SAVOR-TIMI to DECLARE-TIMI: A Review on Cardiovascular Outcome Trials of Incretin-modulators and Gliflozins

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Abstract

Introduction: Since 2008 United State (US) food drug administration mandate, several newer anti-diabetic drugs (ADD) have undergone a mandatory cardiovascular (CV) outcome trial (CVOT) in type diabetes (T2DM) patients with high CV risk. These includes CVOT done with dipeptidyl-peptidase-4 inhibitors, sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide-1 receptor agonist (GLP-1RAs). Several double-blind, randomized, placebo-controlled CVOT have been presented and published in the last decade (2008-2018). **Aims and Objectives:** We systematically searched the database of PubMed and ClinicalTrials.gov from January 1, 2008 to December 31, 2018 using specific key words. Subsequently, we pooled the data of different cardiovascular endpoints and made a comparative forest plot using GraphPad software Inc. Prism Version 8, US. **Results and Conclusion:** Saxagliptin, alogliptin, sitagliptin and linagliptin are CV neutral drugs. Saxagliptin showed a significantly higher hospitalization due to heart failure (HHF). Empagliflozin and canagliflozin have shown a significant reduction in composite of 3-point major cardiac adverse events (3P-MACE). Additionally, empagliflozin, canagliflozin and dapagliflozin significantly reduced the HHF and the composite of CV death or HHF. Moreover, empagliflozin showed significant reduction in CV- and all-cause death in patients with T2DM with established CV disease. While both exendin-backbone-based GLP-1RAs such as lixisenatide and extended-release exenatide were CV neutral; GLP-1-backbone-based GLP-1RAs such as liraglutide, semaglutide and albiglutide shown a significant reduction in the composite of 3-P MACE. Additionally, liraglutide shown a significant reduction in CV- and all-cause death. Moreover, semaglutide reduced non-fatal stroke and albiglutide reduced myocardial infarction, while extended-release exenatide reduced all-cause death; however, *P* value of significance for these outcomes should be considered nominal.

Keywords: Cardiovascular outcome trial, DPP-4 inhibitors, GLP-1 receptor agonist, SGLT-2 inhibitors

Introduction

Several anti-diabetic drugs for type 2 diabetes (T2DM) have underwent cardiovascular (CV) outcome trial (CVOT) since US Food Drug Administration (FDA) and European Medicines Agency mandated this rule in year 2008 and 2012 respectively.[1,2] There are about 12 of these placebo-controlled trials that have been made available in the last one decade (2008-2018), and several of them are still undergoing whose results are expected in very near future [Table 1]. Of the 12 trials, 9 were conducted with the drugs which works through incretin-based pathway and 3 trial with the drug which works primarily through sodium-glucose linked transporter-2 receptor (SGLT-2) inhibition in kidney. From the 9 incretin-based trials, 4 trials were conducted with dipeptidyl peptidase-4 inhibitors (DPP-4Is) and other 5 trials with glucagon-like peptide-1 receptor agonist (GLP-1RAs).

Although, all these CVOTs have been conducted separately with different degree of background CV disease, the patient characteristics are more similar than dissimilar in these trials. Most of these trials have very similar well-defined pre-adjudicated end points, however if any minor differences in ascertainment of the clinical events may exist, that is likely to be minimized by treatment randomization and blinded adjudication process amongst these CVOTs.

About 4 CVOTs that evaluated DPP-4Is on composite of 3-point/4-point MACE (major cardiovascular adverse events)

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Table 1: Cardiovascular outcome trials of anti-diabetes drug currently undergoing or completed

Class/drugs	Trial eponyms	Comparison	Primary outcome	Estimated study completion date
DPP-4 inhibitors				
Saxagliptin	SAVOR-TIMI	Vs. placebo	3P-MACE	Completed
Alogliptin	EXAMINE	Vs. placebo	3P-MACE	Completed
Sitagliptin	TECOS	Vs. placebo	4P-MACE	Completed
Linagliptin	CARMELINA	Vs. placebo	3P-MACE	Completed
	CAROLINA	Vs. glimepiride	3P-MACE	Completed@
Omarigliptin	OMNEON	Vs. placebo	3P-MACE	Completed#
SGLT-2 inhibitors				
Empagliflozin	EMPA-REG	Vs. placebo	3P-MACE	Completed
Canagliflozin	CANVAS Program	Vs. placebo	3P-MACE	Completed
Dapagliflozin	DECLARE-TIMI	Vs. placebo	3P-MACE/Composite of CV death or HHF	Completed
Ertugliflozin	VERTIS-CV	Vs. placebo	3P-MACE	September 2019
Sotagliflozin	SCORED	Vs. placebo	3P-MACE/Composite of CV death or HHF	March 2022
GLP-1 receptor agonist				
Lixisenatide	ELIXA	Vs. placebo	4P-MACE	Completed
Liraglutide	LEADER	Vs. placebo	3P-MACE	Completed
Inj. Semaglutide	SUSTAIN-6	Vs. placebo	3P-MACE	Completed
Exenatide-LAR	EXSCEL	Vs. placebo	3P-MACE	Completed
Albiglutide	HARMONY Outcome	Vs. placebo	3P-MACE	Completed
Dulaglutide	REWIND	Vs. placebo	3P-MACE	Completed@
Oral Semaglutide	PIONEER-6	Vs. placebo	3P-MACE	Completed@
ITCA 650	FREEDOM	Vs. placebo	3P-MACE	Completed@
Basal insulin				
Degludec	DEVOTE	Vs. glargine	3P-MACE	Completed

