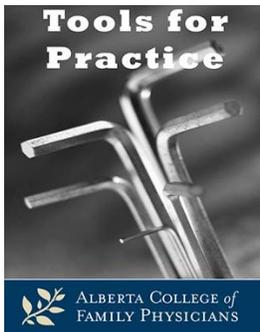


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## **SGLT2 Inhibitors and Diabetics: Does sugar in the pee protect thee?**

**Clinical Question: In patients with type 2 diabetes, do sodium-glucose co-transporter 2 (SGLT2) inhibitors affect mortality or cardiovascular disease (CVD)?**

**Bottom-line: In diabetic patients at high-risk for CVD, empagliflozin reduces mortality for 1 in 39 patients at ~3 years (compared to placebo), while canagliflozin and empagliflozin both reduce CVD death, non-fatal myocardial infarction (MI), and stroke for ~1 in 60 patients. Both medications increased genital infections for ~1 in 6-22 and canagliflozin increased volume depletion (1 in 14-38) and amputations (1 in 96). Cost may limit use.**

### **Evidence:**

- Two placebo-controlled, industry-funded, Randomized Controlled Trials (RCTs) of mostly males, long-standing type 2 diabetics in their 60s with A1cs ~8.<sup>1,2</sup> Patients with GFR <30 ml/min were excluded.
  - Empagliflozin 10 mg or 25 mg daily:<sup>1</sup> 7,020 patients with CVD mostly also on metformin, anti-hypertensives, statins, and ASA. At 3.1 years, empagliflozin significantly effected:
    - CVD death, non-fatal MI, or stroke: 10.5% (empagliflozin) versus 12.1% (placebo), Number Needed to Treat (NNT)=63.
    - Mortality: 5.7% versus 8.3%, NNT=39.
    - Genital infections: 6.4% versus 1.8% (placebo), Number Needed to Harm (NNH)=22.
    - No increase in fractures or volume depletion.
    - Meta-analysis (57 RCTs, six regulatory submissions) had similar findings.<sup>3</sup>
  - Canagliflozin 100 mg or 300 mg daily:<sup>2</sup> 10,142 patients from two different studies (with different enrollment and study lengths), with either CVD or ≥2 CVD risk factors. Concomitant medications unknown. Statistically significant outcomes from combined studies over 3.6 years, except where indicated:
    - CVD death, non-fatal MI, or stroke: 2.7% (canagliflozin) versus 3.2% per year; NNT~61 over 3.6 years.
    - Mortality: 1.7% (canagliflozin) versus 2% per year (approaches statistical significance).
    - Genital infections: NNH=6 (female) to 12 (male).

- 'Volume depletion' (dry mouth/polydipsia to orthostatic hypotension/syncope): NNH=14-38.
- Amputation: NNH=96.
- Fractures: NNH=286.
- Neither RCT demonstrated significant increase in urinary tract infection, acute kidney injury, hypoglycemia, or diabetic ketoacidosis.

**Context:**

- ~50% of diabetics die from CVD.<sup>4</sup>
- Both medications lower systolic blood pressure ~3-4 mmHg, A1c ~0.5%, and weight ~2kg.<sup>1,2</sup>
- CADTH recommends empagliflozin (after Metformin) for diabetics with CVD.<sup>5</sup>
- Post marketing warnings: Acute kidney injury with canagliflozin or dapagliflozin<sup>6</sup> and fractures<sup>7</sup> and amputations<sup>8</sup> with canagliflozin.
- Cost ~\$90 per month.<sup>9</sup>

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Authors do not have any conflicts of interest to declare.

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