TREATMENT AREA: Hyperglycemia, type 2 diabetes

BACKGROUND AND PURPOSE: Agents in the sodium-glucose co-transporter 2 (SGLT2) class are an alternative to DPP-4 inhibitors like sitagliptin (SIT) as add-on therapy when first-line metformin no longer brings patients to goal.4-7 Figure 1 presents indirect comparisons of SGLT2s vs. SIT in this context. How do SGLT2s vs. SIT differ in terms of body weight, body composition, and glucose outcomes, compared to metformin?8

APPROACH: Systematic review and meta-analysis of randomized controlled trials (RCTs) in T2D patients to 9-30 months duration, across studies for canagliflozin (CANA), dapagliflozin (DAPA) and empagliflozin (EMPA) as add-on therapy to metformin (MET). All included studies compared outcomes for add-on therapy to outcomes for a MET+ placebo control. We provided indirect adjusted comparisons of outcomes for SGLT2s vs. MET to SIT vs. MET.

METHODS

SYSTEMATIC REVIEW: We searched the Cochrane Central Register and MEDLINE via Pubmed, using a sensitive search algorithm for RCTs.8 Figure 1 depicts the search and selection process for SGLT2s. To search for SIT studies yielding 964 results. A similar process retained 7 trials that met inclusion criteria, out of 520 de-duplicated records.

CRITERIA: Included trials were phase 2b or 3 RCTs in a single-blind or parallel-group design, a sodium-glucose co-transporter 2 (SGLT2) inhibitor vs. placebo and/or standard of care. T2D patients no longer well controlled on MET monotherapy. All studies had a MET+ placebo (PBO) control. Trials included in the analysis were those with available body weight and body composition data at baseline and at least 1 year follow-up. Trials in which patients were switched from one arm to another were not included.

META-ANALYSIS: Main steps were to:

1. Pool mean and standard deviations for three interventions: FDA-approved "low" and "high" dose SGLT2 and SIT 100 mg, plus the active (MET + PBO) control.
2. Obtain (inverse-variance-weighted) pooled mean change in outcome from baseline for patients receiving SGLT2 or SIT add-on. No difference between MET+ placebo and SIT vs. MET in indirect comparisons, using random-effects models.4, 9
3. Use the pooled, adjusted estimates to gauge whether SGLT2 vs. MET therapy yielded a larger or smaller beneficial or harmful outcome, relative to baseline (PBO) compared to SIT vs. MET. The same control data were used to estimate effects of SGLT2low and SGLT2high.

RESULTS

Table 1 presents study characteristics for SGLT2 trials.

Objectives

- Investigate associaion of SGLT2 therapy with HbA1c, body weight, body composition, and glucose outcomes.
- Identify if SGLT2 vs. MET vs. SIT differ from metformin in terms of body weight, body composition, and glucose outcomes.

RESULTS (cont’d)

Table 2 presents indirect comparisons of SGLT2s vs. MET to SIT vs. MET. Figures 3 and 4 show adjusted indirect comparisons of outcomes. Body weight data were available in all 4 SGLT2s and four of five MET trials. SBP data were available in all SGLT2s and three out of seven SIT trials reported SBP data for SIT+ MET trials were too sparse for bias assessment or to allow indirect comparison.

Indirect comparisons of HbA1c, body weight, and SBP were not statistically significant in all comparisons. There was a 1.7 to 2.1 kg weight loss among patients in the SGLT2 conditions (12-26 weeks), compared to 0 kg weight gain with SIT (2-46 kg, p = 0.0001, 0 kg).

DISCUSSION

Indirect comparisons show that patients on SGLT2s add-on therapy had a clinically meaningful difference. Excess blood glucose is associated with increased cardiovascular risk, typically doubled in T2D.10-12 Overall weight is associated with a diagnosis of T2D.13 A recent two-year long RCT in 7020 T2D patients with known CV disease found EMPA monotherapy vs. placebo was associated with a 38% lower risk of CV death, 32% lower all-cause mortality and 35% fewer heart failures compared to placebo.14 Lower CV risk is thought to be linked to more than reduced weight and BP however, because of its rapid onset during the trial.14-15 Trials to assess long-term CV outcomes with other SGLT2s are currently underway. The results of these studies, expected in 2017 and 2019, will help clarify whether CV protection is a class effect.16-19

CONCLUSIONS

- Indirect comparisons showed parity between the SGLT2s vs. SIT and SGLT2s vs. MET add-on studies. There was a nearly 3% difference in impact on body weight in favor of the SGLT2s – a small but potentially clinically meaningful difference.

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REFERENCES


OTHER CONSIDERATIONS

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