Original Article

PPAR agonists for the treatment of cardiovascular disease in patients with Diabetes

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Abstract

Background: PPAR agonists are drugs that act upon peroxisome proliferator-activated receptors. They are used for treating symptoms like metabolic syndrome, especially for lowering triglycerides and blood sugar.

Objective: PPAR mediated treatment in type 2 diabetes patients and has certain cardiovascular benefits at the post-ischemic stroke. In the Asian diabetic and Hypertension case, patients have additional help from the PPAR therapy for an unknown reason. The objective of this study is to find out the Pioglitazone treatment effectiveness in the patient's body.

Methods: Between 2008 and 2020, admitted patients for ischemic stroke from Taiwan's National health insurance research database were studied. Type II Diabetes mellitus and hypertension patients were also included. Patients were grouped into Pioglitazone and Non-Pioglitazone based on treatment. A propensity score for balancing the baseline characteristics, medication and severe stroke was used. The significant result was achieved for the recurrent ischemic stroke. Subgroup analysis is done in the recurrent ischemic stroke in Pioglitazone and Telmisartan treated patients. Further trend analysis was done for the ischemic stroke risk patients, and a dose-dependent result for the different pioglitazone possession ratio was done under significance level <0.1 and <0.05, respectively.

Results: In the Pioglitazone group, there were 3190 patients, and in the non-Pioglitazone group, there were 32645 patients. Pioglitazone treated patients have a low risk for the Ischemic stroke, as compared to the recurrent and non-Pioglitazone treated group (0.91 sub-distribution hazard ratio; and Confidence interval level is 0.84 to 0.99). Pioglitazone related to the reduced ischemic stroke (p-value for interaction is 0.071). A correlation was found between the PPAR- gamma treatment and ischemic stroke (p-value is 0.076). The dose-specific result also proved that a significant relationship of Pioglitazone in increasing dose causes less recurrent Ischemic stroke (p value=0.068)

Conclusions: According to this study, Pioglitazone treatment in type 2 diabetes patients and hypersensitive Ischemic stroke patients is linked to minor ischemic stroke which is recurrent in Asian people. Pioglitazone and the telmisartan treatment have an increasing pleiotropic effect related to the higher PPAR- gamma effects. Further research needs to be conducted with the PPAR mechanism's details to confirm the PPAR effect on Ischemic stroke treatment. [*Ethiop. J. Health Dev.* 2021; 35(3): 249-257]

Keywords: PPAR agonist, Dyslipidaemia, Thiazolidinediones, Type 2 diabetes, Pioglitazone, PPAR-alpha, PPAR-gamma, Insulin resistance, Alecardio.

Introduction

Diabetes is a well-known chronic disease that catalyzes mortality and reduces life expectancy worldwide. There are two types of diabetes which are based on insulin dependency. Type I diabetes or diabetes mellitus occurs due to a lack of insulin secretion from islets of Langerhans, which are cells of the Pancreas. In contrast, Type II Diabetes or Diabetes insipidus or non-insulin-dependent Diabetes occurs due to a lack of the Anti-diuretic hormone from the Adrenal gland. Diabetes mellitus is associated with Hypertension, dyslipidemia, and abdominal obesity, which results in a high risk of developing cardiovascular disease. According to the report, the number of diabetic patients rose from 108 million to 422 million in 2014 (1). Diabetes is an assembly of cardiometric risk factors like high blood pressure and insulin resistance and high triglyceride conditions. Diabetes leads to neuropathy, such as, severe microvascular complications, and peripheral and cerebral arterial diseases like macrovascular complications. Type II Diabetes or non-insulin-dependent Diabetes is defined by insulin resistance or beta-cell failure and is strongly associated with Hypertension, abdominal obesity, and dyslipidemia. In the patient population, more than 50% of deaths are caused by cardiovascular related diseases.

Microvascular complications like retinopathy are reduced by aggressive glycemic control, but this approach is less applicable to the macrovascular complications of type II diabetes. A study conducted by UKPDS (United Kingdom Prospective Diabetes Study) shows that aggressive glycemic control does not benefit advanced disease treatment (2). According to a recent study, though glycemic treatment has few benefits on cardiovascular disease treatment, there are many hypoglycemia risks. The lack of TCG or tight glycemic control therapy effect proves hyperglycemia is not the only reason for macrovascular complications in type II diabetes. Simultaneously, a more comprehensive treatment approach is needed to deal with all the risk factors. According to the STENO study, multiple risk factors targeting strategies for the treatment of both macro and microvascular disease will be very beneficial (3). Even in the Statin treatment where the cardiovascular disease risk is reduced by 30-55%, there is still a risk for diabetic patients to develop cardiovascular disease compared to non-diabetics (41).

