SGLT2 Inhibitors a Better First Drug in Type 2 Diabetes Than Metformin?

— Observational study suggests some cardiovascular benefit

by Crystal Phend, Contributing Editor, MedPage Today
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Using SGLT2 inhibitors in the first-line treatment of type 2 diabetes lowered some cardiovascular risk, a claims database study showed.

The combined 12-month risk for myocardial infarction (MI), stroke, and death was similar between those who started on an SGLT2 inhibitor and those who started out with metformin (HR 0.96, 95% CI 0.77-1.19), reported HoJin Shin, BPharm, PhD, of Brigham and Women's Hospital and Harvard Medical School in Boston, and colleagues.

However, an advantage in managing heart failure (HF) again appeared with the SGLT2 inhibitors, they noted in the *Annals of Internal Medicine*.

The combined risk for HF hospitalizations or mortality was a relative 20% less likely with these therapies compared with metformin (HR 0.80, 95% CI 0.66-0.97) over a mean follow-up of 12 months.

That fit with findings from the large cardiovascular outcomes trials mandated by the FDA, in which SGLT2 inhibitors reduced HF hospitalization risk by 27% to 35% compared with placebo, Shin's group said.

Newly updated HF guidelines recommend SGLT2 inhibitors for patients with type 2 diabetes and either established cardiovascular disease or high risk for it in order to prevent hospitalization for HF.

"The benefit for reducing HF hospitalizations in these trials predominantly reflects primary prevention of symptomatic HF, because only approximately 10% to 14% of participants in these trials had HF at baseline," the guideline authors wrote. "The mechanisms for the improvement in HF events have not been clearly elucidated but seem to be independent of glucose lowering. Proposed mechanisms include reductions in plasma volume, cardiac preload and afterload, alterations in cardiac metabolism, reduced arterial stiffness, and interaction with the Na^+/H^+ exchanger."

The American Diabetes Association standards of care guidelines stated that "[f]irst-line therapy depends on comorbidities, patient-centered treatment factors, and management needs and generally includes metformin and comprehensive lifestyle modification." They suggested GLP-1 receptor agonists or SGLT2 inhibitors, with or without metformin based on glycemic needs, as "appropriate initial therapy" for type 2 diabetes patients with or at high risk for atherosclerotic cardiovascular disease, HF, and/or chronic kidney disease.

An expert consensus decision pathway from the American College of Cardiology for type 2 diabetes patients similarly recommended starting an SGLT2 inhibitor or GLP-1 receptor agonist, without suggesting one over the other, along with other guideline-directed medical therapy for glucose control and other risk factors in high-risk patients and those with established heart disease.

Shin and colleagues identified use of first-time antidiabetic medication in the Optum Clinformatics Data Mart and IBM MarketScan databases for people ages 18 and older with employer-sponsored commercial health insurance or a Medicare Advantage insurance plan for those 65 and older. They included 8,613 first-line initiators of canagliflozin (Invokana), empagliflozin (Jardiance), or dapagliflozin (Farxiga) matched by propensity score to 17,226 patients who started metformin for type 2 diabetes from April 2013 through March 2020.

Along with the lower risk of HF hospitalizations in the SGLT2 inhibitor initiators (HR 0.78, 95% CI 0.63-0.97), there was a numerically lower risk for MI that just missed statistical significance (HR 0.70, 95% CI 0.48-1.00). Stroke and mortality risk were similar between

groups.

These findings were in line with a 2019 meta-analysis of three cardiovascular outcomes trials, in which there was a relative 11% reduction in MI that was significant, but no reduction in stroke, "suggesting a cardiac preload effect with relatively early manifestation and explaining our finding of a lower MI risk when comparing SGLT2 inhibitors and metformin, particularly among patients with existing cardiovascular disease," Shin's group wrote.

A 2020 meta-analysis of six cardiovascular outcomes trials didn't break down the findings by MI risk, but noted HF hospitalization as "the most consistent observation across the trials," whereas death from cardiovascular causes had heterogeneous results. Cardiovascular mortality couldn't be ascertained in the observational claims data in the current study.

As expected from the trials, the SGLT2 inhibitor initiators had a higher risk for genital infections (HR 2.19, 95% CI 1.91-2.51), but otherwise similar safety compared with metformin initiators.

"Although our findings may support the use of SGLT2 inhibitors as first-line type 2 diabetes treatment of cardiovascular outcomes, further research, that is, a randomized clinical trial, is warranted to establish more robust evidence," Shin's group concluded.

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Disclosures

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Shin disclosed no relevant relationships with industry.

Primary Source

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