COMMENTARY

Should sodium-glucose cotransporter-2 inhibitors be first-line treatment for patients with type 2 diabetes?

Carl van Walraven MD MSc

■ Cite as: *CMAJ* 2020 April 6;192:E375-6. doi: 10.1503/cmaj.200426

See related article at www.cmaj.ca/lookup/doi/10.1503/cmaj.191283

The treatment landscape for type 2 diabetes has expanded extensively over the last few decades. Previously, the only decision required of physicians initiating oral pharmacotherapy for type 2 diabetes was to choose between biguanides and sulfonylureas. Now physicians can consider medications from 5 other drug classes: thiazolidinediones, glinides, glucagon-like peptide (GLP)-1 receptor antagonists, dipeptidyl peptidase-4 (DPP4) inhibitors and sodium–glucose cotransporter-2 (SGLT2) inhibitors. Although having many drug options allows identification of effective and tolerable treatments for each patient, it also complicates treatment decision-making because few adequately powered and randomized studies have directly compared these drug classes in trials that measure micro- or macrovascular outcomes. In this situation, adverse drug effects can become important drivers of drug selection.

Should the findings of related population-based research by Iskander and colleagues[1] — which shows that SGLT2 inhibitors do not cause acute kidney injury (AKI) as previously thought — prompt us to prescribe SGLT2 inhibitors as first-line therapy for type 2 diabetes rather than guideline-recommended metformin? Because the population prevalence of diabetes is high, such a decision could have a large effect on outcomes and should be considered carefully.

The United Kingdom Prospective Diabetes Study (UKPDS) showed that attaining intensive glucose control (i.e., target fasting glucose at 6 mmol/L) in patients with newly diagnosed type 2 diabetes with metformin, sulfonylureas or insulin significantly decreased microvascular complication risks despite a small difference in glycosylated hemoglobin (HbA_{1c}) of only 0.9% between treatment groups.[2] In addition, the study showed that metformin significantly decreased all-cause mortality in those with obesity. Posttrial analyses of UKPDS (with a median follow-up of 18 yr from random assignment) found that intensive control by any treatment significantly decreased risks of diabetes-related outcomes, myocardial infarction and all-cause mortality.[3] These results were attained despite identical HbA_{1c} levels between treatment groups during posttrial monitoring. The Action to Control Cardiovascular Risk in Diabetes (ACCORD)[4] and Action in Diabetes and Vascular Disease: Preterax Diamicron Modified release Controlled Evaluation (ADVANCE)[5] randomized controlled trials (RCTs) both subsequently showed that intensive glucose control significantly decreased microvascular disease in those with long-standing type 2 diabetes. This research highlights the importance of good glucose control in the treatment of type 2 diabetes.

Choosing the best of 7 hypoglycemic drug classes to achieve this goal can be simplified by eliminating those with concerning risks of important adverse effects. This makes drug adverse event warnings by Health Canada and the US Food and Drug Administration important and potentially influential. In October 2015, Health Canada identified SGLT2 inhibitors as contributing to risk of AKI based on reports of 2 patients receiving canagliflozin who had AKI, with additional cases cited by the manufacturers and a literature review that returned "limited evidence on the topic."[6] As is common in detection of adverse events, Health Canada was working with numerators only and were unable to calculate absolute or relative event risks. It concluded in its safety review that "the evidence supported the existence of a link between the use of SGLT2 inhibitors and the risk of acute kidney injury."[6]

KEY POINTS

- Although good glucose control in type 2 diabetes significantly improves patient outcomes, having many options for oral therapy can complicate treatment decisions.
- In this context, a drug's risk of adverse effects can strongly influence choices.
- Health Canada warned in 2015 that sodium–glucose cotransporter-2 (SGLT2) inhibitors were associated with acute kidney injury (AKI), but new, high-quality research has found use of SGLT2 inhibitors to reduce risk of AKI.
- Guidelines still rightly recommend metformin as initial pharmacotheray for patients with type 2 diabetes because of its efficacy, good safety profile and low cost, with SGLT2 inhibitors as second line therapy.

Iskander and colleagues' definitive examination of this proposed association captured every older Ontarian (i.e., > 66 yr of age) who was newly prescribed an SGLT2 inhibitor and had record of a serum creatinine level performed, at the most, 1 year before starting their medication.[1] Patients were followed for 90 days to determine if they visited the emergency department or were admitted to hospital with AKI, defined by standard diagnostic criteria using laboratory data and not diagnostic codes. Risk of AKI in patients prescribed SGLT2 inhibitors was compared with patients prescribed a DPP4 inhibitor. The authors extensively adjusted for covariates and performed multiple sensitivity analyses, and conclusively showed that AKI risk in patients treated with SGLT2 inhibitors does not exceed that for patients treated with DPP4 inhibitors.