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According to several studies, glycemia reduction therapy, like Rosiglitazone and muraglitazar therapy, has antagonistic effects on macrovascular diseases with a high risk of myocardial infarction (40). Due to this, the FDA (Food and drug administration) specifies a licensed glucose-lowering drug criteria, as these will assist in controlling cardiovascular disease. A proactive study has shown that, despite all the complications and controversies, the proliferator-activated receptor drugs like Pioglitazone have an excellent benefit-risk ratio compared to other glucose-lowering medications.

Materials and methods

The NHIRD database was studied from 2009 to 2019. The National health insurance initiative programmed in Taiwan covers about >99% of people. For patients' registration and diagnosis, ICD-9-CM codes are used. The patients included in the study were isolated from the hospitalized patients (ICD-9-M) for all registration. Patients who do not have cerebral palsy are excluded from the research. (ICD code 433-1.0 up to 433-9.0). The study focused on the pleiotropic effect of type2 diabetes mellitus and hypertension. Heart failure patients were not included in the study. Patients were grouped into two parts, Pioglitazone, and non-pioglitazone group. Medication data was taken from the visit data of the pharmacy. If the study drugs were prescribed twice, then the patients used them. If a patients used non-pioglitazone once only, then they were excluded from the study group. The medication possession ratio or ratio was calculated using the following formula.

$$\text{MPR} = \frac{\text{days of prescribed medication}}{\text{days number during a period of 6months post}-\text{index date}}$$

ICD-9-CM diagnostics has been validated from the previous reports: sex, age, hospital-level data extracted from the medical record book. Comorbidity is also taken from the hospital record book. For diagnosis and malignancy detection, the catastrophic illness certificate was used. Stroke and myocardial infarction were placed before the index date. For determining the overall systemic health, CCI data has been used. NHISS was used to determine Ischemic stroke severity. Telmisartan was recorded via the Taiwan NHI reimbursement. Propensity score matching was used the balanced distribution of baseline characteristics. Propensity score was used for covariates like sex, DM period, events and comorbidity was used for the quality of matching, which was assessed by STD (standardized difference) between groups. Cox proportional hazard model was used for risk comparison. Exemplary and Grey sub distribution hazard model was used for non-fatal patients. Sensitivity analysis was done for the recurrent ischemic stroke analysis. Subgroup analysis was also done for the specific groups. SHR model linear trend risk was also tested. Two additional cohort analyses were conducted for the whole cohort adjustment.

Effect of treatment with PPAR gamma agonists

The Thiazolidinediones like Troglitazone, Pioglitazone, and Rosiglitazone are some of the PPAR-gamma agonists, but their effects differ. These drugs work with the PPAR-gamma activation pathway; this is a central controller of glucose and fat metabolism and insulin signaling. The PPAR-gamma agonists increase in the insulin-activated glucose uptake in tissues like adipose, hepatocytes, and skeletal muscle cells and reduce hepatic gluconeogenesis (4). A possible benefit of using PPAR-gamma agonist drugs is that they help minimize glucose level without hypoglycemia or any other side effect found in the other medications, like metformin and sulphonylurea. Glycated haemoglobin A1c is reduced after medication with the thiazolidinediones is about -0.5% to -1.6%, i.e., 5-20 mmol/mol compared to placebo treatments (5). Taking Pioglitazone treatment daily, 15 mg to 45 mg once, decreased plasma glucose level by -39.1% to -65.3% mg/dl (5). A similar effect was found with rosiglitazone therapy (2-6 mg per day) (6). Despite these advantages, PPAR gamma agonists have several adverse effects, including heart failure, retinal oedema, weight gain, and bone fracture (7). PPAR agonists draw attention because they have insulin-sensitizing properties and affect cardiovascular disease risk in type II diabetic patients (8). These agents also improve the lipid profiles, blood pressure, reduce tissue necrosis factor, and redistribute visceral fat to the sub-cutaneous area. The previous study shows that these drugs can decrease systemic inflammation (9) and the potential for affecting vasculature (10). Though these findings are promising, further research needs to be conducted to explore their real treatment benefits in cardiovascular disease.

