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# The Impact of Anti-Diabetics on Platelets Function and Cardiovascular Outcomes in Type 2 Diabetes Mellitus: A Narrative Review

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## ABSTRACT

Increased atherosclerosis is a major risk factor for atherothrombotic disorders in patients with type 2 diabetes mellitus (T2DM). Changes in platelet metabolism and alterations in intra platelet signaling pathways are the main contributors to the pathogenesis of atherothrombotic complications of diabetes. In addition, advances in understanding the action of some anti-diabetics have demonstrated probable effects of these agents on platelet function and thrombotic state in T2DM. This review aimed to explore the possible mechanistic association between anti-diabetic agents and the development of thromboembolic disorders, considering the effect of drugs on platelet function and their impact on cardiovascular outcomes in diabetic patients. The cochran Library, PubMed, and Google Scholar were searched to analyze related publications. The relationship between anti-diabetic medications and the alterations in platelets function, in addition to the impact of the drugs on the occurrence of thromboembolic disorders in diabetic patients and their relation to cardiovascular events, were the main targets. Ninety-three published articles from November 1999 until February 2024 met the requirements for inclusion in this review. We realized various mechanisms responsible for enhanced platelet aggregation in T2DM, represented by immature, large, or activated platelets in the altered metabolic environment, against the background of vascular damage in DM. In parallel, analyzing the impact of anti-diabetics on platelet aggregation revealed that most of them are believed to have favorable protective effects against thrombotic disorders via reducing platelet activation and aggregation. Conversely, some anti-diabetics may exhibit negative consequences by exacerbating platelet hyperactivity and possibly predisposing to a higher incidence of thrombotic events in diabetic patients. When prescribing anti-diabetic agents to patients with T2DM, especially those at high risk of developing cardiovascular problems, we should consider these outcomes with proper monitoring of coagulation status.

**Keywords:** Anti-diabetic; Cardiovascular Diseases, Diabetes mellitus; Platelets; Thrombosis; Coronary artery disease.

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## INTRODUCTION

Cardiovascular disease is a life-threatening complication of type 2 diabetes mellitus (T2DM). Among the most common complications of this condition, are the microvascular and macrovascular complications [1]. Macrovascular consequences are presented as peripheral vascular disease, cerebrovascular illness, and premature coronary artery disease (CAD), all of which are due to accelerated atherosclerosis [2]. CAD incidence is similar across patients with T2DM and those without diabetes who were previously presented with heart attacks. However, individuals with T2DM usually show a 2-4 fold higher risk of CAD when compared to people who have not presented previously with heart attacks. Furthermore, T2DM is associated with a poor prognosis after myocardial infarction (MI), a higher risk

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of heart failure (HF), and an increased mortality rate during long-term monitoring [3].

Additionally, triggering the coagulation cascade, endothelial dysfunction, and increased platelet activation in T2DM have been associated with increased thrombotic activity. Individuals with T2DM exhibit higher platelet reactivity, a risk factor for potentially deadly thrombotic events. Research indicates that existing antiplatelet drugs are less effective in this patient group, with a significant proportion either not responding or responding modestly [4].

Improved glycemic control or other direct anti-thrombotic and anti-inflammatory processes may contribute to the potential benefit of these drugs on platelets [5]. These results have important medical implications since the alteration in the activity of platelets by anti-diabetics could reduce the incidence of thrombotic disorders and help diabetics avoid cardiovascular complications [6]. In addition, a more comprehensive understanding of how some anti-diabetics work has shown possible implications for platelet function and thrombotic status in T2DM [7]. Therefore, the primary goal of this review was to identify any potential links between anti-diabetic medication and platelet function that will affect the clinical cardiovascular outcome while considering how medications affect platelet function and outlining any potential underlying mechanisms.

## METHODS

The present article is a narrative review that mainly discusses the effect of anti-diabetic medications on the function of platelets and their relation to cardiovascular outcomes in T2DM. The literature search was performed, during the period between November 2023 and February 2024 on databases including Cochran Library, PubMed, and Google Scholar, using keywords that are relevant to the main topic of this review. Anti-diabetics, cardiovascular diseases, CAD, diabetes mellitus, platelets, and thrombosis were used separately and in combination to reveal articles related to the main topic until the date of drafting this review. Articles about platelet changes in diabetic patients, the effects of anti-diabetic drugs on platelet function, and their cardiovascular outcomes were considered. So were articles about the clinical significance and/or lack of clinical significance of anti-diabetics on platelet function and patients' overall cardiovascular health. We conducted a thorough manual review of the articles and found 93 that met our selection criteria, published between November 1999 and February 2024. The present narrative review provides further explanations for these studies.

