VOLUME 09
ISSUE 01

CLINICAL PRACTICE UPDATE IN
ENDOCRINOLOGY & DIABETES

Key Learnings from CV trials in T2D

Harpreet Bajaj
MD, MPH, FACE

There has been a rush of CV outcome trials in patients with type 2 diabetes - five in the last 3 years (Table 1). These studies have generated a large set of data. Let's examine how these results might influence our clinical practice, individually and cumulatively.

CLINICAL PEARL #1:

CV Outcome Trials are not designed to test glycemic efficacy of a medication, nor the impact of glucose control itself on outcomes

In 2007, a meta-analysis showed potential CV harm with a then-popular anti-hyperglycemic agent (AHA) called rosiglitazone. The FDA responded by requiring all subsequent new diabetes treatments to demonstrate that they don't contribute to CV harm. The result has been a series of large outcome trials in higher CV risk populations, with follow-up of at least 2 years, and with adjudicated CV endpoints. A key point to note is that this new generation of CV trials are designed with the same A1C targets in both treatment and placebo arms. Indeed, each of the 5 recent trials has shown minimal A1C difference among the trial arms (~0.3%).

CLINICAL PEARL #2:

CV safety with incretins: DPP4i (saxagliptin, sitagliptin and alogliptin) and one GLP-1 RA (lixisenatide)

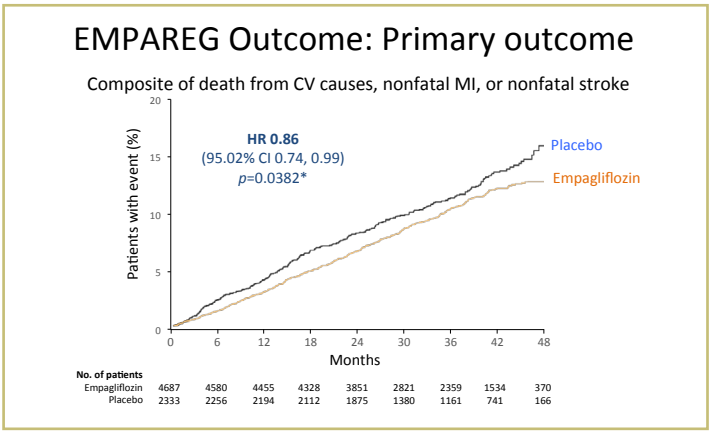
With 3 large trials showing neutrality of the primary CV outcome involving 84,703.2 patient-years of cumulative exposure. Healthcare providers and patients alike can virtually be assured of the CV safety of DPP4i (DPP4 inhibitor) sub-class of incretin therapies.

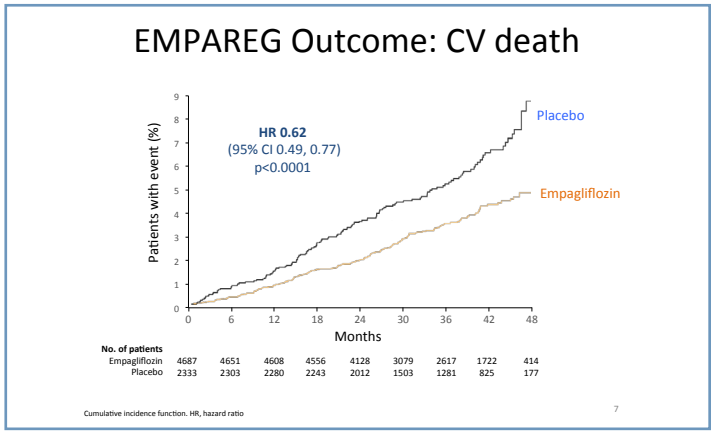
CV Outcome Trials in Diabetes

		Duration of Treatment (as part of usual care)	Patient-years of exposure
SAVOR-TIMI 53	R → Saxagliptin / Placebo	Median 2.1 years	34,633
EXAMINE	R → Alogliptin / Placebo	Median 1.5 years	8,070
TECOS	R → Sitagliptin / Placebo	Median 3.0 years	42,000
ELIXA	R → Lixisenatide / Placebo	Median 2.1 years	12,136
EMPA-REG OUTCOME	R → Empagliflozin / Placebo	Median 3.1 years	21,762

Table 1

The ELIXA trial is the first trial with a GLP-1 RA (GLP-1 receptor agonist) and similarly indicates CV safety in 12,136 patient-years of exposure among subjects with prior acute coronary syndrome. However, a larger trial called LEADER (liraglutide/Victoza™) is scheduled to report this year and has enrolled a broader cohort of T2D patients in secondary prevention.





