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The BRIDGE-DS Study: Improved Glycemic Control and Renal Function in Type 2 Diabetes Mellitus Patients Using the Fixed-Dose Combination of Dapagliflozin and Sitagliptin

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Abstract

Background: Chronic kidney disease (CKD) is characterized by persistent or intermittent albuminuria and a declining glomerular filtration rate (GFR). CKD affects 20-40% of patients with diabetes globally, with significant impacts on health outcomes and healthcare costs. Type 2 diabetes mellitus (T2DM) patients with poor glycemic control are at higher risk of developing CKD, leading to severe complications, including end-stage kidney disease (ESRD).

Methods: A retrospective, multicenter, observational study was conducted using a case-based questionnaire survey to collect data anonymously from diabetologists and endocrinologists across India. The study included T2DM patients with CKD who received a fixed-dose combination (FDC) therapy of dapagliflozin and sitagliptin (D/S). Data were collected digitally and analyzed using SPSS® Version 23.0 software.

Results: Data from 510 patients were collected, comprising 67.6% males and 32.4% females. The median age of the patient cohort was 56 years. After 3 months of FDC D/S treatment, significant reductions in glycated hemoglobin (HbA_{1c}) levels from 9.00% to 7.50%, along with reductions in fasting plasma glucose (FPG) and post-prandial glucose (PPG) levels, were noted. Serum creatinine levels decreased by 0.37 mg/dL, while estimated glomerular filtration rate (eGFR) values improved from 83.83 to 84.00 mL/min/1.73 m^2, indicating a potential improvement in renal function. Adverse events (AEs) included urinary tract infections (UTIs), dehydration, hypoglycemia, and genital mycotic infections.

Conclusion: The study demonstrated that FDC D/S therapy is effective and safe for the management of T2DM and CKD, showing significant improvements in glycemic control and renal function. The combination therapy resulted in notable reductions in HbA_{1c}, FPG, and PPG, along with improved eGFR values, underscoring its renoprotective effects. Despite some AEs, the findings support the use of D/S in combination therapy for patients with T2DM and CKD. However, further research is required to explore the long-term effects and optimal dosing strategies of this drug combination.

Keywords: Blood glucose; Glomerular filtration rate; Creatinine; Hypoglycemia; Urinary tract infection; Glycemic control; Drug combinations

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Introduction

Prevalence and impact of chronic kidney disease (CKD)

CKD is marked by either intermittent or continuous albuminuria and/or a gradual decrease in the glomerular filtration

rate (GFR) [1]. Over 40-50% of patients with diabetes may develop CKD, potentially leading to end-stage kidney disease (ESRD), which requires dialysis or transplantation [1]. It is a significant global health challenge, affecting 20-40% of individuals with diabetes [2].

India, China, and the United States are among the top three countries worldwide with the highest burden of CKD [3]. A systematic review investigating CKD prevalence in South Asia revealed a pooled prevalence of 10.2% among Indian adults (ranging from 4.2% to 21%) [4].

Patients with type 2 diabetes mellitus (T2DM) and poor glycemic control are at higher risk of developing CKD [5]. A cross-sectional study investigating the association between glycated hemoglobin (HbA_{1c}) levels, CKD, and cardiovascular disease (CVD) found that every 1% increase in HbA_{1c} was associated with a 30-40% higher rate of CKD or CVD [6]. In a prospective observational study, researchers found that every 1% reduction in mean HbA_{1c} was associated with a 21% reduction in T2DM-related deaths, a 14% reduction in the risk of myocardial infarction, and a 37% reduction in the risk of developing microvascular complications, all with highly significant P-values ($P < 0.0001$) [7].

CKD is highly prevalent in patients with T2DM for 15 years or more, as well as those with hypertension, hyperlipidemia, and diabetic retinopathy [8]. CKD exacerbates health outcomes, increasing hospitalization risk and deteriorating the quality of life [2]. It exerts a significant economic burden on patients due to the high costs of treatment, including dialysis and transplantation, and the associated healthcare expenditures for managing complications [9]. CKD imposes various restrictions on daily life, affecting patients both physically and mentally, even in the early stages. Patients with CKD have poor health-related quality of life, which worsens as the disease progresses to ESRD [10].

