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Review Article

Define-HF & Emperial Trials: Lessons Learned

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ABSTRACT

Sodium Glucose co-transporter inhibitors (SGLT-2i) have firmly established their position in the management of type 2 diabetes mellitus (T2DM) and have also expanded their indication for use. There were different outcomes benefits with the three SGLT-2i, resulting from differences in patient population studied, primary end-points chosen and statistical testing hierarchy. Although the outcome benefits complemented each other, the subtle differences were blown out of proportion by interested lobbies, eyeing a larger pie of the market share. The corporate war intensified with the publication and top-line results of 2 two recent symptom-based trials in patients with heart failure (DEFINE-HF & EMPERIAL). Once again, the differences were subtle and there were more similarities than differences. Diuretics provide the desired symptom relief whereas SGLT-2i are associated with hard end-point outcome benefits. In view of the profound benefits associated with the use of SGLT-2i two additional categories of studies were launched. The first explored the area of symptomatic relief and the second concentrated on the mechanistic benefits. This review looks in depth at the different types of trials conducted with SGLT-2i and their similarities which is supported by all the recently published guidelines.

Keywords: Type 2 diabetes Mellitus; Major Adverse Cardiac Events; Hospitalization for heart failure; CV death; Chronic kidney disease

Abbreviations: T2DM: Type 2 Diabetes Mellitus; SGLT-2i: Sodium Glucose co-transporter inhibitors; CVOT: Cardiovascular outcome trials; CV: cardiovascular; eASCVD: established atherosclerotic CV disease; MRF: Multiple risk factors; HFrEF: Heart failure with reduced ejection fraction; MACE: Major Adverse Cardiac Events; hHF: hospitalization for heart failure; RRR: Relative risk reduction

INTRODUCTION

The last decade belongs to anti-hyperglycaemic agents as far as making an impact on disease-related adverse outcomes are concerned. It is after a very long period of time (after the era of statins and RAAS blockers) that we have a plethora of agents under the diabetes management fold that positively impacts cardio-renal outcomes. This trend was initiated in 2008 with the regulatory bodies formulating guidelines for the pharmaceutical industry as far as documenting cardiovascular safety was concerned, prior to marketing them [1]. The initial years were sketchy with a lot of effort and focus concentrated on the methodologies required to conduct such rigorous trials. The first group of anti-hyperglycaemic agents to face scrutiny were the gliptins. As far as the primary cardiovascular outcomes were concerned the first two trials with saxagliptin & alogliptin (SAVOR-TIMI 53 & EXAMINE) were neutral [2,3]. However, to the surprise of the medical fraternity, there was an increased risk of hospitalization for heart failure with saxagliptin and a trend towards the same with alogliptin, in type 2 diabetic patients with established cardiovascular disease. These findings seemed to vindicate the regulatory authority's stand as far as cardiovascular outcome trials (CVOTs) were concerned. However, the gliptins story was diverted towards the hospitalization for heart failure (hHF) adverse signal without any positive expectations from future trials. TECOS trial with sitagliptin and CARMELINA with linagliptin proved the same, with neutral outcomes as far as cardiovascular outcomes and hHF were concerned [4,5].

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The exciting period

Just as critics were taking their daggers out on the utility of CVOTs, we were gifted with two blockbuster trials–EMPA REG & LEADER with empagliflozin and liraglutide respectively [6,7]. All of a sudden, the floodgates for positive outcomes from CVOTs opened up and we came across a series of adverse-outcomes modifying anti-hyperglycaemic agents. These included dapagliflozin, canagliflozin, semaglutide, albiglutide, and dulaglutide. There were a variety of adverse outcomes in a wide range of type 2 diabetes (T2DM) population which were positively impacted. Not only did the results stimulated the guidelines committee to get into a hyperactive mode, the pharmaceutical industry also went into a competitive frenzy in order to get a lion's share of the market.

THE SGLT-2i STORY

Sodium glucose cotransporter inhibitor-2 also known as SGLT-2i were at the centre of focus in view of the fact that the positive outcomes were derived from an oral agent which was also much cheaper than its injectable and costly competitor-the glucagon like peptide 1- receptor agonists.

SGLT-2i & CVOTs

The initial competition was between the three (empagliflozin, canagliflozin & dapagliflozin) with their respective CVOTs (EMPA REG, CANVAS Program & DECLARE-TIMI 58) [8,9]. Although each of these studies had completely different patient population recruited, that did not act as an impediment for unfair comparisons (Table 1). Not only were the baseline characteristics different, but so were the positive outcomes. In due course of time, based on the positive outcome results, all the three SGLT-2i got their respective label update. EMPA REG outcomes trial was conducted in T2DM patients with established atherosclerotic cardiovascular disease (eASCVD) and got a label update for reduction in cardiovascular death [10]. In contrast canagliflozin got a label update for major adverse cardiac events (MACE) and dapagliflozin for a combination of cardiovascular death or hHF in a mixed T2DM patient population (eASCVD & multiple risk factors) [11,12].

