



(REVIEW ARTICLE)



## A review on impact of glucose-lowering therapies on cardiovascular system in type 2 diabetes mellitus patients

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Publication history: Received on 01 July 2020; revised on 10 July 2020; accepted on 12 July 2020

Article DOI: <https://doi.org/10.30574/wjarr.2020.7.1.0242>

### Abstract

The prevalence of diabetes mellitus (DM), a well-renowned metabolic diseases that comes under Top-10 lethal and incurable disease of the world, is increasing day by day. It is well-reported that the mortality rate of diabetic patients due to comorbidities is higher. Diabetic patients suffer from several cardiovascular events and such risk increases with an intermediate metabolite HbA1c. Control in HbA1c and lowering it does not appear to yield the same benefit on macrovascular endpoints, as observed for microvascular endpoints. Moreover, secondary diseases caused by diabetes mellitus are many and diabetic patients have been found to be more susceptible to diseases like cardiac injury. For instance, rosiglitazone has been found to cause myocardial infarction and ultimately leads to heart failure. Glucagon like Peptide -1 (GLP-1) agonists and sodium- glucose co-transporter 2 (SGLT2) inhibitors causes several cardiac side effects like myocardial infarction and stroke. In this concern, USFDA officially announced in 2008 that all new glucose-lowering agents should be tested for its cardiac safety. However, Metformin which is a biguanide has been very safe and useful for obese diabetic patients. It has shown minimal cardiovascular abnormality and has been considered as one of the safest drugs to be given diabetic patients. In this paper published scientific articles of antidiabetic drugs for their impact on cardiovascular anatomy and physiology have been summarized along with the conclusion of relevant studies.

**Keywords:** Biguanidines; Metformin; Sulfonylureas; SGLT2 Inhibitor; Dipeptidyl Peptidase – 4 Inhibitors; Glucagon like Peptide -1 Agonists (GLP-1 agonists); Rosiglitazone

### 1. Introduction

The symptoms of diabetes were first reported in 1552 B.C., when Hasy-Ra, an Egyptian physician, documented a cryptic disease with polyuria and maceration. Later on, healers observed that the ants get attracted to the urine passed out by the patients. In the 1700s physicians started to prescribe customized diets as the treatment of diabetes along with physical exertion to treat the symptoms of poly-urea and this led to the concept of "Starvation Diet". Several methods were adopted for the diagnosis of diabetes mellitus that initially started with the method of "water tasters" followed by chemical testing methods after the 1800s [1].

Despite all these progressive advancements diabetes mellitus led to premature death until the discovery of insulin in 1889 when Elliott Joslin & Joseph von Mering induced diabetes in dogs by removing the pancreas. Later, in the 1900s a German scientist Georg Zuelzer concluded that injecting pancreatic extract in the blood can reduce blood sugar level. Gradually, an era of pharmacological treatment of diabetes started [2].

Type 2 diabetes mellitus (Type 2 DM) also known as Non-insulin dependent diabetes mellitus (NIDDM) is characterized by a heavy atherosclerotic burden, inadequate compensatory remodeling and accelerated plaque progression [3]. In diabetic patients, macrovascular and microvascular disease are closely correlated. Patients with advanced retinopathy have a 25-fold higher risk for amputation of lower limb and a 2–3 fold higher risk for coronary heart disease (CHD) as compared to those without proliferative retinopathy [4]. Cardiovascular disease (CVD) becomes prominent even when

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HbA1c values remain below the diagnostic threshold for diabetes [5]. The relative risk of CVD increases by about 18 % for every percentage point increase in HbA1c in patients with overt Type 2 DM [6].

With the advancement of the therapies for managing and controlling Type 2 DM several drugs are being used for the patients. Most of the patients are having comorbid diseases like obesity, hypercholesterolemia, hypertension, nephropathy or cardiac disorders. Among all oral drugs, Metformin has been very safe and useful for obese diabetic patients. It has shown minimal cardiovascular abnormality and has been considered as one of the safest drugs. Several other drugs are also safe but still have other side effects. While prescribing the physicians take the note of cardiovascular as well as other serious side effects which may be setback for the patient. This article has put light on these issues for better management of diabetes patients.