The Proactive study was double-blinded, large, randomized, and explored the pioglitazone effect on the macrovascular complication in type II diabetic patient. Patients were randomly treated with the Pioglitazone (45 mg/day) doses or placebo. They also took care of glucose level, lipid alteration anti-hypersensitivity, and anti-thrombin medications during the trial period. After 34 months, Pioglitazone was able to reduce myocardial infarction, mortality, acute coronary syndrome, and surgical intervention on the coronary or leg arteries by 10% compared to the placebo treatment group, but this result was not statistically significant. A meta-analysis of the pioglitazone trial with 1274 patients shows a 16% reduction in the secondary endpoint (i.e., mortality, stroke, Myocardial infarction) compared to the placebo treatment group, which is a statistically significant result (p-value 0.027) while in the case of the primary endpoint, the result was not significant (p-value 0.016). While Proactive study data after a three-year period with Pioglitazone was also statistically significant (p-value is 0.02) in the Major adverse cardiovascular event-1 endpoint (e.g., myocardial infarction, stroke) reduction compared to placebo patients. Another meta-analysis data with 19 manufacture-funded clinical trials with Pioglitazone effectively prevents vascular complications in diabetic patients. Rosiglitazone also shows a satisfactory result when it is treated for cardiovascular disease in diabetic patients.

Rosiglitazone trial data indicates that these PPAR agonists have different outcomes when it is used in

cardiovascular therapy. After using Rosiglitazone, it was found that cardiovascular deaths and myocardial infarction cases were significantly increased compared to the placebo effect and other glucose-lowering drugs (11). A meta-analysis of the Rosiglitazone trial data shows that the Myocardial infarction death odds ratio was 1.432 (p-value 0.003) and cardiovascular death odds ratio was 1.64 (p-value 0.05), related to the control group (20). Another two meta-analyses by Loke et al., between the Rosiglitazone and Pioglitazone treated group, Myocardial Infarction odds ratio is 1.162 (p-value<0.001), 1.223 for heart failure (p-value<0.001), and for death cases, the odd ratio is 1.143 (p<0.05). While according to Graham et.al., Myocardial infarction hazard ratio is1.06(p-value<0.05) for stroke is 1.272 (p-value<0.05), for heart failure it is 1.251(p<0.05), hazard ratio for death is 1.142 (p<0.05) (20). An open-label RECORD study (10) and another meta-analysis data from 42 trials for the myocardial infarction results were indecisive (11). Due to the cardiovascular safety issue, the European Medicines Agency removed approval for rosiglitazone use in 2010 (12).

Thiazolidinediones decreases insulin resistance and increases glycemic regulation, it has been assumed that thiazolidinediones displays different cardiovascular effects as they have a different impact on the lipid fractions (13). Pioglitazone reduces triglyceride levels and increases HDL cholesterol level, but Rosiglitazone only increases HDL cholesterol. Total cholesterol and low-density lipoprotein levels remain the same after pioglitazone therapy, and significantly increases after rosiglitazone therapy. Different trail reports show that Pioglitazone has satisfactory cardiovascular treatment results over the Rosiglitazone, lipoprotein, serum lipids, and apolipoprotein. Pioglitazone treatment shows significant improvement compared to the rosiglitazone treatment in HDL cholesterol, triglycerides, and LDL particle size (14). Some other thiazolidinediones, like Troglitazone, also show adverse effects like hepatotoxicity after medication. Even though there is no proof that Pioglitazone or Rosiglitazone cause hepatotoxicity (15). Troglitazone has toxicity along with non-receptor facilitated outcomes, perhaps due to mitochondrial interaction (16). The contradictory safety results with the PPAR-gamma agonists are due to different specificities for each PPAR receptors, various gene expression profiles, and other distribution profiles, which results in different outcomes (17). A Gene regulation study using the human pan-genomic micro-assays technique has shown that despite sharing the most target genes PPAR-gamma and PPAR- alpha/gamma agonists induce significant changes in the gene profile of the hepatocytes (17). Selective PPAR-gamma modulators, like S26948 INT131, have been developed to increase glucose metabolism, reducing the side effect of the PPAR-gamma agonists (18).

