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Review Article

# A review of pharmacotherapy in type 2 diabetes mellitus and its possible cardiovascular risk

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**ABSTRACT**

Type 2 diabetes mellitus (T2DM) is characterized by multiple pathophysiologic abnormalities. With time, multiple glucose-lowering medications are commonly required to reduce and maintain plasma glucose concentrations within the normal range. T2DM individuals also are at a very high risk for microvascular and macrovascular complications and the incidence of heart attack and stroke is increased two- to three-fold compared with non-diabetic individuals. Nearly 70 % of deaths occur in diabetes due to macrovascular complications, e.g. myocardial infarction, stroke, heart failure and peripheral vascular disease. Therefore, when selecting medications to normalize glucose levels in T2DM patients, it is important that the agent does not aggravate cardiovascular risk factors (CVRFs), and ideally improves and reduces cardiovascular morbidity and mortality.

**OBJECTIVES**:

This review article focuses on the following objectives:

- Mechanism of action on different cellular level of oral (Biguanides, Sulfonylureas, Meglitinides, Thiazolidinediones, Dipeptidyl peptidase-4 inhibitors (DPP4i), Sodium glucose linked transporter 2(SGLT2) inhibitors, and Alpha-glucosidase inhibitors) and injectable (Glucagon-like peptide-1(GLP-1) receptor agonists and Insulin) glucose-lowering drugs on established CVRFs and long-term studies of cardiovascular outcomes.
- Correlation between the mechanisms behind the antidiabetic medication and its side effects like weight gain, weight loss, increase or decrease of HDL cholesterol, LDL cholesterol and triglycerides and its effects on cardiovascular system (CVS).
- Correlation between coronary artery disease (CAD) risk factors like Hyperglycaemia, hypertension, vascular inflammatory marker (increased c-reactive protein, increased monocyte chemotactic protein-1, increased proinflammatory cytokines),coagulation and thrombotic markers(like decrease antioxidant status, increased von willebrand factor etc..) and endothelial dysfunctions( decreased vascular reactivity, increased degradation of nitric oxide etc.)
- Selection of different antidiabetic agents based on patient's physiological conditions and its possible risk factors to prevent CVD(cardiovascular disease)

**Keywords:** pharmacotherapy, coronary artery disease, type 2 diabetes mellitus, dyslipidemia, vascular inflammation, CVRFs.

## INTRODUCTION:

Cardiovascular diseases (CVD), coronary heart disease (CHD) and cerebro-vascular diseases, are currently the leading cause of death globally, accounting for 21.9 per cent of total deaths, and are projected to increase to 26.3 per cent by 2030[1]. Diabetes is associated with twice the risk of incidence of coronary heart disease (CHD) and ischaemic stroke and 2–4 times increased risk of CHD and stroke mortality compared with patients without diabetes [2–4].

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65% of deaths in patients with diabetes are from cardiovascular causes [5]. More significantly however, the age- and gender-adjusted mortality risk in diabetic patients without pre-existing coronary artery disease was found to be equal to that of non-diabetic individuals with prior myocardial infarction (MI) [6].The management of diabetes mellitus is a challenging multifactorial task because mere treatment of hyperglycaemia is not enough to reduce the mortality rather we have to make multifactorial strategy to identify and target patients cardiovascular risk factors.

A complex mix of mechanistic processes such as oxidative stress, enhanced atherogenecity of cholesterol particles, abnormal vascular reactivity, augmented haemostatic activation, and renal dysfunction have been proposed as features characteristic of T2DM that may confer excess risk of CHD [7]. Similarly with subsequent implications like insulin resistance, visceral adiposity, and excess inflammation [8-10] underlie the pathophysiology of thrombogenesis.These remarkable findings regarding higher risk of mortality[11-13] have led to suspicion that common precursors predispose to diabetes and CHD[14,15]. The actions of oral hypoglycaemic agents and insulin's are not limited to reducing the serum blood glucose level by modifying insulin sensitization or insulin secretion or reducing glucose absorption, but it also leads to vascular inflammations by increasing C - reactive protein, endothelial dysfunction by increased degradation of nitric oxide. The drugs used in the treatment of diabetes have potential CV effects, either beneficial or harmful. In the Framingham Heart Study, men with type-2 diabetes were twice as likely to develop heart failure, whereas this risk was increased by five-fold in women [16]. The epidemiological studies suggest that the risk of stroke may be reduced by 17% for every 1% decrease in glycosylated haemoglobin (HbA1c)[17] so it is important to be screened for fasting blood glucose levels, Hba1c or both for high risk patients regularly and give treatment based on their risk factors. In the meta-analysis in 2007 authors demonstrated a significant increase in risk of myocardial infarction and death from the cardiovascular causes with rosiglitazone use fuelling a lot of controversial issues with respect to prescribing this drug as well as stimulating the debate on whether diabetes drugs should have long term trials showing cardiovascular safety [18, 19]. In its 2008 Guidance for Industry publication, the US Food and Drug Administration (FDA) issued detailed recommendations to drug developers for demonstrating that new and existing therapies will not result in an unacceptable increase in CV risk [20].The European Medicines Agency (EMA) issued similar guidelines in 2012 for drug developers to investigate and rule out potentially harmful drug interactions [21].

## COMMON FACTORS WHICH AFFECTS DIABETIC PATIENTS TO INCREASE CARDIOVASCULAR RISK

Diabetes mellitus with high serum blood glucose level alone is not sufficient to affect cardiovascular risk but different cellular mechanism involved leads to progression and deterioration of CVRFs. DM patients mainly presents with different CVD risk factors (table1) which is associated with insulin resistance in type II DM and some etiological factors. These combinations of insulin resistance and CVD risk factors leads to metabolic syndrome.

