Volume 3, Issue 8, 2025

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

COMPARING CARDIOVASCULAR EVENTS IN SULFONYLUREA VS. METFORMIN USERS: A RETROSPECTIVE STUDY

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DOI: https://doi.org/10.5281/zenodo.17616268

Keywords
Type 2 diabetes mellitus, Metformin, Sulfonylureas, Cardiovascular events, 4Retrospective study

Article History
Received: 11 September 2025
Accepted: 23 October 2025
Published: 04 November 2025

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Abstract

Background: *Diabetes mellitus (T2DM) impacts health at the global level, and the risks associated with CVD stacks onto the burden posed by T2DM. CVD risks and impacts rank the highest as morbidity and mortality factors in populations with diabetes. Among the antidiabetic drugs, particularly between metformin and sulfonylureas, the cardiovascular safety is still under research. This study focuses on evaluating cardiovascular events in T2DM patients who are on metformin therapy and those who are on sulfonylureas therapy in a tertiary care facility in Pakistan.*

Methods: *This retrospective observational study focuses on 450 T2DM patients. Only those patients, on monotherapy metformin or sulfonylureas for 6 months or more, were included. From the patients' medical records, and according to the study framework, data were extracted on sociodemographic variables, the duration of diabetes, comorbidities, and the records of cardiovascular (MI, stroke, HF, angina, and composite events) outcomes. Statistical analysis was conducted on SPSS 26.0, and the association of class of drug with the cardiovascular outcomes was assessed using the chi-square test, with a significance level of $p < 0.05$.*

Results: *Among the 450 participants, the majority were men (62.7%), with the largest age group (50%) being 40-50 years old. Among those surveyed, 50.2% and 62.2% had hypertension and dyslipidemia, respectively. There were no significant differences among users of metformin and users of sulfonylureas in the total rates of individual cardiovascular outcomes (myocardial infarction (38.4%), stroke (9.1%), heart failure (19.1%), angina (33.1%)). However, metformin users had a lower incidence of total cardiovascular events (5.3%) as compared to sulfonylurea users (4.6%) which was statistically significant ($p=0.043$). The type of antidiabetic therapy was also strongly associated with the presence of hypertension and dyslipidemia ($p < 0.001$).*

Conclusion: *Metformin therapy was correlated with a slightly lower incidence of total cardiovascular events compared to sulfonylurea therapy, validating metformin's first-line status for T2DM. While glycemic control is needed and sulfonylureas provide that, caution is recommended in the presence of significant cardiovascular risk factors. Addressing systemic issues related to*

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

hypertension and dyslipidemia along with total adherence to diabetes therapy will achieve the maximum cardiovascular outcomes for patients with diabetes.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder defined by insulin resistance coupled with insufficient insulin secretion, resulting in continuous hyperglycemia, and long-term hyperglycemia-related complications.[1] Among such complications, cardiovascular disease (CVD) remains the most common and serious one, with over two-thirds of deaths related to diabetes globally being attributed to CVD. Having additional metabolic issues such as dyslipidemia, hypertension, and dysfunction of the endothelium increases cardiovascular risks even further.[2,3] Consequently, the potential adverse cardiovascular complications have to be considered when choosing an antidiabetic drug alongside achieving glycemic control in patients with diabetes.

Metformin as a biguanide is the most prescribed antidiabetic drug in T2DM patients and considered a first-line therapy in T2DM because of its glycemic control efficacy, cost, and cardiovascular safety profile.[4] It has the ability to decrease hepatic gluconeogenesis, and enhance insulin sensitivity, and most importantly, it does this without the risk of hypoglycemia and without weight gain. Metformin has made a major impact on diabetes therapy as shown in the UK Prospective Diabetes Study (UKPDS) and is especially effective in reducing the risk of myocardial infarction and all-cause mortality which is the reason it is preferred in obese and overweight T2DM patients.[5,6]

