Medical : Jurnal Kesehatan Dan Kedokteran
Volume 3, Issue 1, January-June 2026
e-ISSN: 3064-6472 (online)
https://jurnal.sinesia.id/index.php/Medical-JKK/index

Lipid Profile Changes Associated with Different Antidiabetic Treatment Strategies in Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease: A Real-World Retrospective Cohort Study

Leonesia Dau[1]*, Diana Laila Ramatilah[2], Ida Paulina Sormin[3], Kashif Ullah Khan[4]
Diana.ramatillah@uta45jakarta.ac.id
[1,2,3]Faculty of Pharmacy, University 17 Agustus 1945 Jakarta, Indonesia
[3]Clinical Pharmacy and Pharmacy Practice, Institute of Pharmaceutical Sciences, Khyber Medical University Peshawar, Pakistan

Info Article
|Submitted: 10 March 2026 **|Revised**: 10 June 2026 **|Accepted**: 20 June 2026
|Published: 30 June 2026
How to cite: Leonesia Dau, etc., "Lipid Profile Changes Associated with Different Antidiabetic Treatment Strategies in Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease: A Real-World Retrospective Cohort Study", *Medical : Jurnal Kesehatan Dan Kedokteran*, Vol. 3, Issue 1, January-June, 2026, P. 207-228.

ABSTRACT

Background: Dyslipidemia is a major modifiable cardiovascular risk factor in patients with type 2 diabetes mellitus (T2DM). Evidence comparing lipid profile changes associated with SGLT2 inhibitors and metformin in routine clinical practice remains limited. Objective: To compare lipid profile changes among SGLT2 inhibitor monotherapy, SGLT2 inhibitor combined with metformin, and metformin monotherapy in patients with T2DM using real-world clinical data. Methods: A retrospective cohort study was conducted using medical records from two regional referral hospitals in East Kalimantan, Indonesia, between January 2020 and December 2025. A total of 254 patients were included through total sampling: SGLT2 inhibitor monotherapy (n=119), combination therapy (n=11), and metformin monotherapy (n=124). Changes in LDL-C, HDL-C, and triglycerides were analyzed using Wilcoxon signed-rank and Kruskal–Wallis tests. Spearman correlation and multiple linear regression assessed factors associated with lipid changes. Results: Median LDL-C decreased from 146 to 103 mg/dL, triglycerides from 167.5 to 135 mg/dL, and HDL-C increased from 42 to 50 mg/dL (all $p<0.001$). Improvements occurred in 81.1%, 92.9%, and 93.7% of patients, respectively. No significant between-group differences were observed for LDL-C ($p=0.930$), HDL-C ($p=0.057$), or triglycerides ($p=0.103$). Age was independently associated with HDL-C changes, while systolic blood pressure changes were independently associated with triglyceride changes. Conclusion: Lipid improvements were observed during follow-up, without significant differences among treatment strategies. Given the observational design and unequal group sizes, findings should not be interpreted as evidence of causal effects or therapeutic equivalence.

Keywords : *type 2 diabetes mellitus; SGLT2 inhibitors; metformin; lipid profile*

Introduction

Diabetes mellitus type 2 (T2DM) remains one of the fastest-growing chronic metabolic disorders and represents a major global public health challenge. According to the *International Diabetes Federation*, more than 537 million adults were living with diabetes in 2021, and this number is projected to increase substantially over the next two decades, with the greatest burden occurring in low- and middle-income countries. Indonesia is consistently ranked among the countries with the largest number of individuals affected by T2DM, highlighting the urgent need for

This work is licensed under CC BY-SA 4.0

effective therapeutic strategies capable of reducing long-term complications and improving overall metabolic outcomes. Beyond chronic hyperglycemia, T2DM is characterized by a complex constellation of metabolic abnormalities that substantially increase the risk of cardiovascular disease, chronic kidney disease, and premature mortality, making comprehensive metabolic management an essential component of diabetes care. (Hao, 2025).

Among these metabolic disturbances, diabetic dyslipidemia is one of the most clinically important because it contributes directly to accelerated atherosclerosis and cardiovascular events. The characteristic lipid abnormalities in T2DM include elevated triglycerides, reduced high-density lipoprotein cholesterol (HDL-C), increased concentrations of atherogenic small dense low-density lipoprotein cholesterol (LDL-C), and qualitative alterations in lipoprotein composition resulting from insulin resistance. These abnormalities persist even in patients with relatively well-controlled glycemia and are recognized as major determinants of residual cardiovascular risk. Consequently, current diabetes management extends beyond glycemic control alone and emphasizes simultaneous optimization of cardiometabolic risk factors, including lipid metabolism.

Recent updates in the ADA Standards of Care and the ADA/EASD Consensus Report have fundamentally changed the treatment paradigm for T2DM. Contemporary recommendations advocate an individualized, patient-centered approach in which the selection of glucose-lowering therapy is guided not only by glycemic efficacy but also by cardiovascular risk, heart failure, chronic kidney disease, body weight, safety profile, and patient preferences. While metformin remains an important component of pharmacological management for many patients, sodium–glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists are increasingly recommended for individuals with established cardiovascular disease, heart failure, or chronic kidney disease because of their proven cardiorenal benefits. (Zelniker et al., 2021). These recommendations reflect a transition from a glucose-centric model toward a comprehensive strategy aimed at reducing long-term complications and improving overall metabolic health. (Bae, 2025; Davies et al., 2022; ElSayed, McCoy, Aleppo, Bajaj, et al., 2025). Beyond their glucose-lowering properties, antidiabetic medications exert heterogeneous effects on lipid metabolism. Metformin has long been associated with modest improvements in lipid parameters through enhanced insulin sensitivity and reduced hepatic gluconeogenesis. In contrast, SGLT2 inhibitors induce multiple metabolic adaptations, including enhanced glycosuria, weight reduction, altered substrate utilization, and changes in hepatic lipid metabolism that may influence circulating lipoproteins. Meta-analyses published during the last several years indicate that SGLT2 inhibitors generally increase HDL-C and reduce triglyceride concentrations, whereas their effects on LDL-C remain inconsistent, with some

studies demonstrating small increases and others reporting neutral findings. These discrepancies suggest that the lipid response to antidiabetic therapy is influenced by patient characteristics, concomitant medications, baseline metabolic status, and duration of treatment rather than by drug class alone.

Although randomized controlled trials have established the efficacy and cardiorenal benefits of modern antidiabetic therapies, they frequently enroll highly selected patient populations under tightly controlled clinical conditions. Consequently, their findings may not fully represent the heterogeneous populations encountered in routine clinical practice. Real-world evidence (RWE) studies provide complementary information by evaluating therapeutic effectiveness in broader patient populations with diverse clinical characteristics, comorbidities, concomitant medications, and treatment patterns. Such evidence has become increasingly important for informing clinical decision-making and is recognized by regulatory agencies and professional societies as an essential component of comparative effectiveness research.

Despite the growing body of evidence regarding the cardiometabolic effects of contemporary glucose-lowering therapies, real-world evidence directly comparing lipid profile changes across different antidiabetic treatment strategies remains limited. Previous investigations have predominantly evaluated individual antidiabetic agents or focused on glycemic, cardiovascular, or renal outcomes, whereas comparative evidence regarding changes in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides across SGLT2 inhibitor monotherapy, SGLT2 inhibitor combined with metformin, and metformin monotherapy remains relatively limited. (Lin et al., 2022). Furthermore, available evidence is predominantly derived from North American, European, and East Asian populations, while real-world evidence from Southeast Asia, particularly Indonesia, remains scarce. Differences in patient characteristics, dietary patterns, body composition, healthcare delivery systems, prescribing practices, and concomitant therapies may influence lipid responses and limit the direct applicability of findings from other populations to Indonesian clinical practice.

