Emerging data on SGLT2 benefits in acute coronary syndromes

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Sodium-glucose co-transporter-2 (SGLT2) inhibitors, initially developed for the management of type 2 diabetes, have demonstrated significant cardiovascular benefits in recent randomized controlled trials (RCTs), including a substantial reduction in cardiovascular mortality.[1–3] Importantly, these agents have shown a marked decrease in the risk of hospitalization for heart failure and cardiovascular death in patients with both reduced and preserved ejection fraction heart failure, independent of diabetes status.[4] Cardiovascular benefits of SGLT2 inhibitors are observed rapidly after therapy initiation and persist with continued use, indicating that their protective effects are likely mediated through mechanisms beyond glycemic control. Furthermore, the consistent cardiovascular advantages seen in patients regardless of type 2 diabetes status underscore the broader therapeutic potential of SGLT2 inhibitors.

Clinical trials with SGLT2 inhibitors have not demonstrated a significant reduction in the risk of fatal or non-fatal myocardial infarction (MI), nor in the risk of first hospitalization for heart failure following an MI.[5,6] The rapid cardiovascular benefits of SGLT2 inhibitors suggest that these agents may reduce heart failure risk post–MI by enhancing cardiac function through multiple mechanisms, including osmotic diuresis-induced volume reduction via glycosuria and natriuresis, decreased systolic blood pressure, and improved myocardial oxygen delivery and cardiac metabolism, with a shift from glucose oxidation to ketone body production providing immediate protective effects against heart failure progression.[7] While additional factors like reduced inflammation, oxidative stress, advanced glycation end products, and decreased epicardial and visceral fat may also contribute, these changes are not immediate and likely do not fully account for the observed rapid decline in heart failure decompensation or hospitalization risk post–MI.

In the current issue of *The Lancet Regional Health–Europe*, Rosen et al.[8] conducted an observational study using data from the SWEDEHEART registry to evaluate cardiovascular outcomes following myocardial infarction in 11,271 patients with type 2 diabetes between 2018 and 2021. Of these patients, 2498 (22.2%) were treated with SGLT2 inhibitors. The study's key findings indicated that SGLT2 inhibitors were associated with significant reduction in the composite outcome of all-cause death and first hospitalization for heart failure, with an adjusted hazard ratio (HR) of 0.70 (95% CI, 0.59–0.82) in Cox models with imputed baseline data. This benefit extended to individual outcomes, showing a reduction in first hospitalizations for heart failure (HR 0.78, 95% CI 0.63–0.98) and all-cause mortality (HR 0.64, 95% CI 0.50–0.80). Complete-case analysis revealed that hazard ratios for all-cause death (HR 0.70; 95% CI, 0.47–1.04) and stroke (HR 0.66; 95% CI, 0.29–1.50) were numerically lower among patients receiving SGLT2 inhibitors, although these reductions did not reach statistical significance.

Sensitivity analysis using inverse probability weighting (IPW) demonstrated hazard ratios for the composite outcome (HR 0.61; 95% CI, 0.49–0.76) and all-cause death (HR 0.49; 95% CI, 0.36–0.66) that were consistent with the primary analysis, supporting the benefit of SGLT2 inhibitors. However, the IPW analysis for first hospitalizations for heart failure (HR 0.76; 95% CI, 0.55–1.03) and stroke (HR 0.76; 95% CI, 0.42–1.38) did not reach statistical significance, indicating that results for these specific outcomes may be more variable or less robust. In a fully adjusted Cox model, non-ST elevation myocardial infarction was the only infarction type associated with a significantly reduced risk (HR 0.65; 95% CI, 0.52–0.81), alongside subgroups with a body mass index (BMI) $\geq$30 kg/m^2 (HR 0.59; 95% CI, 0.44–0.80) and left ventricular ejection fraction $\geq$50% (HR 0.39; 95% CI, 0.20–0.71). The study highlighted that SGLT2 inhibitors rapidly reduced the risk of heart failure hospitalization and mortality, with consistent reductions in heart failure and mortality rates across various patient subgroups. Multiple sensitivity analyses reinforced the robustness of these findings, showing similar outcomes even after adjustment for different variables, including the severity of heart failure risk.

Compared to other RCT's such as DAPA-MI and EMPACT-MI, this study demonstrated a significant reduction in all-cause mortality, a result that was not observed in those RCTs. The observed differences may be attributed to variations in patient populations, as this study included older and sicker patients, suggesting that more targeted RCTs are necessary to confirm these findings. Notably, the SWEDEHEART study indicated that patients with non-ST elevation myocardial infarction, and those with repeated infarctions derived greater benefit from SGLT2 inhibitors, whereas DAPA-MI and EMPACT-MI predominantly included patients with ST-elevation myocardial infarctions.

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Overall, the results suggest that SGLT2 inhibitors may offer significant cardioprotective effects in the early post–MI phase in patients with type 2 diabetes, reducing the risk of cardiovascular mortality and morbidity without any evidence of increased risk of adverse events. Due to the observational nature of this study, cautious interpretation is required, and further randomized studies are needed to fully validate these outcomes.

Declaration of interests

Nothing to declare.

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