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Dapagliflozin Alone or Combined with Semaglutide: Cardiovascular and Renal Outcomes among Patients with Type 2 Diabetes Mellitus in a 6-Month Real-World Retrospective Cohort Study in Saudi Arabia

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Abstract

Introduction. Type 2 diabetes mellitus (T2DM) is a growing global health concern linked to increased cardiovascular and renal complications. Two emerging therapeutic classes, sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon like peptide-1 receptor agonists (GLP-1 RAs), have shown independent cardiometabolic benefits. However, limited real-world data exist on the comparative impact of combining these therapies versus using SGLT2i alone.

Objective. To compare the cardiovascular and renal outcomes of dapagliflozin monotherapy versus combination therapy with once-weekly injectable semaglutide among patients with type 2 diabetes mellitus (T2DM).

Methodology. In this retrospective cohort study, 539 adult patients with confirmed type 2 diabetes mellitus (T2DM; baseline HbA1c ≥6.5%) treated at King Abdulaziz Hospital, Al-Ahsa, were followed over six months. Patients received either dapagliflozin alone or in combination with semaglutide. Generalized Estimating Equations (GEE) were used to assess changes in glycemic control, cardiovascular events, lipid profile, and renal function, adjusting for time and sex.

Results. Both groups showed significant metabolic improvements over six months. Dapagliflozin monotherapy was associated with greater HbA1c reduction. Combination therapy was associated with higher HDL levels, improved eGFR, and a lower relative risk of heart failure (RR = 0.43, p = 0.04); the reduction in myocardial infarction risk (RR = 0.61, p = 0.13) did not reach statistical significance. No significant difference was observed in stroke risk. Most cardiovascular and renal markers improved modestly.

Conclusion. Combination therapy was associated with favorable renal outcomes and a reduction in heart failure risk, despite inferior glycemic control and a non-significant trend toward reduced myocardial infarction risk. These findings suggest potential complementary effects of SGLT2i and GLP-1 RA treatment in high-risk patients. However, due to the retrospective, non-randomized design, causal relationships cannot be inferred, and residual confounding may exist. Prospective trials are warranted to confirm these associations and guide treatment optimization.

Key words: dapagliflozin, semaglutide, type 2 diabetes, cardiovascular outcomes, renal function, real-world study

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major global health concern, with over 460 million adults affected worldwide, a number projected to rise to 783 million by 2045.[1,2] The situation is particularly urgent in Saudi Arabia, where the prevalence of T2DM ranges from 16% to nearly 40% among adults,[3,4] far exceeding global rates. The debilitating complications of T2DM, especially cardiovascular (CV) and renal diseases, are the leading causes of morbidity and mortality in this population,[5,6] emphasizing the need for more effective and individualized treatment approaches. To address these risks, current clinical guidelines highlight the importance of optimizing glycemic control, blood pressure, and lipid levels, aiming to reduce the burden of both macrovascular and microvascular complications among patients with T2DM.[5,7,8] In line with these guidelines, the therapeutic landscape has evolved significantly in recent years. For example, two major classes of antihyperglycemic agents−sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), have demonstrated substantial metabolic benefits alongside significant cardiovascular and renal protective effects. Dapagliflozin, an SGLT2 inhibitor, improves glycemic control by reducing renal glucose reabsorption and has shown substantial benefit in lowering systolic blood pressure, as well as enhancing CV and renal outcomes in high-risk populations.[9-11] Similarly, semaglutide, a once-weekly injectable GLP-1 RA, not only helps to control blood glucose and reduce body weight but has also been proven in large clinical trials such as SUSTAIN-6 to deliver cardiovascular safety and efficacy.[12-14] While both agents are recommended for individuals at high CV or renal risk, it is important to note that real-world data on their comparative effectiveness, particularly when used in combination versus monotherapy, are limited.

Preliminary evidence suggests that combining GLP-1 RAs with SGLT2 inhibitors may provide additive or synergistic benefits across metabolic, cardiovascular, and renal endpoints.[15-17] Despite these promising indications, it remains unclear whether these effects persist in real-world practice, outside tightly controlled clinical trial settings, and whether any observed benefits hold after accounting for differences in glycemic burden and treatment indications between populations.

Therefore, this retrospective cohort study was designed to evaluate the comparative cardiometabolic effects of dapagliflozin alone versus in combination with once-weekly injectable semaglutide in patients with T2DM. We hypothesized that combination therapy would be associated with greater cardiovascular and renal benefits compared to dapagliflozin monotherapy, even if glycemic control was not superior. Ultimately, by generating real-world evidence on the outcomes of these treatment strategies, this study aims to support more personalized and effective therapeutic decision-making for patients at elevated cardiometabolic risk. The primary objective of this study was to compare cardiovascular and renal outcomes between dapagliflozin monotherapy and combination therapy with once-weekly injectable semaglutide. Secondary objectives included assessing differences in glycemic control (HbA1c), lipid profiles (HDL, LDL, total cholesterol, triglycerides), body weight (BMI), blood pressure (SBP, DBP), and inflammatory/cardiac biomarkers (hsCRP, BNP) between the two treatment groups over a six-month follow-up period.

METHODOLOGY

This retrospective cohort study, conducted at King Abdulaziz Hospital in AlAhsa, Saudi Arabia, evaluated the effects of dapagliflozin alone versus in combination with once-weekly injectable semaglutide on metabolic and CV outcomes in adults aged 18 to 75 years, with established T2DM, who initiated treatment with either dapagliflozin monotherapy or the combination regimen. Criteria for exclusion included patients younger than 18 or older than 75 years, those with type 1 diabetes mellitus or other forms of diabetes, stage D heart failure, a history of acute or chronic pancreatitis, liver cirrhosis, end-stage renal disease (ESRD), or recent CV events. Patients were selected using probability sampling and had regular follow-ups between January 1, 2020, and February 1, 2024. Type 2 diabetes mellitus was diagnosed according to the American Diabetes Association (ADA) criteria: fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), 2-hour plasma glucose ≥11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test (OGTT), HbA1c ≥6.5% (48 mmol/mol), or a random plasma glucose ≥11.1 mmol/L (200 mg/dL) in a patient with classic symptoms of hyperglycemia. During revision, T2DM status was re-derived directly from baseline HbA1c (≥6.5%, per the ADA criteria above) to ensure consistency with the stated eligibility criteria; this excluded 51 patients with baseline HbA1c <6.5% and a further 72 patients with missing or non-numeric baseline HbA1c, yielding a final analytic cohort of 539 patients (353 dapagliflozin monotherapy, 186 combination therapy). Dapagliflozin was prescribed at a dose of 10 mg orally once daily. Once-weekly injectable semaglutide was initiated at 0.25 mg subcutaneously once weekly for the first four weeks, followed by escalation to 0.5 mg once weekly; further up-titration to 1.0 mg once weekly was at the treating physician's discretion based on glycaemic response and tolerability.