## EFFECTS OF ELEVATED SERUM BLOOD GLUCOSE

### *EFFECT ON COAGULATION AND THROMBOTIC STATE*

The mechanism behind cardiovascular risk is alteration of the coagulation cascade and its pattern. Hyperglycaemia may lead to increased or decreased clotting factors. Clotting factors IIa (thrombin) and VII are increased in patients with diabetes, whereas protein C, a natural anticoagulant, is decreased. Fibrinolysis is also reduced, further raising the risk of clot formation [22]. This may also lead to inflammation of the artery wall through increased monocyte adhesion to endothelial cells and alterations in the monocytes themselves, causing an accumulation of macrophages [23]. Thromboses in diabetics are bigger as more GPIIb/IIIa receptors are available

on their surfaces. Therefore, platelets can aggregate more easily [24]. The increased receptor availability and clotting factors may cause clot formation easily, and clot may get destabilised and leading to cardiac events. In studies of diabetic patients post mortem, the small coronary arteries appear to be hardened and thickened [25].

**TABLE 1: Cardiovascular risk factors biomarkers associated with type II DM**

| **Risk factors** | |
|---|---|
| Hyperglycaemia | Hyperinsulinemia |
| Obesity | |
| Dyslipidaemia | |
| Decreased high-density lipoprotein cholesterol | |
| Small, dense low-density lipoprotein particle size | |
| Increased triglycerides | |
| Hypertension | |
| Microalbuminuria | |
| Vascular inflammation markers | |
| Increased C-reactive protein | |
| Increased monocyte chemotactic protein-1 | |
| Increased pro-inflammatory cytokines | |
| Coagulation and thrombotic markers | |
| Increased mean platelet volume | |
| Decreased antioxidant status | |
| Increased von Willebrand factor | |
| Decreased antithrombin III | |
| Increased plasminogen activator inhibitor-1 | |
| Increased fibrinogen | |
| Increased matrix metalloproteinase levels | |
| Endothelial dysfunction | |
| Decreased vascular reactivity | |
| Increased degradation of nitric oxide | |
| Reduced release of prostacyclin | |

***ELEVATED FREE FATTY ACIDS***

Elevated blood glucose levels may lead to increase free fatty acids (FFA) and increased FFA may cause cardiovascular complications. It may also lead to endothelial dysfunction, increase lipid deposition, insulin resistance and enhanced coagulation. FFAs also affect cholesterol components by causing an increase in triglycerides (TGs), low-density lipoproteins (LDLs), and very-low density lipoproteins (VLDLs) and a decrease in high-density lipoproteins (HDLs) [26].

***INSUFFICIENT VASODILATION***

High level of serum blood glucose level may decrease nitric oxide level which helps to dilate vascular smooth muscles. Hyperglycaemia leads to decrease or inactivates the nitric oxide level. Diabetic patients also show an increase in endothelin level, which may lead to vasoconstriction [26].

***DIABETES AND HYPERTENTION***

The frequency of hypertension (HTN) in diabetic population is almost twice as compared to non-diabetic population [27]. In India about 50% of diabetics have HTN [28, 29]. In diabetics who are obese, overweight and having dyslipidaemia are more prone to develop HTN. Harry Keen

pointed out two bad companions of diabetes mellitus, viz., hyperglycaemia (glucotoxicity) and high blood pressure both associated with microalbuminuria [30]. Microalbuminuria is a marker for generalized vascular dysfunction. Microalbuminuria interacts with the traditional cardiovascular risk factors; it has an independent relationship to renal and cardiovascular outcomes. Elevated rates of urinary albumin excretion predicts target organ damage, notably renal disease, but are also related to left ventricular dysfunction, stroke, and myocardial infarction [31]. Patients having both HTN and DM have approximately twice the risk to develop cardiovascular complications when compared to non-diabetic people with hypertension alone. Hypertension patients with DM are also at increased risk of micro vascular complications like diabetic retinopathy, nephropathy and neuropathy. Similarly one study shown aortic stiffness as measured from aortic pulse wave velocity (PWV) has been shown to be a predictor of future cardiovascular events in patients with DM and HTN [32, 33].

***ABNORMAL LIPID PROFILES AND OBESITY***

Dyslipidaemia is an established risk factor for CAD in patients with type II DM, as well as in nondiabetic patients, and is likely to play a leading role in the increased CVD risk associated with diabetes [34-36]. Recent guidelines from the National Cholesterol Education Programme and the American Diabetes Association have also advocated lower low-density lipoprotein cholesterol as targets in all patients with diabetes [37]. The level of high density lipoprotein (HDL) decreases while the level of low density lipoprotein (LDL) increases in diabetic patients. Hyperglycaemia affects LDL and become glycosylated, thereby making it difficult to be recognized by LDL receptors. These LDL particles are scavenged by the tissue macrophages creating foam cells, a constituent of the atherosclerotic plaque [38].These plaques may lead to embolism and ischemic heart problems. Blood cholesterol is an important risk factor for CHD but other risk factors such as raised blood pressure, physical activities also play a role, and thus cholesterol screening alone is unlikely to reduce mortality and can be misleading. The load of cardiovascular risk factors (CVRFs) includes hypertension, dyslipidaemia (reduced HDL-cholesterol, elevated triglycerides, and small dense LDL particles), obesity (especially visceral), physical inactivity, sub-clinical inflammation, and endothelial dysfunction. This cluster is referred to as metabolic or insulin resistance syndrome [39-41].

