Cardiovascular Update

January 2019 | Volume 4, Issue 1

A newsletter from the BayCare Cardiovascular Service Line

Advances in Type 2 Diabetes Mellitus and Cardiovascular Disease

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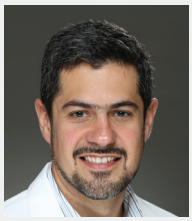

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Tight glucose control with insulin prevents microvascular complications in patients with type 2 diabetes mellitus (DM), but has not been shown to prevent macrovascular complications or improve cardiovascular mortality[1]. Some glucose lowering therapies have shown potential cardiovascular harm[2]. In 2008, the FDA published a guidance to the industry that every new drug for the management of type 2 DM had to prove cardiovascular safety in large, randomized clinical trials[3].

In this setting, two distinct drug classes have changed our understanding of cardio metabolic disease. In 2015, the EMPA-REG outcomes trial was published[4], the first trial ever to show cardiovascular mortality benefit of a drug used to treat diabetes mellitus. This was followed by the LEADER trial[5] in 2016, showing risk reduction of glucagon-like peptide-1 agonist (GLP-1) (Liraglutide) drugs in major cardiovascular adverse events (MACE) in patients with DM and either established cardiovascular disease or risk factors.

The EMPA-REG trial[4] showed a significant 14 percent relative risk reduction of MACE with the use of the sodium glucose co-transporter inhibitor (SGLT-2) Empagliflozin in patients with DM and established cardiovascular disease. It studied a high-risk population with 99 percent having established cardiovascular disease. This MACE risk reduction was mostly driven by a 38 percent relative risk reduction in cardiovascular death. It also showed a significant 35 percent relative risk reduction in hospitalization for congestive heart failure. A surprise finding considering that only about 10 percent of the patients entering the clinical trial were classified as having congestive heart failure. The EMPA-REG clinical trial was followed by other clinical trials with SGLT2 inhibitors, in different patient populations, showing similar results: the Canvas program[6] (Canagliflozin) published in 2017, and the recently published Declare trial[7](Dapagliflozin).

SGLT2 inhibitors are drugs that work mostly on the proximal renal tubule by blocking the reabsorption of sodium and glucose[8]. Diabetic patients have an upregulation of this receptor and thus develop sodium retention. Increased proximal tubule sodium reabsorption reduces distal tubule sodium delivery. This leads to afferent renal arteriole vasodilation via tubule-glomerular feedback mechanism. Afferent renal arteriole vasodilation raises intra-glomerular pressure and leads to albuminuria. Empagliflozin, by prevention proximal tubule sodium reabsorption, significantly reduced albuminuria and prevented progression of renal disease in EMPA-REG renal sub study.

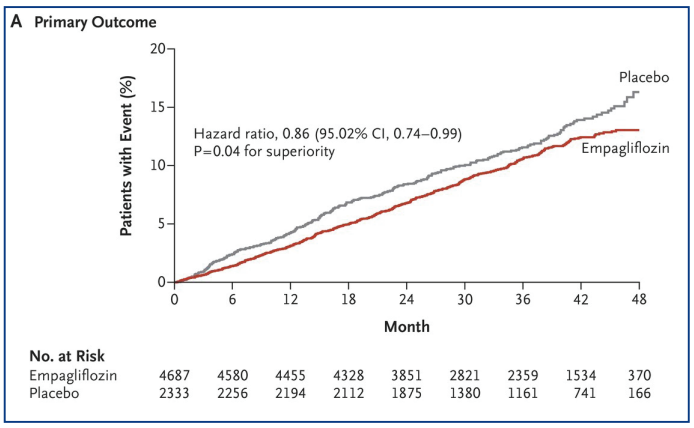
The LEADER[5] trial evaluated the effect of the GLP-1 agonist Liraglutide in patients with diabetes mellitus and high cardiovascular risk. This trial also showed a 14 percent reduction in MACE, 22 percent RRR in cardiovascular death and 15 percent reduction in all-cause death. Microvascular complications were reduced by 22 percent. These results were replicated with the SUSTAIN 6[8] clinical trial in a similar population.

