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Review Article

Advantage of Cardiovascular Outcome Trials (CVOT's) for SGLT2 (Sodium Glucose Transporter 2) Inhibitors in Type 2 Diabetes Mellitus (T2 DM)

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Abstract

Since the discovery of the so-called ''newer T2D agents'' for the treatment of type 2 diabetes mellitus (T2DM) which included dipeptidyl peptidase (DPP4) inhibitors, glucagon like peptide 1 (GLP1) receptor agonists and sodium -glucose transporter 2 (SGLT2) Inhibitors both American food and drug administration (FDA) and European medical agency (EMA) mandated cardiovascular outcome trials (CVOTs) for checking the CV safety of all new glucose lowering drugs. The benefit has been that it has helped us to understand that these newer drugs might not be only glucose lowering but even further help in CV safety. Earlier there had been reports of liraglutide being the best of the GLP1 Receptor agonists. Here we discuss that after CVOT's on SGLT2 inhibitors it is empagliflozin that is best for CV safety of all SGLT2 inhibitors. Thus it is important to carry such studies for all newer antidiabetic agents which is helpful in deciding which antidiabetics will be of help in promoting CV safety and reducing mortality hence these CVOT Trials should continue to be mandatory.

Keywords: *T2DM; SGLT2 Inhibitors; CVOT; Empagliflozin; Liraglutide*

Introduction

Recently the FDA made it essential that cardiovascular (CV) outcome trials (CVOT's) for checking the CV safety of all new glucose decreasing drugs, and the European medical agency (EMA) made the recommendation that either a CVOT or a meta-analysis be done [1,2].

In our earlier article we had already reviewed how Sodium -glucose cotransporter 2 (SGLT2) inhibitors, remain an attractive choice for starting initial combination therapy with metformin. Their mechanism of action is insulin -independent, i.e. by increasing the urinary excretion of glucose. Along with that weight reduction and lowering of blood pressure (BP) occurs in contrast to placebo. Empagliflozin, cana gliflozin, and dapagliflozin have been found to decrease the risk of hospitalization from heart failure and stroke in people having T2DM with established cardiovascular disease or multiple cardiovascular risk factors significantly. Empagliflozin is an SGLT 2 Inhibitor which is in common with other agents in this class and decreases the elevated blood glucose levels by inhibiting SGLT2, that is the main transporter needed for reabsorption of glucose from the glomerular flltrate and hence increases urinary excretion of glucose. Further we discussed the EMPA-REG outcome CVOT (EMPA glozin Removal of Excess Glucose: cardiovascular outcome Event Trial in T2DM Patients)

(NCT011131676) [3]. The primary composite outcome was time to first occurrence of 3 point major adverse CV event (3P-MACE), that is CV death, nonfatal stroke or non-fatal myocardial infarction [MI]). Although EMPA-REG outcome's design was only for testing non inferiority for this outcome, amazingly the study also revealed superiority, with a relative risk reduction of 14%, mainly in view of a 38% decrease in CV death [4]. Hence crucial outcomes were marked improvement once empagliflozin was added to standard of care.

Mutiple secondary CV outcomes also demonstrated decrease, namely hospitalization for heart failure (HHF) by 35% [4]. Death secondary to any reason reduced by 32% along with the number needed to treat [NNT] to prevent one death over 3 years of the study was determined as 39 [4]. But no significant differences to placebos was observed for non-fatal stroke or nonfatal MI [4].

