Editorial

Recent cardiovascular outcome trials of antidiabetic drugs: A comparative analysis

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INTRODUCTION

Since the rosiglitazone controversy, the US Food Drug Administration (USFDA) in the year 2008, mandated that all new antidiabetic agents must undergo an adequately powered, glycemic-equipoised, cardiovascular (CV) outcome trial (CVOT) in high-risk Type 2 diabetic patients, during postmarketing phase to demonstrate its safety by showing noninferiority against placebo. While noninferiority was defined as hazard ratio (HR) of <1.3 for the upper bound of 95% confidence interval (CI), superiority can also be claimed if upper boundary of 95% CI is found to be <1.0 in a subsequent statistical analysis.[1] In 2012, The European Medicines Agency also floated similar guidelines.[2] As a result, since post–2008, all newer antidiabetic agents approved by USFDA have underwent or currently undergoing CVOT. Seven of these trials are already published now. Of these seven trials, six were conducted with the drugs which work through incretin pathway and one trial with the drug which works through sodium-glucose linked transporter-2 receptor (SGLT-2) inhibition. From the six incretin trials, three trials were conducted with dipeptidyl peptidase-4 inhibitors (DPP-4Is) and other three trials with glucagon-like peptide-1 receptor agonists (GLP-1RAs).

Although all these trials have been conducted separately with different types of patient cohort and different degree of background CV disease (CVD), however, the patient population in all the trials was more similar than different. All the trials used almost similar well-defined end-points adjudicated by a blinded committee. Even if subtle differences in ascertainment of the clinical events exist, that is expected to be minimized by blinded adjudication and treatment randomization. Thus, a logic of comparing these trials is perhaps there, especially to find which drugs competes best for the second-line drug after metformin.

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This compendium will comparatively analyze the results from seven CVOTs on different CV end-points and put a perspective on relative merit of each agent to enable clinician to understand merit and demerit of each drugs in the modern management of Type 2 diabetes.

COMPARATIVE ANALYSIS OF CARDIOVASCULAR OUTCOME TRIALS

Of the three CVOTs of DPP-4Is, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in myocardial infarction (SAVOR-TIMI); Examination of CV Outcomes with alogliptin versus Standard of Care (EXAMINE); and Trial Evaluating CV Outcomes with Sitagliptin (TECOS); evaluated saxagliptin, alogliptin, and sitagliptin mainly in high-risk patients (78% of patients in SAVOR-TIMI, 100% patients in EXAMINE, and TECOS had preexisting heart disease) for 2.1, 1.5, and 3 year, respectively.[3-5] Only CVOT of SGLT-2 inhibitors currently available is Empagliflozin Reducing Excess Glucose (EMPA-REG), conducted with empagliflozin, in high-CV risk cases (99% had preexisting CVD) for a median of 3.1 years.[6] The three trials conducted with GLP-1RAs are the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial; Liraglutide Effect and Action in Diabetes: Evaluation of CV Outcome Results (LEADER); and Evaluate CV and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) - conducted with lixisenatide, liraglutide, and semaglutide for a median of 2.1, 3.8 and 2.0 year, respectively.[7-9]

While EXAMINE included most sick patients (acute coronary syndrome [ACS] in preceding 3 months) among the three DPP-4Is trials, ELIXA had most sick patients (ACS within 6 months) among GLP-1RAs trial. EXAMINE had the smallest duration of evaluation among all the seven CVOTs as this study achieved desired event rate very quickly owing to the inclusion of very high-CV risk ACS cases. The similarity and differences in characteristics of the patient profile, treatment received in all the seven CVOTs have been summarized in Table 1.