Result

A Total of 412046 Ischemic stroke patients were hospitalized between 2007 to 2017. A Total of 129556 and 177919 cases did not have Hypertension and type II diabetes (Table 1). Additionally, 11,115 patients have heart failure. 12,312 patients had a follow up period of less than six months. 11900 patients have a recurrent ischemic stroke. About 33344 patients do not get any angiotensin receptor blockers for hypertension control. Lastly, 35,835 Ischemic stroke patients were chosen for analysis. Among them, 32,645 were a non-pioglitazone treated group, and 3190 patients were Pioglitazone treated group. Before Propensity score matching patients with higher dyslipidemia standardize difference value is 0.181), they have minimum National Institutes of Health Stroke Scale Pioglitazone 5.28±3.2 vs non-Pioglitazone: 5.91± 4.0; standardize difference value is -0.164) and follow-up duration is shorter (standardize difference value is -0.104). Post-propensity score matching, and all baseline characters and therapies were balanced within Pioglitazone and non-pioglitazone groups. The propensity score matching comparison between pioglitazone and non-pioglitazone groups is that the Pioglitazone group has less risk of ischemic stroke Pioglitazone 18.81% and non-pioglitazone 20.01%. SHR (sub distribution hazard ratio) is 0.90; 95% Confidence interval is 0.83-0.99) (Table 2). Pioglitazone group was found to have a lesser Ischemic risk after doing inverse-probability-of-treatment sensitivity analysis (Pioglitazone 19.0%; Non-Pioglitazone 21.2%, sub-distribution hazard ratio 0.88; Confidence interval is 0.81-0.99). The other analysis results are that Pioglitazone has lesser Myocardial infarction risk (Pioglitazone 3.68% and Non-Pioglitazone 4.18%; sub-distribution Hazard ratio is 0.80; and a 95% confidence interval is 0.64-0.96). Bladder cancer risk, mortality risks or cardiovascular mortality is not significant between Non-Pioglitazone and Pioglitazone treated group. Simultaneously, the Ischemic stroke subgroup analysis also did not show any major difference to the Pioglitazone effect. However, the chronic kidney disease group and Pioglitazone telmisartan combination group shows a significant effect. In chronic kidney disease group patients and non-Telmisartan medicating groups, pioglitazone effect on ischemic stroke was less significant (Table 3 and Table 4).

Table 1: **Study patients characteristics**

Characteristics	Non-pioglitazone ($n = 6378$) percentage	Pioglitazone ($n = 3189$) percentage	STD
Age, years	66.9 ± 10.3	67.0 ± 10.0	0.008
Age group percentage			
< 65 years	41.00031358	40.82784572	− 0.004
≥ 75 years	22.37378489	23.07933521	0.017
65–74 years	36.62590154	36.09281907	− 0.011
DM duration, (years)	8.59± 3.5	8.58 ± 3.4	− 0.003
Male, n (%)	49.45123863	49.54531201	0.002
Admitted in the medical centre, n (%)	31.27939793	30.00940734	− 0.028
Comorbidity percentage			
Atrial fibrillation	2.414550016	2.790843525	0.024
Malignancy	4.515522107	4.327375353	− 0.009
Myocardial infarction	2.822201317	2.822201317	0
Chronic obstructive pulmonary disease	6.193164001	6.177485105	− 0.001
Chronic kidney disease	7.306365632	6.930072123	− 0.015
Dialysis	0.862339291	0.846660395	− 0.002
Old stroke	9.75227344	8.84289746	− 0.031
Dyslipidemia	51.88146754	52.4615867	0.012
Coronary artery disease	24.99216055	24.67858263	− 0.007
Estimated National Institutes of Health Stroke group			
> 13 age group	4.515522107	4.797742239	0.013
≤ Five age group	77.73596739	77.76732518	0.001
6–13 age group	17.7485105	17.43493258	− 0.008
Anti-hypersensitive agent			
Alpha-blocker	9.093759799	9.031044214	− 0.002
Telmisartan	7.290686736	7.714016933	0.016
Beta-blocker	41.235497	39.98118532	− 0.026
Diuretics (thiazide/loop diuretics/spironolactone)	25.90153653	26.0269677	0.003
Hypertension drugs number on average	2.49± 1.1	2.39 ± 1.1	− 0.0138
CCB	60.12856695	60.45782377	0.007
Antidiabetic agent			
Insulin	17.7641894	17.56036375	− 0.005
Secretagogue (Glinide)	17.56036375	18.12480401	0.015
Biguanide (metformin)	67.84258388	68.54813421	0.015
Alpha-glucosidase	26.19943556	25.96425212	− 0.005
DPP4i	18.31295077	18.06208843	− 0.007
Anticoagulant	3.088742553	3.198494826	0.006
Sulfonylurea	75.24302289	75.50956413	0.006
Other medications (percentage)			
Fibrate	14.22075886	13.92285983	− 0.009
Aspirin	77.21856381	76.23079335	− 0.023
Clopidogrel	16.77641894	16.68234556	− 0.003
Statin	50.45468799	50.67419254	0.004
Follow-up Period	3.9 ± 2.38	4.0 ± 2.4	0.021
Propensity score matching	0.1279 ± 0.071	0.126 ± 0.072	0.0020