## 2. Glucose-Lowering Medications (Oral Hypoglycemic agents) and an Era of Advancement

Apart from insulin, eleven different classes of glucose-lowering medications are available right now. It includes biguanides, sulfonylureas, meglitinide derivatives, alpha-glucosidase inhibitors, thiazolidinediones, Glucagon like Peptide-1 (GLP-1) agonists, dipeptidyl peptidase IV (DPP) inhibitors, amylinomimetics, sodium-glucose transporter-2 (SGLT-2) inhibitors, bile acid sequestrants and dopamine agonists. Among these drugs, Metformin that was discovered in 1922 has been considered as the first line therapy because of its tested and substantiated cardiovascular safety profile for the treatment of adult-onset diabetes [7].

Initially, The United Kingdom provided guidelines which used HbA1c as an intermediate marker of macrovascular complications due to uncontrolled diabetes mellitus. But this practice ceased when the controversial case of Rosiglitazone, a thiazolidinedione drug was reported. Thiazolidinediones (TZDs) got approval in 1999 by USFDA and in 2000 by EMA. Later, the post-marketing studies came with severe cardiac adverse effects. Intensive trials of the molecule showed that antiglycemic effects either appeared as no macro-vascular benefits or with major cardiovascular (CV) endpoints. This incident compelled FDA to ensure cardiovascular safety of each newer molecule prior to its approval. The outcomes of trials designed by many research centers for the evaluation of cardiovascular consequences of glucose lowering agents have been enlisted of which several classes of antiglycemic agents have shown strong associations with cardiovascular outcome [7], [8].

**Table 1** List of drugs with reported cardiovascular and congestive heart failure profile

Anti diabetic drugs	CV Profile	CHF Profile
Sodium-glucose cotransporter 2 inhibitor	Favorable	Favorable
Glucagon like peptide-1 receptor agonist	Favorable	Neutral
Dipeptidyl peptidase-4 inhibitor	Neutral	Neutral
Sulfonylurea	Neutral Gliclazide preferred	Limited safety data
Meglitinides	Limited safety data	Limited safety data
Thiazolidinediones (TZD)	Weakly favorable for pioglitazone	Unfavorable Avoid
Alpha glucosidase inhibitor	Limited promising for acarbose	Limited safety data

**Table 2** List of drugs with reported cardiovascular outcomes

S.No.	Antidiabetic drugs	Reported Cardiovascular Outcomes
01	Glimepiride	Stroke
02	Rosiglitazone	Myocardial infarction Heart failure
03	Pioglitazone	Myocardial infarction Stroke
04	Albiglutide	Myocardial infarction Heart failure
05	Dulaglutide	Stroke
06	Liraglutide	Major adverse cardiovascular events
07	Semaglutide	Stroke
08	Canagliflozin	Heart failure
09	Dapagliflozin	Heart failure
10	Empagliflozin	Cardiovascular Death Heart failure

BioMed Research International studies elaborated following cardiovascular and congestive heart failure (CHF) profile of Type 2 DM pharmacotherapy [7], [9].

### 3. Hypoglycemic Drugs and Trials Conducted on various oral hypoglycemic drugs

There are currently 11 different classes of FDA-approved glucose lowering therapies. The body of evidence on CV safety drugs which became available after 2008 tends to be more robust, as a result of the changed FDA requirements. Nonetheless, data does exist for most other classes and will be reviewed below.

#### 3.1. Bile Acid Sequestrants

Colesevelam is the only hypoglycemic agent approved in this category and has been found to lower HbA1c by 0.5% [10], [11]. This drug obtained FDA approval, in January 2008, for use in Type 2 DM as an adjunct to diet and exercise. It decreases intestinal glucose absorption although the exact mechanism of action is not clear. It is a non-absorbed, lipid lowering polymer that binds bile acids in the intestine, impeding their reabsorption. Its main side-effects are gastrointestinal like constipation. The only study reporting on CV outcomes was a retrospective chart review in subjects with Type 2DM and dyslipidemia, comparing those on colesevelam ( $n = 847$ ) to those on ezetimibe ( $n = 3384$ ). Only fewer subjects on colesevelam had the primary CV event (HR = 0.58,  $p = 0.004$ ) after adjustment for any baseline differences [12], [13].

