Sodium-glucose co-transporter-2 inhibitors: A cardiovascular outcome trial analysis

Viraj Ramesh Suvarna
Department of Medical, Eris Lifesciences Limited, Ahmedabad, Gujarat, India

Abstract

Cardiovascular outcome trials (CVOTs) have to be done by sponsors who wish to launch new antidiabetic drugs in the US, since the December 2008 US Food and Drug Administration ruling, which was subsequently accepted by the European Medicines (Evaluation) Agency (EMA) in 2012. However, the medical community asks the question, “So What?” as they are not convinced of the clinical relevance of CVOTs. The patients selected in CVOTs are necessarily high risk, so that they develop major adverse cardiovascular events quickly, but then, the results are extrapolatable to only a certain percentage of patients seen in the clinical practice. Doctors believe that these trials only serve a regulatory need. At the same time, these trials do provide a lot of good data, but it needs to be interpreted well, and extrapolated appropriately to patients in practice as there are differences between what happens in a randomized control trial and in the real world. Hence, the need for this article which serves to dissect the CVOTs of sodium-glucose co-transporter-2 inhibitors, so that doctors are able to better read this evidence. However, the question of which gliflozin is the best cannot be answered by these trials as these are not head to head trials. All the more reason why one needs to look at the data holistically and be empowered to make the right decision for individual patients, hoping to match the best patient for the best drug, rather than determine which drug is better.

Keywords: Cardiovascular outcome trial, major adverse cardiovascular event, noninferiority, sodium-glucose co-transporter-2 inhibitors, superiority

NEED FOR CARDIOVASCULAR OUTCOME TRIALS

In December 2008, the US Food and Drug Administration (FDA) Endocrinologic Metabolic Drug Advisory Committee (EMDAC) issued a guidance which made it mandatory for companies that wished to market new anti-diabetic drugs to do a cardiovascular (CV) safety metaanalysis pre-approval.[1] In other words, within their pivotal clinical drug development program, they had to include patients who were at high risk for developing major adverse CV events (MACEs). Diabetes is arguably a CAD risk equivalent.[2] The new antidiabetic drug should not further increase one’s risk of developing MACEs. Sponsors should ensure that phase 2 and phase 3 clinical trials are appropriately designed and conducted so that a meta-analysis can be performed at the time of completion of these studies.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Suvarna VR. Sodium-glucose co-transporter-2 inhibitors: A cardiovascular outcome trial analysis. Perspect Clin Res 2021;12:4-8.
ASSESSMENT OF RISK

This is measured by doing what is called a hazard ratio (HR) which is nothing but a comparison of the number of MACE that happen (as a percentage) among patients on the new drug vis a vis the number of MACE that happen (as a percentage) among patients in the control or comparator arm (standard of care). The point estimate is always accompanied by the 95% confidence interval (CI). For example, if the HR is 0.86, then the mean plus or minus 2 standard errors of the mean (on either side of the mean) forms the CI, such as 0.79–1.20. By standard error of the mean is meant standard deviation/square root of the sample size number (n). Basically, when one does a study one tests a representative sample, but the results need to be extrapolated from the sample to the population.

If the upper bound of the 95% CI is less than 1.3, then the new drug will receive regulatory approval. However, if the upper bound of the 95% CI is between 1.3 and 1.8, then the sponsor will be asked to do a CV outcomes trial (CVOT). Moreover, if the upper bound of the 95% CI is more than 1.8, then the new drug will not get regulatory approval. Why 1.3? Diabetes itself increases one’s risk of CVD by 20/1000 patient years and it was decided that the new anti-diabetic drug should not increase this risk by more than 6/1000 patient years. In other words, 20 + 6 = 26/1000 patient years, or 26/20 = 1.3.

DO WE NEED TO DO CARDIOVASCULAR OUTCOME TRIALS?

Why all this brouhaha about the need to do CVOTs, only with new anti-diabetic drugs? The meta-analysis which purported an increased risk of MI and CV death with rosiglitazone was the basis for this guidance.[3] Later, this meta-analysis was shown to have limitations and a study (RECORD) also came to the opposite conclusion, namely that rosiglitazone did not increase MI or CV death.[4] The perception among clinicians is that CVOTs are done only to meet a regulatory mandate, hence sponsors do such studies including only high risk patients so that they get an adequate number of MACE early, so that they meet the regulatory endpoint. However, such studies have the limitation of extrapolatability to clinical practice, as very few patients included in CVOTs are seen by doctors in their routine clinical practice.