Table 2. **Recurrent ischemic stroke subgroup analyses.**

Characteristics	Percentage of Non-pioglitazone	Percentage of Pioglitazone	SHR value
65-74	23.1	18.8	0.88
<65	20.8	19	0.93
≥75	20	18.2	1.02
Female	21	18.5	0.96
Male	21.8	19	0.9
Coronary artery	22	21.2	0.96
No coronary artery	19.3	17.9	0.92
Chronic kidney	17.8	23.1	1.37
No Chronic Kidney	20.1	18.4	0.9
pulmonary disease	23	17.8	0.71
No Chronic obstructive pulmonary disease	19.8	18.8	0.94
Dyslipeadimea	19.6	18.1	0.91
No Dyslipidaemia	20.3	19.5	0.95
< 5 NIHSS	20.2	17.8	0.87
>13 NIHSS	18.1	21.6	1.14
6-13 NIH	19.4	22.1	1.12
Telesmartan	21.7	17.1	0.68
No Telesmaartan	21.3	18.9	0.95
spironolactone	21.6	21.2	0.97
No Spironolactone	19.4	17.9	0.91
1-2 Hypersensitive agent	19	17.4	0.9
≥5 Hypersensitive agent	17.4	20.3	1.2
3-4 Hypersensitive agent	21.6	20.6	0.93
Insulin	20.9	20.9	0.99
No Insulin	19.8	18.3	0.91
Aspirin	20	18.3	0.91
No Aspirin	20	20.1	0.99
Clopidogrel	21.9	23.1	1.01
No clopidogrel	19.6	17.9	0.91

Table 3. **Recurrent ischemic stroke patients treated and non-treated with Pioglitazone.**

	Non pioglitazone	Pioglitazone	SHR(95% Confidence interval) Non-Pioglitazone vs Pioglitazone	P-value
Recurrent ischemic stroke, n (%)	20	18.79	0.91 (0.99,0.84)	0.033
Percentage of ischemic stroke	21.2	19	0.89 (0.99,0.80)	0.025
Secondary outcomes				
Percentage of myocardial infarction (Acute)	4.2	3.7	0.79 (0.97,0.65)	0.021
Percentage of Hospitalization for heart failure,	6.4	6.3	0.99 (1.15,0.85)	0.867
All-cause mortality, n (%)	18.2	17.6	0.94 (1.06,0.83)	0.32
Cardiovascular death, n (%)	11.5	11.4	0.95 (1.11,0.81)	0.523
Bladder cancer, n (%)	0.17	0.31	1.34 (2.88,0.62)	0.456

Table 4. **Dose-dependent peroxisome proliferator-activated receptor-gamma intensity effect on ischemic stroke recurrent and trend test. p < 0.05 significance level.**

	Total number of patients	**No. of occurrence (%)**	**Adjusted trend**	***p* trend**
Pioglitazone and telmisartan effect trend test			0.076	0.087
Telmisartan alone	2259	21.7		
Pioglitazone alone	2944	18.9		
Pioglitazone plus telmisartan	246	17.1		
Pioglitazone's Dose-dependent effect			0.068	0.015
MPR < 80	1784	20.6		
MPR ≥ 80	1406	16.4		
Non-Pioglitazone	32645	21.4		

Discussion

This observation proves that Ischemic Stroke patients under Pioglitazone treatment for Type II Diabetes mellitus control have less risk of developing an Ischemic stroke. The study result supports the beneficial effect of Pioglitazone on Ischemic stroke in patients.