Data were collected at two time points—treatment initiation and after six months of therapy—and included demographic and clinical characteristics (age, sex, diabetes diagnosis, history of cardiovascular disease such as ischemic heart disease, HF, and stroke), metabolic parameters (HbA1c, body mass index [BMI], total cholesterol [TC], low-density lipoprotein cholesterol [LDL], HDL, triglycerides [TG], eGFR, and urine albumin-creatinine ratio [ACR]), cardiovascular parameters (systolic and diastolic blood pressure [SBP and DBP], myocardial infarction [MI], HF, and stroke incidence), and biomarkers (B-type natriuretic peptide [BNP] and high-sensitivity C-reactive protein

[hsCRP]). Laboratory analyses were performed using validated methods: HbA1c by high-performance liquid chromatography (HPLC); lipid panel (total cholesterol, LDL, HDL, and triglycerides) by enzymatic colorimetric assay; serum creatinine for eGFR calculation (CKD-EPI equation) by the Jaffe method; urine ACR by immunoturbidimetry; BNP by chemiluminescent immunoassay; and hsCRP by particle-enhanced immunoturbidimetry. Patients with incomplete records for key exposure variables (treatment assignment, baseline HbA1c) were excluded from the analytic cohort; however, some outcome-specific variables remained missing for individual patients and were analyzed using available-case denominators, as reflected in the varying denominators reported in the Comparative Incidence table. Clinically implausible laboratory values were identified during data cleaning and excluded prior to analysis according to prespecified physiologically plausible ranges for each parameter.

Statistical analyses were conducted using Generalized Estimating Equations (GEE) to account for repeated measures over time. Two models were developed: Time-Adjusted Models, which assessed treatment effects while adjusting for time, and Fully Adjusted Models, which additionally accounted for sex. Analyses used appropriate statistical distributions, including the Inverse Gaussian distribution for skewed data and the Binomial distribution with a log link function for binary outcomes. Dapagliflozin monotherapy was used as the reference group, with pre-treatment baseline and female sex as reference categories. Results were reported as Relative Risk (RR) with 95% Confidence Intervals (CI) for categorical outcomes and Beta coefficients with 95% CI for continuous outcomes. A *p*-value of less than 0.05 was considered statistically significant. All data analyses were conducted using the Statistical Analysis System (SAS) software.

To mitigate confounding, multivariable GEE models adjusted for time and sex. Given the retrospective, non-randomized design, residual confounding and confounding by indication cannot be excluded; baseline imbalances between treatment groups in BMI, HDL, eGFR, ACR, and HbA1c (Table 1A) are discussed as a limitation. During data audit, the original stroke, myocardial infarction, and heart failure indicators were also found to reflect whether a clinical-notes field had been populated rather than a clinically confirmed event; these indicators were cross-validated against event-detail text before the incidence and regression analyses reported here were finalized.

Ethical consideration

The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The study received approval from the Institutional Review Board (IRB) of King Abdullah International Medical Research Center (KAIMRC) under protocol number NRA24A/002/02, with strict adherence to patient confidentiality throughout the research process.

RESULTS

A total of 539 patients with confirmed T2DM (baseline HbA1c ≥6.5%) were included in the final analysis, with 241 (44.7%) males and 298 (55.3%) females (Table 1A). Patients were divided into two groups based on treatment regimen: those receiving dapagliflozin monotherapy and those receiving combination therapy with once-weekly injectable semaglutide (Tables 1A and 1B). Generalized Estimating Equations (GEE) were used to assess both within-group changes over time and between-group differences at six months, with dapagliflozin monotherapy used as the reference group. Results are presented by outcome domain: glycemic control and metabolic parameters, lipid profile and body weight, blood pressure, renal function markers, and incident cardiovascular events. Both time-adjusted and fully adjusted models are reported throughout.

Glycemic control and metabolic parameters

The overall mean HbA1c at baseline was 8.5 ± 1.8%, which significantly decreased to 8.03 ± 1.6% after six months of follow-up (p <0.001. However, compared to dapagliflozin monotherapy, the combination therapy group had significantly higher HbA1c levels at six months (Estimate = 0.069, 95% CI: 0.038 to 0.100; p <0.001; Table 1B). Similarly, the combination therapy group had a higher BMI (Estimate = 0.053, 95% CI: 0.0202 to 0.0875; p = 0.0017), although BMI significantly declined over time in both groups (Estimate = –0.028, 95% CI: –0.040 to –0.016; p <0.001). HDL levels showed a significant increase over time (Estimate = 0.016, 95% CI: 0.0004 to 0.0316; p = 0.043). The combination therapy was also associated with significantly higher HDL compared to dapagliflozin alone (Estimate = 0.061, 95% CI: 0.022 to 0.10; p = 0.0020). In contrast, male sex was significantly associated with lower HDL levels (Estimate = –0.171, 95% CI: –0.208 to –0.135; p <0.001). No significant differences were observed between treatment groups in LDL, total cholesterol, or triglycerides (p >0.05; Table 4).

Cardiovascular outcomes

Systolic blood pressure (SBP) remained stable over the study period, with no significant differences observed between treatment groups (p >0.05). In contrast, diastolic blood pressure (DBP) did not change significantly over time (Estimate = –0.0014, 95% CI: –0.0164 to 0.0135; p = 0.851) (Table 2). In the time-adjusted model, the risk of heart failure (HF) was significantly lower in the combination therapy group compared to dapagliflozin alone (RR = 0.438, 95% CI: 0.201 to 0.957; p = 0.038). The reduction in myocardial infarction (MI) risk (RR = 0.604, 95% CI: 0.314 to 1.165; p = 0.132) did not reach statistical significance. No significant difference in stroke risk was observed between the two treatment groups (RR = 1.211, 95% CI: 0.547 to 2.682; p = 0.637). MI and HF risk both declined significantly over time (p <0.001), as did stroke risk (RR = 0.626, 95% CI not shown; p = 0.031) (Table 3).

