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"DECLARE"-ing New Considerations for Cardiovascular Prevention

LMC

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DECLARE is the most recent and largest cardiovascular (CV) outcome trial to publish results, evaluating the safety of the oral hypoglycemic agent, dapagliflozin. **Dapagliflozin (Forxiga™)** is a once-daily SGLT2 inhibitor (SGLT2i) approved in Canada since 2014. For the past 2 decades, we've followed a key principle that lowering blood glucose is the main-stay for preventing complications. We now have more therapeutic options and emerging clinical trial data than ever before. The current options of antihyperglycemic agents now covers a wider range of glucose-lowering, individualized advantages and proven cardio-renal outcomes. Going forward, our accumulating evidence of cardiac and renal benefits may give us all a clearer pathway for the order of diabetes therapies.

The Context

In 2008, the FDA set out requirements that all new diabetes medications were mandated to undergo a rigorous outcome trial to prove that they are safe in high CV risk patients with type 2 diabetes. Early CV trial outcome programs with the DPP4 inhibitor class demonstrated safety overall. For the first time in 2016, the SGLT2i, **empagliflozin (Jardiance™)**, demonstrated a reduction in the primary endpoint of major adverse cardiovascular events (MACE) (CV death, nonfatal myocardial infarction and nonfatal stroke). This finding meant that empagliflozin was not only safe to use, but also beneficial in decreasing the risk of subsequent CV events for patients with established CV disease. These results were independent of its glucose lowering effect, as participants in the placebo group of CV outcome trials are all treated to the standard of care and typically end up with similar HbA1c results. **Canagliflozin (Invokana™)** was the second SGLT2i to demonstrate a similar CV benefit. GLP-1 receptor agonists, **liraglutide (Victoza™), semaglutide (Ozempic™)**, and **albiglutide** (not available in Canada), have also since each shown these same positive results. **Dulaglutide's (Trulicity™)** CV trial REWIND released its top line result recently, confirming superior primary CV outcome reduction in MACE, and intriguingly in a cohort consisting of only a minority of participants (31%) with established CV disease.

> "...not only safe to use, but also beneficial in decreasing the risk of subsequent CV events for patients with established CV disease."

From the Endocrinology & Diabetes Specialists of LMC Diabetes & Endocrinology. The opinions expressed in this paper are those of the authors and do not necessarily reflect the opinions of LMC Diabetes & Endocrinology or the editorial board of Clinical Practice Update.

DECLARE trial

Most recently, at the American Heart Association, dapagliflozin's CV outcome trial program, DECLARE, presented and simultaneously published its results. DECLARE is the largest CV outcome trial so far, enrolling over 17,000 participants with HbA1c 6.5-12% and creatinine clearance ≥ 60ml/min, and has a slightly more complicated study analysis with dual primary endpoints: MACE and CV death/hospitalization for heart failure (HHF).

MACE Outcomes

The first primary outcome of MACE was non-inferior in the dapagliflozin group compared to the placebo group (8.8% vs. 9.4%; hazard ratio (HR) 0.93; Figure 1). The components of MACE (nonfatal myocardial infarction, nonfatal stroke and CV death) were also each similar in both groups. These results confirmed safety overall, but amongst participants with established CV disease, MACE was not statistically significantly reduced compared to placebo (HR 0.90), which differs from the prior 2 published SGLT2i CV outcome trials.

CV Death HHF Outcomes

The other primary outcome of CV death/HHF was significantly reduced in the dapagliflozin group compared to the placebo group (4.9% vs. 5.8%; HR 0.83; Figure 1). CV death/HHF reductions were superior for both the entire cohort and the sub-cohort of participants with established CV disease (HR 0.83). Interestingly, even though the participants with only CV risk factors just missed statistical significance for superiority (HR 0.84), the point estimate hazard ratios for CV death/HHF were remarkably similar for the entire cohort, sub-cohort of participants with established CV disease, and sub-cohort of participants with only CV risk factors. The reduction in the composite primary endpoint was driven primarily by a 27% relative risk reduction in HHF, and significant benefits were observed for the entire cohort, the sub-cohort of participants with established CV disease, and even in the sub-cohort participants with only CV risk factors. These findings strongly support both primary and secondary prevention of HHF with dapagliflozin, applicable to a broader population of patients. It should be noted that since both primary endpoints did not reach statistical significance for superiority, secondary endpoint analyses for DECLARE are considered exploratory and hypothesis generating.

> "These findings strongly support both primary and secondary prevention of HHF with dapagliflozin, applicable to a broader population of patients."

