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Review

Cardiovascular outcome trials in type 2 diabetes: A critical analysis

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1. Introduction

Diabetes is associated with two-fold excess risk of vascular diseases, which is independent of other traditional risk factors [1]. Patients with type 2 diabetes without any history of preceding cardiovascular disease have similar risk of myocardial infarction as patients with history of previous myocardial infarction without type 2 diabetes [2]. There is 50% increased risk of cardiovascular death and this is one of the main causes of mortality in patients with diabetes [3]. Controversies about the drugs used to control blood sugar and enhanced cardiovascular risk are there in literature since decades. The University Group Diabetes Program (UGDP) raised questions about the enhanced cardiovascular mortality associated with the use of tolbutamide [4]. Subsequent meta-analysis had revealed that second and third generation sulfonylureas are not associated with increased cardiovascular mortality [5]. In 2007 it was reported that rosiglitazone is associated with increased cardiovascular mortality. The report was a meta-analysis of more than forty studies, many studies were of very short duration (24 weeks), and few studies without any cardiovascular mortality were not included in the analysis [6]. Despite all the flaws of the study, it generated extensive discussion in the public and press, which culminated into the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance for the approval of glucose-lowering medications in 2008 and 2012, respectively [7,8]. FDA and EMA made it compulsory to have cardiovascular (CV) safety assessment, if the pre-marketing data revealed a hazard ratio (HR) between 1.3 and 1.8 with a 95% confidence interval (CI). If the premarketing clinical data had already established a H.R < 1.3, then post-marketing trial is not mandatory.

Licensing of any new drug requires multi phased preclinical and clinical studies. Phase 3 clinical trials are most expensive as they account for more than 90% of the total cost involved in the development of the drug [9]. CVOT imposes a great burden in terms of the cost of the development of new antihyperglycemic drugs. This may be unfavorable for innovation and investment. Because of huge financial burden, it leaves the field open only for the bigger pharmaceutical companies. The cost of the development is then transferred to the patients. 79% of 425 million people with diabetes are living in low and middle income countries. The average annual expenditure per person with diabetes is lower than 250 US dollar in this part of world, so they may not be able to afford the newer medication despite pressing need for the same [10].

2. Outcome summary of CVOT

After the advisory by FDA and EMA, several major CV outcome trials (CVOTs) had been conducted till now. Nine trials of different class of drugs have been completed till 2017 (Table 1) which includes three dipeptidyl peptidase–4 inhibitors (DPP-4i), two sodium-glucose co-transporter 2 inhibitor (SGLT-2i) and four glucagon-like peptide-1 analogues (GLP-1a) classes [11]. CV safety has also been established for insulin glargine and degludec [12–14]. Mostly patients with established CVD or high CVD risk were included in the study to ensure statistically significant number of events within a short time span. Recruited participants have long standing diabetes (mean 7.1–16.4 years) with baseline average A1C between 7.2 and 8.7% [11]. The ongoing CVOT has been summarized in Table 2.

3. DPP-4 inhibitors

Five CVOT involving almost 50,000 patients have been intended

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Table 1
Brief overview of completed CVOT till date.

