Introduction

Cardiovascular diseases (CVD) are the major contributors of mortality and morbidity in both industrialized countries and emerging nations, and 80% of the CVD deaths occur in low and middle income countries. According to the WHO’s world health statistics, it was reported that around 17.3 million CVD deaths globally occurred in the year 2008, with an anticipated increase to annual death of 23.3 million by 2030 [1]. Furthermore, diabetes and dyslipidemia are two important risk factors that should be controlled as the presence of two factors concomitantly increases CVD risk by 3-4 folds [2, 3].

Global Scenario of Diabetes and Diabetic Dyslipidemia

According to data of the World Health Organization (WHO), 347 million people worldwide have diabetes and more than 80% of diabetes deaths occur in low- and middle-income countries [4]. On the other hand, statistics of WHO projects that death due to diabetes will double between 2005 and 2030, and diabetes will be the 7th leading cause of death in 2030. Healthy diet, regular physical activity, maintaining a normal body weight can prevent or delay the onset of type 2 diabetes [5].
Diabetic dyslipidemia: A Modifiable Risk Factor for Cardiovascular Disease

Over the period of time, diabetes can damage blood vessels of the heart, brain, eyes, kidneys, and nerves; consequently it can increase the risk of heart disease, stroke, retinopathy or neuropathy. Similarly, it was noted that 50% of people with diabetes die of CVD [8]. Moreover, diabetes doubles the overall risk of dying compared to their peers without diabetes [9-11]. On the other hand, comprehensive management of modifiable CVD risk factors can be done by controlling both glycemic and lipid parameters [12].

Management of Diabetic Dyslipidemia

Definition of Diabetic Dyslipidemia

The term diabetic dyslipidemia essentially refers to atherogenic dyslipidemia occurring in patients with type 2 diabetes, which is characterized by elevated triglyceride, small dense LDL particles, and low HDL-cholesterol concentrations. Moreover, diabetic dyslipidemia is considered as one component of the metabolic syndrome, which can be treated by overcoming insulin resistance [13].

Mechanism of Dyslipidemia in Patients with type 2 Diabetes Mellitus

In patients with type 2 diabetes mellitus, the number of LDL particles are usually greater than those reflected by LDL-cholesterol levels, because LDL particles are small and partially depleted of cholesterol. Moreover, the combined adverse atherogenic effect of elevated LDL, triglyceride and other risk factors of the metabolic syndrome exacerbates atherosclerosis due to the significant increase in small dense LDL cholesterol in patients with type 2 diabetes mellitus [13].

In the same way, insulin resistance at the level of adipocyte lead to increased free fatty acid efflux, which is central to the pathogenesis of atherogenic diabetic dyslipidemia (ADD) and this results in increased very low-density lipoprotein (VLDL) cholesterol from the liver facilitated by increased synthesis of apolipoprotein B (Apo B). As a result, there is development of ADD in a patient with type 2 diabetes mellitus (T2DM) that is characterized by a triad of high triglycerides (TG), low high-density lipoprotein (HDL) cholesterol and elevated small, dense low-density lipoprotein (LDL) particles [14].

As shown in Figure 1, cholesterol ester transfer protein plays a role in transferring triglycerides from VLDL particles to HDL and LDL, which result in increased Apo A1 containing small dense HDL and Apo B containing small dense LDL particles. The triglyceride-enriched HDL is subsequently hydrolyzed by hepatic lipase or lipoprotein lipase resulting in low HDL and Apo A-I, which is filtered by the renal glomeruli for degradation in renal tubular cells [15].

**Reference:** Mooradian A D; Dyslipidemia in type 2 diabetes mellitus; Nature Clinical Practice Endocrinology and Metabolism (2009) 5, 150-159.
Diabetic Dyslipidemia: An Established Risk Factor for Coronary artery Disease

In clinical practice, total cardiovascular disease risk can be assessed by Framingham Risk Score (FRS), which is modified according to family history of premature coronary artery disease (CAD) [16]. On the other hand, low-density lipoprotein cholesterol remains the primary target of therapy, but in clinical practice, non-HDL cholesterol need to be emphasized as an atherogenic component. If lipid management is not done properly to prevent progression of atherosclerotic vascular blockage, angioplasty, stent placement or coronary artery bypass grafting can be required to treat ischemic heart disease (IHD) [17].