Therapeutic strategies for diabetes and CKD management

Risk assessment and early identification can help optimize care and prevention strategies for CKD among individuals with diabetes [5, 11]. A comprehensive understanding of available treatments, particularly glucose-lowering medications, is of paramount importance for effectively managing CKD. Metformin can be given to individuals with T2DM and CKD (estimated glomerular filtration rate (eGFR) ≥ 45 mL/min/1.73 m^2) [12]. The ambiguity surrounding the use of metformin in those with advanced CKD is due to the perceived risk of metformin-associated lactic acidosis [13]. In cases where metformin is contraindicated or not tolerated, or in patients with elevated HbA_{1c} levels unresponsive to metformin, dipeptidyl peptidase-4 inhibitors (DPP4is) and/or sodium-glucose cotransporter-2 inhibitors (SGLT2is) offer promising alternatives [14].

Combination therapy with SGLT2is and DPP4is

SGLT2is and DPP4is have emerged as promising therapies for CKD without an increased risk of hypoglycemia [15]. Dapagliflozin, an SGLT2i, reduces glucose reabsorption in the kidney's proximal tubule, showing efficacy in preventing kidney failure and prolonging survival in CKD patients, regardless of diabetes status [16]. The DECLARE-TIMI 58 trial demonstrated that dapagliflozin effectively prevents and slows CKD progression in patients with T2DM [17]. SGLT2is not only reduce the risk of ESRD but also cardiovascular death and/or hospitalization for heart failure independent of their glucose-lowering effects [18]. A systematic review revealed that DPP4is preserve eGFR and reduce the albumin-to-creatinine ratio in patients with T2DM [19]. Sitagliptin, a DPP4i, boosts insulin secretion and reduces glucagon release [20]. However, sitagliptin is eliminated from the body through the kidneys, and it is important to consider dose adjustments for patients with moderate or severe CKD or those with ESRD on dialysis [21, 22].

The notable benefits of combining dapagliflozin and sitagliptin (D/S) for managing T2DM may lead to optimized treatment strategies and improved patient outcomes within the Indian healthcare landscape. Together, they provide synergistic effects, improving glycemic control beyond monotherapy. This dual approach addresses multiple aspects of glucose regulation simultaneously, potentially leading to more comprehensive control, as shown in several clinical trials [23]. A systematic review conducted to compare the renal outcomes associated with pharmacotherapy administered to patients diagnosed with T2DM reported renoprotective effects for medications like SGLT2is and DPP4is, including slowing the decline of GFR and reducing both albuminuria and renal adverse events (AEs) [24]. This fixed-dose combination (FDC) was approved in India in 2022 [25].

Aim and objectives of the BRIDGE-DS study

The BRIDGE-DS study assessed the effectiveness and safety of FDC D/S in Indian T2DM patients with CKD. The objectives were: 1) to assess the changes in key clinical parameters, such as HbA_{1c}, fasting plasma glucose (FPG), postprandial glucose (PPG), serum creatinine, and eGFR following the administration of FDC D/S; 2) to determine the safety profile of FDC D/S in T2DM patients with varying stages of CKD; and 3) to assess the impact of FDC D/S on CKD progression in T2DM patients across different CKD stages.

The choice of this specific FDC D/S was supported by its unique combination targeting complementary pathways, established individual effectiveness and safety profiles, and clinical relevance to diabetes patients with CKD. Regulatory approval and availability further endorsed its suitability for evaluation in this study.

Materials and Methods

Study design

A retrospective, multicenter, observational, case-based questionnaire survey was conducted to collect data anonymously

from diabetologists and endocrinologists practicing in various locations in India. This multicenter study included data from T2DM patients with CKD from different hospitals and diabetes clinics.

Study population

The study included patients with T2DM and CKD who received FDC D/S (dapagliflozin 10 mg/sitagliptin 100 mg). The inclusion and exclusion criteria are listed below.

Inclusion criteria were: 1) both male and female patients, > 18 years of age, diagnosed with T2DM and CKD with eGFR in the range of 15 - 90 mL/min/1.73 m^2; and 2) patients who received FDC D/S.

Exclusion criteria were: 1) patients with diabetes below the age of 18 years; 2) individuals who did not have CKD; 3) patients who did not receive an FDC D/S combination; 4) pregnant individuals with T2DM; 5) patients with ESRD; and 6) patients intolerant to either dapagliflozin or sitagliptin.

