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Safety of sodium-glucose cotransporter-2 inhibitors for heart failure

Drawing inferences from observational data with possible confounding

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Heart failure is increasing in prevalence and is a major cause of morbidity and mortality worldwide,[1] with prevalence ranging from 1% to 3% of the general adult population in high income countries.[1] Limited data from low and middle income countries suggest high heart failure disease burden.[2,3] Heart failure with reduced ejection fraction, defined as a left ventricular ejection fraction of ≤40%, accounts for around 30-60% of heart failure in epidemiological studies.[1] Increasing evidence of the effectiveness of certain drugs to reduce mortality and morbidity in heart failure with reduced ejection fraction has led to strong recommendations for their use in clinical practice guidelines.[4,5] The foundational therapeutic agents for heart failure with reduced ejection fraction have been shown to improve survival, reduce the risk of readmission to hospital, and improve symptoms by targeting the renin-angiotensin-aldosterone and sympathetic nervous systems. These include angiotensin converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitors, mineralocorticoid receptor antagonists, and β blockers. In recent randomized controlled trials, the addition of a sodium-glucose cotransporter-2 (SGLT-2) inhibitor further reduced the risk of worsening heart failure and death from cardiovascular disease in patients with heart failure with reduced ejection fraction.[4,5] In the linked study (doi:10.1136/bmj-2024-080925), Svanström and colleagues add to this growing evidence by using real world administrative data to show a reduction in mortality but no change in heart failure related hospital admissions with SGLT-2 inhibitor use.[6]

The authors linked data in the Danish heart failure registry to the national civil registration system, including data for patients aged ≥45 years with a left ventricular ejection fraction of ≤40% treated from July 2020 to June 2023. They used a modified prevalent new user design,[7] with an intervention group including patients starting SGLT-2 inhibitor treatment for a heart failure indication and a comparator group including patients without SGLT-2 inhibitors matched on time since diagnosis of heart failure. Results were adjusted using inverse probability of treatment weighting to account for differences in baseline characteristics. The primary outcome was all cause mortality, and secondary outcomes were a composite of cardiovascular mortality or hospital admission with heart failure and its components. The authors used proportional hazards regression to compare outcomes in the intervention and comparator groups. They report a 25% relative risk reduction for all cause mortality and a 23% reduction in cardiovascular mortality but no change in the composite of cardiovascular mortality or hospital admissions due to heart failure associated with SGLT-2 inhibitor use compared with non-users. The magnitude of association with reduction in mortality was consistent across subgroups. They do not report non-heart failure related or all cause hospital admisstions.

Given that observational data on treatment effectiveness are often confounded in ways that cannot be eliminated through risk adjustment, one must be careful in drawing conclusions.[8] Observational data can be useful in examining outcomes or subgroups that were too small to be adequately evaluated in randomized trials. If investigators can first show that the observational outcome is similar to that observed in similar patients in randomized trials, confidence in the observed result will be greater for other populations or other outcomes than for studies in which the investigators cannot reproduce the results of the clinical trials. If the clinical trial results cannot be reproduced, one must have a strong biological plausibility for why the observational studies, with their risk of confounding, are more accurate than the clinical trial results.

Unfortunately, the clinical trial data differ, as noted by Svanström and colleagues. In a meta-analysis of randomized trials of SGLT-2 inhibitors in patients with heart failure with reduced ejection fraction, all cause mortality was reduced with an odds ratio of 0.87 (95% confidence interval 0.77 to 0.98), an effect size half that observed in the linked study.[9] By contrast, hospital admission was markedly reduced in the clinical trials (odds ratio 0.69, 0.62 to 0.78) but not in the registry. How does one reconcile these differences between the randomized controlled trials and observational studies? The authors suggest that their reliance on coding of heart failure for assigning a hospital admission due to heart failure may explain their lack of reduced admissions. Although coding is inferior to adjudication using the medical record, accuracy of coding would have to have been much poorer than has been reported to account for all of the difference.[10] Another possible explanation is that patients not treated with SGLT-2 inhibitors may have had non-heart failure disease that was more severe than their heart failure whereas those treated had heart failure as the major condition. Although the investigators were able to match baseline demographic characteristics between the groups, the patients treated with SGLT-2 inhibitors may be different from those not treated in ways that were not considered or measured but that affect mortality, such as frailty. If risk adjustment was incomplete then these non-treated patients would have worse mortality (from non-cardiovascular causes) and be less likely to be admitted to hospital for heart failure

(and presumably more likely to be admitted for non-heart failure conditions).

In spite of these limitations, these results provide assurance that no unexpected harm results from SGLT-2 inhibitors when they are used for treatment of heart failure outside the clinical trial setting. In addition, the large number of patients treated in the registry shows the rapid uptake of this fourth pillar of pharmacotherapy for heart failure with reduced ejection fraction.[4 5] However, SGLT-2 inhibitors are still underused.[11] Among practitioners, the potential for euglycemic diabetic ketoacidosis, complexity of patients, and drug costs may lead to hesitancy to prescribe SGLT-2 inhibitors.[12] Robust implementation efforts should tackle barriers to prescribing in an effort to increase evidence based prescribing.

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