ORIGINAL RESEARCH

Investigating the Role of New Antidiabetic Agents in Reducing Cardiovascular Events: A Prospective Cohort Study

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ABSTRACT

Aim: This prospective cohort study aimed to evaluate the impact of new antidiabetic agents on the incidence of cardiovascular (CV) events in patients with type 2 diabetes mellitus (T2DM), focusing on SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors. **Materials and Methods**:A total of 100 adult patients (aged ≥ 18 years) with T2DM were enrolled in the study, initiating therapy with one of the new antidiabetic agents. The study followed participants for 12 months, with assessments at baseline, 3, 6, and 12 months. The primary outcome was the occurrence of any major adverse cardiovascular event (MACE), while secondary outcomes included changes in glycemic control, body weight, blood pressure, and lipid profile. **Results**: The baseline characteristics of the study cohort were well-matched across treatment groups. Over the 12-month follow-up, the incidence of MACE was low and did not significantly differ between the three treatment groups (SGLT2i, GLP-1 RA, and DPP-4i). The mean reduction in HbA1c for the entire cohort was 1.5%, with SGLT2i showing the greatest reduction. Weight loss was also observed, with no significant differences between groups. Blood pressure and lipid profile changes were modest and similar across treatment arms. Age, baseline HbA1c, and systolic blood pressure were significant predictors of cardiovascular events. **Conclusion**: This study found no significant differences in cardiovascular events or metabolic changes among patients with T2DM treated with SGLT2 inhibitors, GLP-1 receptor agonists, or DPP-4 inhibitors over 12 months. Age, baseline HbA1c, and systolic blood pressure were identified as significant predictors of cardiovascular outcomes. Longer-term studies with larger sample sizes are needed to further assess the cardiovascular benefits of these newer antidiabetic agents.

Keywords: Type 2 diabetes, cardiovascular events, SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors

INTRODUCTION

Diabetes mellitus, particularly type 2 diabetes, has become one of the most significant global health challenges of the 21st century. Characterized by chronic hyperglycemia and disturbances in carbohydrate, fat, and protein metabolism, it arises due to varying degrees of insulin resistance and deficiency. While the primary concern of diabetes management has traditionally focused on glycemic control to prevent microvascular complications such as retinopathy, nephropathy, and neuropathy, growing attention has shifted toward macrovascular complications—specifically cardiovascular disease (CVD)—which remains the leading cause of morbidity and mortality among diabetic patients.[1]Cardiovascular complications in diabetes are not merely a byproduct of elevated blood glucose levels. Rather, they result from a complex interplay of metabolic, inflammatory, and hemodynamic abnormalities associated with insulin resistance, dyslipidemia, endothelial dysfunction, and chronic low-grade inflammation. Consequently, effective diabetes management now requires a broader therapeutic approach—one that not only targets glycemic control but also addresses the heightened cardiovascular risk inherent in this population.Over the past decade, the landscape of diabetes pharmacotherapy has evolved significantly, marked by the development of novel antidiabetic agents with mechanisms that extend beyond traditional glucose-lowering effects. Among these, sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as promising therapies with demonstrated cardiovascular benefits. Their unique modes of action—promoting glucose excretion via the kidneys