Data collection

Data from 510 patients were collected from clinicians using digitalized case report forms (CRFs) over a 7-month period, from September 2023 to April 2024.

Data analysis and interpretation

Statistical analyses were conducted using the SPSS® Version 23.0 software. Median and interquartile ranges (IQRs) for variables before and after the use of FDC D/S were calculated.

Ethical consideration

Approval from the Institutional Review Board (IRB) was obtained from the primary study site. Data were collected anonymously from the study participants. All information was kept confidential using codes and document locking through login details. This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Results

Patient demographics

The study included 510 patients with a median age of 56 years (IQR: 49 - 64 years). Of these, 67.6% (N = 345) were male and 32.4% (N = 165) were female. The medical history of the patients included diuretic use, dyslipidemia, physical inactivity, prior history of CVD, smoking, and use of medications like statins, the details of which are summarized in Table 1.

Table 1. Medical History of the Patient

Medical history	N	%
Statin use	321	62.9
Dyslipidemia	297	58.2
Physical inactivity	276	54.1
Smoking	232	45.5
Prior CVD history	167	32.7
Diuretic use	111	21.8

CVD: cardiovascular disease.

The reasons for adding D/S to these patients' therapeutic regimens are listed in Table 2.

CKD progression in terms of eGFR is summarized in Table 3 [26], while Table 4 [26] summarizes CKD progression by albuminuria.

Effects of FDC D/S after 3 months of treatment

Table 5 presents a pairwise comparison of variables before and after treatment with FDC D/S for 3 months. The median HbA_{1c} level significantly decreased from 9.00% to 7.50% after treatment with FDC D/S, indicating improved glycemic control ($P < 0.001$). All other variables showed significant P-values (< 0.05).

AEs that occurred during the treatment are illustrated in Table 6.

The most common AEs observed were urinary tract infections (UTIs) (24.51% of patients), dehydration (15.88% of patients), hypoglycemia (10.20% of patients), and genital mycotic infection (7.65% of patients). Other AEs included changes in serum uric acid, a decrease in renal creatinine clearance, diabetic ketoacidosis, hypotension, vulvovaginitis, and hypovolemia. Sitagliptin dose adjustments are recommended for individuals with moderate-to-severe CKD or ESRD; however, it was not adjusted in our study. Of note, no specific increase in AEs was observed in these participants (n = 41/510).

Discussion

CKD secondary to diabetes poses a significant global health challenge, affecting up to 40% of individuals with diabetes, with India bearing a substantial burden of the disease [3].

Previous studies have identified various risk factors associated with CKD in patients with T2DM. A cross-sectional study evaluated the risk factors for CKD, including older age, lower body mass index (BMI), smoking habits, albuminuria, hypertension, CVD, duration of diabetes, HbA_{1c}, dyslipidemia, and medications (diuretics, antiplatelets, antihypertensives), among others [5]. This study showed that the highest CKD prevalence rates were found in individuals aged over 75 years and those with an HbA_{1c} of 8% or higher [5]. Another study on patients with stages 3-5 CKD (n = 3,303) showed that varying lipid profiles had an independent association with

Table 2. Reasons for the Addition of FDC D/S to the Patients' Therapeutic Regimen

Reasons	N	%
To improve HbA_{1c}	470	92.16
Glycemic variability	348	68.24
Weight gain	186	36.47
Hypoglycemia due to other GLP-1 analog/insulin/other OADs	171	33.53
Metformin intolerance	10	34.48
Improvement in CKD conditions	10	34.48
Reduction in nephropathy progression	3	10.34
Reduction in eGFR values	2	0.39
Obesity	2	6.90
Change in albumin-to-creatinine ratio	1	0.20
Antihypertensive, nephroprotective, cardioprotective effects	1	3.45
CKD	1	3.45
Hypothyroidism	1	3.45
Reduction in albuminuria	1	3.45

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; FDC D/S: fixed-dose combination of dapagliflozin and sitagliptin; GLP-1: glucagon-like peptide-1; HbA_{1c}: glycated hemoglobin; OADs: oral antidiabetic drugs.

renal replacement therapy and rapid CKD progression [12]. Individuals with a history of smoking had significantly higher eGFR and hemoglobin levels [27]. While metformin is a common therapy, several therapeutic approaches for CKD, including FDCs, have been explored.