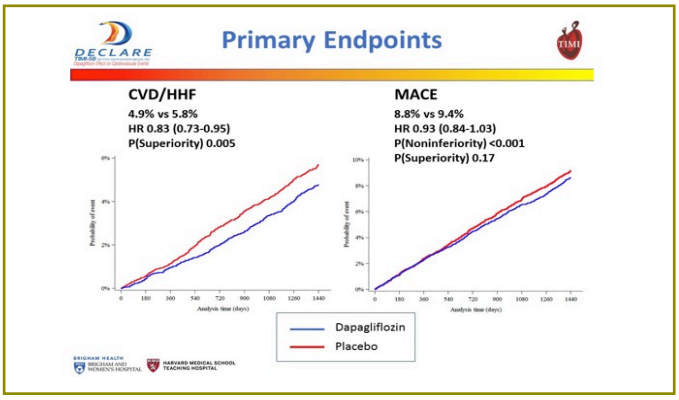

Figure 1 – DECLARE Results: Primary Outcomes

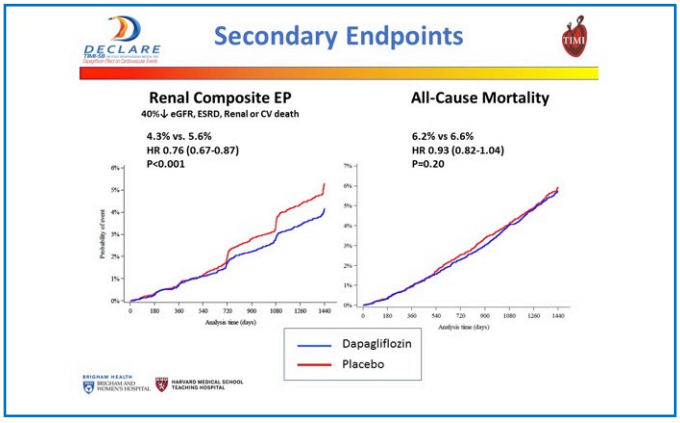

Figure 2 – DECLARE Results: Secondary Endpoints

Renal Outcomes

As seen in other SGLT2i CV outcome trials, the renal composite (≥40% decrease in eGFR, new end-stage renal disease, or death from a renal or cardiovascular cause) endpoint was significantly reduced by 24% in the dapagliflozin group compared to the placebo group (4.3% vs. 5.6%; Figure 2).

Key Safety Endpoints

Amongst key safety endpoints, genital infections and diabetic ketoacidosis were increased in the dapagliflozin group. Favourably, acute kidney injury was decreased in the dapagliflozin group. And reassuringly, amputations and urinary tract infections were similar in both groups (Table 1).

Key Safety Events

	Dapagliflozin (%)	Placebo (%)	Between Group Comparison
Genital Infections	0.9	0.1	p<0.001
Diabetic Ketoacidosis (DKA)	0.3	0.1	p=0.02
Acute Kidney Injury	1.5	2.0	p=0.002
Urinary infections	1.5	1.6	p=NS
Amputations	1.4	1.3	p=NS

Table 1 – DECLARE Results: Key Safety Events

SGLT2i: Are we seeing a class-effect for CV benefits?

A recent meta-analysis of the EMPA-REG outcome, CANVAS program and DECLARE trial published in the Lancet compares the magnitude of the effect of SGLT2i on specific cardiovascular and renal outcomes, and evaluates whether heterogeneity is based on key baseline characteristics. Data from 34,322 patients (60.2% with established CV disease) was collected. SGLT2i reduced major adverse cardiovascular events by 11% (HR 0.89), with these benefits only seen in patients with established CV disease (HR 0.86), and not in those with only risk factors (HR 1.00). SGLT2i also reduced the risk of CV death and HHF by 23%, with similar benefits in patients with or without established CV disease, and in those with or without a history of heart failure. SGLT2i reduced the risk of progression of renal disease by 45%. The magnitude of benefit of SGLT2i varied with baseline renal function, with greater reductions in HHF and lesser reductions in progression of renal disease in patients with more severe kidney disease at baseline.

We can conclude from these results that SGLT2i have moderate benefits on atherosclerotic MACE that seem confined to patients with established CV disease, and have robust benefits on reducing HHF and the progression of renal disease regardless of baseline CV disease.

So what will I do differently on Monday morning in my practice? With relatively recent data, there is expectedly some ongoing debate on the applicability of some of these beneficial effects for individual agents vs. classes of agents, and for specific at CV risk groups of patients.

