Commentary

SGLT2-Inhibitors and cardiovascular outcomes : inferences for clinical practice

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Cardiovascular risk is the keyconsideration in the management of type 2 diabetes mellitus. Evolving evidence suggests possible cardiovascular protection with certain agents of the SGLT2 inhibitors (SGLT2-i) class. It is important to understand the meaning of the available evidence, for the clinical practice setting. This review attempts to interpret the finer aspects of the available evidence, for appropriate translation to practice.

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The present understanding of cardiovascular disease (CVD) in type-2 diabetes mellitus (T2DM) has evolved considerably. Diabetes and CVD are known to share common antecedent factors. The risk of CVD increases progressively across the continuum of dysglycemia, beginning from the pre-diabetic stage. Subclinical CVD is prevalent in 2 out of every 3 patients of diabetes, andis associated with 2-fold greater risk of CV events[1]. Intensive control of glycemia has notconsistently demonstrated reduction in risk of macrovascular events, or improvement in survival[2-7]. Aholistic multi-factorial CV risk management is key to improve clinical outcomes. However, CVD still remains the leading cause of mortality in T2DM, accounting for nearly 2 of every 3 deaths[7].

Recent advances from the CV outcome trials of the SGLT2-inhibitors (SGLT2-i) and GLP-1 receptor agonists (GLP1-RAs), has prompted optimism in the management of T2DM from CVD risk perspectice[8-11]. The CV benefits demonstrated in EMPA-REG OUTCOME, LEADER, SUSTAIN-6, and CANVAS program,haveushereduniqueopportunities for improving the standards of care. This review attempts to infer the evidence on CV outcomes with the SGLT2-i agents, from a clinical practice perspective.

The Story of 2 CVOTs : CANVAS Program and EMPA-REG OUTCOME —

CANVAS program was a pooled analysis of 2 randomized controlled trials, CANVAS and CANVAS-R[11,12]. The pooled analysis had a hierarchialstatistical assessment plan, as described in Fig 1.

What is the CV benefit : 3P-MACE in CANVAS Program and EMPA-REG OUTCOME ?

The CANVAS program was statistically designedto detect CV safety of canagliflozin, in terms of 'non-inferiority' for 3P-MACE[12]. The analysis did provethe same; further, a significant 14% reduction in the risk of 3P-MACE events was also demonstrated with canagliflozin. As per the statistical analysis plan of CANVAS program, 'superiority' of canagliflozin for 3P-MACE was considered, based on the hazard ratio of 3P-MACE demonstrating upper bound of 95% confidence interval as <1.0[11,12]. However, the statistical assessment plan of the CANVAS program did not assume statistical power to detect 'superiority'for 3P-MACE[12]. In the statistical considerations, a balance between the possibility of false-positive (alpha) error, andthe power of study, should be optimized for maintaining robustness[13]. In the CANVAS program, since the superiority of 3P-MACE was not considered in the hierarchial assessment plan, a greater statistical power should have been required to optimally reduce the chances of falsely positive 3P-MACE results, which was not the case. However, if the statistical-assumptions of the CANVAS program are reconsidered in the hindsight, it remains uncertain whether such a stricter interpretation should prevail. For demonstration of superiority, the left-truncated dataset that excludes the events accrued in CANVAS before Nov 2012 should have been more appropriate. This is because the events accrued in CANVAS before Nov 2012, were partially unblinded for safety assessments[12]. In the CANVAS program, an additional aspect needing further explanation is that the patients receiving diuretic therapy in the background, had demonstrated significantly greater 3P-MACE benefit; this subgroup analysis suggested that background diuretic use could have considerably in-

