Current Research in Diabetes & Obesity Journal
ISSN: 2476-1435

Juniper Publishers
key to the Researchers

Review Article
Volume 13 Issue 5 - November 2020
DOI: 10.19080/CRDOJ.2020.13.555874

Curr Res Diabetes Obes J

What Have We Learnt from Cardiovascular Outcome Studies of New Anti-diabetic Therapies in Last Decade?

Ashok Jaiswal[1]*, Banshi Saboo[2] and Sadanand R Shetty[3]

[1]*Medical Advisor, Zydus Healthcare Limited, India*

[2]*Consultant Diabetologist, Diabetes Care & Hormone Clinic, India*

[3]*Consultant Cardiologist, Sadanand Healthy Living Center, India*

Submission: October 02, 2020; **Published:** November 05, 2020

***Corresponding author:** Ashok Jaiswal, Zydus Healthcare Limited, Zydus Tower, IB Patel Road, Goregaon East, Mumbai – 400063, India

Abstract

Diabetes has become a major health concern worldwide with a rapid increase in its prevalence rate. Cardiovascular complications are the leading cause of morbidity and mortality in diabetes. A 2007 meta-analysis of rosiglitazone showed significant increase in the risk of cardiovascular events with rosiglitazone therapy and that raised an alarm regarding cardiovascular safety of anti-diabetic drugs. Post this incidence in 2008, the UF FDA issued a guidance for the industry to conduct CVOT on new anti-diabetic therapies before they are approved for clinical use. Since then, all new anti-diabetic therapies underwent CVOTs for their cardiovascular safety evaluation. The objective of this paper is to review the key learnings from CVOTs of new anti-diabetic therapies published post 2008 FDA guidance.

Keywords: T2DM; CVOT; Anti diabetic; MACE; SGLT-2; DPP-IV; GLP-1

Introduction

The prevalence of diabetes and associated complications are rising rapidly. Diabetes has become a major health issue worldwide. According to 9th Edition, International Diabetes Federation (IDF) Diabetes Atlas released in 2019, there are 463 million people living with diabetes worldwide, and the number is projected to reach to 700 million by 2045 and this is alarming [1]. Increasing diabetes prevalence is also associated with increasing prevalence of associated comorbidities and complications. A meta-analysis of 102 studies showed that the hazard ratio (HR) for coronary heart disease (CHD) and coronary death were 2.0 (95%CI 1.83 to 2.19) and 2.3 (95%CI 2.05 to 2.60) respectively in people with diabetes compared to those without diabetes [2]. According to a systemic review analysis including more than 4.5 million type 2 diabetes (T2DM) patients, CVD has been observed as a major cause of morbidity (around 32% prevalence of CVD in T2DM) and mortality (accounting for almost 50% of all death) amongst T2DM patients [3]. Looking into this strong positive association between diabetes and CVD, one would always expect the treatment modalities of diabetes to be associated with at least no further increase in the risk of CVD if not reduced.

Rosiglitazone and cardiovascular events

Rosiglitazone was introduced in 1999 and became one of the most widely used medicine either as a monotherapy or in combination with other anti-diabetic drugs in the management of T2DM. In the year 2007, a meta-analysis was carried out including 42 trials showed that the treatment with rosiglitazone was associated with significant increase in the risk of myocardial infarction (odds ratio 1.43; 95%CI 1.03 – 1.97) and death due to cardiovascular (CV) causes (odds ratio 1.64; 95%CI 0.98 – 2.74) [4]. The results of this meta-analysis triggered a discussion on CV safety of anti-diabetic drugs. As a result, the United States Food & Drug Administration (US FDA) issued a guidance in the year 2008 for pharmaceutical companies to carry out cardiovascular outcome trials (CVOT) for all new anti-diabetic drugs before they get authorization for the clinical treatment of diabetes [5]. After this development, the CVOT became mandatory for all new research molecule in T2DM.

The US FDA 2008 guidance on new anti-diabetic therapy evaluation

According to the 2008 guidance by US FDA, the agency advised

that the analysis of premarketing data (either a meta-analysis of phase II and phase III studies or an exclusively conducted large randomized controlled study) comparing the CV events (typically a composite of nonfatal myocardial infarction [MI], nonfatal stroke or CV death) in the test arm with control arm should rule out the upper limit (two-sided 95% CI) of hazard ratio of 1.8. For the new drug therapy whose 95% CI upper limit falls within 1.3 to 1.8 in premarketing studies analysis, completion of post marketing trial or continuation of premarketing trial after approval may be needed to conclusively show that the upper limit of the two-sided 95% CI is 1.3 with a reassuring point estimate of overall CV risk [5]. Post 2008, many new antidiabetic therapies from various categories, like DDP-IV inhibitors, GLP-1 agonists and SGLT2 inhibitors have been evaluated under long-term CVOTs.