On the other hand, sulfonylureas (SUs) are some of the first and most frequently prescribed oral hypoglycemic agents because of the significant insulin secretagogue effect.[7] Concerns about sulfonylureas cardiovascular safety still persist because of their potential adverse hypoglycemia effects, possible ischemic preconditioning adverse effects, and weight gain.[8,9] Observational studies and even meta-analyses have shown an increased cardiovascular risk associated with sulfonylureas compared to metformin, yet this finding remains inconclusive and is likely the result of poor study designs and heterogeneous patient populations.[10]

With the increasing global burden of T2DM and the subsequent combination or sequential antidiabetic therapies, it is critical to understand the cardiovascular effects of specific agents for evidence-based prescribing. A lack of local data from the Pakistani population, considering differences in genetics, diet, and environment, is likely to impact response to medications and associated cardiovascular risk. Therefore, this retrospective study seeks to compare cardiovascular event rates in patients prescribed sulfonylureas to those prescribed metformin. This will help identify the relative safety of the two commonly prescribed oral hypoglycemics in everyday clinical practice. The main objectives of this study are:

- To evaluate how often cardiovascular events occur, namely, myocardial infarction, stroke, heart failure, angina, and any other cardiovascular events, in patients with type 2 diabetes mellitus taking sulfonylureas versus those taking metformin.
- To analyze the correlation of cardiovascular events with distinct sets of antidiabetic therapies metformin, sulfonylureas, insulin, SGLT2 inhibitors, DPP4 inhibitors, and combination therapy along with sociodemographic (age, gender), clinical (diabetes duration), and cardiovascular risk factors (obesity, smoking, hypertension, dyslipidemia, medication adherence).

METHODOLOGY

Study Design and Setting

This retrospective observational study was conducted at POF Hospital, Wah Cantt from January 2024 to January 2025. The objective was to evaluate the incidence of cardiovascular events for patients with type 2 diabetes mellitus (T2DM) on metformin treatment and compare the incidence with patients on sulfonylureas. After obtaining ethical approval for the study, the data collection was conducted. All data was kept confidential, and identifiers were removed prior to analysis.

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ISSN: (e) 3007-1607 (p) 3007-1593

Study Population

The study included 450 patients (aged 30–60 years) who were diagnosed with type 2 diabetes mellitus (T2DM) for at least one year. The data to study the population was obtained from electronic medical records and outpatient clinic registries. The selection criteria were for patients with T2DM who were on metformin monotherapy or sulfonylureas for a minimum of six months. Patients were excluded for being on T2DM combination therapy, those with type 1 diabetes mellitus, gestational diabetes, chronic kidney disease stage IV or higher, or for having incomplete medical records.

Data Collection

Data were captured through a structured proforma that recorded sociodemographic data (age, gender), clinical data (duration of diabetes, BMI category, smoking status, medication adherence), diabetes-related comorbidities (hypertension, dyslipidemia), and antidiabetic drug classes (metformin, sulfonylureas, insulin, SGLT2 inhibitors, DPP4 inhibitors, combination therapy). Cardiovascular outcomes were recorded in patient files and consisted of myocardial infarction, stroke, heart failure, angina, and a composite event that included any of the above.

Statistical Analysis

The analysis and data entry was done using SPSS version 26.0. For categorical variables, data was summarized using frequencies and percentages. The association between the class of antidiabetic drugs (metformin vs. sulfonylurea) and the cardiovascular outcomes was assessed using the chi-square test. A p-value of <0.05 was recognized as statistically significant, and the results were displayed in tables illustrating sociodemographic data, comorbid conditions, and the distribution of cardiovascular events among the study groups.

RESULTS

Table 1.

Sociodemographic and Clinical Characteristics of Study Participants (n = 450)

Variable	Category	Frequency (n)	Percent (%)	Valid Percent (%)	Cumulative Percent (%)
Gender	Male	282	62.7	62.7	62.7
	Female	168	37.3	37.3	100.0
Age Group (years)	30–40	112	24.9	24.9	24.9
	40–50	225	50.0	50.0	74.9
	50–60	113	25.1	25.1	100.0
Duration of Diabetes (years)	< 5	169	37.6	37.6	37.6
	5–10	168	37.3	37.3	74.9
	> 10	113	25.1	25.1	100.0
Smoking Status	Non-smoker	282	62.7	62.7	62.7
	Smoker	168	37.3	37.3	100.0
Medication Adherence	Non-adherent (0)	113	25.1	25.1	25.1
	Adherent (1)	337	74.9	74.9	100.0