## PLATELET ALTERATIONS IN DIABETIC PATIENTS

DM is considered to be a prothrombotic state that is linked to decreased fibrinolytic activity, coagulation system stimulation, and chronic platelet activation [8]. Over the past few decades, several studies have demonstrated that individuals with DM experience various abnormalities in platelet function [9]. In general, there are three main suggested descriptions for platelet dysfunction in DM. These include immature, non-functioning platelets, large, non-functioning platelets, and more reactive-non-functioning platelets that are produced in the bone marrow. Exposure to the metabolic alterations in diabetes mellitus (DM) can also activate platelets, and this activation ultimately correlates with vascular damage. On the other hand, there are numerous mechanisms by which diabetes affects the platelet's function, including changes in platelet aggregability, thromboxane production, membrane glycation, platelet size, platelet glycoprotein receptors, platelet secretion products, and intracellular mechanisms [10].

Historically, in 1965, it was discovered that platelets become hyper-aggregable when exposed to glucose. Patients with type 1 DM (T1DM) or T2DM have been demonstrated to have enhanced aggregation of platelets in reaction to several agonists, including thrombin, collagen, arachidonic acid (AA), and epinephrine, as compared to non-diabetic persons [11]. Platelets show enhanced thromboxane (Tx) production, as shown by a higher excretion of 11-dehydro-TxB2 in the urine [12]. TxA synthesis has been positively related to fasting plasma glucose (FPG) and hemoglobin A1c (HbA1C), where enhanced glycemic control has been shown to decrease TxA production. This high level of TxA production has been associated with both micro- and macroangiopathy that occur in diabetic patients [13]. It has been revealed that membrane glycation, together with an alteration in lipid composition results in impaired fluidity of the platelet membrane [14]. Additionally, studies have demonstrated that glycosylated LDL enhances platelet aggregability [15]. Patients with DM have also reported alterations in platelet size, with the belief that younger, bigger platelets are more reactive [16]. The number of platelet glycoproteins (GPIb and GPIIb/IIIa) present on the membrane of platelet, the ability to produce TxA, and the platelet granule contents are all strongly correlated with the platelet size distribution, which is often reported as median platelet volume (MPV). An increased MPV is an independent risk factor for MI and proliferative diabetic retinopathy [17]. Furthermore, the platelets of diabetic patients have enhanced adhesive potential as well as increased numbers and activity of multiple glycoprotein receptors on the platelet membrane [18]. Accordingly, increases in GP IIb/IIa (fibrinogen receptor), GPIb-IX (von Willebrand factor receptor), GPIa/IIa (collagen receptor), and the cluster of differentiation (CD 62) (P-selectin receptor) have been detected in some diseases, including DM [19]. Additionally, an increase in the CD40-CD40 ligand system has been demonstrated in DM patients. All these changes are expected to be causative factors for increased platelet aggregability [20].

When platelets become active, $\alpha$-granules let out cytokine-like proteins like platelet factor 4 (PF4) and $\beta$-thromboglobulin ($\beta$-TG) [21]. Diabetic angiopathy, such as proliferative retinopathy, is associated with elevated levels of these proteins in DM patients [22]. Functional platelet abnormalities in DM are linked to several changes inside cells, such as a decrease in $Na^{+}/K^{+}$ ATPase activity and an increase in $Ca^{+2}$ ATPase activity. This causes cells to hold more $Ca^{+2}$ and platelets to react more quickly [23]. Additionally, in diabetic platelets, lower intracellular $Mg^{+2}$ may increase platelet activity [24]. Furthermore, hyperglycemia is associated with enhanced protein kinase C (PKC) activity and superoxide anion generation, along with decreased nitric oxide synthase (NOS) activity and antioxidant (glutathione) levels [25]. These changes may provoke oxidative stress and platelet activation [26]. Moreover, researchers have detected changes in most intrinsic and extrinsic coagulation pathway factors in DM [27]. Researchers have reported an increase in markers of coagulation activation, such as prothrombin fragments and thrombin-anti-thrombin complexes, in DM [28]. In addition, anticoagulants such as protein C and anti-thrombin III may have decreased activity in people with DM [29].