Evidence suggests that this dysfunctional adipose tissue is less sensitive to insulin and has reduced hormone-sensitive lipase activity compared with normal adipose tissue. As a result, there is an increased breakdown of intracellular TG and increased release of FFAs into the circulation, leading to fatty infiltration in the liver, muscles and possibly pancreatic β-cells. Other hand scientific studies have shown that cardiovascular disease (CVD) has multiple risk factors, including unhealthy diet, physical inactivityand abdominal obesity [42] and a simple reduction of 5-10% of body weight has been demonstrated to improve metabolic profile and cardiovascular health [43]. Maintaining of weight and keeping cholesterol level normal would be the one more step to maintaining our blood glucose and subsequently preventing the possible risk of cardiovascular complications.

***ENDOTHELIAL AND VASCULAR WALL DYSFUCTIONS***

The endothelial dysfunction is the change in vascular tone, vascular permeability and imbalance in angiogenesis. The vascular endothelial dysfunction plays an important role in the development and progression of subclinical atherosclerosis. Hyperglycaemia [44], impaired anti-oxidant balance [45], dyslipidaemia and the increased free fatty acids [46] are thought to cause endothelial damage. The impaired endothelium includes reduced vasoactive capability, increased ability to support thrombosis, increased permeability and increased adhesion molecule expression [47, 48]. Due to changes of such endothelial functions, it produces increased adhesion of leukocytes and platelets, increased responsiveness to cardiovascular agents (eg, angiotension II, endothelin-I and thrombin) and increased

transmigration of leukocytes [48, 49]. Prostacyclin and nitric oxide (NO), produced by normal endothelium, inhibit platelet activation and relax vascular smooth muscle, promoting normal blood flow. People with DM have a reduced release of prostacyclin and NO [50] and chronic impairment of endothelial NO synthase activity, this leads to increase chance of atherosclerosis in DM. Overall all these mechanism finally leads to impairment in the cardiovascular system.

***INFLAMMATION AND CV RISK***

Inflammation and endothelial dysfunctions are closely associated with insulin resistance, atherogenic dyslipidaemia, hypertension, impaired fibrinolysis/increased risk of thrombosis, and inflammation. The evidence which explain that low grade inflammation would reflect a widespread activation of the innate immune system is closely involved in the pathogenesis of type II DM dyslipidaemia and atherosclerosis [51]. Similarly chronic inflammation of the endothelial cell and vascular environment impairs endothelium-dependent vasodilation, induces the expression of cell surface adhesion molecules by endothelial cells and increases cardiovascular risk [52-54]. Inflammatory markers like C-reactive protein (CRP) play a significant role as it amplifies the inflammatory response by stimulating the production of Tumour necrotic factor (TNF) alpha and Interleukin 1 (IL-1) by tissue macrophages [54]. Overall the vascular inflammation plays an important role in the development of atherosclerosis and plaque stability [55]. It is now beyond dispute that inflammation is one of the important causes of CVD and a key player in the development of atherothrombosis, leading to adverse clinical events [56].

**AVAILABLE ORAL HYPOGLYCEMIC AGENTS AND INSULIN USE TO TREAT DIABETES MELLITUS**

**BIGUANIDES (METFORMIN)**

Metformin is an insulin sensitizer which inhibits gluconeogenesis, decrease glucose absorption from gastrointestinal system and increase the peripheral glucose uptake by tissue (mainly skeletal muscles) in the presence of insulin. Metformin belongs to the class of biguanides; it acts by reducing insulin resistance, mainly in liver and skeletal muscles, suppressing hepatic gluconeogenesis and increasing insulin sensitivity and peripheral glucose utilizations [57]. The cellular mechanism involves activation of an adenosine monophosphate (AMP) kinase enzyme which plays an important role in carbohydrate and lipid metabolism, inhibition of mitochondrial respiration leading to inhibition of hepatic glucose production, increased glucose uptake in contracting muscle, increased fatty-acid oxidation, decreased lipolyisis and enhanced insulin sensitivity, it does not produce side effects like weight gain or hypoglycaemia [58-62]. Metformin is commonly prescribed oral hypoglycaemic agent world-wide and is commonly recommended as first line therapy by the American Diabetes Associations (ADA), European Association for the study of Diabetes, and international Diabetes Federation [63]. Metformin, when used as monotherapy has been associated with a reduction in glycated haemoglobin (HbA1c) of between -1.1% to -3% [64]. Metformin is the drug of choice for the treatment of overweight and obese patients and it has other effects too which includes lowering of lipid levels and improvements in fibrinolysis, inflammatory markers, and platelet anti aggregating effect. It also decreases in triglycerides, LDL- cholesterol level by approximately 10-15%. HDL levels may be remain unchanged or slightly increased, and there is moderate weight loss (2-3 kg) associated with metformin [65-67] (fig. 2) so it is beneficial for overweight patients and hypertensive patients. Metformin doesn't have direct effect on beta cell so it doesn't cause hypoglycaemia. The common side effects includes diarrhoea and may increase plasma level of homocysteine which is risk factors for CAD by impairing absorption of vitamins and especially folate in the chronic treatment[68,69]. Lactic acidosis is a serious complication occurring rarely, with approximately 5 cases per 100,000 patients per year [70].

