscript provides insights into their practice. Based on contemporary evidence, the universal use of SGLT-2 inhibitors in patients following acute MI is not warranted. A further role of these drugs in post-MI HF will be clarified in ongoing trials.

Keywords: Empagliflozin, heart failure, left ventricular ejection fraction, NT pro-BNP

Trial Summary

EMMY trial was a multicenter, double-blinded randomized controlled trial of sodium-glucose cotransporter-2 inhibitor (SGLT-2i) in a post-myocardial infarction scenario. In this trial, patients with acute myocardial infarction accompanied by a large creatine kinase elevation (>800 IU/L) were randomly assigned to empagliflozin 10 mg or matching placebo once daily within 72 h of percutaneous coronary intervention. Patients with estimated glomerular filtration rate (e-GFR) <45 mL/min, urinary tract infection, unstable hemodynamics, previous SGLT-2i use, acidosis (pH < 7.3) and type 1 diabetes mellitus (DM) were excluded. The primary outcome was the N-terminal pro-brain natriuretic peptide (NT-pro-BNP) level change over a period of 26 weeks. The secondary outcome included changes in the echocardiographic parameters. Over a period of 5 years, 476 patients between the ages of 18 and 80 years were enrolled from 11 sites across Austria. The median age of the study population was 57 years and the baseline median (interquartile range) NT-proBNP was 1294 (757–2246) pg/mL. More than 95% of patients were initiated on guideline-directed medical therapy and only 1/8th of the population had a previous diagnosis of DM.

A decline in NT-pro-BNP levels at 26 weeks was observed in both arms of the study but the reduction was significantly greater (by 15%) in the empagliflozin group, as compared with the placebo group, after adjusting for baseline NT-proBNP, sex, and diabetes status ($P = 0.026$). The NT-proBNP advantage with empagliflozin was evident by 12 weeks and observed across the entire range of baseline values.

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With respect to secondary outcomes, in the empagliflozin group absolute left-ventricular ejection fraction improvement was significantly greater by 1.5% (95% confidence interval [CI]: 0.2–2.9%, $P = 0.029$), mean left ventricular E/e' reduction was 6.8% greater (95% CI: 1.3–11.3%, $P = 0.015$), left-ventricular end-systolic and end-diastolic volumes were lower by 7.5 mL (95% CI: 3.4–11.5 mL, $P = 0.0003$) and 9.7 mL (95% CI: 3.7–15.7 mL, $P = 0.0015$), as compared with the placebo group. Weight loss was significantly higher with empagliflozin (by 1.76 Kg, $P = 0.02$) compared to placebo. Seven patients were hospitalized for heart failure (HF) (three in the empagliflozin group). Other predefined serious adverse events were rare and did not differ significantly between groups.

To summarize, in patients with a recent MI, empagliflozin was associated with a significantly greater NT-proBNP reduction over 26 weeks, accompanied by a significant improvement in functional and structural echocardiographic parameters.

Comments

Sodium–glucose co-transporter 2 inhibition reduces the risk of hospitalization for HF and death in patients with symptomatic HF. There are many subsets of HF, where SGLT-2 inhibitors have won the battle and have been approved for use by major international guidelines.

SGLT 2 Inhibitors were initially developed for glycemic control in diabetes mellitus but benefits were observed not only in terms of diabetes control but also for cardiovascular outcomes, and renal improvement and there was an especially significant reduction in hospitalization for HF was observed in studies such as CANVAS,[1] CREDANCE,[2] DECLARE TIMI 58,[3] and EMPA REG OTCOME TRIAL.[4]

Bolstered by these results, the subsequent generation trials enrolled HF patients *per se* irrespective of the presence of DM and reproduced benefits with SGLT-2i in a population of HF with reduced EF (HFrEF) patients in DAPA HF trial[5] and EMPEROR REDUCED TRIAL.[6] After that, trials were initiated with SGLT-2i in HF with preserved EF (HFpEF) and benefits were shown in EMPEROR PRESERVED[7] and DELIVER[8] studies. Finally, in acute HF, promising results with these agents were recently reported from the EMPULSE trial and SOLOIST-WHF [Figure 1].[9]

However, trials investigating the effects of this drug class in patients in post-MI scenario are scarce. The only data available concerning the effect of SGLT2 inhibitor on post-MI NT-proBNP concentrations derives from the EMBODY trial,[10] which analyzed the impact of empagliflozin treatment on post-MI sympathomimetic activity. This trial reported a decline of NT-proBNP concentrations in the empagliflozin and the placebo group. However, no statistically significant difference was reported, potentially due to the rather small number of participants and the later treatment initiation compared with EMMY.