According to the IRIS study of non-diabetic patients with Ischemic, the risk of Myocardial infarction is lower after being treated with the Pioglitazone than the non-Pioglitazone group. A prospective clinical trial with Pioglitazone proves that Pioglitazone minimizes the stroke risk of Diabetic patients (19). There is a need for more research in this field because only 19% of the prospective study had a stroke previously (20). Though Pioglitazone's effect of reducing the cardiovascular risk was not supported by the junto study organized in Japan (21). Pioglitazone effect was also not significant in the case of the IRIS study (22). According to Chan et al., Pioglitazone and metformin have less cardiovascular complications than the Sulfonyl and metformin combination (23). While a Korea centred study proved Pioglitazone to be beneficial (23). In the case of the Asian patients having Ischemic stroke, who had undergone Pioglitazone treatment for Diabetes, their risk of developing an ischemic stroke was reduced. According to the collected data, Pioglitazone can cause Ischemic stroke in Type II diabetes mellitus patients. This observation is compatible with the other meta-analysis results (24). Additionally, the study shows that Ischemic stroke patients without chronic kidney disease or simultaneous telmisartan medication may obtain more protection when using Pioglitazone for Diabetes. PPAR-gamma has a neuroprotective and metabolism controlling effect and protects from chronic kidney disease and atherosclerosis (25). Several studies also show the vascular protection potential of Pioglitazone (20). Pioglitazone also has potential good effects on the neuroprotection and cerebral ischemic study effect (26). Pioglitazone also induced adiponectin levels in the body, which may relate to elevated insulin sensitivity and energy consumption (27). The increased adiponectin has anti-thrombin, anti-atherosclerotic effects (28). Though Telmisartan induces adiponectin secretion, the relation between clinical consequences and adiponectin levels remains unresearched and requires more research (29). PPAR-gamma effect on vascular disease remains unidentified. As a PPAR-gamma activator, Rosiglitazone has more potential than Pioglitazone, but Rosiglitazone negatively affects atherogenic lipid profiles, with highly induced LDL cholesterol results in high cardiovascular risks. Pioglitazone also induces LDL lipoprotein cholesterol levels, but it also increases HDL cholesterol levels and reduces triglyceride levels and non-HDL cholesterol levels (14). According to this study, dyslipidemia in the Pioglitazone medicating group was greater than the non-Pioglitazone treated group. So, the Pioglitazone treated patients have a higher risk of developing an Ischemic stroke. Telmisartan is a limited PPAR- gamma agonist and, it is the only angiotensin blocker that produces PPAR-gamma modulating effects (30). PPAR-gamma modulation by Telmisartan is much less compared to Pioglitazone. According to the previous studies, the Telmisartan is not a very good stroke preventer (31). Telmisartan and Pioglitazone bind to the PPAR-gamma receptor differently. Therefore, the use of these two drugs in clinical practice is recommendable (32). This study uses previously published papers to show the difference between the different PPAR agonists' effects on cardiovascular disease treatment. This study shows a significant tendency of reduced Ischemic stroke while medicating with Pioglitazone and Telmisartan rather than only using Telmisartan and Pioglitazone (p value=0.076). These indicate increased protection from using the intensive PPAR-gamma controlling treatments for Ischemic stroke patients with type II diabetes mellitus and Hypertension. Our analysis resonated with the observation of the Insulin Resistance Intervention After Stroke (IRIS) trial, i.e., Pioglitazone treated patient have a hazard ratio for recurrent Ischemic stroke which is more than 80% (33). Chronic kidney disease patients' insulin resistance is a major cause of cardiovascular risk factors (34). Pioglitazone improves insulin resistance by activating PPAR-gamma in the case of a chronic kidney disease patient (35). The PROactive (PROspective pioglitazone Clinical Trial in Macro-Vascular Events) study data shows that chronic kidney disease patients who go through pioglitazone medication for Type II Diabetes Mellitus may have higher death rates, and Myocardial Infarction compared to non-chronic kidney disease patients (36). A similarity to the PROactive trial in this study also shows that non- chronic kidney disease patients experience less Ischemic strokes after taking pioglitazone. Pioglitazone in low doses decreases

weight gain and fluid retaining in kidney disease patients (37). According to our study, it is observed that Pioglitazone's protective effect in kidney disease arises from the cardiovascular effect of renal disease than the refusal of drugs. This study also proves that there is less Myocardial infarction in Pioglitazone users (38). In this study, the data from Taiwan shows that Pioglitazone users have induced bladder cancer risk by up to 34%. However, this observation is not statistically significant due to the limited number of sample data. Though the bladder cancer risk due to Pioglitazone is still doubtful due to less evidence, the FDA (Food and drug administration) is limited to the pioglitazone use in bladder cancer patients (39). Population dependent observations show less evidence than the RCT (randomized control trial). Our study shows less evidence than RCT (randomized control trials). This research will help future studies in PPAR agonists treatment-related research work.

Conclusion

We recommend lipid metabolism, cell proliferation, PPARs and modulators for metabolic disorder treatment, considering its immense benefits on glucose. The glucose and lipid-related disorders inhibition and treatment must consider the potential and affinity of few PPAR and their carcinogenic effects. Hence, natural compounds and their close derivatives are being targeted as future drugs against metabolic diseases. It is necessary to evaluate new PPAR agonists' clinical properties and their influence on patient health soon.