Key Takeaways from Major CVOTs of Various New Anti-Diabetic Therapies Conducted Post 2008 US FDA Guidance

Table 1: Summary of CVOTs conducted post FDA 2008 guidance on new anti-diabetic therapies.

Therapy Class	Study	Study groups (Number of Subjects)	Median Follow-up (Years)	Primary Endpoint	HR (95%CI) of Primary Endpoint	HR (95%CI) of all-cause Mortality
DPP-IV inhibitors	SAVOR-TIMI 53 [6]	Saxagliptin (8280) vs. placebo (8212)	2.1	Composite of CV death, nonfatal MI, or nonfatal ischaemic stroke	1.00 (0.89 to 1.12)	1.11 (0.96 to 1.27)
	EXAMINE [7]	Alogliptin (2701) vs. placebo (2679)	1.5	Composite of CV death, nonfatal MI, or nonfatal ischaemic stroke	0.96 (≤1.16)*	0.98 (0.86 to 1.12)
	TECOS [8]	Sitagliptin (7257) vs. placebo (7266)	3	4-point MACE (composite of CV death, nonfatal MI, nonfatal stroke, or hospitalisation for unstable angina)	0.99 (0.89 to 1.10)	1.01 (0.90 to 1.14)
	CARMELINA [9]	Linagliptin (3494) vs. placebo (3485)	2.2	Composite of CV death, nonfatal MI, or nonfatal ischaemic stroke	1.02 (0.89 to 1.17)	0.98 (0.84 to 1.13)
	CAROLINA [10]	Linagliptin (3023) vs. glimepiride (3010)	6.3	Composite of CV death, nonfatal MI, or nonfatal stroke	0.98 (0.84 to 1.14	0.91 (0.78 to 1.06)
GLP-1 receptor agonist	ELIXA [11]	Lixisenatide (3034) vs. placebo (3034)	2.1	Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalisation for unstable angina	1.02 (0.89 to 1.17)	0.94 (0.78 to 1.13)
	LEADER [12]	Liraglutide (4668) vs. placebo (4672)	3.8	Composite of CV death, nonfatal MI or nonfatal stroke	0.87 (0.78 to 0.97)	0.85 (0.74 to 0.97)
	SUSTAIN-6 [13]	Semaglutide (1648) vs. placebo (1649)	2.1	Composite of CV death, nonfatal MI, or nonfatal stroke	0.74 (0.58 to 0.95)	1.05 (0.74 to 1.50)
	EXSCEL [14,15]	Exenatide (5394) vs. placebo (5388)	3.2	Composite of CV death, nonfatal MI, and nonfatal stroke	0.90 (0.82 to 1.00)	0.88 (0.77 to 1.00)
	HARMONY outcomes [16]	Albiglutide (4731) vs. placebo (4732)	1.6	Composite of CV death, MI, and stroke	0.78 (0.68 to 0.90)	0.95 (0.79 to 1.16)
	PIONEER 6 [17]	Oral semaglutide (1591) vs. placebo (1592)	1.32	Composite of CV death, nonfatal MI, or nonfatal stroke	0.79 (0.57 to 1.11)	0.51 (0.31 to 0.84)
	REWIND [18]	Dulaglutide (4949) vs. placebo (4952)	5.4	Composite of non-fatal MI, non-fatal stroke, or CV death	0·88 (0·79 to 0·99)	0·90 (0·80 to 1·01)
SGLT-2 inhibitors	EMPA-REG [19]	Empagliflozin (4687) vs. placebo (2333)	3.1	Composite of CV death, nonfatal MI, or nonfatal stroke	0.86 (0.74 to 0.99)	0.68 (0.57 to 0.82)
	CANVAS [20]	Canagliflozin (2888) vs. placebo (1442)	2.4	Composite of CV death, nonfatal MI, or nonfatal stroke	0.88 (0.75 to 1.03)	0.84 (0.70 to 1.01)
	DECLARE-TIMI 58 [21]	Dapagliflozin (8582) vs. placebo (8578)	4.2	Composite of CV death, MI, or ischaemic stroke	0.93 (0.84–1.03)	0.93 (0.82–1.04)
	CREDENCE [22]	Canagliflozin (2202) vs. placebo (2199)	2.6	One of the secondary outcomes was - Composite of CV death, MI, or stroke	0.80 (0.67 to 0.95) #	0.83 (0.68 to 1.02)
	DAPA-HF [23]	Dapagliflozin (2373) vs. placebo (2371)	1.5	Composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or CV death	0.74 (0.65 to 0.85)	0.83 (0.71 to 0.97)
	VERTIS-CV [24]	Ertugliflozin (5493) vs. placebo (2745)	3	Composite of CV death, nonfatal MI, or nonfatal stroke	0.97 (0.85 to 1.11)	0.93 (0.80 to 1.08)