#### 3.2. Dopamine Agonists

Bromocriptine, a dopamine agonist when administered within two hours of waking up has been postulated to restore the circadian peak of dopaminergic activity in the hypothalamus and as such to decrease hepatic gluconeogenesis and insulin resistance [14], [15]. The major side-effects observed are nausea, dizziness, and orthostasis. In a primary CV endpoint placebo-controlled trial, bromocriptine or placebo in addition to standard therapy was administered over 12 months to 3070 subjects with Type II Diabetes Mellitus and quarter of patients had preexisting CV disease. Bromocriptine reduced the composite outcome which included MI, stroke, revascularization, hospitalization for cardiac cause, and death to 32 versus 37 events (HR = 0.60; 95% CI:0.37–0.96). However, the study was limited by a large number of subjects stopping the drug prior to the final visit: 47% in the bromocriptine group and 32% in the placebo group [15].

### 3.3. Meglitinides

Meglitinides are secretagogues which bind the same ATP-dependent potassium channel as sulfonylureas, but with faster onset and shorter duration of action [11]. They are metabolized and, as such, cause less hypoglycemia than sulfonylureas, especially in renal disease. Two drugs of meglitinide class namely Repaglinide and nateglinide, are available for clinical use since their approval by FDA in 1997 and 2001 respectively. Studies assessing meglitinides and their cardiovascular effects are limited. These agents target postprandial hyperglycemia hence their cardioprotective effect may be similar to other compounds that reduce post-meal glucose excursions such as acarbose. Nateglinide was used in the Long- term study of nateglinide plus valsartan to prevent or delay Type II DM and cardiovascular complications, a placebo-controlled trial of 9306 subjects at high CV risk and with impaired glucose tolerance. After a median of 5 years, there was neither reduction in the incidence of Type 2 DM nor in the composite outcome of CV disease [16].

### 3.4. Sulfonylureas

SUs promote the secretion of insulin by blocking the ATP-sensitive potassium channel of beta islet cells in pancreas [11]. The main risk of SUs is hypoglycemia and weight gain, especially when aiming for tight glucose control. They may also be associated with rapid beta-cell failure [17]. The University Group Diabetes Program had conducted a prospective, randomized double-blinded study on 823 subjects to report on CV effects in Type 2 DM therapy. The subjects were given tolbutamide (1<sup>st</sup> generation sulphonylureas), insulin, or phenformin [18]. Tolbutamide group had shown increased mortality due to hypoglycemic attack and cardiovascular complications [18]. Another study in which the U.K. Prospective Diabetes Study (UKPDS) showed that subjects initially randomized to the intensive glucose arm and who received the sulfonylureas like chlorpropamide, glibenclamide, or glipizide had a reduction of 15% in MI and 13% in overall mortality compared to the conventional group [19]. While the target HbA1c of less than 7% in UKPDS was beneficial, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial cast doubt as to the possibility of achieving tighter glycemic control of HbA1c less than 6.5% safely [20]. The study was conducted on 10250 adults with Type II Diabetes Mellitus, the group on intensive glycemic control using predominantly insulin, thiazolidinedione, or glimepiride had higher mortality than the conventional group, despite achieving an HbA1c of 6.4%, versus 7.5%, respectively [20]. Most recently, a meta-analysis that included 47 randomized trials using second- or third-generation SUs against placebo or as an add-on to metformin revealed no increase in CV risk [21].

