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Review Article

Cardiovascular outcomes and safety with antidiabetic drugs

Khaled K. Aldossari

Department of Family and Community Medicine, College of Medicine, Prince Sattam Bin Abdulaziz University, Al-Kharj, Saudi Arabia

Address for correspondence:
Khaled K. Aldossari, Alkharj Public Library, Sa'ad Ibn Mu'adh, Al Kharj 16278, Saudi Arabia. Tel.: +966(11)5886136. Mobile: +966553335159.
E-mail: khalid317@gmail.com

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ABSTRACT

Type 2 diabetes is a debilitating disease that impacts the life expectancy, quality of life, and health of an individual. Cardiovascular disease (CVD) is a common diabetes-associated complication and a principal cause for death in diabetic patients. This review aims to investigate and summarize the effect of Type 2 diabetes mellitus (T2DM) medications on CVD issues. A comprehensive literature review mainly from level 1 evidence was performed. Thirty-seven articles were extracted from Google Scholar, ScienceDirect, ProQuest, and PubMed Database using a combination of keywords. The findings suggest that different glucose-lowering agents have been tested for their efficacy and safety in T2DM with CVD. Some of the recent trials such as the "United Kingdom Prospective Diabetes Study," "Empagliflozin (EMPA) Cardiovascular (CV) Outcome Event Trial in T2DM Patients-Removing Excess Glucose" (EMPA-REG OUTCOME), "Liraglutide Effect and Action in Diabetes: Evaluation of CV Outcome Results," and "Trial to Evaluate CV and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes" (SUSTAIN6) have shed important light on this vital clinical concern, thus demonstrating a convincing effect of liraglutide, semaglutide, and EMPA on CVD outcomes, while metformin is thought to be the first-line optimal oral agent to manage Type 2 diabetics. Some classes of drugs demonstrate CV protection, some of them may be a result of a class effect, and some differences might be based on the population enrolled individually. Most of the trials failed to show a significant benefit with regard to mortality and morbidity in spite of intensive glycemic control. This study, therefore, enabled us to develop a guide of potential antidiabetic medication that can influence or promote CV health. Health professionals in future should weigh the CV risk against possible advantages while prescribing antidiabetic medications.

Keywords: Antidiabetic drugs, cardiovascular impact, cardiovascular risk, diabetes medications, type 2 diabetes

Introduction

Individuals with type 2 diabetes mellitus (T2DM) face significantly higher risk of developing cardiovascular diseases (CVD) compared to the general population. Diabetes mellitus and CVD are common chronic progressive disorders and major public health issue in Saudi Arabia.[1] The World Health Organization stated that Saudi Arabia ranks 7th globally in terms of the rates of diabetes.[2] One of the major impacts of T2DM is its high incidence of premature deaths and morbidity that primarily results from macrovascular and microvascular complications.[3-5] In the previous years, the condition of diabetes has demonstrated a 10-fold increase among Saudi population.[6] It has been estimated that 2 of 5 diabetic adults are undiagnosed in the Middle East.[7] The resultant shift in the lifestyle and modernization to a more sedentary life with consumption of high-fat diets and obesity are the primary cause of increased diabetes mellitus prevalence within the Saudi community.

According to the Centers for Disease Control and Prevention (CDC),[8] CVD tends to be the principal cause of morbidity and mortality in individuals suffering from T2DM. The medication used in the treatment of T2DM has potential cardiovascular (CV) effect (harmful, beneficial, or neutral). Thus, the Food and Drug Administration (FDA) in 2008/2010 and the "European Medicines Agency" indicated that novel compounds that are mainly being developed for T2DM need to go through different clinical trials to guarantee safety from CVD.[9,10] Moreover, for majority of the antidiabetic drugs, the effects of CV are not as yet clarified.[11] The FDA[9] published a report, namely "Guidance for Industry: Diabetes Mellitus - Evaluating CV Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes," now demands novel drugs being

licensed for diabetes to show that no adverse CV effects are caused during the trials.

Limited evidence is available from the randomized trials with regard to how well T2DM can be treated in the CVD population. The "European Association for the Study of Diabetes and American Diabetes Association" have shown a consensus algorithm for the purpose of managing T2DM, wherein metformin was known to be the initial pharmacologic agent of choice that can be merged with other drugs in triple and double therapy.[12] The study will be of substantial assistance for all medical physicians, who are treating the patients of diabetes such as diabetologists, endocrinologists, internal medicine doctors, primary care physicians, and experienced personnel including young doctors. The study will further help in prioritizing add-on drug choices for managing diabetes. Hence, this article seeks to establish why people suffering from diabetes are at a greater risk of developing CVD and then considers to summarize the impact of type 2 diabetes drugs on CV outcomes.

METHODS

Garrad[13] suggested that an intensive and wide literature on the topic must be in place before conducting any informative literature review. Therefore, a search strategy was performed using the following key words: "CV impact, CV risk, diabetes medications, and antidiabetic drugs" to retrieve relevant evidence from the electronic database selected such as "Google Scholar, ScienceDirect, ProQuest, and PubMed." Furthermore, Boolean operators such as OR, AND, and NOT were also used for combining both the set of search terms, thus instructing the databases to retrieve relevant material. Primarily, English articles were incorporated. Cross-reference lists and regulatory guidelines were also included in the review.