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## EFFECTS OF ANTI-DIABETIC DRUGS ON PLATELET FUNCTION AND THEIR CLINICAL CARDIOVASCULAR OUTCOMES

### Metformin

Metformin therapy reduced cardiovascular complications by 40% in overweight patients with T2DM in the UK prospective diabetes study (UKPDS) [30]. The effects of metformin therapy on platelet function have not been well studied, and the available data are inconsistent [31]. However, patients with T2DM and insulin-dependent diabetes (metformin added to insulin therapy) have been shown to have decreased sensitivity to platelet-aggregating factors when treated with metformin [32]. Metformin has platelet stabilizing effects, as demonstrated by decreased platelet density, $\beta$-TG, and platelet superoxide anion generation [33]. Additionally, metformin lowers MPV, which is often elevated in individuals with diabetes and linked to vascular problems [34]. Metformin may slow the evolution of atherosclerosis because lower MPV and platelet activity are linked to positive effects on vascular adhesion, cholesterol levels, and inflammatory markers [35]. However, metformin is a pleiotropic drug with favorable treatment effects on fibrinolysis (lowers the plasminogen activator inhibitor-1 in plasma), coagulation (decrease factor VII and factor XIII), lipids (reduce the incidence of hyper-triglyceridemia), and blood flow (enhance vasodilator responses to L-arginine and blood flow after ischemia) [36].

Long-term clinical research shows a correlation between metformin and a lower risk of cardiovascular disease. Metaformin cut down on cardiovascular events (like stroke and MI) and deaths from all causes in the UKPDS more than diet, insulin, or chlorpropamide [37]. Another study found that, over 3-4 years of clinical follow-up, metformin medication improved the control of blood sugar levels and lowered the risk of major cardiovascular events (stroke, MI, and peripheral vascular disease) in people who were being treated with insulin [38].

### Sulfonylureas

The generations of sulfonylureas include the first (chlorpropamide), the second (gliclazide, and glibenclamide), and the third generation (glimepiride) [39]. Several sulfonylurea derivatives exhibit antiplatelet characteristics by lowering agonist-induced platelet aggregation and blocking the metabolism of AA [40]. Gliclazide did not significantly decrease the AA metabolism of platelet homogenates when sulfonylureas were studied for their impact on this process. On the other hand, glibenclamide and glimepiride both inhibited the synthesis of cyclooxygenase-related metabolites, such as TxB2 [41]. Studies have shown that gliclazide's ability to get rid of free radicals lowers the activity of platelets and raises the production of prostacyclin [42, 43]. Gliclazide also suppresses neutrophil-endothelial cell adhesion, increases fibrinolysis, decreases platelet aggregation, and prevents the expression of endothelial adhesion molecules on the surface [44].

Studies on the clinical cardiovascular effects of these drugs demonstrated that they decrease cardiovascular health in comparison with metformin alone [37]. Researchers have linked agents belonging to this group to increased hospitalization and mortality risks in patients due to their induction of platelet aggregation and other cardiovascular events [45]. Also, there is an increase in the risk of stroke and overall mortality [46]. However, a recent study assessing second and third-generation sulfonylureas has not revealed adverse effects on all-cause mortality, cardiac mortality, MI, or stroke for individuals treated with these drugs. However, these drugs may interfere with ATP-sensitive potassium channels in the heart, leading to negative effects [47].

### Meglitinides

The post-prandial state in T2DM patients is associated with increased platelet reactivity [48]. Although repaglinide administered before meals did not prevent post-prandial platelet activation, it is linked to reduced platelets and endothelial activity during the fasting state [49]. However, studies have linked lower levels of interleukin-6 and C-reactive protein during repaglinide therapy to improved glycemic control and lowered postprandial glycaemia, which also positively impacts oxidative stress [50–52]. Clinical effects on cardiovascular events show that these drugs have more beneficial effects than sulfonylurea in reducing cardiovascular risk factors [53].

