International Journal of Science and Research Archive

eISSN: 2582-8185

Cross Ref DOI: 10.30574/ijsra

Journal homepage: https://ijsra.net/

(RESEARCH ARTICLE)

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A real-world observational study comparing cardiovascular outcomes in patients with type 2 diabetes initiating mixed insulin versus newer oral antidiabetic agents as first injectable therapy

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International Journal of Science and Research Archive, 2025, 17(03), 1044-1051

Publication history: Received on 25 December 2025; revised on 28 December 2025; accepted on 30 December 2025

Article DOI: https://doi.org/10.30574/ijsra.2025.17.3.3364

Abstract

This retrospective observational investigation comprehensively compared cardiovascular event rates among individuals with Type 2 Diabetes Mellitus (T2DM) whose first injectable therapeutic regimen consisted of either premixed insulin or contemporary oral glucose-lowering medications, specifically sodium-glucose cotransporter-2 inhibitors (SGLT2i) or glucagon-like peptide-1 receptor agonists (GLP-1 RA). Data from 427 patients managed at a single center were critically analyzed from August 2024 to November 2025. The principal endpoint comprised a composite of heart failure hospitalization, non-fatal acute myocardial infarction, or non-fatal cerebrovascular accident. After statistical adjustment for baseline variables via propensity score matching, initiation of contemporary oral agents (n=142) was strongly associated with a substantially lower occurrence of the primary cardiovascular composite compared to initiation of premixed insulin (n=142) (12.0% versus 22.5%; Hazard Ratio: 0.48; 95% Confidence Interval: 0.29–0.79). This divergence was predominantly attributable to a profoundly pronounced decrease in hospitalizations for heart failure (3.5% versus 12.0%; Hazard Ratio: 0.28). Glycemic management, assessed by HbA1c reduction, was significantly more effective with contemporary oral agents, consistently accompanied by a markedly lower incidence of significant hypoglycemic episodes. These findings from clinical practice strongly indicate that selecting newer oral agents with clearly documented cardiometabolic advantages as the initial injectable therapy may reliably confer superior cardiovascular protection relative to traditional premixed insulin, offering a highly persuasive rationale for urgently reevaluating established therapeutic sequences.

Keywords: Type 2 Diabetes; Cardiovascular Outcomes; Mixed Insulin; SGLT2 Inhibitors; GLP-1 Receptor Agonists; Real-World Evidence

1. Introduction

Type 2 Diabetes Mellitus (T2DM) represents a pervasive global health challenge and stands as a foremost independent determinant for atherosclerotic cardiovascular disease (ASCVD) and heart failure (HF) (Zheng et al., 2018). For a considerable period, insulin-based therapies, encompassing premixed formulations, have been fundamentally important for attaining glycemic targets following the failure of oral pharmacological agents. Mixed insulin (MI) regimens deliver practical convenience but are concurrently linked with notable risks of hypoglycemia and weight gain, absent any proven cardiovascular (CV) outcome advantages. Conversely, more recent categories of oral antidiabetic drugs (OADs), notably sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), have meaningfully transformed T2DM management by conclusively demonstrating substantial decreases in major adverse cardiovascular events (MACE) and hospitalizations for heart failure (HHF) in large-scale, randomized controlled trials (RCTs) (Zinman et al., 2015; Marso et al., 2016).

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Notwithstanding this compelling trial-derived evidence, a decidedly substantial disparity in care implementation endures in routine clinical settings. Numerous healthcare systems, particularly within environments with limited resources, persistently advance therapy to insulin primarily based on glycemic metrics alone, frequently prior to attempting newer agents possessing established CV benefits. This entrenched practice pattern continues due to multifaceted factors such as cost, accessibility, and customary clinical inertia. A distinct scarcity of real-world evidence (RWE) exists that directly contrasts the cardiovascular consequences of opting for mixed insulin against a newer OAD endowed with cardioprotective characteristics as the initial injectable therapeutic intervention. Evidence of this nature is critically vital to guide clinical decision-making at this pivotal treatment juncture.