**Table 2: Pharmacotherapy of anti-diabetic medications and its effects on body**

| DRUGS | EFFECTON WEIGHT | EFFECTS ON BP | EFFECTON CHOLESTEROL | EFFECTS ON BLOOD VESSELS | EFFECTS ON HEART | INFLAMMATION | SIDE EFFECTS | OVERALL CV EFFECTS |
|---|---|---|---|---|---|---|---|---|
| **Biguanides (Metformin)** | Loss(around 0.6-2.9kg) or neutral | Neutral or decrease | Increase in HDL Decrease in LDL Decrease in TG | It protect endothelial lining | May have cardio protective Effects and improve LVF | Anti-inflammatory and anti-thrombotic properties | Lactic acidosis (rare) Caution indicated in older with CHF, renal and hepatic insufficiency patients | Somewhat beneficial |
| **Sulfonylureas** Tolbutamide, Chlorpropamide Cliclazide Glipizide Climepiride Glyburide Glibenclamide | Gain (around 1-2 kg) | Neutral | decrease in HDL decrease or neutral in LDL increase or neutral TG | May damage endothelial | May increase risk of CV(gliclazide and glimepiride may be safer) | May inhibits platelet aggregation | May cause CV side effects | May increase CV risk |
| **TZD** Rosiglitazone Pioglitazone | Gain (around 1-2 kg) | Neutral or decrease | Increase in HDL Neutral or increase LDL Decrease TG | It may prevent atherosclerosis | Fluid retention and oedema, May increase the chances of HF | Anti-inflammatory properties | Increase the risk of MI, CHF and mortality | Caution with Heart disease Pioglitazone is Safer than Rosiglitazone |
| **DPP-4 inhibitors** Sitagliptin Saxagliptin Vildagliptin Linagliptin Alogliptin | Neutral | Neural or moderately decrease | Neutral or increase HDL Neutral or increase LDL Decrease TG | Vasodilation action and antithrombotic effect | May have cardio protective action | Improve fibrinolysis | May cause HF | CV safety Unclear |
| GLP-1 RA Exenatide Liraglutide | Loss (around 3-5 kg) | Decrease | Neutral HDL Decrease LDL Decrease TG | Improve endothelial by improving vasodilation | May improve LVF and reduce arrhythmias | Anti-thrombotic and anti-inflammatory property | May cause acute pancreatitis with exenatide | May have cardio Protective effect |
| SGLT-2i | Loss (around 2-3 kg) | Decrease | Increase HDL Increase LDL Decrease TG | Reduce arterial stiffness and improve endothelial functions | Not significant effect on heart and have risk of volume depletion | Decrease CV risk markers like albuminuria, uric acid | Genital react infection and osmotic diuretic effect | It shows beneficial effect but still clinical trials are going on |
| Alpha-glucosidase inhibitors | | | | | | | | |
| Insulin | Gain (around 1-3 kg) | Neutral | Neutral HDL Decrease LDL Decrease TG | May have anti atherosclerotic effects | CV effects due to risk of hypoglycaemia | Inhibits platelet aggregation | Hypoglycaemia | Cardiovascular Safety unclear |

## SAFETY PROFILE OF METFORMIN IN CVS

Studies have reported as a cardio protective effect of metformin in diabetes mellitus. UKPDS (UK Prospective Diabetes Study) reported improved cardiovascular outcomes in obese patients receiving metformin monotherapy but it shows increased cardiovascular mortality in patients taking combination of metformin and sulfonylurea [71]. According to UKPDS, it concluded that as compared to conventional therapy, metformin was able to reduce any diabetes related problems, diabetes related death and all causes mortality. As compared to insulin and sulfonylureas, metformin showed a more beneficial effect for any diabetes related endpoint, all-cause mortality and stroke [72]. Similarly another study also concluded that, treatment of diabetic patients having coronary heart disease with metformin for a 5 years period found that metformin alone also reduces the risk of macrovascular disease [73-74]. A recent study reviewed and explained that metformin is safer anti-diabetic drug not only to reducing the blood glucose level but it also effective in HF patients, it improves left Ventricular ejection fraction [75]. Although long term treatment of metformin impairs gastrointestinal absorption of vitamin B, mainly folate [76, 77] and rarely cause lactic acidosis [78] metformin shows cardio protective effects, it also reduces the body weight so it is good for obese patients, it also reduces the TG and HDL cholesterol and has neutral effects on HDL cholesterol and have anti-inflammatory, anti-thrombotic actions. So basically its cardio protective drug but clinical trials are ongoing on to overcome the controversial conclusion.

## *SULFONYLUREAS*

Sulphonylureas (SU) are insulin secretagogues, these exert their effect by binding to adenosine triphosphate (ATP) sensitive potassium channels situated on the Beta-cells inhibiting potassium efflux leading to subsequent depolarization of beta cell, which lead to insulin secretion [79,80]. These receptors are also present in cardiac myocytes thereby leading to cardiac side effects of SUs [81]. SUs reduce the HBA1c level by around 0.9-2.5% and are used as monotherapy or with combination of first line agent (metformin) mainly non obese patients [82, 83]. The well-known side effects of SU is hypoglycaemia and weight gain. SU exert their effect by binding to sulfonylurea receptor 1 (SUR1) on pancreatic beta cell and shows insulinotropic effect [79]. and it also bind to SUR2 A/B on the myocardium and coronary smooth muscle and prevent development of protective ischemic preconditioning [84]. Sulfonylureas directly act by stimulating insulin secretion. Therefore, the effect of sulfonylureas is limited to the patients with compromised beta cell function [85]. SUs are very effective with first line medications (metformin) than as monotherapy. According to a 2013 meta-analysis, SU can cause a slight reduction of HDL-c with no effects on BP and other lipid profile [86]. However, a very recent meta-analysis revealed that SU have only a small effect on lipids, with a significant increase in both free fatty acids (FFA) and TG levels, and a decrease in LDL-c and HDL-c if treated alone [87]. Metformin and second generation SUs (glimepiride, glibenclamide) have good effect on lipids as compared to metformin and glitazone. Sulfonylurea alone do not reduce the triglyceride and LDL, it may cause weight gain around 2-3 kg mainly with first generations. Hypoglycaemia appears to be more frequent with glyburide [88] while glimepiride is associated with lower risk of hypoglycaemia and less weight gain [89].