Studies	**T2DM (%)	*eASCVD (%)	Primary end-point(s)	Label updates based on outcomes benefit
EMPA REG6	100	100	***MACE	+CV death[10]
CANVAS8	100	65.6	MACE	MACE11
DECLARE TIMI 589	100	40.6	MACE & CV death or hHF	MACE & CV death or ++hHF[12]
CREDENCE14	100	51	Composite outcome of ESKD, doubling of serum creatinine, or renal or CV death	Composite outcome of +++ESKD, doubling of serum creatinine, or renal or CV death[11]
DAPA-HF15	41.8	All ##(HFrEF)	Composite of worsening #HF or death from CV causes	Composite of worsening HF or death from CV causes[12]

*eASCVD: established atherosclerotic cardiovascular disease; **T2DM: type 2 diabetes mellitus; ***MACE: major adverse cardiac events; +CV: cardiovascular; ++hHF: hospitalization for heart failure; +++ESKD: end-stage kidney disease; #HF: heart failure; ##HFrEF: heart failure with reduced ejection fraction

The initial SGLT-2i pharma war: Battle of outcomes

With three different label updates from the recommending bodies, the marketing turf opened up for a pitched battle on one Manship. While proponents of empagliflozin harped on the hard end point (CV death) benefits, competitors focussed on the small proportion (approximately 14%) of T2DM patients presenting with eASCVD and hence the lack of generality of empagliflozin in a broader population [13]. Since CANVAS program and DECLARE-TIMI 58 were conducted in a mixed population of patients, they were considered to be applicable to a wider population range.

Advantage empagliflozin?

EMPA REG outcomes trial documented significant benefits of adding empagliflozin on top of standard of care in T2DM patients with eASCVD as far as reducing CV deaths were concerned. This was a hard end point which was not matched by any of its competitors. However, the population studied included patients with eASCVD and not those with multiple risk factors (MRF). In a subsequent analysis an attempt was made to dissect the paper and identify approximately 35% of patients who did not have established myocardial infarction (MI) or stroke at enrolment [14]. However, the attempt to perform such a post-hoc analysis as a reactionary strategy to match the CANVAS Program cohort was met with justified criticism. Why were patients with intermediate to low CV risk exposed to coronary angiography in the first place? Hence for all practical purposes EMPA REG outcomes trial remains a study conducted on T2DM patients with eASCVD demonstrating an impressive 38% relative risk reduction in CV death [6]. This aspect of benefit with empagliflozin is a unique advantage not seen in any other studies with SGLT-2i.

The challenger

Canagliflozin was the first challenger off the block with CANVAS Program. 35% of patients included in this trial had MRF with 65% having eASCVD [8]. The only positive coming out of this trial was reduction in 3-P MACE. Although a positive trial from the primary outcomes point of view, CANVAS Program was dragged into controversy in view of increased rates of lower limb amputations. Such a morbid and serious adverse event offset the CV benefit especially when it was not clear whether the risk was due to the molecule per se or as a result of some specific risk factors. In due course of time a black box warning was incorporated in canagliflozin's package insert specifying two areas where to avoid canagliflozin – those with a diagnosis of peripheral arterial disease (PAD) and prior amputation.

The publication of CREDENCE trial demonstrating an impressive reduction in composite renal outcomes was a boost in the arm for canagliflozin [15]. Not only did CREDENCE establish the concept of cardio-renal benefits in a broader CV risk population, but also did not show any increase in amputation rates. These data definitely helped canagliflozin get a broader positioning than empagliflozin.

A bigger challenge: Dapagliflozin posted the strongest challenge to other flozins in the SGLT-2i group. DECLARE TIMI 58 & DAPA-HF were the two blockbuster trials with dapagliflozin with the former documenting a 17% relative risk reduction (RRR) in CV death or hHF composite as a co-primary end-point and the later associated with a 26% RRR in worsening of HF or CV death [9,16]. hHF was the outcomes of interest in EMPA REG, CANVAS Program & DECLARE-TIMI 58 trials. None of these trials objectively studied heart failure (HF). DAPA-HF was the first to get published on the same. This expanded the indication of use of a SGLT-2i even further, especially since DAPA-HF was conducted in patients with (42%) and without (58%) T2DM. Both, the co-primary from DECLARE-TIMI 58 as well as the worsening of HF or CV death benefits found their way into the package insert.

And the winner is: All-The different population being studied as well as the divergent outcomes benefit results opened up the corporate war, with each highlighting their positives superior to the others. However, in reality what we came across was that the different SGLT-2i were tested in different scenarios in order to explore and expand their indications for use. The very recent update from the EASD/ADA consensus statement mentions use of SGLT-2i in T2DM patients with HF or chronic kidney disease (CKD) without specifying any particular agent [17]. Hence, the winner is the class as a whole and none of the individual agents, irrespective of their individual label updates (Table 1).

The Emperor's New Clothes?