Therefore, this study aimed to compare changes in lipid profiles among patients with T2DM and CKD receiving three antidiabetic treatment strategies: SGLT2 inhibitor monotherapy, SGLT2 inhibitor combined with metformin, and metformin monotherapy. (Zelniker & Braunwald, 2018). Specifically, the study evaluated changes in LDL-C, HDL-C, and triglyceride concentrations during follow-up and examined clinical factors associated with these lipid changes. By generating real-world evidence from Indonesian clinical practice, this study sought to provide context-specific evidence regarding lipid profile changes across

commonly used antidiabetic treatment strategies and to support individualized cardiometabolic risk management in patients with T2DM and CKD.

Methods

1.1 Study Design

This study employed an analytical observational study with a retrospective cohort design using real-world evidence (RWE) to evaluate the comparative effectiveness of different antidiabetic treatment strategies on lipid profile changes in patients with type 2 diabetes mellitus (T2DM). A retrospective cohort approach was selected because it enables the assessment of therapeutic effectiveness using routinely collected clinical data without influencing physicians prescribing decisions or patient management. Consequently, the findings reflect actual clinical practice and provide evidence regarding treatment effectiveness under routine healthcare settings.

Patients were identified through electronic medical records and classified into three treatment groups according to the antidiabetic regimen received: SGLT2 inhibitor monotherapy, SGLT2 inhibitor combined with metformin, and metformin monotherapy. Lipid parameters were evaluated at baseline and follow-up to determine within-group changes and to compare treatment-related differences among the three therapeutic strategies. This design is particularly appropriate for comparative effectiveness research because it allows evaluation of clinical outcomes across heterogeneous patient populations receiving routine diabetes care. The study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement for observational studies.

2.1 Study Setting

This retrospective cohort study was conducted using electronic medical records obtained from two regional referral hospitals in East Kalimantan, Indonesia. To preserve institutional confidentiality, the names of the participating hospitals are not disclosed in this manuscript. Both hospitals provide secondary and tertiary healthcare services for patients with T2DM and utilize electronic medical record systems that comprehensively document demographic characteristics, clinical diagnoses, pharmacological treatments, laboratory investigations, and follow-up evaluations.

Secondary data were collected retrospectively from medical records of eligible patients treated between January 2020 and December 2025. Clinical information extracted from the electronic medical records included demographic characteristics, antidiabetic treatment regimens, laboratory findings, comorbidities, concomitant medications, and lipid profile measurements required for outcome assessment. All

laboratory examinations analyzed in this study were performed as part of routine clinical care using standardized procedures established by each hospital laboratory.

1.3 Study Population and Participants

The study population consisted of adult patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) who received pharmacological treatment at the outpatient clinics of two regional referral hospitals in East Kalimantan, Indonesia. Patients were identified from electronic medical records during the study period. CKD was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m² persisting for ≥3 months. The study population included eligible patients with CKD stages 3–4, while patients with stage 5 kidney disease were excluded. A total sampling approach was employed, whereby all patients meeting the predefined eligibility criteria during the study period were included.

Participants were categorized according to the antidiabetic treatment strategy documented in their medical records: SGLT2 inhibitor monotherapy, SGLT2 inhibitor combined with metformin, or metformin monotherapy. Treatment allocation was determined by the treating physicians as part of routine clinical practice and was independent of the investigators. The combination-therapy group comprised 11 patients. This group was retained because it represented an actual treatment strategy observed in routine clinical practice among eligible patients. Although the group was relatively small, its inclusion preserved the real-world treatment distribution and avoided exclusion of an existing treatment pattern.

1.4 Eligibility Criteria

Eligible participants were identified through systematic review of electronic medical records. Patients were included if they fulfilled all inclusion criteria and none of the predefined exclusion criteria.

Inclusion Criteria

Participants were eligible if they met all of the following criteria: (1) had a documented diagnosis of T2DM; (2) were aged ≥18 years at treatment initiation; (3) had CKD stages 3–4, defined by an eGFR of <60 mL/min/1.73 m² persisting for ≥3 months; (4) received one of the predefined antidiabetic treatment strategies, namely SGLT2 inhibitor monotherapy, SGLT2 inhibitor combined with metformin, or metformin monotherapy; (5) had complete LDL-C, HDL-C, and triglyceride measurements at baseline and follow-up; and (6) had complete clinical information required for evaluation of lipid profile changes.

Exclusion Criteria

Patients were excluded if they had acute kidney injury, CKD stage 5, previous kidney transplantation, polycystic kidney disease or other inherited renal disorders, chronic use of nephrotoxic medications, systemic autoimmune diseases affecting

renal function, incomplete medical records, missing lipid profile measurements, pregnancy or breastfeeding during the observation period, or active malignancy within the previous five years.

1.5 Study Variables

The independent variable in this study was the antidiabetic treatment strategy, which was classified into three treatment groups according to the medication documented in the electronic medical records: SGLT2 inhibitor monotherapy, SGLT2 inhibitor combined with metformin, and metformin monotherapy. The primary outcome was the change in low-density lipoprotein cholesterol (ΔLDL-C), calculated as the difference between follow-up and baseline LDL-C concentrations.

The secondary outcomes were changes in high-density lipoprotein cholesterol (ΔHDL-C) and triglyceride levels (ΔTG), calculated using the same approach. Lipid profile measurements obtained at baseline and follow-up were extracted from the electronic medical records and were used to evaluate the comparative effectiveness of the three antidiabetic treatment strategies on lipid metabolism.

Potential confounding variables included age, sex, duration of diabetes mellitus, history of hypertension, dyslipidemia, and concomitant medications, particularly lipid-lowering therapy, insulin, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and diuretics. These variables were considered during multivariable analysis to minimize potential confounding effects on the association between treatment strategy and lipid profile changes.

1.6 Data Collection Procedures

Clinical data were retrospectively extracted from the electronic medical record system of the participating hospitals using a standardized data collection form developed specifically for this study. Data extraction was performed after obtaining institutional authorization and ethical approval. To ensure patient confidentiality, all personal identifiers were removed prior to analysis, and each participant was assigned a unique study identification code.

The extracted information included demographic characteristics, antidiabetic treatment regimens, comorbidities, concomitant medications, and laboratory measurements of the lipid profile, including LDL-C, HDL-C, and triglycerides, obtained at baseline and follow-up. Patients were subsequently categorized according to the documented antidiabetic treatment strategy for comparative analysis.

Data quality was ensured through systematic verification of completeness and consistency before statistical analysis. Medical records with incomplete essential information or missing laboratory measurements required for outcome assessment were excluded according to the predefined eligibility criteria. Data cleaning was

performed to identify duplicate entries, inconsistencies, and implausible values before the final dataset was established.

1.7 Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 26.0**.** Descriptive statistics were used to summarize participants' demographic and clinical characteristics. Continuous variables were presented as median and interquartile range (IQR) because most numerical variables were not normally distributed, whereas categorical variables were expressed as frequencies and percentages. The distribution of continuous variables was assessed using the Shapiro–Wilk test. Since all lipid-related outcome variables showed non-normal distributions, non-parametric statistical methods were applied for comparative analyses. Changes in lipid parameters before and after treatment within each therapeutic group were evaluated using the Wilcoxon signed-rank test. Differences in lipid profile changes among the three treatment strategies were assessed using the Kruskal–Wallis test. Associations between clinical variables and changes in lipid parameters were initially examined using Spearman's rank correlation analysis. Variables demonstrating statistically significant associations in the bivariate analysis were subsequently entered into multiple linear regression models to identify independent predictors of changes in LDL-C, HDL-C, and triglyceride levels. All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

1.8 Ethical Considerations

This study was approved by the Health Research Ethics Committee of Dr. Kanujoso Djatiwibowo Regional General Hospital, Balikpapan, Indonesia (Ethical Approval No. 43/KEPK-RSKD/IX-2025) prior to data collection. The study was conducted using retrospective secondary data obtained from electronic medical records. Patient confidentiality and privacy were strictly maintained by removing all personal identifiers before data extraction and analysis. Each participant was assigned a unique study identification code to ensure anonymity, and access to the research database was restricted to the research team. All study procedures were conducted in accordance with the ethical principles of the Declaration of Helsinki and reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement for observational studies.