Mechanisms via which SGLT2is and DPP4is lower blood glucose levels are as follows.

Role of SGLT2is in CKD management

SGLT2is have been found to significantly reduce the risk of acute kidney injury (AKI) by 36-60%, despite being associated with higher incidences of AEs related to hypovolemia [28]. A systematic review and meta-analysis consisting 50,820 participants showed that although SGLT2is are associated with a heightened risk of genital infections (risk ratio (RR) of 3.30 (95% confidence interval (CI): 2.74 - 3.99)), there were no significant differences between the SGLT2i group and the control group [29]. These findings highlight the importance of weighing the benefits of renal protection against the risk of AEs when considering SGLT2i therapy in patients with CKD. The DAPA-CKD trial also showed that the use of dapagliflozin (versus a placebo) was associated with minimal kidney and cardiovascular AEs, and that there were no significant differences between groups having participants with and without CVD. The study demonstrated, however, that dapagliflozin usage was associated with a reduced risk of kidney failure (haz-

Table 3. CKD Progression by eGFR [26]

Categories	N	%
Normal or high (≥ 90 mL/min/1.73 m^2)	162	31.8
Mildly decreased (60 - 89 mL/min/1.73 m^2)	188	36.9
Mildly to moderately decreased (45 - 59 mL/min/1.73 m^2)	119	23.3
Moderately to severely decreased (30 - 44 mL/min/1.73 m^2)	34	6.7
Severely decreased (15 - 29 mL/min/1.73 m^2)	7	1.4

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

Table 4. CKD Progression by Albuminuria [26]

Categories	N	%
Normal to mildly decreased (ACR: < 30 mg/g; < 3 mg/mmol)	255	50.00
Moderately increased (ACR: 30 - 300 mg/g; 3 - 30 mg/mmol)	239	46.86
Severely increased (ACR: > 300 mg/g; > 30 mg/mmol)	16	3.14

ACR: albumin-creatinine ratio; CKD: chronic kidney disease.

Table 5. Effect on Various Parameters After Treatment With FDC D/S

Parameters	N	%	Median	Q1 - Q3	P-value
HbA_{1c} (%) before FDC D/S	464	90.98	9.00	8.50 - 9.80	< 0.001
Current HbA_{1c} (%) after FDC D/S	464	90.98	7.50	7.00 - 8.20	
FPG before FDC D/S	437	85.69	181.50	156.00 - 220.00	< 0.001
FPG after FDC D/S	437	85.69	141.00	124.65 - 175.00	
PPG before FDC D/S	428	83.92	255.00	212.00 - 301.00	< 0.001
PPG after FDC D/S	428	83.92	182.00	170.00 - 210.00	
Serum creatinine (mg/dL) before FDC D/S	386	75.69	1.90	1.30 - 20.00	< 0.001
Serum creatinine (mg/dL after FDC D/S	386	75.69	1.53	1.10 - 18.00	
eGFR before FDC D/S	386	75.69	83.83	52.00 - 107.80	< 0.001
eGFR after FDC D/S	386	75.69	84.00	61.00 - 105.81	

HbA_{1c}: glycated hemoglobin; FDC D/S: fixed-dose combination of dapagliflozin and sitagliptin; FPG: fasting plasma glucose; PPG: post-prandial glucose; eGFR: estimated glomerular filtration rate.

ard ratio (HR) 0.61, 95% CI: 0.48 - 0.78) [16]. The landmark DECLARE-TIMI 58 trial further supports the renal benefits of SGLT2is. This study followed up on patients with T2DM over a median period of 4.2 years. Those treated with dapagliflozin (46%) experienced a notable decrease in the rate of decline of eGFR to less than 60 mL/min per 1.73 m^2 (by at least 40%) compared to the placebo group. Moreover, the incidence of severe renal complications such as ERSD/renal death was significantly lower in those receiving dapagliflozin compared to those receiving a placebo (P = 0.012). These results highlight the potential of SGLT2is in improving renal outcomes independent of cardiovascular status [17].

The KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease suggests using SGLT2is for individuals with T2DM, CKD, and an eGFR of ≥ 20 mL/min/1.73 m^2 and continuing when eGFR falls below 20 mL/min/1.73 m^2, unless not tolerated by the patient [30]. In line with the American Diabetes Association (ADA) Standards of Care in Diabetes 2024, SGLT2is are indicated for reducing CKD progression and cardiovascular events in individuals with T2DM, an eGFR of ≥ 20 mL/min/1.73 m^2, and urinary albumin of ≥ 200 mg/g creatinine [12, 18]. These recommendations emphasize the growing recognition of SGLT2is as valuable therapeutic agents for CKD management in T2DM patients.

Table 6. AEs During FDC D/S Use

AEs	N	%
Urinary tract infections	125	24.51
Dehydration	81	15.88
Hypoglycemia	52	10.20
Genital mycotic infection	39	7.65
Changes in serum uric acid	32	6.27
Decreases in renal creatinine clearance	31	6.08
Diabetic ketoacidosis	28	5.49
Hypotension	21	4.12
Vulvovaginitis/balanitis	12	2.35
Hypovolemia	8	1.57

AEs: adverse effects; FDC D/S: fixed-dose combination of dapagliflozin and sitagliptin.

Role of DPP4is in CKD management

DPP4is represent another class of antidiabetic agents with potential benefits in patients with CKD. In a prospective study, T2DM patients (N = 49) with renal dysfunction switched from other DPP4is (vildagliptin, linagliptin, or alogliptin) to a low dose of sitagliptin based on their renal function. Results showed stable renal function and glycemic control with no AEs [31]. The TECOS study involving individuals with CKD showed that sitagliptin was generally well tolerated by CKD patients (at a median follow-up period of 2.8 years) [32]. These studies suggest that low-dose sitagliptin, adjusted to renal function, is a safe and effective option for treating T2DM patients with CKD.

Combination therapy with SGLT2is and DPP4is

The combination of SGLT2is and DPP4is offers a synergistic approach to T2DM management, as demonstrated in this study and supported by previous research. At the same time, SGLT2is enhance the effects of DPP4is by improving beta-cell function and insulin sensitivity [33]. This combination decreases glycemic variability, reduces the risk of hypoglycemia, and offers cardiovascular and renal protection in patients with T2DM [34]. Additional benefits include once-daily dosing that improves adherence and accelerates the attainment of target HbA_{1c} levels, offering enhanced glycemic control with a simplified regimen [14].

Patient profiles considered suitable for FDC D/S include: 1) patients with uncontrolled glycemic parameters; 2) elderly patients; 3) those at high risk of CVD; 4) those with T2DM

and heart failure (HF); 5) those with T2DM and atherosclerotic cardiovascular disease (ASCVD); 6) T2DM patients with CKD; and 7) individuals at high risk of hypoglycemia [34].

In the retrospective Real DAPSI study, 358 patients with T2DM were treated with FDC D/S. After 12 weeks, significant reductions in mean HbA_{1c} levels (from 8.9% to 7.2%), mean fasting blood glucose levels (from 178.8 to 124.0 mg/dL), and PPG levels (from 273.9 to 176.0 mg/dL) were observed. Of note, no serious AEs were reported, thus proving that this combination was effective and safe in managing T2DM [23]. Furthermore, a systemic review by Li et al in patients with T2DM (n = 4,828) revealed that compared to using DPP4is alone, the combination therapy not only improved glycemic control but also led to a significant reduction in body weight (by 2.05 kg) and systolic blood pressure (by 5.90 mm Hg). The combination reduced HbA_{1c} levels by 0.31%, FPG by 8.94 mg/dL, triglyceride levels by 3.25%, and total cholesterol levels by 1.48% [33]. Interestingly, even low doses of SGLT2is in the combination exhibited comparable or superior efficacy in some aspects compared to high doses of monotherapy [33].

Contraindications of FDC D/S include [34]: 1) individuals with eGFR of < 45 mL/min/1.73 m^2; 2) individuals with a history of diabetic ketoacidosis; and 3) individuals with a history of pancreatitis.