Table 1: Baseline characteristics of patients in all seven CVOTs

Parameters	TECOS	SAVOR	EXAMINE	EMPA-REG	ELIXA	LEADER	SUSTAIN-6
Patients number	14 735	16 492	5380	7020	6068	9340	3297
HbA1C entry criteria (%)	6.5–8	6.5–12	6.5–11	7-10	5.5-11	≥7	≥7
Established CVD (%)	100	78	100	99	100	81	58.8
Age (year)	≥50	≥40	≥18	≥18	≥30	≥50	≥50
Mean age (year)	65.5	65	61	63.1	60.3	64.3	64.6
Number of events accrued	1690	1,222	621	772	844	1302	254
Primary outcome	4P-MACE	3P-MACE	3P-MACE	3P-MACE	4P-MACE	3P-MACE	3P-MACE
Median duration of trial (year)	3.0	2.1	1.5	3.1	2.1	3.8	2.1
Asian population (%)	22.3	10.7	20.2	19.2	12.7	7.6	8.3
Mean duration of diabetes (year)	11.6	10.3	7.3	>10 (57%)	9.3	12.8	13.9
Mean baseline A1C (%)	7.2	8	8	8.1	7.7	8.7	8.7
Mean BMI (Kg/M^2)	30.2	31.2	28.7	30.6	30.2	32.5	32.8
Hypertension, %	86	82	83	94	75.5	90	92.8
Dyslipidemia, %	77	71	NR	NR	NR	77	NR
Current smoker, %	11	NR	14	13	11.7	12.1	NR
Previous heart failure, %	18	13	28	10	22.4	17.9	23.6
Metformin (%) –	81.0 (Sita)	69.9 (Saxa)	67.4 (Alo)	73.8 (Empa)	67.2 (Lixi)	75.8 (Lira)	73.5 (Sema)
	82.2 (PBO)	69.2 (PBO)	65.0 (PBO)	74.3 (PBO)	65.4 (PBO)	77.0 (PBO)	72.9 (PBO)
Insulin (%)	23.5 (Sita)	41.6 (Saxa)	30.3 (Alo)	48.1 (Empa)	39.2 (Lixi)	43.6 (Lira)	58.0 (Sema)
	22.9 (PBO)	41.2 (PBO)	29.4 (PBO)	48.6 (PBO)	39.0 (PBO)	45.5 (PBO)	58.0 (PBO)
SU (%)	45.6 (Sita)	40.5 (Saxa)	46.2 (Alo)	43.0 (Empa)	32.6 (Lixi)	50.6 (Lira)	42.4 (Sema)
	45.0 (PBO)	40.0 (PBO)	46.9 (PBO)	42.5 (PBO)	33.5 (PBO)	50.5 (PBO)	43.2 (PBO)
TZD (%)	2.7 (Sita)	6.2 (Saxa)	2.4 (Alo)	4.3 (Empa)	1.4 (Lixi)	6.3 (Lira)	2.2 (Sema)
	2.7 (PBO)	5.7 (PBO)	2.5 (PBO)	4.3 (PBO)	1.7 (PBO)	6.0 (PBO)	2.5 (PBO)
Aspirin	78.6 (Sita)	75.5 (Saxa)	90.6 (Alo)	82.7 (Empa)	97.6^ (Lixi)	63.7 (Lira)	63.8 (Sema)
	78.4 (PBO)	75.0 (PBO)	90.6 (PBO)	82.6 (PBO)	97.4^ (PBO)	62.1 (PBO)	64.1 (PBO)
Statin	79.8 (Sita)	78.3 (Saxa)	90.6 (Alo)	77.5 (Empa)	93.3 (Lixi)	72.7 (Lira)	72.8 (Sema)
	80.0 (PBO)	78.4 (PBO)	90.3 (PBO)	76.0 (PBO)	92.2 (PBO)	71.4 (PBO)	72.8 (PBO)
Beta-blockers	63.4 (Sita)	61.6 (Saxa)	81.7 (Alo)	65.2 (Empa)	83.6 (Lixi)	56.7 (Lira)	56.7 (Sema)
	63.7 (PBO)	61.6 (PBO)	82.2 (PBO)	64.2 (PBO)	85.3 (PBO)	54.0 (PBO)	58.2 (PBO)
RAAS-blocker	78.3 (Sita)	81.8 (Saxa)	81.5 (Alo)	81.1 (Empa)	84.9 (Lixi)	83.5 (Lira)	83.6 (Sema)
	79.2 (PBO)	82.5 (PBO)	82.5 (PBO)	80.1 (PBO)	85.0 (PBO)	82.1(PBO)	83.5 (PBO)

