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Detection and Assessment of Drug-Related Problems Associated with Dapagliflozin in Patients with Type 2 Diabetes Mellitus: A Retrospective Cross-Sectional Study

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Abstract

Background: Dapagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, has emerged as a front-line therapy for type 2 diabetes mellitus (T2DM) with expanding indications including heart failure and chronic kidney disease. While its cardiorenal protective effects are well-established, the comprehensive profile of drug-related problems (DRPs) in real-world clinical settings requires further characterization.

Objective: To evaluate the drug-related problems associated with dapagliflozin therapy in patients with T2DM, including adverse drug reactions, drug-drug interactions, and side effect distribution across demographic subgroups.

Methods: A retrospective cross-sectional study was conducted over three months at Paalana Hospital, Palakkad. Nineteen patients (14 males, 5 females) aged ≥18 years with T2DM who had received SGLT2 inhibitors for at least six months were included. Data were collected using patient data entry forms, quality of life questionnaires, and WHO ADR reporting forms. Glycemic parameters (FBS, PPBS, RBS, HbA1c) were assessed at baseline, three months, and six months. Statistical analysis was performed using appropriate methods with significance set at $p<0.05$.

Results: The study population comprised 73% males and 27% females, with 89.5% aged 40-80 years. Significant glycemic improvements were observed over six months: FBS reduced from 171.22±22.27 to 121.58±19.31 mg/dL ($p<0.001$), PPBS from 251.07±3.28 to 224.47±317.38 mg/dL ($p<0.001$), and HbA1c from 7.72±0.65% to 6.40±0.87% ($p<0.001$). Nine drug-drug interactions were identified, predominantly moderate in severity, involving combinations with glimepiride, insulin aspart, and cardiovascular medications. Adverse drug reactions included urinary tract infections (54.54%), burning sensation in genital area (36.36%), and hypoglycemia (9.08%). Side effects reported were hypoglycemia (33.3%), dehydration (26.7%), hypotension (20%), and weight loss (20%), with notable gender-specific patterns.

Conclusion: Dapagliflozin demonstrates significant glycemic efficacy in real-world practice but is associated with predictable drug-related problems, particularly genitourinary infections and hypoglycemia when combined with insulin secretagogues. Gender-sensitive prescribing, age-tailored monitoring, and initiative-taking medication management are essential to optimize the benefit-risk profile. The findings underscore the importance of comprehensive DRP assessment frameworks in improving long-term outcomes for patients with T2DM receiving SGLT2 inhibitor therapy.

Keywords: Dapagliflozin, SGLT2 inhibitors, drug-related problems, type 2 diabetes mellitus, adverse drug reactions, drug interactions, glycemic control

Introduction

Diabetes mellitus has emerged as one of the most significant global health challenges of the twenty-first century, with its prevalence reaching epidemic proportions across both developed and developing nations. According to the International Diabetes Federation, approximately 537 million adults aged 20-79 years were living with diabetes in 2021, a number projected to rise to 783 million by 2045 (1). Type 2 diabetes mellitus (T2DM) accounts for over 90% of these cases and is associated with substantial morbidity, mortality, and healthcare expenditure worldwide (2). The management of T2DM has evolved over the past two decades, moving beyond simple glycemic control to encompass cardiovascular and renal risk reduction as equally important therapeutic objectives (3). This paradigm shift has been driven by the emergence of two medication classes—sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists—which have demonstrated unprecedented cardiorenal protective effects in large-scale cardiovascular outcome trials (4).

Among the SGLT2 inhibitors, dapagliflozin has emerged as a front-line therapy with expanding indications beyond its original approval for type 2 diabetes. First approved by the United States Food and Drug Administration in 2014 for glycemic control in adults with T2DM, dapagliflozin has since received regulatory approval for additional indications including heart failure with reduced ejection fraction (2019), chronic kidney disease (2021), and heart failure with preserved ejection fraction (2023) (5). This expanding therapeutic landscape reflects the growing recognition that SGLT2 inhibition produces beneficial effects that extend far beyond glucose lowering, encompassing hemodynamic improvements, weight reduction, blood pressure control, and direct cardiorenal protective mechanisms (6). The DAPA-HF trial demonstrated that dapagliflozin reduced the composite of worsening heart failure or cardiovascular death by 26% in patients with heart failure and reduced ejection fraction, regardless of diabetes status (7). Similarly, the DAPA-CKD trial showed a 39% reduction in the composite of sustained decline in estimated glomerular filtration rate, end-stage kidney disease, or death from renal or cardiovascular causes in patients with chronic kidney disease, with or without diabetes (8).

The mechanism of action of dapagliflozin is fundamentally different from other glucose-lowering agents. By selectively inhibiting SGLT2 receptors located in the proximal convoluted tubule of the nephron, dapagliflozin reduces glucose reabsorption, leading to glucosuria and subsequent lowering of plasma glucose concentrations (9). This insulin-independent mechanism offers several advantages, including a low intrinsic risk of hypoglycemia when used as monotherapy and the potential for combination with other antidiabetic agents without overlapping mechanisms (10). The resulting glucosuria typically amounts to 50-80 grams of glucose excreted daily, which translates to a calorie loss of 200-320 kilocalories per day and contributes to modest weight reduction (11). Additionally, the osmotic diuresis induced by glucosuria produces mild volume contraction, blood pressure reduction, and favorable hemodynamic effects that underlie many of the cardiovascular benefits observed in clinical trials (12).

However, the very mechanism that confers therapeutic benefit—glucosuria—also creates a distinct and predictable profile of drug-related problems. The presence of glucose in urine provides a favorable environment for microbial growth, predisposing patients to genitourinary tract infections (13). Clinical trials and real-world studies have consistently demonstrated that

SGLT2 inhibitors increase the risk of genital mycotic infections by three to five times compared to placebo, with women affected more frequently than men due to anatomical and physiological factors (14). The relationship with urinary tract infections is more nuanced, with meta-analyses suggesting that dapagliflozin, unlike some other agents in its class, may be associated with a modest but statistically significant increase in UTI risk (15). These infectious complications, while mild to moderate in severity and responsive to standard antimicrobial therapy, represent the most common drug-related problem encountered in clinical practice and require initiative-taking patient education and monitoring (16).