Consistent with the trend toward "Evidence-Based Medicine," the level of evidence is also considered to assess the quality of the research articles selected. The studies are primarily assessed based on two dimensions: Study quality and level of evidence. It is an establishment of a hierarchy of the study design based on the ability of the design to protect against bias. Randomized controlled trials (RCTs) are least susceptible to bias and are considered the gold standard for evaluating efficacy in clinical research [Figure 1].

RESULTS AND DISCUSSION

In the present review, we encountered a range of clinical trials related to the T2DM and CVD-associated risk. Diabetes is a primary risk factor for CVD and its development, such as stroke, hypertension, heart, and vascular, or CV, diseases. Our study retrieved 37 trials summarizing the outcome of T2DM medications on CVD-related outcomes. In total, 37 clinical trials were included (7 trials including

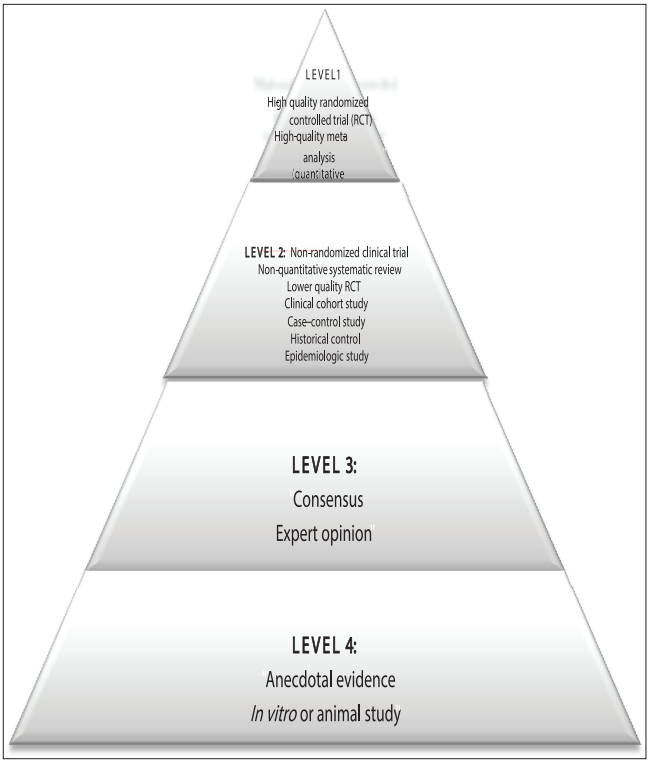

Figure 1: Evidence hierarchy[14]

thiazolidinediones [TZDs] [with sub-classes pioglitazone and rosiglitazone],[15-21] 2 trials: Biguanides [metformin],[22,23] 4 trials: Second-generation sulfonylureas [glimepiride, glipizide, and glyburide],[24-26] 2 trials: Meglitinides (nateglinide and repaglinide),[27,28] 2 trials: Alpha-glucosidase inhibitors [AGIs] [acarbose, and miglitol],[29,30] 7 trials: Glucagon-like peptide-1 [GLP-1] receptor agonist [exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, and semaglutide],[31-37] 1 trial: Amylin analogs [pramlintide][38] trial, 5 trials: Dipeptidyl peptidase-4 inhibitors [DPP-IV] [saxagliptin, sitagliptin, linagliptin, and alogliptin],[39-43] 2 trials: Insulins [glargine],[44,45] and 5 trials: Sodium-glucose cotransporter 2 [SGLT2] [canagliflozin, dapagliflozin, and empagliflozin (EMPA)][46-50]).

The findings of the trials demonstrate that T2DM patients have an increased and inherent risk for CVD. CV benefits with metformin are promising with evidence demonstrating reduction to some extent in diabetes-associated deaths, diabetes-associated end points, along with all-cause mortality.[22] Studies for the sulfonylureas (SUs) therapy and its safety are still conflicting; however, when compared with metformin, SU use is concomitant to an increased risk for causing heart failure (HF), explicitly at a higher dose.[25,26] Pioglitazone is also known to reduce the composite of stroke and non-fatal myocardial infarction (MI) besides all-cause mortality in T2DM patients who are at a high risk for macrovascular event.[15] While, use of TZDs predominantly rosiglitazone is contra-indicated in HF patients as it is well known to intensify HF-related risk.[18,20] On the other hand,

DPP-4 and GLP-1 agonist are known to potentially show positive effects on the CV system.[31-37,39-43] Exenatide, a GLP-1 analog, is linked with a substantial decline in the CVD-related risk and hospitalization among individuals with T2DM.[32] Although "SGLT2 inhibitors" are unique glucose-lowering oral agents, the potential for CVD-related benefits from the SGLT2 inhibitors remains to be established.[46,47] A large body of evidence specifies a different multifactorial approach to the care of diabetes that mainly targets glycemic control besides treatment of dyslipidemia as well as hypertension that will considerably reduce the CVD-related risk. Hence, the findings obtained from the ongoing clinical trials will further provide indications regarding CV safety in addition to diabetic drug efficacy. Such trials will most likely assist to further refine the therapeutic guideline in the near future. Tables 1-10 summarize key diabetes and CV trials. The results of each selected trials are discussed in detail in the sections below.