^Includes all anti-platelet drugs, CVD: Cardiovascular disease, 3P-MACE: 3 point major adverse cardiac events (composite of cardiovascular death, nonfatal stroke and nonfatal myocardial infarction), 4-P MACE: Composite of 3P-MACE plus unstable angina, ACS: Acute coronary syndrome, BMI: Body mass index, SU: Sulfonylureas, TZD: Thiozoliendiones, RAAS: Rennin-angiotensin-aldosterone system, Sita-: Sitagliptin, Saxa: Saxagliptin, Alo: Alogliptin, Empa: Empagliflozin, Lixi: ILixisenatide, Lira: Liraglutide, Sema- semaglutide, PBO: Placebo, NR: Not reported

COMPARATIVE ANALYSIS OF MAJOR ADVERSE CARDIAC EVENT OUTCOME IN ALL CARDIOVASCULAR OUTCOME TRIALS

All the three DPP-4Is trials achieved the noninferiority margin on major adverse cardiac event (MACE) end-points as laid down by the FDA in 2008, thereby suggesting that saxagliptin, alogliptin, and sitagliptin all are CV neutral drugs. However, no superiority on MACE was observed with any of the three DPP-4Is.[3-5] Surprisingly, empagliflozin in EMPA-REG not only achieved the noninferiority but also demonstrated a substantial superiority against placebo. EMPA-REG found a significant relative risk reduction in the primary outcome of 3P-MACE (composite of CV death, nonfatal myocardial infarction [MI], and nonfatal stroke) by 14% (HR = 0.86, 95% CI = 0.74–0.99, $P = 0.04$ for superiority) compared to the placebo.[6] From the three GLP-1RAs trials, ELIXA found lixisenatide to be noninferior (4P MACE, HR = 1.02; 95% CI = 0.89–1.17; $P < 0.001$ for noninferiority) to placebo while liraglutide and semaglutide showed superiority on 3P-MACE compared to placebo. LEADER found 13% relative risk reduction (HR = 0.87; 95% CI = 0.78–0.97; $P = 0.01$) and SUSTAIN-6 demonstrated even a larger 26% relative risk reduction (HR = 0.74; 95% CI = 0.58–0.95; $P = 0.02$) in 3P-MACE.[7-9] Interestingly, both LEADER and SUSTAIN-6 also demonstrated a significant reduction on the expanded composite outcome (death from CV causes, nonfatal MI, nonfatal stroke, revascularization or hospitalization for unstable angina, or heart failure) by 12% (HR = 0.88; 95% CI = 0.81–0.96; $P = 0.005$) and 26% (HR = 0.74; 95% CI = 0.62–0.89, $P = 0.002$), respectively, whereas EMPA-REG could not demonstrate a significant reduction (HR = 0.89; 95% CI = 0.78–1.01; $P = 0.08$) on expanded 4P-MACE (3P-MACE plus unstable angina). Forest plot in Figure 1 depicts the reduction in MACE in all seven CVOTs.