Beyond genitourinary infections, dapagliflozin produces several other clinically significant drug-related problems that warrant attention. The osmotic diuresis induced by glucosuria can lead to intravascular volume depletion, particularly in susceptible populations including elderly patients, those with impaired renal function, and individuals receiving concomitant diuretic therapy (17). Volume depletion may manifest as symptomatic hypotension, dizziness, orthostatic hypotension, and in severe cases, acute kidney injury (18). The DECLARE-TIMI 58 trial, which included over 17,000 patients, documented higher rates of volume depletion events with dapagliflozin compared to placebo, though serious events were uncommon (19). This hemodynamic effect, while well-tolerated, necessitates careful patient selection and monitoring, particularly when dapagliflozin is used in combination with other blood pressure-lowering medications (20).

Hypoglycemia represents another important consideration in the safety profile of dapagliflozin. While the drug has low intrinsic hypoglycemia risk due to its insulin-independent mechanism, the risk increases substantially when dapagliflozin is combined with insulin or insulin secretagogues such as sulfonylureas (21). The significant glycemic improvements achieved with dapagliflozin, typically reducing HbA1c by 0.8-1.2%, may necessitate dose reduction of concomitant glucose-lowering agents to prevent hypoglycemic events (22). This interaction underscores the importance of comprehensive medication review and initiative-taking dose adjustment at the time of dapagliflozin initiation (23).

A rare but serious drug-related problem associated with SGLT2 inhibitors is euglycemic diabetic ketoacidosis. This condition presents with the metabolic features of ketoacidosis—including elevated anion gap metabolic acidosis and ketonemia—without the marked hyperglycemia typically seen in diabetic ketoacidosis (24). The mechanism involves SGLT2 inhibitor-induced shifts in fuel metabolism toward increased fat oxidation and ketone body production, combined with reduced renal clearance of ketones (25). While the absolute risk is low (approximately 0.3% in the DECLARE-TIMI 58 trial), euglycemic DKA carries significant morbidity and requires prompt recognition and management (26). Risk factors include prolonged fasting, acute illness, surgery, excessive alcohol consumption, and reduced insulin doses. Patient education about "sick day" protocols—including temporary discontinuation of dapagliflozin during intercurrent illness—is essential for risk mitigation (27).

Drug-drug interactions represent another dimension of dapagliflozin's safety profile that requires consideration. While SGLT2 inhibitors have a low propensity for clinically significant pharmacokinetic interactions, emerging literature has identified several important interactions in clinical practice (28). The combination of dapagliflozin with loop diuretics produces synergistic natriuresis, increasing the risk of volume depletion and hypotension (29). Recent case reports have raised concern about potential rhabdomyolysis risk when dapagliflozin is combined with rosuvastatin, though the mechanism and true incidence remain to be defined (30). Interactions with lithium, tacrolimus, and angiotensin-receptor-neprilysin inhibitors have also been documented, highlighting the need for comprehensive medication review in complex patients with polypharmacy (31).

The demographic characteristics of patients receiving dapagliflozin therapy add another layer of complexity to the management of drug-related problems. The typical patient population includes middle-aged and older adults with multiple comorbidities, placing them at increased risk for polypharmacy, age-related physiological changes, and reduced physiological reserve (32). Elderly patients are particularly vulnerable to volume depletion, hypotension, and falls, necessitating enhanced monitoring and individualized therapeutic approaches (33). Gender differences in drug response and adverse effect profiles are increasingly recognized, with emerging evidence suggesting that women may experience greater glycemic and weight loss responses to SGLT2 inhibitor therapy, potentially increasing their susceptibility to certain adverse effects while deriving greater therapeutic benefit (34).

Real-world evidence has become increasingly important in understanding the complete safety profile of dapagliflozin, complementing data from randomized controlled trials (35). While trials provide rigorous evidence of efficacy and safety under control conditions, real-world studies capture the full spectrum of patients encountered in clinical practice, including those with multiple comorbidities, complex medication regimens, and varying levels of adherence and monitoring (36). Post-marketing pharmacovigilance databases, such as the FDA Adverse Event Reporting System, have identified potentially overlooked adverse reactions including signals for bladder cancer, cholangiocarcinoma, and thrombotic stroke, underscoring the importance of ongoing safety surveillance (37).

The comprehensive assessment of drug-related problems associated with dapagliflozin requires integration of data across multiple domains: patient demographics and clinical characteristics, glycemic efficacy, blood pressure and hemodynamic effects, drug-drug interactions, and adverse event profiles (38). Gender- and age-stratified analyses are essential for identifying differential risks and benefits that may inform personalized prescribing decisions (39). The relationship between glycemic improvement and adverse effects must be carefully balanced, recognizing that the therapeutic success of dapagliflozin in lowering HbA1c may simultaneously increase the risk of predictable adverse effects such as genitourinary infections and, in susceptible patients, hypoglycemia (40).

This study aims to comprehensively evaluate the drug-related problems of dapagliflozin in a real-world patient population, examining the distribution of adverse effects across demographic subgroups, characterizing drug-drug interaction patterns, and assessing the relationship between glycemic efficacy and safety outcomes. By integrating clinical, demographic, and safety data, this research seeks to provide clinically actionable insights that can optimize the benefit-risk profile of dapagliflozin therapy and guide personalized approaches to prescribing, monitoring, and adverse effect management. The findings will contribute to the growing body of real-world evidence on SGLT2 inhibitor safety and support the development of evidence-based strategies for maximizing therapeutic benefits while minimizing drug-related harm in this expanding patient population.

METHODOLOGY

A cross-sectional survey is planned to conduct detection and assessment of drug related problems associated with SGLT2 inhibitors in diabetes population. Questionnaire was distributed to Department of general medicine in Paalana hospital, Palakkad. Collected data will be analyzed using suitable statistical methods.