TZDs

TZDs are known to act as insulin sensitizers and ligands of the "transcription factor peroxisome proliferator-activated receptor γ (PPAR-γ). The 'Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication' trial found no increase in the rates of CV event with rosiglitazone, while the rosiglitazone group significantly developed supplementary HF events.[18] On the other hand, 'Rosiglitazone Evaluated for CV Outcomes and Regulation of Glycemia in Diabetes' (RECORD) trial confirmed that rosiglitazone fails to increase the risk of overall mortality and morbidity, whereby confirming an elevated HF risk.[51] Issues with regard to data integrity and design led FDA to call for an independent reevaluation of data RECORD, which reported comparable results.[17] Another meta-analysis revealed that rosiglitazone is linked with a significant increase in the MI risk as well as deaths caused due to CV.[52] RECORD clinical trial exhibited no increased

Table 1: Cardiovascular outcome trials for antidiabetics (TZDs) in type 2 diabetes

Antidiabetics	Generic name	Brand name	Therapeutic class	Mechanism of action	Cardiovascular outcomes
TZDs	Pioglitazone	Actos	682028	Insulin sensitizers; Responsible to modulate the gene transcription involved in metabolism of glucose	**(Level 1 evidence; RCT)** "PROactive 'PROspective pioglitAzone Clinical Trial In macroVascular Events' clinical trials (5238 type 2 diabetics with established CVD) •10% non-statistically significant decline in the relative risk–primary composite end points (all-cause death, ACS, and MI); •16% statistically significant decline was observed in the main secondary end point (death, MI, and stroke)[15] Pioglitazone treatment failed to yield any significant reductions in the primary CV events rates[16]
	Rosiglitazone	Avandia	-	Antidiabetic	**(Level 1 Evidence; RCT)** "RECORD clinical trial, •No increased risk for heart attack or maybe death in individuals offered treatment with rosiglitazone versus diabetes medications[17] Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial •Found no increase in CV event rates with rosiglitazone, although the rosiglitazone group developed significantly more HF events[18] Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial (randomized 2368 patients) •Among T2DM patients and CAD rosiglitazone is not associated with an escalation in major ischemic CV events[19] **(Level 1 Evidence; Meta-Analysis)** •Both rosiglitazone and pioglitazone seem to increase the HF risk; nevertheless, the CV death risk is not increased[20] •Cochrane meta-analysis demonstrated that PPAR-γ agonists confirmed to lessen the overall events of CV deaths and recurrent stroke, and it will also improve carotid plaque stabilization and insulin sensitivity[21]"

TZDs: Thiazolidinediones, RCT: Randomized controlled trials, CVD: Cardiovascular disease, ACS: Acute coronary syndrome, MI: Myocardial infarction, CV: Cardiovascular, T2DM: Type 2 diabetes mellitus, CAD: Coronary artery disease, HF: Heart failure, PPAR-γ: Peroxisome proliferator-activated receptor γ, RECORD: Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes

risk of heart attack or death in individuals who were provided rosiglitazone versus diabetes medications as a treatment[17] [Table 1]."

"PROspective pioglitAzone Clinical Trial In macroVascular Events" trials recruited 5238 type 2 diabetics with established CVD. Results demonstrated a non-statistically significant 10% relative risk (RR) reduction within primary composite end-points (MI, acute coronary syndrome [ACS], and all-cause death); and 16% statistically significant decline was observed for the core secondary end point (MI, death, and plus stroke).[15] Moreover, treatment with pioglitazone failed to produce any substantial reductions in the primary CV event rate.[16] On the contrary, both rosiglitazone and pioglitazone seem to increase the HF risk; nevertheless, the risk of death caused due to CV is not increased.[20] A Cochrane meta-analysis considerably demonstrated that PPAR-γ agonists tend to lessen the overall events of CV deaths and recurrent stroke. However, it considerably improved carotid plaque stabilization and insulin sensitivity[21] [Table 1].

Biguanides

One of the biguanides, metformin is widely consumed in treating diabetes and is one of the first-line treatments for majority of the patients. If it is administered at a lower dose, gently titrated, metformin can be well tolerated. It has been potentially associated with losing weight. With respect to the United Kingdom Prospective Diabetes Study (UKPDS) results, it is a well-known cardioprotective drug. Individuals being treated with metformin often have a reduced risk of diabetes-related deaths, any diabetes-related clinical end point, in addition to all-cause mortality that was considered to be primary outcome measures.[8] Consequently, some of the individuals in the metformin-treated arm of the work (just over 300) led to a review of additional studies, where this drug was used for determining that whether being cardioprotective is justified.[53] The study supported the metformin use for its cardioprotective properties over and above its role as an oral hypoglycemic agent. Hence, this drug makes it an ideal first choice for population with type 2 diabetes, explicitly holding a less purchase cost. On the other hand, "A Diabetes Outcome Progression Trial" trial failed to show any benefit with regard to the CV events and the risk of deaths over rosiglitazone or glibenclamide.[9] Glimepiride, however, might be safe in CVD patients as it has no detrimental effects on ischemic preconditioning as demonstrated in Table 2.[24,25]

Second-generation sulfonylureas

If strengthening of treatment is required for improving glycemic control along with getting HbA1c to target, several physicians offer SUs as a second-line treatment in accordance to the National Institute for Health and Care Excellence guidelines.[4] SUs are associated to hypoglycemia and weight gain, due to which it might not be an ideal choice, exclusively as several other drug classes have become available. Frier *et al*.[54] suggested that hypoglycemia may lead to an amplified risk of CV events. It is, therefore, argued that medications with a higher risk of triggering hypoglycemia need to be avoided. With regard to the SUs effect on CV health, limited clarity is available. Few of the studies demonstrated no detrimental effects on ischemic preconditioning by glimepiride.[24,25] Others offer a more reassuring picture with an increase in CVD events, possibly associated with an increased hypoglycemia risk[28] [Table 3].