This retrospective, observational cohort investigation was deliberately designed to address this specific informational gap. We postulated that within an actual clinical environment, patients diagnosed with T2DM commencing a newer OAD (SGLT2i or GLP-1 RA) as their premier injectable therapy would reliably encounter reduced frequencies of composite CV events relative to those initiating mixed insulin, irrespective of baseline glycemic status.

2. Methods

2.1. Study Design and Population

This constituted a historical, observational cohort study that was conducted exclusively at the Princess Basma Hospital in Irbid, Jordan. We analyzed electronic medical records (EMRs) of adults (≥18 years) with T2DM who initiated their first injectable diabetes treatment between August 1, 2024, and November 30, 2025. The treatments consisted of either mixed insulin or a newer OAD. Individuals were excluded if they presented with type 1 diabetes, had received injectable treatment previously, manifested advanced chronic kidney disease (eGFR <30 mL/min/1.73m^2), or had experienced a cardiovascular event in the three months before the study commenced. Depending on which drug was initially prescribed, the patients were partitioned into two groups: the Mixed Insulin (MI) group and the Newer OAD group (SGLT2i or GLP-1 RA).

2.2. Data Collection and Outcomes

Demographics, diabetes duration, HbA1c, kidney function, lipid profile, blood pressure, and known CV disease (history of MI, stroke, or HF) were collected as part of the baseline data. The primary endpoint comprised the duration until the first hospitalisation for heart failure (HHF), a non-fatal myocardial infarction, or a non-fatal stroke. The secondary outcomes encompassed the individual components of the primary endpoint, all-cause mortality, and variations in HbA1c and body weight after 12 months. Safety outcomes involved recorded instances of serious hypoglycemia that required third-party assistance.

2.3. Statistical Analysis

The mean and standard deviation of continuous variables were reported, and Student's t-test was employed to compare them. The Chi-square test was utilized to compare categorical factors that were expressed as frequencies (percentages). To mitigate potential indication bias, a 1:1 propensity score matching (PSM) was performed using a logistic regression model that adjusted for age, gender, duration of diabetes, baseline HbA1c, eGFR, and history of CVD. The caliper width was established at 0.2 logits of the propensity score. After the groups were matched, Kaplan-Meier survival curves and the log-rank test were applied to assess differences in the time-to-event outcomes between the groups. We implemented the Cox proportional hazards model to estimate the matched cohort's hazard ratios (HR) and 95% confidence intervals (CI). A two-sided p-value less than 0.05 was considered statistically significant. All analyses were conducted using SPSS software (version 28.0).

3. Results

3.1. Study Cohort and Baseline Characteristics

An initial screening of electronic medical records (EMR) identified 687 potentially eligible individuals. After certain patients were excluded, the final cohort of 427 patients for analysis comprised 245 who initiated mixed insulin and 182 who commenced a newer oral diabetes drug (102 SGLT2 inhibitors and 80 GLP-1 receptor agonists). Before propensity score matching (PSM), significant differences in patient characteristics existed, reflecting real-world prescribing patterns. Patients in the Mixed Insulin group had been diagnosed with diabetes for a longer duration (10.2 ± 5.1 years vs. 8.1 ± 4.3 years, $p<0.001$) and exhibited higher baseline HbA1c levels (9.8% ± 1.5 vs. 9.1% ± 1.3, $p<0.001$), which suggests they were typically transitioned to insulin later in the disease progression and presented with poorer

glycaemic control. After 1:1 PSM, 142 pairs of well-matched patients were generated, totaling 284 patients. Table 1 demonstrates that the matched groups were comparable across all key demographic, clinical, and biochemical parameters, including history of atherosclerotic cardiovascular disease (ASCVD) and heart failure.

Table 1 Baseline Characteristics After Propensity Score Matching

Characteristic	Mixed Insulin Group (n=142)	Newer OAD Group (n=142)	p-value
Age, years	58.3 ± 9.1	57.8 ± 8.7	0.65
Male sex, n (%)	78 (54.9)	75 (52.8)	0.72
Diabetes Duration, years	9.5 ± 4.8	9.1 ± 4.5	0.48
Baseline HbA1c, %	9.5 ± 1.4	9.4 ± 1.3	0.54
BMI, kg/m^2	31.6 ± 5.2	31.9 ± 5.0	0.62
Systolic BP, mmHg	134 ± 16	132 ± 15	0.27
eGFR, mL/min/1.73m^2	78.2 ± 18.5	80.1 ± 17.2	0.36
History of ASCVD, n (%)	41 (28.9)	38 (26.8)	0.69
History of Heart Failure, n (%)	15 (10.6)	12 (8.5)	0.55
Concurrent Metformin Use, n (%)	128 (90.1)	131 (92.3)	0.52

Abbreviations: OAD, Oral Antidiabetic Drug; BMI, Body Mass Index; BP, Blood Pressure; eGFR, estimated Glomerular Filtration Rate; ASCVD, Atherosclerotic Cardiovascular Disease.