- ✓ Study type: Retrospective cross-sectional study.
- ✓ Study duration: 3 months.
- ✓ Study population: patients from Paalana hospital Palakkad.
- ✓ Study tools: patient data entry form, Questionnaire for QOL, WHO ADR reporting form

✓ Study criteria**:**

a. Inclusion criteria:

- Both sex of age above 18 years.
- Patients with type 2 diabetes mellitus(T2DM).
- Diabetic patients using SGLT2 inhibitors at least 6 months as a diabetic drug.

b. Exclusion criteria:

- Diabetic ketoacidosis history
- Active urinary tract infection or history of recurrent UTIs
- Pediatrics, Pregnant and lactating women
- Know hypersensitivity to dapagliflozin or any component of the medication

RESULTS

Table no.2: DISTRIBUTION OF POPULATION ACCRODING TO GENDER

Gender	Population	Percentage
Female	5	27%
Male	14	73%

Out of total population of nineteen individuals, males constitute the majority.

- Male: fourteen individuals (73%)
- Female: five individuals (27%)

Table no 3: DISTRIBUTION OF POPULATION ACCRODING TO AGE

Age	Male	Percentage	Female	Percentage
18-40	0	0%	0	0%
40-60	6	31.57%	2	10.52%
60-80	6	31.57%	3	15.78%
>80years	1	5.26%	1	5.26%

Out of the total nineteen people, most belongs to the 40–80yearsagegroup.

- 40–60years:8people(6males,2females)
- 60–80years:9people(6males,3females)
- Above80years: 2people(1male,1female)
- 18–40years: No individuals

Table No 4: DISTRIBUTION OF BLOOD PRESSURE LEVEL IN PATIENTS

Bood Pressure	Male	Percentage	Female	Percentage
110/80	3	15.78%	1	5.26%
120/80	2	10.52%	0	0%
130/80	2	10.52%	2	10.52%
140/80	1	5.26%	0	0%
150/80	1	5.26%	0	0%
160/80	2	10.52%	1	5.26%
130/90	1	5.26%	0	0%
140/90	2	10.52%	1	5.26%

Out of nineteen people, most have normal to high blood pressure, and males are more than females in all categories.

- Normal blood pressure is seen in a few people.
- Many people have slightly high or high blood pressure.
- Males show higher blood pressure more often than females.
- Only a few females are seen, mostly with normal or moderately high blood pressure.

Table No 6: DISTRIBUTION OF PULSE RATE IN PATIENTS

Pulse Rate	Male	Percentage	Female	Percentage
60-69	4	21.05%	1	5.26%
70-79	3	15.78%	2	10.52%
80-89	5	26.31%	2	10.52%
90-99	2	10.52%	0	0

Out of the total of nineteen people, pulse rates are mostly within the normal range. Five people have a pulse rate of 60–69bpm, with more males than females.
Another five people fall in the 70–79 bpm range, including both males and females. The highest number of people (seven) have a pulse rate of 80–89bpm, males. Only two people have a pulse rate of 90–99 bpm, and both are males.

TableNo8: DISTRIBUTION OF RESPIRATION RATE IN PATIENTS

Respiration Rate	Male	Percentage	Female	Percentage
20	5	26.31%	1	5.26%
22	7	36.84%	3	15.78%
24	0	0%	1	5.26%
26	2	10.52%	0	0%

Outofthe19people, most have a respiration rate of 20–22 breaths per

minute. Six people have a respiration rate of twenty, with more males than females.
Ten people have a respiration rate of twenty-two, including both males and females. Only one female has a respiration rate of twenty-four.
Two males have a respiration rate of twenty-six.

Table no 9. Distribution of Average Blood Sugar Levels in Study Population (N=19)

Types of Blood Sugar Levels	At initiation of therapy	At Third month	At sixth month	P value
FBS	171.22±22.269	134.78±27.258	121.58±19.305	<0.001*
PPBS	251.07±3.275	235.48±36.274	224.47±317.376	<0.001*
RBS	178.29±31.651	168.45±11.028	164.36±16.826	<0.001*
HBA1C	7.720±0.654	6.46±0.731	6.400±0.873	<0.001*

*Significant at p value <0.05

FBS levels decreased significantly from 171.22±22.269 at before the initiation of therapy to 134.78±27.258 and 121.58±19.305over the treatment period ($p < 0.001$).

PPBS value shows a significant reduction from 251.07±3.275 to 235.48±36.274 throughout the course of study period.

RBS levels decreased significantly from 178.29±31.651 at before the initial therapy to 168.45±11.028 and 164.36±16.826 over the follow-up period ($p < 0.001$).

HBA1C decreased significantly from 7.720±0.654 before the initiation of therapy to 6.46±0.731 and 6.400±0.873 over the study duration ($p < 0.001$).

Table No 10: DRUG INTERACTION CHART

S no	Drug interaction	Type	Management
1	Aspirin+Bisoprolol	Minor	Use caution/monitor
2	Aspirin+ticagrelor	Moderate	Use caution/monitor
3	Glymipride+Dapagliflozi n	Moderate	Modifytherapy/monitorclosely
4	Ofloxacin+Metformin	Moderate	Usecaution/monitor
5	Pantoprazole+Digoxin	Mild	Avoid/usealternatedrug
6	Ticagrelor+Rosvastatin	Moderate	use monitor/caution
7	Aspirin+Enalapril	Mild	Avoid/usealternatedrug
8	Dapaglifloxin+Insulin Aspart	Moderate	Use caution/monitor
9	levothyroxine+Metformi	Mild	Use caution/Monitor

	n		

In the study population of nineteen patients, several drug interactions were identified. Most of the interactions were mild to moderate in nature.
The common management approach was use with caution and regular monitoring.
Aspirin showed interactions with bisoprolol, ticagrelor, and enalapril, requiring monitoring or alternative therapy.
Antidiabetic drugs such as glimepiride, dapagliflozin, insulin aspart and metformin showed moderate interactions, so close monitoring or therapy modification is needed.
Some combinations, like pantoprazole with digoxin, should be avoided or replaced with an alternative drug.
Overall, careful monitoring and appropriate management can reduce the risk of adverse effects.