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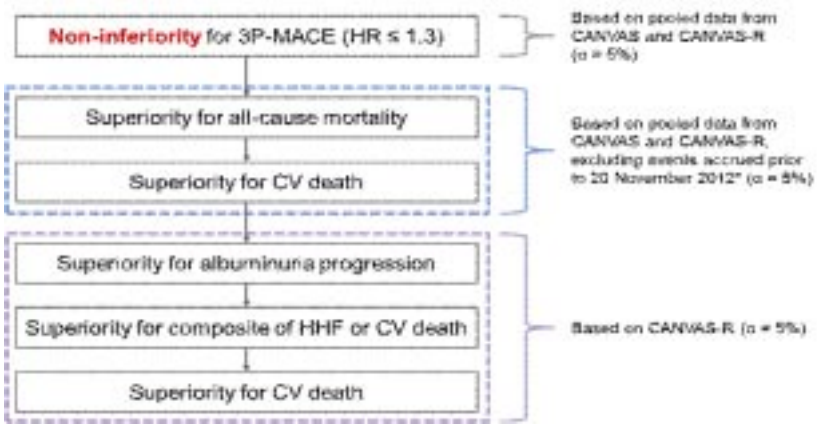

Fig 1— CANVAS Program: Sequential Statistical Analysis Plan

fluenced the overall CV benefit observed with canagliflozin, with the p value for interaction being <0.001[11]. However, in the EMPA-REG OUTCOME study, such discordant beneficial effect based on the background diuretic use, had not been observed with empagliflozin.8Based on all these considerations, the accurateestimation of 3P-MACE from the left-truncated dataset, using optimized statistical power and alpha-error assumptions, whether canagliflozin would have consistently demonstrated superiority for 3P-MACE, remains uncertain. Overall, the results of the CANVAS program do suggest the possibility ofCV protection with another SGLT2-i agent, in patients of T2D with high CV risk. Based on these observations with their strengths and limitations, the ADA has considered 3P-MACE benefit of canagliflozin as Level C evidence (Conflicting evidence with weight of evidence supporting recommendation).

In the EMPA-REG OUTCOME study, a significant 14% reduction was observed with empagliflozin for 3P-MACE events.8In EMPA-REG OUTCOME as well as in CANVAS program, silent myocardial infarction was excluded from the primary analysis of 3P-MACE[8,11]. Since a precise and timely ascertainment of silent MI is not possible in CVOTs, including silent MI in the primary outcome of 3P-MACE leads to increased uncertainty in the CV safety assessments; hence to maintain robustness of 3P-MACE endpoints, silent MI is generally excluded from primary assessments in CVOTs.

For any therapy, a reduction in all-cause deathis the strongest evidence of benefit; the endpoint of all-cause deathcannot be manipulatedby considering different definitions for specific causes of death[14]. In terms of all-cause death, empagliflozin demonstrated significant 32% reduction in the EMPA-REG OUTCOME study[8]. The mortality benefits of empagliflozin, including all-cause death and CV death, remained consistent even after excluding the 'non-assessable CV deaths' from the analyses[15]. In the CANVAS program, significant reduction in risk of all-cause death or CV death was not observed with canagliflozin, even in those 6,656 patients who had a prior history of CVD[11,28]. Thus, empagliflozin and liraglutide are presently the only 2 antidiabetic agents, which have conclusively proven mortality benefitsin robust studies[8,9].

The overall CV outcomes observed in EMPA-REG OUTCOME, and in the CANVAS program, have been summarized in Table 1.

At what stage of CVD, is the benefit more plausible?

The antidiabetic CVOTs are required to include patients of T2DM with high CV-risk[18]. The definitions of high CV-risk may vary across the CVOTs.The seminal work of Preiss and colleagues suggested that in patients with diabetes, the presence of underlying CVD would yield a 3.5 to 4.6 fold higher CV event rate[19]. Preiss and colleagues defined underlying CVD based on objective criteria for ascertaining coronary artery disease, peripheralarterial disease, or cerebrovascular disease. Objective identification included either a prior CV event history or con-

Table 1 — *CV Outcomes in EMPA-REG OUTCOME and CANVAS Program. Relative Risk Reductions (dark boxes imply statistically significant reductions)*
This is not a head-to-head comparison