Table 1A. Baseline demographic and clinical characteristics by treatment group (T2DM-confirmed cohort, n = 539)

Parameter	Dapagliflozin monotherapy (n = 353)	Combination therapy (n = 186)	*p*-value
Age (years), mean (SD)*	61.97 (11.52)	57.83 (10.84)	<0.001
Sex, n (%) male	163 (46.2%)	78 (41.9%)	0.395
BMI (kg/m²)	33.92 (6.77)	36.11 (7.08)	0.001
SBP (mmHg)	139.33 (18.12)	136.31 (16.40)	0.079
DBP (mmHg)	71.43 (10.27)	70.85 (9.61)	0.566
HDL (mmol/L)	1.05 (0.27)	1.13 (0.28)	0.004
LDL (mmol/L)	2.43 (0.91)	2.48 (1.04)	0.666
Total cholesterol (mmol/L)	4.02 (1.01)	4.16 (1.18)	0.208
Triglycerides (mmol/L)	1.58 (1.09)	1.63 (0.99)	0.593
eGFR (mL/min/1.73m²)	74.53 (23.38)	82.00 (21.42)	<0.001
ACR (mg/g)	38.79 (54.72)	23.56 (39.26)	0.008
BNP (pg/mL)	286.42 (607.67)	279.45 (707.55)	0.972
hsCRP (mg/L)	22.58 (62.90)	20.64 (27.83)	0.827
HbA1c (%)	8.64 (1.58)	9.20 (1.76)	0.001
Comorbidities (baseline)			
Hypertension, n (%)	19 (5.4%)	9 (4.8%)	0.947
Chronic kidney disease, n (%)	26 (7.4%)	4 (2.2%)	0.021
Heart failure (history), n (%)	5 (1.4%)	1 (0.5%)	0.622
Ischemic heart disease, n (%)	11 (3.1%)	0 (0.0%)	0.035
Atrial fibrillation, n (%)	4 (1.1%)	0 (0.0%)	0.353
Obesity, n (%)	11 (3.1%)	4 (2.2%)	0.710
Concomitant medications (baseline)			
ACEi/ARB use, n (%)	169 (47.9%)	101 (54.3%)	0.184
Statin use, n (%)	257 (72.8%)	147 (79.0%)	0.138
Insulin use, n (%)	144 (40.8%)	95 (51.1%)	0.028

*Age recorded in source records as 10-year bands; values reflect band midpoints (see Strengths and Limitations). Comorbidity and concomitant medication flags were derived from the single primary-diagnosis field and free-text medication list per encounter, not a complete problem list; prevalence figures should be interpreted as minimum estimates.

Table 1B. Six-month follow-up characteristics by treatment group (T2DM-confirmed cohort, n = 539)

Parameter	Dapagliflozin monotherapy (n = 353)	Combination therapy (n = 186)	*p*-value
BMI (kg/m²)	33.22 (6.70)	35.03 (7.25)	0.008
SBP (mmHg)	137.13 (18.14)	135.10 (18.53)	0.281
DBP (mmHg)	70.33 (10.23)	72.85 (9.71)	0.013
HDL (mmol/L)	1.08 (0.28)	1.13 (0.26)	0.050
LDL (mmol/L)	2.46 (0.90)	2.44 (0.99)	0.819
Total cholesterol (mmol/L)	4.09 (1.06)	4.08 (1.16)	0.994
Triglycerides (mmol/L)	1.58 (1.16)	1.55 (0.92)	0.816
eGFR (mL/min/1.73 m²)	75.22 (24.14)	82.53 (20.40)	0.001
ACR (mg/g)	41.72 (62.43)	23.09 (37.97)	0.003
BNP (pg/mL)	349.39 (716.89)	353.58 (780.11)	0.986
hsCRP (mg/L)	38.59 (170.48)	13.56 (14.59)	0.238
HbA1c (%)	7.97 (1.36)	8.72 (1.89)	<0.001

Table 2. Time-adjusted GEE model for continuous metabolic and cardiovascular outcomes

Parameters	Drug	*P*-value	Time	*P*-value
BMI	0.0578 [0.0215 – 0.0940]	0.002	-0.0238 [-0.0338 – -0.0137]	<0.001
SBP	-0.0184 [-0.0393 – 0.0025]	0.084	-0.0136 [-0.0274 – 0.0002]	0.054
DBP	0.0136 [-0.0086 – 0.0358]	0.231	-0.0014 [-0.0164 – 0.0135]	0.851
HDL	0.0604 [0.0164 – 0.1045]	0.007	0.0170 [0.0001 – 0.0339]	0.048
LDL	0.0047 [-0.0615 – 0.0708]	0.890	0.0030 [-0.0311 – 0.0371]	0.864
TC	0.0176 [-0.0284 – 0.0636]	0.454	0.0048 [-0.0185 – 0.0280]	0.688
TG	0.0099 [-0.0990 – 0.1188]	0.858	-0.0171 [-0.0768 – 0.0427]	0.576
eGFR	0.0942 [0.0452 – 0.1432]	<0.001	0.0083 [-0.0088 – 0.0254]	0.342
ACR	-0.5435 [-0.8983 – -0.1887]	0.003	0.0279 [-0.1409 – 0.1968]	0.746
BNP	-0.0102 [-1.2912 – 1.2707]	0.988	0.2047 [-0.0570 – 0.4665]	0.125
hsCRP	-0.4708 [-1.1906 – 0.2489]	0.200	0.1771 [-0.6854 – 1.0396]	0.687
HbA1c	0.0759 [0.0441 – 0.1076]	<0.001	-0.0719 [-0.0880 – -0.0557]	<0.001

For drug dapagliflozin was set as the reference group. Time before the follow up period was set as the reference group.

Table 3. Time-adjusted GEE model for binary cardiovascular outcomes (stroke, myocardial infarction, and heart failure)

Dependent Variables	Drug	*P*-value	Time	*P*-value
Stroke	1.211 [0.547 – 2.682]	0.636	0.626 [0.409 – 0.959]	0.031
MI	0.604 [0.314 – 1.165]	0.132	0.526 [0.381 – 0.727]	<0.001
HF	0.438 [0.201 – 0.957]	0.038	0.531 [0.386 – 0.730]	<0.001

Measures displayed are relative risk (RR) with drug dapagliflozin was set as the reference group. Time before the follow up period was set as the reference group.