Table No 11: DISTRIBUTION OF ADVERSE DRUG REACTION IN PATIENTS

Name of Adverse Drug Reaction	**frequency**	**percentage**
Urinary Tract Infection	6	54.54%
Burning sensation genital area	4	36.36%
Hypoglycemia	1	9.08%

Among the19patients, the most common adverse drug reaction was urinary tract infection, seen in14 patients (54.54%).
Four patients (36.36%) reported a burning sensation in the genital area.
Hypoglycemia was observed in one patient (9.08%), making it the least common adverse reaction.

Table No 12: DISTRIBUTION OF SIDE EFFECTS IN PATIENTS

Side Effect	Male	Percentage	Female	Percentage
hypoglycemia	2	13.3%	3	20%
Hypotension	1	6.7%	2	13.3%
Weight loss	1	6.7%	2	13.3%
dehydration	3	20%	1	6.7%

Out of the total nineteen patients, side effects were present in both males and females. Hypoglycemia was observed in two males and three females.
Hypotension was seen in one male and two female.
Weight loss was reported in1male and 2females.
Dehydration was noted in three males and one female.

DISCUSSION

Gender-Based Distribution in the Context of Dapagliflozin's Drug-Related Problems

The study population consisted of nineteen participants, with a marked difference in gender distribution: fourteen were male (73%) and five were female (27%). This predominance of male subjects is a significant demographic characteristic that must be considered when interpreting the study's findings on drug-related problems (DRPs) associated with dapagliflozin. The existing literature provides important context for understanding how this gender imbalance might influence the observed safety profile of the drug.

1. Increased Susceptibility of Females to Genital Infections

The most well-documented DRP for SGLT2 inhibitors like dapagliflozin is an increased risk of genital mycotic infections. Crucially, multiple studies and drug information sources indicate that this risk is not evenly distributed between genders. The FDA-approved prescribing information for dapagliflozin explicitly states that genital mycotic infections were "more frequently reported in females than in males."

This finding is strongly supported by a recent prospective observational study from 2025, which found that among patients on SGLT2 inhibitors (98.5% of whom were on dapagliflozin), the incidence of genital infections was higher in females (36.25%) compared to males (30.8%). The mechanism is attributed to enhanced glucosuria caused by the drug, which creates a favorable environment for microbial growth, a risk that is inherently higher in the female genitourinary tract.

Therefore, the underrepresentation of females in our sample (only 27%) means that the full scope of this major, gender-linked adverse event may not be accurately captured. A study with a more balanced or female-predominant population would report a higher overall incidence of genital infections.

2. Gender-Neutral Safety Profile for Other Serious Events

While females are more prone to genital infections, large-scale clinical trials suggest that the safety profile for other serious adverse events is comparable between men and women. A pre-specified analysis of the landmark DECLARE-TIMI 58 trial, which included over 17,000 patients, concluded that "the overall safety profile of dapagliflozin was similar for women and men". This trial data showed no significant difference between genders in the occurrence of serious events like renal-related adverse events, fractures, or major hypoglycemia.

However, some nuances exist. The same trial data showed a trend, though not always statistically significant, for different risks. For instance, the odds ratio for volume depletion was slightly higher in males (OR 1.46) than in females (OR 1.39) when comparing dapagliflozin to placebo. This suggests that while the overall safety profile is similar, the specific types of DRPs and their relative risk might vary.

3. Underrepresentation of Women in Clinical Research

The significant gender imbalance in our study (73% male, 27% female) reflects a broader issue in medical research. Recent literature critically highlights the "underrepresentation of women in clinical trials for kidney and cardiovascular protective drugs, such as SGLT2 inhibitors". This underrepresentation is a concern because it can lead to a less complete understanding of sex-specific adverse reactions. As one review notes, women are sometimes "more likely to experience adverse events" from certain treatments, and the lack of female subjects in trials prevents a "sex-informed approach in prescribing practices." Our study's demographic profile, with only 27% female participation, may inadvertently perpetuate this gap in knowledge by providing limited data on how dapagliflozin affects female patients.

4. Analysis of Our Study's Gender Distribution

Given the literature, the predominance of males in our sample suggests that our results may be more representative of the DRP profile in men. While the study may accurately capture the types and rates of problems experienced by male patients (such as the abdominal pain noted in one study as being more common in males), it is underpowered to detect the full range and frequency of DRPs that affect women, particularly genital infections. To provide a complete picture, any discussion of DRPs in this cohort must acknowledge this gender imbalance as a limitation and compare the findings against the established literature showing a higher infectious risk for women.

Age-Based Distribution in the Context of Dapagliflozin's Drug-Related Problems

The study population comprised 19 participants distributed across three age brackets, with the majority (n=17, 89.5%) being over 40 years of age. Specifically, eight participants (42.1%) were in the 40–60-year range, 9 (47.4%) were in the 60–80-year range, and 2 (10.5%) were over 80 years old. There were no participants, there were under forty. This age distribution is highly characteristic of the typical patient population for which dapagliflozin is indicated, namely middle-aged and older adults with type 2 diabetes, heart failure, or chronic kidney disease. The concentration of patients in the 60–80-year bracket (47.4%) is particularly significant, as this demographic is known to be at the highest risk for both polypharmacy and age-related physiological changes that can precipitate drug-related problems.

1. Increased Risk of Volume Depletion and Hypotension in Older Adults
Literature consistently identifies advanced age as a risk factor for volume depletion events with SGLT2 inhibitors like dapagliflozin. The physiological changes associated with aging—including reduced renal function, decreased thirst sensation, and diminished baroreceptor sensitivity—make older patients more vulnerable to the diuretic effects of the drug.

A pooled analysis of phase 3 clinical trials specifically examining the safety of dapagliflozin in elderly patients (≥65 years) found that while the efficacy and overall safety profile were consistent with younger adults, there was a slightly higher incidence of adverse events related to volume depletion (e.g., dehydration, hypotension) in the older cohort . This finding is echoed in the FDA-approved labeling, which advises consideration of volume status and renal function in elderly patients due to the higher risk of volume depletion.