Table 2: Cardiovascular outcome trials for antidiabetics (biguanides) in type 2 diabetes

Antidiabetics	Generic name	Brand name	Therapeutic class	Mechanism of action	CV outcomes
Biguanides	Metformin	Glucophage, Fortamet, Glumetza, Riomet	682004	Decrease hepatic glucose production	**(Level 1 Evidence; RCT)** The UKPDS: •A landmark study of the CV benefits from consumption of metformin •Metformin was capable to reduce any diabetes-associated endpoint, diabetes- associated death, and all-cause mortality than any other conventional treatment group •In comparison to chlorpropamide, insulin, or glibenclamide, metformin demonstrated a more pronounced effect for any all-cause mortality, diabetes-associated end point, and stroke[22] The ADOPT •Metformin failed to show any benefits with regard to the death risk or CV events over rosiglitazone or glibenclamide[23]

UKPDS: United Kingdom Prospective Diabetes Study, RCT: Randomized controlled trials, CV: Cardiovascular, ADOPT: A Diabetes Outcome Progression Trial

Meglitinides

In comparison to SUs, the meglitinides are structurally different as they apply their effects through sulfonylurea receptor-1. It acts likewise through regulating ATP-dependent potassium channels in pancreatic beta-cells, thus increasing insulin secretion. Repaglinide fails to be concomitant to elevated mortality and risk of CVD as compared to metformin in one of the large cohort of diabetics either without or with MI.[55] One uncontrolled randomized study involved 112 patients with insufficiently controlled type 2 diabetes that were not treated formerly with oral hypoglycemic agents. The repaglinide use was likely associated with positive outcomes in most of the CVD risk parameters, for example, homocysteine, lipoprotein (a), and plasminogen activator inhibitor.[56] Another "The Nateglinide and Valsartan in Impaired Glucose Tolerance (IGT) Outcomes Research" trial showed that nateglinide failed to demonstrate any beneficial result in discontinuing the progression from prediabetes to diabetes compared to placebo [Table 4].[27]

Table 3: Cardiovascular outcome trials for antidiabetics (sulfonylureas - second generation) in type 2 diabetes

Antidiabetics	Generic name	Brand name	Therapeutic class	Mechanism of action	Cardiovascular outcomes
Sulfonylureas - second generation	Glimepiride	Glucotrol, Diabeta, Micronase, Glynase	682020	It is mainly responsible to stimulate the release of insulin through inhibition of "ATP-dependent potassium channel in the beta-cells of pancreas"	•In patients with CVD, glimepiride might be safer, as it leaves no detrimental effects on ischemic preconditioning[24,25]
	Glipizide		-	It partially blocks potassium channels among beta-cells of pancreatic islets of Langerhans	**(Level 1 Evidence; RCT)** Diabetic patients with documented CAD, glyburide, and glipizide were accompanied with elevated mortality,[26] the latter may be due to its capability to impair ischemic preconditioning[26]
	Glyburide		-	It reduces the blood glucose acutely by encouraging insulin release from the pancreas, an effect dependent on beta-cells functioning within the pancreatic islet	

CVD: Cardiovascular disease, RCT: Randomized controlled trials, CAD: Coronary artery disease

Table 4: Cardiovascular outcome trials for antidiabetics (meglitinides) in type 2 diabetes

Antidiabetics	Generic name	Brand name	Therapeutic class	Mechanism of action	Cardiovascular outcomes
Meglitinides	Nateglinide	Starlix	682016	Reduce levels of blood glucose by means of stimulating secretion of insulin from the pancreas	**(Level 1 Evidence; RCT)** The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study (diabetes prevention RCT) •In comparison to placebo, nateglinide failed to demonstrate any beneficial effect in discontinuing the progression from prediabetes to diabetes[27]
	Repaglinide	Prandin	**682016**	It is primarily responsible to reduce the levels of glucose through blocking the "ATP-dependent potassium channels within pancreatic beta-cells," thereby stimulating the insulin secretion	**(Level 1 Evidence; RCT)** •The study population for this uncontrolled RCT trial included 112 patients with defectively controlled type 2 diabetes mellitus not formerly treated with oral hypoglycemic agents •The repaglinide use was related with positive improvements in few of the parameters of cardiovascular risk, for example, lipoprotein (a), plasminogen activator inhibitor, and homocysteine[28]

RCT: Randomized controlled trials

AGIs

AGIs are a unique class of drugs that tend to inhibit the carbohydrate absorption from gut and might be utilized in treating T2DM patients or people suffering from IGT. AGIs are drugs that prevent absorption of carbohydrates from the gut and it might be utilized in the management and handling of individuals with type 2 diabetes or IGT. Acarbose CV Evaluation Trial (ACE) trial reported that acarbose can prevent individuals with IGT and coronary heart disease (CHD) from dying or experiencing additional strokes or heart attacks. This trial further reported if acarbose reduces blood glucose following a meal can either delay or prevent people progressing from IGT to type 2 diabetes.[29] The results of the trial failed to show superiority for the primary end point, without reductions observed with acarbose in the risk of major adverse CV events. Conversely, it demonstrated a significant 18% reduction in the new-onset incidence of diabetes cases with acarbose than placebo.[56] Thus, ACE offers reassurance that acarbose can be safely consumed for improving the glucose levels in individuals with impaired glucose regulation and CHD without impacting the rates of HF or CV complications. Thus, a reduced incidence of diabetes observed in this trial may, however, help in reducing the risk for CV conditions in future by delaying the diabetes onset among high-risk population under study.[56] These findings extended the knowledge of the acarbose safety as well as efficacy for delaying the diabetes onset in a population with both CHD and IGT. Conversely, miglitol, another AGI, showed improved postprandial endothelial dysfunction in ACS patient other than new-onset postprandial hyperglycemia, thus referring to a potential use of class effect[30] [Table 5].