and enhancing insulin secretion while suppressing glucagon, respectively—have introduced new dimensions in the treatment paradigm of type 2 diabetes.[2] What sets these newer agents apart from earlier treatments is their potential to influence cardiovascular outcomes directly. Traditionally used medications such as sulfonylureas and insulin have shown limited, if any, benefit in reducing major adverse cardiovascular events (MACE), and in some cases, concerns have been raised regarding their safety profiles. In contrast, a growing body of clinical trial evidence suggests that SGLT2 inhibitors and GLP-1 RAs may reduce the risk of heart failure, stroke, myocardial infarction, and cardiovascular death—benefits that appear to be independent of their glucose-lowering effects.This paradigm shift stems, in part, from regulatory changes that have redefined the priorities in antidiabetic drug development. In response to earlier concerns about the cardiovascular safety of certain glucose-lowering medications, regulatory agencies mandated that new antidiabetic drugs must undergo rigorous cardiovascular outcome trials (CVOTs) before approval. These trials, while initially intended to ensure cardiovascular safety, have uncovered unexpected benefits in some drug classes, thereby changing the trajectory of diabetes care.[3] The role of SGLT2 inhibitors in cardiovascular protection has been particularly notable in patients with established atherosclerotic cardiovascular disease or at high risk of such events. These agents have demonstrated significant reductions in hospitalization for heart failure and cardiovascular death, and they appear to confer renal protective effects as well. The mechanisms underlying these benefits are multifactorial and still under investigation, involving hemodynamic effects, reductions in blood pressure and body weight, and improvements in cardiac energy metabolism.Similarly, GLP-1 receptor agonists have shown favorable outcomes, particularly in reducing major cardiovascular events such as stroke and myocardial infarction. Their benefits are thought to be mediated through anti-inflammatory effects, weight loss, improved lipid profiles, and modulation of endothelial function. Importantly, these agents also offer the advantage of promoting satiety and aiding in weight management, which is a critical component of diabetes care.[4] The growing emphasis on cardiovascular risk reduction in diabetes management has important clinical implications. It necessitates a more individualized treatment strategy that considers not only glycemic control but also the patient's cardiovascular risk profile, comorbidities, and preferences. As a result, contemporary guidelines have begun to prioritize the use of SGLT2 inhibitors and GLP-1 RAs in patients with type 2 diabetes and coexisting cardiovascular disease or high cardiovascular risk, often regardless of baseline glycemic control or the presence of prior therapy.Despite these advances, challenges remain. Access to these newer therapies can be limited by cost and availability, and their use requires careful consideration of contraindications and potential side effects. Moreover, while clinical trials provide strong evidence in select populations, translating these findings into real-world settings requires ongoing research and evaluation. There is also a need for further exploration into how these drugs may benefit subgroups of patients, such as those with preserved ejection fraction heart failure, chronic kidney disease without diabetes, or varying racial and ethnic backgrounds.[5] In light of these developments, investigating the role of new antidiabetic agents in reducing cardiovascular events is both timely and essential. It reflects a broader shift in the understanding of type 2 diabetes as a complex systemic disease with far-reaching implications beyond blood glucose. As the field continues to evolve, the integration of cardioprotective strategies into diabetes management holds the potential to significantly improve long-term outcomes, reduce healthcare burdens, and enhance the quality of life for millions of individuals living with diabetes.

MATERIALS AND METHODS

This was a prospective cohort study conducted a tertiary care center with a dedicated endocrinology and cardiology department. The study aimed to evaluate the impact of new antidiabetic agents on the incidence of cardiovascular (CV) events in patients with type 2 diabetes mellitus (T2DM).A total of 100 adult patients (aged ≥ 18 years) with a confirmed diagnosis of T2DM were enrolled consecutively from outpatient endocrinology and internal medicine clinics. All participants were initiating therapy with one of the following new antidiabetic agents: sodium-glucose co-transporter-2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1 RA), or dipeptidyl peptidase-4 inhibitors (DPP-4i).

Inclusion Criteria

- Adults aged ≥ 18 years.
- Diagnosed with T2DM for at least 1 year.
- Naïve to or switching to one of the new antidiabetic agents (SGLT2i, GLP-1 RA, or DPP-4i).
- Provided informed written consent.

Exclusion Criteria

- History of type 1 diabetes mellitus.
- Existing cardiovascular disease at baseline (e.g., myocardial infarction, stroke, heart failure).
- End-stage renal disease (eGFR < 30 mL/min/1.73 m^2).
- Pregnant or breastfeeding women.
- Inability to provide informed consent or comply with follow-up.

Intervention and Follow-Up

Participants were initiated on the selected antidiabetic agent according to physician discretion based on

clinical profile and guidelines. Patients were followed prospectively for a period of 12 months with scheduled visits at baseline, 3, 6, and 12 months. At each visit, clinical and laboratory data were collected, including HbA1c, fasting glucose, lipid profile, renal function, blood pressure, and body weight.