Table 4. Fully adjusted GEE Model (adjusted for time and sex) for metabolic and cardiovascular parameters

Dependent Variables	Drug	*P*-value	Time	*P*-value	Sex	*P*-value
BMI	0.0470 [0.0124 – 0.0816]	0.008	-0.0241 [-0.0338 – -0.0144]	<0.001	-0.1181 [-0.1513 – -0.0849]	<0.001
SBP	-0.0196 [-0.0403 – 0.0011]	0.064	-0.0133 [-0.0271 – 0.0005]	0.059	-0.0137 [-0.0338 – 0.0064]	0.182
DBP	0.0177 [-0.0036 – 0.0391]	0.104	-0.0023 [-0.0174 – 0.0128]	0.766	0.0530 [0.0314 – 0.0746]	<0.001
HDL	0.0502 [0.0101 – 0.0904]	0.014	0.0136 [-0.0029 – 0.0301]	0.107	-0.1858 [-0.2251 – -0.1465]	<0.001
LDL	0.0033 [-0.0633 – 0.0700]	0.922	0.0004 [-0.0341 – 0.0349]	0.980	-0.0682 [-0.1303 – -0.0061]	0.031
TC	0.0134 [-0.0322 – 0.0591]	0.564	0.0022 [-0.0215 – 0.0258]	0.858	-0.0843 [-0.1268 – -0.0417]	<0.001
TG	0.0153 [-0.0934 – 0.1240]	0.782	-0.0169 [-0.0776 – 0.0439]	0.586	0.0470 [-0.0616 – 0.1556]	0.396
eGFR	0.0942 [0.0453 – 0.1431]	<0.001	0.0083 [-0.0088 – 0.0253]	0.342	0.0011 [-0.0502 – 0.0524]	0.966
ACR	-0.5404 [-0.8953 – -0.1855]	0.003	0.0319 [-0.1381 – 0.2019]	0.713	-0.0393 [-0.3902 – 0.3116]	0.826
BNP	-2.8847 [-3.6148 – -2.1547]	<0.001	0.4317 [-0.3302 – 1.1935]	0.267	3.9658 [2.9542 – 4.9774]	<0.001
hsCRP	-0.5118 [-1.0067 – -0.0168]	0.043	0.3550 [-0.2131 – 0.9230]	0.221	-0.9879 [-1.5104 – -0.4654]	<0.001
HbA1c	0.0741 [0.0424 – 0.1059]	<0.001	-0.0719 [-0.0881 – -0.0558]	<0.001	-0.0273 [-0.0555 – 0.0010]	0.058

For drug dapagliflozin was set as the reference group. Time before the follow up period was set as the reference group.

Cardiac biomarkers

In the time-adjusted model, BNP did not differ significantly between treatment groups (Estimate = –0.010; p = 0.988); a significant association emerged only in the fully adjusted (sex-inclusive) model (Estimate = –2.885; p <0.001; Table 4), suggesting the unadjusted BNP comparison in the original submission was confounded by the sex distribution between groups. No significant differences were observed between the two groups in high-sensitivity C-reactive protein (hsCRP) levels (p >0.05) (Table 2).

Renal function

The combination therapy was associated with a persistently higher estimated glomerular filtration rate (eGFR) throughout follow-up compared to dapagliflozin monotherapy (Estimate = 0.094, p <0.001), consistent with the higher eGFR already present at baseline (Table 1A). It was also associated with persistently lower urine albumin–creatinine ratio (ACR) (Estimate = –0.544, p = 0.003) (Table 2) (Figure 2).

Multivariate analysis

In the fully adjusted model—which accounted for time and sex—the combination therapy remained significantly associated with higher body mass index (BMI) (p = 0.008), higher high-density lipoprotein cholesterol (HDL) (p = 0.014), higher estimated glomerular filtration rate (eGFR) (p <0.001), and lower B-type natriuretic peptide (BNP) levels (p <0.001) (Table 4). Combination therapy was also associated with a modest reduction in high-sensitivity C-reactive protein (hsCRP) (p = 0.043); although statistically significant, the magnitude of this effect was small and its clinical relevance is uncertain. Male sex was independently associated with lower BMI (p <0.001) and lower HDL levels (p <0.001). DM diagnosis was removed as a covariate following restriction of the cohort to confirmed T2DM patients (Methodology).

In summary, in the fully adjusted (sex-inclusive) model, combination therapy was not significantly associated with a reduced risk of stroke (RR = 1.188; p = 0.667) or myocardial infarction (RR = 0.605; p = 0.133). Combination therapy remained significantly associated with a lower risk of heart failure (HF) (RR = 0.434; p = 0.036). Stroke, MI, and HF risk all declined significantly over time (p <0.001).

After adjustment for treatment group and time, sex was not significantly associated with the risk of stroke (RR = 0.616; p = 0.244), MI (RR = 1.035; p = 0.901), or HF (RR = 0.777; p = 0.410) in this T2DM-confirmed cohort. DM diagnosis, included as a covariate in the original submission, was removed following exclusion of non-T2DM patients (see Methodology).

These findings are summarized in Figure 1, which illustrates the modest, non-significant sex differences and the significant time-related decline in cardiovascular event risk across this T2DM-confirmed cohort.

DISCUSSION

Over the past decade, the management of type 2 diabetes (T2D) has evolved significantly with the introduction of novel pharmacologic classes targeting distinct pathophysiological pathways. Among these, SGLT2i and GLP-1 RAs have demonstrated not only robust glucose-lowering efficacy but also substantial cardiovascular and renal benefits. SGLT2 inhibitors, including empagliflozin, dapagliflozin, and canagliflozin, improve glycemic control while also reducing heart failure events and slowing the progression of kidney disease.[18] GLP-1 RAs—such as liraglutide, dulaglutide, and semaglutide—enhance insulin secretion, suppress glucagon release, delay gastric emptying, and promote weight loss, with favorable cardiovascular effects shown in major outcome trials.[19]

Given these complementary mechanisms of action, there is growing interest in combining SGLT2i and GLP-1 RAs to maximize metabolic and cardiovascular outcomes in patients with T2D. Emerging data suggest that these drug classes may act through largely independent pathways, potentially allowing additive or even synergistic effects. This raises the question of whether combining these agents could enhance outcomes beyond those achievable with monotherapy.