In our study, 53% of the population (n=10) is over 60 years old, and two patients are over 80. This demographic is precisely the group identified in the literature as being at elevated risk. Therefore, any reports of dizziness, orthostatic hypotension, or dehydration in this study should be scrutinized, particularly in patients taking concurrent diuretics.

2. Renal Function and Age-Related Decline
Dapagliflozin's efficacy and safety are dependent on adequate renal function, as its mechanism of action requires glomerular filtration. The prescribing information recommends against initiating dapagliflozin in patients with an eGFR below 25-30 mL/min/1.73m², depending on the indication (diabetes vs. heart failure), and recommends discontinuation once eGFR falls persistently below this threshold.

The risk of age-related renal impairment is significant. The 60-80 year and >80-year cohorts (n=11, 57.9%) are at the highest risk of having some degree of chronic kidney disease (CKD). Literature reviews emphasize that while dapagliflozin provides renal protective benefits, it must be monitored closely in older adults to ensure that a decline in renal function does not go undetected. Our study's data would need to be correlated with eGFR values to determine if any DRPs related to renal function (e.g., acute kidney injury, further eGFR decline) occurred in these older age groups.

3. Polypharmacy and Drug-Drug Interactions in the Middle-Aged and Elderly
The 40-60 year and 60–80-year groups represent a population where the prevalence of comorbidities—such as hypertension, dyslipidemia, and coronary artery disease—increases substantially. This often leads to polypharmacy, which is a primary driver of DRPs.

As noted in the previous discussion, dapagliflozin has documented interactions with loop diuretics (increasing risk of volume depletion) and potential interactions with drugs like lithium (affecting lithium levels) and antihypertensives. The risk of these interactions is amplified in patients over sixty who are taking multiple medications. A recent study on DRPs in diabetic patients found that the number of medications was a significant predictor of DRPs, and that over sixty patients were overrepresented in the group experiencing at least one DRP. Our study's data showing a high concentration of patients in the 40–80-year range (89.5%) suggests that polypharmacy is a relevant factor in this cohort.

4. The "Oldest Old" (>80 Years) and Limited Evidence
The inclusion of two patients over 80 years old (10.5%) is noteworthy. Clinical trial data for the "oldest old" is often limited, as these patients are frequently excluded from landmark trials due to frailty or multiple comorbidities. Real-world evidence and post-marketing studies become crucial for this demographic.

Literature focusing on very elderly patients (≥75-80 years) suggests that while dapagliflozin can be used safely, it requires a higher degree of vigilance. A study by Yu et al. (2024) on very elderly patients with heart failure found that while the benefits were maintained, the incidence of frailty-related adverse events and the need for dose adjustments due to renal decline were higher compared to younger old patients. The two patients over eighty in our study represent a vulnerable population where the risk-benefit ratio must be assessed on an individual basis, and any DRPs observed in this small subgroup warrant specific attention.

5. Absence of Younger Patients (18-40 Years)
The complete absence of patients under forty is expected, given that dapagliflozin is primarily indicated for conditions (T2DM, HF, CKD) that are far more prevalent in older populations. While early-onset type 2 diabetes is increasing, the overall prescribing patterns skew heavily toward older adults. Therefore, our sample is reflective of the real-world patient population, and the lack of data in the 18-40 bracket is not a limitation but rather an accurate representation of the drug's target demographic.

Blood Pressure Distribution in the Context of Dapagliflozin's Drug-Related Problems
The study population of nineteen patients exhibits a diverse range of baseline blood pressure (BP) readings, spanning from 110/80 mmHg to 160/80 mmHg and including various diastolic pressures such as 130/90 mmHg and 140/90 mmHg. The distribution shows that a massive portion of patients (n=10, 52.6%) have a systolic blood pressure (SBP) of 130 mmHg or higher, indicating a prevalence of elevated BP or hypertension within the cohort. This distribution is clinically significant when evaluating the safety and drug-related problems (DRPs) associated with dapagliflozin therapy, as the drug's antihypertensive effect and its interaction with baseline BP can influence both efficacy and adverse outcomes.

1. Antihypertensive Effect of Dapagliflozin Across the BP Spectrum
The literature consistently demonstrates that dapagliflozin exerts a modest but clinically meaningful reduction in blood pressure. A comprehensive review of SGLT2 inhibitors published in Hypertension confirms that dapagliflozin, along with other agents in its class, reduces blood pressure through multiple mechanisms, including osmotic diuresis, natriuresis, and weight loss. The magnitude of this effect is well-documented.

Recent prospective studies provide precise estimates of these changes. A 2024 Italian multicenter study in patients with diabetic kidney disease found that after 12 weeks of dapagliflozin 10 mg/day, office SBP declined by -7.9 mmHg (P = 0.009), while 24-hour ambulatory monitoring revealed a nighttime SBP reduction of -3.0 mmHg and a daytime

SBP reduction of -2.4 mmHg. Importantly, this study also demonstrated that dapagliflozin improves circadian blood pressure rhythm, increasing the prevalence of normal dipping (nighttime BP fall) from 31.3% to 50.6% (P = 0.005). The DAPA-HF trial similarly reported a placebo-corrected reduction in SBP of -2.54 mmHg in 2 weeks, with the effect being slightly smaller in patients with the lowest baseline SBP.

In the study, the wide range of baseline BP values means that patients will experience varying degrees of BP reduction. Those with higher baseline readings (e.g., 150/80, 160/80 mmHg) may derive greater absolute BP-lowering benefit, potentially contributing to improved hypertension control—a secondary therapeutic advantage of dapagliflozin beyond glycemic management.

2. Risk of Hypotension in Patients with Lower Baseline BP

The primary safety concern related to dapagliflozin's BP-lowering effect is the potential for symptomatic hypotension, particularly in patients who already have lower baseline BP or are taking concomitant antihypertensive medications.

Data shows that 4 patients (21.0%) had a baseline BP of 110/80 mmHg (n=4) or 120/80 mmHg (n=2, though the latter are not hypotensive but represent the lower-normal range). According to drug prescribing information, patients with SBP < 110 mmHg were included in clinical trials only if they were not symptomatic, but caution is advised. The MIMS prescribing information specifically identifies elderly patients and those on loop diuretics as being at increased risk for volume depletion or hypotension.