@Full results yet to be published, #Early terminated study, CV death: cardiovascular death, 3P-MACE: 3-point composite of major cardiac adverse events (CV death, non-fatal myocardial infarction, non-fatal stroke), 4P-MACE: 3P-MACE plus unstable angina, HHF: Heart failure hospitalization

includes saxagliptin in SAVOR-TIMI (Saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus – Thrombolysis in myocardial infarction), alogliptin in EXAMINE (Examination of cardiovascular outcomes with alogliptin versus standard of care), sitagliptin in TECOS (Trial evaluating cardiovascular outcomes with sitagliptin) and linagliptin in CARMELINA (Cardiovascular and renal microvascular outcome study with linagliptin in patients with type 2 diabetes mellitus).[3-6] Similarly, 3 CVOT that evaluated SGLT-2 inhibitors (SGLT-2Is) includes empagliflozin in EMPA-REG (Empagliflozin reducing excess glucose, canagliflozin in CANVAS Program (CANagliflozin cardiovascular assessment study) and dapagliflozin in DECLARE-TIMI (Trial to evaluate the effect of dapagliflozin on the incidence of cardiovascular events).[7-9] The 5 CVOT that was conducted with GLP-1Rs are lixisenatide in ELIXA (Evaluation of lixisenatide in acute coronary syndrome), liraglutide in LEADER (Liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results), semaglutide in SUSTAIN-6 (Evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes), exenatide in EXSCEL (Exenatide study of cardiovascular event lowering trial), and albiglutide in HARMONY outcome (Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease).[10-14]

All these trials compared DPP-4Is/SGLT-2Is/GLP-1RAs respectively to the placebo at the top of background conventional ant-diabetic drugs in T2DM with high CV risk. The similarity and differences in the patient characteristics in all the 12 CVOTs have been summarized in Table 2.

There are few other CVOTs which has been recently published other than the twelve placebo-controlled USFDA-mandated trials discussed above. These includes DEVOTE (Trial comparing cardiovascular safety of insulin degludec versus insulin glargine in subjects with type 2 diabetes at high risk of cardiovascular events), TOSCA-IT (Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin), ACE (Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance), and IRIS (Pioglitazone after ischemic stroke or transient ischemic attack).[15-18] We did not include these four trials in this comparative review as both DEVOTE and TOSCA-IT were active-controlled trial not the placebo-controlled, while ACE trial was conducted in patients with impaired glucose tolerance and IRIS was conducted in non-diabetics.

AIMS AND OBJECTIVES

We systematically searched the database of PubMed and ClinicalTrials.gov from January 1, 2008 to December 31, 2018 using MeSH and specific key words and retrieved all the placebo-controlled CVOT done in T2DM with

Table 2: Similarities and differences in 12 cardiovascular outcome trials of anti-diabetic drugs

Parameters	SAVOR-TIMI	EXAMINE	TECOS	CARMELINA	EMPA-REG	CANVAS Program	DECLARE-TIMI	ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY
n	16,492	5,380	14,735	6,979	7,020	10,142	17,160	6,068	9,340	3,297	14,752	9,463
Mean age (year)	65	61	65.5	66	63.1	63.3	63.9	60.3	64.3	64.6	63	64
HbA1C entry criteria (%)	6.5-12	6.5-11	6.5-8	6.5-10	7-10	7-10.5	6.5-12	5.5-11	≥7	≥7	6.5-10	≥7
Diabetes duration (mean, year)	10.3	7.3	11.6	15	>10 (57%)	13.5	11.0	9.3	12.8	13.9	12	14
Mean HbA1C (%)	8	8	7.2	8	8.1	8.2	8.3	7.7	8.7	8.7	8.0	8.7
Mean BMI (Kg/M2)	31.2	28.7	30.2	31.3	30.6	32	32	30.2	32.5	32.8	31.8	32
Current smoker, (%)	NR	14	11	10.2	13	17.8	14.5	11.7	12.1	NR	NR	16
Asian (%)	10.7	20.2	22.3	9.0	19.2	12.7	13.4	12.7	7.6	8.3	9.9	5
HTN (%)	82	83	86	91	94	90	89.4	75.5	90	92.8	NR	86
CVD (%)	78	100	100	57	100	65.6	40.6	100	81	72.2	73.1	100
Heart failure (%)	13	28	18	27	10.1	14.4	10	22.4	17.9	23.6	16.2	20
eGFR <60 ml ((%)	16.6	29.1	9.3	62.3	25.9	20.1	7.4	23.2	21.7	24.1	18.6	23
Median trial duration (year)	2.1	1.5	3.0	2.2	3.1	2.4	4.2	2.1	3.8	2.1	3.2	1.6
Events accrued (*n*)	1,222	621	1690	854	772	1011	1559	805	1302	254	1744	766
Primary outcome	3P-MACE	3P-MACE	4P-MACE	3P-MACE	3P-MACE	3P-MACE	3P-MACE/CV Death + HHF	4P-MACE	3P-MACE	3P-MACE	3P-MACE	3P-MACE