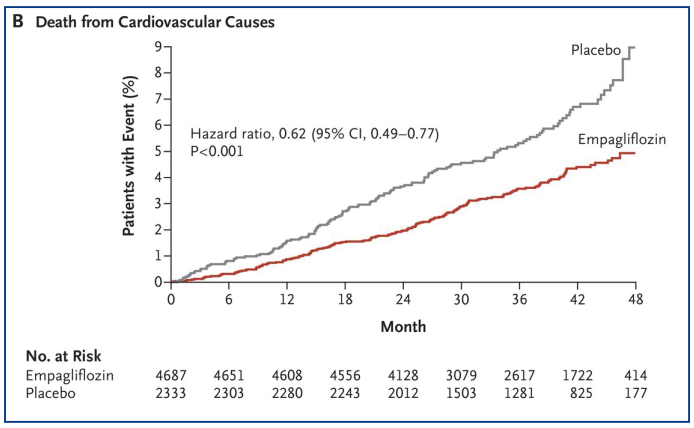
GLP-1 agonists have multiple effects[10]. In the pancreas, to increase insulin and reduce glucagon secretion, in the brain to increase satiety and in the stomach to decrease gastric emptying. It also has an effect on the vasculature. These effects combined lead to improved glucose control, weight loss and lower blood pressure. The mechanism by which GLP-1 agonists reduce cardiovascular mortality is not known.

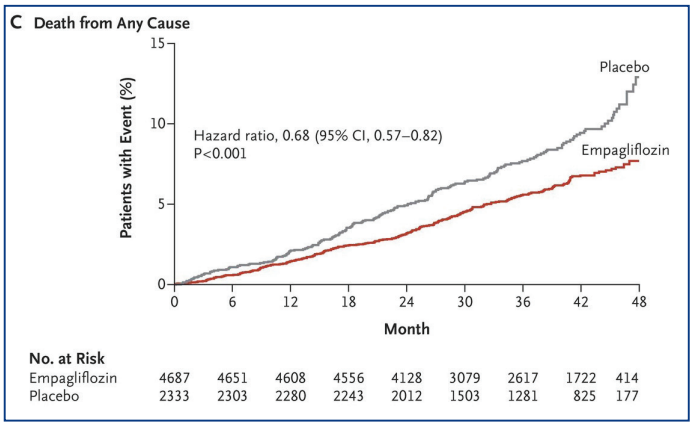
Based on these published clinical trial results, the American College of Cardiology has recently published a consensus statement on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. This consensus statement emphasizes the high risk of macrovascular events on the diabetic population and recommend the use of SGLT2 inhibitors and GLP-1 agonists individually, or in combination, in order to significantly lower this risk.

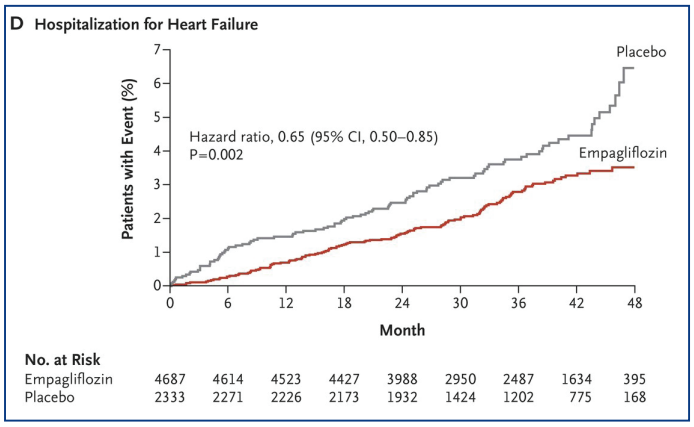
Continued on page 2

At BayCare, the SGLT2 drug Empagliflozin has been on formulary across the hospitals to be used in patients with DM and high cardiovascular risk in order to improve cardiovascular mortality and CHF risk.









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