The differences in the metabolic parameters across these three positive trials are summarized in Table 2. While all these three trials, EMPA-REG, LEADER, and

SUSTAIN-6 demonstrated a statistical significant relative risk reduction in 3P-MACE (by 14%, 13%, and 26%, respectively), there appears to be some difference even on this end-point, especially when judged by a different sensitivity analysis method. While the statistical benefit in 3P-MACE of EMPA-REG was just achieved ($P = 0.04$), 3P-MACE in LEADER had statistically more robust P value ($P = 0.01$) despite almost similar risk reduction in 3P-MACE (13% vs. 14% reduction in EMPA-REG). Interestingly, the magnitude of 3P-MACE reduction was clearly larger in SUSTAIN-6 (26%) compared to EMPA-REG (14%) and also had more robust P value (0.02 vs. 0.04, respectively). This difference of P value among the three trials perhaps could be the reason as to why LEADER and SUSTAIN-6 still show significant P value irrespective of the sensitive analysis used, whereas EMPA-REG no longer remains significant in other sensitive analysis [Table 3]. Moreover, 3P-MACE in EMPA-REG no longer remain significant, when silent MI was included (HR = 0.91; 95% CI = 0.73–1.13) and nonassessable deaths were excluded (HR = 0.90; 95% CI = 0.77–1.06) as suggested in an independent analysis by USFDA.[10]

Ironically, the two groups that did not show a significant benefit in 3P-MACE in LEADER included patients without established CVD (19% of the overall cohort) and patients with estimated glomerular filtration rate >60 ml/min. It is also not yet clear whether this lack of benefit in these two groups was also observed with respect to CV or all-cause death.[8]

COMPARATIVE ANALYSIS OF CARDIOVASCULAR DEATH IN ALL CARDIOVASCULAR OUTCOME TRIALS

No benefit was observed in reducing CV death in any CVOTs with DPP-4Is against placebo. Similarly, two GLP-1RAs, lixisenatide, and semaglutide could not show any significant reduction in the CV death in ELIXA and SUSTAIN-6, respectively. However, both empagliflozin in EMPA-REG and liraglutide in LEADER, significantly reduced CV death by 38% (HR = 0.62; 95% CI = 0.49–0.77; $P < 0.0001$) and 22% (HR = 0.78; 95% CI = 0.66–0.93; $P = 0.007$), respectively. This suggests that EMPA-REG showed much larger reduction in CV deaths compared to LEADER (38% vs. 22%) with more persuasive P value (<0.0001 vs. 0.007). Forest plot in Figure 2 depicts the outcome of CV death in all seven CVOTs.

It should also be noted that while the reduction in CV death in EMPA-REG was evidently robust (2.3% absolute risk reduction), a large proportion (~40%) of CV deaths were also attributed to "other" CV causes (this category is not as diagnostically sound as the others).[10] No reduction in CV death was observed with SUSTAIN-6.
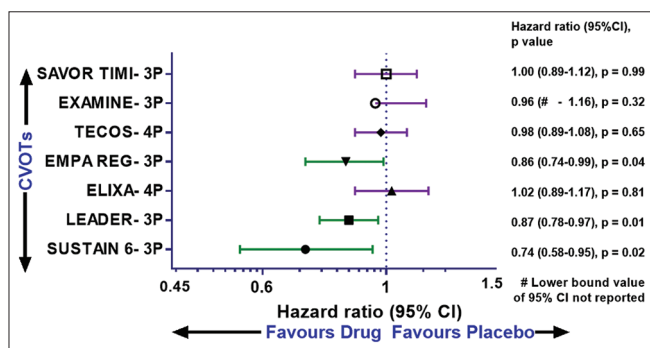

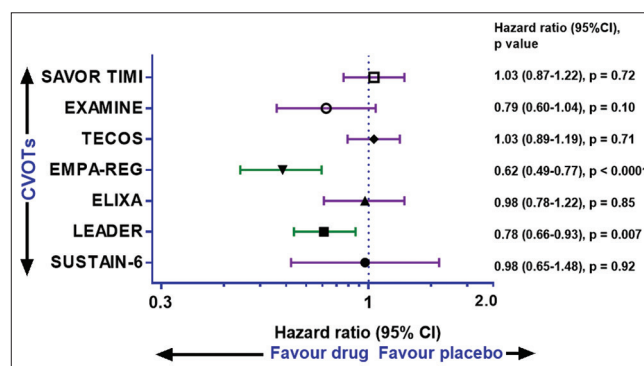**Figure 1:** Primary major adverse cardiac event in cardiovascular outcome trials

