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SGLT2 Inhibitors - Cardiac & Renal Outcomes Key Pearls

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We know that, in Canada, diabetes continues to confer a 2 to 5-fold increase in the risk of heart failure and remains the leading cause of kidney disease. Cardiovascular disease continues to be the leading cause of death in type 2 diabetes (T2D). There is therefore an ongoing need for therapies that reduce the cardiorenal burden of type 2 diabetes. Three SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin) have been available in Canada since 2014-2015. These agents reduce the reabsorption of glucose in the proximal renal tubule, resulting in increased glycosuria, with the resulting osmotic diuresis and associated natriuresis. Phase 3 trials have already demonstrated A1C reductions of 0.5 to 1.3% with only rare hypoglycemia, weight loss of 2 to 3 kg, and systolic BP reductions of 3 to 5 mmHg. Head-to-head studies have shown similar or better A1C lowering than sulfonylureas and DPP-4 inhibitors with the added benefit of weight loss and rare hypoglycemia. In addition to these benefits, the results seen in recent CV outcome trials with empagliflozin and with canagliflozin even further increase their potential impact for clinical practice due to their positive cardiorenal results.

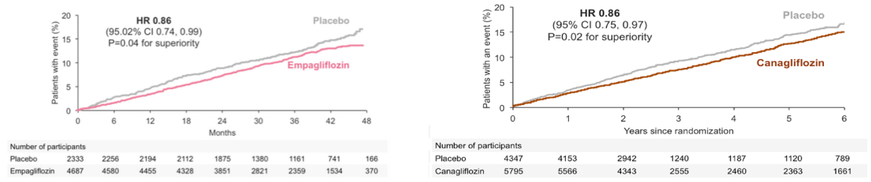
EMPA-REG OUTCOME

The EMPAgliflozin Removal of Excess of Glucose OUTCOME trial (EMPA-REG OUTCOME) trial randomized 7020 patients with type 2 diabetes and clinical cardiovascular disease (CVD) to empagliflozin or placebo on top of standard care. The primary outcome of major adverse cardiovascular events (MACE), a composite of cardiovascular death, nonfatal MI or nonfatal stroke, was reduced in the empagliflozin group compared to the placebo group (10.5% vs.12.1%; hazard ratio [HR], 0.86; p=0.04 for superiority) (*Figure 1*). The reduction in the primary endpoint was driven mainly by a 38% relative risk reduction (p<0.001) in cardiovascular death. Empagliflozin therapy was also associated with a 35% relative risk reduction (p=0.002) of hospitalization for heart failure (*Figure 2*) and a 32% relative risk reduction (p<0.001) of total mortality. Further, new or worsening nephropathy was reduced by 39%. Each component of the nephropathy composite endpoint showed significant reductions - including new macroalbuminuria, doubling of serum creatinine, and initiation of kidney replacement therapy (*Figure 3*). There was a similar renal benefit in the subgroup with prevalent kidney disease at baseline (eGFR <60 mL/min/1.73m2 and/or macroalbuminuria). Empagliflozin treated patients showed remarkable stability of GFR after an initial decline observed at one month (vs. a progressive decline seen in the placebo arm).

In the study, there were modest metabolic benefits that likely do not account for the cardio-

FIGURE 1

Primary Composite Endpoint – CV Death, Non-fatal MI, or Non-fatal Stroke

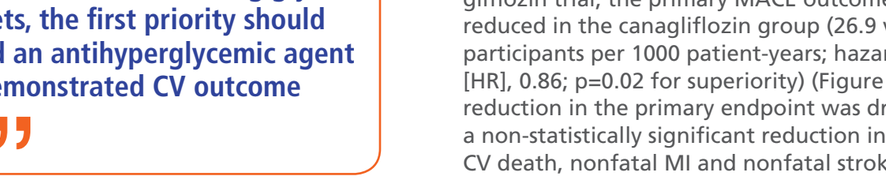


Number of participants									
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370

Number of participants							
Placebo	4347	4153	2942	1240	1187	1120	789
Canagliflozin	5795	5566	4343	2555	2460	2363	1661

FIGURE 2

Hospitalization for Heart Failure



Number of participants									
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395