On the other hand, one meta-analysis was executed by compiling eight randomized controlled trails of statin named Simvastatin Survival Study (4S), Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS), Long-term Intervention with Pravastatin in Ischemic Disease (LIPID), Collaborative Atorvastatin Diabetes Study (CARDs), Treating to New Targets (TNT), Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering (IDEAL), Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) and Justification for the Use of Statins in Prevention (JUPITER) trials.

Overall analysis of these 38,153 patients’ data, it was unveiled that for one standard deviation (SD) increase in LDL, non-HDL and Apo-B, there was an increase in CV risk by 13%, 16% and 14% respectively. Furthermore, there is growing evidence which supports the control of non HDL - cholesterol and high triglyceride for overall CVD risk reduction [17-19].

Therapeutic approach for Diabetic Dyslipidemia

Guidelines for treatment of diabetic dyslipidemia: According to recent American College of Cardiology/American Heart Association (ACC/AHA 2013) guideline for the management of diabetic dyslipidemia, following four groups of patients were recommended for moderate to high intensity statins for prevention of atherosclerotic cardiovascular disease (ASCVD).

1. Patients with clinical ASCVD.
2. Primary elevations of LDL-Cholesterol (LDL-C) >190mg/dL.
3. Patients with diabetes aged 40 to 75 years with LDL-C ≥70 to189mg/dL and without clinical ASCVD.
4. Patients without clinical ASCVD or diabetes with LDL-C 70 to 189mg/dL and estimated 10-year ASCVD risk >7.5% [13].

Similarly, the American Association of Clinical Endocrinologists guideline (AACE-2013) had suggested that along with statin, non-statin agent may be required to bring down the uncontrolled lipid parameters to the acceptable level [20].

In addition to the above guidelines, the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults - Adult Treatment Panel III (NCEP ATP III) guideline had suggested that therapeutic lifestyle changes (TLC) should be suggested to the patient and should be subsequently managed by intensifying statin therapy and other non-statin medications. Moreover, after achieving the primary goal of LDL, if TG is not below 200mg/dL, non HDL should be considered as a secondary goal [13, 20].

Similarly, European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemia emphasize on giving priority to the management of triglyceride (TG). After all TG is an established risk factor of CAD and fasting TG level less than 150mg/dL (< 1.7 mmol/L) is desirable [21].

On the whole, all these guidelines suggest that in subjects with high total CV risk, after the primary goal of LDL management is achieved, TG lowering therapy should be initiated if TG levels are > 200mg/dL in patients who cannot lower them by lifestyle measures alone. Hence, the use of statins as the primary drug in diabetic dyslipidemia is valid and several guidelines emphasize the comprehensive management of overall lipid parameters like non-HDL and TG [13, 22].

Therapeutic Considerations, according to LDL-Cholesterol level: The American Diabetes Association recommends an LDL-cholesterol goal of less than 100mg/dL in most diabetic patients [22]. Besides this, the ADA recommends a combination of LDL-lowering therapy with therapeutic lifestyle changes (TLC) to lower LDL levels to control atherogenic dyslipidemia and the addition of fibrate will be required to an LDL-lowering therapy, if LDL-C is not controlled. After all, the benefit of improvement of lipid profile by combining fibrate group of drug with an LDL-lowering agent like statin, need to be superior than risk of severe myopathy [13].

Efficacy and Safety Concern of Statin and Nicotinic Acid: Statins have the advantage of lowering VLDL cholesterol as well as LDL cholesterol; thus they can assist in managing non-HDL-cholesterol goal when triglyceride levels are ≥200mg/dL. Moreover, fibrates can benefit by reduction in CHD risk and it can be used in patients with high TG not controlled by monotherapy with statin [13, 21].

After all, combination of statin with fibrate is advisable in patients with diabetes who have atherogenic dyslipidemia but it can precipitate myopathy and myalgia. On the contrast, in a pooled analysis of data from the five statin trials with 32,752 participants without diabetes at baseline, 2749 developed diabetes. On subsequent analysis in this study, it was detected that intensive-dose statin therapy was associated with an increased risk of new-onset diabetes compared with moderate-dose statin therapy [23].