Here's what we know and agree on: SGLT2i are safe, and effective at reducing HHF and renal outcomes. DECLARE also provided further reassurance on important safety endpoints, particularly amputations and fractures. Here's what we are still debating and hoping for answers soon: Can we still consider all SGLT2 inhibitors equally beneficial for patients with established CV disease if dapagliflozin showed non-inferior results for MACE (i.e. reduced, but not statistically

"SGLT2i have moderate benefits on atherosclerotic MACE that seem confined to patients with established CV disease, and have robust benefits on reducing HHF and the progression of renal disease regardless of baseline CV disease."

significantly, compared to placebo)? Could this be explained by examining the specific population of participants in the 3 SGLT2i CV outcome trials? Are the reductions in HHF seen in DECLARE in primary prevention patients applicable to dapagliflozin or to the entire class of SGLT2i? It will also be interesting to see how Diabetes Canada incorporates the DECLARE trial into future iterations of the clinical practice guidelines. As of now, the 2018 Diabetes Canada guidelines recommend:

"In adults with type 2 diabetes with clinical CV disease in whom glycemic targets are not achieved with existing antihyperglycemic medication(s) and with an eGFR > 30 mL/min/1.73 m2, an antihyperglycemic agent with demonstrated CV outcome benefit should be added."

Make sure to check our back page to hear the perspectives from 6 DECLARE primary investigators at LMC Diabetes & Endocrinology, responsible for enrolling about 5% of the entire cohort across 3 Canadian provinces.

REFERENCES:
1) Wiviott SD et al. "Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes." N Engl J Med (2018).
2) Zelniker TA et al. "SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials." Lancet (2018).
3) Verma S et al. "Pump, pipes, and filter: do SGLT2 inhibitors cover it all?." Lancet (2018).

DECLARE Q&A:

Perspectives from our Primary Investigators

JEAN-FRANCOIS YALE – LMC Montreal Glenn

What impact might the DECLARE results have on our clinical decisions?

"Since the FDA started requesting cardiovascular outcome trials for all new antihyperglycemic agents, we have focused primarily on evaluating MACE. DECLARE provides impactful evidence for a more frequent, often forgotten, fatal cardiovascular complication: heart failure. We will need to consider beneficial affects other than MACE (such as impact on heart failure and renal outcomes) when choosing individualized regimens of antihyperglycemic agents best suited for our patients."

HARPREET BAJAJ – LMC Brampton

What was unique about the trial design and clinical applicability?

"Two trial design characteristics set DECLARE apart from other cardiovascular outcome trials:
1. Magnitude - a total of 69,547 patient-years of follow-up in this trial provides sufficient power to test the cardiovascular efficacy and overall safety of dapagliflozin vs. placebo in a randomized fashion
2. Broad inclusion criteria: meant that DECLARE was the easiest trial to recruit in LMC's history (558 subjects randomized at 5 of our sites) – and makes the results broadly applicable to the majority of people living with type 2 diabetes who visit outpatient clinics."

RON GOLDENBERG – LMC Vaughan

What do you think is the mechanism of action in reducing the risk of hospitalization for heart failure/ CV death demonstrated in the DECLARE trial?

"Although the exact reason for heart failure reduction with SGLT2 inhibition remains unexplained, multiple mechanisms have been proposed, including natriuresis, reduction in interstitial edema, reduced preload and afterload with a reduction in LV wall stress, inhibition of cardiac sodium-hydrogen exchange and improved cardiac bioenergetics. The recent EMPA-HEART trial demonstrated a reduction in LV mass with SGLT2 inhibition, an important mechanistic study that suggests that LV remodelling may contribute to the reduction in heart failure/CV death in SGLT2i trials."

BUKI AJALA – LMC Calgary

How do you think the DECLARE results impact the management of primary and secondary prevention patients?

''The fact that there is now a medication shown to reduce major adverse cardiovascular events in people with diabetes without established CVD, and despite fairly good baseline glycemic control is truly impressive".

DAVID TWUM BARIMA – LMC Oakville

What are your perspectives on the DECLARE trial establishing the CV benefits of SGLT2 inhibitors as a "class-effect"?

"1. The DECLARE trial, taken in conjunction with the two previous trials (EMPA-REG, CANVAS), confirms CV safety for SGLT2i as a class for patients with type 2 diabetes with or without prior cardiovascular disease. DECLARE, with its large cohort of primary prevention patients, demonstrated a significant protective effect against heart failure, which is a major source of morbidity in patients with type 2 diabetes.
2. The Lancet meta-analysis shows that SGLT2i, as a class, have the greatest and most robust effect on reducing the relative risk of HHF (both in patients with and without a history of prior HF). Their effect on MACE is more modest and appears to be confined to patients with established atherosclerotic CV disease.
3. Thus, SGLT2i do satisfy the regulatory requirement for CV safety, but also show additional CV benefits (for MACE and HHF)."

RONNIE ARONSON – LMC Mid-Toronto

How did Canada come to play such a big role in the DECLARE study?

"I'm actually very proud to look back upon LMC's first two decades in clinical research and look upon our contribution to the DECLARE study as one of our biggest achievements. Three of the top five contributing sites in the world were LMC sites and our LMC group as a whole contributed and supported 5% of the entire global DECLARE cohort. We're thrilled to be part of the Canadian group of investigators and to have the chance to play such a meaningful role in advancing our knowledge in type 2 diabetes."