Number of participants							
Placebo	4347	4198	3011	1274	1236	1180	829
Canagliflozin	5795	5653	4437	2643	2572	2498	1782

renal benefits. The reduction in heart failure and CV death is likely driven by a hemodynamic effect, with reduction in cardiac preload and afterload. The renal benefit may be at least partially explained by the particular effect of the osmotic diuresis on "tubuloglomerular feedback", restoring the physiologic ability to constrict the afferent (incoming) arteriole and therefore, reduce glomerular pressure, improving their survival. Overall, empagliflozin was well tolerated, although genital infections occurred at a higher rate in patients treated with empagliflozin. In summary, EMPA-REG OUTCOME demonstrated a positive benefit of empagliflozin therapy on MACE, CV death, heart failure and nephropathy in patients with T2D and clinical CVD.

> **"Diabetes Canada updated their recommended pharmacotherapy algorithm for the management of T2D, suggesting that in patients with clinical CVD who are not achieving glycemic targets, the first priority should be to add an antihyperglycemic agent with a demonstrated CV outcome benefit."**

In 2016, following the results of EMPA-REG OUTCOME and the LEADER study (using liraglutide), Diabetes Canada updated their recommended pharmacotherapy algorithm for the management of T2D, suggesting that in patients with clinical CVD who are not achieving glycemic targets, the first priority should be to add an antihyperglycemic agent with a demonstrated CV outcome benefit.

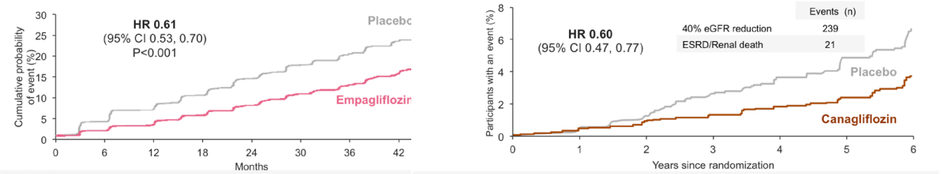
CANVAS Program

The CANagliflozin cardioVascular Assessment Study (CANVAS) program randomized 10,142 patients with type 2 diabetes to canagliflozin or placebo, on top of their usual care. Two thirds of the group had established CV disease, as in EMPA-REG OUTCOME, but one third only had risk factors for developing CV disease. Similar to the empagliflozin trial, the primary MACE outcome was reduced in the canagliflozin group (26.9 vs. 31.5 participants per 1000 patient-years; hazard ratio [HR], 0.86; p=0.02 for superiority) (Figure 1). The reduction in the primary endpoint was driven by a non-statistically significant reduction in each of CV death, nonfatal MI and nonfatal stroke. Canagliflozin therapy was also associated with a 33% relative risk reduction of the exploratory outcome of hospitalization for heart failure (Figure 2). Renal benefits were also seen with canagliflozin, seen in a 27% lower incidence of albuminuria progression and a 70% greater rate of albuminuria regression. Furthermore, the hard renal outcome (either sustained (40%) reduction in eGFR, need for renal-replacement therapy, or death from renal causes) was reduced by 40% in the canagliflozin arm (Figure 3). Adverse effects of canagliflozin included an increase in genital mycotic infections, osmotic and volume related adverse effects, fractures and lower extremity amputations. Although the hazard ratio for amputations was 1.97, the absolute increase in risk was 0.29% per year, with the greatest risk increase occurring in the 2.3% of patients who already had a prior amputation at baseline (absolute risk increase of 3.7% per year). 71% of all amputations were minor (toes or metatarsals) and 29% were major (ankle or above). Weighing the potential advantages vs disadvantages is best done by looking at the number needed to treat over 5 years for each outcome (*Figure 4*). For example, to prevent one patient having a MACE, heart failure or major renal outcome, 44-63 would need to be treated for 5 years. On the other hand, for amputation, 96 people would need to be treated to cause a minor amputation and 223 would need to be treated to cause a major amputation, over 5 years. It would appear that the cardiorenal benefits generally outweigh the lower risk of amputation.