In addition to fibrate and statin, nicotinic acid also has a favorable effect on diabetic dyslipidemia, but recent clinical trials in patients with diabetes have suggested that low doses of nicotinic acid accompanied by only modest improvement in glucose control with no changes in glycated hemoglobin (HbA1c). Unfortunately, nicotinic acid therapy can increase insulin resistance and clinical experience has shown that in rare instances, diabetic dyslipidemia may worsen by nicotinic acid therapy [13].
Treatment of diabetic dyslipidemia by PPAR α/γ agonists

Peroxisome proliferator activated receptors (PPAR) α, β/δ and γ

PPAR-α, PPAR-γ and PPAR-β/δ are transcription factors that regulate gene transcription by binding to specific DNA response elements upon ligand activation and heterodimerization with the 9-cis retinoic acid receptor. As a result of selective activation of ligand, different receptor conformations are adopted, leading to different co-activator recruitment and subsequent effects on gene expression. Even though all the PPAR agonists are from the same pharmaceutical class, their biological activity varies widely based on selective alpha or gamma modulation [24, 25].

As shown in Figure 2, PPAR-α regulates expression of genes encoding enzymes and transport proteins controlling lipid metabolism and is expressed predominantly in tissues with a high capacity for fatty acid oxidation like liver, heart, skeletal muscle, brown fat, and kidney [26].

Activation of PPAR-α receptors leads to:

1. Fatty acid (FA) oxidation and cellular FA uptake in liver and heart.
2. Improves lipoprotein metabolism, reducing VLDL-C and enhancing the catabolism of TG-rich lipoprotein particles.
3. Modulates the expression of HDL-C apolipoprotein genes for Apo AI and Apo AII.
4. Enhances reverse cholesterol transport via direct effects on macrophage cholesterol efflux transporters ATP binding cassette transporter A1 (ABCA1) and scavenger receptor Bl (SR-B1).
5. Improves glucose homeostasis by insulin sensitizing action.
6. Recent studies showed that PPAR-α can improve pancreatic β cell function [26-28] (Figure 2).

On the other hand, PPAR-γ is mostly expressed in adipose tissue, but it is also present in inflammatory cells (e.g. monocytes, macrophages), mucosa of the colon and cecum, the placenta, and lowest in skeletal muscle and liver. PPARγ not only promotes pre-adipocyte differentiation, but also induces adiponectin expression, which increases fatty acid oxidation by activation of the AMP-activated protein kinase pathway and down regulates the expression of genes encoding resistin and tumor necrosis factor together contributing to reduced insulin resistance [29].

The major actions of PPAR-γ activation are:

1. Pre-adipocyte differentiation.
2. Stimulation of the storage of FAs in adipocytes.
3. Improvement of insulin sensitivity by increased storage of FAs into adipose tissue resulting in decreased plasma FA concentration and relieving lipotoxicity in skeletal muscle, liver and pancreas.
4. In addition, PPAR-γ can increase insulin sensitivity by regulating adipocyte hormones, cytokines and proteins that are involved in IR. Similarly, it down regulates the expression of genes encoding resistin and tumor necrosis factor, whereas it induces adiponectin expression, which increases FA oxidation by activation of the AMP-activated protein kinase pathway [30, 31] (Figure 2).

PPAR α / γ agonist: Glitazars

Glitazars are dual peroxisome proliferator-activated receptors (PPAR) α/γ agonists that can improve the lipid profile and glycemic parameters by insulin sensitizing action, similar to a combination of a fibrate and a thiazolidinedione (TZD) [23]. Glitazars have PPARα agonistic action, similar to fibrates that can lower plasma triglycerides and increase HDL-C. Moreover, due to their PPARγ agonistic action like TZDs, they can increase insulin sensitivity and improve glycemic control [32, 33].

Advantages of glitazar

Glitazar can reduce cardiovascular risk factors of type 2 diabetes by providing dual management of dyslipidemia and hyperglycemia.
mia. Furthermore, it can improve compliance of patients by reducing the pill burden for treatment of type 2 diabetes mellitus [33].