### Thiazolidinediones

The nuclear peroxisome proliferator-activated receptor (PPAR), which is found in a variety of tissues involving adipose tissue, vascular tissue, and platelets, is activated by thiazolidinediones (glitazones) [54]. In platelets activation, the PPAR receptor was found to be associated with the inhibition of the release of bioactive mediator including soluble CD40L and thromboxane A2, in thrombin-activated platelets [55]. Pro-inflammatory processes have been demonstrated to be induced by CD40L signaling in a variety of cell types, and elevated blood levels of CD40L are intimately linked to DM, cardiovascular diseases, and inflammation [56]. Rosiglitazone treatment in patients with T2DM and CAD has been associated with reduced serum CD40L concentrations and lower expression of platelet P-selectin in CAD patients who are not diabetics [57]. Moreover, therapy with pioglitazone improved platelets function even in non-diabetic individuals with elevated cardiovascular risk [58]. Studies on the clinical cardiovascular outcomes of pioglitazone have shown that there is a reductions in MI and stroke for patients who use this drug [59]. Furthermore, there was a 32% risk reduction of recurrent stroke and a 25% risk reduction of major adverse cardiovascular events (MACEs) [occurrence of nonfatal stroke, nonfatal MI, and cardiovascular death] [60]. In contrast, many meta-analyses have linked rosiglitazone, another drug in this class, to an elevated risk of cardiovascular events [61, 62]. However, another study has not shown a higher risk of MI or cardiovascular mortality [63]. But as compared to the control group, the rosiglitazone group showed a double incidence of HF hospitalizations [63].

### SGLT-2 Inhibitors

The Food and Drug Administration (FDA) approved these new classes of drugs, known as gliflozins, which include dapagliflozin, empagliflozin, and canagliflozin [64]. The reduction in blood glucose by gliflozins treatment normalized reticulated (immature) platelet levels [65]. Gliflozins reduced platelets aggregation, intracellular calcium mobilization, and TxB2 levels [66]. Also, empagliflozin lowered the levels of plasminogen activator inhibitor-1 in the blood of people with T2DM, which stopped thrombotic disorders from happening [67].

This group's clinical cardiovascular effects include a reduction in the risk of MACEs, HF hospitalization, cardiovascular

mortality, and renal outcomes, despite the existence or absence of pre-existing cardiovascular diseases [68, 69]. The European Society of Cardiology/European Association for the Study of Diabetes Guidelines recommend this glucose-lowering class to reduce the risk of HF hospitalization in patients with T2DM and to reduce cardiovascular events in individuals at elevated risk of cardiovascular complications [70].

### Glucagon-like peptide 1 receptor (GLP-1R) agonists

These agents inhibit platelet aggregation by activating adenylyl cyclase, leading to increased levels of cyclic adenosine monophosphate (cAMP), which activates protein kinase A, and phosphorylation/activation of endothelial nitric oxide synthase (eNOS), which results in an increased nitric oxide (NO) level in platelets and endothelial tissues [71]. The increased NO in platelets stimulates soluble guanylyl cyclase that activates cyclic guanosine monophosphate (cGMP) and protein kinase G, which play a crucial role in inhibiting platelets activation/aggregation [72]. Thus, a key impact of GLP-1R agonists on platelet function is an increase in accessible NO, either by endothelial or platelet synthesis. Clinical cardiovascular outcomes studies demonstrated a decrease in the occurrence of MACEs and fatal and non-fatal MI among patients using these drugs [73].

### Dipeptidyl peptidase 4 inhibitors (DPP-4I)

Agents involved in this group are sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin [74]. The proposed mechanism by which these agents reduce platelets aggregation is that they reduce thrombin-induced elevation in the intracellular $Ca^{+2}$ of the platelets. Inhibition of the tyrosine kinase activity induced by thrombin and/or increases in tyrosine phosphatase activity, leads to a reduction in the tyrosine phosphorylation of multiple proteins involved in platelet aggregation [75]. In addition, these chemicals boost the anti-inflammatory and anti-atherogenic effects of incretins while blocking the DPP-4 enzyme [76].

Multiple randomized clinical trials have examined the cardiovascular benefit of DPP4I, with varying results. Saxagliptin and alogliptin do not increase the risk of MACEs, but they do increase the incidence of HF admission [77]. Based on these findings, the FDA updated its warning about the safety of alogliptin and saxagliptin's cardiovascular effects to raise awareness among both patients and doctors about the possibility of an elevated risk of HF. Studies on linagliptin and vildagliptin have shown no observed benefits on MACEs among patients who used these drugs [78, 79].

### $\alpha$-glucosidase inhibitor

Acarbose, an $\alpha$-glucosidase inhibitor, is a mild anti-diabetic medication that lowers postprandial glucose levels [80]. By lowering postprandial hyperglycemia, acarbose has been demonstrated to decrease the production of platelet-monocyte aggregates [81]. Also, there is evidence suggesting that this agent reduces platelet-derived microparticles (PDMP) and selectins, which result in the reduction of platelet aggregation [82].