CLINICAL PEARL #3:
CV risk reduction with an SGLT2i (empagliflozin, Jardiance™)

The growing number of these negative CV trials had been leading to an air of futility by mid-2015 until the presentation of the EMPA REG outcome trial last September - the first finding of significant CV risk reduction with a T2D therapy. Led by Toronto's own Dr. Bernie Zinman, the study team outlined their finding of significant reductions in major CV events (14% relative risk reduction), CV death (38% relative risk reduction) and overall mortality (32% relative risk reduction) with empagliflozin; with the only significant downside being an increased rate of genital tract yeast infections (6.4% in the empagliflozin vs. 1.8% in placebo treated arms). It's important to recall that in the UKPDS findings of nearly two decades ago, a small substudy of metformin in overweight patients had shown a 39% lower rate of MI and a 36% reduction in all-cause mortality. The EMPA REG study found a 'number needed to treat' (NNT) of 39 to prevent a death, over a 3-year treatment period. With this secondary prevention T2D trial, empagliflozin joins the ranks of comparable established CV reduction strategies in T2DM such as ACE inhibitors and statins.

> "...empagliflozin joins the ranks of comparable established CV reduction strategies in T2DM such as ACE inhibitors and statins."

CLINICAL PEARL #4:
Continue to individualize vascular protection strategies and the choice of AHA add-on for your patients as per CDA guidelines

The current approach of individualizing our AHA choice is based on a number of factors: 1) severity of hyperglycemia, 2) risk for hypoglycemia, 3) effects on body weight, 4) cost, and 5) co-morbidities (especially renal function). The composite of these clinical + economic parameters should continue to be followed when deciding on which anti-hyperglycemic agent (AHA) to add-on-to-metformin in a majority of patients with T2D.

Vascular protection strategies in patients with T2D should also continue to focus on CDA-guideline recommended ABCDEs (A1C, BP, Cholesterol, Drugs for CV prevention, Exercise & Eating healthy and Smoking cessation). For the minority of patients meeting EMPA REG study criteria (i.e. T2D not meeting A1C target + prior history of CVD) and with no cautions attached (especially those with eGFR > 60), empagliflozin should be considered as the preferred AHA for secondary CV prevention, ahead of other AHA add-on options. Our Canadian and other national guidelines are being reviewed to take the new findings into account.

UNANSWERED QUESTION #1:
Do DPP4i agents have any potential adverse effects?

Over the last nine years of clinical use, DPP4i's have commanded an exemplary track record as the safest AHA to date, with minimal impact on either hypoglycemia or weight gain. Note that the CDA guideline table listing add-on AHAs to metformin does not include a single adverse

effect attributed to the DPP4i class. The large sample sizes and extended duration of DPP4i CV outcome trials have allowed expanded power to detect rare outcomes - and led to questioning of their clean adverse effects slate:

Pancreatitis? None of the individual CVOTs with DPP4i (SAVOR, EXAMINE or TECOS) met statistical significance for worse pancreatitis outcomes, however each of the 3 trials did suggest a similar numerical possibility of pancreatitis in the respective DPP4i arms. Indeed, a meta-analysis presented at EASD 2015 by another Toronto researcher, Dr. Robert Josse (data not yet published), did suggest a statistically significant pancreatitis signal with DPP4i's (HR= 1.6; number needed to harm > 1000). It should be noted that ELIXA with lixisenatide, which excluded patients with a history of pancreatitis, did not show a numerical increase in pancreatitis outcomes during the trial period. Pooled, patient-level meta-analysis of the CV outcome trials for pancreatitis are expected, and results of the upcoming LEADER trial might clarify lingering unease on this topic. We continue to believe that the overall benefits of the incretin class likely outweigh this small potential risk of pancreatitis.

"...the overall benefits of the incretin class likely outweigh this small potential risk of pancreatitis."

Hospitalizations for heart failure (HF)?
Among all the CV trials, SAVOR with saxagliptin (Onglyza™) unexpectedly suggested an increased risk of HF (HR=1.27). No other prior nor subsequent studies have found such a harm signal. While TECOS (sitagliptin, Januvia™) and a subsequent meta-analysis of the DPP4i trials have put to rest any concern of HF harm for DPP4i as a class, the potential risk needs to be further clarified for saxagliptin with further mechanistic studies and/or clinical trials.

UNANSWERED QUESTION #2:
Do the CV benefits observed in the EMPA REG study extend to the whole SGLT2i class and to primary CV prevention?

Three noteworthy CV benefit observations in EMPA REG Outcome trial are:

a) 38% reduction in CV mortality was the main contributor to the effect on the primary composite CV outcome; there was actually no difference found in incidence of either MI or stroke;
b) the CV benefit occurred very early (within months) after randomization
c) empagliflozin (Jardiance™) also reduced the risk for hospitalization for heart failure by 39%.

