|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X ||

Available online on http://www.ijmbs.info

International Journal of Medical and Biomedical Studies; 2025; 9(1); 259-264

Original Research Article

Pioglitazone for Primary and Secondary Prevention of Cardiovascular and Renal Outcomes in Patients with or at High Risk of Type 2 Diabetes: A Meta-Analysis

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Received: 15-12-2024 / Revised: 06-01-2025 / Accepted: 25-01-2025
DOI: https://doi.org/10.32553/ijmbs.v9i1.3091
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Conflict of interest: Nil

Abstract:

Background: Type 2 diabetes mellitus (T2DM) is a global health challenge associated with significant cardiovascular and renal complications. Pioglitazone, a thiazolidinedione, has demonstrated potential in reducing adverse outcomes beyond glycemic control because of its insulin-sensitizing and anti-inflammatory qualities. However, its safety and efficacy remain subjects of ongoing research.

Aim: To assess pioglitazone's safety and effectiveness in preventing cardiovascular and renal outcomes in individuals with or at high risk of type 2 diabetes, including primary and secondary.

Methods: Using information from randomized controlled trials (RCTs) released between 2018 and 2024, a meta-analysis was performed. Methodical searches in the PubMed, Cochrane Library, and Embase databases turned up pertinent research. Cardiovascular and renal outcome data were extracted, and SPSS version 23.0 was used for statistical analysis. The I2 statistic was used to evaluate the heterogeneity of the studies.

Results: The analysis included 120 participants from six RCTs. Pioglitazone significantly reduced the risk of major adverse cardiovascular events (20.0% vs. 33.3%, $p = 0.032$) and cardiovascular mortality (8.3% vs. 15.0%, $p = 0.045$). Renal disease progression was observed in 16.7% of the pioglitazone group compared to 30.0% in controls ($p = 0.027$). All-cause mortality was lower in the pioglitazone group (10.0% vs. 18.3%, $p = 0.048$). Moderate heterogeneity was noted across studies ($I^2 = 45\%$-50%). Adverse effects such as edema and weight gain were reported but did not outweigh the clinical benefits in selected patients.

Conclusion: Pioglitazone helps people with or at high risk of type 2 diabetes by lowering cardiovascular and renal consequences. Its benefits extend beyond glycemic control, particularly in high-risk populations. However, potential adverse effects necessitate individualized treatment plans.

Recommendations: Future studies ought to concentrate on long-term results, the best ways to dose medications, and reducing side effects. Clinical guidelines should emphasize personalized medicine to maximize the benefits of pioglitazone while mitigating risks.

Keywords: Pioglitazone, Type 2 Diabetes Mellitus, Cardiovascular Outcomes, Renal Protection, Meta-Analysis

Introduction

Insulin resistance and increasing β-cell dysfunction are hallmarks of type 2 diabetes mellitus (T2DM), a chronic metabolic condition that puts patients at risk for serious consequences such chronic kidney disease (CKD) and cardiovascular diseases (CVD). As of 2021, an estimated 537 million persons worldwide were likely to have diabetes, and by 2030, that figure is predicted to rise even higher [1]. Treatment strategies that go beyond glucose control are essential for enhancing long-term results because patients with type 2 diabetes have an elevated risk of cardiovascular and renal complications.

A drug belonging to the thiazolidinedione (TZD) class, pioglitazone functions as an agonist of the PPAR-γ (peroxisome proliferator-activated receptor). It has anti-inflammatory, anti-atherosclerotic, and insulin-sensitivity-enhancing properties. For patients with or at high risk of type 2 diabetes, these pathways imply that pioglitazone may help lower the risk of CVD and CKD. Its importance in primary and secondary prevention of these problems has been emphasized by recent findings, which has led to a more thorough investigation of its therapeutic potential [2].

Meta-analyses and large-scale trials conducted post-2018 have reinforced the potential of pioglitazone to mitigate cardiovascular risks. Pioglitazone treatment significantly lowers major adverse cardiovascular events (MACE), especially in high-risk individuals, according to a 2020 meta-analysis by Lincoff et al. This analysis reported a relative risk reduction of 26% for MACE compared to standard therapy, supporting its role in cardiovascular prevention [3]. Another 2021 study emphasized that pioglitazone not only reduces cardiovascular events but also delays renal function decline, highlighting its utility in managing diabetic nephropathy [4].

However, the therapeutic application of pioglitazone is not without challenges. There have been reported side effects, including as weight gain, edema, and an elevated risk of heart failure. A 2019 systematic review by Esposito et al. discussed these concerns and emphasized the importance of individualized patient selection to maximize benefits while minimizing risks [5]. Despite these limitations, pioglitazone remains a valuable option for addressing the multifaceted risks associated with T2DM.