ARNI in Post MI scenario -*Paradise Lost!*

The journey of angiotensin receptor blocker and neprilysin inhibitor (ARNI) started from HFrEF, then moved to acute HF, HFpEF, and finally to acute MI mirroring SGLT 2 inhibitors. However, in the PARADISE MI study, the use of ARNI was not associated with a significantly lower incidence of death

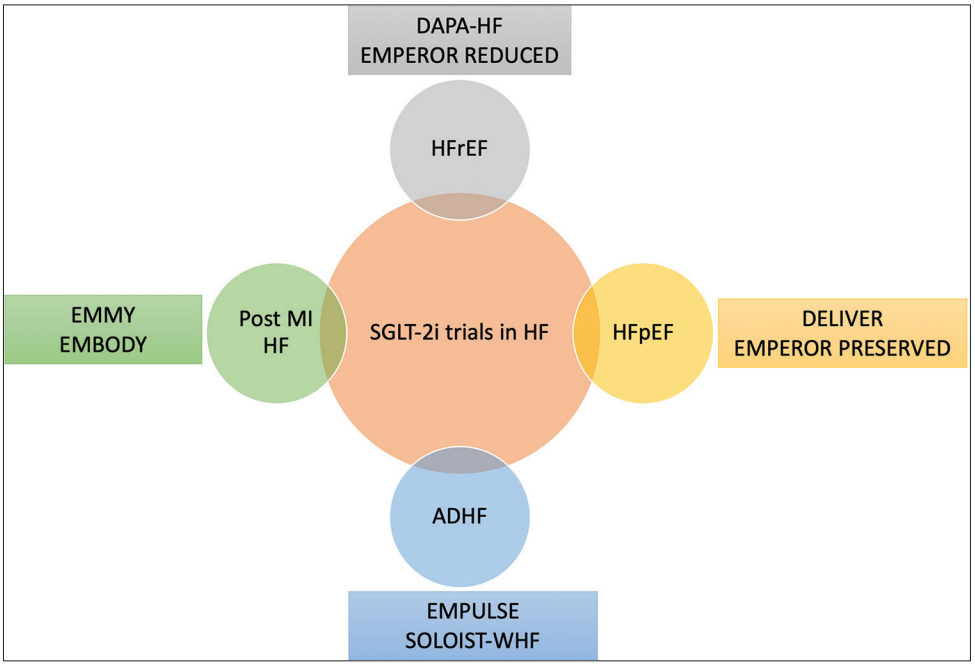

Figure 1: Pivotal trials of SGLT-2 inhibitors in various subsets of heart failure

from cardiovascular cause or incident HF than ramipril among patients with acute MI.[11] Positive outcome data in HF trials with ARNI (PARADIGM-HF and PIONEER-HF) did not necessarily translate into positive outcomes in post-MI trials, as observed in the PARADISE-MI trial.

The positive results of the EMMY trial become more prominent, considering the disappointing results with ARNI in the PARADISE MI study. Natriuretic peptides (Nt-pro BNP and BNP) are important prognostic markers in both acute and chronic HF. Hence, their reduction is routinely utilized as a surrogate for benefits in clinical event reduction in many trials. They similarly predict outcomes in the post-MI scenario even when the LV dysfunction is not apparent. Hence, the EMMY trial can be considered as a positive proof of concept study enabling the design of further studies of SGLT2i in post-MI scenarios. However, several caveats within the EMMY study are noteworthy. First and foremost, the absence of hard clinical endpoints as outcomes precludes routine use in post-MI scenarios. The small sample size and the very short 4-month follow-up could be additional spoilers. However, we need to reconcile that the COVID-19 pandemic must have impacted the latter half of the trial follow-up process. Also, large and robust RCTs with good follow-up entail a huge financial and logistic burden too.

The Way Forward

The post-MI scenario is a high-risk condition for HF and the incidence varies from anywhere between 7% and 38%.[12] The occurrence of HF adds to morbidity and mortality in such a situation and is an area of unmet need. The EMMY trial demonstrated that the addition of empagliflozin led to a greater reduction in NT-pro-BNP and better recovery of left ventricular function than the standard of care. Though the study size was small and had a limited follow-up, it attests to the safety of empagliflozin in the scenario. The role of SGLT2i in acute MI patients will be further clarified when the robust outcome data from the two ongoing studies—EMPACT-MI (NCT04509674) with empagliflozin and DAPA-MI (NCT04564742) with dapagliflozin, which are powered for differences in the composite outcome of hospitalization for HF and cardiovascular or all-cause mortality, are reported.

Implications for Clinical Practice

Management of HF needs good interaction and coordination between the primary care physician, cardiologist and the HF specialist. The primary care physician plays a vital role in the outpatient care of HF patients and it is imperative that he should have good insight into the evolving landscape of medical management of HF. The pharmacotherapy of HF has undergone rapid strides in the past decade like none other. SGLT-2 inhibitors and ARNI have emerged as two pivotal pillars of HF management in the past decade. SGLT-2 inhibitors stand out as an HF therapy effective across the entire spectrum of HF–both acute or chronic states and both preserved or reduced EF. However, the post-MI scenario is an unmet need with a high risk of HF and CV events despite optimal therapy. The failure of ARNI in the PARADISE MI study has shifted the spotlight back to SGLT-2i in this scenario. The EMMY trial demonstrated that empagliflozin use led to lower levels of NT-pro-BNP in the short term in patients with acute MI. This was complemented by an improvement in the echocardiographic parameters of the LV function. However, whether this will translate into hard clinical outcomes will be clarified only by future trials. Currently, their use in post-MI scenarios should be restricted to underlying diabetes mellitus and HF only.

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Conflicts of interest

There are no conflicts of interest.

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