The adjective definitive at the start of the previous paragraph is not used lightly to describe Iskander and colleagues' study. It has numerous and considerable strengths including large numbers of unselected people from the population of Ontario; an absence of any selection bias because every person meeting the reasonable inclusion criteria was included; in-depth adjustment for possible confounding; and use of gold-standard data to define both exposures and outcomes. When considering these findings alongside those from a 2019 systematic review involving 58 181 patients in 30 RCTs that found a significantly decreased risk of AKI with use of SGLT2 inhibitors (odds ratio [OR] 0.64, 95% confidence interval [CI] 0.48–0.80),[7] we can be confident that initiating SGLT2 inhibitors does not increase AKI risk.

But does it then follow that SGLT2 inhibitors should become our first choice for treatment of type 2 diabetes? A 2019 meta-analysis involving 34 322 patients from 3 placebo-controlled RCTs found significant reductions in the risk of heart failure and cardiovascular death (OR 0.77, 95% CI 0.71–0.84) and renal disease progression (OR 0.55, 95% CI 0.48–0.64) in patients taking SGLT2 inhibitors, and, in those with established atherosclerosis, major adverse cardiovascular events (OR 0.89, 95% CI 0.83–0.96).[8] However, despite these encouraging findings, SGLT2 inhibitors should not become first-line pharmacologic treatment for type 2 diabetes. Regardless of its comparator drug class, metformin achieved equivalent or better intermediate outcomes (including glucose control, patient weight and hypoglycemic events) compared with sulfonylureas and moderate evidence exists for reduced cardiovascular mortality with metformin.[9] Furthermore, no RCT has directly compared long-term outcomes for metformin versus SGLT2 inhibitors.

This explains why 2 recent guidelines[10,11] recommended metformin for initial pharmacotherapy for type 2 diabetes because of its efficacy, good safety profile, our long-term experience with it and its low cost. When additional treatment is required and the patient's estimated glomerular filtration rate exceeds 45 (and probably 30) mL/min/1.73 m^2, these guidelines recommended SGLT2 inhibitors as the next agent to be started in almost all patients with type 2 diabetes, including those with concurrent atherosclerotic cardiovascular disease, heart failure or chronic kidney disease; concerns about weight gain; and situations where avoidance of hypoglycemic events is important.[10] The only group of patients with diabetes in whom SGLT2 inhibitors are not recommended after metformin are those for whom cost of treatment is an issue. Framed like that, treatment of type 2 diabetes today is not that much more complicated than it used to be.

References

1. Iskander C, Cherney DZ, Clemens KK, et al. Use of sodium–glucose cotransporter-2 inhibitor and risk of acute kidney injury in older adults with diabetes: a population-based cohort study. *CMAJ* 2020;192:E351-60.
2. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group [published erratum in *Lancet* 1998;352:1558]. *Lancet* 1998;352:854-65.
3. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577-89.
4. Action to Control Cardiovascular Risk in Diabetes Study Group; Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545-59.
5. ADVANCE Collaborative Group; Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560-72.
6. Summary safety review: Sodium-glucose cotransporter-2 (SGLT2) inhibitors INVOKANA (canagliflozin) and FORXIGA (dapagliflozin) — Evaluation of a potential risk of acute kidney injury. Ottawa: Health Canada; 2015. Available: www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-sodium-glucose-cotransporter-2-sglt2-inhibitors-invokana-canagliflozin-forxiga-dapagliflozinl-risk.html (accessed 2020 Mar. 10).
7. Menne J, Dumann E, Haller H, et al. Acute kidney injury and adverse renal events in patients receiving SGLT2-inhibitors: a systematic review and meta-analysis. *PLoS Med* 2019;16:e1002983.
8. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials [published erratum in *Lancet* 2019;393:30]. *Lancet* 2019;393:31-9.
9. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med* 2016;164:740-51.
10. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018;41:2669-701.
11. Qaseem A, Barry MJ, Humphrey LL, et al.; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline update from the American College of Physicians. *Ann Intern Med* 2017;166:279-90.

Competing interests: None declared.

This article was solicited and has not been peer reviewed.

Affiliations: Departments of Medicine, and Epidemiology and Community Medicine, University of Ottawa; Ottawa Hospital Research Institute; ICES uOttawa, Ottawa, Ont.

Correspondence to: Carl van Walraven, carlv@ohri.ca