HbA1c: Glycated hemoglobin, BMI: Body mass index, HTN: Hypertension, CVD: Cardiovascular disease, NR: Not reported, 3P-MACE: 3-point major adverse cardiac events (composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), 4P-MACE: 3P-MACE plus hospitalization due to unstable angina, HHF: Hospitalization due to heart failure

anti-diabetic drugs, post-2008 USFDA mandate. Specific key words include DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1R agonists, sulfonylureas, pioglitazone, insulin, cardiovascular outcome trials. Subsequently, we pooled the data of different cardiovascular endpoints and made a comparative forest plot using GraphPad software Inc. Prism Version 8, US.

This review is an update to our previous systematic review of 2016, which included 7 CVOTs published at that point of time.[19,20] Here we have aimed to provide readers a latest ready-reckoner monograph of comparative forest plot on major CV endpoints observed in twelve placebo-controlled CVOT of anti-diabetic drugs (ADD), published in last decade (2008-2018).

RESULTS

Comparative analysis of MACE outcome in CVOTs

While 3P-MACE (CV death, non-fatal myocardial infarction [MI], non-fatal stroke) was primary objective in all these CVOTs, sitagliptin in TECOS and lixisenatide in ELIXA kept 4P-MACE (component of 3P-MACE plus hospitalization due to unstable angina) as a primary endpoint.

All the 4 DPP-4Is that underwent CVOT such as saxagliptin, alogliptin, sitagliptin and linagliptin achieved the non-inferiority margin on MACE endpoints against placebo, however, no superiority was observed with either agents in the class. With regards to SGLT-2Is, both empagliflozin in EMPA-REG and canagliflozin in CANVAS Program demonstrated a significant superiority in composite of 3P-MACE against placebo (HR = 0.86, 95% CI 0.74-0.99, P = 0.04; HR = 0.86, 95% CI 0.75-0.97, P = 0.02; all P for superiority). While dapagliflozin in DECLARE-TIMI achieved the non-inferiority, it missed to demonstrate the superiority on 3P-MACE (HR = 0.93, 95% CI 0.84-1.03, P = 0.17). Nevertheless, dapagliflozin demonstrated a significant reduction in the composite of CV death or hospitalization due to heart failure (HHF), a prespecified co-primary endpoints (HR = 0.83, 95% CI 0.73-0.95, P = 0.005) studied exclusively in DECLARE-TIMI.

Amongst the 5 GLP-1RAs trials, both exendin-backbone-based compound such as lixisenatide and extended-releasing exenatide was found to be non-inferior compared to placebo and could not demonstrate superiority. Extended-releasing exenatide missed the statistical significance by a flicker (HR = 0.91, 95% CI 0.83-1.00, P = 0.06). In contrast, all GLP-1-backbone-based compound like liraglutide, semaglutide and albiglutide showed superiority on 3P-MACE, compared to placebo (HR = 0.87, 95% CI 0.78-0.97, P = 0.01; HR = 0.74, 95% CI 0.58-0.95, P = 0.02; HR = 0.78, 95% CI 0.68-0.90, P = 0.0006 respectively; all P for superiority). Forest plot in Figure 1 depicts the reduction in MACE in all 12 CVOTs.

Comparative analysis of CV death in CVOTs

None of DPP-4Is demonstrated a significant reduction in CV death in any of the CVOTs when compared to the placebo. Similarly, amongst the GLP-1RAs class, neither lixisenatide,

nor semaglutide or albiglutide have shown any significant reduction in the CV death in ELIXA, SUSTAIN-6 and HARMONY outcomes respectively. However, liraglutide have demonstrated a significantly reduction in CV death (HR = 0.78, 95% CI 0.66-0.93, P = 0.007 for superiority). In the SGLT-2Is class, only empagliflozin shown significant reduction in CV death (HR = 0.62, 95% CI, 0.49-0.77, P < 0.0001 for superiority) compared to placebo in patient with type 2 diabetes and established CV disease. No significant reduction in CV death was observed with canagliflozin and dapagliflozin in CANVAS and DECLARE-TIMI respectively. Forest plot in Figure 2 depicts the reduction in CV death in all 12 CVOTs.