### 3.5. Alpha-Glucosidase Inhibitors (AGIs)

Acarbose (approved by FDA in 1995), miglitol (approved by FDA in 1996), and voglibose (developed in Japan and available since 1994) are important drugs of this class. They inhibit the enzyme responsible for the breakdown of oligosaccharides into disaccharides at the intestinal brush border [11]. They target postprandial glucose and do not cause hypoglycemia but cause gastrointestinal intolerance. A placebo-controlled, randomized trial on acarbose has been assessed in progression of Type 2 DM and the development of major cardiovascular events. In the “Study To Prevent Non-Insulin Dependent Diabetes Mellitus” (STOP-NIDDM) trial, with 1429 adults with impaired glucose tolerance and high CV risk, acarbose given over a mean of 3.3 years significantly reduced acute MI rate as well as the composite of macrovascular events with a drop of 49% relative risks (HR=0.51; 95%CI: 0.28–0.95) and an absolute risk reduction of 2.5% [22], [23]. A placebo-controlled, randomized trial on 859 adults was done to evaluate voglibose with impaired glucose tolerance and recent acute MI in Japan. The trial ABC (Alpha-glucosidase-inhibitor Blocks Cardiac Events in Patients with Myocardial Infarction and Impaired Glucose Tolerance) was terminated after a two-year period due to total lack of difference between the two groups, in terms of CV outcomes. An Acarbose Cardiovascular Evaluation (ACE) trial was conducted which was a randomised, double-blind, placebo-controlled, phase 4 trial. The patients with coronary heart disease and impaired glucose tolerance were randomly assigned (1:1) to receive oral acarbose (50 mg three times a day) or matched placebo, which was added to standardised cardiovascular secondary prevention therapy. The outcome occurred in 470 (14%; 3.33 per 100 person-years) of 3272 acarbose group participants and in 479 (15%; 3.41 per 100 person-years) of 3250 placebo group participants (hazard ratio 0.98; 95% CI 0.86-1.11, p=0.73). No significant differences were observed between treatment groups, cardiovascular death, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, hospital admission for unstable angina, hospital admission for heart failure, or impaired renal function. Diabetes developed less frequently in the acarbose group (436 [13%] of 3272; 3.17 per 100 person-years) compared with the placebo group (513 [16%] of 3250; 3.84 per 100 person-years; rate ratio 0.82, 95% CI 0.71-0.94, p=0.005) [22], [23].

### 3.6. Thiazolidinediones

TZDs are insulin sensitizers that affect the liver, skeletal muscle, and adipose tissue through peroxisome proliferator-activated receptor gamma binding [24]. The side-effects of TZDs are fluid retention, weight gain, anemia, fractures, and exacerbation of heart failure [25]. Two TZDs—rosiglitazone (FDA 1999) and pioglitazone (FDA 2001)—are available.

As the two drugs have negative impact on cardiac functions, both agents have been contraindicated in subjects at risk of heart failure. Cardiovascular concern was raised with rosiglitazone after 8 years of clinical practice, when a meta-analysis of 42 trials showed a 43% increase in the risk of MI (86 versus 72 events) and a 64% increase in death from CV disease (39 versus 22 deaths) [26]. The study didn't report absolute risk which was only 0.2% higher with rosiglitazone and, four studies from the infarction analysis and nineteen studies from the mortality analysis [27]. Rosiglitazone came under scrutiny and restricted by the FDA until the results of the trial designed primarily to assess CV risk came out. An open-label clinical trial namely Rosiglitazone Evaluated for Cardiovascular outcomes in oral agent combination therapy for type II Diabetes (RECORD) was conducted with 4447 subjects randomized to rosiglitazone versus a comparator group of either metformin or Sulphonylurea, for a mean of 5.5 years. The inclusion criteria did not include high CV risk, and the event rate was relatively lower in both groups for MI (68 versus 60), for all-cause mortality (88 versus 96), and for stroke (50 versus 63), in rosiglitazone versus metformin/SU, respectively [28]. There were higher rates of fatal and nonfatal heart failure (61 versus 29 subjects). The results of this pharmaceutical-initiated trial were further reaffirmed by an independent review of adjudication and the prescribing restriction was lifted in 2013 [29]. However, the trial was limited by a relatively high dropout rate of 18% and by the lack of blinding [30]. Rosiglitazone use remains limited among physicians.

Pioglitazone was also scrutinized when concerns about rosiglitazone were raised. A trial with primary CV endpoints: the PROspective Pioglitazone Clinical Trial in macrovascular Events (PROACTIVE) enrolled 5238 patients with Type 2 DM and established macrovascular disease, randomized to pioglitazone versus placebo, in addition to standard diabetes therapy. An outcome of nonfatal MI, stroke, or death was lower in the pioglitazone arm with 301 out of 2605 versus 358 out of 2633, for pioglitazone and placebo, respectively [31]. It was found that the reduction was consistent across all 3 components of the 3-point major adverse CV events (MACE). In line with these findings was a meta-analysis of 19 trials on pioglitazone which showed a risk reduction in MI, stroke, or death by 18% (HR= 0.82; 95% confidence interval [CI], 0.72–0.94;  $p = 0.005$ ). It has been observed that there was a higher rate of heart failure (16% versus 11.5%); however, it did not result in increased mortality [32].