## *SAFETY PROFILES OF SULFONYLURES IN CVS*

The negative cardio-vascular outcome related to sulfonylureas treatment and studies suggests that some SUs can impair ischemic preconditioning in the cardiac myocardium [90]. The study analysed from Diabetes Audit and Research in Tayside Scotland (DARTS) diabetes information system and the Medicines Monitoring Unit (MEMO) revealed that patients receiving sulfonylurea treatment, either alone or in combination with metformin, exhibited significantly increased cardiovascular morbidity and mortality as well as all-cause mortality compared to patients treated with metformin alone [91]. Similarly meta-analysis looking at cohort and case-control studies showed that SU monotherapy or in combination treatment was

associated with higher all-cause and cardiovascular mortality risks when compared to patients receiving non-SU treatment. They explained that the potential causes for this could be due to some specific effects of SU therapy namely hypoglycaemia, weight gain, increased proinsulin release and activation of SU receptors on myocardial muscle cells [92]. Similarly a meta-analysis concluded that an increased risk of stroke and a significant increase in mortality, without affecting the overall incidence of major adverse cardiac events (MACE) with SU treatment [93]. Likewise another study has shown an increase in CV risk and mortality with all SU, except for gliclazide which was associated with a lower risk [94]. Similarly another retrospective study in US veterans showed an increase in the hospitalization for acute MI or stroke, or death, in the patients with the long term treatment of SUs as compared with metformin [95]. In another double-blind randomized trial study in the patients with diabetes and CAD, they preferred first line agent (metformin) over SUs [96].So overall the treatment of diabetes with SUs should be limited for the high risk patients like obese and CAD until unless first line agent is not enough to control high serum glucose level.

## ***THIAZOLIDINEDIONES***

Thiazolidinediones (TZDs) (rosiglitazone, pioglitazone) are insulin sensitizers. It works by activating the peroxisome proliferator-activated receptor (PPAR) γ which leads to increased transcription of genes involved in glucose and lipid metabolism as well as energy balance. PPAR-γ in adipocytes and endocrine enhances the adipogenesis and decreases fat breakdown which lead to reduction in liver fat and improvement in insulin sensitivity in liver and muscles [97, 98]. PPARs belong to nuclear receptors family, having three isoforms alpha, beta and gamma. These receptors balance the lipolysis, glucose balance, local inflammation, tumour development, and thrombosis. And they have antiatherogenic effects [99]. TZDs decreases glucose and HbA1c at moderate level around 10-20%, it increases HDL level up to 5-10% and moderately increases LDL level also around 5-10% [100]. Generally small LDL particles are more atherogenic; TZDs treatments may reduce the atherosclerosis by increasing the LDL level in moderate amount [101]. TZDs treatment may cause weight gain around 2 kg. When used in combination with metformin, it decreases the blood pressure slightly, increases insulin mediated vasodilation and raise insulin sensitivity. Similarly it inhibits intracellular calcium and myocyte contractility and inhibits endothelium secretions [101].

## ***SAFETY PROFILES OF THIAZOLIDINEDIONES IN CVS***

Generally two drugs mainly used in this class of diabetic medicine (rosiglitazone and pioglitazone). Rosiglitazone has an increased risk of ischemic cardiac events and has been withdrawn from the market in the EU in 2010 by the European Medicines Agency (EMA) and restricted to use by the FDA [102,103].

The common side effects of TZDs include weight gain, fluid retention which may lead to peripheral oedema associated with cardiovascular risk [104]. Similarly in meta-analysis done by Nissen and Wolski in 2007 explained that there was a significant increased risk of myocardial infarction, angina and cardiovascular mortality in patients taking rosiglitazone when compared to metformin, SU or placebo [105]. Another meta-analysis for pioglitazone was found not to increase cardiovascular risk [106]. But rosiglitazone and pioglitazone does not increase risk of new onset of heart failure, but worsen the pre-existing heart failure [107]. Another study also explained that Pioglitazone reduces CV surrogate markers such as endothelial dysfunction, blood pressure, dyslipidemia, circulating levels of inflammatory cytokines, and prothrombotic factors [108-110]. But safety profile of rosiglitazone in CV still remains controversial [108].

## ***INCRETIN THERAPY***

In DM there is Decreased insulin sensitivity and progressive loss of pancreatic beta-cell insulin secretion. In the incretin therapy, the researcher focused on the incretin system and its role in contributing to hyperglycaemia. The two main incretin hormones thought to maintain euglycemia are GLP-1 and glucose-

dependent insulinotropic peptide (GIP). Both hormones are secreted because of carbohydrate and fat consumption, and both result primarily in increased glucose-dependent insulin secretion and decreased glucagon secretion. Both hormones are rapidly metabolized in the circulation by dipeptidyl peptidase-4 (DPP-4). Two incretin based therapy involves are given below.