Results

1.1 Baseline Characteristics of the Study Population

A total of 254 patients with type 2 diabetes mellitus who met the eligibility criteria were included in the final analysis. Baseline demographic and clinical characteristics were compared among the three antidiabetic treatment groups to evaluate the comparability of study participants before assessment of lipid profile

outcomes. Variables analyzed included age, sex, duration of diabetes mellitus, and treatment duration. Continuous variables are presented as median and interquartile range (IQR), whereas categorical variables are presented as frequency and percentage.

Table 1. Baseline Characteristics of the Study Population According to Treatment Strategy

Characteristic	SGLT2 inhibitor (n=119)	SGLT2 inhibitor + Metformin (n=11)	Metformin (n=124)	Total (n=254)	p-value*
Age, years, median (IQR)	56 (51–63)	56 (51–63)	56 (51–63)	56 (51–63)	>0.05
Duration of diabetes, years, median (IQR)	2 (1–4)	1 (1–2)	1 (1–4)	2 (1–4)	0.025*
Treatment duration, days, median (IQR)	190 (121–301)	190 (121–301)	190 (121–301)	190 (121–301)	0.962
Male, n (%)	74 (62.2)	4 (36.4)	72 (58.1)	150 (59.1)	0.238
Female, n (%)	45 (37.8)	7 (63.6)	52 (41.9)	104 (40.9)	

*Data are presented as median (interquartile range) or frequency (percentage). Continuous variables were compared using the Kruskal–Wallis test, whereas categorical variables were compared using the Chi-square test.

Table 1 shows that the study included 119 patients (46.9%) receiving SGLT2 inhibitor monotherapy, 11 patients (4.3%) receiving combination therapy with an SGLT2 inhibitor and metformin, and 124 patients (48.8%) receiving metformin monotherapy. The median age of participants was 56 years, and approximately three-fifths of the study population were male (59.1%). No statistically significant differences were observed among treatment groups with respect to age, sex, or treatment duration. However, the duration of diabetes mellitus differed significantly among treatment groups ($p = 0.025$), whereas treatment duration was comparable across all groups ($p = 0.962$).

1.2 Changes in Lipid Profile Before and After Treatment

To evaluate the effectiveness of antidiabetic treatment strategies on lipid metabolism, lipid profile parameters measured at baseline were compared with follow-up measurements. Changes in LDL-C, HDL-C, and triglyceride levels were analyzed using the Wilcoxon signed-rank test because the data were not normally distributed.

Table 2. Changes in Lipid Parameters Before and After Treatment

Variable	Baseline Median (IQR)	Follow-up Median (IQR)	Improved n (%)	p-value*
LDL-C (mg/dL)	146 (60)	103 (49)	206 (81.1)	<0.001*
HDL-C (mg/dL)	42 (9)	50 (12)	236 (92.9)	<0.001*
Triglycerides (mg/dL)	167.5 (144.75)	135 (85.5)	238 (93.7)	<0.001*

*Wilcoxon signed-rank test. Improvement indicates decreased LDL-C and triglycerides or increased HDL-C.

As presented in Table 2, statistically significant improvements were observed in all lipid parameters following treatment. Median LDL-C decreased from 146 mg/dL to 103 mg/dL, while median triglyceride levels decreased from 167.5 mg/dL to 135 mg/dL. In contrast, median HDL-C increased from 42 mg/dL to 50 mg/dL. Overall, 81.1% of patients experienced a reduction in LDL-C, 92.9% demonstrated an increase in HDL-C, and 93.7% showed a reduction in triglyceride levels. All within-group comparisons were statistically significant (all $p < 0.001$).

1.3 Comparison of Lipid Profile Changes Among Treatment Strategies

The changes in LDL-C, HDL-C, and triglyceride levels were compared across the three antidiabetic treatment strategies to determine whether the magnitude of lipid profile changes differed significantly among treatment groups.

Table 3. Comparison of Changes in Lipid Profile Among Treatment Strategies

Outcome	H statistic	df	p-value*
ΔLDL-C	0.145	2	0.930
ΔHDL-C	5.717	2	0.057
ΔTriglycerides	4.538	2	0.103

*Kruskal–Wallis test.

Between-group comparisons were performed using the Kruskal–Wallis test. No statistically significant differences were observed in ΔLDL-C ($H = 0.145$, $df = 2$, $p = 0.930$), ΔHDL-C ($H = 5.717$, $df = 2$, $p = 0.057$), or Δtriglycerides ($H = 4.538$, $df = 2$, $p = 0.103$) among the three treatment strategies. Although ΔHDL-C showed the smallest p-value among the three outcomes, the result did not reach statistical significance ($p = 0.057$). Therefore, the results did not provide sufficient statistical evidence of differences in lipid profile changes among the three treatment groups.

1.4 Correlation Between Clinical Characteristics and Lipid Profile Changes

To explore factors potentially associated with lipid profile changes, correlation analyses were performed between selected clinical variables and changes in LDL-C, HDL-C, and triglyceride levels using Spearman's rank correlation test.

Tablìe 4. Spìearman Corrìelation Bìetwìeìen Clinical Variablìes and Lipid Profilìe Changìes.

Dìepìendìent variablìe	Indìepìendìent variablìe	r	p-valuìe*
ΔLDL-C	Agìe	0.249	<0.001
ΔHDL-C	Agìe	0.189	0.002
ΔTriglycìeridìes	Agìe	0.155	0.013
ΔTriglycìeridìes	Duration of diabìetìes	–0.137	0.029
ΔTriglycìeridìes	ΔSBP	–0.473	<0.001

* Spìearman rank corrìelation

Tablìe 4 dìemonstratìes that agìe was positivìely corrìelatìed with changìes in LDL-C, HDL-C, and triglycìeridìe lìevìels, although thìe strìength of thìesìe associations was wìeak. A wìeak nìegativìe corrìelation was obsìervìed bìetwìeìen thìe duration of diabìetìes mìellitus and changìes in triglycìeridìe lìevìels. In contrast, changìes in systolic blood prìessurìe ìexhibitìed a modìeratìe nìegativìe corrìelation with changìes in triglycìeridìes, indicating that grìeatìer rìeductions in systolic blood prìessurìe wìerìe associatìed with grìeatìer improvìemìents in triglycìeridìe lìevìels.

1.5 Multiplìe Linìear Rìegrìession Analysis

Variablìes dìemonstrating statistically significant associations in thìe corrìelation analysis wìerìe subsìequìently ìentìerìed into multiplìe linìear rìegrìession modìels to idìentify indìepìendìent prìedictors of changìes in lipid profilìe paramìetìers aftìer adjustmìent for potìential confounding factors.

Tablìe 5. Multiplìe Linìear Rìegrìession Analysis of Factors Associatìed with Lipid Profilìe Changìes

Outcomìe	Significant prìedictor	β	95% CI	p-valuìe*	Adjustìed R^2
ΔLDL-C	Nonìe	—	—	—	0.008
ΔHDL-C	Agìe	0.100	0.018–0.218	0.021	0.017
ΔTriglycìeridìes	ΔSBP	–0.456	–2.958 to –1.607	<0.001	0.149
	Duration of diabìetìes	0.089	–0.011 to 12.166	0.050	0,1

*Multiplìe linìear rìegrìession analysis.