Study	TECOS	SAVOR-TIMI 53	EXAMINE	ELIXA	SUSTAIN-6	EXSCEL	LEADER	EMPA-REG OUTCOME	CANVAS Program
Class of drug	DPP-4 Inhibitor			GLP-1 Analogue				SGLT-2 Inhibitor	
Drug	Sitagliptin	Saxagliptin	Alogliptin	Lixisenatide	Semaglutide	Exenatide QW	Liraglutide	Empagliflozin	Canagliflozin
Drug class	DPP-4 I	DPP-4 I	DPP-4 I	GLP-1 A	GLP-1 A	GLP-1 A	GLP-1 A	SGLT-2 I	SGLT-2 I
Intervention	Sitagliptin/ placebo	Saxagliptin/ placebo	Alogliptin/ placebo	Lixisenatide/ placebo	Semaglutid/ placebo	Exenatide QW/ placebo	Liraglutide/ placebo	Empagliflozin/ placebo	Canagliflozi/ placebo
N	14,671	16,492	5380	6068	3297	14,752	9340	7020	10,142
Follow-up (years)	3.0	2.1	1.5	2.1	2.1	3.2	3.8	3.1	2.4
Established CVD (%)	100	78	100	100	58.8	73.1	81	99	65.6
Diabetes duration (years)	11.6	10.3	7.1	9.3	13.9	12	12.8	.> 10 (57%)	13.5
Mean age (year)	65.5	65	61	60.3	64.6	62	64.3	63.1	63.3
Number of events accrued	1690	1222	621	805	254	1744	1302	772	1011
CHF(%)	18	13	28	22.4	23.6	16.2	17.9	10	14.4
Primary outcome	4-point MACE	3-point MACE	3-point MACE	4-point MACE	3-point MACE	3-point MACE	3-point MACE	3-point MACE	3-point MACE
HR for Primary outcome	0.98	1.00	0.96	1.02	0.74	0.91	0.87	0.86	0.86
Key secondary outcome	3-point MACE	Expanded MACE	4-point MACE	Expanded MACE	Expanded MACE	Individual components of MACE	Expanded MACE	4-point MACE	All-cause and CV mortality
CV death	1.03	1.03	0.85	0.98	0.98	0.88	0.78	0.62	0.96
MI	0.95	0.95	1.08	1.03	0.74	0.97	0.86	0.87	0.89
Stroke	0.97	1.11	0.91	1.12	0.61	0.85	0.86	1.18	0.87
HF hospitalization	1.00	1.27	1.19	0.96	1.11	0.94	0.87	0.65	0.67
All-cause mortality	1.01	1.11	1.11	0.94	1.05	0.86	0.85	0.68	0.87
Progressive nephropathy		1.08			0.64		0.78	0.61	0.60

Table 2
Ongoing CVOT.

Study	CAROLINA	CARMELINA	REWIND	ITCA650	PIONEER 6	HARMONY Outcomes	DECLARE-TIMI	VERTIS CV
Drug class	DPP-4 Inhibitor		GLP-1 Analogues				SGLT-2 Inhibitor	
Drug	Linagliptin	Linagliptin	Dulaglutide	Exenatide in DUROS	Oral Semaglutide	Albiglutide	Dapagliflozin	Ertugliflozin
Intervention	Sitagliptin/ glimipride	Linagliptin/ placebo	Dulaglutide/ placebo	ITCA650/placebo	Oral Semaglutide/placebo	Albiglutide/ placebo	Dapagliflozin/ placebo	Ertugliflozin/ placebo
N	6000	7003	9901	4156	3176	9400	17,276	8000
CV status	CVD or age ≥ 70 years or ≥ 2 CV risk factors	High risk for CV events	CVD or ≥ 2 CV risk factors	Preexisting CAD,CVA,PAD	Preexisting CAD or > 60y with one CV risk factor	Preexisting CAD,CVA,PAD	High risk for CV events	Preexisting CAD
HbA1c levels (%)	7.5–8.5	6.5–10	≤9.5	≥6.5	–	>7.0	–	7.0–10.5
Age (years)	˃ 45 ˂ 85	≥18	≥50	≥40	≥50	≥40	≥40	≥40
Primary outcome	3-P MACE	3-point MACE	4-point MACE	4-P MACE	3-point MACE	3-point MACE	3-P MACE + HF hospitalization	3-point MACE

to evaluate the CV safety of DPP-4 inhibitors. Three of them has been completed, SAVOR-TIMI (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in myocardial infarction), EXAMINE (Examination of CV Outcomes with Alogliptin versus Standard of Care) and TECOS (Trial Evaluating CV Outcomes with Sitagliptin). Majority of patients had established CVD (78% in SAVOR-TIMI, 100% in EXAMINE, and TECOS). Patient included in EXAMINE had acute coronary syndrome during last 3 months. All the three completed trials achieved the primary endpoint of CV safety but none of them were associated with any evidence of CV benefit [15–17]. Saxagliptin in the SAVOR-TIMI-53 was found to be associated with 27% increased risk of hospitalization for heart failure (HR 1.27 [95% CI 1.07–1.51], P = 0.007), similar but statistically non-significant trend was noted with Alogliptin in the EXAMINE (HR 1.19 [95% CI 0.90–1.58], P = 0.220). This lead to a warning by the FDA particularly in patients who are having established heart and kidney disease [18]. CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes) including 7003 patient and CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus) including 6072 patients are ongoing trials to compare the non-inferiority of Linagliptin relative to glimepiride and to assess the CV safety of Linagliptin respectively [19,20]. CARMELINA trial met its primary endpoint of 3 point major adverse cardiovascular events (MACE) with no additional safety concern coming out, demonstrating long term CV safety with linagliptin. The full data including renal outcome would be read out on 4th October 2018 during European Association for the Study of Diabetes [21].