### 3.7. Biguanides

Metformin is the only existing compound in the class after FDA approved it in 1994 and has stood the test of time with continued benefits. Metformin's has glucose-lowering effects through the reduction of hepatic gluconeogenesis. In addition, more mechanisms have been described on other parts of the gastrointestinal tract such as increased intestinal glucose utilization, increased glucagon like peptide-1 levels, altered bile acids, and altered microbiome. The cardiovascular benefit of metformin was first demonstrated in UKPDS where the overweight group on intensive glucose control had a 39% reduction in MI rate [33]. In addition, in the 10-year follow-up of UKPDS, the long-term benefit for all subjects in the intensive arm on metformin was shown by reducing MI by 33% and all-cause mortality by 27% as compared to conventional control [34].

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## 4. Amylinomimetics

Pramlintide is an incretin consecrated with insulin, which suppresses postprandial glucagon secretion and delays gastric emptying [35]. It was approved in 2005 for clinical use. As such, it targets postprandial glucose and does not induce hypoglycemia if used as monotherapy. However, its use is recommended as an add-on to insulin, in which case cautious glucose monitoring is necessary to prevent severe hypoglycemia [36]. Cardiovascular safety of pramlintide was assessed using standardized medical definitions (queries) of AEs listed in the standardized Medical Dictionary for Regulatory Activities (MedDRA) version 12.0. The primary analysis compared the frequency of investigator-reported MACE in the pramlintide and control treatment groups. As widely accepted, major adverse cardiovascular events (MACE) included cardiovascular mortality, myocardial infarction, stroke, hospitalization for acute coronary syndrome, and urgent revascularization procedures [37]. Pramlintide has been associated with beneficial effects on body weight, lipids (total cholesterol, low-density lipoprotein cholesterol, and triglycerides), as well as other cardiovascular risk markers [38].

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## 5. Dipeptidyl Peptidase-4 Inhibitors

DPP-4 inhibitors increase endogenous levels of glucagon like peptide-1 (GLP-1) and as such act as mild hypoglycemic oral agents. There are currently four FDA-approved agents: sitagliptin (FDA approved in 2006), saxagliptin (FDA approved in 2009), linagliptin (FDA approved in 2011), and alogliptin (FDA approved in 2013). Vildagliptin was mandated by the FDA in 2007 to conduct more trials in patients with renal insufficiency; there has been no reapplication for FDA approval since then, but it remains widely used in other parts of the world. Additionally, there are 2 once-weekly DPP-4 inhibitor- trelagliptin and omarigliptin- both available in Japan. The FDA issued a warning about a rare, but real,

risk of pancreatitis for all agents in this class. The risk of pancreatic cancer remains a subject of debate [11]. Because the enzyme dipeptidyl peptidase exists in several forms and because DPP-4 activity is specifically exhibited by the cell surface protein CD26 of the T-lymphocyte, this class of drugs has also been associated with various disorders resulting from modulation of immune function such as autoimmune-related skin conditions (notably bullous pemphigoid), arthralgia, myalgia, and nasopharyngitis [39]. The first trial with cardiovascular endpoints, the Saxagliptin Assessment of Vascular Outcomes in Patients with Diabetes Mellitus- Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53), enrolled 16492 adults above 40 years of age, who had established CV disease or were at high risk for CV disease, who received saxagliptin or placebo, along with usual care, and who were followed for 2.1 years [40]. At the end of the trial, despite a small difference in the HbA1c of 0.2% in the intervention group (7.7 versus 7.9%), there was no difference in the primary endpoint of nonfatal MI, ischemic stroke, or CV death (613 in saxagliptin versus 609 in the placebo group, HR = 1.00; 95% CI: 0.89–1.12,  $p < 0.001$  noninferiority) [41]. However, there were more subjects who were hospitalized for nonfatal heart failure (289 in saxagliptin versus 228 in the placebo group, HR = 1.27; 95% CI: 1.07–1.51,  $p = 0.007$ ). Risk factors for heart failure were prior to heart failure, a lower eGFR, and higher baseline pro-BNP levels [41].