Role of empagliflozin in diabetics at greater CV Risk

It is better to find those who won't benefit by empagliflozin since it is a drug which is both safe and has high efficacy. Empagliflozin seems to act as a double agent tackling both hyperglycemia, in addition to CV risk factors and hence best for both type 2 diabetes (T2D) and cardiovascular disease (CVD), accepted now internationally [5-8]. The EMPA-REG OUTCOME study took patients with established CVD, a meta-analysis of 8 randomized controlled trials (RCT's) of empagliflozin examined the results from 11292 individuals, that included those who were at low and medium, along with high risk of CV events [9]. Primary endpoint being CV death, nonfatal stroke or non-fatal myocardial infarction (MI), and hospitalization for unstable angina (4P-MACE), with a secondary endpoint of 3P-MACE [9], 4P-MACE resulted in 365 (9.5%) patients getting placebo and 635 (8.5%) patients getting empagliflozin (HR 0.86; 95% CI 0.76 - 0.98). 3P-MACE took place in 307 (8.0%) subjects getting placebo and 522 (7.0%) subjects getting empagliflozin (HR 0.84; 95% CI 0.73 - 0.96) [42]. From these data conclusions can be drawn that empagliflozin is accompanied by decreased risk of CV morbidity and mortality in T2DM, in all be it low/medium CV risk that got included in the analysed population. For the analysis of HHF outcome (endpoint prespecified) in EMPA-REG OUTCOME demonstrated that the good effects of empagliflozin were similar in both subjects that had or didn't have any baseline HF, indicating prevention at the primary level for the ones not having baseline HF, while secondary prevention for subjects having HF at baseline. On analysis 1,8% of individuals getting empagliflozin in absence of HF at baseline underwent an event in contrast to 3.1% for placebo (HR 0.6; 95%CI 0.43 - 0.82); while for those presenting with baseline HF, the incidence of HHF was 10.4and 12.3% respectively (HR 0.75; 95%CI 0.48 - 1.19) [4,10]. American Heart Association (AHA) and American College of Cardiology (ACC) has started accepting the proof of primary prevention of HF with empagliflozin and laid guidelines [8] and there studies ongoing which are trying to get more insight on this potential advantage; although it has to be taken into account that empagliflozin is right now not indicated for the treatment of HF.

Decreases in CV death were same in patients with and without HF at baseline. CV events took place in 3.2% of patients receiving empagliflozin vs 5.3% with placebo (HR 0.6; 95%CI 0.47 - 0.77) for no baseline HF, and 8.2% vs 11.1% (HR 0.71; 95%CI 0.43 - 1.16) for those patients with baseline HF [10]. EMPRISE will evaluate CV death outcomes in a wide CV risk population in routine clinical practice, but these data have not yet been reported [11].

The CANVAS Program

The CANVAS Program represents a pooled evaluation of 2 subsidiary studies: CANVAS, a CV safety study besides CANVAS RENAL (CANVAS-R) that included albuminuria progression as a crucial outcome besides CV outcomes [12].

Study design of the CANVAS Program

The CANVAS CVOT represents a RCT with the design to examine safety on canaglifolozin vs placebo, over standard care, where 4330 subjects having T2DM and either symptomatic CVD (one or more of coronary arterial disease (CAD), cerebrovascular disease, peripheral vascular disease (PVD) or multiple CV risk factors (age ≥ 50 and 2 or more of dyslipidaemia, hypertension, current smoker, ≥ 10yrs DM duration or albuminurea) at baseline [12]. A public revelation of interim analyses was needed for regulatory fillings, and further plans for assessing CV protection via an expansion of the study were finished at that time [12-14]. Rather to get sufficient power to assess CV

assessment, the additional CANVAS-R CVOT (N = 5813) was clubbed with CANVAS into the CANVAS Program, helping in a pooled analysis, but excluded events collected prior to November 2012, that was the date of last unblinding [12-14]. CANVAS-R was a shorter study with median follow up 2.1 years [12].

As a sequential hypothesis testing plan of the pooled data from CANVAS and CANVAS-R to give a total of 5795 subjects that were treated using canaglifolozin and 4347 placebo controls statistical analysis were carried out [12]. Just like with EMPA-REG -OUTCOME, the primary endpoint in the CANVAS Program was time to first occurrence OF 3P-MACE (first testing for non-inferiority and then superiority [12]. Next step was a test for superiority for death [12]. On finding a non-significant result, further analyses was exploratory only.

Crucial results in the CANVAS program

The primary evaluation gave a positive result, having 26.9 participants getting canagliflozin who experienced an event/1000 patients years in contrast to 31.5 in the placebo group (HR 0.86; 95%CI 0.75 - 0.97, p = 0, 02 for superiority); but superiority was not demonstrated for the 1st secondary outcome (death by any cause, (HR 0.87; 95%CI 0.74 - 1.01), hence the sequential analysis examination was finished here [12], that meant that the results of all consequent secondary analysis couldn't be considered as significant but instead an exploratory analyses [12]. Superiority for death by any cause and CV death were, what was further summated in an independent trial steering committee for the CANVAS Program on revision of the initial analysis plan. The idea of performing these changes were thinking that the results regarding subject mortality outcomes would have greater strength as compared to the composite outcome of 3P-MACE, the way it has been observed in EMPA-REG OUTCOME [13,14]. By involving CV death in the form of outcome also gave a method to show superiority of an individual outcome. But absence of superiority regarding all-cause mortality in the pooled data implies that the consequent analysis of CV death was only exploratory [12].