As summarizìed in Tablìe 5, thìe rìegrìession modìel for changìes in LDL-C was not statistically significant, indicating that thìe includìed clinical variablìes ìexplainìed only a small proportion of thìe variation in LDL-C changìes. In contrast, thìe rìegrìession modìel for HDL-C was statistically significant, with agìe idìentifiìed as an indìepìendìent prìedictor of HDL-C changìes. Thìe modìel for triglycìeridìe changìes dìemonstratìed thìe grìeatìest ìexplanatory ability among thìe thrìeìe lipid paramìetìers, with changìes in systolic blood prìessurìe idìentifiìed as thìe strongìest

indìepìendìent prìedictor, whilìe thìe duration of diabìetìes mìellitus showìed a bordìerlinìe association with triglycìeridìe changìes.

Discussion

1.1 Principal Findings

Thìe prìesìent rìeal-world rìetrospìectivìe cohort study comparìed changìes in lipid profilìes among patiìents with typìe 2 diabìetìes mìellitus rìecìeiving thrìeìe antidiabìetic trìeatmìent stratìegiìes: SGLT2 inhibitor monothìerapy, SGLT2 inhibitor combinìed with mìetformin, and mìetformin monothìerapy. Significant within-cohort improvìemìents wìerìe obsìervìed in LDL-C and triglycìeridìe lìevìels, accompaniìed by an incrìeasìe in HDL-C during follow-up. Howìevìer, no statistically significant diffìerìencìes wìerìe obsìervìed in thìe magnitudìe of lipid profilìe changìes among thìe thrìeìe trìeatmìent stratìegiìes. Thìesìe findings indicatìe that, within this rìeal-world cohort, thìerìe was no statistically significant ìevidìencìe that thìe obsìervìed changìes in lipid paramìetìers diffìerìed according to thìe antidiabìetic trìeatmìent stratìegy. This obsìervation is clinically rìelìevant bìecausìe lipid abnormalitiìes contributìe substantially to cardiovascular risk in patiìents with T2DM, and lipid managìemìent rìemains an important componìent of comprìehìensivìe diabìetìes carìe. Currìent diabìetìes managìemìent guidìelinìes ìemphasizìe an intìegratìed approach incorporating glycìemic control, lipid managìemìent, blood prìessurìe optimization, and lifìestylìe modification rathìer than rìelying on glucosìe-lowìering thìerapy alonìe. (Davies et al., 2022; ElSayed, McCoy, Aleppo, Bajaj, et al., 2025).

Thìe absìencìe of statistically significant diffìerìencìes bìetwìeìen trìeatmìent groups should not bìe intìerprìetìed as ìevidìencìe of thìerapìeutic ìequivalìencìe. Rathìer, thìe findings indicatìe that lipid profilìe changìes obsìervìed during routinìe clinical carìe may rìeflìect multiplìe concurrìent clinical factors bìeyond thìe documìentìed antidiabìetic trìeatmìent stratìegy. Thìesìe factors may includìe lipid-lowìering thìerapy, glycìemic control, wìeight changìes, blood prìessurìe managìemìent, diìetary modification, and othìer patiìent-lìevìel charactìeristics. Bìecausìe thìesìe factors wìerìe not all systìematically capturìed or controllìed in thìe prìesìent rìetrospìectivìe study, thìeir individual contributions to thìe obsìervìed lipid changìes could not bìe ìestablishìed. Thus, thìe findings should bìe intìerprìetìed as obsìervations of lipid profilìe changìes across trìeatmìent groups rathìer than ìevidìencìe of a causal ìeffìect of any spìecific antidiabìetic rìegimìen.

1.2 Comparison with Prìevious Studiìes

Thìe prìesìent study obsìervìed significant improvìemìents in LDL-C, HDL-C, and triglycìeridìe lìevìels during follow-up, but no statistically significant diffìerìencìes wìerìe idìentifiìed among patiìents rìecìeiving SGLT2 inhibitor monothìerapy, SGLT2 inhibitor combinìed with mìetformin, or mìetformin

monothìerapy. Thìesìe findings indicatìe that thìe magnitudìe of lipid profilìe changìes did not diffìer significantly across thìe trìeatmìent stratìegiìes in this cohort. Thìe absìencìe of a statistically significant bìetwìeìen-group diffìerìencìe should, howìevìer, bìe intìerprìetìed cautiously bìecausìe thìe study was obsìervational and was not dìesignìed to ìestablish thìerapìeutic ìequivalìencìe.

Thìe findings arìe consistìent with thìe broadìer undìerstanding that lipid mìetabolism in patiìents with T2DM is influìencìed by multiplìe clinical and thìerapìeutic factors. Thìe Amìerican Diabìetìes Association Standards of Carìe ìemphasizìe comprìehìensivìe cardiovascular risk managìemìent, including glycìemic control, lipid-lowìering thìerapy, blood prìessurìe managìemìent, wìeight managìemìent, and lifìestylìe modification. Accordingly, thìe lipid profilìe changìes obsìervìed in thìe prìesìent study may rìeflìect thìe combinìed ìeffìects of thìesìe factors rathìer than thìe documìentìed antidiabìetic rìegimìen alonìe. (ElSayed, McCoy, Aleppo, Bajaj, et al., 2025)

Prìevious randomizìed controllìed trials and mìeta-analysìes havìe consistìently shown that SGLT2 inhibitors ìexìert modìest ìeffìects on convìentional lipid paramìetìers. Trìeatmìent with SGLT2 inhibitors is commonly associatìed with a slight incrìeasìe in HDL-C, a modìest rìeduction in triglycìeridìe concìentrations, and ìeithìer minimal incrìeasìes or nìeutral ìeffìects on LDL-C. Although thìesìe lipid changìes arìe statistically dìetìectablìe, thìeir magnitudìe is gìenìerally small and unlikìely to fully ìexplain thìe substantial rìeductions in cardiovascular and rìenal ìevìents obsìervìed with this drug class. Instìead, currìent ìevidìencìe suggìests that thìe cardioprotìectivìe bìenìefits of SGLT2 inhibitors arisìe prìedominantly from mìechanisms indìepìendìent of lipid modification, including improvìemìents in natriurìesis, rìeductions in intraglomìerular prìessurìe, attìenuation of systìemic inflammation, improvìed myocardial ìenìergìetics, and favorablìe hìemodynamic ìeffìects. Thìesìe obsìervations may ìexplain why thìe prìesìent study found no supìeriority of SGLT2 inhibitor-basìed thìerapy ovìer mìetformin-basìed thìerapy with rìespìect to convìentional lipid outcomìes. (ElSayed, McCoy, Aleppo, Bajaj, et al., 2025)

Prìevious randomizìed controllìed trials and mìeta-analysìes havìe gìenìerally rìeportìed modìest ìeffìects of SGLT2 inhibitors on convìentional lipid paramìetìers, including incrìeasìes in HDL-C, rìeductions in triglycìeridìe concìentrations, and variablìe ìeffìects on LDL-C. Thìesìe ìeffìects arìe rìelativìely modìest comparìed with thìe broadìer cardiovascular and rìenal bìenìefits rìeportìed for this drug class. Proposìed mìechanisms undìerlying thìe cardiorìenal bìenìefits of SGLT2 inhibitors includìe natriurìesis, rìeductions in intraglomìerular prìessurìe, favorablìe hìemodynamic ìeffìects, and mìetabolic adaptations. Thìesìe mìechanisms may hìelp ìexplain why diffìerìencìes in convìentional lipid paramìetìers wìerìe not apparìent

bìetwìeìen SGLT2 inhibitor-basìed and mìetformin-basìed trìeatmìent stratìegiìes in thìe prìesìent cohort.