The DAPA-HF trial provides reassuring data on this point: among 1,205 patients with baseline SBP < 110 mmHg, the benefit of dapagliflozin was consistent with the overall trial (hazard ratio 0.76), and study drug discontinuation did not differ between dapagliflozin and placebo across SBP categories. However, the trial excluded patients with SBP < 95 mmHg, and the rate of the primary outcome was actually higher in the lowest SBP category (20.6 per 100 person-years) compared to the highest SBP category (13.8 per 100 person-years), reflecting the well-known "BP paradox" in heart failure where lower BP is associated with worse prognosis .

In the study, the four patients with BP 110/80 mmHg warrant closer monitoring for symptoms of hypotension (dizziness, lightheadedness, syncope) after initiating dapagliflozin, particularly if they are also on diuretics or other BP-lowering medications.

3. Concomitant Antihypertensive Therapy and Drug Interactions

The literature emphasizes that dapagliflozin is often used in patients already receiving multiple antihypertensive agents, which can potentiate the risk of hypotension. A health advisory publication notes that combining dapagliflozin with ACE inhibitors, ARBs, and nitrates increases the chance of dizziness or fainting, especially when standing up. Similarly, the combination of diuretics (loop or thiazide) raises the risk of dehydration, hypotension, and kidney stress.

Notably, research has demonstrated a synergistic interaction between dapagliflozin and loop diuretic natriuresis is increased by 36% after one week of dapagliflozin, due to enhanced delivery of sodium chloride to the loop of Henle. Conversely, dapagliflozin natriuresis is increased 3-fold after one week of bumetanide. This bidirectional constructive interaction means that patients on combination therapy require careful monitoring.

In study population, the presence of elevated BP readings (e.g., 140/90, 150/80, 160/80 mmHg) suggests that many patients have hypertension and may already be prescribed antihypertensive medications. Therefore, the potential for drug-drug interactions and additive BP-lowering effects should be considered when evaluating DRPs.

Pulse Rate Distribution in the Context of Dapagliflozin's Cardiovascular Effects

The study population of nineteen patients exhibits a pulse rate distribution ranging from the 60-69 bpm bracket to the 90-99 bpm bracket. Most patients (n=15, 78.9%) have a pulse rate between 60 and 89 bpm, with the largest group (n=7, 36.8%) falling in the 80-89 bpm range. Two male patients (10.5%) are in the 90-99 bpm range, indicating a higher resting heart rate. This distribution is clinically relevant when evaluating the cardiovascular effects of dapagliflozin, as heart rate is both a potential modifier of treatment response and, in some contexts, a parameter that may be modestly influenced by the therapy.

1. Dapagliflozin's Effect on Heart Rate: Evidence of a Reducing Effect

Recent literature provides compelling evidence that dapagliflozin therapy is associated with a modest but statistically significant reduction in heart rate. This finding is important because elevated resting heart rate is an established risk factor for cardiovascular events.

A 2024 study published in a cardiovascular journal investigated the effect of dapagliflozin on blood pressure and cardiac function in patients with type 2 diabetes and hypertension. After 24 weeks of treatment, the dapagliflozin group showed a significantly lower heart rate (70.28 ± 11.94 beats/min) compared to the conventional treatment group (75.76 ± 12.35 beats/min, $P < 0.05$). This represents a mean reduction of approximately 5.5 bpm attributable to dapagliflozin therapy.

This finding is corroborated by another research. A 2019 study examining the effects of dapagliflozin on electrocardiogram parameters in patients with type 2 diabetes reported that heart rate was found to be significantly lower at control admission ($p<0.05$) after treatment initiation. Furthermore, a large-scale study on SGLT2 inhibitors in diabetic patients with implantable cardiac devices found that at one year of follow-up, SGLT2i-users had a lower heart rate along with improved clinical status and reduced inflammatory markers.

The consistency of these findings across different study populations suggests that heart rate reduction may be a genuine, albeit modest, effect of dapagliflozin therapy. The proposed mechanisms include improved cardiac efficiency, reduced sympathetic tone, and favorable hemodynamic changes.

2. Heart Rate as a Prognostic Marker and Effect Modifier

The distribution of pulse rates in our study, particularly the presence of patients in higher ranges, must be interpreted considering the well-established relationship between heart rate and cardiovascular risk.

A landmark patient-level pooled analysis of the DAPA-HF and DELIVER trials (n=6,401 patients in sinus rhythm) provides critical context. This study demonstrated that:

Among patients in sinus rhythm, the rate of the primary outcome (worsening heart failure or cardiovascular death) was higher in those with higher heart rates: 16.8 per 100 person-years for patients with heart rate ≥80 bpm versus 7.7 per 100 person-years for those with heart rate <60 bpm.

The relationship between heart rate and risk was particularly steep in patients with heart failure with reduced ejection fraction.

Importantly, the benefit of dapagliflozin was consistent across the entire heart rate range. For patients with sinus rhythm with heart rate <60 bpm, the hazard ratio for dapagliflozin versus placebo was 0.72 (95% CI, 0.55-0.95); for those with heart rate ≥80 bpm, the hazard ratio was 0.77 (95% CI, 0.61-0.97). This indicates that dapagliflozin provides cardiovascular protection regardless of baseline heart rate.

However, the same analysis found that heart rate was not associated with outcomes in patients with atrial fibrillation, regardless of heart failure phenotype. This distinction is important, as approximately 25-40% of heart failure patients may have atrial fibrillation.

Respiratory Rate Distribution in the Context of Dapagliflozin's Pulmonary Effects

The study population of nineteen patients exhibits a respiratory rate distribution ranging from 20 to 26 breaths per minute. Most patients (n=16, 84.2%) have respiratory rates between 20 and 22 breaths per minute, with the largest group (n=10, 52.6%) at 22 breaths per minute. Two male patients (10.5%) have a respiratory rate of twenty-six breaths per minute, which represents the upper end of the normal range (typically 12-20 breaths per minute for healthy adults, though slightly higher rates can be normal in certain patient populations). This distribution is clinically relevant when evaluating the emerging evidence regarding dapagliflozin's effects on pulmonary function, respiratory disorders, and potential drug-related problems affecting the respiratory system.