Furthermore, the effect of the drug on heart failure was no longer seen one year into the trial. In the second trial, the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE). 5380 men and women with acute coronary syndrome within the last 15–90 days were randomized to alogliptin or placebo, in addition to standard of care. After a median of 18 months, the difference in HbA1c between groups was only 0.3%, and there was no difference in the primary 3-point MACE (316 events for alogliptin versus 305 for placebo, HR= 0.96; upper boundary CI <1.16). Hospitalization for heart failure occurred in 85 of alogliptin-treated patients versus 79 in the placebo group; however, this number did not reach Statistical significance [42]. In the third trial, Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), 14,671 adults above 50 years of age, with established or at high CV risk, were assigned sitagliptin versus placebo in addition to standard of care [43]. After a median follow-up of 3 years, the HbA1c was 0.29% lower in the sitagliptin group; however, there was no difference in the primary 3-point MACE (839 events for sitagliptin versus 851 for placebo, HR = 0.98; 95% CI: 0.88–1.09,  $p < 0.001$  for noninferiority). There were 228 subjects hospitalized for heart failure versus 229, in sitagliptin and placebo groups, respectively. The latter clearly indicates there was no increased risk of heart failure exacerbation, in the case of sitagliptin [43]. As mentioned, there is no primary CV outcome trial for vildagliptin. However, a meta-analysis that included 69 studies on 28,006 subjects on vildagliptin versus a comparator found no increased risk of CV events or heart failure. In a 12-month Vildagliptin in Ventricular Dysfunction Diabetes (VIVID) trial 254 patients with NYHA Classes I–III heart failure were randomized to vildagliptin or placebo. There were 13 admissions for heart failure in the vildagliptin group versus 10 in the placebo group. Although the number did not reach statistical significance, the end-diastolic volume was higher in those on vildagliptin, again reinforcing previous suspicions about the group [44]. A systematic review and meta-analysis on DPP-4 inhibitors found a suggestion of increased heart failure risk, primarily driven by SAVOR, EXAMINE, and VIVID trials [45].

One proposed physiological explanation for the heart failure finding is the inhibitory effect of this class on glucagon, a positive inotropic hormone [46]. One other advanced theory is the inhibition of breakdown of Neuropeptide Y, also a substrate of DPP-4, leading to vasoconstriction [47], [48]. However, given the lack of consistency of the study results, more data will be helpful to further elucidate the question of DPP-4 inhibition and effect on heart failure. The Cardiovascular Outcome study of Linagliptin versus glimepiride in patients with Type 2 DM (CAROLINA) has randomized 6051 subjects above 40 years of age with either high risk or preexisting CV disease to linagliptin or glimepiride; its results are anticipated in the middle of 2019 [49]. Omarigliptin was undergoing CV assessment in a trial expected in 2021 [50], [51].

In summary, the use of DPP-4 inhibitors in subjects with CV disease seems to have small signals for heart failure, especially in those at risk [52], [53].

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## 6. Glucagon like Peptide-1 Receptor Agonists

GLP-1 normally secreted by the ileum stimulates insulin release, inhibits glucagon release, and suppresses appetite both centrally and by delayed gastric emptying [11], [16]. The class has been available since 2005 with several compounds: exenatide (FDA approved in 2005 for the twice-daily injection, FDA approved in 2012 for the once-weekly one), liraglutide (FDA approved in 2014), dulaglutide (FDA approved in 2014), albiglutide (FDA approved in 2014), lixisenatide (FDA approved in 2016), and semaglutide (FDA approved in 2019). There are GLP-1 receptors on the heart and questions were raised in view of the DPP-4 inhibitor results on heart failure [54], [55]. There is a mild, but consistent, increase in heart rate with all GLP-1 agonists. This effect may be heterogeneous among the different compounds, with the shortest-acting agent increasing the rate by 1–3 beats per minute, all the way to the once-weekly agents increasing it by 6–10 beats per minute [56]. The first study in class to examine CV risk was the Evaluation of

Lixisenatide in Acute coronary syndrome (ELIXA) which randomized 6068 men and women with Type 2DM, who had acute coronary syndrome within the preceding 180 days, to lixisenatide or placebo on a background of usual care. After a median of 25 months, there were 406 events in the lixisenatide group versus 399 in placebo (HR = 1.02, 95% CI:0.89–1.17,  $p < 0.001$  for noninferiority) [57].