Reference

1. https://www.who.int/news-room/fact-sheets/detail/diabetes
2. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR. Glucose control and vascular complications in veterans with type 2 diabetes. New England journal of medicine. 2009 Jan 8;360(2):129-39.
3. Gæde P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. New England Journal of Medicine. 2003 Jan 30;348(5):383-93.
4. Tan MH. Current treatment of insulin resistance in type 2 diabetes mellitus. International journal of clinical practice. Supplement. 2000 Oct 1(113):54-62.
5. Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride monotherapy improves glycemic control in treating patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group. Diabetes Care. 2000 Nov 1;23(11):1605-11.
6. Raskin P, Rappaport EB, Cole ST, Yan Y, Patwardhan R, Freed MI. Rosiglitazone short-term monotherapy lowers fasting and post-prandial glucose in patients with type II diabetes. Diabetologia. 2000 Mar 1;43(3):278-84.
7. Bando Y, Ushiogi Y, Okafuji K, Toya D, Tanaka N, Fujisawa M. Troglitazone combination therapy in obese type 2 diabetic patients poorly controlled with α-glucosidase inhibitors. Journal of international medical research. 1999 Mar;27(2):53-64.
8. Yoshimoto TA, Naruse MI, Nishikawa ME, Naruse KI, Tanabe AK, Seki TO, Imaki TO, Demura RE, Aikawa EI, Demura HI. Antihypertensive and vascular-and renoprotective effects of Pioglitazone in genetically obese diabetic rats. American Journal of Physiology-Endocrinology and Metabolism. 1997 Jun 1;272(6):E989-96.
9. Marx N, Kehrle B, Kohlhammer K, Grub M, Koenig W, Hombach V, Libby P, Plutzky J. PPAR activators as antiinflammatory mediators in human T lymphocytes: implications for atherosclerosis and transplantation-associated arteriosclerosis. Circulation research. 2002 Apr 5;90(6):703-10.
10. Caballero AE, Saouaf R, Lim SC, Hamdy O, Abou-Elenin K, O'Connor C, LoGerfo FW, Horton ES, Veves A. The effects of Troglitazone, an insulin-sensitizing agent, on the endothelial function in early and late-type 2 diabetes: a placebo-controlled randomized clinical trial. Metabolism. 2003 Feb 1;52(2):173-80.
11. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ, RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomized, open-label trial. The Lancet. 2009 Jun 20;373(9681):2125-35.
12. Diamond GA, Bax L, Kaul S. Uncertain effects of Rosiglitazone on the risk for myocardial infarction and cardiovascular death.
13. Staels B, Fruchart JC. Therapeutic roles of peroxisome proliferator–activated receptor agonists. Diabetes. 2005 Aug 1;54(8):2460-70.
14. Goldberg RB, Kendall DM, Deeg MA, Buse JB, Zagar AJ, Pinaire JA, Tan MH, Khan MA, Perez AT, Jacober SJ. A comparison of lipid and glycemic effects of Pioglitazone and Rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care. 2005 Jul 1;28(7):1547-54.
15. Tolman KG. The safety of thiazolidinediones. Expert opinion on drug safety. 2011 May 1;10(3):419-28.
16. Feinstein DL, Spagnolo A, Akar C, Weinberg G, Murphy P, Gavrilyuk V, Russo CD. Receptor-independent actions of PPAR thiazolidinedione agonists: is mitochondrial function the key?. Biochemical pharmacology. 2005 Jul 15;70(2):177-88.
17. Rogue A, Lambert C, Jossé R, Antherieu S, Spire C, Claude N, Guillouzo A. Comparative gene expression profiles induced by PPARγ and PPARα/γ agonists in human hepatocytes. PloS one. 2011 Apr 18;6(4):e18816.
18. Carmona MC, Louche K, Lefebvre B, Pilon A, Hennuyer N, Audinot-Bouchez V, Fievet C, Torpier G, Formstecher P, Renard P, Lefebvre P. S 26948: a New Specific Peroxisome