	EMPA-REG OUTCOME	Pooled CANVAS Program
3P-MACE	14% (HR 0.86, 95%CI 0.74-0.99)	14%* (HR 0.86, 95%CI 0.75-0.97)
CV Death	38% (HR 0.62, 95%CI 0.49-0.77)	HR 0.87 (95%CI 0.72-1.06)
All-cause Death	32% (HR 0.68, 95%CI 0.57-0.82)	HR 0.87 (95%CI 0.74-1.01)
Nonfatal MI	HR 0.87 (95%CI 0.7-1.09)	HR 0.85 (95%CI 0.69-1.05)
Nonfatal Stroke	HR 1.24 (95%CI 0.92-1.67)	HR 0.90 (95%CI 0.71-1.15)
HHF	35% (HR 0.65, 95% CI 0.50-0.85)	33% (HR 0.67, 95% CI 0.52-0.87)
HHF or CV Death	34% (HR 0.66, 95%CI 0.55-0.79)	22% (HR 0.78, 95%CI 0.67-0.91)

* Analysis not powered to detect superiority for 3P MACE

firmation through gold-standard assessments, like vascular imaging in asymptomatic or symptomatic patients. Such objective definitionfor underlying CVD ensures greaterhomogeneity of underlying CVD risk in the study populations, and has been followed as inclusion criteria in TECOS and EMPA-REG OUTCOME[8,20].

In clinical practice setting, an objective assessment of underlying CVD by vascular imaging is not routinely recommended inasymptomatic patients of T2DM[21]. Silent ischemiais of common occurrence in asymptomatic patients of T2DM, often with significant underlying atherosclerotic obstruction, and may manifest as serious events like silent MI or sudden death. It is known that in diabetes, the underlying atherosclerotic plaques are diffuse, andremain asymptomatic for a longer duration[22]. The Framingham offspring study suggested that 2/3rd of the patients of diabetes have underlying subclinical CVD[1]. Further, a post-mortem assessment in patients of diabetes haddemonstrated high-grade coronary atherosclerosis, in 3/4th of the patients who had been asymptomatic; half of the patients having multi-vessel disease. Hence, if the assessment of underlying CVD is based merely on clinical symptoms, one may miss out on a significant proportion of patients with subclinical CVD, who also have high CV risk. In the CVOTs, if objective assessment for underlying CVD is not considered as the inclusion criterion, enrollment of participants with high CV risk may be maximized by including those with multiple uncontrolled CV risk-factors. CVOTs like LEADER, CANVAS program, and DECLARE TIMI 58 have included patients of high CV risk based on these lines[9,11].

In CANVAS program, 66% of enrolled patients had symptomatic atherosclerotic CVD, whereas 34% had multiple CV risk-factors, without a known history of CVD. In these 34% of study participants, the CVD status was not excluded by vascular imaging[11]. The mean age of the study patients was 63 years,and average duration of diabetes was 14years; hypertension was present in 90% of these patients[11]. As the CVD status was not excluded through vascular imaging, it would be inappropriate to assume absence of underlying CVD, in these 34% of patients with high CV risk, enrolled in the CANVAS program.

In the CVOTs, the 3P-MACE event rates in placebo groups indicate the background CV risk in the respective study participants. As demonstrated in Fig 2, in the placebo groups across most of the CVOTs, the 3P-MACE event-rates were comparable (Fig 2)[8-12,20,24]; this is suggestive of similar background CV-risk in the participants across these CVOTs. Since all the CVOTs include patients with high CV-risk profiles, attempts to extrapolate the beneficial CV outcomes observed in these CVOTs, to patients with lower CV-risk profiles, may befutile.

Trial	High CV Risk: Definition (Established CVD / Presence of CV Risk-factors)	Incidence rate of 3P-MACE Events (Placebo group)
LEADER	Age ≥50 and CHD / Cerebrovascular disease / PVD / CKD stage ≥3 / CHF (NYHA 2-3) **OR** Age ≥60 with ≥1 CV risk-factor (proteinuria, HT and LVH, LVSD or DD, ABPI <0.9)	3.4 per 100 pt-yrs
SUSTAIN-6	Similar to LEADER	4.4 per 100 pt-yrs
SAVOR TIMI-53	Age ≥40, and clinical atherosclerotic event (coronary / cerebral / peripheral vascular) **OR** Age ≥55 (men) / 60 (women), and dyslipidemia / HT / active smoking	3.5 per 100 pt-yrs
TECOS	H/o major CAD / ischemic cerebrovascular disease, or atherosclerotic PAD	3.6 per 100 pt-yrs
EMPA-REG OUTCOME	Single-vessel CAD / Multi-vessel CAD / PAD / H/o MI / H/o Stroke / H/o UA with CAD	4.4 per 100 pt-yrs
CANVAS Program	Age ≥30, with Symptomatic ASCVD Age ≥50, with ≥2 CV risk-factors	3.2 per 100 pt-yrs