Comparative analysis of non-fatal MI in CVOTs

There was no significant reduction in non-fatal MI in any of the twelve CVOTs except HARMONY Outcomes. While albiglutide reduced MI (both fatal and non-fatal) in HARMONY (HR = 0.75, 95% CI 0.61-0.90, P = 0.003), trends of nonsignificant increase in non-fatal MI was noticed with linagliptin in CARMELINA (HR = 1.15, 95% CI 0.91-1.45, P = 0.23). Forest plot in Figure 3 depicts the reduction in non-fatal in all 12 CVOTs.

Comparative analysis of nonfatal-stroke in CVOTs

EXAMINE, TECOS and CARMELINA demonstrated a neutral outcome on non-fatal stroke with alogliptin, sitagliptin and linagliptin respectively, while saxagliptin had a non-significant trend in increase in stroke (including both fatal and non-fatal) in SAVOR-TIMI, compared to the placebo (HR = 1.11, 95%CI 0.88-1.39, P = 0.38). In SGLT-2Is class, both canagliflozin and dapagliflozin shown neutral outcome on stroke in CANVAS Program and DECLARE-TIMI respectively, however, empagliflozin had non-significant trend in increase in stroke in EMPA-REG (HR = 1.24, 95% CI, 0.92-1.67, P = 0.16). In an independent analysis of FDA, following subgroups of patients that had significantly higher stroke in EMPA-REG which includes[21]

a. patients with age <65 years of age (HR = 1.6, 95% CI 1.03-2.49)
b. patients from Europe (HR = 2.04, 95% CI 1.26-3.29)
c. patients with baseline HbA1c ≥8.5% (HR = 2.13, 95% CI 1.21-3.74)
d. patients treated with insulin (HR = 1.57, 95% CI 1.03-2.41).

With regards to GLP-1RAs class, while liraglutide, extended-releasing exenatide and albiglutide demonstrated neutral outcome in LEADER, EXSCEL and HARMONY outcome respectively, semaglutide showed significant reduction in non-fatal stroke (HR = 0.61, 95% CI, 0.38-0.99, P = 0.04) in SUSTAIN-6 against placebo. Lixisenatide showed a non-significant trend in increase in stroke in ELIXA against placebo. Forest plot Figure 4 summarizes the non-fatal stroke outcome of all 12 CVOTs.

Comparative analysis of all-cause mortality in CVOTs

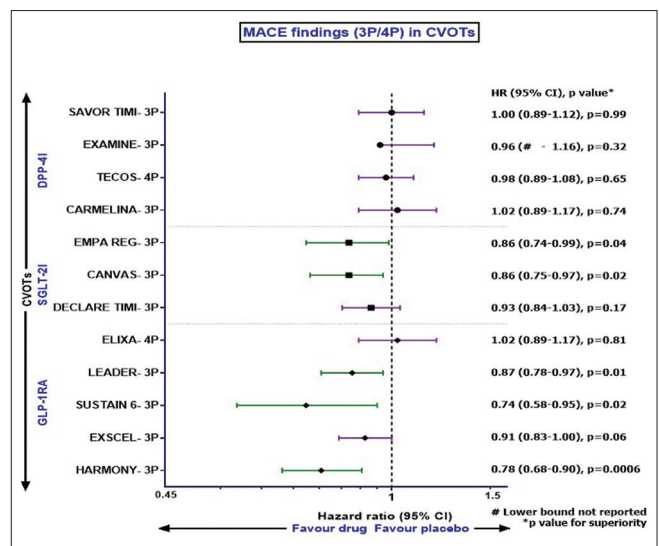No significant increase or decrease in all-cause mortality was observed with alogliptin, sitagliptin and linagliptin