Proliferator–Activated Receptor γ Modulator With Potent Antidiabetes and Antiatherogenic Effects. Diabetes. 2007 Nov 1;56(11):2797-808.
19. Wilcox R, Bousser MG, Betteridge DJ, Schernthaner G, Pirags V, Kupfer S, Dormandy J. Effects of Pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspectivepioglitAzone Clinical Trial In macroVascular Events 04). Stroke. 2007 Mar 1;38(3):865-73.
20. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefèbvre PJ, Murray GD, Standl E. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspectivepioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. The Lancet. 2005 Oct 8;366(9493):1279-89.
21. Tanaka R, Yamashiro K, Okuma Y, Shimura H, Nakamura S, Ueno Y, Tanaka Y, Miyamoto N, Tomizawa Y, Nakahara T, Furukawa Y. Effects of Pioglitazone for secondary stroke prevention in patients with impaired glucose tolerance and newly diagnosed Diabetes: the J-SPIRIT study. Journal of atherosclerosis and thrombosis. 2015 Dec 1;22(12):1305-16.
22. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, Guarino PD, Lovejoy AM, Peduzzi PN, Conwit R, Brass LM. Pioglitazone after ischemic stroke or transient ischemic attack. N engl J med. 2016 Apr 7;374:1321-31.
23. Chan CW, Yu CL, Lin JC, Hsieh YC, Lin CC, Hung CY, Li CH, Liao YC, Lo CP, Huang JL, Lin CH. Glitazones and alpha-glucosidase inhibitors as the second-line oral antidiabetic agents added to metformin reduce cardiovascular risk in type 2 diabetes patients: a nationwide cohort observational study. Cardiovascular diabetology. 2018 Dec 1;17(1):20.
24. Woo MH, Lee HS, Kim J. Effect of Pioglitazone in acute ischemic stroke patients with Diabetes mellitus: a nested case–control study. Cardiovascular diabetology. 2019 Dec 1;18(1):67.
25. Kaundal RK, Sharma SS. Peroxisome proliferator-activated receptor gamma agonists as neuroprotective agents. Drug news & perspectives. 2010 May;23(4):241.
26. Gliem M, Klotz L, van Rooijen N, Hartung HP, Jander S. Hyperglycemia and PPARγ antagonistically influence macrophage polarization and infarct healing after ischemic stroke. Stroke. 2015 Oct;46(10):2935-42.
27. Yadav A, Kataria MA, Saini V, Yadav A. Role of leptin and adiponectin in insulin resistance. Clinicachimica Acta. 2013 Feb 18;417:80-4.
28. Gairolla J, Kler R, Modi M, Khurana D. Leptin, and adiponectin: pathophysiological role and possible therapeutic target of inflammation in ischemic stroke. Reviews in the Neurosciences. 2017 Apr 1;28(3):295-306.
29. Mori D, Miyagawa S, Matsuura R, Sougawa N, Fukushima S, Ueno T, Toda K, Kuratani T, Tomita K, Maeda N, Shimomura I. Pioglitazone strengthen therapeutic effect of adipose-derived regenerative cells against ischemic cardiomyopathy through enhanced expression of adiponectin and modulation of macrophage phenotype. Cardiovascular diabetology. 2019 Dec;18(1):1-3.
30. Benson SC, Pershadsingh HA, Ho CI, Chittiboyina A, Desai P, Pravenec M, Qi N, Wang J, Avery MA, Kurtz TW. Identification of Telmisartan as a unique angiotensin ii receptor antagonist with selective pparγ–modulating activity. Hypertension. 2004 May 1;43(5):993-1002.
31. Yusuf S, Diener HC, Sacco RL, Cotton D, Ôunpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, Bornstein N. Telmisartan to prevent recurrent stroke and cardiovascular events. New England Journal of Medicine. 2008 Sep 18;359(12):1225-37.
32. Tagami T, Yamamoto H, Moriyama K, Sawai K, Usui T, Shimatsu A, Naruse M. A selective peroxisome proliferator-activated receptor-γ modulator, Telmisartan, binds to the receptor differently from thiazolidinediones. Endocrinology. 2009 Feb 1;150(2):862-70.
33. Spence JD, Viscoli CM, Inzucchi SE, Dearborn-Tomazos J, Ford GA, Gorman M, Furie KL, Lovejoy AM, Young LH, Kernan WN. Pioglitazone therapy in patients with stroke and prediabetes: a post hoc analysis of the IRIS randomized clinical trial. JAMA neurology. 2019 May 1;76(5):526-35.
34. Chan DT, Watts GF, Irish AB, Dogra GK. Insulin resistance and vascular dysfunction in chronic kidney disease: mechanisms and therapeutic interventions. Nephrology Dialysis Transplantation. 2017 Aug 1;32(8):1274-81.
35. Xu H, Carrero JJ. Insulin resistance in chronic kidney disease. Nephrology. 2017 Dec;22:31-4.
36. Schneider CA, Ferrannini E, DeFronzo R, Schernthaner G, Yates J, Erdmann E. Effect of Pioglitazone on cardiovascular outcome in Diabetes and chronic kidney disease. Journal of the American Society of Nephrology. 2008 Jan 1;19(1):182-7.
37. Satirapoj B, Watanakijthavonkul K, Supasyndh O. Safety and efficacy of low dose pioglitazone compared with standard-dose Pioglitazone in type 2 diabetes with chronic kidney disease: A randomized controlled trial. PloS one. 2018 Oct 31;13(10): e0206722.
38. Young LH, Viscoli CM, Curtis JP, Inzucchi SE, Schwartz GG, Lovejoy AM, Furie KL, Gorman MJ, Conwit R, Abbott JD, Jacoby DL. Cardiac outcomes after ischemic stroke or transient ischemic attack: effects of Pioglitazone in patients with insulin resistance without diabetes mellitus. Circulation. 2017 May 16;135(20):1882-93.
39. Drug Safety Communication. Update to ongoing safety review of Actos (Pioglitazone) and increased risk of bladder cancer. In: FDA, editor. 2019 (. http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm)

40. Odom J, Williamson B, Carter L. Rosiglitazone and pioglitazone in the treatment of diabetes mellitus. American Journal of Health-System Pharmacy. 2008 Oct 1;65(19):1846-50.

41. Martín-Timón I, Sevillano-Collantes C, Segura-Galindo A, del Cañizo-Gómez FJ. Type 2 diabetes and cardiovascular disease: have all risk factors the same strength? World journal of diabetes. 2014 Aug 15;5(4):444.