WHY ARE HIGH-RISK PATIENTS RECRUITED IN EVENT-DRIVEN TRIALS?

High-risk patients are recruited in event driven trials only so that they have a higher risk of developing MACE. One has to balance between homogeneity (e.g., all patients have established CV disease) and heterogeneity (e.g., some have established CV disease/history of MACE, and some do not). The former design is more likely to succeed as was seen in the landmark EMPA-REG OUTCOME study.[5] However, then it limits extrapolatability, as the study results are generalizable only to the kind of high-risk patients in the CVOT who had established CVD. The latter design is fraught with risk as was seen in the CANVAS Program.[6]

CAN ONE CLAIM PRIMARY PREVENTION IN CARDIOVASCULAR OUTCOME TRIALS?

While one may wish to claim primary prevention, if the drug prevents myocardial infarction (MI) or stroke in those who did not have it at baseline, one should remember that in a CVOT all patients are at high risk. If one really wants to assess primary prevention, one needs to do a UKPDS like study with recently diagnosed diabetics who may or may not have established renal and/or cardiac comorbidity. However, then one will need to follow-up these patients for years before some get MACE, as these are low-risk patients. These low-risk patients form the majority of patients seen by doctors in the practice. However, results from CVOTs that include high-risk patients cannot be extrapolated to such low-risk patients. Hence, doctors have asked the question, “So What?” when CVOTs read out, as they believe that such trials are done only to satisfy regulatory requirements, and are not clinically as relevant.

SUBGROUP ANALYSIS

We must understand the difference between P value (for interaction) and the usual P value. In the case of the latter, the P value needs to be less than 0.05 for it to be significant. In other words, it means that the result or difference between the two comparator arms is not because of chance, and if the study was repeated 100 times, in 95 of the 100 times the result would be the same and the difference would favor the new drug. However, the other P value (for interaction) is computed to find out if there is any interaction between a subgroup and the overall results. In such cases, the P value for interaction needs to be not significant for us to be able to say that the subgroup did not interact with the overall results, meaning that the study results are robust and consistent across all subgroups. Needless to say, the subgroups need to be defined a priori or prespecified and not post hoc, as the latter has limitations.

Interpretation of subgroup analysis may also involve looking at the “direction of point estimate,” and “magnitude of effect size,” e.g., in the CANVAS integrated analysis, for MACE endpoint analysis in the subgroup of patients with
established ASCVD and multiple risk factors, respectively, the $P$ value for interaction was nonsignificant, but the effect size was very small for patients with multiple risk-factors. Hence, canagliflozin received the indication approval for MACE, only for patients with established ASCVD.

**STATISTICAL HIERARCHICAL SEQUENTIAL TESTING PLAN**

Another important aspect of reading CVOTs is to understand the statistical hierarchical plan (Hochberg 2-stage test) which has to be prespecified or defined *a priori* in the statistical analysis plan. In the EMPA-REG OUTCOME trial, the plan was to first test for noninferiority for the 3-P MACE, then noninferiority for the 4-P MACE (both of which were achieved), then superiority for 3-P MACE which again was achieved, and finally, superiority for 4-P MACE which was not achieved, as for the 4th $P$, namely, hospitalization due to unstable angina, the difference was not statistically significant.

In the case of the CANVAS Program-integrated analysis, the plan was different. After noninferiority for 3-P MACE was achieved, per the statistical hierarchical sequential testing plan, one tested superiority for all-cause mortality. Moreover, if one achieved that then the next step was to test the superiority for CV mortality. Moreover, in both these very important endpoints, superiority was not met. After which all analyses were to be considered exploratory. Did canagliflozin achieve superiority for the 3-P MACE? A $P = 0.0158$ or 0.02 for superiority is mentioned but is it a nominal $P$ value as the alpha function was spent? Per the integrated analysis paper by Neal *et al.*, it is mentioned that if noninferiority for the 3-P MACE is met, then the null hypothesis would be rejected, and if the upper bound of the 95% CI is less than 1.0 (in this case it was 0.97) then superiority would be considered to have been met.