GLP-1 receptor agonist (GLP-1RA)

The GLP-1 actions are mediated through GLP-1R mainly expressed in peripheral tissues in addition to pancreatic islet cells. Consequently, this wide distribution of GLP-1R and GLP-1 tends to exert extrapancreatic actions which have beneficial effects on CNS, gastrointestinal, and CV systems.[57] At present, the GLP-1 RA that is accepted for type 2 diabetes treatments includes extended-release exenatide, dulaglutide, exenatide, lixisenatide, liraglutide and albiglutide.[58] The Exenatide Study of CV Event-Lowering Trial is a phase 3 randomized placebo-controlled trial, which determines the outcomes of CV after exenatide use. An estimated 14,752 individuals were randomized and obtained exenatide either on one occasion weekly or placebo. CV-related outcomes entail time to initially confirm CV-related event, all-cause mortality, ACS hospitalization, or HF.[31] The results show Type 2 diabetes, without or with prior CVD conditions, and the incidence of major adversative CV events did not significantly

Table 5: Cardiovascular outcome trials for antidiabetics (A - glucosidase inhibitors) in type 2 diabetes

Antidiabetics	Generic name	Brand name	Therapeutic class	Mechanism of action	Cardiovascular outcomes
AGIs	Acarbose	Precose	682002	Delayed absorption of glucose from the gastrointestinal tract by means of hindering enzymes that transform carbohydrate to monosaccharides	**(Level 1 Evidence; RCT)** ACE •Population: 6526 patients with IGT who have recognized ACS or CAD. •The acarbose therapy impacts on CV-related mortality and morbidity (non-fatal MI, CV death, and non-fatal stroke)[29] •The study was completed on April 18, 2017 •The primary results of the study were presented at the European Association of the Study of Diabetes in Lisbon on September 13, 2017 •Acarbose did not have any effect on the composite cardiovascular outcome
	Miglitol	Glyset	-	It has an antihyperglycemic action that in turn results from reversible inhibition of "membrane-bound intestinal α-glucoside hydrolase enzymes"	**(Level 1 Evidence; RCT)** •Miglitol, another AGI, has demonstrated to improve postprandial endothelial dysfunction in individuals with ACS and postprandial hyperglycemia (new-onset), indicating a significantly beneficial class effect[30]

RCT: Randomized controlled trials, AGIs: Alpha-glucosidase inhibitors, ACE: Acarbose Cardiovascular Evaluation Trial, MI: Myocardial infarction, CV: Cardiovascular, ACS: Acute coronary syndrome

vary between individuals who received exenatide compared to those receiving placebo.[32] The "Liraglutide Effect and Action in Diabetes: Evaluation of CV Outcome Results" (LEADER) trial demonstrated the long-term liraglutide effect on CV events in T2DM patients. CV risk over the period of 4 years dropped significantly.[3] The "Evaluation of CV Outcomes in Patients With Type 2 Diabetes After ACS During Treatment With Lixisenatide" (ELIXA) trial demonstrated counting lixisenatide to conventional therapies in diabetic patients with a recent ACS holding neutral effect on CV-related outcomes.[34] Conversely, "Effect of Albiglutide, When Added to Standard Blood Glucose-Lowering Therapies, on Major CV Events in Subjects with T2DM" (HARMONY) trial outcomes and "Researching CV Events With a Weekly INcretin in Diabetes" trials are still ongoing.[35,36] Marso *et al*.[37] addressed a lower CV event rate among T2DM patients who received semaglutide (GLP-1 analog) than individuals receiving placebo. The results of this trial were consistent with the LEADER trial that examined the effects of liraglutide [Table 6].

Amylin analogs

Amylin analogs are injectable medication which are being consumed for treating diabetics and are considerably taken before meals and work correspondingly to the amylin hormone. CV safety evaluation with pramlintide was performed using accepted regulatory medical AE definitions in five of the previous randomized controlled phase and four trials of

Table 6: Cardiovascular outcome trials for antidiabetics (glucagon-like peptide-1 receptor agonist) in type 2 diabetes

Antidiabetics	Generic name	Brand name	Therapeutic class	Mechanism of action	Cardiovascular outcomes
GLP-1 receptor agonist	Exenatide	Byetta	682092	Stimulate glucose-dependent insulin secretion	**(Level 1 Evidence; RCT)** "The EXSCEL Trial study • Population: 14,752 patients obtained exenatide either once weekly or placebo • CV-related outcomes consist of time to initially confirm the CV event, all-cause mortality, ACS hospitalization, or HF[31] • This study has been completed on April 21, 2017 • The results were presented to the general audience at the "EASD annual meeting" on September 14, 2017, in Lisbon, Portugal • The findings demonstrated that exenatide had no adverse effects on the CV health, i.e., the drug may have an acceptable CV safety profile in individuals with type 2 diabetes who may be suffering from a wide array of existing cardiovascular conditions[32]
	Liraglutide	Victoza	-	Stimulate glucose-dependent insulin secretion	**(Level 1 Evidence; high-quality RCT)** LEADER "Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results" trial The LEADER trial determined the liraglutide long-term effects on CV events in subjects with T2DM. CV risk over the period of 4 years: • Reduced primary CV-related deaths • Reduced CV causes, non-fatal MI, or non-fatal stroke. • Reduced death caused due to other reason[33]

(contd....)