With the guidelines signalling a slowing down of the intense competition between the individual SGLT-2i, a couple of trials evaluating the symptomatic benefits of SGLT-2i in patients with heart failure with reduced ejection fraction (HFrEF) rekindled it. Before evaluating these trials, we need to understand the aims of conducting outcomes-oriented trials (Figure 1). The initial randomised controlled trials with SGLT-2i were looking at hard, objective outcome benefits. Since the major focus of advantage with SGLT-2i shifted to HF, subsequent trials were designed to evaluate symptomatic benefits as well as the mechanisms leading to them.

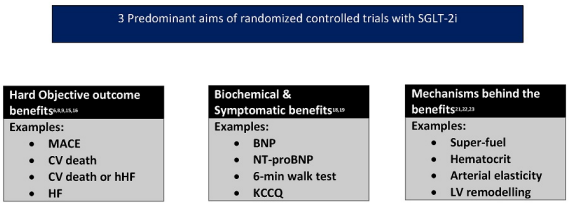

Figure 1: Aims of randomized controlled trials with SGLT-2i.

Defining the new debate: DEFINE-HF Trial

The DEFINE-HF trial recruited patients with HFrEF and an eGFR ≥ 30 ml/min [18]. Patients were initiated dapagliflozin versus placebo on top of standard of care. There was no impact on the NT-proBNP, the biochemical marker for HF. However, there was a significant improvement in a dual primary outcome - NT-proBNP or Kansas City Cardiomyopathy Questionnaire (KCCQ) score. The KCCQ-OS (overall summary) was not significant when assessed individually. However, the truncated version -KCCQ-CS (clinical summary) was significant at the end of 12 weeks, being statistically insignificant for ≥ 5 points increase at end of 6 weeks. Scoring systems have their share of estimation problems. In DEFINE-HF trial another objective and validated test (six-minute walk distance) was evaluated although as a secondary end point. At the end of 12 weeks there was no significant improvement in the six-minute walk distance test.

EMPERIAL Trials: Losing out to dapagliflozin?

Very recently the top-line results of the EMPERIAL-Reduced and EMPERIAL-Preserved were announced. At 12 weeks there was no significant improvement in the six-minute walk test in patients with HFrEF and HFpEF [19].

And the winner is? None

In view of the renewed corporate war it is important to clarify the differences between the trials and the futility in comparing them thereof. The primary end point of EMPERIAL trials was the six-minute walk test which was one of the secondary end-points in DEFINE-HF trial. In both these trials this assessment parameter was not significantly impacted by the SGLT-2i. Since DEFINE-HF combined NT-proBNP and KCCQ-OS scores it was statistically significant. However, individually both NT-proBNP and KCCQ-OS (12-weeks) were statistically insignificant.

This issue was addressed more objectively a year ago when empagliflozin was used either alone or in combination with a loop diuretic in patients with HFrEF and their exercise capacity was assessed using VO2 (peak oxygen consumption) [20]. Improvement in peak VO2 was seen with adequate use of loop diuretic which was not achieved with the use of empagliflozin alone.

CONCLUSION

SGLT-2i are being evaluated from three different angles.

First is the hard end-point outcomes benefit. SGLT-2i have passed this test in flying colours. The benefits of SGLT-2i encompasses a wide range of indications in patients with T2DM. EMPA REG outcome trial established the role of SGLT-2i in patients with eASCVD [6]. The results have been so robust that guidelines recommend substituting/adding a SGLT-2i to an existing regimen in the backdrop of eASCVD, which constitutes about 14% of T2DM patients visiting a physician. CANVAS Program, DECLARE-TIMI 58 & CREDENCE expanded the indication of use of SGLT-2i to a broader population and introduced the concept of cardio-renal benefit [8,9,15]. Now, we have a new indication for the use of SGLT-2i (apart from CV risk reduction), preventing onset and progression of CKD. Approximately 28% of patients presents to a physician with the cardio-renal dysfunction [12]. DAPA-HF expanded the scope of SGLT-2i use further making it the second drug after Angiontensin Receptor Neprilysin Inhibitor (ARNI) in recent times to make a significant impact on HF-related adverse outcomes [16].

The second area of research is focussed on symptomatic relief in patients with HF. Results from both the DEFINE-HF and top-line results of EMPERIAL trials proved the futility of SGLT-2i on improvement of symptoms in patients with HF [18,19]. This is where the role of diuretics is extremely important. Both these groups of drugs complement each other -SGLT-2i delivers the outcomes benefit whereas diuretics provide symptomatic relief.

The third area of research is focussed on finding the mechanisms behind such dramatic outcomes benefits with SGLT-2i. There are several hypotheses doing rounds–the super-fuel hypothesis, restoration of the QTc interval, improvement in arterial elasticity, improvement in left ventricular mass index and many more [21,22,23]. Once results related to these outcomes starts flowing in, we will experience another bout of corporate war.

All the studied SGLT-2i behave in the same way as far as their effect on the cardio-renal outcomes and adverse effects are concerned. The differences seen emanates from the differences in the population being studied, the primary end-points being assessed and the statistical analysis being employed.

The emperor remains the same. It is only his changing clothes that fool us from time to time.

CONFLICT OF INTEREST

None to declare

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