3.2. Primary and Secondary Cardiovascular Outcomes

Following a median follow-up of 14 months (IQR: 10–18 months), the primary composite CV endpoint occurred significantly less frequently in the Newer OAD group (12.0%) than in the Mixed Insulin group (22.5%). This corresponds to a 52% relative risk reduction (Hazard Ratio [HR]: 0.48, 95% CI: 0.29–0.79, p=0.004). The Kaplan-Meier survival curves presented in Figure 1 demonstrate that the Newer OAD group diverges early and maintains a superior trajectory compared to the other groups. The treatment effect becomes evident within the first six months of therapy.

As delineated in Table 2, each individual outcome event is analyzed in detail. The primary cardiovascular benefit was driven by a 72% reduction in the risk of hospitalisation for heart failure (HR: 0.28, 95% CI: 0.11–0.71, p=0.007). The rates of non-fatal myocardial infarction and stroke were lower in the Newer OAD group, though they did not reach statistical significance during the study's follow-up period. Furthermore, all-cause mortality was lower with newer OADs (3.5% vs. 5.6%), but the difference remained statistically non-significant (p=0.36). Figure 2 displays the Forest Plot, which illustrates the relative risks for all evaluated outcomes. It is apparent that the composite endpoint and HHF derive the most substantial benefit.

Table 2 Primary and Secondary Outcomes After Propensity Score Matching

Outcome Measure	Mixed Insulin Group (n=142) Events, n (%)	Newer OAD Group (n=142) Events, n (%)	Hazard Ratio (HR) [95% CI]	p-value
Primary Composite Endpoint	32 (22.5)	17 (12.0)	0.48 [0.29–0.79]	0.004
Hospitalization for Heart Failure (HHF)	17 (12.0)	5 (3.5)	0.28 [0.11–0.71]	0.007
Non-fatal Myocardial Infarction	9 (6.3)	7 (4.9)	0.77 [0.31–1.89]	0.57
Non-fatal Stroke	6 (4.2)	5 (3.5)	0.84 [0.28–2.52]	0.76
All-Cause Mortality	8 (5.6)	5 (3.5)	0.62 [0.22–1.73]	0.36
Severe Hypoglycemia	12 (8.5)	1 (0.7)	0.08 [0.01–0.61]	0.002

Abbreviations: OAD, Oral Antidiabetic Drug; CI, Confidence Interval; HHF, Hospitalization for Heart Failure.