Figure 2: Cardiovascular death in cardiovascular outcome trials

Table 2: Difference in metabolic changes at the end of trial in three positive CVOTs

	EMPA-REG		LEADER		SUSTAIN-6		
	Baseline	ΔEOT	Baseline	ΔEOT	Baseline	ΔEOT (0.5 mg)	ΔEOT (1.0 mg)
HbA1c, %	8.1	−0.3	8.7	−0.4	8.7	−0.66	−1.05
SBP, mm Hg	135	−4.0	136	−1.2	135.6	−1.3	−2.6
DBP, mm Hg	77	−1.0	77	+0.6	77	0.04	+0.14
Weight, Kg	86	−2.0	92	−2.3	92.1	−2.9	−4.4
LDL-C, mg/dL	86	+5.3	89.5	−1.6	82.3	−3.3	−0.8
HDL-C, mg/dL	44.5	+2.0	45.5	+0.3	43.7	0.0	+1.7
Heart rate, bpm	71	0.0	72	+3.0	72	+2.0	+2.5

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, ΔEOT: Changes at the end of trial

COMPARATIVE ANALYSIS OF NONFATAL MYOCARDIAL INFARCTION IN ALL CARDIOVASCULAR OUTCOME TRIALS

There was a nonstatistical trend in reduction of nonfatal MI in almost all CVOTs except EXAMINE and ELIXA. Forest plot in Figure 3 depicts this outcome. Silent MI was assessed in all patients in LEADER, and SUSTAIN-6 but only in ~ 50% patient in EMPA-REG. Intriguingly, there was 28% increased trend of silent MI in EMPA-REG although statistically insignificant.

COMPARATIVE ANALYSIS OF NONFATAL-STROKE IN ALL CARDIOVASCULAR OUTCOME TRIALS

EXAMINE, TECOS, and LEADER had neutral outcome on nonfatal stroke. SAVOR-TIMI and ELIXA showed a nonsignificant trend in the increase in stroke. Stroke also increased by 24% in empagliflozin arm (HR = 1.24; 95% CI = 0.92–1.67; $P = 0.16$), although it was statistically not significant. In contrast, SUSTAIN-6 showed a significant 39% relative risk reduction in nonfatal stroke (HR = 0.61; 95% CI = 0.38–0.99; $P = 0.04$). While SUSTAIN-6 lowered nonfatal stroke by a huge margin (39%), but its P value just reached statistical significance ($P = 0.04$). Forest plot Figure 4 depicts the nonfatal stroke outcome of all seven CVOTs. Ironically, four subgroups of patients that had significantly higher stroke in EMPA-REG in an independent analysis of FDA included in the study as follows:[10]

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

COMPARATIVE ANALYSIS OF HOSPITALIZATION DUE TO UNSTABLE ANGINA IN ALL CARDIOVASCULAR OUTCOME TRIALS

No difference in hospitalization due to unstable angina was observed in these CVOTs except SAVOR-TIMI and ELIXA, the latter two had increased trend although it was statistically insignificant. Figure 5 depicts this outcome in all CVOTs.

