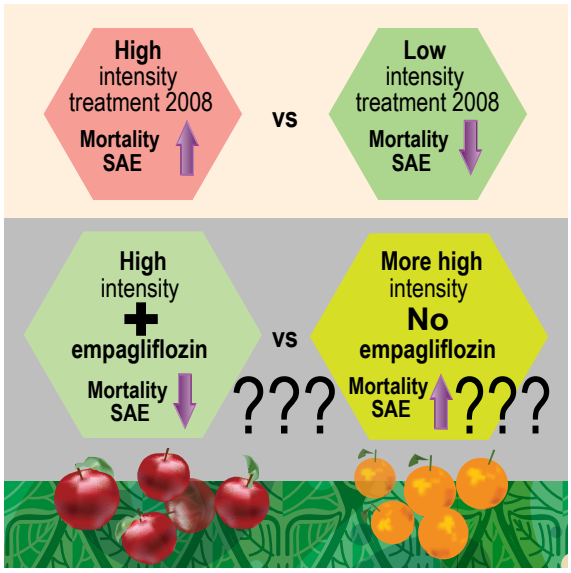
THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

EMPA-REG OUTCOME Trial What does it mean?

Empagliflozin (Jardiance) inhibits the sodium-glucose co-transporter 2 (SGLT2), which is the predominant mechanism responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. By inhibiting SGLT2, empagliflozin increases urinary glucose excretion.[1] Empagliflozin was approved by Health Canada in 2015 to improve glycemic control in adult patients with type 2 diabetes (T2DM).[2] In 2016, Health Canada and the U.S. Food and Drug Administration (FDA) approved an additional claim that empagliflozin reduces the incidence of cardiovascular death in patients with T2DM who have established cardiovascular disease. This was based on the results of a single trial, EMPA-REG OUTCOME, which was conducted as a requirement by the FDA to rule out a 30% (relative) increase in cardiovascular events by empagliflozin.[3,4]

The EMPA-REG OUTCOME Trial tested adding empagliflozin to 'standard of care'

In this trial, 7028 T2DM patients with established cardiovascular disease were randomized to 1 of 3 arms: empagliflozin 10 mg or empagliflozin 25 mg or placebo and were followed for a median of 3.1 years.[3] Participants were eligible if their glycated haemoglobin (HbA1c) was 7.0% to 10.0% (mean 8.1%). Other parameters: mean age 63, 72% white, 72% male, mean BMI 31 kg/m^2, 95% taking antihypertensives, 81% taking lipid-lowering drugs, and 83% taking antiplatelet medications. Most had a diagnosis of T2DM for >5 years, more than half had a diagnosis for >10 years. At baseline 98% of participants were receiving other glucose-lowering medications; 68% were receiving 2 or more. Metformin, insulin and sulfonylureas were prescribed to 74%, 48%, and 43% of participants, respectively. The net health effect of the various glucose-lowering drugs and drug combinations prescribed to participants at baseline and throughout the trial is not known.[5]



The results using our usual outcome hierarchy are shown in Table 1. The 2 empagliflozin arms have been combined; the outcomes were similar for the 2 doses.

If this trial had been conducted in a way that empagliflozin was the only difference between the groups, these results would suggest that empagliflozin causes a net health benefit in people with T2DM and a history of cardiovascular disease. Unfortunately, empagliflozin was not the only difference between the groups. During the trial, HbA1c was not blinded and investigators could escalate medications in an effort to achieve a glucose target ≤6.5-7.0% in accordance with aggressive 'standards of care'. As a result, other glucose-lowering medications were added more frequently and at higher doses in the placebo group[3,7] (see Table 2).

Interpretation

There are thus at least 3 possible interpretations of the EMPA-REG OUTCOME Trial:

1. Empagliflozin decreases mortality and serious adverse events when added to 'standard of care'.
2. The more aggressive use of other glucose-lowering medications in the placebo group increases mortality and serious adverse events.
3. A combination of 1 and 2.