Role of canagliflozin in diabetics at greater CV Risk

Significant 3P-MACE finding simulates that in EMPA-REG OUTCOME for empagliflozin, but absence of significance for both CV death and death due to any other cause came as a disappointment on the clinical front, since these parameters might be of interest for clinicians, knowing how common CV risk is in patients with T2D [12].

The population that underwent study in The CANVAS Program comprised of 58.9% of patients that presented with symptomatic CVD in CANVAS and 70.7% in the CANVAS-R; with the pooled figures being 65.6% [17]. The figures regarding CV involvement have more heterogeneity than the EMPA-REG OUTCOME population, where 99% of participants had established CVD [4]. Canafliglozin was found to be superior to placebo for 3P-MACE in the secondary prevention group only on evaluation, but with no difference from placebo when one looks only at primary prevention [15,16]. But on analysis of interactions between the primary, secondary and overall populations, no statistically significant difference was seen (p = 0.18) [16]. Those 35% cases of CANVAS Program who had CV risk factors, although were asymptomatic are a challenge, as lack of symptoms does not mean an absence of disease, as proven by studies that show that people having T2DM are known to have a great burden of asymptomatic CVD and that CAD might present silently [17].

DECLARE TIMI 58

1st reports of dapagliflozin regarding DECLARE-TIMI 58 CVOT were discussed late. DECLARE-TIMI 58 CVOT was the 1st CVOT in the SGLT2 inhibitor group which has included most of primary prevention patients, implicating 59% of patients had lot of CV risk factors (males with age ≥ 55 or females with age ≥ 60 having one or more of CAD, ischaemic cerebrovascular disease or PAD [18,19].

Original design of the study with primary safety endpoint was noninferiority for 3P-MACE and the primary efficacy endpoint was superiority for 3P-MACE, like with EMPA-REG outcome and the CANVAS Program. But after EMPA-REG outcome, a new co-primary composite efficacy endpoint of HHF and CV death got included, with the permission from the regulators, in view of the idea that outcomes of these might be very important for SGLT2 inhibitors [4,18,20].

Just like other drugs, DECLARE TIMI 58 showed that dapagliflozin was noninferior to placebo in the form of an add on to the standard of care in the study population, and hence it met the primary safety endpoint [18]. Further DECLARE TIMI 58 gave further proof of decrease in HHF is consistent with other SGLT2 inhibitors group in view of the co-primary efficacy end point of HHF and CV death was also achieved, mainly due to a reduced risk of HHF, although no difference between dapagliflozin and placebo in the risk of CV death [18].

But this study could not achieve the primary efficacy endpoint of superiority for 3P-MACE with no marked difference between dapagliflozin and placebo [18]. Moreover, even on consideration only of patients with the baseline atherosclerotic CVD that is established (a similar size cohort to EMPA-REG outcome) no significant benefit remained in either 3P-MACE or CV death with dapagliflozin [15,18]. Death risk secondary to any cause was also not significantly decreased with dapagliflozin vs placebo [18].

Comparison of the 3 programs alongside each other

Inspite of recent CANVAS Program and DECLARE TIMI 58 results empagliflozin is the only member of the SGLT2 inhibitor class till now which has proved to cause significant decrease in CV death (38%RRR) in a dedicated and heavy CVOT which had a design, and power for testing the superiority in CVOT outcomes versus placebo [16-18]. Moreover, the decreased risk of CV death was consistent with prespecified evaluation [4]. In contrast no significant decrease with either canagliflozin, in the CANVAS Program, or dapagliflozin in DECLARE TIMI 58, versus placebo was observed and it was true that when trying to evaluate each study population as a whole or only subjects with baseline symptomatic atherosclerotic CVD [12,15,16,18]. But, HHF and renal endpoint suggested that all SGLT2 inhibitors gave a benefit for these outcomes, though these evaluations were only exploratory in CANVAS Program and DECLARE TIMI 58 in view of the hierarchical statistical testing plan design [4,12,18,21,22]. Safety outcomes also displayed changes, with risk of lower limb amputation and bone fracture in the CANVAS Program but not in EMPA-REG outcome, or DECLARE TIMI 58, though risk of genital infection was consistent across the class and those who prescribe should be advised regarding the possibility of DKA events with all the 3 agents [4,5,12, 18,23].