Fig 2 — 3P-MACE Event Rates in CVOTs (Placebo Groups)

In the CANVAS program, in the subgroup of patients with multiple CV risk factors, a meaningful effect was not demonstrated for 3P-MACE (hazard ratio was 0.98), although the p-value for interaction was non-significant.This means that although the overall results of 3P-MACE were consistent across the subgroups, a clear benefit was not demonstrated in patients with multiple CV risk-factors. A CV safety meta-analysis of empagliflozin, including pooled events from 8 randomized controlled trials, demonstrated consistent CV benefitswith empagliflozin in patients of T2DM with low-medium or high CV risk. On exclusion of EMPA-REG OUTCOME study from this analysis, significant CV benefits still remained for 4P-MACE and hospitalizations for heart-failure or CV death. However, this meta-analysis included trials of 24-52 weeks duration, and fewer CV events. Hence, this evidence of possible CV benefit with empagliflozin, in patients with lower CV-risk profiles, is also exploratory in nature[26].

Real-world studies like CVD-REAL study furnish additional evidence of possible CV benefitsof the SGLT2-i agents, in patients with varied extent of CV-risks[27]. In this retrospective real-world analysis including diverse database records, the use of SGLT-2i agents was associated with significant 51% lower risk of mortality, and 39% lower risk of HHF. The analysis does suggest an overall benefit of SGLT2-i agents compared to the other glucose-lowering therapies. However, real-world evidence does not give a conclusive proof, because of the inherent limitations in

such observational study designs. In CVD REAL study, the two comparator groups were matched for only[28-34] possible confounding variables, through 1:1 propensity-score matching. A clear discordance was observed in the findings of the US-cohort of CVD-REAL study. This US-cohort included patients who mainly received canagliflozin. A significant reduction in all-cause death was observed in this US cohort; however, in the CANVAS program, canagliflozin failed to demonstrate a benefit for all-cause death. This discordance is possibly explained by immortal time bias, which maybe prevalent in real-world studies, as explained earlier[29].

Conclusion :

Hence, contemporary evidence does not confirm the possibility of primary CVD prevention with SGLT2-i agents, as far as the 3P-MACE outcomes are concerned. The diverse cardio-metabolic effects of SGLT2-inhibitiors, like improvement in blood pressure, reduction in interstitial fluid volume, reduction in arterial stiffness, delay in onset and progression of chronic kidney disease, or lusitropic effect, suggest possible benefits of preventing CVD, if used optimally in patients of T2DM with apposite risk.

References

1 Ingelsson E Sullivan LM, Murabito JM, Fox CS, Benjamin EJ, Polak JF, *et al* — Prevalence and Prognostic Impact of Subclinical Cardiovascular Disease in Individuals With the Metabolic Syndrome and Diabetes. *Diabetes* 2007; **56:** 1718-26.

2 Bergenstal RM, Bailey CJ, Kendall DM — Type 2 diabetes: assessing the relative risks and benefits of glucose-lowering medications. *Am J Med* 2010; **123:** 374.e9-e18.

3 Genuth S, Ismail-Beigi F — Clinical implications of the ACCORD trial. *J Clin Endocrinol Metab* 2012; **97:** 41-8.

4 Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, *et al* — Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010; **376:** 419-30.

5 Hayward RA, Reaven PD, Wiitala WL, Bahn GD, Reda DJ, Ge L, *et al* — Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015; **372:** 2197-206.

6 Zoungas S, Chalmers J, Neal B, Billot L, Li Q, Hirakawa Y, *et al* — Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* 2014; **371:** 1392-406.