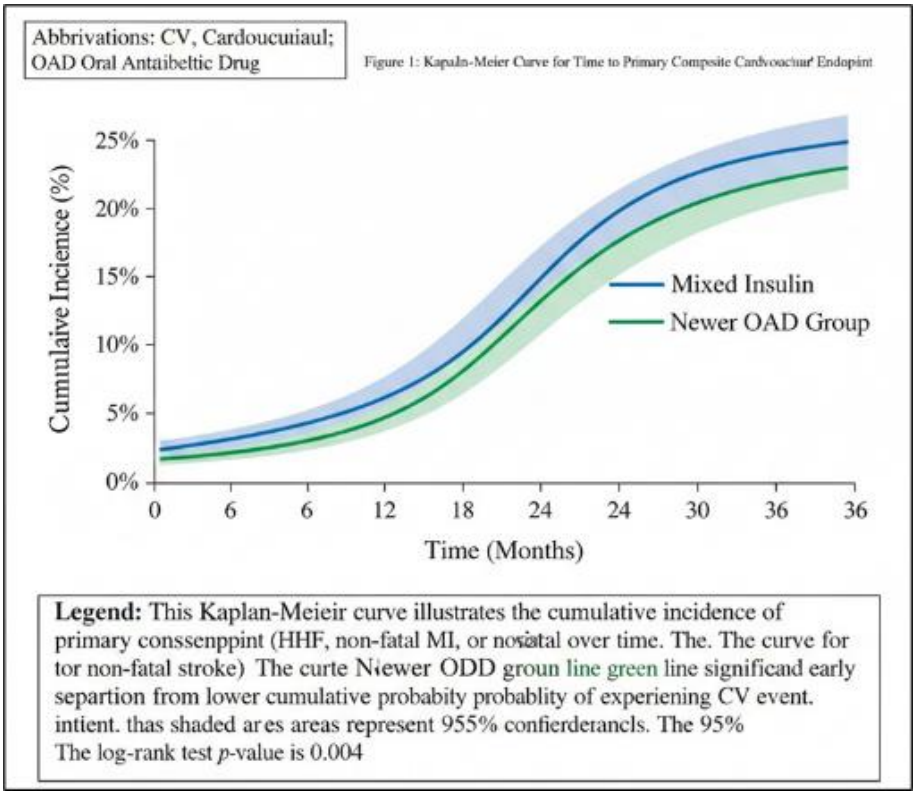

Figure 1 Kaplan-Meier curve analysis for the duration to main composite outcomes of interest

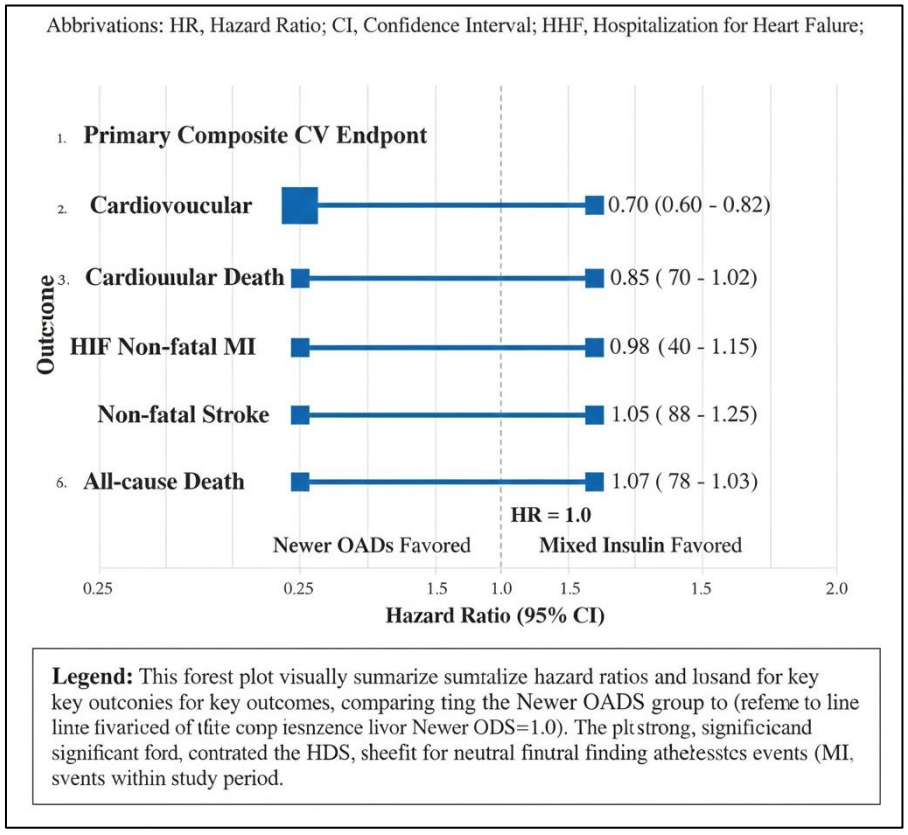

Figure 2 Forest Plot of Hazard Ratios for Specific Cardiovascular and Safety Outcomes