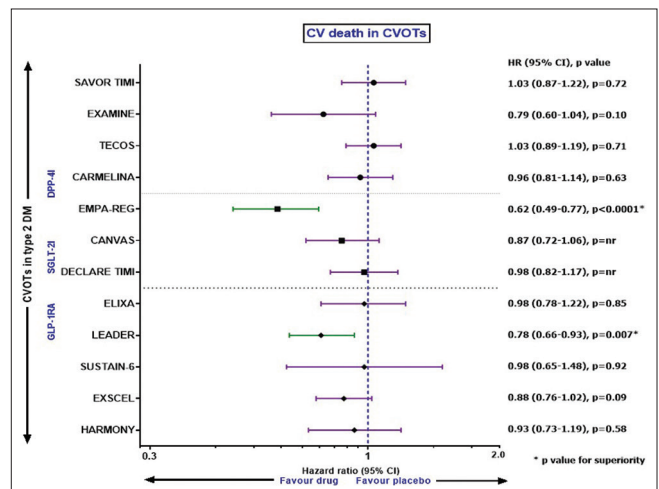

Figure 1: MACE outcomes in CVOTs
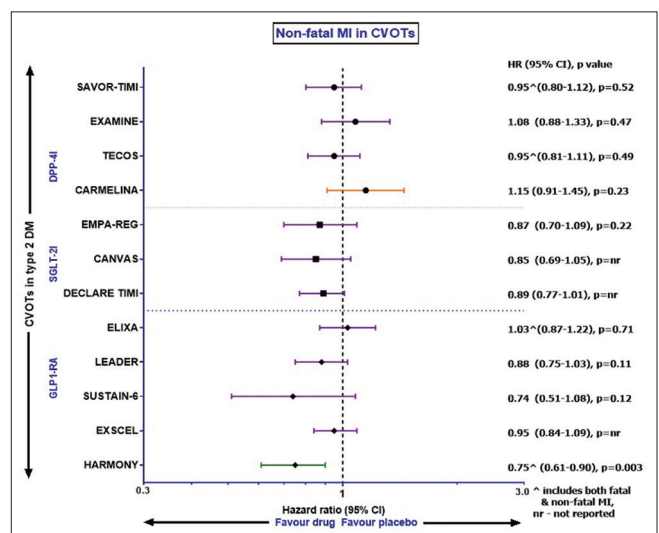

Figure 2: Cardiovascular death in CVOTs

Figure 3: Non-fatal myocardial infarction in CVOTs
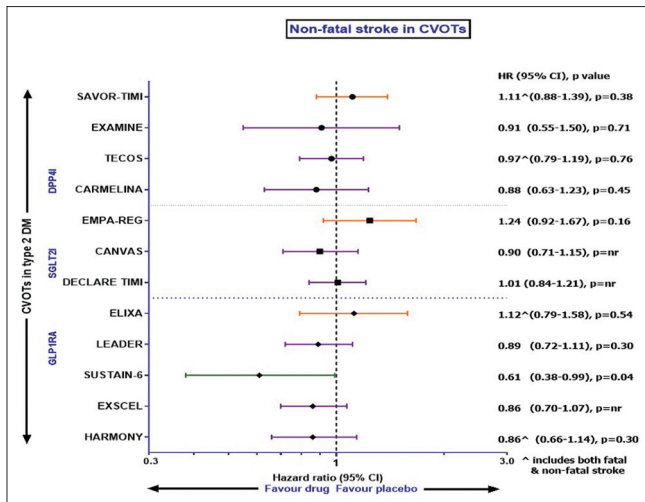
Figure 4: Non-fatal stroke in CVOTs

Figure 5: All-cause death in CVOTs

in EXAMINE, TECOS and CARMELINA respectively. Only saxagliptin had non-significant increased trend in SAVOR-TIMI (HR = 1.11, 95% CI 0.96-1.27, $P = 0.15$) against placebo. Amongst the SGLT-2Is class, while empagliflozin significantly reduced all-cause mortality (HR = 0.68, 95% CI, 0.57-0.82, $P < 0.0001$), canagliflozin and dapagliflozin did not demonstrate any significant reduction. With regards to GLP-1RAs class, while liraglutide and extended-releasing exenatide demonstrated a significant reduction in all-cause mortality in LEADER and EXSCEL (HR = 0.85; 95% CI, 0.74-0.97, $P = 0.02$; HR = 0.86, 95% CI 0.77-0.97, $P = 0.02$) respectively, no reduction was observed with lixisenatide, semaglutide and albiglutide in ELIXA, SUSTAIN-6 and HARMONY outcomes respectively. Forest plot in Figure 5 depicts the all-cause mortality across all 12 CVOTs.