The primary outcome of the study was the occurrence of any major adverse cardiovascular event (MACE), which was defined as a composite of non-fatal myocardial infarction (MI), non-fatal stroke, cardiovascular death, and hospitalization for heart failure. Secondary outcomes included changes in glycemic control (HbA1c), body weight, blood pressure, and lipid profile. Data collection was performed using standardized case report forms and entered into a secure electronic database. All cardiovascular events were independently adjudicated by a blinded cardiologist, who reviewed medical records, imaging, and laboratory reports to confirm the events.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics. The incidence of cardiovascular events was expressed as event rates per 100 person-years. Comparisons between groups (e.g., different drug classes) were performed using Chi-square tests for categorical variables and t-tests or ANOVA for continuous variables, as appropriate. A Cox proportional hazards model was used to identify independent predictors of cardiovascular events, adjusting for potential confounders such as age, sex, duration of diabetes, baseline HbA1c, and blood pressure. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 21.0.

RESULTS

Table 1: Baseline Demographic and Clinical Characteristics of Participants (N = 100)

This table presents the baseline demographic and clinical characteristics of the 100 participants included in the study, who were divided into three groups based on the antidiabetic agent prescribed: SGLT2i (33 patients), GLP-1 RA (33 patients), and DPP-4i (34 patients). The mean age of the participants was 58.4 ± 7.1 years, with no significant differences between the three groups ($p = 0.512$). The gender distribution was fairly balanced, with 60.00% of the participants being male, and there were no significant gender differences between the groups ($p = 0.836$). The mean duration of diabetes was 8.1 ± 3.4 years, with no significant differences among the groups ($p = 0.723$). Participants had a mean BMI of 31.3 ± 5.2 kg/m², indicating obesity, and this did not differ significantly between groups ($p = 0.877$). Baseline HbA1c levels were 8.2 ± 1.1%, with no significant differences between groups ($p = 0.452$). Systolic blood pressure (BP) was 135 ± 14 mmHg, and diastolic BP was 85 ± 9 mmHg, with no significant variations across the groups ($p = 0.731$ and $p = 0.812$, respectively). These results indicate that the baseline characteristics of participants were well-matched across the three treatment groups.

Table 2: Incidence of Major Adverse Cardiovascular Events (MACE)

Table 2 shows the incidence of major adverse cardiovascular events (MACE) during the study period. In total, 4.00% (4 patients) of the participants experienced non-fatal myocardial infarction (MI), with the incidence being slightly higher in the GLP-1 RA group (6.06%) compared to the SGLT2i and DPP-4i groups (both 3.03% and 2.94%, respectively). Non-fatal stroke occurred in 3.00% (3 patients) of the total cohort, with similar rates across all treatment groups (3.03% for SGLT2i and GLP-1 RA, and 2.94% for DPP-4i). Cardiovascular death was observed in 2.00% (2 patients) of the participants, with no deaths occurring in the SGLT2i group, and one death each in the GLP-1 RA and DPP-4i groups (3.03% and 2.94%, respectively). Hospitalization for heart failure occurred in 5.00% (5 patients), with the highest incidence in the SGLT2i and GLP-1 RA groups (6.06% each) compared to the DPP-4i group (2.94%). Overall, the incidence of MACE was low across all treatment groups, and no significant differences were found between the groups (p-values ranging from 0.583 to 1.000).

Table 3: Changes in Glycemic Control and Weight Over 12 Months

Table 3 summarizes the changes in glycemic control and weight over the 12-month study period. The mean reduction in HbA1c for the entire cohort was 1.5 ± 0.8%, with the SGLT2i group experiencing the greatest reduction (1.7 ± 0.7%), followed by the DPP-4i group (1.4 ± 0.8%) and the GLP-1 RA group (1.3 ± 0.9%). However, the differences between the groups were not statistically significant ($p = 0.315$). In terms of weight change, the total cohort experienced a mean reduction of -2.1 ± 2.5 kg. The SGLT2i group had the largest weight loss (-2.6 ± 2.7 kg), followed by the DPP-4i group (-2.0 ± 2.4 kg) and the GLP-1 RA group (-1.8 ± 2.3 kg), though the differences were again not statistically significant ($p = 0.712$). Fasting glucose levels decreased from 120 ± 15 mg/dL at baseline to similar levels across all groups, with no significant differences ($p = 0.764$).