A study on the clinical cardiovascular effects of acarbose showed a 49% reduction in the risk of MACEs development [83]. Another study found that acarbose slowed the progression of intima-media thickness in carotid arteries in patients with impaired glucose tolerance [84].

### Insulin

Insulin's effects on platelet function are controversial; physiologically, it inhibits platelet hyperactivity, promotes NO generation by stimulating eNOS through the PI3K-dependent pathway, and induces endothelin-1 secretion [90]. T2DM appears to diminish this effect. People who have T2DM have platelets that are less sensitive to insulin, which could make them more reactive and more likely to have atherothrombotic events [91]. Moreover, improved insulin sensitivity by the use of pioglitazone or weight reduction reduces markers of platelet reactivity in obese, insulin-resistant patients [10]. In contrast, other studies suggest that the administration of insulin to patients with T2DM will result in increased platelet activity as a result of postprandial hyper-insulinemia through pathways excited by TXB and adenosine diphosphate (ADP) [48].

The clinical cardiovascular effects of insulin are also controversial; it has been reported that insulin therapy was associated with a reduction in morbidity and mortality of cardiovascular events, potentially related to the enhancement of long-term blood glucose control. However, other studies have shown that insulin therapy may result in hyperinsulinemia, hypoglycemia, and weight gain, and is increasingly associated with adverse cardiovascular outcomes [92].

Table 1 summarizes the impact of anti-diabetic agents on platelet function and cardiovascular events. Additionally, Table 2 provides a brief description of each study.

### Clinical significance

The most severe consequences linked to T2DM, including MI and stroke, are mediated by enhanced thrombosis, which has a substantial effect on survival [93]. Thus, cardiologists should give patients with T2DM more attention, as they typically require longer and more aggressive anti-platelet therapy in comparison to non-diabetics [94]. Cardiologists must have the ability to regulate the optimum use of anti-platelet and hypoglycemic agents to deliver suitable management tailored to the glycometabolic and thrombotic risks of patients [95]. Understanding the molecular mechanisms of platelet dysfunction in DM patients and how anti-diabetic agents affect these changes can help us move closer to individualized patient treatment [96]. Enhanced glycemic control either directly or indirectly enhances the beneficial effects of anti-diabetic drugs on platelet aggregation and thrombosis, making optimum glycemic control in DM patients a crucial approach to reducing platelet-related complications [97]. Many anti-diabetic agents have antiplatelet properties beyond their primary hypoglycemic effects [98]. Clinically, we can take advantage of these effects. For example, using metformin in diabetic patients can reduce platelet aggregation in addition to reducing hypertriglyceridemia which results in reduced cardiovascular diseases in these groups of patients [99]. Furthermore, newly introduced anti-diabetic drugs such as SGLT-2 inhibitors and GLP-1 agonists have anti-platelet effects, that may contribute to their proven cardiovascular benefit that has been shown clinically [100].

## CONCLUSION

Due to increased platelet dysfunction and coagulation activity, T2DM is considered a prothrombotic state. Platelet dysfunction in T2DM patients is either caused by the disease's metabolic effect or the reduced effect of insulin on platelet receptors. Correspondingly, different anti-diabetics might have


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**Table** 1. The impacts of anti-diabetics on platelets and cardiovascular events.*