A similar thing happened in SUSTAIN-6 where a $P = 0.02$ was mentioned for superiority but since this was not prespecified, the NEJM paper concluded that semaglutide achieved noninferiority (not superiority) for the primary composite endpoint of 3-P MACE. When the US FDA appointed EMDAC dissected the CANVAS Program results in October 2018, this bone of contention became clearer, and they recommended that in the label for canagliflozin, an additional claim of reduction in risk of the 3-P MACE (CV death, nonfatal MI < nonfatal stroke) in the high risk patients included in the integrated CANVAS program, can be included, which the US FDA also accepted later.

**COMPARISONS ARE ODIOUS**

The two CVOTs (the CANVAS Program and EMPA-REG OUTCOME) should not be compared as trial populations, designs, analyses, and methodologies are different. If canagliflozin was evaluated in an EMPA-REG OUTCOME setting, for example, a hypothetical CANA-REG OUTCOME, would it have fared as well as empagliflozin did? Moreover, if empagliflozin was evaluated in a CANVAS program like setting, would empagliflozin have fared as well as it did in its own CVOT? If patients included are of two different high-risk categories, so that one might be able to claim primary and secondary prevention, then the study needs to be longer (to give enough time for the MACE to accrue), the sample size needs to be larger, and the number of events needs to be higher before deciding on study closure (outcomes driven). Which is what DECLARE TIMI-58 seems to have done, results for which were read out on November 10, 2018, at the AHA meeting, and it was shown that dapagliflozin did not meet the primary endpoint of 3-P MACE for superiority, but it did meet the coprimary endpoint of CV death and hospitalization due to heart failure (HHF) for superiority, and this was driven by the HHF results, and not CV death. Since ~60% of patients did not have a history of or evidence of established CVD, a claim of primary prevention has been attempted, though this is arguable since primary prevention is generally claimed when one includes low-risk patients and then follows them up for years till they develop MACE.

**EMPA-REG OUTCOME STUDY: TOO GOOD TO BE TRUE?**

On September 17, 2015, for the first time an anti-diabetic was shown, in a dedicated CVOT, to be not just safe (noninferior) but also have benefits (cardioprotection). Empagliflozin not only met the primary endpoint of 3-P MACE for superiority, but it did meet the coprimary endpoint of CV death and hospitalization due to heart failure (HHF) for superiority, and this was driven by the HHF results, and not CV death. Since ~60% of patients did not have a history of or evidence of established CVD, a claim of primary prevention has been attempted, though this is arguable since primary prevention is generally claimed when one includes low-risk patients and then follows them up for years till they develop MACE.

On December 2, 2016 the US FDA approved the additional label claim of cardioprotection for empagliflozin (it reduces CV mortality in adult type 2 diabetics with established CVD). Since the $P$ value for superiority for the 3-P MACE was not statistically persuasive (0.04; not <0.001) the 3-P MACE benefit did not appear in the Indication in the label. In
any case there was no significant reduction in nonfatal MI (13%) or nonfatal stroke (24%, in the wrong direction).

The event curves separated very early (6–12 weeks) which did not support an anti-atherosclerotic effect. More likely it was a hemodynamic effect consequent to the glucuretic (glucose-induced osmotic diuretic) effect in the immediate term and perhaps a metabolic effect in the long-term as well as an increase in hematocrit (shift of oxyhemoglobin curve to the right) which improves tissue oxygenation, the only mechanism in the mediation analysis to reach significance.[9] Kaul did a Bayesian analysis[10] and showed that at least for CV mortality and all-cause mortality the results were good and true and the $P < 0.001$ was so statistically compelling that it had to be credible.

Stroke going in the wrong direction was a concern initially. However, in the per-protocol or on treatment analysis it was closer to 1.0. An interesting finding was that there was no imbalance in stroke during the trial and even during the 30 days after stopping empagliflozin. The imbalance (18 strokes) happened more than 90 days after empagliflozin was discontinued. A recent paper in the journal stroke by Zinman et al.[11] has dissected out this finding and concluded that empagliflozin is not linked to the nonsignificant increase in nonfatal stroke. The critical EMDAC report of June 28, 2016 also stated that it could be due to a play of chance and that empagliflozin is not causally associated with stroke.[12]