**DPP-4 INHIBITORS**

DPP-4 inhibitors (sitagliptin, saxagliptin, vildagliptin, linagliptin, teneligliptin) are the new class of oral anti-diabetic agents. They control high blood sugar by inhibiting the enzymatic degradation of glucagon like peptide 1 (GLP-1). GLP-1 is an incretin hormone produced by the distal part of small intestine and released in to bloodstream. It controls blood sugar by delaying gastric emptying, by suppressing glucagon release and insulin release by glucose dependent stimulation. It is used to reduce the postprandial plasma glucose level by endogenous production of GLP-1 hormone. [111] the retrospective studies suggested that DPP-4 inhibitors reduce the LDL cholesterol, total cholesterol and triglyceride levels. [112] and increases the HDL cholesterol. [113] Its effective drugs who is having comorbid condition like CVD because it reduces or normalise the blood pressure and improve lipid profile.[114,115] Other than biological effects of incretins, DPP-4 inhibitors have some pleiotropic effects in the CV system, it involve cytokines, chemokines, inflammation, immunity and vascular function.[116] DPP-4 inhibitors helps to improve the vasodilation by substance P and bradykinin and may improve fibrinolysis by stimulating tissue plasminogen activator (tPA). [117] it does not cause weight gain and hypoglycaemia. [118] Some Studies have shown that these drugs are generally well tolerated, reduce HbA1c by around -0.8% are weight neutral and by themselves are not associated with hypoglycaemia, thus the FDA has approved them for both monotherapy as well as in combination with other anti-hyperglycaemic drugs in the treatment of type 2 diabetic patients. [119-121]

**SAFETY PROFILES OF DPP-4 INHIBITORS IN CVS**

The study have shown that use of sitagliptin to patients with coronary artery disease led to increased ejection fraction and improved contractile function of the ischemic areas [122] Studies also shown that DPP-4 reduces blood pressure and have positive effect on cardiovascular system [123] Similarly other studies also explained that DPP-4 inhibitors induces improvements in blood pressure and lipids, so it is effective in patients with pre-existing cardiovascular diseases. [124,125] DPP-4 inhibitors reduces atherosclerotic lesions and the pro-inflammatory cytokines, [126] and it also reduces monocyte activation and chemotaxis. [127] But in some studies they have shown that the use of saxagliptin did not alter the rate of ischemic events, rather the rate of hospitalization for heart failure was increased. [128] Some meta-analysis of randomized trials found a marked reduction in CV risk with DPP-4 inhibitors and as compared to metformin, it shown beneficial effects to high-risk patients (coronary artery disease). [129]

In the clinical trials of Alogliptin is not associated with CV risk in patients with diabetes when compared to other therapies or placebo. [130] In the other hand another clinical trial of saxagliptin use vs placebo over a 2.1 years period on the primary endpoint of a composite of CV death, MI, or ischemic stroke in 16,492 patients with a history of type 2 diabetes mellitus or a risk for CV events. [131] but further evaluation is needed for this controversial conclusion. Furthermore currently ongoing clinical trials of linagliptin, the cardiovascular safety and renal microvascular outcome study with linagliptin in patients with type 2 DM, lasting till 2018, has been designed to assess the long term impact on CV morbidity and mortality with linagliptin. [132]

**GLP-1 RA**

Glucagon like peptide-1 receptor agonists (GLP-1 RA) act as same way like DPP-4 inhibitors, it is a peptide hormones, under the stimulation, insulin will be secreted by regulation of intracellular glucose level and it also reduce glucagon secretion from the alpha cells which

lead to lowering of HbA1c level by 0.8-2%. GLP-1 RA also delays the gastric emptying as well as early satiety as a result decrease oral intake. Thereby GLP-1 deceases postprandial glucose excursions. Mainly two drugs (exenatide, liraglutide) are used subcutaneously of this class of drugs. Exenadie is a short acting drug which is given twice daily and liralutide is long acting drugs and will be given once daily. It's more effective for reducing HbA1c level if we give combination with metformin, sulfonylureas and sometimes with thiazolidinediones. [133,134] they don't cause hypoglycaemia and it may losses the weight by 2-3 kg and it also have shown beneficial effects on blood pressure. [135,136] similarly it also reduces the triglycerides, Free fatty acids, LDL level and has neutral effects on HDL. [137] nausea and vomiting is most common side effects seen with the use of these drugs but we can manage it by some antiemetic medication. Similarly in few cases pancreatitis have been seen reported with the use of exenatide.

**SAFETY PROFILES OF GLP-1 RA IN CVS**

GLP-1 agonist have beneficial effect on heart, it reduces the systolic and diastolic blood pressure along with controlling blood sugar. In the clinical trials it's seen that GLP-1 agonists have direct effect on the vascular smooth muscles and kidney and lead to vasodilation and induce diuresis as a result reduction in systolic blood pressure. [138] thus GLP-1 RA are having beneficial effect on diabetes with CV comorbidity. Similarly it has seen beneficial effect on cardiovascular marker, which lead to increasing left ventricular ejection fraction in the patients having cardiac insufficiency and myocardial infarction. [139] Likewise one meta-analysis also concluded that, they haven't find any evidence related increase CV risk and its morbidity with the use of GLP-1 RA when compared to placebo or other drugs. [140]

In another retrospective study also showed regarding the use of exenadie and significantly reduced the risk of cardiovascular disease and its CVD-related hospitalization in the patients with type 2 diabetes mellitus. [141] So the reduced risk of hypoglycaemia, well controlled Systolic blood pressure, reduced LDL, TG, weight loss and improved cardiac ejection fraction of these incretin based medication appears to have a very good beneficial effect on CV risk factors in patients with diabetes, but long term beneficial effects is not shown clearly so further vigilance is required for that.