CV: Cardiovascular; MI: Myocardial Infarction; HR: Hazard Ratio; DPP-IV: Dipeptidyl Peptidase-IV; SGLT-2: sodium glucose co-transporter 2; GLP-1: Glucagon like Peptide-1; CI: confidence interval. *Only upper range of 95% CI is reported. # HR of one of the secondary outcomes of composite of CV death, MI or stroke

How to cite this article: Ashok J, Banshi S, Sadanand R S. What Have We Learnt from Cardiovascular Outcome Studies of New Anti-diabetic Therapies in Last Decade?. Curre Res Diabetes & Obes J 2020; 13(5): 555874. DOI: 10.19080/CRDOJ.2020.13.555874.

The various CVOTs of new anti-diabetic therapies are briefly summarized in table 1.

DPP-IV inhibitors and CVOTs

None of the studies of DPP-IV inhibitors, as mentioned in table 1, have shown increase or decrease in the risk of MACE (major adverse cardiovascular events) [6-10]. These studies have also endorsed that DPP-IV inhibitors are not associated with increased risk of all-cause mortality. The results from SAVOR-TIMI 53 study showed that saxagliptin therapy is associated with significant increase in the risk of hospitalization for heart failure compared to placebo group (HR 1.27; 95% CI, 1.07 to 1.51; P = 0.007) [6]. All these studies were placebo controlled except for CAROLINA study wherein linagliptin was compared with glimepiride. For primary MACE outcome, linagliptin was found to be non-inferior to glimepiride [10].

GLP-1 receptor agonist and CVOTs

The results from available CVOTs as briefed in table 1. have established that GLP-1 receptor agonist is not associated with increase in the risk of CV events [11-18]. Certain studies have shown significant CV risk reduction with certain GLP-1 agonist compared to placebo arm. LEADER, SUSTAIN-6, HARMONY OUTCOMES and REWIND studies showed significant reduction in the risk of MACE with liraglutide, semaglutide, albiglutide and dulaglutide respectively [12,13,16,18]. Two studies, LEADER and PIONEER 6 studies, have additionally shown significant reduction in the risk of all-cause mortality with liraglutide and oral semaglutide respectively compared to placebo group [12,17].

SGLT-2 inhibitors and CVOTs

First published CVOT with SGLT-2 inhibitor was EMPA-REG outcome study with empagliflozin [19] and it showed that the treatment with empagliflozin is associated with significant reduction in the risk of MACE and all-cause mortality compared to placebo arm. Empagliflozin and placebo arms were not significantly different in terms of incidence of MI or stroke, however, empagliflozin significantly reduced the risk of CV death by 38% compared to placebo arm. Based on the results from EMPA-REG outcome study, empagliflozin is also indicated to reduce the risk of CV death in adult patients with type 2 diabetes and established CVD. After EMPA-REG outcome study, the results from many CVOTs with different SGLT-2 inhibitors were published and they showed that SGLT-2 inhibitors are not associated with increased risk of CV events [20-24].

The primary objective of CREDENCE study was to evaluate the renal outcome with canagliflozin compared with placebo. The results of this study showed that canagliflozin produced significant 20% relative risk reduction in one of the secondary objectives of 3-point MACE [22]. DAPA-HF study is an exceptional study, evaluating the effect of dapagliflozin in NYHA class II, III, and IV heart failure with or without diabetes [23]. The results showed that dapagliflozin produced significant 26% relative risk reduction in primary outcome of composite of worsening of heart failure or CV death and 17% significant relative risk reduction in all-cause mortality compared to placebo arm in patients with NYHA II, III and IV patients irrespective of presence of diabetes [23]. As a result of DAPA-HF study, dapagliflozin is additionally approved to reduce the risk of CV death and hospitalization for heart failure in adults with NYHA II-IV heart failure with reduced ejection fraction.