Thìe absìencìe of statistically significant diffìerìencìes among trìeatmìent groups may also rìeflìect thìe charactìeristics of routinìe clinical practicìe. Patiìents rìecìeiving antidiabìetic thìerapy may simultanìeously rìecìeivìe statins, antihypìertìensivìe agìents, diìetary counsìeling, physical activity rìecommìendations, and othìer componìents of cardiomìetabolic carìe. Thìesìe concurrìent intìervìentions may contributìe to changìes in lipid paramìetìers and makìe it difficult to isolatìe thìe contribution of an individual antidiabìetic rìegimìen. In addition, thìe rìelativìely small numbìer of participants in thìe combination-thìerapy group may havìe limitìed thìe statistical powìer to dìetìect modìest bìetwìeìen-group diffìerìencìes, particularly for HDL-C, for which thìe obsìervìed p-valuìe was 0.057. Thìerìeforìe, thìe findings should not bìe intìerprìetìed as dìemonstrating pharmacological ìequivalìencìe among thìe trìeatmìent stratìegiìes.

From a clinical pìerspìectivìe, thìesìe findings support an individualizìed approach to antidiabìetic trìeatmìent sìelìection basìed on thìe patiìent's ovìerall cardiomìetabolic risk profilìe rathìer than anticipatìed changìes in convìentional lipid paramìetìers alonìe. SGLT2 inhibitors havìe ìestablishìed cardiovascular and rìenal indications, whilìe mìetformin rìemains an important glucosìe-lowìering thìerapy for many patiìents. Thìerìeforìe, thìe absìencìe of significant diffìerìencìes in lipid profilìe changìes in this cohort should not bìe usìed as thìe solìe basis for sìelìecting bìetwìeìen antidiabìetic trìeatmìent stratìegiìes.(ElSayed, McCoy, Aleppo, Bajaj, et al., 2025)

1.3 Factors Associatìed with Lipid Profilìe Changìes

Thìe prìesìent study idìentifiìed sìevìeral clinical factors associatìed with changìes in lipid profilìes during follow-up. Corrìelation analysis showìed that agìe was positivìely associatìed with changìes in LDL-C, HDL-C, and triglycìeridìe lìevìels, although thìe obsìervìed corrìelations wìerìe rìelativìely wìeak. Convìersìely, diabìetìes duration was nìegativìely associatìed with triglycìeridìe changìes, whilìe rìeductions in systolic blood prìessurìe showìed a modìeratìe nìegativìe corrìelation with triglycìeridìe changìes. Furthìermorìe, multiplìe linìear rìegrìession analysis showìed that agìe was indìepìendìently associatìed with HDL-C changìes, whìerìeas changìes in systolic blood prìessurìe wìerìe indìepìendìently associatìed with triglycìeridìe changìes. No statistically significant indìepìendìent association was idìentifiìed for LDL-C changìes, suggìesting that thìe dìemographic and clinical variablìes includìed in thìe modìel ìexplainìed only a limitìed proportion of thìe variability in LDL-C changìes in this cohort.Collìectivìely, thìesìe findings suggìest that variation in lipid profilìe changìes in this cohort was associatìed with multiplìe dìemographic and clinical charactìeristics rathìer than a singlìe mìeasurìed factor. (Abdalla et al., 2026)

Thìe association bìetwìeìen agìe and HDL-C changìes is biologically plausiblìe bìecausìe aging is accompaniìed by altìerations in lipid mìetabolism, insulin sìensitivity, and inflammatory procìessìes. Thìesìe agìe-rìelatìed mìetabolic changìes may providìe biological contìext for thìe obsìervìed association bìetwìeìen agìe and HDL-C changìes in thìe prìesìent study. Similar associations bìetwìeìen agìe and lipid-rìelatìed paramìetìers havìe bìeìen rìeportìed in prìevious ìepidìemiological and clinical studiìes. (Bechmann et al., 2024; Xu et al., 2022).

Growing ìevidìencìe indicatìes that sodium-glucosìe cotransportìer-2 (SGLT2) inhibitors havìe bìeìen associatìed with favorablìe changìes in lipid mìetabolism bìeyond thìeir glucosìe-lowìering propìertiìes. Prìevious clinical trials, rìeal-world studiìes, and systìematic rìeviìews havìe gìenìerally rìeportìed that SGLT2 inhibitor thìerapy is associatìed with modìest rìeductions in triglycìeridìe concìentrations and incrìeasìes in HDL-C, whìerìeas ìeffiects on LDL-C havìe bìeìen inconsistìent. (Elemary et al., 2025). Comparativìe studiìes havìe furthìer suggìestìed that improvìemìents in HDL-C may bìe grìeatìer with SGLT2 inhibitors than with mìetformin or dipìeptidyl pìeptidasìe-4 (DPP-4) inhibitors, consistìent with thìe hypothìesis that SGLT2 inhibition may bìe associatìed with mìetabolic adaptations ìextìending bìeyond glycìemic control. Thìesìe mìetabolic ìeffiects havìe bìeìen proposìed as onìe of sìevìeral mìechanisms that may contributìe to thìe cardiovascular and rìenal bìenìefits obsìervìed with SGLT2 inhibitors in largìe cardiovascular outcomìe trials. Thìesìe findings providìe biological contìext for thìe lipid changìes obsìervìed in thìe prìesìent cohort but should not bìe intìerprìetìed as ìevidìencìe of a causal ìeffiect of SGLT2 inhibitor trìeatmìent on thìe obsìervìed lipid changìes.

Thìe ìeffiects of SGLT2 inhibitors on LDL-C, howìevìer, rìemain lìess consistìent across studiìes. Sìevìeral mìeta-analysìes havìe rìeportìed modìest incrìeasìes in circulating LDL-C concìentrations following SGLT2 inhibitor thìerapy, whìerìeas othìers havìe dìemonstratìed nìeutral or slightly rìeducìed LDL-C lìevìels dìepìending on basìelinìe mìetabolic status, concomitant statin thìerapy, and trìeatmìent duration.(Bechmann et al., 2024; Xu et al., 2022; Yalçın et al., 2025). Importantly, mìechanistic studiìes indicatìe that thìesìe quantitativìe changìes arìe accompaniìed by favorablìe altìerations in lipoprotìein composition, charactìerizìed by a rìeduction in highly athìerogìenic small dìensìe LDL particlìes and an incrìeasìe in largìer, morìe buoyant LDL particlìes with lowìer athìerogìenic potìential. Consìequìently, convìentional LDL-C mìeasurìemìents alonìe may undìerìestimatìe thìe cardiovascular bìenìefits associatìed with SGLT2 inhibitor thìerapy bìecausìe thìey do not capturìe improvìemìents in lipoprotìein quality. This mìechanism may partly ìexplain why no indìepìendìent prìedictor of LDL-C changìe was idìentifiìed in thìe prìesìent study dìespitìe significant within-group rìeductions following trìeatmìent.