COMPARATIVE ANALYSIS OF ALL-CAUSE MORTALITY IN ALL CARDIOVASCULAR OUTCOME TRIALS

SAVOR-TIMI had increased trend, while TECOS, EXAMINE, and ELIXA were neutral. Empagliflozin reduced all-cause mortality by 32% (HR = 0.68; 95% CI = 0.57–0.82; $P < 0.0001$), while LEADER reduced it by 15% (HR = 0.85; 95% CI = 0.74–0.97; $P = 0.02$). This suggests that EMPA-REG had larger and robust reduction in all-cause mortality compared to LEADER (32% vs. 15%, respectively) with persuasive P value (<0.0001 vs. 0.02, respectively). SUSTAIN-6 did not find any benefit in all-cause mortality. Forest plot in Figure 6 depicts the all-cause mortality across all CVOTs.
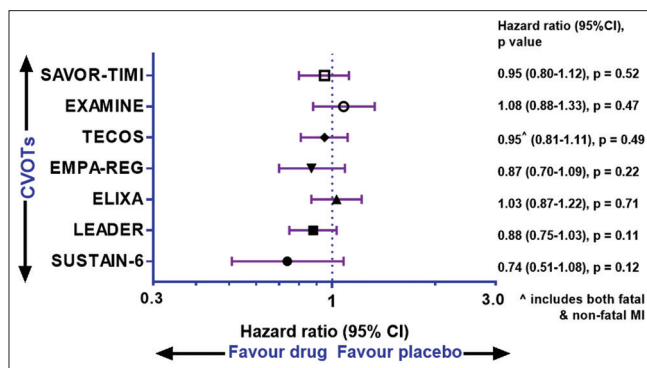

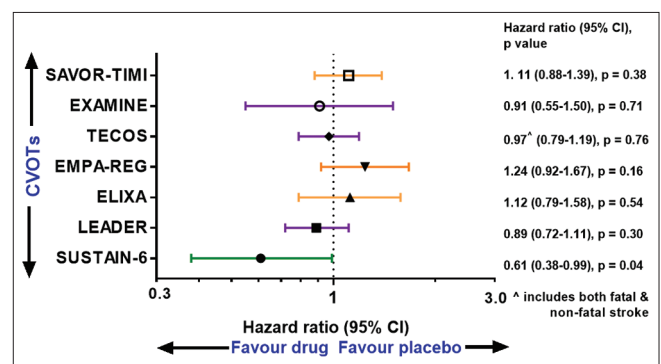**Figure 3:** Nonfatal myocardial infarction in cardiovascular outcome trials

Figure 4: Nonfatal stroke in cardiovascular outcome trials

Table 3: Results of 3P-MACE assessed through different sensitivity analysis in three positive CVOTs

	EMPA-REG		LEADER		SUSTAIN-6	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Intention-to-treat analysis	0.86 (0.74-0.99)	0.04	0.87 (0.78-0.97)	0.01	0.74 (0.58-0.95)	0.02
Per-Protocol analysis	0.86 (0.75-1.00)	0.05	0.85 (0.75-0.96)	NR	0.71 (0.54-0.95)	NR
On-Treatment analysis	0.86 (0.75-1.02)	0.09	0.83 (0.73-0.95)	NR	0.73 (0.56-0.96)	NR

COMPARATIVE ANALYSIS OF HEART FAILURE HOSPITALIZATION IN ALL CARDIOVASCULAR OUTCOME TRIALS

Hospitalization due to heart failure (HHF) was a prespecified exploratory end-point in all the trials. Saxagliptin in SAVOR-TIMI showed a statistically significant 27% increase in the relative risk of HHF (HR = 1.27; 95% CI = 1.07–1.51, $P = 0.007$). This HHF in SAVOR-TIMI was more pronounced within its first year of randomization. Similar trend of increase (19%) was also observed with alogliptin in EXAMINE (HR = 1.19; 95% CI = 0.89–1.58; $P = 0.24$), although it was statistically insignificant. Intriguingly, the *post hoc* analyses from both SAVOR-TIMI and EXAMINE found that certain subgroups had a significant increase in HHF that included, patients with a history of heart failure and renal disease.[11-13] Curiously, a *post hoc* analysis of EXAMINE also suggested a significant increase in HHF in patients without any history of heart failure (HR = 1.76, 95% CI = 1.07–2.90; $P = 0.026$).[14] On the contrary, sitagliptin in TECOS found no signal of HHF. Further extensive analysis of TECOS also could not find any signal of the heart failure, regardless of time, subgroups, and method of statistical analysis applied.[15,16] Meanwhile, FDA put a warning on April 5, 2016 which states that "safety review has found that Type 2 diabetes medicine containing saxagliptin and alogliptin may increase the risk of heart failure particularly in the patients who already have heart or kidney disease."[17] It should however be noted that HHF was neither a primary or secondary objective of these studies and thus any subanalysis could be subject to statistical error or may be a play of chance.