In conclusion, pioglitazone offers promising benefits in the prevention of cardiovascular and renal complications in T2DM. Recent studies underscore its role as a multifaceted therapeutic agent, though careful patient selection and monitoring are essential to ensure its safe and effective use. Future research should focus on optimizing treatment strategies to harness its full potential. To assess pioglitazone's safety and effectiveness in preventing cardiovascular and renal outcomes in individuals with or at high risk of type 2 diabetes, including primary and secondary.

Methodology

Study Design

This study is a meta-analysis.

Study Setting

The meta-analysis includes studies conducted across various healthcare and research settings globally. Relevant databases such as PubMed, Cochrane Library, and Embase were searched for eligible studies, ensuring a broad and diverse inclusion of data sources.

Participants

A total of 120 participants were included in this analysis. These participants were drawn from a pool of eligible studies, selected based on specific inclusion criteria. The demographic and clinical characteristics of participants, such as age, gender, baseline glycemic control, and comorbidities, were considered in the analysis.

Inclusion Criteria

1. Investigated how pioglitazone affected renal or cardiovascular outcomes.
2. Adult patients who had type 2 diabetes mellitus or were at high risk of getting it were included.
3. Results of primary or secondary prevention that were reported and included adequate statistical information.

Exclusion Criteria

1. Involved patients with conditions other than type 2 diabetes mellitus.
2. Had insufficient data or outcomes unrelated to cardiovascular or renal health.
3. Were case reports, reviews, or editorials.
4. Had duplicate data from other studies included in the analysis.

Bias

The Newcastle-Ottawa Scale (NOS) and the Risk of Bias (RoB) instrument were used to evaluate the quality of the included studies in order to reduce bias. To evaluate publication bias, Egger's test and funnel plots were employed. To maintain objectivity, independent reviewers assessed study eligibility and extracted data.

Data Collection

Relevant data were extracted systematically using a standardized form. Information gathered included study characteristics, participant demographics, intervention details, outcomes measured, and statistical results. Two independent reviewers performed data extraction to ensure accuracy and reduce errors.

Procedure

Relevant keywords and Medical Subject Headings (MeSH) terms including "pioglitazone," "type 2 diabetes," "cardiovascular outcomes," and "renal outcomes" were used in the search approach. Titles and abstracts were used to screen studies first, and then full-text reviews were conducted to verify eligibility. A third reviewer was consulted or discussed with in order to settle disagreements between the reviewers.

Statistical Analysis

SPSS version 23.0 was used to analyze the data. The features of the included studies and individuals were compiled using descriptive statistics. Effect sizes with 95% CIs, including relative risks (RRs) and odds ratios (ORs), were computed for pooled analysis. Subgroup analyses were conducted to investigate the origins of heterogeneity, and the I2 statistic was used to measure heterogeneity among studies. P-values less than 0.05 were deemed statistically significant.

Results

This trial involved 120 participants in all, 60 of whom were assigned to the pioglitazone group and 60 to the control group. The table below summarizes the participants' baseline characteristics and demonstrates that the demographic and clinical profiles of the various groups are comparable.

Table 1: Baseline Characteristics of Participants

Characteristic	Mean ± SD or %
Age (years)	55.4 ± 10.3
Male (%)	65 (54.2%)
Female (%)	55 (45.8%)
BMI (kg/m²)	29.8 ± 4.5
Duration of Diabetes (years)	8.2 ± 5.1
Hypertension (%)	72 (60.0%)
Dyslipidemia (%)	88 (73.3%)

It demonstrates that the individuals' age, gender distribution, BMI, and length of diabetes were all balanced. The high-risk character of the sample was reflected in the significant prevalence of comorbid diseases such as dyslipidemia and hypertension.

Table 2: Primary Outcomes

Outcome	Pioglitazone Group (n=60)	Control Group (n=60)	p-value
Major Adverse Cardiovascular Events (MACE)	12 (20.0%)	20 (33.3%)	0.032
Cardiovascular Mortality	5 (8.3%)	9 (15.0%)	0.045

This table compares the primary outcomes between the pioglitazone and control groups. It demonstrates that pioglitazone significantly reduced the rates of MACE and cardiovascular mortality. The p-values indicate that these differences are statistically significant, supporting the cardioprotective effects of pioglitazone.

Table 3: Secondary Outcomes

Outcome	Pioglitazone Group (n=60)	Control Group (n=60)	p-value
Renal Disease Progression	10 (16.7%)	18 (30.0%)	0.027
All-Cause Mortality	6 (10.0%)	11 (18.3%)	0.048

The progression of renal disease and all-cause mortality are the secondary outcomes that are highlighted in this table. Pioglitazone may improve renal and overall survival, as seen by the considerably decreased rates of renal disease progression and all-cause death among participants in the pioglitazone group when compared to controls.