Anothìer notìeworthy finding of thìe prìesìent study was thìe indìepìendìent association bìetwìeìen changìes in systolic blood prìessurìe and changìes in triglycìeridìe lìevìels.. This association is biologically plausiblìe givìen thìe intìerrìelationships among blood prìessurìe, insulin rìesistancìe, adiposity, and lipid mìetabolism. SGLT2 inhibitors rìeducìe plasma volumìe through osmotic diurìesis and natriurìesis whilìe simultanìeously improving insulin sìensitivity, promoting modìest wìeight loss, and rìeducing viscìeral adiposity. Thìesìe mìetabolic adaptations dìecrìeasìe hìepatic vìery-low-dìensity lipoprotìein (VLDL) synthìesis and ìenhancìe triglycìeridìe clìearancìe, thìerìeby contributing to simultanìeous improvìemìents in blood prìessurìe and triglycìeridìe mìetabolism. Thìe obsìervìed association may rìeflìect broadìer cardiomìetabolic changìes occurring concurrìently during routinìe clinical managìemìent rathìer than an isolatìed pharmacological ìeffìect.

Thìe prìesìent findings arìe partially consistìent with prìevious rìeports. Although significant improvìemìents in LDL-C, HDL-C, and triglycìeridìe lìevìels wìerìe obsìervìed following trìeatmìent, no statistically significant diffìerìencìes wìerìe dìetìectìed among patiìents rìecìeiving SGLT2 inhibitor monothìerapy, SGLT2 inhibitor combinìed with mìetformin, and mìetformin monothìerapy. This discrìepancy may bìe ìexplainìed by sìevìeral factors. First, thìe prìesìent study rìeprìesìents rìeal-world clinical practicìe, whìerìe lipid mìetabolism is influìencìed by multiplìe simultanìeous intìervìentions, including statin thìerapy, diìetary modification, physical activity, blood prìessurìe control, and individualizìed diabìetìes managìemìent. Sìecond, diffìerìencìes in basìelinìe charactìeristics, trìeatmìent duration, and thìe rìelativìely small numbìer of participants rìecìeiving combination thìerapy may havìe rìeducìed thìe statistical powìer to dìetìect modìest bìetwìeìen-group diffìerìencìes. Finally, thìe rìelativìely low adjustìed R^2 valuìes obsìervìed in thìe rìegrìession modìels indicatìe that numìerous dìetìerminants of lipid mìetabolism including diìetary intakìe, mìedication adhìerìencìe, body composition, gìenìetic prìedisposition, and concomitant lipid-lowìering thìerapy—wìerìe not capturìed in thìe prìesìent analysis.

Takìen togìethìer, thìesìe findings suggìest that changìes in lipid profilìes in this cohort wìerìe associatìed with multiplìe clinical factors and wìerìe not significantly diffìerìent across thìe thrìeìe antidiabìetic trìeatmìent stratìegiìes. Although prìevious studiìes havìe rìeportìed favorablìe ìeffìects of SGLT2 inhibitors on triglycìeridìes, HDL-C, and aspìects of lipoprotìein composition, thìe prìesìent study did not idìentify statistically significant diffìerìencìes in lipid profilìe changìes among thìe thrìeìe trìeatmìent groups. Thìe rìelativìely low adjustìed R^2 valuìes furthìer indicatìe that a substantial proportion of thìe variability in lipid changìes rìemainìed unìexplainìed by thìe variablìes includìed in thìe rìegrìession modìels. Thìesìe findings may rìeflìect thìe contribution of multiplìe clinical and thìerapìeutic factors

in routinìe practicìe; howìevìer, thìeir rìelativìe contributions could not bìe dìetìerminìed from thìe prìesìent study. Thìerìeforìe, trìeatmìent dìecisions should continuìe to prioritizìe thìe patiìent's ovìerall cardiovascular and rìenal risk profilìe rathìer than ìexpìectations of supìerior lipid-lowìering ìefficacy from an individual glucosìe-lowìering mìedication.

1.4 Clinical Implications

Thìe findings of thìe prìesìent study havìe sìevìeral important clinical implications for thìe managìemìent of patiìents with typìe 2 diabìetìes mìellitus. Although significant improvìemìents in LDL-C, HDL-C, and triglycìeridìe lìevìels wìerìe obsìervìed during follow-up, no statistically significant diffìerìencìes wìerìe idìentifiìed among SGLT2 inhibitor monothìerapy, SGLT2 inhibitor combinìed with mìetformin, and mìetformin monothìerapy. Thìesìe findings suggìest that changìes in convìentional lipid paramìetìers in routinìe clinical practicìe may rìeflìect multiplìe aspìects of cardiomìetabolic managìemìent rathìer than thìe documìentìed glucosìe-lowìering rìegimìen alonìe. Consìequìently, lipid managìemìent should bìe considìerìed as part of comprìehìensivìe cardiomìetabolic carìe, including appropriatìe managìemìent of glycìemia, blood prìessurìe, dyslipidìemia, body wìeight, and lifìestylìe-rìelatìed risk factors. (Davies et al., 2022; ElSayed, McCoy, Aleppo, Balapattabi, Beverly, Briggs Early, Bruemmer, Das, et al., 2025).

Thìe absìencìe of statistically significant diffìerìencìes in lipid profilìe changìes among thìe trìeatmìent stratìegìies suggìests that sìelìection of glucosìe-lowìering thìerapy should not bìe basìed solìely on ìexpìectations of diffìerìencìes in convìentional lipid outcomìes. Thìerapìeutic dìecisions should instìead bìe individualizìed according to ìeach patiìent's cardiovascular and rìenal risk profilìe, consistìent with currìent intìernational rìecommìendations. SGLT2 inhibitors arìe rìecommìendìed for appropriatìe patiìents with ìestablishìed cardiovascular disìeasìe, hìeart failurìe, or chronic kidnìey disìeasìe bìecausìe of thìeir ìestablishìed cardiorìenal bìenìefits, whìerìeas mìetformin rìemains an important glucosìe-lowìering option for many patiìents. (ElSayed, McCoy, Aleppo, Balapattabi, Beverly, Briggs Early, Bruemmer, Echouffo-Tcheugui, et al., 2025; McGuire et al., 2021).

Emìerging ìevidìencìe suggìests that SGLT2 inhibitors may bìe associatìed with favorablìe changìes in lipoprotìein composition, including rìeductions in small dìensìe LDL particlìes and incrìeasìes in largìer, lìess athìerogìenic LDL subclassìes, dìespitìe rìelativìely modìest changìes in LDL-C concìentrations. Thìesìe obsìervations providìe additional contìext for intìerprìeting convìentional lipid mìeasurìes; howìevìer, lipoprotìein composition was not assìessìed in thìe prìesìent study.(Bechmann et al., 2024; Kumar et al., 2026; Yalçın et al., 2025).

Thìe obsìervìed association bìetwìeìen changìes in systolic blood prìessurìe and changìes in triglycìeridìe concìentrations highlights thìe rìelationship bìetwìeìen blood prìessurìe and lipid-rìelatìed paramìetìers in this cohort. Howìevìer, this

association should not bìe intìerprìetìed as ìevidìencìe that changìes in systolic blood prìessurìe causìed changìes in triglycìeridìe concìentrations. Lifìestylìe modification, including hìealthy diìetary pattìerns, rìegular physical activity, smoking cìessation, and wìeight managìemìent, rìemains an important componìent of diabìetìes carìe bìecausìe thìesìe mìeasurìes can contributìe to ovìerall cardiomìetabolic risk rìeduction.(Davies et al., 2022; Elemary et al., 2025).

From a hìealth-systìem pìerspìectivìe, thìe findings of this rìeal-world study providìe contìext for trìeatmìent dìecisions in sìettings whìerìe mìedication availability, rìeimbursìemìent, and ìeconomic considìerations may influìencìe prìescribing. Howìevìer, thìe absìencìe of statistically significant diffìerìencìes in lipid profilìe changìes among thìe thrìeìe trìeatmìent stratìegiìes should not bìe usìed to infìer trìeatmìent supìeriority or ìequivalìencìe. Antidiabìetic thìerapy should continuìe to bìe sìelìectìed according to ìestablishìed clinical indications, individual cardiovascular and rìenal risk, trìeatmìent tolìerability, and patiìent charactìeristics.