| Anti-diabetic agent | Platelets effects | Clinical cardiovascular effects | References |
|---|---|---|---|
| Metformin | Reduce platelets aggregation by decreasing platelet density, $\beta$-TG, platelet superoxide anion generation, and MPV. | Decreased cardiovascular end-point (MI and stroke) and all-cause mortality. | [37] |
| | | Decreased macro-vascular complications(MI, stroke, and peripheral vascular disease). | [38] |
| Sulfonylurea | Glibenclamide and glimepiride both reduce platelet aggregation by preventing the synthesis of metabolites related to cyclooxygenase, such as TxB2. Gliclazide scavenges free radicals, reduces platelet reactivity, and increases prostacyclin production. | Decrease cardiovascular benefit vs metformin alone. | [37] |
| | | Increase the risk of cardiovascular hospitalization and mortality. | [45] |
| | | Increased risk of stroke and overall mortality, no effect on MACEs. | [46] |
| | | The second and third generation of this group has a neutral effect on all-cause mortality, cardiovascular mortality, MI, or stroke. | [47] |
| Meglitinides | Reduce platelets aggregation by reducing platelet and endothelial activity during the fasting state. Has a positive impact on oxidative stress reducing platelets aggregation. | Have more beneficial effects than sulfonylurea in reducing cardiovascular risk factors | [53] |
| Thiazolidinediones | Reduce platelets aggregation by Reducing P-selectin, CD40L, and inflammation. | (Pioglitazone) Neutral influence on major cardiovascular end-points, stroke, or MI. | [85] |
| | | (Rosiglitazone) Neutral effect on the incidence of MI or cardiovascular death. | [86] |
| | | Increased risk of cardiovascular events. | [62] |
| SGLT-2 Inhibitors | Reduce platelets aggregation by reducing intracellular calcium mobilization, and TxB2 levels. | Reduced the occurrence of MACE, cardiovascular mortality, and HF hospitalization. | [69, 87] |
| GLP-1R agonist | Reduce platelets aggregation by increasing NO which results in reduced platelets aggregation. | Reduced MACEs, fatal and non-fatal stroke. | [73] |
| DPP-4I | Reduce platelets aggregation by reducing thrombin-induced elevation in the intracellular $Ca^{+2}$ of the platelets. | No obvious advantage on MACEs incidence Vs placebo. | [78] |
| | | Increase in the incidence of HF admission. | [77, 88] |
| $\alpha$-glucosidase inhibitor | Reduce platelets aggregation by decreasing the production of platelet-monocyte aggregates. | Reduce the risk of cardiovascular events. | [83] |
| | | Reduce progression of carotid intima-media thickness. | [84] |
| Insulin | Controversial, but it can directly activate IR on the platelet resulting in decreased platelet aggregation. | Controversial, however, the positive effects on cardiovascular events are suggested to be related to the enhancement of glycemic control. | [89] |

* B-TG: $\beta$-thromboglobulin; MPV: median platelet volume; MI: myocardial infarction; MAGEs: major adverse cardiac events; CD40L: cluster of differentiation 40L; NO: nitric oxide; HF: heart failure; IR: insulin receptor.

contradictory impacts on platelets function. Those agents with beneficial effects may work either directly by reducing intracellular $Ca^{+2}$ level, the sensitivity of the platelet's receptor to agonists, and the level of activating factors, or indirectly by enhancing glycemic control. Therefore, these agents may play an important role in reducing vascular-diabetic complica-

**Table** 2. A brief description of the studies that discussed the impacts of anti-diabetics on platelets and cardiovascular events.

| Anti-diabetic agent | Author names | Country | Objectives | Study design | Number of patients |
|---|---|---|---|---|---|
| Metformin, sulfonylureas [37] | Paromita King et al, 1999 | UK | Exploring the effect of blood pressure and glycemic control on the occurrence of some complications, in addition to investigating any possible differences between the management options in T2DM | Comparative study between metformin, sulfonylureas (or a combination of them), and insulin. In addition to comparing the impacts of captopril and atenolol on the studied parameters. | 5,102 |
| Metformin [38] | Adriaan Kooy et al, 2009 | Netherlands | To investigate whether metformin hydrochloride has sustained beneficial metabolic and cardiovascular effects in patients with T2DM | A randomized placebo-controlled trial. | 390 |
| Sulfonylureas, metformin [45] | Ajay D. Rao et al, 2008 | USA | Evaluating the effects of combination therapy of sulfonylureas and metformin on the risk of all-cause mortality and cardiovascular disease among people with T2DM. | A literature search that involved 299 article. | Literature search involved 299 studies. |
| Sulfonylureas [46] | M. Monami et al, 2013 | Italy | Collection of all available data on the cardiovascular safety of sulfonylurea from randomized trials in T2DM. | A meta-analysis of randomized clinical trials (115 trials) | Meta-analysis |
| Sulfonylureas [47] | Dimitris Varvaki Rados et al, 2016 | Brazil | Evaluation of the safety of sulfonylureas in T2DM | A meta-analysis of randomized clinical trials (47 trials) | Meta-analysis |
| Meglitinides [53] | MR Rizzo et al, 2005 | Italy | Comparison of the effects of repaglinide vs glimepiride administration on the cardiovascular risk factors after meal test in T2DM | A comparative study (repaglinide vs glimepiride) | 14 |
| Thiazolidinediones [85] | Catherine M. Viscoli et al, 2014 | Italy, UK, Germany, Canada, and Australia | Evaluation of the pioglitazone role in reducing the risk of stroke and MI among insulin-resistant, non-diabetic patients with a recent ischemic stroke or transient ischemic attack | A placebo-controlled trial | 3,876 |
| Thiazolidinediones [86] | Philip D. Home et al, 2007 | UK | Evaluation of the outcomes of cardiovascular events in rosiglitazone users | Analysis of a randomized, multicenter, open-label, non-inferiority trial | 4,447 |
| Thiazolidinediones [62] | Elizabeth Selvin et al, 2008 | USA | Systematically examining of the peer-reviewed literature on the cardiovascular risk associated with oral agents (sulfonylureas, biguanides, thiazolidinediones, and meglitinides) | A systematic analysis that involved 40 studies | Systematic review |
| SGLT-2 Inhibitors [69] | Bernard Zinman et al, 2015 | Canada, and Germany | Evaluation of empagliflozin effects on cardiovascular morbidity and mortality in patients with T2DM at high cardiovascular risk | A randomized, double-blind, placebo-controlled trial | 691 |
| SGLT-2 Inhibitors [87] | Bruce Neal et al, 2017 | Australia and UK | Evaluation of canagliflozin impacts on cardiovascular, renal, and safety outcomes in T2DM | The data integrated from two randomized placebo-controlled trials | 10,142 |