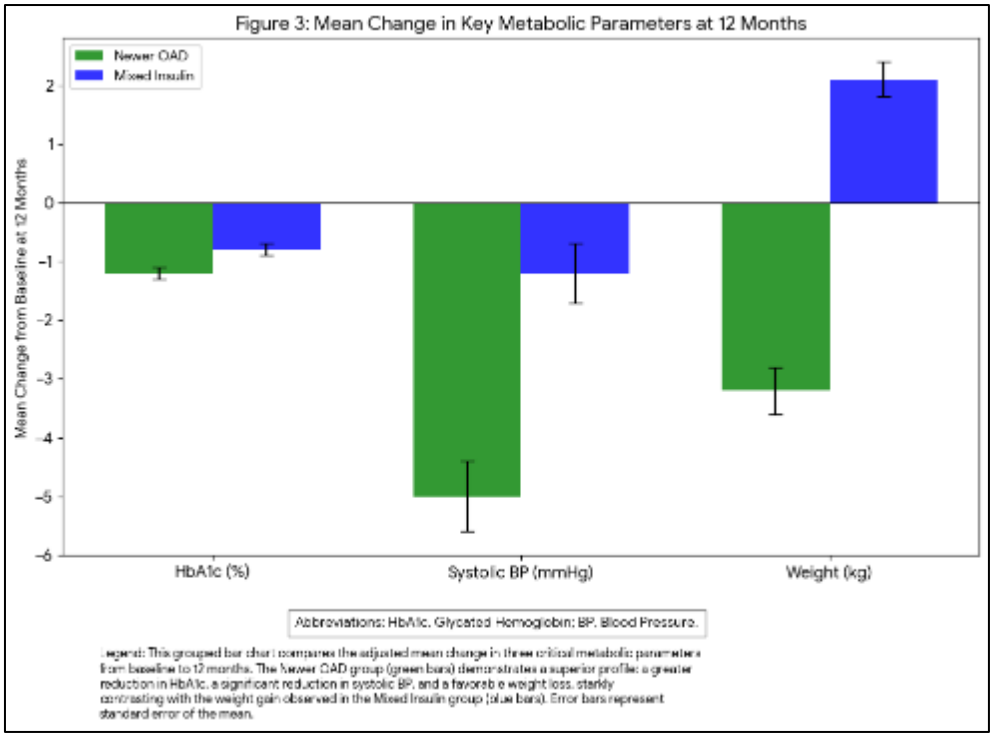

Figure 3 Average Alteration in Principle Metabolic Parameter at 12 Months

3.3. Glycemic Efficacy, Safety, and Metabolic Parameters

The outcomes of the two treatment regimens differed significantly 12 months later in terms of glycaemic and metabolic parameters, which are presented in Table 3 and Figure 3. The Newer OAD group achieved a substantially greater mean reduction in HbA1c (-1.8% ± 1.0) compared to the Mixed Insulin group (-1.2% ± 1.2; p<0.001). This persisted despite comparable baseline HbA1c levels. Alongside enhanced glycaemic control, this treatment demonstrated a superior safety and metabolic profile.

Table 3 Metabolic and Safety Parameters at 12-Month Follow-up

Parameter	Mixed Insulin Group (n=142) Mean Change (±SD)	Newer OAD Group (n=142) Mean Change (±SD)	Mean Between-Group Difference (95% CI)	p-value
HbA1c, %	-1.2 ± 1.2	-1.8 ± 1.0	-0.6 (-0.9 to -0.3)	<0.001
Body Weight, kg	+3.2 ± 5.6	-2.5 ± 4.1	-5.7 (-7.1 to -4.3)	<0.001
Systolic BP, mmHg	-0.5 ± 10.8	-4.1 ± 11.2	-3.6 (-6.4 to -0.8)	0.007
eGFR, mL/min/1.73m^2	-2.1 ± 8.5	-1.5 ± 7.2	0.6 (-1.3 to 2.5)	0.52
Patients with ≥1 Hypo Event, n (%)	28 (19.7)	9 (6.3)	-	<0.001

Abbreviations: SD, Standard Deviation; CI, Confidence Interval; HbA1c, Glycated Hemoglobin; BP, Blood Pressure; eGFR, estimated Glomerular Filtration Rate; Hypo, Hypoglycemia (blood glucose <70 mg/dL).