Table 6: ***(Continued)***

Antidiabetics	Generic name	Brand name	Therapeutic class	Mechanism of action	Cardiovascular outcomes
	Lixisenatide	Lyxumia	-	Stimulate glucose-dependent insulin secretion	**(Level 1 Evidence; high-quality RCT)** ELIXA "Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With Lixisenatide" trial Neutral CV results with recent ACS were reported in ELIXA trial[34]
	Albiglutide	Tanzeum	-	Stimulate glucose-dependent insulin secretion	**(Level 1 Evidence; high-quality RCT)** HARMONY "Effect of Albiglutide, When Added to Standard Blood Glucose-Lowering Therapies, on Major Cardiovascular Events in Subjects with Type 2 Diabetes Mellitus" trial outcomes ♦ Is an ongoing study ♦ It is evaluating if albiglutide has an impact in major CVD event occurrences, for example, strokes and heart attack in T2DM either when used alone or used additionally with other treatments for diabetes[35]
	Dulaglutide	Trulicity	-	Stimulate glucose-dependent insulin secretion	**(Level 1 Evidence; high-quality RCT)** **REWIND "researching cardiovascular events with a weekly incretin in diabetes" trial** ♦ Is an ongoing study ♦ Evaluating if dulaglutide is effective to reduce major CV-related events in diabetic population[36]
	Semaglutide	-		Stimulate glucose-dependent insulin secretion	• Semaglutide 0.5 mg versus semaglutide 1.0 mg versus placebo • Population: 3297 T2DM patients (with CVD or high CV risk) • SUSTAIN-6 trial demonstrated that treatment with semaglutide (once in a week) for 2 years considerably reduces the risk for CVD that also supports the class effect acting with long-acting GLP-1RAs[37]

GLP-1: Glucagon-like peptide-1, RCT: Randomized controlled trials, EXSCEL: Exenatide Study of Cardiovascular Event-Lowering, CV: Cardiovascular, ACS: Acute coronary syndrome, HF: Heart failure, EASD: European Association for the Study of Diabetes, MI: Myocardial infarction, CVD: Cardiovascular disease, T2DM: Type 2 diabetes mellitus

16–52 weeks duration in type 2 diabetes adults. Mealtime pramlintide with insulin demonstrated no increase in the risk for CV AEs type 2 diabetics using insulin[38] [Table 7].

DPP-IV

The DPP-IV inhibitors belong to the antihyperglycemic agent class that is shown to improve the glycemic control in type 2 diabetics. Initially, there were no concerns with reference to the risk of CVD in individuals taking DPP4 inhibitors. Currently published data about HF admissions among individuals using DPP4 inhibitors revealed that such a risk should be considered before initiating individuals on treatment with gliptin. Other studies also showed that inherent difference in drugs is observed with the DPP4 inhibitor class, which may be influenced, if the risk of HF exists. "CV and Renal

Microvascular Outcome Study with Linagliptin in Patients with T2DM" (CARMELINA) study was designed to assess the long-term CV influence on CV mortality, morbidity, in addition to the renal function of treatment with linagliptin.[41] Alternatively, "Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in MI" study found an increased number of HF admissions of individuals on saxagliptin, while "Trial Evaluating CV Outcomes with Sitagliptin"[40] study reported that sitagliptin fails to have a similar effect.[40] The impact of alogliptin on patient with high CVD risk was assessed in the "Examination of CV Outcomes with Alogliptin versus Standard of Care"

Table 7: Cardiovascular outcome trials for antidiabetics (amylin analogs) in type 2 diabetes

Antidiabetics	Generic name	Brand name	Therapeutic class	Mechanism of action	Cardiovascular outcomes
Amylin analogs	Pramlintide	Symlin	682092	Analog of human amylin	**(Level 1 evidence; meta-analysis)** • Cardiovascular care of pramlintide was performed by utilizing accepted regulatory medical AE definitions in 5 previously conducted RCTs (16–52-week duration) in T2DM (adults). Mealtime pramlintide is considered to be an adjunct to insulin that advised no elevated cardiovascular AEs risk in type 2 diabetics using insulin[38]

RCT: Randomized controlled trials, T2DM: Type 2 diabetes mellitus

Table 8: Cardiovascular outcome trials for antidiabetics (DPP-IV inhibitors) in type 2 diabetes

Antidiabetics	Generic name	Brand name	Therapeutic class	Mechanism of action	Cardiovascular outcomes
DPP-IV	Saxagliptin	Onglyza		Preserve beta cell function	**(Level 1 Evidence; RCT)** The Saxagliptin Assessment of Vascular Outcomes Thrombolysis in Myocardial Infarction (SAVOR-TIMI) study • 16,492 T2DM individuals (either at a risk for CV events or having a CVD-related history) (patients received either placebo or saxagliptin) • The use of saxagliptin failed to change the ischemic events rate while the rate of hospitalization for HF was higher[39]
	Sitagliptin	Januvia		Incretin hormones (slow inactivation) (for example, GLP-1) that stimulates glucose-dependent insulin secretion	**(Level 1 Evidence; Meta-Analysis)** TECOS (Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin) • This study signified that an amplified HF risk is not a DPP-4 inhibitor class effects • Population: 14,671 patients assigned either to sitagliptin or placebo other than present antidiabetic therapy • The three trials directed that DPP-4 inhibitors are considerably harmless from a CV perspective; however, it does not improve CV end points at any rate in short term[40]

(contd....)