Building on this rationale, the present study aimed to test the hypothesis that adding once-weekly semaglutide to ongoing dapagliflozin therapy would provide incremental cardiovascular and renal benefits beyond those of dapagliflozin alone, even if the improvement in glycemic control was not superior. This hypothesis draws on accumulating evidence from clinical trials and real-world data indicating that the two agents may independently target different aspects of cardiometabolic risk.

In this retrospective cohort analysis, we compared dapagliflozin monotherapy with its combination with semaglutide across key metabolic, cardiovascular, and renal outcomes. While both groups showed significant improvements over time, combination therapy was associated with greater increases in HDL levels, improved eGFR, and a reduction in heart failure risk, with a non-significant trend toward lower myocardial infarction risk. Conversely, dapagliflozin monotherapy was associated with greater reductions in HbA1c levels. These findings provide real-world insights into the potential role of combination therapy in high-risk cardiometabolic populations, although interpretation must account for study limitations and potential confounding.

Glycemic control and metabolic parameters

Over the six-month follow-up period, both treatment groups showed a statistically significant reduction in HbA1c levels. However, patients receiving combination therapy maintained higher HbA1c values than the monotherapy group during follow-up, likely reflecting greater baseline glycemic burden rather than a smaller treatment response, since between-group change from baseline was not separately modeled; this contrasts with previous studies suggesting synergistic glycemic effects when combining SGLT2 inhibitors with GLP-1 receptor agonists.[20,21] In our cohort, patients receiving combination therapy had higher baseline HbA1c levels, possibly reflecting the selection of individuals with more advanced or poorly controlled diabetes for more intensive treatment.[22,23]

Despite these differences in HbA1c reduction, the overall improvement across both groups is clinically meaningful, given the well-established benefits of improved glycemic control in reducing microvascular complications such as nephropathy and retinopathy.[24,25] Nonetheless, the results highlight that combination therapy did not outperform monotherapy in glycemic control in this real-world population. These findings should be interpreted considering potential confounding by indication.

In addition to glycemic outcomes, both treatment groups experienced modest but significant reductions in body mass index (BMI). Dapagliflozin's weight loss effect is known to result initially from osmotic diuresis, followed by sustained reductions in visceral fat.[26] GLP-1 RAs, including semaglutide, contribute to weight reduction primarily through appetite suppression and delayed gastric emptying.[27,28] Although combination therapy was associated with a slightly higher BMI overall, weight declined in both groups over time, further supporting the metabolic benefit of either approach.

Interestingly, a previous study found greater reductions in HbA1c, fasting blood glucose, and BMI with combination therapy, as well as improvements in lipid markers; however, that study differed in design and patient population.[15] In our cohort, by contrast, HDL cholesterol increased significantly in the combination group, consistent with the known lipid-modulating effects of GLP-1 Ras.[29,30] This change is clinically relevant, as elevated HDL levels are linked to lower cardiovascular risk. Mechanistically, GLP-1 RAs such as semaglutide increase HDL levels through multiple pathways: upregulation of hepatic apolipoprotein A-I (ApoA-I) synthesis, enhancement of reverse cholesterol transport, reduction of hepatic lipase activity, and attenuation of systemic inflammation that otherwise promotes HDL catabolism. Dapagliflozin may further support HDL elevation indirectly through reductions in insulin resistance, visceral adiposity, and oxidative stress—all of which are known suppressors of HDL synthesis. The additive HDL-raising effect observed with combination therapy in this study is consistent with these mechanistic

considerations and supports the potential cardioprotective synergy of the two agents.[31,32]

However, no statistically significant changes were observed between the groups in LDL, total cholesterol, or triglycerides, suggesting that the lipid effects of combination therapy may be specific to HDL modulation rather than broad-spectrum lipid lowering.[33,34] Concerning blood pressure, systolic blood pressure (SBP) remained essentially unchanged in both groups, while diastolic blood pressure (DBP) showed a small but statistically significant reduction. This pattern aligns with prior studies, some of which report selective effects on SBP,[35] while others have observed reductions in both SBP and DBP.[36,37]

Renal and cardiovascular outcomes

Combination therapy with dapagliflozin and semaglutide was associated with favorable renal and cardiovascular parameters compared to dapagliflozin alone in this study. Specifically, combination therapy showed persistently higher estimated glomerular filtration rate (eGFR) and lower albumin-to-creatinine ratio (ACR) throughout follow-up; however, both measures were already higher/lower, respectively, at baseline (Table 1A). This likely reflects an observed between-group difference rather than a demonstrated treatment-induced improvement. These findings are consistent with prior evidence supporting the renal protective effects of both GLP-1 RAs and SGLT2 inhibitors when used individually.[16,38] Moreover, the dual treatment may offer complementary benefits through mechanisms including reduced glomerular hyperfiltration, natriuresis, and attenuation of intrarenal inflammation and oxidative stress. Regarding glomerular hemodynamics specifically, dapagliflozin exerts its renoprotective effect primarily by reducing proximal tubular sodium-glucose reabsorption, which increases sodium delivery to the macula densa and restores tubuloglomerular feedback. This results in afferent arteriolar constriction and a reduction in intraglomerular pressure, thereby mitigating glomerular hyperfiltration—a key driver of CKD progression. Semaglutide complements this mechanism by attenuating systemic and renal inflammation, reducing oxidative stress via GLP-1 receptor signaling in tubular epithelial cells and podocytes, and improving endothelial function. The combination of these distinct hemodynamic and anti-inflammatory pathways may account for the additive renoprotective effects observed in this cohort, manifested as improved eGFR and lower ACR in the combination therapy group.[39,40]

However, it is essential to note that while these improvements in renal markers were statistically significant, the absolute changes were modest, and the potential influence of baseline disease severity cannot be entirely excluded. Given that this was a non-randomized retrospective cohort, differences in renal outcomes may reflect confounding by indication or baseline patient characteristics rather than direct effects of therapy.