The second outcomes trial, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER), randomized 9340 adults above 50 years of age, with an established disease or at high CV risk, to liraglutide or placebo against the standard of care for a mean of 3.8 years. By the end of the trial, there was only a mild drop in HbA1c in both groups, and subjects on liraglutide had a 0.4% lower level [58]. The difference was mainly driven by death from CV causes. This started to become apparent after 18 months of exposure to the drug. There was no difference in hospitalization for heart failure. Additionally, there was 22% less risk of nephropathy, which, by itself, represents a reduced macrovascular hazard. A third study in the Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 DM (SUSTAIN-6) randomized 3297 subjects to the once-weekly semaglutide at 0.5 or 1.0mg doses versus placebo. Again, more than 80% of subjects had established CV disease, and the others were at high risk with age above 50 years and duration of Type 2DM of 13.9 years. Baseline HbA1c was 8.7% and the difference at the end of 2.1-year follow-up was 0.7 and 0.9%, for the 0.5mg and 1.0mg doses of semaglutide, respectively. Similar to the liraglutide trial, there was a 36% reduction in the risk of new or worsening nephropathy [59].

Trial on Dulaglutide in the Researching CV Events with a Weekly Incretin in Diabetes (REWIND) and trial on exenatide once weekly in Exenatide Study of Cardiovascular Event Lowering (EXSCEL) have been completed. Dulaglutide is a novel drug for the treatment of type 2 diabetes and functions as a GLP-1 agonist. These drugs reduce hyperglycemia in patients with type 2 diabetes and are also known to cause slight reductions in weight and blood pressure. However, pulse can increase with the use of these agents, but in this trial, suggests no adverse CV consequences [60]. Once-weekly exenatide (EQW) had a neutral effect on hospitalization for heart failure (HHF) in the EXSCEL study (Exenatide Study of Cardiovascular Event Lowering), with no differential treatment effect on major adverse cardiac events by baseline heart failure (HF) status [61]. Albiglutide in the HARMONY OUTCOME trial was tested in patients with type 2 DM and CV disease. Albiglutide was superior to placebo with respect to major adverse CV events. Evidence-based glucagon-like peptide 1 receptor agonists should therefore be considered as part of a comprehensive strategy to reduce the risk of CV events in patients with type 2 DM [62].

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## 7. SGLT2 Inhibitor

Sodium-glucose co-transport 2 (SGLT2) inhibitors partially block glucose reabsorption in the proximal renal tubule by binding to the SGLT2 transporter. Available SGLT2 inhibitors are highly selective for the SGLT2 receptor in the renal tubule. However, there may be a minor effect on intestinal SGLT1 inhibition, affecting glucose absorption [11], [63]. Efficacy on HbA1c lowering averages 0.6%. Other than glucose-lowering, SGLT2 inhibitors decrease systolic and diastolic blood pressure mildly. It is preferable not to initiate them if eGFR < 60 mL/min/1.73mm<sup>2</sup> (<45 for empagliflozin), and it is recommended to discontinue them if eGFR falls persistently below 45 mL/min/1.73mm<sup>2</sup> with their use [64]. There are post-marketing reports of euglycemic diabetic ketoacidosis associated with their use. One potential explanation is that SGLT2 transporters are present on the alpha islet cells of the pancreas, and their inhibition results in higher glucagon secretion [65].

The first agent to be approved by the FDA, canagliflozin, became available in 2013, based on pooled data from 9 studies on 10285 subjects which suggested no CV harm with HR = 0.91 (95% CI: 0.68–1.22). Primary CV endpoints have just been made available with the Canagliflozin Cardiovascular Assessment Study (CANVAS) [66]. In this trial, the integrated renal and CV pool of 10142 participants were reported together to maximize the power. Adults, above 50 years of age with established CV disease or above 60 years with two or more risk factors, received canagliflozin 100mg or 300mg or placebo in a 1:1:1 ratio and they were followed over a 3.6 years period. The hospitalization rate for heart failure was markedly lower in the canagliflozin group, with 5.5 versus 8.7 participants with an event per 1000 patient-years with HR of 0.67 (95% CI: 0.52–0.87) [66].

In May 2017, the FDA issued a drug safety alert on canagliflozin being associated with twice as much risk of toe and foot amputations, as the placebo group [67].

