Sodium-glucose cotransporter 2 inhibitors for Type 2 diabetes: a systematic review and meta-analysis

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CRD summary
This well-conducted review concluded that sodium-glucose cotransporter 2 inhibitors may improve some short-term outcomes in adults with type 2 diabetes, but the effects on long-term outcomes and safety were unclear. These cautious conclusions reflect the limitations of the evidence identified and are likely to be reliable.

Authors' objectives
To assess the efficacy and safety of sodium-glucose cotransporter 2 inhibitors in adults with type 2 diabetes.

Searching
MEDLINE, EMBASE, and The Cochrane Library databases were searched up to April 2013 with no language restrictions. Search strategies were reported in a separate online appendix. Relevant regulatory authorities’ reports and conference abstracts, web sites of pharmaceutical companies, trial registries and reference lists of relevant studies were also searched.

Study selection
Randomised controlled trials (RCTs) that compared a sodium-glucose cotransporter 2 inhibitor versus placebo or another anti-diabetic medication in adults with type 2 diabetes were eligible for inclusion. The primary efficacy outcome was change from baseline in glycated haemoglobin (HbA1c) level. Secondary efficacy outcomes included changes in body weight, systolic and diastolic blood pressures, all-cause mortality, and cardiovascular events (myocardial infarction, stroke, death due to cardiovascular disease or hospitalisation for unstable angina). The harmful outcomes included incidence of any hypoglycaemia, urinary tract infections, genital tract infections, hypotension, bladder cancer, breast cancer, or any serious adverse event.

The included trials evaluated a range of sodium-glucose cotransporter 2 inhibitors, including dapagliflozin, canagliflozin, ipragliflozin, empagliflozin, luseogliflozin, tofogliflozin, ertugliflozin and remogliflozin. Most trials used placebo as controls; the rest used an active comparator (metformin, sitagliptin or sulfonylurea) as monotherapy or add-on treatment. The duration of the intervention ranged from 12 days to 104 weeks. Mean glycated haemoglobin level at baseline ranged from 6.9% to 9.2% (where reported). All but one of the trials excluded patients with severe renal impairment.

Two reviewers independently assessed studies for inclusion, with any disagreements resolved by consensus with a third reviewer.

Assessment of study quality
The quality of included trials was assessed using the Cochrane Collaboration risk of bias tool. The criteria included randomisation sequence generation, allocation concealment, blinding, selective outcome reporting, incomplete outcome reporting and other bias (sponsor bias). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the strength of evidence.

Quality assessment was performed independently by two reviewers, with any disagreements resolved by consensus.

Data extraction
For continuous outcomes, data were extracted on mean and standard deviation to calculate mean differences and 95% confidence intervals. For dichotomous variables, data were extracted on event rates to enable the calculation of odds ratios with 95% confidence intervals. Intention-to-treat data were extracted where possible. Additional data were requested where necessary.

Data extraction was performed independently by two reviewers and checked by one reviewer.
**Methods of synthesis**
The analysis of efficacy outcomes was restricted to trials with at least 12 weeks’ duration. A random-effects model was used to calculate weighted mean differences and 95% confidence intervals for continuous outcomes. A fixed-effect Mantel-Haenszel model was used to calculate the pooled odds ratios with 95% confidence intervals for dichotomous outcomes (with continuity correction for zero events). Statistical heterogeneity was assessed using I².

Sensitivity analyses were performed by incorporating unpublished data. Subgroup analyses were performed by different types of comparator treatment.

Publication bias was assessed using Egger's test.

**Results of the review**
Forty-nine RCTs and nine extension trials were included in the review. Forty-five trials (11,232 participants) compared sodium-glucose cotransporter 2 inhibitors with placebo and 13 trials (5,175 participants) compared sodium-glucose cotransporter 2 inhibitors with active comparators. The sample size ranged from 18 to 1,237 participants. Most trials had high overall risk of bias, mainly due to high discontinuation rate or use of inadequate imputation method to deal with missing data. All but three of the trials had a double-blind design. Fourteen studies had a high attrition rate (>20%) or unbalanced rate between treatment groups (where reported). Almost all trials were sponsored by pharmaceutical companies. Nine trials had an unclear overall risk of bias. The quality of evidence was rated as low for the primary outcome, and low or moderate for the remaining outcomes.

Sodium-glucose cotransporter 2 inhibitors were associated with a significant reduction in glycated haemoglobin level compared with placebo (WMD -0.66%, 95% CI -0.73 to -0.58; I²=77%; 26 trials), but there was a non-significant reduction in glycated haemoglobin level when compared with active comparators (WMD -0.06%, 95% CI -0.18% to 0.05%; I²=71%, nine trials). Sensitivity analyses by incorporating unpublished data showed similar effect estimates.

Compared with active comparators, sodium-glucose cotransporter 2 inhibitors were associated with a significant reduction in body weight (WMD -1.80kg, 95% CI -3.5 to -0.11; I²=97%; five trials) and systolic blood pressure (WMD -4.45mmHg, 95% CI -5.73 to -3.18; I²=34%; six trials).

Compared with active comparators, sodium-glucose cotransporter 2 inhibitors were significantly associated with a higher rate of urinary tract infections (OR 1.42, 95% CI 1.06 to 1.90; I²=25%, eight trials) and genital tract infection (OR 5.06, 95% CI 3.44 to 7.45; I²=0%; eight trials). The results for cardiovascular outcomes and death were inconclusive. An imbalance in incidence of bladder and breast cancer was found in trials that compared dapagliflozin with controls.

**Authors’ conclusions**
Sodium-glucose cotransporter 2 inhibitors may improve some short-term outcomes in adults with type 2 diabetes, but the effects on long-term outcomes and safety were unclear.

**CRD commentary**
The review question was clear and supported by appropriate inclusion criteria. A range of relevant databases was searched. Efforts were made to find both published and unpublished studies, which minimised the potential for publication bias. No language restriction was applied to the search, which minimised the risk of language bias. Sufficient attempts were made to minimise errors and biases during the review process.

Appropriate criteria were used assess trial quality, indicating that most trials had high overall risk of bias. Statistical heterogeneity was assessed and appropriate methods were used to pool the results. However, the value of some pooled results may have been compromised by the high level of heterogeneity.

Overall, the authors’ conclusions reflect the limitations of the evidence identified, and are likely to be reliable.

**Implications of the review for practice and research**
Practice: The authors did not state any implication for practice.

Research: The authors stated that further research should investigate differences among individual sodium-glucose...
cotransporter 2 inhibitors and differences between sodium-glucose cotransporter 2 inhibitors and other antidiabetic agents. Further research was also required to clarify their effects on long-term clinical outcomes, diabetic complications, and safety.

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