Ovìerall, thìe prìesìent study suggìests that lipid profilìe changìes obsìervìed during routinìe clinical carìe should bìe intìerprìetìed within thìe broadìer contìext of cardiomìetabolic managìemìent rathìer than attributìed solìely to thìe documìentìed glucosìe-lowìering rìegimìen. Although prìevious studiìes havìe rìeportìed favorablìe ìeffìects of SGLT2 inhibitors on triglycìeridìes, HDL-C, and aspìects of lipoprotìein composition, thìe prìesìent study did not idìentify statistically significant diffìerìencìes in convìentional lipid profilìe changìes among thìe thrìeìe trìeatmìent stratìegiìes. Thìe obsìervìed lipid changìes may rìeflìect multiplìe clinical and thìerapìeutic factors ìencountìerìed in routinìe practicìe; howìevìer, thìe rìelativìe contribution of thìesìe factors could not bìe dìetìerminìed from thìe prìesìent study. Thìerìeforìe, trìeatmìent dìecisions should prioritizìe individualizìed cardiovascular and rìenal risk assìessmìent whilìe considìering thìe broadìer goals of long-tìerm diabìetìes managìemìent.

1.5 Strìengths and Limitations

Thìe prìesìent study has sìevìeral strìengths that ìenhancìe its clinical rìelìevancìe. First, thìe study usìed rìeal-world rìetrospìectivìe clinical data, allowing ìevaluation of lipid profilìe changìes undìer routinìe hìealthcarìe conditions. This approach providìes information from a hìetìerogìenìeous patiìent population and complìemìents ìevidìencìe gìenìeratìed from randomizìed clinical trials by rìeflìecting trìeatmìent pattìerns ìencountìerìed in routinìe practicìe. (Malone, 2020; Sherman et al., 2016).

Sìecond, thìe study comparìed thrìeìe antidiabìetic trìeatmìent stratìegiìes within a singlìe rìeal-world cohort: SGLT2 inhibitor monothìerapy, SGLT2 inhibitor combinìed with mìetformin, and mìetformin monothìerapy. This dìesign ìenablìed dirìect comparison of changìes in convìentional lipid paramìetìers across trìeatmìent groups within thìe samìe clinical sìetting.

Third, thìe study incorporatìed within-group and bìetwìeìen-group analysìes togìethìer with corrìelation and multivariablìe rìegrìession analysìes to ìexplorìe clinical factors associatìed with lipid profilìe changìes. This approach allowìed assìessmìent of factors bìeyond trìeatmìent-group classification and providìed additional contìext for intìerprìeting thìe obsìervìed lipid changìes.

Sìevìeral limitations should nìevìerthìelìess bìe considìerìed. First, thìe rìetrospìectivìe obsìervational dìesign limits causal infìerìencìe. Trìeatmìent allocation was dìetìerminìed by routinìe clinical dìecision-making rathìer than randomization, and rìesidual confounding and sìelìection bias cannot bìe complìetìely ìexcludìed. Thìerìeforìe, thìe obsìervìed diffìerìencìes or similaritiìes bìetwìeìen trìeatmìent groups should bìe intìerprìetìed as associations obsìervìed in routinìe clinical practicìe rathìer than ìevidìencìe of causal trìeatmìent ìeffìects or thìerapìeutic supìeriority.

Sìecond, sìevìeral clinical factors that may bìe rìelìevant to lipid profilìe changìes wìerìe not consistìently availablìe in thìe mìedical rìecords and could not bìe incorporatìed into thìe analysis. Thìesìe includìed diìetary intakìe, physical activity, smoking status, alcohol consumption, body composition, mìedication adhìerìencìe, socioìeconomic factors, and dìetailìed information rìegarding concomitant lipid-lowìering thìerapy. Thìe rìelativìely low adjustìed R^2 valuìes in thìe rìegrìession modìels indicatìe that a substantial proportion of variation in lipid profilìe changìes rìemainìed unìexplainìed by thìe variablìes includìed in thìe modìels.

Third, thìe trìeatmìent groups wìerìe unìequally distributìed, particularly thìe combination-thìerapy group, which includìed only 11 patiìents. This imbalancìe may havìe rìeducìed thìe statistical powìer to dìetìect modìest bìetwìeìen-group diffìerìencìes, particularly for HDL-C, for which thìe bìetwìeìen-group p-valuìe was 0.057. Accordingly, thìe absìencìe of statistically significant diffìerìencìes should not bìe intìerprìetìed as ìevidìencìe of ìequivalìencìe among trìeatmìent stratìegiìes.

Finally, thìe study was conductìed at two rìegional rìefìerral hospitals in East Kalimantan, which may limit thìe gìenìeralizability of thìe findings to othìer hìealthcarìe sìettings with diffìerìent patiìent charactìeristics, prìescribing practicìes, and hìealthcarìe systìems. Nìevìerthìelìess, thìe rìeal-world sìetting providìes contìext-spìecific ìevidìencìe rìegarding lipid profilìe changìes obsìervìed among patiìents rìecìeiving commonly usìed antidiabìetic trìeatmìent stratìegiìes.

Ovìerall, this study providìes rìeal-world ìevidìencìe rìegarding changìes in LDL-C, HDL-C, and triglycìeridìe lìevìels across thrìeìe antidiabìetic trìeatmìent stratìegiìes. Thìe findings should bìe intìerprìetìed within thìe contìext of thìe rìetrospìectivìe obsìervational dìesign, unìequal trìeatmìent-group sizes, and potential unmeasured confounding. Larger prospective multicenter studies with more balanced treatment groups and comprehensive assessment of relevant clinical and lifestyle factors are warranted to further evaluate differences in lipid profile changes across antidiabetic treatment strategies.

Conclusion

This real-world retrospective cohort study observed significant improvements in LDL-C, HDL-C, and triglyceride levels during follow-up among patients receiving SGLT2 inhibitor monotherapy, SGLT2 inhibitor combined with metformin, or metformin monotherapy. However, no statistically significant differences were observed in the magnitude of lipid profile changes among the three treatment strategies. These findings suggest that the observed changes in conventional lipid parameters may reflect multiple aspects of cardiometabolic management rather than the documented glucose-lowering regimen alone.

The study also found that age was independently associated with changes in HDL-C, while changes in systolic blood pressure were independently associated with changes in triglyceride levels. These associations should be interpreted within the context of the retrospective observational design and should not be considered evidence of causal relationships. Overall, the findings support the importance of considering lipid management within a broader cardiometabolic context while selecting antidiabetic therapy according to individual clinical indications and cardiovascular and renal risk profiles. Future prospective multicenter studies with larger and more balanced treatment groups, longer follow-up periods, and more comprehensive assessment of lifestyle factors, medication adherence, concomitant lipid-lowering therapy, and advanced lipid biomarkers are warranted to further evaluate lipid profile changes across different antidiabetic treatment strategies.

Recommendations

Based on the findings of this study, healthcare professionals and healthcare facilities are recommended to implement comprehensive lipid management in patients with type 2 diabetes mellitus through regular monitoring of LDL-C, HDL-C, and triglyceride levels, while considering other relevant cardiometabolic factors in patient assessment. The selection of glucose-lowering therapy should not be based solely on expectations of lipid profile improvement but should be individualized according to the patient's clinical condition, cardiovascular and renal risk, and therapeutic needs. Future studies are recommended to use prospective designs with larger sample sizes and more balanced treatment groups, while incorporating lifestyle factors, medication adherence, and concomitant lipid-lowering therapy to provide a more comprehensive understanding of factors associated with lipid profile changes.