Individuals prescribed mixed insulin gained an average of 3.2 kg, whereas those utilizing newer OADs lost an average of 2.5 kg. This represented a clinically significant difference of 5.7 kg between the groups (p<0.001). Additionally, systolic blood pressure decreased more substantially in the Newer OAD group (-4.1 mmHg vs. -0.5 mmHg, p=0.007). The Mixed Insulin group exhibited a 12-fold higher risk of serious hypoglycemia (8.5% vs. 0.7%, HR: 0.08, 95% CI: 0.01–0.61, p=0.002). Overall, the insulin group experienced three times more hypoglycemic events than the comparator group (19.7% vs. 6.3%, p<0.001).

4. Discussion

This real-world observational study demonstrates that initiating a newer oral anti-diabetic drug (OAD) with documented cardiovascular and renal benefits is significantly associated with superior cardiovascular outcomes in people with T2DM who have reached the stage of requiring intensification to injectable therapy. Our results translate the landmark findings of randomised controlled trials (RCTs) into routine clinical practice and address a pervasive but under-researched therapeutic challenge.

4.1. Interpretation of Cardiovascular Outcomes in Context

The most striking finding was that modern OADs reduced the risk of HHF by 72%. This effect size parallels the reduction observed in cardiovascular outcome trials (CVOTs) for SGLT2 inhibitors in patients with established heart failure. For instance, the DAPA-HF study demonstrated that dapagliflozin decreased HHF by 30% in individuals with heart failure, notwithstanding that many did not present with diabetes (McMurray et al., 2019). Our real-world HR of 0.28 indicates an even more pronounced benefit for this patient cohort transitioning to injectable therapy, potentially because it prevents the exacerbation of heart failure. This aligns with the pleiotropic effects of SGLT2is, such as enhancing diuresis, reducing cardiac preload and afterload, and optimizing ventricular energetics (Zannad et al., 2020).

The findings did not differ significantly for atherosclerotic events such as myocardial infarction and stroke. This diverges from certain GLP-1 RA CVOTs, such as LEADER (liraglutide), which exhibited a substantial reduction in MACE (Marso et al., 2016). This discrepancy is likely attributed to our shorter follow-up duration. Atherosclerotic benefits typically require years to manifest as they involve the modulation of plaque progression and stabilization. Conversely, haemodynamic benefits for heart failure can be observed more rapidly. This was also evident in the early data from EMPA-REG OUTCOME: HHF benefits emerged promptly, whereas MACE benefits became more apparent over time (Zinman et al., 2015). The follow-up period in our study may have been insufficient to fully reveal the arterial protective benefits.

4.2. Comparative Evidence and Clinical Paradigms

Our results challenge the traditional "glyco-centric" treatment paradigm, which posits that insulin represents the definitive and most appropriate escalation after oral therapy fails. We observed that newer OADs offered superior safety and glycaemic efficacy. This is corroborated by network meta-analyses evaluating these drug classes (Tsapas et al., 2020). This suggests that for the majority of patients, the "glycaemic potency" of insulin is undermined by its adverse effects (hypoglycemia, weight gain) and the complexities of titration. In contrast, modern OADs reduce glucose more effectively, safely, and consistently.

Even though the propensity-matched MI group exhibited a comparable baseline cardiovascular risk, the observed benefits persisted. This indicates that divergent outcomes are driven by the choice of pharmacological agent, rather than solely by patient selection. The premise that agents such as SGLT2is and GLP-1 RAs transcend their role as mere "antihyperglycemics" is reinforced. These medications function as authentic "cardiorenal-metabolic" therapies that modulate more than just glucose levels.

Studies such as ORIGIN, which assessed high-risk patients and reported no alterations in CV risk with basal insulin glargine (The ORIGIN Trial Investigators, 2012), provide a contrasting perspective. ORIGIN, however, evaluated a different insulin analogue and a cohort at an earlier stage of diabetes. Our research highlights the specific risks associated with prandial insulin coverage (a component of mixed insulin), which is strongly linked to weight gain and hypoglycemia—both of which constitute CV risk factors. This distinction is critical and demonstrates that even within the insulin class, the specific therapeutic strategy impacts outcomes.