**CANVAS PROGRAM: TWO GOOD TO BE TRUE?**

Against this backdrop the CANVAS Program Results were eagerly awaited during this year’s ADA meeting on June 12. Janssen had started CANVAS in 2009 and canagliflozin was approved on March 29, 2013 so the regulator did look at data from this CVOT (4330 patients of which data on 4327 patients was unblinded). There was a safety signal. The upper bound of the 95% CI for the HR had crossed 1.3 and it was felt that there was no point to then do cohort B (another 10,000 patients). Rather they decided to do CANVAS-R on 5812 patients (similar to CANVAS but they had renal impairment and reduction in progression of regression of albuminuria and slowing a 40% reduction in eGFR were added as endpoints) and got the US FDA permission to do an integrated or pooled analysis of 10,142 patients with a better chance of showing superiority. But if not for what eventually transpired, it could have been a single large CVOT, rather than a pooled analysis of two randomized control trials.

Perhaps because it was a mixed population the results were not as homogeneous as EMPA-REG OUTCOME. The ~34% high risk patients were without a history of established CVD [by this they meant stroke, MI, hospitalization for unstable angina, coronary artery bypass grafting, percutaneous coronary intervention, peripheral revascularization (surgical or percutaneous), and symptomatic with documented hemodynamically significant carotid or peripheral vascular disease or amputation secondary to vascular disease] and hence were not as high risk as the remaining 65.6% who did have the history of established CVD. However, all had diabetes for 13.5 years on average and this “primary prevention” cohort had patients above the age of 50 years with at least 2 risk factors for CVD. So it is possible that they may have had sub-clinical CVD though there was no objective evidence for confirming the same, in contrast to EMPA-REG OUTCOME where almost all patients had evidence of established CVD, though 35% of these patients did not have a past history of MI or stroke.

Importantly, glycemic equipoise was not achieved as the difference in HbA1c was 0.58%. To be fair to canagliflozin, all three individual component endpoints of the composite primary endpoint of 3-P MACE went in the right direction (lower side of 1.0) but all three were not significant. Stroke went in the right direction and gives reassurance for the class. The HHF and renal outcomes were also replicated in both CVOTs. Hence the CANVAS Program Results prove that EMPA-REG OUTCOME was not a flash in the pan.

**TAKE AWAY MESSAGE FOR CLINICAL PRACTITIONERS**

So what should a practising diabetologist take from both CVOTs? How many patients in a CVOT are seen by doctors in their daily practice? Can we extrapolate results of CVOTs to the lower risk patients who we see more often in our practice? What is the clinical relevance of CVOTs or are they done more to satisfy the US FDA? Is it a class effect? The results of DECLARE TIMI-58 have been declared and there is some talk about “primary prevention”. Top line and subsequently the full results have shown that dapagliflozin met the 3-P MACE primary endpoint for noninferiority but it did achieve superiority in the co-primary endpoint of CV death or hospitalization due to heart failure. There was no increased risk of amputations in the dapagliflozin arm.

**CONCLUSION**

To conclude, CVOT, but so what? Typically strengths, weaknesses, threats and opportunities (SWOT) analysis stands for SWOT. I believe that the real question is not about whether one drug is better than another. It is about
identifying patient substrates who respond to a given drug or regimen the best. Companies should come together in the spirit of competitive collaboration and facilitate investigator initiated pragmatic clinical trials in the real world that can help answer clinically relevant questions that matter most to doctors and their patients.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabet. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf. [Last accessed on 2017 Aug 05].
2. Haffner SM, Lehto S, Rönemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229-34.
3. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457-71.
4. Home PD, Pocock SJ, Beck-Nielsen H, Caritis PS, Gomis R, Hanefeld M, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): A multicentre, randomised, open-label trial. Lancet 2009;373:2125-35.
5. 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.
6. 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;377:644-657.
7. 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.
8. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834-44.
9. Ferrannini E, Mark M, Mayoux E. CV Protection in the EMPA-REG OUTCOME trial: A “Thrifty Substrate” hypothesis. Diabetes Care 2016;39:1108-14.
10. Kaul S. Is the mortality benefit with empagliflozin in type 2 diabetes mellitus too good to be true? Circulation 2016;134:94-6.
11. 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.
12. FDA Briefing Document Endocrine and Metabolic Drug Advisory Committee Meeting June 28, 2016. Available from: https://www.fda.gov/downloads/AdvisoryCommittees/UCM508422.pdf. [Last accessed on 2017 Aug 05].