Comparative analysis of heart failure hospitalization (HHF) in CVOTs

DPP-4 inhibitors have shown a very differential outcome on HHF. While saxagliptin showed a significant increase in HHF (HR = 1.27, 95% CI, 1.07-1.51, $P = 0.007$) in SAVOR-TIMI, alogliptin showed a similar trend of increase in EXAMINE (HR = 1.19, 95% CI, 0.89-1.58, $P = 0.24$). The post-hoc analyses of SAVOR-TIMI and EXAMINE both suggested that a certain subgroups had a significant increase in HHF in patients with a history of heart failure and or renal disease.[22-24] Moreover, another post-hoc analysis of EXAMINE suggested a significant increase in HHF in patients even without any history of prior heart failure (HR = 1.76, 95% CI 1.07-2.90, $P = 0.026$).[25] These findings could be misleading because HHF was neither a primary nor a secondary objective in EXAMINE and it was post-hoc analysis and could be subjected to the statistical error. Nonetheless, this outcome is in sharp contrast to sitagliptin (TECOS) and linagliptin (CARMELINA) CVOT where no signals of HHF observed. The subsequent exclusive analysis of HF in TECOS and CARMELINA did not find any signals of the heart failure regardless of the subgroups or the method of statistical analysis applied.[26,27]
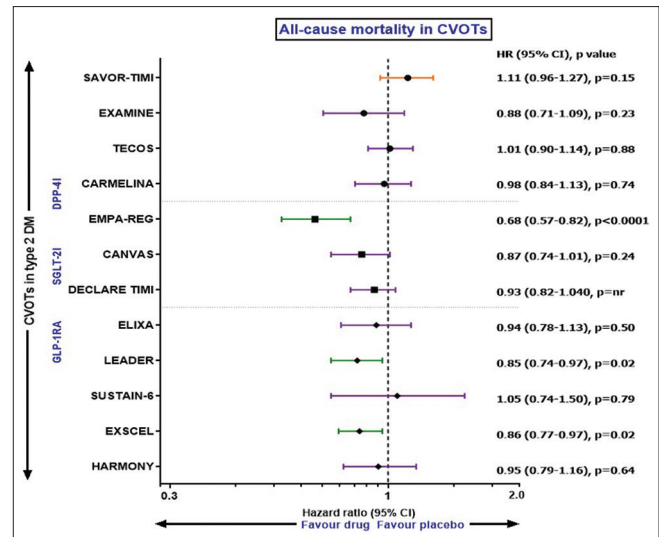
In contrast to SAVOR-TIMI findings, SGLT-2Is class have shown a consistent reduction in HHF. Empagliflozin, canagliflozin and dapagliflozin reduced HHF significantly in EMPA-REG (HR = 0.65, 95% CI, 0.50-0.85, $P = 0.002$), CANVAS program (HR = 0.67, 95% CI 0.52-0.87, P not reported) and DECLARE-TIMI (HR = 0.73, 95% CI 0.61-0.88, P not reported), respectively. With regards to GLP-1RAs, none of them have shown any harm or benefit except semaglutide in SUTAIN-6 which had non-significant trend in increase in HHF (HR = 1.11, 95% CI 0.77-1.61, $P = 0.57$). No increased signals of HHF with liraglutide in LEADER was more encouraging as previous two trials conducted in patients with heart failure had somewhat discordant noise. FIGHT (Functional impact of GLP-1 for heart failure treatment in patient with advanced heart failure) study (N = 300) conducted with liraglutide (Median left ventricular ejection fraction of 25%) had a nonsignificant trend of increase in HHF (HR = 1.30, 95% CI 0.89-1.88, $P = 0.17$) and death (HR = 1.10, 95% CI, 0.57-2.14, $P = 0.78$).[28] Another study LIVE (Liraglutide on Left Ventricular Function in Chronic Heart Failure Patients With and Without Type 2 Diabetes Mellitus) also found a significant increase in serious adverse cardiac events with liraglutide (12 vs. 3, $P = 0.04$), compared to placebo.[29] Forest plot in Figure 6 summarizes the HHF outcomes in all CVOTs.

Comparative safety analysis of CVOTs

No significant increase in pancreatitis was observed with any of these trials of either DPP-4Is or GLP-1RAs when compared to the placebo. However, meta-analysis of pooled data of pancreatitis events from all the 4 CVOTs of DPP-4Is, do find increased signals of pancreatitis with this class versus placebo, although significantly high heterogeneity across these trials may limits this conclusion.[30] Interestingly, no such signals of increase in pancreatitis observed in the pooled meta-analysis of GLP-1RAs CVOTs. There was a significant increased rate of genital infection and increased trend of diabetic keto-acidosis
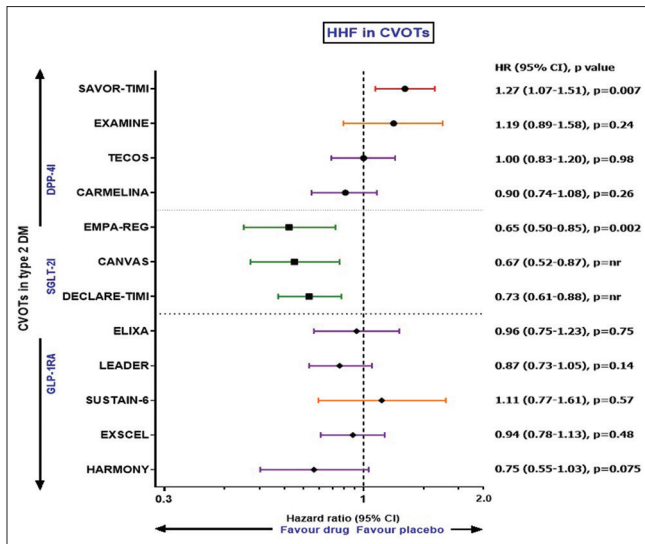
Figure 6: Heart failure hospitalization in CVOTs

with all the SGLT-2Is. Surprisingly, some of the newer issues have also emerged from these CVOTs of anti-diabetic drugs, which was not observed during their phase 2/3 developmental program. Canagliflozin had significantly higher lower limb amputation rate (HR = 1.97, 95% CI 1.41-2.75) compared to the placebo in CANVAS program. Similarly, increase trend in fractures (HR = 1.23, 95% CI 0.99-1.52) was also noticed with canagliflozin in CANVAS program. No such increased signals of amputation and fractures were observed during prospective evaluation with dapagliflozin in DECLARE-TIMI and retrospective evaluation with empagliflozin in EMPA-REG. A significant increase in acute gall stone disease ($P < 0.001$) and acute cholecystitis ($P = 0.046$) was observed with liraglutide in LEADER. A significant increase (HR = 1.76; 95% CI 1.11-2.78, $P = 0.02$) in composite of retinopathy complication was observed with semaglutide in SUSTAIN-6. Liraglutide had similar non-significant increase trend in retinopathy complication (HR = 1.15, 95% CI, 0.87-1.52; $P = 0.33$).