A study by Li et al showed that AEs were generally similar between the combination therapy and when each drug was used alone, except for an increased risk of genital infections with the combination as compared to DPP4is alone (RR = 5.31) and a consistent risk of genital infections compared to SGLT2is alone (RR = 0.61) [33]. In individuals receiving SGLT2is, dehydration or orthostatic hypotension resulting from volume reduction due to osmotic diuresis and natriuresis may also be a potential concern, although these AEs have been infrequently documented in randomized controlled trials [35]. In addition, the TECOS study showed that within the CKD cohort, when comparing sitagliptin to placebo groups, the occurrence of severe hypoglycemia was twice as common in CKD versus non-CKD cohorts; however, treatment groups showed no differences despite slightly lower HbA_{1c} levels in the sitagliptin group [32]. Safety data from 12 randomized, placebo-controlled phase 2b/phase 3 trials were analyzed, revealing that treatment with dapagliflozin at various doses is linked to an elevated risk of vulvovaginitis or balanitis due to glucosuria induction [36]. A systematic review and meta-analysis illustrated that DPP4is may mitigate the risk of patients developing genitourinary tract infections associated with SGLT2is use [37].

The current study supports previous research findings regarding the effectiveness and safety of FDC D/S in T2DM patients with CKD. Notably, the FDC D/S therapy led to significant reductions in HbA_{1c} levels ($P < 0.001$) after 3 months of treatment. There were consistently significant reductions in FPG, PPG levels, and serum creatinine levels. A significant improvement in eGFR values was also observed, underscoring its role in preserving renal function. This study provides compelling evidence validating the effectiveness and safety of the combination therapy of SGLT2is and DPP4is in the management of T2DM and CKD. Common AEs included UTIs, dehydration, hypoglycemia, and genital mycotic infections.

Strengths of the study

The multicenter, observational design of the study facilitated the assessment of real-world outcomes. Comprehensive data collection encompassing patient demographics, medical history, and CKD progression offered an understanding of the study population. Additionally, the utilization of objective outcome measures such as HbA_{1c}, FPG, PPG, serum creatinine, and eGFR further strengthened the validity of the outcomes.

Limitations of the study

This retrospective, questionnaire-based study design posed inherent limitations, introducing bias and affecting the reliability of the findings. Dose adjustments for sitagliptin are recommended in those with moderate-to-severe CKD or ESRD [38]; however, the dosage remained unchanged in our study. In addition, there was no control group, which prevented the effectiveness of the treatment under investigation from being compared. Potential confounding variables, such as comorbidities, concomitant medications, and lifestyle factors, might not have been adequately accounted for, potentially influencing treatment outcomes.

Conclusion

This real-world evidence on using FDC D/S in treating T2DM patients with CKD risk showed that it effectively decreases HbA_{1c}, FPG, and PPG levels and improves eGFR values. This study contributes to the evidence supporting the effectiveness and safety of the combination of SGLT2is and DPP4is in the management of T2DM and CKD. The findings underscore the importance of individualized treatment approaches tailored to renal function and cardiovascular risk profiles. More research is required to elucidate the long-term effects and optimal dosing strategies of combination therapy in diverse patient populations.

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Conflict of Interest

The present study was initiated and supported by USV Primate Limited. The authors Rohan Narayan Kesarkar, Ashish Prasad

and Abhijit Pednekar are employees of USV, and the rest of the authors have indicated that they have no other conflict of interest regarding the content of this article.

Informed Consent

The data collected were from the patient's past records and as the data collected were anonymous from the patient's health records, informed consent was not taken.

Author Contributions

Animesh Maiti, Rohan Narayan Kesarkar, Ashish Prasad, and Abhijit Pednekar have contributed to the study design, data support, data analysis, manuscript development, review, and revisions. Rest of the authors have contributed to the data support and manuscript review.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

ADA: American Diabetes Association; AE: adverse event; AKI: acute kidney injury; ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; CRF: case report form; CI: confidence interval; CVD: cardiovascular disease; D/S: dapagliflozin and sitagliptin; DPP4i: dipeptidyl peptidase-4 inhibitor; eGFR: estimated glomerular filtration rate; ESRD: end-stage kidney disease; FPG: fasting plasma glucose; FDC: fixed-dose combination; GLP-1: glucagon-like peptide-1; GFR: glomerular filtration rate; HbA_{1c}: glycated hemoglobin; HR: hazard ratio; IRB: Institutional Review Board; PPG: post-prandial glucose; OAD: oral antidiabetic drug; RR: risk ratio; SGLT2i: sodium-glucose cotransporter-2 inhibitor; T2DM: type 2 diabetes mellitus; UTI: urinary tract infection

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