These observations suggest that the CV benefit observed achieved cannot be completely explained by the metabolic effects of SGLT2i (reduced A1C, BP and body weight). Ongoing CVOTs with other agents in the class (CANVAS – canagliflozin/Invokana™; DECLARE – dapagliflozin/ Forxiga™) may answer the important clinical questions of:
a) whether CV benefits observed in the secondary prevention population enrolled in the EMPA REG trial will be found with the other members of the SGLT2i class
b) whether their use in a primary CV prevention population will achieve similar benefits.

Summary

The impact of anti-hyperglycemic therapies on CV events should become a preeminent clinical consideration, now that important efficacy and safety information is available through 5 large published CV outcome trials. Current CV trial data indicate that there is no CV safety concern for the DPP4i class and the GLP1 RA lixisenatide, while empagliflozin has been shown to reduce CV death and heart failure in patients with history of T2D and established CVD.

References
1. Scirica BM, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369:1317-26.
2. White WB, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369:1327-35.
3. Green JB et al. TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; N Engl J Med. 2015 Jul 16;373(3):232-42
4. Pfeffer MA et al. The Evaluation of Lixisenatide in Acute Coronary Syndrome —ELIXA. N Engl J Med 2015;373:2247-57.
5. Zinman B, et. al; EMPA-REG OUTCOME - Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov26;373(22):2117-28.

Improving Patient Adherence:
The GIFT of Getting More with Less

In T2D, an increasingly popular clinical trend has been addition of a DPP4 inhibitor (eg Januvia™, Onglyza™ or Trajenta™) as the 2nd-choice medication if metformin monotherapy fails to achieve glycemic control targets. Should the DPP4i be added with a separate prescription? Or should it be added as part of a fixed dose combination (FDC) of the DPP4 inhibitor + metformin (eg Janumet™, Komboglyze™ and Jentadueto™)? We know from earlier studies, that fewer medications and fewer tablets lead to improved adherence - but the value of metformin + DPP4i combinations has not yet been systematically investigated.

We know from earlier studies, that fewer medications and fewer tablets lead to improved adherence - but the value of metformin + DPP4i combinations has not yet been systematically investigated.

Our LMC group recently investigated this question in a retrospective cohort study of our Ontario clinics. The **GIFT (Glycemic Improvement with a Fixed-dose combination DPP-4 inhibitor + metformin in patients with Type 2 Diabetes)** study aimed to characterize glycemic control in patients who were switched from separate dual therapy with metformin and a DPP4i to an FDC of metformin + DPP4i. We studied all patients between May 2011 and March 2015, who had progressed from dual therapy to an FDC. The study was self-funded by LMC alone.

GIFT Cohort and Results

The GIFT study included patients with T2D, between 18-80 years of age, who had consented to participation in research and were using both a DPP4 inhibitor + metformin for > 3 months. We excluded patients with eGFR < 40 mL/min/1.73m2. We identified 568 patients who then had also progressed to using an FDC (mean age = 63.6 years, T2D duration = 12.7 years, 56% male). The Primary Outcome of A1C was 7.7% at baseline and improved to 7.4% three months after the switch to FDC (Table). FPG similarly improved from 8.1 mmol/L to 7.6 mmol/L. In fact, among patients who had been uncontrolled, one quarter were able to achieve target glycemic control (A1C ≤ 7%) after the switch to FDC. Similar improvements in A1C were also observed for varying subgroups of patients: age ≥ 65 years; diabetes duration ≥ 10 years; Caucasian, South Asian or other ethnicities; and even among those patients whose metformin dosage was unchanged. The effect was primarily seen among patients with a baseline pill burden of > 10 pills/day, who showed a significant reduction in A1C (from 7.5% to 7.1%, p=0.02).

"...among patients who had been uncontrolled, one quarter were able to achieve target glycemic control (A1C ≤ 7%) after the switch to FDC."

Clinical implications:

With no change in therapy other than combining two separate medications into one FDC, we achieved better glycemic control in real-world clinical practice likely due to improved medication adherence.

FPG = Fasting plasma glucose

		Dual SeparateTherapy (metformin + DPP4 Inibitor	Fixed Dose Combination (metformin + DPP4 Inibitor	P-value
Full cohort	A1C	7.7%	7.4%	<0.01
	FPG (mmol/L)	8.1	7.6	<0.01
Subgroup-baseline A1C 7-10%	A1C	8.1%	7.7%	<0.01
	FPG (mmol/L)	8.4	7.8	<0.01

Table. Change in A1C and FPG after switch from Dual Therapy to Fixed-Dose Combination (FDC) of metformin + a DPP4 inhibitor

Supported by educational grants from members of the pharmaceutical industry.