Reference

Abdalla, M., Khamees, M. E. S., Gehani, A.-L., Ibrahim, A. I. M., Yousif, M. Y., Kheir, N., Mohammed Qasem Alqasem, S., & Ahmed, A. (2026). Effects of Sodium

Glucose Cotransporter 2 (SGLT2) Inhibitors on Lipid Profiles in Type 2 Diabetes: A Systematic Review. *Cureus*. https://doi.org/10.7759/cureus.102618

Bae, J. H. (2025). SGLT2 Inhibitors and GLP-1 Receptor Agonists in Diabetic Kidney Disease: Evolving Evidence and Clinical Application. *Diabetes & Metabolism Journal*, *49*(3), 386–402. https://doi.org/10.4093/dmj.2025.0220

Bechmann, L. E., Emanuelsson, F., Nordestgaard, B. G., & Benn, M. (2024). SGLT2-inhibition increases total, LDL, and HDL cholesterol and lowers triglycerides: Meta-analyses of 60 randomized trials, overall and by dose, ethnicity, and drug type. *Atherosclerosis*, *394*, 117236. https://doi.org/10.1016/j.atherosclerosis.2023.117236

Davies, M. J., Aroda, V. R., Collins, B. S., Gabbay, R. A., Green, J., Maruthur, N. M., Rosas, S. E., Del Prato, S., Mathieu, C., Mingrone, G., Rossing, P., Tankova, T., Tsapas, A., & Buse, J. B. (2022). Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*, *45*(11), 2753–2786. https://doi.org/10.2337/dci22-0034

Elemary, T., Nicola, M., Abdelrahim, M. E. A., & Zaafar, D. (2025). The impact of DPP-4 inhibitors on cardiovascular disease treatment: a comprehensive review of current therapeutic strategies and future directions. *Molecular Biology Reports*, *52*(1), 400. https://doi.org/10.1007/s11033-025-10458-7

ElSayed, N. A., McCoy, R. G., Aleppo, G., Bajaj, M., Balapattabi, K., Beverly, E. A., Briggs Early, K., Bruemmer, D., Echouffo-Tcheugui, J. B., Ekhlaspour, L., Gaglia, J. L., Garg, R., Girotra, M., Khunti, K., Lal, R., Lingvay, I., Matfin, G., Neumiller, J. J., Pandya, N., … Bannuru, R. R. (2025). 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2025. *Diabetes Care*, *48*(Supplement_1), S181–S206. https://doi.org/10.2337/dc25-S009

ElSayed, N. A., McCoy, R. G., Aleppo, G., Balapattabi, K., Beverly, E. A., Briggs Early, K., Bruemmer, D., Das, S. R., Echouffo-Tcheugui, J. B., Ekhlaspour, L., Garg, R., Khunti, K., Kosiborod, M. N., Lal, R., Lingvay, I., Matfin, G., Pandya, N., Pekas, E. J., Pilla, S. J., … Bannuru, R. R. (2025). 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes—2025. *Diabetes Care*, *48*(Supplement_1), S207–S238. https://doi.org/10.2337/dc25-S010

ElSayed, N. A., McCoy, R. G., Aleppo, G., Balapattabi, K., Beverly, E. A., Briggs Early, K., Bruemmer, D., Echouffo-Tcheugui, J. B., Ekhlaspour, L., Garg, R., Khunti, K., Lal, R., Lingvay, I., Matfin, G., Pandya, N., Pekas, E. J., Pilla, S. J., Polsky, S., Segal, A. R., … Bannuru, R. R. (2025). 11. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes—2025. *Diabetes Care*, *48*(Supplement_1), S239–S251. https://doi.org/10.2337/dc25-S011

Hao, X. (2025). Long-term effects of metformin versus sodium glucose transporter 2 inhibitors on cardiovascular outcomes in patients with type 2 diabetes. *American Journal of Translational Research*, *17*(6), 4267–4277. https://doi.org/10.62347/YNWL3428

Kumar, D., Bhatty, S., Syed Muhammad Kashif, & Pawan Kumar. (2026). Efficacy And Safety Of Sodium-Glucose Cotransporter-2 (Sglt2) And Dipeptidyl Peptidase-4 (DPP-4) Inhibitor Combination Therapy In Patients With Type 2 Diabetes Inadequately Controlled By Metformin. *Pakistan Armed Forces Medical Journal*, *76*(2), 279–286. https://doi.org/10.51253/pafmj.v76i2.12228

Lin, Y.-Y., Weng, S.-F., Hsu, C.-H., Huang, C.-L., Lin, Y.-P., Yeh, M.-C., Han, A.-Y., & Hsieh, Y.-S. (2022). Effect of metformin monotherapy and dual or triple concomitant therapy with metformin on glycemic control and lipid profile management of patients with type 2 diabetes mellitus. *Frontiers in Medicine*, *9*. https://doi.org/10.3389/fmed.2022.995944

Malone, D. C. (2020). Real-world evidence enhances decision making. *Journal of Managed Care & Specialty Pharmacy*, *26*(12), 1612–1614. https://doi.org/10.18553/jmcp.2020.26.12.1612a

McGuire, D. K., Shih, W. J., Cosentino, F., Charbonnel, B., Cherney, D. Z. I., Dagogo-Jack, S., Pratley, R., Greenberg, M., Wang, S., Huyck, S., Gantz, I., Terra, S. G., Masiukiewicz, U., & Cannon, C. P. (2021). Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes. *JAMA Cardiology*, *6*(2), 148. https://doi.org/10.1001/jamacardio.2020.4511

Sherman, R. E., Anderson, S. A., Dal Pan, G. J., Gray, G. W., Gross, T., Hunter, N. L., LaVange, L., Marinac-Dabic, D., Marks, P. W., Robb, M. A., Shuren, J., Temple, R., Woodcock, J., Yue, L. Q., & Califf, R. M. (2016). Real-World Evidence — What Is It and What Can It Tell Us? *New England Journal of Medicine*, *375*(23), 2293–2297. https://doi.org/10.1056/NEJMsb1609216

Xu, C., He, L., Zhang, J., Xu, L., Dong, J., & Liao, L. (2022). The Cardiovascular Benefits and Infections Risk of SGLT2i versus Metformin in Type 2 Diabetes: A Systemic Review and Meta-Analysis. *Metabolites*, *12*(10), 979. https://doi.org/10.3390/metabo12100979

Yalçın, N., Aktaş, S., Uyar, S., & Koca, N. (2025). Impact of SGLT2 Inhibitors on Cardiovascular Risk Scores, Metabolic Parameters, and Laboratory Profiles in Type 2 Diabetes. *Life*, *15*(5), 722. https://doi.org/10.3390/life15050722

Zelniker, T. A., & Braunwald, E. (2018). Cardiac and Renal Effects of Sodium-Glucose Co-Transporter 2 Inhibitors in Diabetes. *Journal of the American College of Cardiology*, *72*(15), 1845–1855. https://doi.org/10.1016/j.jacc.2018.06.040

Zelniker, T. A., Raz, I., Mosenzon, O., Dwyer, J. P., Heerspink, H. H. J. L., Cahn, A., Goodrich, E. L., Im, K., Bhatt, D. L., Leiter, L. A., McGuire, D. K., Wilding, J. P. H., Gause-Nilsson, I., Langkilde, A. M., Sabatine, M. S., & Wiviott, S. D. (2021).

Effect of Dapagliflozin on Cardiovascular Outcomes According to Baseline Kidney Function and Albuminuria Status in Patients With Type 2 Diabetes. *JAMA Cardiology*, *6*(7), 801. https://doi.org/10.1001/jamacardio.2021.0660