So, what do we learn from all these CVOTs published in 2010s? One common learning from all these studies is that "these drugs are safe and none of the studies showed increase in the risk of MACE compared to placebo". Hence, the point of discussion now in 2020 is "Do we require to conduct CVOTs for new drug therapies in Diabetes?" This is important as conducting CVOT before the drug approval has its own impact on the cost of drug development. Finally, in March 2020, the US FDA has eliminated the previous 2008 guidance for the industry which was asking the sponsor to conduct CVOT mandatorily before they get new anti-diabetic drug approval. After eliminating the previous 2008 guidance, the US FDA has now issued a new draft guidance "Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control" for public comment on its revised proposal for broad safety evaluations before new drug approval [25]. Once this new safety evaluation guidance March 2020 is implemented, we will come to know more about its implications on new anti-diabetic drug development in future.

Summary

Diabetes and associated complications are rising, and CVD has become the leading cause of morbidity and mortality in people with diabetes. Hence, it would always be considered counterproductive if any drug therapy in diabetes increases the risk of CV events. The rosiglitazone matter in the year 2007 raised a CV safety alarm and subsequently the US FDA made CVOT mandatory for all new anti-diabetic therapies in 2008. After this, many CVOTs have been conducted with various new anti-diabetic therapies and none of them showed increase in the risk of MACE, instead some of the studies have shown beneficial effect on MACE/CV mortality/all-cause mortality. After reviewing all these CVOTs, the US FDA has eliminated the 2008 guidance of CVOT for new anti-diabetic therapies and issued a new draft guidance for soliciting public comment on its revised proposal for broader safety evaluation of new drugs before approval.

References

1. IDF Diabetes Atlas (2019) 9th Edition.
2. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, et al. (2010) Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 375(9733): 2215-2222.

How to cite this article: Ashok J, Banshi S, Sadanand R S. What Have We Learnt from Cardiovascular Outcome Studies of New Anti-diabetic Therapies in Last Decade?. Curre Res Diabetes & Obes J 2020; 13(5): 555874. DOI: 10.19080/CRDOJ.2020.13.555874.

3. Einarson TR, Acs A, Ludwig C, Panton UH (2018) Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol 17(1): 83.
4. Nissen SE, Wolski K (2007) Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 356(24): 2457-2471.
5. US Food and Drug Administration Guidance for industry: Diabetes mellitus-Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes.
6. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, et al. (2013) SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 369(14): 1317-1326.
7. Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, et al. (2015) Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. Lancet 385(9982): 2067-2076.
8. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, et al. (2015) Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 373(3): 232-242.
9. Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, et al. (2019) Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults with Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. JAMA 321(1): 69-79.
10. Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, et al. (2019) CAROLINA Investigators. Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients with Type 2 Diabetes: The CAROLINA Randomized Clinical Trial. JAMA 322(12): 1155–1566.
11. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, et al. (2015) ELIXA Investigators. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. N Engl J Med 373(23): 2247-2257.
12. Marso SP, Daniels GH, Brown Frandsen K, Kristensen P, Mann JF, et al. (2016) LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 375(4): 311-322.
13. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, et al. (2016) SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 375(19): 1834-1844.
14. Mentz RJ, Thompson VP, Aguilar D, Lokhnygina Y, Buse JB, et al. (2018) Effects of once weekly exenatide on clinical outcomes in patients with preexisting cardiovascular disease. Prespecified analysis from EXSCEL. Circulation 138: 2576-2578.
15. Bethel MA, Mentz RJ, Merrill P, Buse JB, Chan JC, et al. (2018) Renal outcomes in the EXenatide study of cardiovascular event lowering (EXSCEL). Diabetes 67(1): 522-P.
16. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB Sr, Granger CB, et al. (2018) Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (harmony outcomes): a double-blind, randomised placebo-controlled trial. Lancet 392(10157): 1519-1529.
17. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, et al. (2019) PIONEER 6 Investigators. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 381(9): 841-851.
18. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, et al. (2019) Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 394(10193): 121-130.
19. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, et al. (2015) EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 373(22): 2117-2128.
20. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, et al. (2017) CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 377(7): 644-657.
21. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, et al. (2019) DECLARE–TIMI 58 Investigators. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 380(4): 347-357.
22. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, et al. (2019) CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med 380(24): 2295-2306.
23. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, et al. (2019) DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 381(21): 1995-2008.
24. Cannon CP, Pratley R, Dagogo Jack S, Mancuso J, Huyck S, et al. (2020) VERTIS CV Investigators. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. N Engl J Med 383(15): 1425-1435.
25. Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control Guidance for Industry - DRAFT GUIDANCE.

DOI: 10.19080/CRDOJ.2020.13.5574

How to cite this article: Ashok J, Banshi S, Sadanand R S. What Have We Learnt from Cardiovascular Outcome Studies of New Anti-diabetic Therapies in Last Decade?. Curre Res Diabetes & Obes J 2020; 13(5): 555874. DOI: 10.19080/CRDOJ.2020.13.555874.