Table 4: Changes in Blood Pressure and Lipid Profile Over 12 Months

Table 4 presents the changes in blood pressure and lipid profile over the study period. The mean systolic blood pressure (SBP) decreased by -6.1 ± 8.3 mmHg overall, with the SGLT2i group showing the greatest reduction (-7.2 ± 9.1 mmHg). The DPP-4i and GLP-1 RA groups showed slightly smaller reductions in SBP (-5.6 ± 8.7 mmHg and -5.8 ± 7.5 mmHg, respectively), but the differences were not statistically

significant (p = 0.682). Diastolic blood pressure (DBP) decreased by -3.3 ± 5.1 mmHg on average, with no significant differences among the groups (p = 0.895). Total cholesterol levels decreased by -12.2 ± 20.1 mg/dL overall, with the SGLT2i group showing the largest reduction (-13.3 ± 18.5 mg/dL). HDL cholesterol increased by 5.6 ± 8.1 mg/dL across all participants, with no significant differences between groups (p = 0.802). LDL cholesterol levels decreased by -8.3 ± 14.6 mg/dL, with similar reductions in all treatment groups (p = 0.773). Overall, there were no significant differences in blood pressure or lipid changes across the three groups.

Table 5: Cox Proportional Hazard Analysis for Predictors of Cardiovascular Events

Table 5 presents the results of the Cox proportional hazards analysis, which identifies the independent predictors of cardiovascular events. The analysis revealed that age (per 10 years) was a significant predictor of cardiovascular events, with a hazard ratio (HR) of 1.25 (95% CI: 1.05 - 1.50, p = 0.014), indicating that older age was associated with a higher risk of cardiovascular events. Baseline HbA1c levels were also a significant predictor, with a HR of 1.18 (95% CI: 1.02 - 1.36, p = 0.027), suggesting that higher HbA1c levels at baseline were associated with an increased risk of cardiovascular events. Systolic blood pressure (per 10 mmHg) was another significant predictor (HR = 1.20, 95% CI: 1.05 - 1.38, p = 0.010), indicating that higher blood pressure was associated with a greater risk of cardiovascular events. However, the type of antidiabetic agent (SGLT2i or GLP-1 RA) did not significantly affect the risk of cardiovascular events when compared to DPP-4i (HR for SGLT2i = 0.54, p = 0.173; HR for GLP-1 RA = 0.80, p = 0.618).

Table 1: Baseline Demographic and Clinical Characteristics of Participants (N = 100)

Characteristic	Total (N = 100)	SGLT2i (n = 33)	GLP-1 RA (n = 33)	DPP-4i (n = 34)	p-value*
Age, years (mean ± SD)	58.4 ± 7.1	59.2 ± 6.3	57.7 ± 7.2	58.2 ± 7.0	0.512
Gender (Male, %)	60.00%	58.00%	62.00%	58.00%	0.836
Duration of T2DM, years (mean ± SD)	8.1 ± 3.4	7.9 ± 3.2	8.4 ± 3.6	8.0 ± 3.3	0.723
BMI, kg/m² (mean ± SD)	31.3 ± 5.2	30.8 ± 5.1	31.4 ± 5.5	31.5 ± 5.3	0.877
Baseline HbA1c (%) (mean ± SD)	8.2 ± 1.1	8.3 ± 1.0	8.0 ± 1.2	8.3 ± 1.0	0.452
Systolic BP, mmHg (mean ± SD)	135 ± 14	136 ± 13	134 ± 15	135 ± 14	0.731
Diastolic BP, mmHg (mean ± SD)	85 ± 9	84 ± 8	85 ± 10	86 ± 9	0.812

Table 2: Incidence of Major Adverse Cardiovascular Events (MACE)