Table 8: ***(Continued)***

Antidiabetics	Generic name	Brand name	Therapeutic class	Mechanism of action	Cardiovascular outcomes
	Linagliptin	Tradjenta		Reduces the breakdown of insulinotropic hormone GLP-1 for improved control of glycemia	**(Level 1 Evidence; RCT)** *The Cardiovascular safety and renal microvascular outcome study with LINAgliptin in patients with T2DM (CARMELINA):* • Assessed the long-term impact on mortality, morbidity of CV as well as renal function of linagliptin treatment[41] • The study is still ongoing
	Alogliptin	Nesina		Inhibits DPP-4	**(Level 1 Evidence; RCT)** The EXAmination of CV outcomes with alogliptIN versus Standard of Care (EXAMINE) study • Population: 5380 Type 2 diabetics who needed hospitalization during the previous 15–90 days because of either unstable angina or acute MI. • Alogliptin failed to increase MACE such as HF, stroke, or MI in comparison to individuals receiving placebo[42] • A *post hoc* EXAMINE trial analysis with alogliptin that mainly enrolled high-risk diabetic individuals and recent cases of ACS patients demonstrated no elevated heart failure risk Comparatively, FDA safety review suggested that T2DM medicines containing either alogliptin or saxagliptin may increase the heart failure risk. Thus, FDA has issued a warning on the use of alogliptin[43]

DPP-IV: Dipeptidyl peptidase-4 inhibitors, RCT: Randomized controlled trials, CVD: Cardiovascular disease, T2DM: Type 2 diabetes mellitus, CV: Cardiovascular, HF: Heart failure, GLP-1: Glucagon-like peptide 1, MI: Myocardial infarction, ACS: Acute coronary syndrome

(EXAMINE) study. The study found evidence of CV harm while no increase in HF was stated. This study also failed to demonstrate any benefit. Conversely, a recent FDA safety review suggested that T2DM medicines containing either alogliptin or saxagliptin may increase the HF risk. Thus, FDA has issued a warning on the use of alogliptin and saxagliptin mainly in patients who already have either a kidney or heart disease[59] [Table 8].

Insulins

The insulin resistance in Type 2 diabetics is accompanied with higher insulin levels, which has also been associated with the risk of CVD. It has been demonstrated that if insulin is associated with higher CVD risk, then exogenous insulin might do the same.[60] While only limited evidence exists to determine if it is true. Another evidence associates hypoglycemic events to CVD though, indicating that the use of insulin is linked with hypoglycemia risk. Hence, it is believed that individuals being offered insulin treatment may be at an elevated CVD risk.[54] The Outcome Reduction with Initial Glargine Intervention trial together with long-acting insulin glargine randomized 12,000 patients (to standard care or glargine) with early or new T2DM, IGT, or impaired fasting glucose, with higher CVD risk and prior event of CVD. No association was demonstrated with macrovascular events in both the groups. A positive association was found in both hypoglycemia and weight gain[45] [Table 9].

SGLT2

SGLT2 inhibitors are one of the latest class of oral hypoglycemic agents which were introduced in the diabetes market. SGLT2 inhibitors tend to inhibit the glucose reabsorption through kidneys so that it can be excreted in the urine. Such a glucose loss in the urine reduces the levels of blood glucose and consequently results in the loss of weight.[61] SGLT2 inhibitors,

Table 9: Cardiovascular outcome trials for insulins in type 2 diabetes

Antidiabetics	Generic name	Brand name	Therapeutic class	Mechanism of action	Cardiovascular outcomes
Insulins	Glargine	Lantus	682008	Is responsible to stimulate uptake of peripheral glucose through skeletal muscle and fat together with impeding the hepatic glucose production	**(Level 1 Evidence; RCT)** The Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial • Population: 12,000 patients (early or new-onset T2DM, impaired glucose tolerance, or impaired fasting glucose, with previous CV event or at a higher risk of CVD) • Patients were randomized either to standard care or glargine • In both the groups, no association was found with macrovascular events • A positive association was observed in both hypoglycemia and weight gain[44] The ORIGIN "Outcome Reduction with Initial Glargine Intervention" trial/ (ORIGINALE) • Patients were followed up for 2.5 years • Insulin glargine was known to have neutral effects on CV health[45]

T2DM: Type 2 diabetes mellitus, CV: Cardiovascular, RCT: Randomized controlled trials

Table 10: Cardiovascular outcome trials for antidiabetics (sodium-glucose cotransporter 2) in type 2 diabetes