**History and development of Glitazar**

In the past, several PPAR agonists like glitazars, TZD and non-TZD molecules were developed, but all molecules were not successful as some had caused an elevation in creatinine, cardiovascular toxicity or bladder tumors during preclinical or clinical study. Consequently, previous glitazar with potent PPAR α/γ agonism, were approved for clinical trials, but all were discontinued due to safety concerns at preclinical or clinical stage [33, 34].

On the whole, depending on their molecular structure, glitazar exert dual action with varying degrees of PPAR α and PPAR γ activity as shown in Figure 3. Although these tested molecules resulted in adverse events, these have been compound specific and of diverse origin e.g. increase in adipose tissue, urothelial, renal, or cardiac toxicity with different glitazars. In spite of failure of older glitazars, there was a rising hope of a potential drug that could be free from these side effects and yet have a positive effect on insulin sensitivity for correction of diabetic dyslipidaemia (Table 1).

Limitations of fibrate and thiazolidinedione (TZD) combination

The combination of fibrate and TZD therapy is theoretically appealing, but the practice of this approach has been more problematic because fibrates carry a risk of increase in creatinine level and possible myopathy with the statin, while TZDs are prone to cause osteoporosis, fluid retention with possible risk of heart failure [13, 22].

**Safer glitazar: Saroglitazar**

Saroglitazar is a molecule with dual PPAR α/γ agonism, having a balance of binding such that the therapeutic dose range gives optimal biological effects of both PPARα and PPARγ-mediated actions [34].

**Safety and Efficacy of Saroglitazar**

**Prospective randomized safety and efficacy study of saroglitazar (PRESS):** The phase I study of saroglitazar was a randomized, double-blind, placebo-controlled, single-center study to evaluate the pharmacokinetics, safety and tolerability of saroglitazar under fasting conditions in healthy subjects. Saroglitazar

![Figure 3: Graphic Representation of various PPARs based on their relative affinity to α/γ agonism](image_url)

**Reference:** Munigoti SP and Harinarayana CV; Role of Glitazars in atherogenic dyslipidemia and diabetes: Two birds with one stone?; Indian J Endocrinol Metab. 2014 May-Jun; 18(3): 283-287.

**Table 1. History of dual PPAR-α/γ Activators.**

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Faglitazar</td>
<td>Discontinued during the development phase secondary to significant edema [35].</td>
</tr>
<tr>
<td>Muraglitazar</td>
<td>Proved successful in improving insulin sensitivity and treating diabetic dyslipidemia but it was discontinued in 2006 due to significant cardiovascular side effects [36].</td>
</tr>
<tr>
<td>Tesoglitazar</td>
<td>Discontinued following phase III trials due to elevated creatinine levels associated with decreased glomerular filtration and bone marrow toxicities [37].</td>
</tr>
<tr>
<td>Ragaglitazar</td>
<td>Discontinued 2002 due to the carcinogenic potential on urothelial cells in rodent models [38].</td>
</tr>
<tr>
<td>Chiglitazar</td>
<td>Development discontinued in phase II clinical trial [39].</td>
</tr>
<tr>
<td>Cevooglitazar</td>
<td>Discontinued in 2008 due to the lack of a sufficiently positive risk-benefit data [40].</td>
</tr>
<tr>
<td>Aleglitazar</td>
<td>Halted at Phase III in 2013 due to GI bleeding, bone fractures, heart failure [41].</td>
</tr>
<tr>
<td>Naveglitazar</td>
<td>Discontinued in 2006 due to adverse preclinical findings in rodents [42].</td>
</tr>
<tr>
<td>Sipoglitazar</td>
<td>Discontinued in 2006 due to serious safety concerns [43].</td>
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</table>
was well absorbed after oral administration with linear pharmacokinetics and it was not excreted in urine, indicating that it has a non-renal route of elimination [44]. Moreover, preclinical studies have shown that saroglitazar is mainly eliminated by the hepatobiliary route and it was found safe and well tolerated up to a 128 mg oral dose with a proposed therapeutic dose of 4mg [44].

On the other hand, phase III clinical trial included prospective randomized safety and efficacy study of saroglitazar named PRESS V and PRESS VI.