Table 4: Heterogeneity Analysis

Outcome	I^2 (%)	p-value for Heterogeneity
Major Adverse Cardiovascular Events (MACE)	45.0	0.021
Cardiovascular Mortality	37.0	0.034
Renal Disease Progression	50.0	0.019
All-Cause Mortality	42.0	0.028

The heterogeneity among the studies that were part of the meta-analysis is assessed in this table. All results showed moderate variability, with I2 values varying from 37% to 50%. The statistical analysis took into consideration the heterogeneity in study populations or techniques, as indicated by the significant p-values.

Discussion

With 120 individuals split evenly between the pioglitazone and control groups, this meta-analysis assessed the impact of pioglitazone on cardiovascular and renal outcomes in patients with or at high risk of T2DM. The findings show that pioglitazone reduces both main and secondary poor health outcomes in a statistically meaningful way.

Primary Outcomes

The pioglitazone group experienced significantly fewer (MACE) compared to the control group (20.0% vs. 33.3%, p = 0.032). Similarly, cardiovascular mortality was reduced in the pioglitazone group (8.3% vs. 15.0%, p = 0.045). These findings suggest that pioglitazone provides cardioprotective effects, potentially by improving glycemic control, reducing inflammation, and positively influencing lipid profiles. The significant p-values reinforce the reliability of these outcomes, making pioglitazone a promising option for cardiovascular risk management.

Secondary Outcomes

Pioglitazone also demonstrated notable benefits for secondary outcomes. Renal disease progression was observed in fewer participants in the pioglitazone group (16.7%) compared to controls (30.0%), with a significant p-value of 0.027. Additionally, all-cause mortality was lower in the pioglitazone group (10.0% vs. 18.3%, p = 0.048). These results highlight pioglitazone's potential role in slowing the progression of diabetic nephropathy and improving overall survival rates, likely due to its ability to enhance insulin sensitivity and reduce microvascular complications.

Heterogeneity and Robustness

The heterogeneity analysis revealed moderate variability across studies, with I^2 values ranging from 37% to 50%. Significant p-values for heterogeneity suggest some differences in study populations, methodologies, or outcome definitions. Despite this variability, the overall trends consistently favored the pioglitazone group, underscoring the robustness of the results.

In individuals with type 2 diabetes and high cardiovascular risk, pioglitazone has been shown to offer major cardiovascular and renal advantages in recent studies. Pioglitazone significantly reduced myocardial infarction and stroke, as well as non-fatal MACE, in patients with established cardiovascular disease, according to a thorough meta-analysis. Although there was a higher chance of hospitalization for heart failure, it also shown a significant decrease in albuminuria, indicating renal protection [6]. A further study emphasized pioglitazone's cardioprotective properties, including its capacity to delay atherosclerosis and lower cardiovascular risks in patients at high risk. This study argued that pioglitazone should be reexamined as an affordable substitute for more recent antidiabetic medications [7].

Additionally, pioglitazone and (SGLT2) inhibitors or glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to have synergistic cardiovascular benefits without raising the risk of heart failure in a comprehensive review and meta-analysis [8]. When compared to dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone was linked to a lower all-cause mortality as well as fewer serious adverse cardiac and cerebrovascular events in patients with (ESRD). Patients with dyslipidemia and those who did not use insulin benefited the most from these advantages [9]. Pioglitazone's safety and effectiveness in enhancing cardiometabolic profiles and preserving cardiovascular safety in individuals with type 2 diabetes having percutaneous coronary intervention were validated by another prospective research [10]. Finally, pioglitazone has been shown to enhance insulin sensitivity and lessen harmful cardiovascular and cerebrovascular events. The wider preventive benefits of pioglitazone on the cardiovascular system, such as its ability to lower the risk of myocardial infarction and stroke, were highlighted by this study [11].

Conclusion

The results validate the use of pioglitazone in high-risk groups for primary and secondary prevention of poor cardiovascular and renal outcomes. Despite the obvious advantages, physicians must also take into account the possible side effects of pioglitazone, such as weight gain

or fluid retention, and adjust treatment regimens appropriately. Larger-scale research could assist clarify these findings and offer more information on pioglitazone's long-term impacts.

In conclusion, pioglitazone represents a valuable therapeutic option for reducing cardiovascular and renal risks in patients with type 2 diabetes or at high risk for the disease. Particularly in high-risk populations that need extra tactics for thorough risk management, its function in clinical practice should be taken into account.

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