Review: Sodium–glucose cotransporter 2 inhibitors reduce HbA_{1c} and weight but increase infections

Vasilakou D, Karagiannis T, Athanasiadou E, et al. ***Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis.*** *Ann Intern Med. 2013;159:262-74.*

Clinical impact ratings: GM ★★★★★★☆ En ★★★★★★☆

Question

In adults with type 2 diabetes, what are the efficacy and safety of sodium–glucose cotransporter 2 (SGLT2) inhibitors?

Review scope

Included studies compared SGLT2 inhibitors, as monotherapy or add-on therapy, with placebo or other active type 2 diabetes medications in adults with type 2 diabetes. Outcomes included changes in hemoglobin A_{1c} (HbA_{1c}) level and body weight, cardiovascular (CV) events (myocardial infarction, stroke, death due to CV disease, or hospitalization for unstable angina), and urinary or genital tract infections.

Review methods

MEDLINE, EMBASE/Excerpta Medica, and Cochrane Library (all to Apr 2013); meetings of relevant associations (2009 to 2012); Web sites of relevant pharmaceutical companies; reports from regulatory authorities; clinical trial registries; and reference lists were searched for randomized controlled trials (RCTs). 49 RCTs and 9 extension studies (n = 16 407, duration 12 d to 104 wk) met selection criteria. SGLT2 inhibitors included dapagliflozin (21 RCTs), canagliflozin (12 RCTs), ipragliflozin (8 RCTs), empagliflozin (3 RCTs), luseogliflozin (2 RCTs), and tofogliflozin, ertugliflozin, and remogliflozin (1 RCT each). The comparator was placebo in 45 RCTs and an active medication in 13 RCTs (metformin, sitagliptin, or sulfonylurea). Trials had high risk for sponsorship bias (55 RCTs), incomplete data (47 RCTs), and overall risk for bias (50 RCTs).

Main results

Main results are in the Table.

Conclusions

In adults with type 2 diabetes, sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce hemoglobin A_{1c} more than placebo but do not differ from other active medications. SGLT2 inhibitors reduce weight, increase urinary and genital tract infections, and do not affect cardiovascular events.

Source of funding: No external funding.

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Sodium–glucose cotransporter 2 inhibitors vs placebo or active medication for adults with type 2 diabetes*

Outcomes	Number of trials (n)	Comparator	WMD (95 %CI)	
Mean change in HbA_{1c}	26 (8648)	Placebo	–0.66% (–0.73 to –0.58)	
	9 (3827)	Active	–0.06% (–0.18 to 0.05)	
Change in body weight	15 (3340)	Placebo	–1.7 kg (–2.0 to –1.5)	
	4 (1148)	Active	–1.1 kg (–1.5 to –0.8)	
			RRR/RRI (CI)	NNH (CI)
CV events†	25 (17 180)	All	RRR 11% (–14 to 30)	NS
UTI	21 (4003)	Placebo	RRI 32% (3 to 67)	60 (28 to 666)
	8 (2930)	Active	RRI 39% (6 to 81)	46 (22 to 310)
GTI	20 (4030)	Placebo	RRI 234% (140 to 364)	23 (15 to 39)
	8 (2930)	Active	RRI 365% (227 to 553)	13 (9 to 21)

**CV = cardiovascular; GTI = genital tract infection; HbA_{1c} = hemoglobin A_{1c}; UTI = urinary tract infection; WMD = weighted mean difference; other abbreviations defined in Glossary. RRR, RRI, NNH, and CI calculated from control event rates and odds ratios in article using a fixed-effect model. Sodium–glucose cotransporter 2 inhibitors were prescribed as monotherapy or add-on therapy.*

†Myocardial infarction, stroke, death due to CV disease, or hospitalization for unstable angina.

Commentary

Due to a novel extra-pancreatic mechanism of action, SGLT2 inhibitors can be used at any stage for treatment of type 2 diabetes. Canagliflozin is approved in the USA, and dapagliflozin is approved in regions including Europe and Australia. Vasilakou and colleagues show that, aside from a durable glucose-lowering effect, these convenient, once-daily oral agents can potentially improve metabolic parameters, including weight and blood pressure. Although generally well-tolerated with low incidence of hypoglycemia, they increase risk for genital and urinary tract infections to which individuals with diabetes may already be susceptible. A major limitation is that these agents may not be used with moderate or severe renal impairment since glucosuric efficacy is dependent on sufficient glomerular filtration (1). The authors have noted the concern about higher rates of bladder and breast cancer with dapagliflozin, although this may be a result of frequent surveillance during clinical trials leading to earlier detection. Long-term CV safety, including risk for stroke, remains to be established.

Due to the well-established efficacy, safety, and affordability of metformin, these SGLT2 inhibitors are unlikely to be used as monotherapy or first-line therapy unless metformin is not tolerated. These agents can fit into dual- or triple-therapy regimens that may include insulin when diabetes control is inadequate, especially when obesity-related comorbid conditions, such as hypertension or sleep apnea, are concerns. Canagliflozin was similar to sulfonylurea for glycemic control, with reduced incidence of hypoglycemia (2). They can be effective even in individuals with reduced insulin secretion when other noninsulin medications may not be effective. The doses of sulfonylurea and insulin may need to be reduced when combined with SGLT2 inhibitors to reduce risk for hypoglycemia. In combination with insulin, SGLT2 inhibitors can reduce the need to escalate insulin dosing and attenuate some of the weight gain (3). The higher cost of SGLT2 inhibitors may be prohibitive for wide-scale use. Ultimately, in the growing pool of diabetes treatment options, SGLT2 inhibitors may provide clinicians an additional choice in this era of individualizing care for patients.

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References

1. **Kasichayanula S, Liu X, Pe Benito M, et al.** Br J Clin Pharmacol. 2013;76:432-44.
2. **Cefalu WT, Leiter LA, Yoon KH, et al.** Lancet. 2013;382:941-50.
3. **Wilding JP, Woo V, Soler NG, et al; Dapagliflozin 006 Study Group.** Ann Intern Med. 2012;156:405-15.