However, empagliflozin showed a robust reduction in HHF by 35% (HR = 0.65, 95% CI = 0.50–0.85; $P = 0.002$) in EMPA-REG. LEADER had a nonsignificant reduction in HHF, which definitely sounds encouraging for liraglutide as earlier two trials conducted in patients with exclusive heart failure subjects, had disappointing results. While functional impact of GLP-1 for heart failure treatment ($n = 300$) conducted in patient with advanced heart failure (median left ventricular ejection fraction of 25%) with liraglutide (FIGHT) 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; $P = 0.78$), the effect of liraglutide on left ventricular function in chronic heart failure patients with and without Type 2 diabetes mellitus (LIVE) also had a significant increase in serious adverse cardiac events when compared to placebo (12 vs. 3, respectively, $P = 0.04$).[18,19] Intriguingly, SUSTAIN-6 had a nonsignificant increase in trend of HHF. Forest plot in Figure 7 depicts the HHF in all CVOTs.
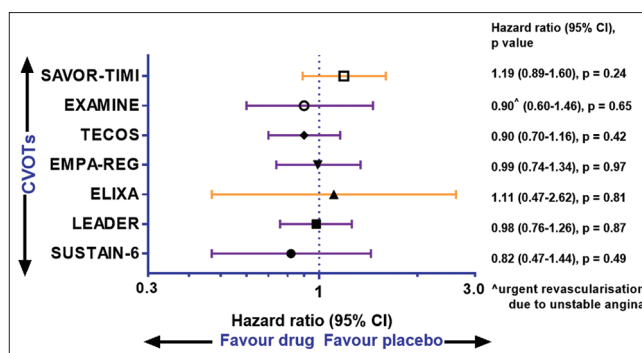

Figure 5: Unstable angina hospitalization in cardiovascular outcome trials
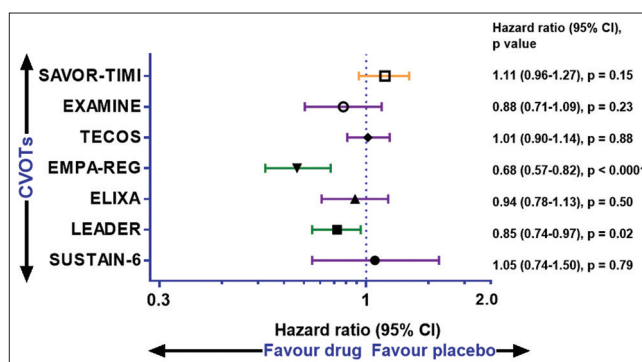

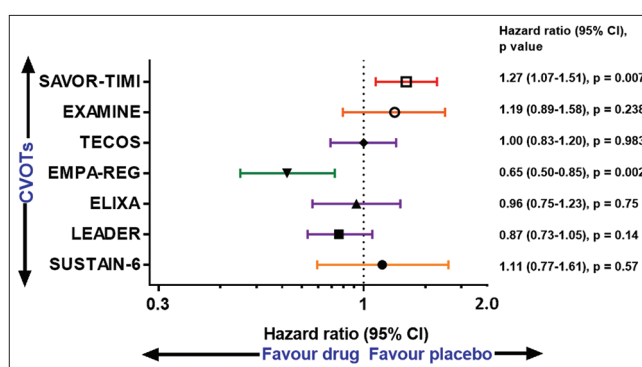**Figure 6:** All-cause mortality in cardiovascular outcome trials