In terms of cardiovascular outcomes, combination therapy was associated with a significantly lower risk of heart failure (HF) events over six months compared to dapagliflozin monotherapy, an association that remained significant in both the time-adjusted and fully adjusted models, though more modest than in the original, unvalidated analysis. The reduction in myocardial infarction (MI) risk observed in earlier analyses did not reach statistical significance after restricting the cohort to confirmed T2DM patients and validating cardiovascular event ascertainment (see Methods), and should be interpreted as a non-significant trend rather than a confirmed effect. This observation is consistent with prior landmark trials demonstrating the cardioprotective effects of GLP-1 RAs (e.g., SUSTAIN-6, REWIND) and SGLT2 inhibitors (e.g., DECLARE-TIMI 58, EMPA-REG) when used individually.[11,14,22,41] Furthermore, a recent meta-analysis has also suggested additive improvements in cardiac structure and function when both classes are used together.[17]

Nonetheless, the retrospective design limits causal inference. Patients prescribed the combination therapy may have undergone more intensive clinical monitoring, benefited from more aggressive risk factor management, or had favorable unmeasured health characteristics that contributed to the observed outcomes. Despite statistical adjustment for sex and time, residual confounding cannot be ruled out.

For cerebrovascular events, no significant difference in stroke risk was observed between the treatment groups. This finding is consistent with mixed results reported in the literature regarding cerebrovascular outcomes from SGLT2i and GLP-1 RA trials.[22,42] In fact, in our cohort, stroke risk declined over time in both groups, which may reflect overall improvement in risk factor control rather than treatment-specific effect.

Even with adjustment for key covariates, unmeasured factors such as disease duration, medication adherence, or prior cardiovascular history could have influenced the associations observed. As a result, causal relationships cannot be inferred from these findings.

Taken together, the observed reductions in renal and cardiovascular risk markers with combination therapy are promising; however, they must be interpreted with caution and should be interpreted as associations, not definitive evidence of superiority. Future prospective randomized trials are needed to determine whether dual therapy provides a genuine incremental benefit beyond monotherapy in high-risk real-world populations.

Strengths and limitations

One of the strengths of this study is its relatively large sample size and the use of real-world data from a diverse patient population, which enhances the external validity and generalizability of the findings. Additionally, the

application of advanced statistical methods such as Generalized Estimating Equations (GEE) allowed for the analysis of repeated measures over time and adjustment for selected covariates, providing more robust estimates of treatment effects.

However, several limitations should be acknowledged. First, the retrospective design inherently introduces potential biases, particularly selection bias and confounding by indication, where patients receiving combination therapy may have had more severe disease or higher baseline risk, which could have influenced both the treatment decision and the observed outcomes. Although adjustments were made for sex and time, several other baseline differences between groups — including age, BMI, HbA1c, eGFR, ACR, CKD prevalence, ischemic heart disease prevalence, and insulin use — were not included as covariates in the final models. These, together with unmeasured factors such as disease duration, comorbidity burden, or medication adherence, may have contributed to residual confounding. Therefore, observed associations between treatment type and outcomes should be interpreted with caution, and not assumed to indicate causality.

Additionally, baseline age was recorded in the source records as 10-year bands rather than exact age, and figures reported in Table 1A/1B reflect band midpoints. A small number of records (n = 18, 3.3% of the corrected cohort) fell outside the stated 18–75-year eligibility window. Given the very small proportion of such cases, these patients were retained, and this is acknowledged as a limitation of the study. Baseline imbalances between treatment groups in BMI, HDL, eGFR, ACR, and HbA1c (Table 1A) indicate the two groups were not fully comparable at treatment initiation, which may confound the between-group comparisons reported. In particular, the combination therapy group appeared to represent a clinically different population, with higher BMI, higher HbA1c, greater insulin use, and lower prevalence of CKD and ischemic heart disease than the monotherapy group; readers should weigh this substantial baseline confounding by indication when interpreting all between-group comparisons in this study. Age and several other baseline clinical differences between groups were not included as covariates in the final models and may have contributed to residual confounding. Baseline event variables (stroke, MI, heart failure) were derived from encounter documentation rather than a structured disease registry and may not completely capture historical disease burden; for example, baseline heart failure history was similar between groups (1.4% vs. 0.5%, $p = 0.622$) while baseline heart failure admission rates differed more substantially (10.5% vs. 4.7%, $p = 0.043$), a discrepancy that likely reflects differences in encounter documentation rather than true differences in disease history. Because treatment allocation was not randomized and baseline differences existed between groups, the observed associations should be interpreted as hypothesis-generating rather than confirmatory. Of the 662 patients with a recorded baseline HbA1c value or drug assignment, 51 did not meet the ADA HbA1c criterion for T2DM and 72 had missing or non-numeric baseline HbA1c; the original dataset's exclusions for incomplete baseline or follow-up records at other timepoints were not separately quantified in the source records, and a formal STROBE-style flow diagram was not constructed for this cohort. This is acknowledged as a limitation of the reporting.

Second, the follow-up period was limited to six months, which may not be sufficient to capture long-term cardiovascular or renal outcomes, particularly for chronic disease processes. Future studies with longer follow-up and prospective designs are needed to validate and extend these findings. Lastly, the study was conducted at a single tertiary care center, which may limit generalizability to broader healthcare settings or populations. Additionally, several clinical realities must be acknowledged. Long-term cost barriers represent a significant practical challenge: both semaglutide and dapagliflozin are high-cost medications, and real-world adherence may be substantially lower than observed in controlled settings, particularly in lower-resource healthcare systems. The complex dosing regimen of once-weekly injectable semaglutide—with its staged titration schedule—introduces additional complexity compared to monotherapy and may adversely affect treatment adherence in routine clinical practice. Furthermore, the broad phenotypic heterogeneity of chronic kidney disease (CKD) presents a challenge to generalizing these findings. Patients with CKD exhibit diverse underlying etiologies (diabetic nephropathy, hypertensive nephropathy, glomerular disease), varying degrees of proteinuria, and distinct rates of eGFR decline. This heterogeneity means that the renoprotective response to SGLT2i/GLP-1 RA combination therapy may differ considerably depending on the predominant CKD phenotype. Regarding concomitant therapy, a notable proportion of patients in this cohort were prescribed renin-angiotensin-aldosterone system (RAAS) blockers, including angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), as well as mineralocorticoid receptor antagonists (MRAs) in some cases. Although these agents were not formally analyzed as effect modifiers in the current study, their use as background therapy—particularly given their established renoprotective and cardioprotective roles—may have contributed to the overall outcomes observed in both groups and should be considered when interpreting the results. Future analyses should account for RAAS blocker use as a covariate.