MACE Type	Total (N = 100)	SGLT2i (n = 33)	GLP-1 RA (n = 33)	DPP-4i (n = 34)	p-value*
Non-fatal Myocardial Infarction (MI), n (%)	4 (4.00%)	1 (3.03%)	2 (6.06%)	1 (2.94%)	0.811
Non-fatal Stroke, n (%)	3 (3.00%)	1 (3.03%)	1 (3.03%)	1 (2.94%)	1.000
Cardiovascular Death, n (%)	2 (2.00%)	0 (0.00%)	1 (3.03%)	1 (2.94%)	0.583
Hospitalization for Heart Failure, n (%)	5 (5.00%)	2 (6.06%)	2 (6.06%)	1 (2.94%)	0.728

Table 3: Changes in Glycemic Control and Weight Over 12 Months

Parameter	Total (N = 100)	SGLT2i (n = 33)	GLP-1 RA (n = 33)	DPP-4i (n = 34)	p-value*
HbA1c Reduction (%) (mean ± SD)	1.5 ± 0.8	1.7 ± 0.7	1.3 ± 0.9	1.4 ± 0.8	0.315
Weight Change (kg) (mean ± SD)	-2.1 ± 2.5	-2.6 ± 2.7	-1.8 ± 2.3	-2.0 ± 2.4	0.712
Fasting Glucose (mg/dL) (mean ± SD)	120 ± 15	118 ± 16	121 ± 14	122 ± 15	0.764

Table 4: Changes in Blood Pressure and Lipid Profile Over 12 Months

Parameter	Total (N = 100)	SGLT2i (n = 33)	GLP-1 RA (n = 33)	DPP-4i (n = 34)	p-value*
Systolic BP (mmHg) (mean ± SD)	-6.1 ± 8.3	-7.2 ± 9.1	-5.8 ± 7.5	-5.6 ± 8.7	0.682
Diastolic BP (mmHg) (mean ± SD)	-3.3 ± 5.1	-3.6 ± 5.2	-3.4 ± 5.0	-3.1 ± 5.3	0.895
Total Cholesterol (mg/dL) (mean ± SD)	-12.2 ± 20.1	-13.3 ± 18.5	-10.5 ± 22.4	-12.1 ± 19.2	0.762
HDL Cholesterol (mg/dL) (mean ± SD)	+5.6 ± 8.1	+6.1 ± 7.2	+5.2 ± 8.5	+5.4 ± 8.3	0.802
LDL Cholesterol (mg/dL) (mean ± SD)	-8.3 ± 14.6	-9.2 ± 13.8	-7.9 ± 15.2	-8.1 ± 14.9	0.773

Table 5: Cox Proportional Hazard Analysis for Predictors of Cardiovascular Events

Variable	Hazard Ratio (HR)	95% CI	p-value
Age (per 10 years)	1.25	1.05 - 1.50	0.014
Baseline HbA1c (%)	1.18	1.02 - 1.36	0.027
Systolic BP (per 10 mmHg)	1.20	1.05 - 1.38	0.010

Antidiabetic Agent (SGLT2i vs. DPP-4i)	0.54	0.22 - 1.30	0.173
Antidiabetic Agent (GLP-1 RA vs. DPP-4i)	0.80	0.33 - 1.96	0.618

DISCUSSION

The baseline characteristics of the study participants were well-balanced across the three treatment groups, which is crucial for ensuring that the observed outcomes are primarily influenced by the treatment rather than baseline differences. The participants in this study had a mean age of 58.4 years and a mean HbA1c of 8.2%. These characteristics are similar to those found in the study by Buse et al. (2019), where the participants had a mean age of 59.5 years and a mean HbA1c of 8.4%. In both studies, the participants had a relatively high burden of diabetes, which is indicative of moderate to poor glycemic control.[6] These baseline characteristics were consistent across the three treatment arms (SGLT2i, GLP-1 RA, and DPP-4i), supporting the homogeneity of the study cohort and minimizing confounding factors. Such baseline comparability has been emphasized in previous research, such as by Inzucchi et al. (2017), which highlighted the importance of baseline characteristics matching when comparing new diabetic treatments.[7]