7 Low Wang CC, Hess CN, Hiatt WR, Goldfine AB — Clinical Update: Cardiovascular Disease in Diabetes Mellitus: Atherosclerotic Cardiovascular Disease and Heart Failure in Type 2 Diabetes Mellitus - Mechanisms, Management, and Clinical Considerations. *Circulation* 2016; **133:** 2459-502.

8 Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, *et al* — Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015; **373:** 2117-28.

9 Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, *et al* — Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016; **375:** 311-22.

10 Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, *et al* — Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2016; **375:** 1834-44.

11 Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, *et al* — Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017. doi: 10.1056/NEJMoa1611925.

12 Neal B, Perkovic V, Mahaffey KW, Fulcher G, Erondu N, Desai M, *et al* — Optimizing the analysis strategy for the CANVAS Program: A prespecified plan for the integrated analyses of the CANVAS and CANVAS-R trials. *Diabetes Obes Metab* 2017; **19:** 926-35.

13 Murphy KR, Myors B, Wolach A — Statistical power analysis: a simple and general model for traditional and modern hypothesis tests. 4th Ed. New York and London: Routledge (Taylor & Francis Group); 2014.

14 Lauer MS, Blackstone EH, Young JB, Topol EJ — Cause of death in clinical research: time for a reassessment? *J Am Coll Cardiol* 1999; **34:** 618-20.

15 FDA Briefing document. Endocrine and Metabolic Drug Advisory Committee Meeting. June 2016. sNDA 204629 and sNDA 206111.

16 Leavell HR, Clark EG — Preventive Medicine for the Doctor and his Community. 3rd Ed. New York: McGraw-Hill; 1965.

17 Strasser T — Reflections on cardiovascular diseases. *Interdisciplinary Science Review* 1978; **3:** 225-30.

18 FDA — Guidance for Industry. Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type-2 Diabetes. 2008. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071627.pdf. Accessed Jun 28, 2017.

19 Preiss D, Sattar N, McMurray JJ — A systematic review of event rates in clinical trials in diabetes mellitus: the importance of quantifying baseline cardiovascular disease history and proteinuria and implications for clinical trial design. *Am Heart J* 2011; **161:** 210-9.

20 Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, *et al* — Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2015; **373:** 232-42.

21 American Diabetes Association — Cardiovascular disease and risk management. Sec. 9. In Standards of Medical Care in Diabetesd2017. Diabetes Care 2017;40(Suppl. 1): S75-S87.

22 Tavares CAF, Wajchjenberg BL, Rochitte C, Lerario AC — Screening for asymptomatic coronary artery disease in patients with type 2 diabetes mellitus. *Arch Endocrinol Metab* 2016; **60:** 143-51.

23 Goraya TY, Leibson CL, Palumbo PJ, Weston SA, Killian JM, Pfeifer EA, *et al* — Coronary atherosclerosis in diabetes mellitus: a population-based autopsy study. *J Am Coll Cardiol* 2002; **40:** 946-53.

24 Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, *et al* — Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013; **369:** 1317-26.

25 Salsali A, Kim G, Woerle HJ, Broedl UC, Hantel S, *et al* — Cardiovascular safety of empagliflozin in patients with type 2 diabetes: a meta-analysis of data from randomized placebo-controlled trials. *Diabetes Obes Metab* 2016; **18:** 1034-40.

26 Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, *et al* — Lower Risk of Heart Failure and Death in Patients Initiated on SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study. Circulation. 2017 May 18. pii:CIRCULATIONAHA.117.029190.

27 Zinman B, Inzucchi SE, Lachin JM, Wanner C, Fitchett D, Kohler S, *et al* — Empagliflozin and Cerebrovascular Events in Patients With Type 2 Diabetes Mellitus at High Cardiovascular Risk. *Stroke* 2017; **48:** 1218-25.

28 Mahaffey KW, Neal B, Perkovic V, de Zeeuw D, Fulcher G, Erondu N, *et al* — Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). *Circulation* 2017; pii: CIRCULATIONAHA.117.032038.

29 Suissa S — Reduced Mortality With Sodium-Glucose Cotransporter-2 Inhibitors in Observational Studies: Avoiding Immortal Time Bias. *Circulation* 2018; **137:** 1432-4.