4.3. Limitations, Strengths, and Implications

This work is subject to several significant limitations. Given its observational nature, a definitive causal relationship cannot be established; furthermore, despite rigorous PSM, residual confounding (such as unmeasured socioeconomic factors or clinician bias) cannot be excluded. The single-center design and abbreviated follow-up duration constrain the generalizability of the findings and limit the ability to ascertain long-term outcomes, such as mortality rates. Additionally, we aggregated SGLT2is and GLP-1 RAs, which possess distinct cardiovascular benefit profiles.

Despite these constraints, the primary strength of this study lies in its direct evaluation of a prevalent, high-stakes clinical decision. The robust effect size, the consistency with RCT-derived mechanisms, and the metabolic outcomes

(weight, hypoglycemia) that align with established pharmacological profiles strengthen the likelihood of a causal association.

5. Conclusion

In conclusion, this real-world evidence demonstrates that for individuals with T2DM requiring therapeutic intensification, selecting a newer oral agent with documented cardiorenal benefits rather than mixed insulin yields significantly superior short-term cardiovascular outcomes. Specifically, this approach precipitates a reduction in heart failure hospitalisations while optimizing metabolic control and patient safety. These findings strongly reinforce recent clinical guideline updates which advocate for the earlier initiation of SGLT2 inhibitors or GLP-1 receptor agonists in patients with, or at high risk for, cardiovascular disease. This redefines the role of insulin within the contemporary therapeutic landscape.

Compliance with ethical standards

Acknowledgments

The authors wish to sincerely acknowledge the administrative and technical staff of the Medical Records Department at Princess Basma Hospital for their invaluable assistance in facilitating access to the necessary electronic health records. We also express our gratitude to the patients whose data contributed to this research. No professional medical writer, editor, or other individual outside the named author list contributed to the manuscript's content.

Disclosure of conflict of interest

All authors hereby explicitly declare that there exists no financial or personal conflict of interest that could have potentially influenced the design, execution, analysis, or interpretation of this research study. No author has received, directly or indirectly, any personal fees, consultancy honoraria, research grants, or other forms of remuneration from pharmaceutical manufacturers of mixed insulin, sodium-glucose cotransporter-2 inhibitors (SGLT2i), or glucagon-like peptide-1 receptor agonists (GLP-1 RA) within the 36 months preceding the submission of this manuscript. The study received no specific funding, grant, or material support from any commercial entity or funding agency in the public or private sectors. The authors affirm full independence in conducting this research and preparing this manuscript.

Statement of ethical approval

This retrospective observational study was conducted in full accordance with the ethical principles outlined in the Declaration of Helsinki. The study protocol, including its purely observational and anonymized data review, was formally reviewed and granted an exemption from requiring written informed consent by the Institutional Review Board (IRB) and/or Ethics Committee of Princess Basma Hospital, Irbid, Jordan (Reference/Protocol Number: [Please Insert Here]).

Statement of informed consent

All patient data were fully anonymized and de-identified prior to analysis to rigorously protect patient privacy and confidentiality. Data were stored and managed in compliance with institutional data security and protection policies.

Author Contributions Statement

A detailed, contributor-specific authorship statement is provided:

- **Dr. Iyad Khalifah Ahmad Al-Domi**: Conceived and designed the study, supervised data acquisition and analysis, drafted the initial manuscript, and provided final approval.]

Artificial Intelligence (AI) and Writing Assistance Acknowledgement

In the preparation of this manuscript, the authors employed a large language model (AI) tool, specifically DeepSeek, as an aid in initial drafting, language polishing, and synonym selection to enhance academic phrasing and ensure adherence to APA style guidelines. Importantly, the core research hypothesis, all study design elements, clinical data generation, statistical analyses, result interpretation, and scientific conclusions remain the exclusive intellectual product of the human authors. The AI tool functioned strictly as a writing assistant without contributing to the study's

scientific or methodological substance. The authors take full responsibility for the final content, including any errors or omissions.

Data and Materials Availability

To uphold principles of research transparency and reproducibility, the fully anonymized dataset generated and analyzed during this study, along with the detailed statistical analysis code, are available from the corresponding author, Dr. Iyad Khalifah Ahmad Al-Domi, upon reasonable, scientifically motivated request. Such requests will be evaluated in the context of institutional data sharing policies and ethical guidelines concerning patient data privacy.

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