The incidence of major adverse cardiovascular events (MACE) observed in this study was relatively low, with a combined incidence of 4% for non-fatal myocardial infarction (MI) and 5% for hospitalization due to heart failure. The rates of MI and stroke were comparable across all three treatment groups, and no significant differences were found. These findings align with the results from a study by Zelniker et al. (2019), which assessed the cardiovascular outcomes of patients on SGLT2 inhibitors and reported a low but consistent rate of cardiovascular events (MI and stroke) across treatment groups.[8] In contrast, a larger meta-analysis by Li et al. (2018) reported a slightly higher incidence of MACE in patients on GLP-1 receptor agonists, particularly those with pre-existing cardiovascular disease, which is in contrast to the findings in this study where no treatment group had a significantly higher incidence. The low MACE incidence observed in this study may reflect the relatively short duration of follow-up (12 months), as most cardiovascular outcomes are typically more pronounced in longer-term studies.[9]

The changes in glycemic control and weight observed in this study also mirrored those seen in similar studies. The overall HbA1c reduction of 1.5% observed in this study was comparable to the reductions seen in other studies involving new antidiabetic agents. For example, in the EMPA-REG OUTCOME trial, patients on SGLT2 inhibitors had an HbA1c reduction of approximately 1.0%, which was associated with a reduction in cardiovascular events (Zelniker et al., 2019).8 In our study, the SGLT2i group showed the greatest reduction in HbA1c (1.7%), consistent with findings from a systematic review by Pasternak et al. (2018), where SGLT2 inhibitors consistently provided a greater glycemic reduction compared to other newer agents like GLP-1 RA and DPP-4i.[10] Weight loss was also observed in this study, with a mean weight reduction of 2.1 kg overall, which is in line with previous findings such as the LEADER trial by Marso et al. (2016), which demonstrated that GLP-1 receptor agonists resulted in significant weight loss in patients with diabetes.[11] However, no significant differences were found in weight loss among the treatment groups, which is consistent with findings from the DURATION-8 study (Yamada et al., 2017), where no significant difference in weight reduction was observed between GLP-1 RA and other antidiabetic therapies.[12]

The blood pressure and lipid changes observed in this study were relatively modest, with no significant differences between groups. Systolic blood pressure decreased by 6.1 mmHg on average across all participants, which is similar to results from the CANVAS program, which demonstrated a reduction in systolic blood pressure of around 3 to 5 mmHg with SGLT2 inhibitors (Neal et al., 2017).[13] Additionally, the reduction in total cholesterol and LDL cholesterol in this study is consistent with the findings of the SUSTAIN-6 trial, which also demonstrated small reductions in total cholesterol and LDL cholesterol with GLP-1 receptor agonists (Marso et al., 2016). Although the observed changes were not statistically significant, these findings support the notion that the newer antidiabetic agents have modest but beneficial effects on cardiovascular risk factors, including blood pressure and lipid profile.[11]

The Cox proportional hazards analysis in this study revealed that age, baseline HbA1c, and systolic blood pressure were significant predictors of cardiovascular events, which aligns with results from previous studies. In the ADVANCE trial, higher baseline HbA1c and age were strong predictors of cardiovascular outcomes (Miller et al., 2015).[14] The finding that the type of antidiabetic agent did not significantly affect the risk of cardiovascular events is consistent with the results from the TECOS trial, which found that while DPP-4 inhibitors did not significantly affect cardiovascular outcomes, they were considered to be neutral in terms of heart failure and other cardiovascular events (Green et al., 2015). However, the failure to find a significant effect of SGLT2 inhibitors or GLP-1 receptor agonists on cardiovascular outcomes in this study might be attributed to the relatively short follow-up duration and the relatively low number of cardiovascular events observed, which limits the ability to detect such differences.[15]

CONCLUSION

In conclusion, this prospective cohort study did not find significant differences in the incidence of major adverse cardiovascular events (MACE) among patients with type 2 diabetes treated with SGLT2 inhibitors, GLP-1 receptor agonists, or DPP-4 inhibitors over 12 months. While improvements in glycemic control, weight, blood pressure, and lipid profiles were observed, these changes were modest and not statistically significant across treatment groups. Age, baseline HbA1c, and systolic blood pressure emerged as significant predictors of cardiovascular events. Further long-term studies with larger sample sizes are needed to fully assess the cardiovascular benefits of these newer antidiabetic agents.

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