1. Dapagliflozin's Effects on Pulmonary Function: Evidence of Neutral or Beneficial Effects

Recent literature provides growing evidence that dapagliflozin and other SGLT2 inhibitors may have neutral or even beneficial effects on pulmonary function, rather than causing respiratory depression or impairment. Multiple studies have specifically investigated pulmonary function tests, including spirometry and diffusing capacity, in patients treated with dapagliflozin.

A 2021 study examining the short-term effects of dapagliflozin on pulmonary function in heart failure with reduced ejection fraction (HFrEF) patients found that spirometry values did not change after 2-4 weeks of therapy. This study specifically measured standard spirometry and diffusing capacity of the lungs for carbon monoxide (DLCO) and found no significant alterations following dapagliflozin initiation. Similarly, a more comprehensive 2025 study evaluating dapagliflozin's effects on exercise performance, cardiac remodeling, and pulmonary function in HFrEF patients reported that pulmonary function tests showed no significant changes in lung diffusion or spirometry after 6 months of treatment.

The recently published DAPA-LUNG-HF trial (2025) provides the most detailed assessment to date, confirming that after 6 months of dapagliflozin therapy, pulmonary function tests and overnight respiratory monitoring showed no significant changes in lung diffusion or spirometry. The study specifically noted that the apnea-hypopnea index remained unchanged (from 5.0 [1.1-16.6] at baseline to 6.2 [0.7-13.8]/h; p = n.s.). These findings collectively suggest that dapagliflozin does not adversely affect basic pulmonary mechanics or respiratory rate in a clinically meaningful way.

2. Dapagliflozin and Respiratory Rate: Potential Mechanisms and Clinical Implications
The absence of dapagliflozin-induced changes in respiratory rate is physiologically consistent with the drug's mechanism of action. Unlike medications that directly affect the central nervous system respiratory centers (e.g., opioids, benzodiazepines) or those that cause bronchospasm (e.g., beta-blockers), SGLT2 inhibitors work primarily through renal glucose excretion and have no known direct effects on respiratory control centers or bronchial smooth muscle.

However, the literature does identify indirect effects that could theoretically influence respiratory rate in specific patient populations:

Volume depletion and metabolic compensation: In patients who develop significant volume depletion or dehydration from dapagliflozin's diuretic effects, a compensatory increase in respiratory rate would not be expected as a primary response. However, if volume depletion leads to metabolic acidosis (a rare but serious adverse effect), tachypnea could develop as part of the compensatory respiratory response. The literature notes that dapagliflozin treatment results in increased fasting β-hydroxybutyrate (BHBA) in some patients, indicating a shift toward ketone body production. In rare cases, this can progress to euglycemic diabetic ketoacidosis, which presents tachypnea (Kussmaul breathing) as a cardinal sign.

Improved ventilatory efficiency: Interestingly, while resting respiratory rate may remain unchanged, studies have documented improvements in exercise ventilatory efficiency (VE/VCO2 slope) with dapagliflozin therapy. A 2025 study reported that the VE/VCO2 slope improved from 34.2 (31.1-39.2) at baseline to 33.7 (30.2-37.6) after 6 months (p = 0.006), suggesting that patients require less ventilatory effort for a given level of carbon dioxide production during exercise. This improvement in ventilatory efficiency may reflect beneficial effects on pulmonary congestion and cardiac function.

3. Respiratory Safety Profile: Evidence from Large-Scale Meta Analyses
A comprehensive 2024 network meta-analysis of SGLT2 inhibitors involving over 100,000 patients provides robust evidence regarding respiratory safety. This analysis assessed ten respiratory outcomes, including acute respiratory failure, pulmonary edema, COPD, dyspnea, asthma, respiratory tract infection, lower respiratory tract infection, and pneumonia. The findings revealed that dapagliflozin may be the best gliflozin for preventing asthma among the five agents assessed (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and sotagliflozin)

Glycemic Control Parameters in the Context of Dapagliflozin Therapy

Table No. 9 presents longitudinal data on four key glycemic parameters—Fasting Blood Sugar (FBS), Postprandial Blood Sugar (PPBS), Random Blood Sugar (RBS), and Glycated Hemoglobin (HbA1c)—measured at three time points: initiation of therapy, third month, and sixth month. The data demonstrates a consistent and statistically significant improvement ($p < 0.001$ for all parameters) across all glycemic indices over the six-month study period. These findings are robustly supported by the existing literature on dapagliflozin's efficacy and provide important context for understanding both the therapeutic benefits and potential drug-related problems associated with medication.

1. Magnitude of HbA1c Reduction: Consistent with Landmark Trials

The reduction in HbA1c from 7.72% at baseline to 6.46% in three months and 6.40% in six months represents a mean reduction of approximately 1.32% over the study period. This finding is highly consistent with the efficacy data reported in major clinical trials and meta-analyses of dapagliflozin.

A comprehensive 2019 meta-analysis of dapagliflozin clinical trials published in Diabetes, Obesity and Metabolism reported that dapagliflozin 10 mg/day consistently reduced HbA1c by 0.8-1.2% compared to placebo, with the magnitude of reduction depending on baseline HbA1c and patient characteristics. The slightly larger reduction observed in our study (1.32%) may reflect the high baseline HbA1c (7.72%), as the literature consistently demonstrates that patients with higher baseline HbA1c experience greater absolute reductions with SGLT2 inhibitor therapy.

The landmark DECLARE-TIMI 58 trial, which enrolled over 17,000 patients, documented a mean HbA1c reduction of 0.42% with dapagliflozin compared to placebo at 48 months, though this included patients with well-controlled diabetes at baseline. A more recent 2024 real-world study in Indian patients with type 2 diabetes reported HbA1c reductions of 1.1-1.4% at 6 months, closely mirroring our findings and suggesting that real-world effectiveness often exceeds efficacy observed in tightly controlled clinical trials.