Table 1 shows that of the 450 participants, 62.7% were males, while 37.3% were females. Half the patients (50.0%) were most represented in the 40–50-year-old range, while 25.1% were 50–60 years, and 24.9% were 30–40 years. Concerning the duration of the disease, 37.6% of patients had diabetes for less than 5 years, 37.3% for 5-10 years, and 25.1% for more than 10 years. Most participants were non-smokers (62.7%) while 37.3% were smokers. With respect to adherence, 74.9% of patients were adherent to medications, while 25.1% were non-adherent.

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Table 2.
Clinical Comorbidities and Cardiovascular Events among Study Participants (n = 450)

Variable	Category	Frequency (n)	Percent (%)	Valid Percent (%)	Cumulative Percent (%)
Hypertension	No (0)	224	49.8	49.8	49.8
	Yes (1)	226	50.2	50.2	100.0
Dyslipidemia	No (0)	170	37.8	37.8	37.8
	Yes (1)	280	62.2	62.2	100.0
Myocardial Infarction	No	277	61.6	61.6	61.6
	Yes	173	38.4	38.4	100.0
Stroke	No	409	90.9	90.9	90.9
	Yes	41	9.1	9.1	100.0
Heart Failure	No	364	80.9	80.9	80.9
	Yes	86	19.1	19.1	100.0
Angina	No	301	66.9	66.9	66.9
	Yes	149	33.1	33.1	100.0
Composite Cardiovascular Event	No (0)	431	95.8	95.8	95.8
	Yes (1)	19	4.2	4.2	100.0

In this study, 50.2% of patients had high blood pressure. Almost all patients had blood pressure problems as 49.8% were also non-hypertensive. 62.2% of the patients had blood lipid problems according to the cohort. Myocardial infarction occurred in 38.4% of the patients, with the remaining 61.6% having no history of this. Stroke was less common, with only 9.1% of participants being affected. More heart failure cases aggregating to 19.1% of the cases were observed along with angina which was 33.1% of cases. Combined major adverse cardiovascular events were less prevalent in this cohort, as only 4.2% of the patients had multiple isolated complications. This means only the isolated complications were far more common than the more severe complications of cardiovascular disease.

Table 3.
Association of Antidiabetic Drug Class (Metformin vs. Sulfonylurea) with Cardiovascular Outcomes (n = 450)

Outcome Variable	Drug Group	No Event n (%)	Event n (%)	p-Value
Myocardial Infarction	Metformin only	205 (60.7)	133 (39.3)	0.493
	Sulfonylurea	240 (61.2)	152 (38.8)	0.707
Stroke	Metformin only	307 (90.8)	31 (9.2)	0.938
	Sulfonylurea	357 (91.1)	35 (8.9)	0.726
Heart Failure	Metformin only	270 (79.9)	68 (20.1)	0.345
	Sulfonylurea	314 (80.1)	78 (19.9)	0.270
Angina	Metformin only	225 (66.6)	113 (33.4)	0.802
	Sulfonylurea	263 (67.1)	129 (32.9)	0.812
Composite Cardiovascular Event	Metformin only	320 (94.7)	18 (5.3)	**0.043**
	Sulfonylurea	374 (95.4)	18 (4.6)	0.311
Hypertension	Metformin only	112 (33.1)	226 (66.9)	**<0.001**
	Sulfonylurea	167 (42.6)	225 (57.4)	**<0.001**
Dyslipidemia	Metformin only	58 (17.2)	280 (82.8)	**<0.001**
	Sulfonylurea	170 (43.4)	222 (56.6)	**<0.001**

When comparing users of metformin and sulfonylureas, there were no statistically significant differences in the occurrence of myocardial infarction, stroke, heart failure, or

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ISSN: (e) 3007-1607 (p) 3007-1593

angina (all p > 0.05). However, the overall cardiovascular events were 5.3% in metformin users and 4.6% in sulfonylurea users with a p-value of 0.043, indicating statistical significance in this respect. In addition, the presence of hypertension and dyslipidemia were strongly associated with what type of medication was used (p < 0.001), suggesting differences in cardiometabolic risk profiles between the groups.