**ALPHA-GLUCOSIDASE INHIBITORS**

Acarbose, meglitol, voglibose, these are the drugs used for diabetes mellitus on this class of drugs. The mechanism involved on this class of drugs is to inhibit the enzyme called alpha-glucosidase such as maltase, isomaltase, sucrase and glucoamylase. They act by inhibition of those enzymes that breaks down polysaccharides into monosaccharides. Inhibition of the absorption of carbohydrate from intestinal wall to blood stream leads to lowering of postprandial blood glucose level. They reduce the HbA1c level around 0.6-1.3% and used as monotherapy or combination with other anti-diabetic drugs. [142] The use of this drugs loss the weight around 1.5 kg but have neutral effect on cholesterol and BP. [142] The common side effects with the use of this drugs are gastrointestinal side effects like flatulence and diarrhoea. [142-144] They are less effective as compare to other drugs to reduce HbA1c level so it's commonly given with other medication to reduce postprandial hyperglycaemia. They have very less hypoglycaemic potential as compared to metformin and sulfonylureas. [145]

**SAFETY PROFILES OF ALPHA-GLUCOSIDASE INHIBITORS IN CVS**

Alpha-glucosidase inhibitors are considered as a second line anti-diabetic drugs either alone or with combination with other. These drugs reduce the post prandial hyperglycaemia, because of such action it doesn't show any harmful effects on oxidative stress and atherosclerosis so it contributes to reduction of risk of developing CVD and hypertension. [146-148] Similarly STOP-NIDDM also shown that decreasing postprandial hyperglycaemia was associated with a 49% reduction of risk developing cardiovascular complications like MI. [149] Similarly STOP-NIDDM had performed a long term clinical trials of AGIs on cardio-

vascular disease, and have shown reduced the risk of developing of hypertension by 25% of type 2 diabetes mellitus with the treatment of AGIs. [150]

But long term effects of these drugs on diabetic microvascular and macrovascular complications are not clearly known yet. [151] so over all AGIs seems one of the effective drugs to control postprandial hyperglycaemia with CVDs but its controversial regarding superior action to other drugs. Additional long term clinical trials required for confirmation.

**SGLT-2 INHIBITORS**

SGLT2 inhibitors inhibit the SGLT2 in the proximal part of nephron, subsequently reducing the reabsorption of filtered glucose. Excretion of glucose in the urine is increased by up to 80g per day [152]. These agents provide modest weight loss as the result of increased loss of urinary glucose and reduction in blood pressure by means of osmotic diuresis effects [153]. An additional advantage of SGLT2 inhibitors is that these agents are effective at all stages of type 2 diabetes mellitus (T2DM) [154,155]. Several clinical studies have shown that SGLT2 inhibitors have safer and effective for the treatment of patients with T2DM [156-158]. SGLT2 inhibitors as monotherapy or in combination with another anti-diabetic treatment such as metformin or sulfonylurea have demonstrated efficacy in glycaemic control with HbA1c reduction of 0.5-1.0 %. Similarly large meta-analysis studies of randomized controlled trials of these agents have found effective glycaemic control, weight reduction and blood pressure control [159,160].SGLT-2 inhibitors are new class of antidiabetic medications, the FDA and EMA have approved mainly three drugs named canagliflozin, dapagliflozine and empagliflozin and several other being under clinical trials[161]. Talking about the advantages of SGLT-2 inhibitors it protect the proximal tubular cells by blocking glucose entry into the cell and have less chance to be diabetic nephropathy [162] and it indirectly reduces insulin secretion, improve insulin sensitivity and increase the peripheral glucose uptake [163]. SGLT-2 inhibitors have very low chances to induce hypoglycaemia as compared to SU or insulin [164].

It also have effect on body weight and it loss around 2-3 kg over the 6-12 months of treatment [165,166]. Similarly it has small increase in LDL and HDL cholesterol level and moderate reduction in triglycerides [167]. Apart from the beneficial action of SGLT-2 inhibitors, It also have some side effects, which includes Hypotension, dizziness, and dose-related increase in LDL cholesterol have seen because of diuretic action. Fractures and bladder cancer are rare, but have occurred in susceptible patients. Due to the renal mechanism of action of SGLT2 inhibitors, it is contraindicated in patients with severe renal function including eGFR<30mL/min/1.73m [168], end-stage renal disease. It's common to develop fungal infections on the genital area due to high glucose execration with these drugs.

**SAFETY PROFILES OF SGLT-2 INHIBITORS IN CVS**

Due to diuretic action of SGLT-2 inhibitor, it inhibits the sodium reabsorption in proximal tubules, and they lead to mild to moderate intravascular volume depletion and decease in BP [169,170]. The reduction of blood pressure with chronic hypertensive patients and controlling of hyperglycaemia may help to reduce the cardiovascular problems. SGLT-2 inhibitors also showed improved endothelial functions [171] and reduction of arterial stiffness [172]. On September 27, 2015 the New England Journal of Medicine published the results of a randomized clinical trial involving 7020 diabetic patients using 10 mg or 25 mg of Empaglifozin, compared to placebo, during 3.1 years. The primary outcome was death due to cardiovascular disease and other events such as non-fatal MI, non-fatal stroke, and unstable angina [173]. Similarly in 490 of 4687 patients using empagliflozin, compared to 282 of 2333 patients in the placebo group, there were no significant differences between those groups in the rates of myocardial infarction or stroke were found, but in the empagliflozin group there were significantly lower rates of death from cardiovascular cause's hospitalization for heart failure and death [173]. The reduction of weight, improvement of HDL and reduction if TG level and reduction of inflammatory markers like albuminuria and uric acid, similarly

improvements of endothelial functions and reduction of arterial stiffness etc. may promote the reductions of possible cardiovascular events. But researcher still did not clearly concluded with those entire inflammatory markers and its possible CV impact so further clinical trials are required.