There might be a possible reason for differing outcomes between the SGLT2 inhibitor CVOT's might be the difference in study design, some of which have been described earlier. But another cause might be dissimilarities in molecular structure which cause separate relative selectivity for SGLT2 over SGLT1 [24]. SGLT1 inhibition is known to cause gastrointestinal problems and investigations into the earliest SGLT2 inhibitors were given up in view of absence of selectivity between SGLT2 and SGLT1 [25]. Other repercussions of different molecular structures have not been found till now.

Real world evidence (RWE)

CVD-REAL, EASEL and EMPRISE (reviewed in ref 26) were the ones to compare clinical and health economic outcomes with SGLT2 inhibitors in routine clinical practice and ongoing RWE studies have the role to give more light on this in future years to come. RWE get captured in natural, uncontrolled settings outside a traditional RCT's and supposed to represent a measure of understanding healthcare data collected under real-life practice circumstances [27].

RWE data in context

RWE need to be used with precaution in the context of CVOT's, since data that is generated from the observational studies cannot be compared with the RCT's that are the gold standard, and residual confounding e.g. selection bias can't be excluded. Flaws were seen in CVD-REAL. Concern over the possibility of immortal time bias was addressed in the study design for EMPRISE, where patients are matched for number of DM therapies and the study design is to compare treatments with the same position in the treatment pathway [11].

RWE studies can be of use where the data support and agree with results of RCT'S. E.g. the evidence from RWE supports the findings from CVOT's show a decrease in HHF with SGLT2 inhibitors, that suggests that the decrease in HHF shown in CVOTs might be observed in T2D patients across a broad continuum of CVD in routine clinical practice.

SGLT2 inhibitors and class effect

With the results from SGLT2 inhibitor CVOT's it is still very early to safely assume a class effect. Different results in CV death, death by any cause and safety cause put doubts on the potential effect of a class effect, despite similar decreases in HHF and renal outcomes between the 3 CVOT's. It has been seen that a variability in a class in CV death outcomes has a implicit precedence in CVOT's among GLP-1 receptor agonist CVOT's, a decrease in CV death was observed with liraglutide or the unlicensed agent albiglutide [28-31,32].

Hence guidelines globally have been updated in the light of CVOT's with the recognition of these differences, recommending an SGLT2 inhibitor or GLP1 receptor agonist that has beneficial effects that have been proved regarding CV action for patients with T2DM in an atherosclerotic CVD setting [6,7], or an SGLT inhibitor with proven HF or CKD benefit in patients where HF or CK predominates [6,7].

Adverse effects

In view of these agents belonging to the newest class of drugs for treating T2DM, clinical experience is limited. Because of increased urinary glucose, urinary and vaginal infections are the most frequent side effects encountered. Usually tend to be mild to moderate and are easily manageable with standard therapy. Although no increased acute kidney injury risk was seen in the major trials, the mechanism of action of these drugs needs caution when administered to patients having extracellular fluid depletion or with drugs that affect renal haemodynamics. Canagliflozin raised the risk of amputations and the rate of fractures in the CANVAS trial, although data are required before any definite conclusions are drawn. Risk of euglycaemic diabetic ketoacidosis seems to be minimal when the drugs are prescribed properly. As far as other side effects are concerned, SGLT2 Inhibitors don't increase the risk of hypo glycaemia even on coadministration with insulin, but a reduction in the dose of sulfonylureas is needed Although available data do not point to a causative role in malignancy risk, As part of the FDA approval in 2013, post marketing studies for CVS outcomes and for monitoring bladder and urinary cancer risk are underway., but these drugs should be used with caution in patients with known haematuria or history of bladder cancer. Thus although safe studies are needed to assess their long term safety [35].

Conclusion

Investigation of SGLT2 inhibitors regarding CVOTs have pointed that they are of benefit beyond glucose lowering, confirmed by RWE studies [4,11,12,18,21-34], that has caused guidelines to support these agents favourably in the treatment of patients with T2DM presenting in a scenario of CV risk, HF and renal disease [5-8]. But empagliflozin is the only drug within this class that has shown proven action along with safety across the most relevant endpoints, namely CV and renal outcomes [4,12,18].

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