Table 1: The EMPA-REG OUTCOME Trial Outcomes[3,6]

Outcome	Placebo N=2333	Empagliflozin N=4687	RR [95%CI]	ARR %
Death from any cause (ITT)	8.3%	5.7%	0.69 [0.57, 0.82]	2.6
Death from any cause (On treatment)	4.7%	3.4%	0.72 [0.57, 0.92]	1.3
Total serious adverse events (On treatment)	42.3%	38.2%	0.90 [0.85, 0.96]	4.1
Total CV serious adverse events (ITT)	12.1%	10.5%	0.86 [0.75, 0.99]	1.6

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Table 2: The EMPA-REG OUTCOME Trial
Medication changes after randomization[3]

Participants with additional:	Placebo	Empagli-flozin
Glucose-lowering medications added in concordance with an escalated 'standard of care'	31.5%	19.5%
Insulin	11.5%	5.8%
Dipeptidyl peptidase 4-inhibitor	8.3%	5.6%
Sulfonylurea	7.0%	3.8%
Thiazolidinedione	2.9%	1.2%

After a detailed examination of the published trial[3], the U.S. FDA review[7], the European Medicines Agency (EMA) review[8], and the German Institute for Quality and Efficiency in Health Care (IQWiG) review[9], we are not confident in explanation #1. In support of explanation #2 there are 2 RCTs that have shown that more intensive therapy in T2DM increases total mortality and cardiovascular mortality.[10,11] Whether these findings are attributable to the pursuit of an intensive HbA1c target or to the use of any specific drug or drug-combination remains uncertain.

We are not alone in not accepting the results of this trial. **In June 2016, a 23-member FDA advisory committee voted on whether, based on this single trial, the company could claim that empagliflozin reduces cardiovascular mortality. The vote was 12 for and 11 against.[12,13]**

Did empagliflozin cause harm?

Harms were increased in those taking empagliflozin in the EMPA-REG OUTCOME Trial (Table 3). The increase in genital infections in both men and women means that during a 3 year time period, 1 in 29 men and 1 in 14 women will have their quality of life adversely affected by a genital infection.

Other reasons for scepticism

The FDA review of the EMPA-REG OUTCOME Trial rejected the manufacturer's claim that empagliflozin reduces the risk of heart failure and nephropathy.[7] In addition, analyses of outcomes by geography identified unexplained regional differences: the magnitude of effect of empagliflozin on mortality was less in North America and Europe compared to Latin America and Asia.[6] Another independent drug bulletin has critically appraised this trial and identified these and many other concerns.[14] It should also be clear that this trial tells us nothing about the use of empagliflozin in other T2DM clinical settings.

Conclusions

- The EMPA-REG OUTCOME Trial tested the addition of empagliflozin to a 'standard of care' for T2DM whose impact on clinically important outcomes is currently unknown.
- **It is uncertain whether the reduction in mortality and serious adverse events in the EMPA-REG OUTCOME Trial is attributable to empagliflozin or to less use of other glucose-lowering therapies.**
- The results of this trial are not applicable to people with T2DM in other clinical settings.
- **Until there is a body of evidence informed by large, independently conducted comparative effectiveness trials of different therapeutic strategies, we will not know the optimal treatment of T2DM at various stages of the diagnosis.**

Table 3: The EMPA-REG OUTCOME Trial Harms[3]

Outcome	Placebo N=2333	Empagli-flozin N=4687	RR [95%CI]	ARI %
Urosepsis	0.1%	0.4%	2.83 [0.83, 9.66]	0.3
Genital infection (women)	2.6%	10.0%	3.84 [2.34, 6.30]	7.4
Genital infection (men)	1.5%	5.0%	3.47 [2.27, 5.30]	3.5

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For a complete list of references go to: **www.ti.ubc.ca/letter107**

The draft of this Therapeutics Letter was submitted for review to 75 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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