**INSULIN**

Insulin is mainly used to treat type I diabetes but it's also used in type 2 diabetes if OHAs are not sufficient to control high serum blood glucose level. [174,175] Insulin reduces HbA1c level around 3-4.9% [176]. Insulin action occurs after its binding to the insulin receptor, which leads to the activation of two major pathways of considerable complexity: the mitogenic pathway, mediating the growth effects of insulin through the mitogen-activated protein kinase (MAPK), and the metabolic pathway which regulates nutrient metabolism by activation of phosphatidylinositol 3-kinase (PI3K). Some authors believe that individuals with insulin resistance, mainly affecting the PI3K pathway, need greater amounts of insulin to achieve a similar glycaemic control, whilst MAPK pathway overstimulation leads to an acceleration of the atherosclerotic process within the vessel wall.[177] The in vivo studies of insulin provided the evidence of anti-thrombotic action.[178] Similarly several studies also explained that the possible anti-thrombotic effect of insulin mediated is by nitric oxide release[179]. Insulin may lead to weight gain depend on how much unit they get and it has decreased or no effect on cholesterol and have side effect of hypoglycaemia and weight gain.

**SAFETY PROFILES OF INSULIN IN CVS**

Several studies have reported that the risk of CV disease with the chronic use of insulin [180] some researcher believes that CV risk is due to hypoglycaemic episode of insulin therapy[181] Similarly many retrospective and case control studies of insulin treatment have reported a higher prevalence of CVD in insulin treatment patients[182,183]. But in other hand United Kingdom Prospective Diabetes Study (UKPDS), they have explained that, there was no association between the use of insulin and CVD incidents, even after 10 years of follow-up[184]. In other clinical trials of ORIGINAL with more than 2.5 years of follow up they have confirmed that insulin glargine had neutral effects on CV system [185]. Similarly in another clinical trials the relation between hyperglycaemia and its effect after acute myocardial infarction on cardiovascular outcomes in patients with type 2 diabetes mellitus (HEART2D) and to study the effects of either prandial (lispro) or basal (NPH twice daily or insulin glargine once daily) insulin on CV outcomes in 1,115 patients after myocardial infarction (MI).There was no differences in respect of CV events between prandial versus basal strategies were found [186].

Cardiovascular risk caused by hypoglycaemia, weight gain and other inflammatory changes with the used of insulin have not clearly explained so further long term clinical trials are required.

**CONCLUSION**

It is very difficult to select the best treatment over different anti-diabetic agents, but we can select those agents based on different physiological conditions of different patients. So while choosing agents over different comorbid condition we should focus on both pathophysiological conditions and glycaemic controlling level. Normally maintaining of glucose levels at a normal point with pharmacological agents in long term is known to decrease the morbidity and mortality rates by reducing macrovascular and microvascular complications. So to prevent other cardiovascular complications we should select such agents which maintain or control the risk factors for cardiovascular disease. Generally risk factors to contribute cardiac complications are hyperinsulinemia, obesity, dyslipidaemia, hypertension, vascular inflammation, coagulation and thrombotic markers and endothelial dysfunctions which I have already explained. As far we know sulfonylureas lead to weight gain, hyperlipidaemia and hypoglycaemia. so while choosing agents we should also consider patient's pathological conditions like we should limit the use SU over obese patients and we should look at atherosclerotic conditions too. So physician

should have some target regarding weight lose which is done by some other anti-diabetic medications like SGLT-2 inhibitors. Similarly TZDs treatments lead to fluid accumulation and oedema so we should target on alternative treatment for the patients who is having comorbid conditions like CHF/IHD. Similarly in some patients having diabetes with hypertension and first line treatment alone is not sufficient to control diabetes at that condition we can choose the agents which can control hyperglycaemia as well as hypertension, in this condition SGLT-2 inhibitors would be the best choice because it will not only reduce the glucose level but also reduces the blood volume as it acts like diuretics. As I have already mentioned the actions and its effects on biological risk factors, all the anti-diabetic medications have capacity to reduce blood glucose level in different waysbut we have to select such agents according to patients physiological conditions so at the last I would like to say while selection anti-diabetic medication we have to consider the effect on different biological system and its changes in the body mainly weight, cholesterol, inflammations etc.to prevent possible cardiovascular disease.

**ABBREVIATION**

T2DM= type 2 diabetes mellitus
DPP4i= dipeptidyl peptidase 4 inhibitors
SGLT2= sodium glucose linked transporter 2 inhibitors
CVRFs= cardiovascular risk factors
CVS= cardiovascular system
CVD= cardiovascular disease
PPAR-γ= peroxisome proliferative activator receptor gamma
MI= myocardial infraction
HbA1c= haemoglobin A 1 c
EMA= European medicines agency
FFA= free fatty acids
HTN= hypertension
ADA= American diabetes association
LDL= low density lipoprotein
HDL= high density lipoprotein
TG= triglycerides
LVF= left ventricular functions
GLP-1 RA= glucagon like peptide 1 receptor agonists
TZD= thiazolidinediones
UKPDS= UK prospective diabetes study
HF= heart failure
SU= sulfonylureas
SUR= sulfonylurea receptors
DARTS= diabetes audit and research in Tayside sotland
MEMO= medicines monitoring unit
MACE= major adverse cardiac events
GIP= glucose dependent insulinotropic peptide
tPA= tissue plasminogen activator, AGIs= alpha glucosidase inhibitors

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28. Blood pressure should be measured in supine, sitting, and standing postures in a diabetic patient to detect existence of autonomic neuropathy and drug induced postural hypotension.
29. Tight BP control (Target level 130/80 or below) prevents or retards the progress of

both micro- and macro-vascular complications.

**30.** Tight control of blood sugar prevents or retards the progress only of micro-vascular complications. It is difficult to achieve, and is attended with more risks of hypoglycaemia.

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