Antidiabetics	Generic name	Brand name	Therapeutic class	Mechanism of action	Cardiovascular outcomes
Sodium-glucose cotransporter 2	Canagliflozin	Invokana		Limits the reabsorption of glucose from renal tubules	**(Level 1 Evidence; RCT)** Canagliflozin Cardiovascular Assessment Study (CANVAS) (an ongoing trial) • This trial evaluated adverse CV events with canagliflozin usage in diabetics having higher CV risk • Canagliflozin did not intensify the overall risk of CV • In patients devoid of CV disease, canagliflozin-treated patients performed statistically better than the comparator therapies in accordance to the key CV events[46] • FDA warns of escalated risk of foot/ leg amputations, mostly distressing the toes, with canagliflozin[47] Landmark CANVAS Program study: • Integrated analysis of the CANVAS-R and CANVAS trials • Population: 10,142 with type 2 diabetes and high cardiovascular risk • Patients being treated with canagliflozin had a reduced cardiovascular event risk versus patients who received placebo • This study also exhibited a potential renal protective effects[48]
	Dapagliflozin	Farxiga		It blocks the reabsorption into kidney, which results in blood glucose elimination through urine	**(Level 1 Evidence; RCT)** DECLARE-TIMI58 - A Multicenter Trial • Is a continuing trial, to estimate the dapagliflozin effects on the incidence of cardiovascular events[49]

(contd....)

Table 10: ***(Continued)***

Antidiabetics	Generic name	Brand name	Therapeutic class	Mechanism of action	Cardiovascular outcomes
	Empagliflozin	Jardiance		Inhibitor of SGLT2	**(Level 1 Evidence; RCT)** "EMPA-REG 'Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose' OUTCOME study • Demonstrated exciting CV results with empagliflozin • When compared with placebo, empagliflozin-reduced deaths among individuals with type 2 diabetics and established CVD • In three-point MACE primary end points, 14% reductions were exhibited by the patients • It was primarily due to advantages related to CV deaths, as empagliflozin failed to reduce the rate of non-fatal strokes or non-fatal MI • Empagliflozin displayed - All-cause mortality (32% reduction); CV death (38% reduction); HF hospitalization (35% reduction)[50]

CV: Cardiovascular, RCT: Randomized controlled trials, CVD: Cardiovascular disease, HF: Heart failure, MI: Myocardial infarction, SGLT2: Sodium-glucose cotransporter 2

as the latest market additions, had to meet the FDA standards and demonstrated the evidence of CVD risk[62] [Table 10]. EMPA-REG reported the long term EMPA effects versus placebo on the mortality and morbidity in about 7000 patients with type 2 diabetes together with higher CVD events. Results indicated that EMPA limited the RR for 3-point MACE (non-fatal stroke, non-fatal MI, and time to initial incidence of CVD death) by 14%. It was also known to reduce the RR of hospitalization for HF by 35%, survival improvements by reducing RR of all-cause mortality by 32%, and reduced CV death RR by 38%[50] [Table 10]. It was likely that this study tends to raise the SGLT2 inhibitor consumptions, specifically in groups at higher risk following the diabetic ketoacidosis warning among individuals on SGLT2 inhibitors that came last year.[63] Overall, additional experience and research with SGLT2 inhibitors are warranted in future.

A canagliflozin CV assessment study (CANVAS) program and landmark study currently published in the New England Journal of Medicine[48] combined data from two of the trials CANVAS-R and CANVAS, which involved recruiting of a total of 10,142 diabetic and cardiac patients. The CANVAS patients were randomized 1:1:1 to canagliflozin 300 mg or 100 mg or placebo, while CANVAS-R patients were randomized to placebo or 100 mg (having an option to elevate to 300 mg after 13 weeks). The results demonstrated that INVOKANA® (canagliflozin) considerably reduces the combined risk of non-fatal stroke, MI, and CV death versus placebo in diabetic patients either with a CV disease history or at risk. Thus, treatment with canagliflozin is often associated with a reduced hospitalization from HF risk and also showed protective renal effects. However, FDA issued warning of escalated risk of foot/leg amputations mostly distressing the toes, with canagliflozin.[59]

CONCLUSION

This study highlighted issues related to CVD risk and diabetes and has also identified possible concern areas while prescribing blood glucose-lowering therapies with respect to its impact on the risk of CVD. Diabetes is thought to be a multifaceted illness that considerably carries a significant burden with regard to the complications of CVD. Even though, medication and lifestyle interventions aimed at treating blood pressure and lipids are of great significance during diabetes management, considerably glycemia control is also required for reducing such a risk. There are a number of classes of drugs available for treating high blood glucose levels. Most of the trials failed to demonstrate a significant benefit with regard to mortality and morbidity in spite of intensive glycemic control. Some of the recent trials such as EMPA-REG OUTCOME, UKPDS, SUSTAIN6, and LEADER have shed important light on this vital clinical concern, thus demonstrating a convincing effect of liraglutide, semaglutide, and EMPA on CVD outcomes. Trials are ongoing for CVD safety in novel classes of drugs. Drugs within classes often provide different levels of risk. Personalized care should take account of tailored treatment plans for every patient. Hence, physicians need to be aware of the benefits and risk of such therapies with respect to the CV outcomes and impact. Since the findings obtained from trials are uncertain or contradictory. Therefore, it is essential to tailor all therapies to every individual case by case, and physicians should be vigilant of the new findings from different clinical trials as they become available. As diabetic patients are at an

increased risk for CV mortality and morbidity, considering the CV safety of such drugs unquestionably constitutes knowledge of vital importance for all clinicians dealing with this condition in the future.

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