> **"The CANVAS and the EMPA-REG OUTCOME trials suggest a cardiorenal benefit with canagliflozin and empagliflozin in high-risk T2D patients."**

FIGURE 3

Major Renal Outcomes

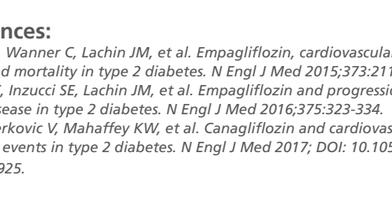


Number of participants								
Placebo	2061	1946	1836	1703	1433	1016	833	521
Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219

Number of participants							
Placebo	4347	4227	3029	1274	1229	1173	819
Canagliflozin	5795	5664	4454	2654	2576	2495	1781

FIGURE 4

CANVAS Program: Benefits on Cardiorenal Outcomes (NNT5Y) vs Risk of Minor or Major Amputations (NNH5y)



Summary

The CANVAS and the EMPA-REG OUTCOME trials suggest a cardiorenal benefit with canagliflozin and empagliflozin in high-risk T2D patients. Since there is an ongoing cardiorenal burden in patients with T2D, these agents should be considered when adding-on antihyperglycemic agents for not only the benefit on A1C with rare hypoglycemia, weight loss, and BP reduction, but also for the benefit on MACE outcomes, hospitalization for heart failure and renal outcomes. While currently not indicated for initiation in patients with eGFR < 60 ml/min, EMPA-REG OUTCOME and CANVAS did consistently show a cardiorenal benefit in those with GFR between 30-59 ml/min. Ongoing studies with SGLT2 inhibitors will help determine the impact of these agents in patients with heart failure and with established renal disease in people both with, and without, T2D.

References:

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Wanner C, Inzucci SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323-334.
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I'M SICK.
what should I do differently for my Diabetes today?

Blood glucose can be difficult for patients to manage on even the best of days. A further layer of difficulty is added when the body is fighting an illness. To optimize recovery, as well as potentially avoid a trip to an Emergency Department, provide these simple but effective steps:

1 Some diabetes medications must be continued; others must be held

To optimize recovery, reasonable glycemia needs to be maintained, so most diabetes medications should be continued through illness and, in some cases, insulin may even need to be temporarily increased. Explain to patients they may experience higher blood glucose (BG) values when they are sick, as the hormones that are part of our physiological response to illness (cortisol and catecholamines) can also cause BG to rise and insulin to be less effective.

Some medications, however, must be held during illnesses that may cause volume depletion and the possibility of kidney function decline. Eg - if a patient is at risk of dehydration from vomiting and/or diarrhea, they must temporarily discontinue medications that are renally cleared, in order to avoid any possible toxicity.

An effective way to help remember which medications must be held is by using the following acronym:

- **S** Sulfonylurea
- **A** ACE-inhibitors
- **D** Diuretics, direct rennin inhibitors
- **M** Metformin
- **A** Angiotensin receptor blockers
- **N** Non-steroidal anti-inflammatory
- **S** SGLT2 inhibitors

2 Increased frequency of self blood glucose monitoring

At least 3-4 blood glucose tests per day is necessary to help prevent hypo and hyperglycemia.

3 Choose easy-to-digest carbohydrates

Carbohydrates provide the body with energy it needs to fight off infection or illness. Some easy to digest examples include:

- *½ cup unsweetened applesauce*
- *1 piece of toast*
- *½ cup of Glucerna*
- *½ a banana*
- *7 crackers*
- *½ cup jello*
- *½ cup hot cereal*

Note: these portions are equal to approximately 15 grams of carbohydrates

4 Stay hydrated

Aim to drink at least 1 cup of sugar-free, caffeine-free fluids every hour. Water or clear broth are excellent options.

5 Know when to seek help

In the following situations, consider sending your patient to hospital:

- Illness lasting >3 days
- unable to take medication or insulin
- cannot keep food / fluids down
- Severe or frequent vomiting or diarrhea

Patients with type 1 diabetes should check their ketones daily while fighting illness. If ketones > 3, patients should go directly to their local ED. Clinical signs of progressing ketosis include nausea and/or vomiting, abdominal pain, difficulty breathing, drowsiness and excessive thirst.

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