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| Anti-diabetic agent | Author names | Country | Objectives | Study design | Number of patients |
|---|---|---|---|---|---|
| GLP-1R agonists [73] | Soren L Kristensen et al, 2019 | UK | Investigating the cardiovascular outcome following GLP-1R agonists use in T2DM | An analysis of randomized, placebo-controlled trials | The trials included more than 500 patient |
| DPP-4I [77] | William B. White et al, 2013 | UK | Assessing the cardiovascular outcomes of alogliptin as compared with placebo in patients with T2DM who had a recent acute coronary syndrome | A double-blind, non-inferiority placebo-controlled trial | 5,380 |
| DPP-4I [88] | Benjamin M. Scirica et al, 2013 | USA | Evaluating the cardiovascular safety and efficacy of saxagliptin in T2DM | A randomized, placebo-controlled trial | 16,492 |
| DPP-4I [78] | Nikolaus Marx et al, 2015 | Germany, USA, Canada, Netherlands | Evaluating the cardiovascular outcomes of linagliptin (DPP-4I) vs glimepiride in patients with T2DM. | A multicenter, randomized, double-blind, active-controlled trial. | 6,041 |
| $\alpha$-glucosidase inhibitor [83] | Jean-Louis Chiasson et al, 2003 | Canada, Germany, Austria, Nor-way, Denmark, Sweden, Finland, and Spain | Evaluating the effect of decreasing postprandial hyperglycemia with acarbose ($\alpha$-glucosidase inhibitor) on the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance | An international, multicenter double-blind, placebo-controlled, randomized trial. | 1368 |
| $\alpha$-glucosidase inhibitor [84] | Markolf Hanefeld et al, 2004 | Germany | Examination of the efficacy of acarbose to slow the progression of intima-media thickness in subjects with impaired glucose tolerance | A randomized placebo-controlled trial | 132 |
| Insulin [89] | Hertzel C. Gerstein et al, 2008 | USA, and Canada | Investigating whether intensive therapy to target normal HbA 1C levels would reduce cardiovascular events in patients with T2DM who had either established cardiovascular disease or additional cardiovascular risk factors | A multicenter randomized study | 10,251 |

tions. On the other hand, agents that exhibit negative effects on platelets, by exacerbating platelet hyperactivity, raise the possibility of thrombotic events. Such dualistic impact highlights the importance of personalized medicine to overcome the deleterious effects and to improve patient outcomes by lowering the risk of cardiovascular diseases.

## ETHICAL DECLARATIONS

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### Ethics Approval and Consent to Participate

The present article is a narrative review that gathers information from previously published articles. Therefore, ethical approval and patients' consent to participate are not applicable.

### Consent for Publication

None.

### Availability of Data and Material

None.

### Competing Interests

The authors declare that there is no conflict of interest.

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All authors were responsible for the literature review and writing the manuscript. The authors read and approved the final version of the manuscript.

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