Conclusion, Commentary and Future Ahead

Collectively from the available evidence, it can be concluded that saxagliptin, alogliptin, sitagliptin and linagliptin are CV neutral drugs. Unexpected increase in HHF with saxagliptin and possibly alogliptin led USFDA to put an additional label of HHF in April 2016 recommending avoidance of both of these drugs in patients with established CVD and or chronic kidney disease.[31] Interestingly, scientific statement by American Heart Association (AHA) and European Society of Cardiology (ESC) HF guidelines in 2016 also warned about HHF with the entire class of DPP4Is, despite knowing well that there were no signals of hHF with sitagliptin in TECOS which was published in 2015.[32,33] Although, this move of AHA and ESC was criticized by a group of authors in Lancet.[34] We are still unclear whether HHF with saxagliptin is truly molecule specific or due to the statistical noise, because no such signals were observed with either sitagliptin or linagliptin. Mechanistic

evaluation of glucose-lowering strategies in patients with heart failure (MEASURE-HF) is a 24 week, double-blind, randomized, multi-centric placebo-controlled study (N = 330) is currently evaluating the effects of saxagliptin and sitagliptin on cardiac dimensions and function (change in left ventricular end diastolic volume [LVEDV] index measured by MRI) in patients with type 2 diabetes and heart failure.[35] This study might enlighten us about differential HHF effect between two DPP-4 inhibitors, once it is completed in 2019.

All 3 SGLT-2Is studied so far have shown a consistent benefit on reducing CV risk, especially the HHF. 3P-MACE reduction with both empagliflozin and canagliflozin is noteworthy. CV death and all-cause death reduction with empagliflozin is unique amongst the SGLT-2Is class but this benefit seems to be extending only to the patients with type 2 diabetes and established CVD (secondary prevention cohort). Benefit in HHF and composite of CV death or HHF observed with dapagliflozin in patients with type 2 diabetes with high CV risk (apparently primary prevention cohort) is another unique finding amongst the SGLT-2Is class. It should however be noted that while the results of HHF outcome with SGLT-2Is are in line with some of the recent mechanistical trials, few trials could not demonstrate significant benefit. EMPA-HEART (N = 97) studied for 6-month in patients with T2DM with established CV disease (6% with chronic HF), found a significantly reduction in left ventricular (LV) mass (Δ -3.35; 95% CI -5.9, -0.81; $P = 0.01$) with empagliflozin compared to placebo, indicating reverse remodelling with SGLT-2Is.[36] This result is exciting but it has a limitation of including a very small number of patients, requiring larger and longer trials to conclusively reproduce similar results. Another small-scale, prospective, observational, pilot study (N = 15) of empagliflozin could not demonstrate any significant improvement in exercise tolerance in patients with T2DM with HF with reduced ejection fraction (HFrEF).[37] REFORM (Safety and Effectiveness of SGLT-2 Inhibitors in patients with heart failure and diabetes), a double-blind, placebo-controlled, discovery-study (N = 58) conducted with dapagliflozin in patients with T2DM with HFrEF has failed to show any significant benefit compared to placebo, although improvement was observed in subgroups with heart failure with preserved ejection fraction (HFpEF) only.[38]

Like these, there are many exclusive heart failure trials, which are currently under progress and expected to add evidence to the available literature with regards to HF lowering capabilities of SGLT-2Is in patients with or without diabetes, but with established heart failure (both HF with preserved or reduced ejection fraction, Table 3). VERTIS-CV (Ertugliflozin treatment in type 2 diabetes mellitus participants with vascular disease) and SCORED (Effect of sotagliflozin on cardiovascular and renal events in patients with type 2 diabetes and moderate renal impairment who are at cardiovascular risk) are next two CVOT being conducted with ertugliflozin and sotagliflozin respectively, that will also add evidence to the available literature for SGLT-2Is.[39,40]