Figure 7: Heart failure hospitalization in cardiovascular outcome trials

COMPARATIVE SAFETY ANALYSIS OF ALL CARDIOVASCULAR OUTCOME TRIALS

All six CVOTs conducted with incretin-based therapy almost ruled out any real increase in pancreatitis or pancreatic cancer as was perceived earlier; however, there was a slight trend of increase in pancreatitis in DPP-4Is arm compared to the placebo. However, two newer issues have also emerged in these studies. While LEADER showed a significant increase in acute gallstone disease ($P < 0.001$) and acute cholecystitis ($P = 0.046$), SUSTAIN-6 showed a significant increase (HR = 1.76; 95% CI = 1.11–2.78, $P = 0.02$) in retinopathy complication (includes vitreous hemorrhage, onset of diabetes-related blindness, and

the need for treatment with an intravitreal agent or retinal photocoagulation). It should also be noted that liraglutide in LEADER also reported an increased trend in retinopathy complication (HR = 1.15; 95% CI = 0.87–1.52; P = 0.33), although it was nonsignificant.

COMMENTARY AND CONCLUSION

From the available evidence so far gathered, it is apparent that all the three DPP-4Is studied are CV neutral drugs although saxagliptin had undoubted increase in HHF in certain subgroups of patients. Alogliptin somehow had controversial results on HHF. In this regard, sitagliptin in TECOS came out cleanest and showed no signal of HHF. Among the GLP-RAs trials, lixisenatide was found to be CV neutral without any obvious safety signals. LEADER had a concordant reduction in all the CV end-points, some statistically significant and some nonsignificant. SUSTAIN-6 had the largest reduction in 3P-MACE but no reduction in the CV death, all-cause death, and HHF. EMPA-REG had the largest and the most robust reduction in the CV death, all-cause death, and HHF, but a discordant nonsignificant increase in silent MI (assessed in half patients only) and nonfatal stroke, that is somewhat worrying.

It should be worthwhile to mention that both CV- and all-cause deaths are prespecified secondary end-points across the CVOTs, and these individual end-points have not undergone the strategic statistical hierarchical testing similar in line like the composite of primary 3P or 4P MACE. It is possible that α (alpha) error had already been spent during the calculation of 3P/4P and thus any subsequent analyses of other end-points including CV- and all-cause mortality should be deemed as exploratory. Nevertheless, the hard core Bayesian analysis of these secondary end-points (CV death and all-cause mortality) and even the exploratory end-points (HHF) in EMPA-REG, also suggested a robust reduction in these outcomes.[20] It should also be pointed that while 3P-MACE reduction in EMPA-REG was mainly attributed to reduction in the CV death which was majorly due to the reduction in death from HHF; 3P-MACE reduction in LEADER was derived from summation of all CV end-points although here also reduction in the CV death contributed majorly. In contrast, the 3P-MACE reduction in SUSTAIN-6 was primarily attributed to a significant reduction in the nonfatal stroke.

Nonetheless, the available evidences from seven CVOTs, it can be proposed that the following drugs may be preferable in decreasing order of preference, to reduce CV outcomes in type 2 diabetes patients with known CVD:
a. 3P-MACE: Semaglutide >> liraglutide = empagliflozin >> lixisenatide = sitagliptin = alogliptin = saxagliptin

b. CV-death, all-cause death, HHF: Empagliflozin >> liraglutide >> lixisenatide = sitagliptin = alogliptin = semaglutide = saxagliptin
c. Nonfatal stroke: Semaglutide >> liraglutide > alogliptin = sitagliptin = saxagliptin = lixisenatide = empagliflozin.

Several future CVOT trials are being conducted with linagliptin (CARMELINA, CAROLINA), canagliflozin (CANVAS, CANVAS-R), dapagliflozin (DECLARE-TIMI), ertugliflozin (VERTIS-CV), exenatide once weekly (EXCEL), dulaglutide (REWIND) and albiglutide (HARMONY) which will further enlighten us in future.[21-29]

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