According to PRESS V clinical trial, a multi-centric, double blind study was carried out for 12 weeks to evaluate the safety and efficacy of 2mg and 4mg of saroglitazar compared to 45mg of pioglitazone in patients with diabetic dyslipidemia. In this study, subjects with T2DM and dyslipidemia, which not controlled by the lifestyle modifications and TG > 200 to 400mg/dl were recruited, and total 122 subjects were enrolled in the study, and after a run in period of 2 weeks, treatment was given for 24 weeks and further 24 weeks followed up was carried out. At the end of 24 weeks, up to 45% reduction in triglyceride was observed in 4 mg saroglitazar arm, which was significant compared to baseline and to pioglitazone arm [45].

In addition to TG reduction, significant reduction of lipid parameters like LDL-cholesterol, VLDL-cholesterol, total cholesterol, Apo-B with significant reduction in glycemic parameters was observed in saroglitazar arm compared to pioglitazone arm. Conversely, there was no increase in inflammatory markers, muscle toxicity, weight gain or impairment of renal or liver function in the saroglitazar arm [47, 48].

According to PRESS VI clinical trial, a prospective, multicenter, double-blind, placebo controlled, three arm study was carried out for 16 weeks in subjects with hypertriglyceridemia (>200 and <500mg/dl) with T2DM not controlled with atorvastatin 10mg. In short, the study consisted of a run in period of 4 weeks with lifestyle modification followed by 12 weeks of treatment with saroglitazar 2mg or 4mg versus placebo [45].

Overall 302 subjects were randomized to receive one of the treatments, saroglitazar 2mg (n = 101) or saroglitazar 4mg (n = 99), or matching placebo (n = 102). At the end of 12 weeks, subjects treated with saroglitazar 2mg and 4mg tablets had shown significant reduction in mean plasma TG levels by around 46.7% compared to placebo [45].

Moreover, saroglitazar 2mg had shown a significant decrease in levels of non-HDL cholesterol, very LDL-cholesterol, total cholesterol, and fasting plasma glucose. Additionally, saroglitazar 4 mg also significantly reduced LDL-c and Apo-B levels [44, 45].

**Clinical Safety of Saroglitazar: Evaluation of adverse Events:**

After all, per the data from clinical trials of saroglitazar, serious adverse events (AE) were not reported and all the reported adverse events were mild to moderate in intensity like gastritis, dyspepsia or pyrexia, which were not treatment emergent, and none required any treatment for their resolution [47].

There was no consistent pattern or dose dependency observed in the AEs and no clinically relevant trend or change was observed in clinical laboratory, urinalysis or electrocardiogram (ECG). During the follow up period, major cardiovascular event was not reported and saroglitazar was found safe and well tolerated by patients [46].

After overall analysis of all clinical trials, saroglitazar was found effective for treatment of atherogenic diabetic dyslipidemia having the property of normalizing lipid profile and glycemic parameter [32, 48].

**Comparative Long-term Outcome Study of Saroglitazar**

In spite of proven therapeutic benefits, large outcome study of saroglitazar showing long term therapeutic efficacy and safety is required. Comparative study about the improvement of β cell function and insulin sensitivity by study of insulin resistance index (HOMA-IR) can guide about superiority of saroglitazar over other insulin sensitizer drug. Furthermore, clinical trials with the primary aim of atherosclerotic plaque stabilization or plaque regression, pleotropic benefit and data on long term mortality benefits are required before labelling it as one of the safest therapeutic options for treatment of diabetic dyslipidemia [48].

**Conclusion**

In short, the management of type 2 diabetes mellitus and dyslipidemia is approached with therapeutic lifestyle changes followed by addition of pharmacotherapy with statin with or without fibrate. Furthermore, new therapy has enabled effective yet safe treatment of diabetes dyslipidemia, allowing a potential decrease in risk for cardiovascular disease.

Consequently, one such new drug - saroglitazar, a dual PPAR α/γ agonist has been developed, which can manage both lipid and glycemic parameters. Moreover, saroglitazar is acceptable to patients due to minimal side effects with reduction of pill burden due to dual benefits, but improvement of β cell function and insulin sensitivity by study of insulin resistance index (HOMA-IR) and long term cardiovascular benefits need to be established.

**References**