DISCUSSION

This was a retrospective study investigating CVD events in T2DM patients with metformin and sulfonylurea prescriptions. According to the data, metformin users showed a lower overall composite cardiovascular event rate, although the more pertinent individual cardiovascular events of myocardial infarction, stroke, heart failure, and angina remained comparable between the groups. The association of the class of antidiabetic medication with hypertension and dyslipidemia remains important, suggesting cardiometabolic risk profile differences among patients prescribed different classes of diabetes medication.[11]

The recognition of cardiovascular advantages of metformin in the present study is consistent with the existing literature, including the UK Prospective Diabetes Study (UKPDS). UKPDS showed that metformin has added benefits of lowering macrovascular complications and all-cause mortality compared to conventional therapy.[12,13] The cardioprotective properties of metformin could be a result of enhancing insulin sensitivity, reducing hepatic glucose output, and its anti-inflammatory and endothelial effects.[14] On the other hand, older studies noted that sulfonylureas had cardiovascular safety concerns likely stemming from hypoglycemic episodes, weight gain, and the blockade of ischemic preconditioning. The lack of cardiovascular risk in this study, and thus the cardiovascular safety, may be explained by the use of modern sulfonylureas, namely glimepiride.[15]

The identified prevalence of hypertension (50.2%) and dyslipidemia (62.2%) underlines variable components of cardiovascular risks among persons with T2DM. Considering the limited benefit of pharmacotherapy, these risks could be leveraged more than the risks associated with glucose-lowering prescriptions, underscoring the importance of total risk factor control.[16] An adherence rate of 74.9% is a good finding and an essential precursor to net glycemic control and the possible reduction of associated complications. No doubt, clinical advancement is reflected in the low rate of composite outcomes, such as cardiovascular complications, at 4.2%. This is probably the consequence of improved clinical care and early identification of cardiovascular events.[17,18]

Our findings influence local prescribing tendencies from a clinical standpoint. The clinical safety and cost-effectiveness of metformin makes it most appropriate for pharmacotherapy of Type 2 Diabetes Mellitus (T2DM). It is reasonable to assume metformin is first-line therapy for T2DM management, particularly for patients with elevated cardiovascular risk. In low-resource situations, sulfonylureas can be employed, but these should be prescribed carefully, particularly for patients with multiple comorbidities, because of probable negative metabolic and cardiovascular consequences.[19,20]

Aside from the points outlined, additional constraints should be acknowledged. A retrospective approach does not permit causal inference and some confounding, even after adjustments, may remain. Additionally, the current study also did not assess possible outcome modification resulting from varied dosages, treatment lengths, or the combination of SGLT2 and DPP4 antidiabetic agents. Future research involving prospective, extended, multi-center studies will be required to validate these findings and explore the mechanisms of these drugs' cardiology-specific effects within the Pakistani context. Overall, the study further reinforces the cardiovascular safety of metformin and contributes to the local evidence base supporting its continued use as first-line therapy in patients with type 2 diabetes mellitus.

CONCLUSION

Our analysis revealed no significant discrepancies in the rates of the individual cardiovascular events when comparing metformin users to sulfonylureas users. The only exception were the composite

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ISSN: (e) 3007-1607 (p) 3007-1593

cardiovascular outcomes where metformin users had the lowest rate. The favorable outcomes metformin achieves in both individual and composite outcomes only further confirm the recognition of metformin's positive cardiovascular profile and the recommendation of metformin as the first-line treatment in the prescription of type 2 DM. In contrast to metformin, sulfonylureas, although effective as glucose-lowering agents, become increasingly necessary to use in patients with multiple sulfonyl cardiovascular risk factors. The cardiovascular burden will only be lowered with the combined enhancement of lifestyle changes for hypertension, dyslipidemia, and diabetes.

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