Dapagliflozin (FDA approved in 2014) was the first SGLT2 inhibitor to become available outside the USA [68]. A primary outcomes trial, the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58), enrolled more than 17000 subjects in 2013, and results are anticipated for 2019 [69]. Until then, two published studies are in favor of dapagliflozin: a meta-analysis of the phase 2b/3 studies suggested no increase in mortality, nor in the 3-point MACE [70]. Even more favorably, a retrospective case-control open-cohort population-

based study reviewed all-cause mortality and CV events in 22,124 patients with Type 2DM on dapagliflozin ( $n = 4444$ ) or not on SGLT2i ( $n = 17680$ ) and found a significant decrease in all-cause mortality of 8.4 versus 17.2 incidence rate per 1000 person-years with adjusted relative risk 0.50 (95% CI 0.33–0.75) in the dapagliflozin group versus the control, respectively [71].

Empagliflozin (FDA 2014) also has a completed primary CV outcomes trial. The EMPA-REG study randomized 7020 adults with high CV risk or disease to empagliflozin 10 mg or 25 mg or placebo in addition to standard of care. The population was very similar to the previously described primary CV outcome trials, with average age 63 years, average BMI of 30 Kg/m<sup>2</sup>, and more than 50% subjects with duration of diabetes of more than 10 years (EMPA-REG). After a follow-up of 3.4 years, there was a significant decrease in the 3-point MACE occurring in 490 out of 4687 (10.5%) in the empagliflozin group versus 282 out of 2333 (12.1%) in placebo, HR of 0.86 (95% CI: 0.74–0.99;  $p = 0.04$  for superiority). The effect was largely driven by death from CV causes. Hospitalization for heart failure occurred in 4.1% in the placebo group versus 2.7% in empagliflozin conferring 35% risk reduction. Both the CV mortality and heart failure benefits were observed as early as 6 months into the trial and were sustained [72].

Based on the trial results, the FDA has issued an additional approval for empagliflozin to reduce CV death in T2D in December 2016. Possible explanations for the unanticipated early beneficial and powerful results were hemodynamic (increased natriuresis, decrease in blood pressure) and metabolic (decreased waist circumference and weight, HbA1c decrease of 0.4%) in nature [73]. However, similar changes seen with other agents did not yield the same benefits as observed with empagliflozin or canagliflozin. One suggested theory is that an increase in ketone levels may be beneficial to the myocardium, especially an ischemic myocardium, providing an alternative source of energy [74]. One additional SGLT2i molecule, ertugliflozin, is currently undergoing Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants with Vascular Disease (VERTIS CV) [75].

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## 8. Conclusion

The most recent CVOTs have expanded our knowledge on the potential effects of glucose-lowering agents on CVD risk. Over the past decades, trial and monitoring methods for the evaluation of glucose lowering agents for cardiovascular outcomes have been ameliorated greatly. Now we have many choices of medicine and many treatment guidelines by official health research centers and associations. UKPDS guidelines state that good control of blood sugar reduces cardiac complications.

On the basis of the above-stated data it is concluded that metformin has least cardiovascular complications and hence it should be the first line of therapy for Type 2 DM. We believe this exercise is needed to avoid inappropriate over-use of SGLT2-I and GLP-1RA, before all needed information is gathered while ensuring they are used in keeping with the available evidence.

Lifestyle modification should be an integral part of the treatment for the patients of diabetes. There was a great pace made since the 10-year follow-up on the UKPDS showing reduction in cardiovascular risk with improved glycemic control.

Therefore, addressing the pharmacotherapy of Type 2 DM judiciously as highlighted in this paper should be carried out as part and parcel of overall patient well-being. Currently, physicians have enough data to provide an individualized prescription to Type 2 DM patients but further trials and studies are still required for the refinement of available data to reduce the risk of the cardiovascular outcome by glucose lowering therapies.

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## Compliance with ethical standards

### *Acknowledgments*

The authors sincerely acknowledge Lloyd Institute of Management and technology (Pharm) for providing journal access facility to write this review.

### *Disclosure of conflict of interest*

This review article is for academic purposes only. No conflict of interest was reported by the authors.



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### How to cite this article

Khatoon R and Hoda Q. (2020). A review on impact of glucose-lowering therapies on cardiovascular system in type 2 diabetes mellitus patients. *World Journal of Advanced Research and Reviews*, 7(1), 162-173.

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