CONCLUSION

In this retrospective cohort study, both dapagliflozin monotherapy and its combination with once-weekly injectable semaglutide were associated with improvements in metabolic, cardiovascular, and renal parameters over six months. While dapagliflozin alone was linked to better glycemic control, combination therapy demonstrated additional benefits in HDL levels, renal function (eGFR, ACR), and a reduced risk of heart failure, with a non-

significant trend toward reduced myocardial infarction risk. These findings support the potential value of individualized treatment strategies, particularly for patients with elevated cardiovascular or renal risk profiles. However, given the study's observational nature and possible residual confounding, these associations should be interpreted with caution. Prospective, randomized controlled trials are warranted to confirm these results and guide evidence-based treatment pathways that optimize personalized care in patients with T2DM.

In particular, a future prospective randomized controlled trial should pre-specify primary renal endpoints including urine albumin excretion rate (or albumin-to-creatinine ratio) and rate of eGFR decline over time, together with primary cardiovascular endpoints such as major adverse cardiovascular events (MACE). Secondary outcomes should encompass glycemic control (HbA1c), body weight and BMI, lipid parameters, blood pressure, and biomarkers (BNP and hsCRP), thereby providing the level of evidence needed to guide personalized treatment decisions in this high-risk population.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
RA: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **MA:** Conceptualization, Methodology, Validation, Formal analysis, Resources, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision; **MA:** Conceptualization, Methodology, Validation, Investigation, Writing – review and editing, Supervision; **SAM:** Conceptualization, Methodology, Validation, Investigation, Writing – review and editing; **AA:** Conceptualization, Methodology, Validation, Investigation, Writing – review and editing, Supervision; **AA:** Conceptualization, Methodology, Validation, Investigation, Writing – review and editing; **AK:** Conceptualization, Methodology, Software, Resources, Writing – review and editing, Visualization; **NA:** Conceptualization, Methodology, Software, Formal analysis, Resources, Data curation, Writing – review and editing, Visualization; **AA:** Conceptualization, Methodology, Validation, Investigation, Writing – review and editing, Visualization; **NA:** Conceptualization, Methodology, Validation, Investigation, Writing – review and editing; **MA:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing – review and editing, Formal analysis, Writing – review and editing; **AA:** Conceptualization, Methodology, Validation, Writing – review and editing; **TA:** Conceptualization, Methodology, Formal analysis, Resources, Writing – review and editing; **RA:** Conceptualization, Methodology, Validation, Writing – review and editing; **GA:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – review and editing; **JA:** Conceptualization, Methodology, Validation, Writing – review and editing; **AA:** Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing – review and editing; **TA:** Conceptualization, Methodology, Validation, Writing – review and editing; **AA:** Conceptualization, Methodology, Validation, Resources, Writing – review and editing; **IA:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – review and editing; Supervision; **SK:** Conceptualization, Software, Validation, Formal analysis, Supervision; **AAQ:** Conceptualization, Validation, Investigation; **YT:** Conceptualization, Data curation, Writing – original draft preparation; **MAH:** Conceptualization, Software, Investigation, Supervision.

Data Sharing and Availability
Datasets generated and analyzed are included in the published article.

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References
1. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019;157:107843. PMID: 31518657 DOI: 10.1016/j.diabres.2019.107843
2. Magliano DJ, Boyko EJ; IDF Diabetes Atlas 10th Edition Scientific Committee. IDF Diabetes Atlas, 10th ed. Brussels, Belgium: International Diabetes Federation; 2021. Bookshelf ID: NBK581934
3. Aljulifi MZ. Prevalence and reasons of increased type 2 diabetes in Gulf Cooperation Council countries. Saudi Med J. 2021;42(5): 481-90. PMID: 33896777 PMCID: PMC9149705 DOI: 10.15537/smj.2021.42.5.20200676
4. Jarrar M, Abusalah MAH, Albaker W, et al. Prevalence of type 2 diabetes mellitus in the general population of Saudi Arabia, 2000-2020: A systematic review and meta-analysis of observational studies. Saudi J Med Med Sci. 2023;11(1):1-10. PMID: 36909010 PMCID: PMC9997860 DOI: 10.4103/sjmms.sjmms_394_22
5. American Diabetes Association. 9. Cardiovascular disease and risk management. Diabetes Care. 2017;40(Suppl 1):S75-87. PMID: 27979896 DOI: 10.2337/dc17-S012
6. Alguwaihes AM, Alhozali A, Yahia MM, et al. The prevalence of cardiovascular disease in adults with type 2 diabetes mellitus in Saudi Arabia-CAPTURE study. Saudi Med J. 2023;44(1):57-66. PMID: 36634941 PMCID: PMC9987684 DOI: 10.15537/smj.2023.44.1.20220402
7. Wareham NJ. Personalised prevention of type 2 diabetes. Diabetologia. 2022;65(11):1796-803. PMID: 35916901 PMCID: PMC9522721 DOI: 10.1007/s00125-022-05774-7
8. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical update: Cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus-mechanisms, management, and clinical considerations. Circulation. 2016;133(24):2459-502. PMID: 27297342 PMCID: PMC4910510 DOI: 10.1161/CIRCULATIONAHA.116.022194
9. Kalra S. Sodium-glucose cotransporter 2 (SGLT2) inhibitors and cardiovascular disease: A systematic review. Cardiol Ther. 2016; 5(2):161-8. PMID: 27539303 PMCID: PMC5125111 DOI: 10.1007/s40119-016-0069-z
10. McGurnaghan SJ, Brierley L, Caparrotta TM, et al. The effect of dapagliflozin on glycaemic control and other cardiovascular disease risk factors in type 2 diabetes mellitus: A real-world observational study. Diabetologia. 2019;62(4):621-32. PMID: 30631892 DOI: 10.1007/s00125-018-4806-9
11. Furtado RH, Bonaca MP, Raz I, et al. Dapagliflozin and cardiovascular outcomes in patients with type 2 diabetes mellitus and previous myocardial infarction: Subanalysis from the DECLARE-TIMI 58 trial. Circulation. 2019;139(22):2516-27. PMID: 30882239 DOI: 10.1161/CIRCULATIONAHA.119.039996
12. Goldenberg RM, Steen O. Semaglutide: Review and place in therapy for adults with type 2 diabetes. Can J Diabetes. 2019;43(2):136-45. PMID: 30195966 DOI: 10.1016/j.jcjd.2018.05.008
13. Frías JP, Auerbach P, Bajaj HS, et al. Efficacy and safety of once-weekly semaglutide 2.0 mg versus 1.0 mg in patients with type 2 diabetes (SUSTAIN FORTE): A double-blind, randomised, phase 3B trial. Lancet Diabetes Endocrinol. 2021;9(9):563-74. PMID: 34293304 DOI: 10.1016/S2213-8587(21)00174-1
14. Leiter LA, Bain SC, Hramiak I, et al. Cardiovascular risk reduction with once-weekly semaglutide in subjects with type 2 diabetes: a post hoc analysis of gender, age, and baseline CV risk profile in the SUSTAIN 6 trial. Cardiovasc Diabetol. 2019;18(1):73. PMID: 31167654 PMCID: PMC6551895 DOI: 10.1186/s12933-019-0871-8
15. Lunati ME, Cimino V, Bernasconi D, et al. Type 2 diabetes mellitus pharmacological remission with dapagliflozin plus oral semaglutide. Pharmacol Res. 2024;199:107040. PMID: 38128857 DOI: 10.1016/j.phrs.2023.107040

16. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019; 380(24):2295-306. PMID: 30990260 DOI: 10.1056/NEJMoa1811744
17. Zhang DP, Xu L, Wang LF, Wang HJ, Jiang F. Effects of antidiabetic drugs on left ventricular function/dysfunction: Systematic review and network meta-analysis. Cardiovasc Diabetol. 2020;19(1):10. PMID: 31969144 PMCID: PMC6977298 DOI: 10.1186/s12933-020-0987
18. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021;44(Suppl 1):S111-24. PMID: 33298420 DOI: 10.2337/dc21-S009
19. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes-state-of-the-art. Mol Metab. 2021; 46:101102. PMID: 33068776 PMCID: PMC8085572 DOI: 10.1016/j.molmet.2020.101102
20. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018;41(12):2669-701. PMID: 30291106 PMCID: PMC6245208 DOI: 10.2337/dci18-0033
21. Frias JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med. 2021; 385(6):503-15. PMID: 34170647 DOI: 10.1056/NEJMoa2107519
22. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015; 373(22):2117-28. PMID: 26378978 DOI: 10.1056/NEJMoa1504720
23. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016; 375(4):311-22. PMID: 27295427 PMCID: PMC4985288 DOI: 10.1056/NEJMoa1603827
24. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) group. Lancet. 1998;352(9131):837-53. PMID: 9742976
25. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. BMJ. 2000;321(7258): 405-12. PMID: 10938048 PMCID: PMC27454 DOI: 10.1136/bmj.321.7258.405
26. Barnett AH. Impact of sodium glucose cotransporter 2 inhibitors on weight in patients with type 2 diabetes mellitus. Postgrad Med. 2013;125(5):92-100. PMID: 24113667 DOI: 10.3810/pgm.2013.09.2698
27. Blundell J, Finlayson G, Axelsen M, et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. Diabetes Obes Metab. 2017;19(9):1242-51. PMID: 28266779 PMCID: PMC5573908 DOI: 10.1111/dom.12932
28. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): An open-label, cluster-randomised trial. Lancet. 2018;391(10120):541-51. PMID: 29221645 DOI: 10.1016/S0140-6736(17)33102-1
29. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016; 375(19):1834-44. PMID: 27633186 DOI: 10.1056/NEJMoa1607141
30. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): A double-blind, randomised placebo-controlled trial. Lancet. 2019;394(10193): 121-30. PMID: 31189511 DOI: 10.1016/S0140-6736(19)31149-3
31. Barter P, Gotto AM, LaRosa JC, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med. 2007;357(13):1301-10. PMID: 17898099 DOI: 10.1056/NEJMoa064278
32. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation. 1989;79(1):8-15. PMID: 2642759 DOI: 10.1161/01.cir.79.1.8
33. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372(25):2387-97. PMID: 26039521 DOI: 10.1056/NEJMoa1410489
34. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376(18):1713-22. PMID: 28304224 DOI: 10.1056/NEJMoa1615664
35. Gorgojo-Martínez JJ, Serrano-Moreno C, Sanz-Velasco A, Feo-Ortega G, Almodóvar-Ruiz F. Real-world effectiveness and safety of dapagliflozin therapy added to a GLP-1 receptor agonist in patients with type 2 diabetes. Nutr Metab Cardiovasc Dis. 2017;27(2): 129-37. PMID: 28077257 DOI: 10.1016/j.numecd.2016.11.007
36. Kim HS, Lee WJ. Clinical efficacy of sodium-glucose cotransporter 2 inhibitor and glucagon-like peptide-1 receptor agonist combination therapy in type 2 diabetes mellitus: Real-world study (Diabetes Metab J 2022;46:658-62). Diabetes Metab J. 2022;46(4):665-6. PMID: 35929176 PMCID: PMC9353569 DOI: 10.4093/dmj.2022.0166
37. Saroka RM, Kane MP, Busch RS, Watsky J, Hamilton RA. SGLT-2 inhibitor therapy added to GLP-1 agonist therapy in the management of T2DM. Endocr Pract. 2015;21(12):1315-22. PMID: 26307900 DOI: 10.4158/EP15877.OR
38. Mann JF, Ørsted DD, Brown-Frandsen K, et al. Liraglutide and renal outcomes in type 2 diabetes. N Engl J Med. 2017;377(9):839-48. PMID: 28854085 DOI: 10.1056/NEJMoa1616011
39. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15): 1436-46. PMID: 32970396 DOI: 10.1056/NEJMoa2024816
40. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): A multicentre, open-label, randomised trial. Lancet Diabetes Endocrinol. 2018;6(8):605-17. PMID: 29910024 DOI: 10.1016/S2213-8587(18)30104-9
41. Furtado RHM, Bonaca MP, Raz I, et al. Dapagliflozin and cardiovascular outcomes in patients with type 2 diabetes and previous myocardial infarction. Circulation. 2019;139(22):2516-27. PMID: 30882239 DOI: 10.1161/CIRCULATIONAHA.119.039996
42. McMurray JJ, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019; 381(21):1995-2008. PMID: 31535829 DOI: 10.1056/NEJMoa1911303