Table 3: Heart failure trials of SGLT-2 inhibitors currently under progress

Eponyms	n	Duration (Month)	Background disease	Primary objective	Expected results (year)	ClinicalTrial.gov identifier
Empagliflozin						
RECEDE-CHF	34	1.5	T2DM with stable HFrEF on loop diuretics	Changes in urinary output and sodium	February 2019	NCT03226457
EMBRACE-HF	60	3	T2DM with HF (HFrEF or HFpEF, ischemic or non-ischemic)	Impact on pulmonary artery diastolic pressure in patients on CardioMEMs device implanted	June 2019	NCT03030222
Empire-HF	189	3	Patients with HFrEF	Changes in NTproBNP	October 2019	NCT03198585
EMPA-VISION	86	3	Patients with HFrEF/ HFpEF	Change from baseline to week 12 in PCr/ATP ratio in the resting state measured by 31P MRS	October 2019	NCT03332212
EMPA-RESPONSE	80	1	Patients with acute decompensated HF	Change in dyspnea, weight change, hospital stay, NTproBNP, HF readmission, all-cause mortality	December 2019	NCT03200860
ELSI	84	3	Patients with HFrEF/ HFmEF	Tissue sodium content assessed by 23Na-MRI	December 2019	NCT03128528
EMPERIAL-Reduced	300	3	Patients with HFrEF	Exercise capacity by 6-min walk test	December 2019	NCT03448419
EMPERIAL-Preserved	300	3	Patients with HFpEF	Exercise capacity by 6-min walk test	December 2019	NCT03448406
SUGAR	130	10	T2DM with HFrEF	LVESVI and LV strain measured by cardiac MRI	February 2020	NCT03485092
EMMY	476	6.5	Acute MI with or without T2DM	Changes in NTproBNP and EF	April 2020	NCT03087773
EMPA Acute HF	56	1	T2DM with acute heart failure	Changes in cardiac output measured by ClearSight system	May 2020	NCT03554200
ERA-HF	128	2	Patients with HFrEF	Measuring PVC by ICD/CRTD device	June 2020	NCT03271879
EMPEROR-Reduced	2850	38	Patients with or without T2DM with HFrEF	Composite of CV death or hHF	June 2020	NCT03057977
EMPEROR-Preserved	4126	38	Patients with or without T2DM with HFpEF	Composite of CV death or hHF	June 2020	NCT03057951
EMPA-TROPISM	80	6	Patients with HFrEF	LVESV and LVEDV	December 2020	NCT03485222
EMPA	50	1	T2DM with stable HF loop diuretics	Effect on natriuresis measuring urinary Na at day 36	June 2022	NCT03027960
Dapagliflozin						
DEFINE-HF	250	3	T2DM with HFrEF (ischemic or non-ischemic)	Effect on BNP and NTproBNP, symptoms and quality of life	April 2019	NCT02653482
PRESERVED-HF	320	3	T2DM or IGT with HFpEF	Changes in NTproBNP	September 2019	NCT03030235
DAPA-HF	4744	36	T2DM with HFrEF	Composite of CV death or hHF or urgent HF	December 2019	NCT03036124
DELIVER	4700	33	Patients with HFpEF	Composite of CV death or hHF or urgent HF	June 2021	NCT03619213
Canagliflozin						
CANDLE	250	6	Canagliflozin versus glimepiride in T2DM with NYHA Class I/III HF	Changes in NTproBNP	December 2017	UMIN000017669
-	88	3	Canagliflozin versus sitagliptin in T2DM with NYHA Class I/III HF	Changes in aerobic exercise capacity	March 2019	NCT02920918
Ertugliflozin						
ETRU-GLS	120	6	T2DM with stage B HF	Changes in global longitudinal strain	October 2020	NCT03717194
ERADICATE-HF	36	3	T2DM with HFrEF or HFpEF	Changes in proximal Na+ reabsorption	March 2021	NCT03416270

Contd...

Table 3: Contd...

Eponyms	*n*	Duration (Month)	Background disease	Primary objective	Expected results (year)	ClinicalTrial.gov identifier
Sotagliflozin						
SOLOIST-WHF	4000	32	T2DM with HFrEF	Composite of CV death or hHF	January 2021	NCT03521934

CV: Cardiovascular, T2DM: Type 2 diabetes mellitus, HF: Heart failure, EF: Ejection fraction, HFrEF: Heart failure with reduced ejection fraction, HFpEF: Heart failure with preserved ejection fraction, HFmEF: Heart failure with moderately reduced ejection fraction, SITA: Sitagliptin, LV: Left ventricular, LVESV: Left ventricular end systolic volume, LVEDV: Left ventricular end diastolic volume, LVESI: Left ventricular end systolic index, Na: Sodium, NYHA: New York heart association

With regards to GLP-1RAs, while lixisenatide and extended-release exenatide are CV neutral; liraglutide, semaglutide and albiglutide has shown a significant CV risk reduction (3P-MACE). Moreover, both liraglutide and extended-release exenatide have shown a significant reduction in all-cause death, while only liraglutide has shown a significant reduction in CV death. Furthermore, semaglutide has shown a significant reduction in non-fatal stroke, while albiglutide has shown a nominally significant reduction in MI.

Finally, we need to exercise some cautions while interpreting these CVOTs results. As because HHF, CV death and all-cause deaths are a pre-specified secondary or exploratory end point or based on post-hoc analysis (EXAMINE), these end-points are not included in the statistical hierarchical testing strategies like primary outcomes of 3P/4P-MACE. Thus, any conclusion on these outcomes should be deemed exploratory.

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Conflicts of interest
There are no conflicts of interest.

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