The fact that most of the HbA1c reduction occurred within the first three months (1.26% reduction) with minimal additional reduction in the subsequent three months (0.06%) is consistent with the drug's known pharmacokinetics and pharmacodynamics. Dapagliflozin's maximal glycemic effects are typically observed within 12-24 weeks of treatment initiation.

2. Fasting Blood Sugar Reduction: Rapid and Sustained Effect

The FBS data show a progressive decline from 171.22 mg/dL at baseline to 134.78 mg/dL at three months and 121.58 mg/dL at six months, representing a mean reduction of 49.64 mg/dL (29%) over the study period. This finding aligns closely with published literature.

A pooled analysis of phase 3 clinical trials found that dapagliflozin 10 mg/day reduced FBS by 25-35 mg/dL compared to placebo at 24 weeks. The slightly larger reduction in our study reflects the higher baseline FBS values. The DAPPER trial in Japanese patients with type 2 diabetes reported FBS reductions of 28.7 mg/dL with dapagliflozin monotherapy at 24 weeks, while combination therapy with other agents produced reductions of up to 45 mg/dL.

The progressive nature of the FBS reduction—with continued improvement between months three and six (additional 13.2 mg/dL reduction)—suggests that the full glycemic benefits of dapagliflozin may extend beyond the initial titration period and may be augmented by concomitant lifestyle modifications or weight loss, which are known to occur with SGLT2 inhibitor therapy.

3. Postprandial Blood Sugar Reduction: A Key Mechanism of Action

The PPBS data demonstrates a reduction from 251.07 mg/dL at baseline to 235.48 mg/dL in three months and 224.47 mg/dL at six months, representing a mean reduction of 26.6 mg/dL (10.6%) over six months. This finding is particularly important as it reflects dapagliflozin's unique mechanism of action.

Unlike medications that stimulate insulin secretion or enhance insulin sensitivity, SGLT2 inhibitors lower blood glucose by increasing urinary glucose excretion, regardless of insulin levels. This mechanism results in reductions in both fasting and postprandial glucose. A mechanistic study published in Diabetes Care demonstrated that dapagliflozin reduces postprandial glucose excursions by delaying intestinal glucose absorption and increasing glucose excretion, with effects on postprandial glucose that are independent of insulin secretion.

However, it is important to note the substantial standard deviation in the six-month PPBS measurement (±317.376), which suggests considerable variability in postprandial glucose responses among patients. This variability may reflect differences in dietary adherence, concomitant medications, or individual patient factors affecting glucose metabolism. The presence of such variability underscores the importance of individualized patient education regarding meal planning and medication timing.

4. Random Blood Sugar Reduction: Real-World Effectiveness

The RBS data shows a reduction from 178.29 mg/dL at baseline to 168.45 mg/dL in three months and 164.36 mg/dL at six months, representing a mean reduction of 13.93 mg/dL (7.8%) over the study period. The more modest reduction in RBS compared to FBS and PPBS reflects the inherent variability of random glucose measurements, which are influenced by timing of meals, physical activity, and other factors.

Nevertheless, the statistically significant improvement ($p < 0.001$) across all three time points confirms that the glycemic benefits of dapagliflozin are robust enough to be detected even with less standardized measurements, supporting the drug's effectiveness in real-world clinical settings where random glucose monitoring is commonly used.

5. Clinical Significance: Achievement of Glycemic Targets

The achievement of a mean HbA1c of 6.40% at six months is clinically significant, as this value falls well within the American Diabetes Association's recommended target of <7.0% for most non-pregnant adults with diabetes. Furthermore, the mean FBS of 121.58 mg/dL approaches the recommended target of 80-130 mg/dL. These findings suggest that dapagliflozin therapy, either as monotherapy or in combination with other agents, enabled most patients to achieve glycemic control within six months of treatment initiation.

The rapid achievement of glycemic targets within three months (HbA1c 6.46%) is particularly noteworthy, as it may improve patient adherence and confidence in the treatment regimen. The literature suggests that early achievement of glycemic targets is associated with improved long-term outcomes, including reduced risk of diabetes-related complications.

6. Relationship Between Glycemic Improvement and Drug-Related Problems
The substantial glycemic improvements observed in this study must be considered in the context of potential drug-related problems associated with dapagliflozin. Several important relationships merit discussion:

Genitourinary infections: As discussed previously, the mechanism of dapagliflozin—increasing urinary glucose excretion—directly increases the risk of genital mycotic infections and, to a lesser extent, urinary tract infections. The magnitude of glycemic improvement observed in this study (FBS reduction of 49.6 mg/dL, HbA1c reduction of 1.32%) implies significant glucosuria, which would be expected to increase infectious risk. Therefore, patients achieving excellent glycemic control may paradoxically face higher risk of this specific adverse effect. The literature notes that the risk of genital infections is highest in the first few months of therapy, coinciding with the period of maximal glycemic improvement.

Hypoglycemia risk: Importantly, dapagliflozin as monotherapy has a low intrinsic risk of hypoglycemia because its mechanism does not depend on insulin secretion. However, when used in combination with insulin or insulin secretagogues (e.g., sulfonylureas), the risk of hypoglycemia increases. The substantial reductions in FBS, PPBS, and HbA1c observed in this study suggest that patients on concomitant insulin or sulfonylureas may require dose reductions of these agents to prevent hypoglycemia. Prescribing information for dapagliflozin recommends considering a lower dose of insulin or insulin secretagogue to reduce the risk of hypoglycemia when initiating dapagliflozin.

Weight loss and metabolic effects: The glycemic improvements observed are typically accompanied by modest weight loss (2-3 kg) with dapagliflozin therapy, which further contributes to improved metabolic control. This weight loss effect is considered a therapeutic benefit but should be monitored in elderly or frail patients who may be at risk for sarcopenia or unintended weight loss.

Ketone body elevation: As noted in previous discussions, dapagliflozin treatment results in increased fasting β-hydroxybutyrate levels in some patients. The substantial improvement in glycemic control observed in this study suggests effective SGLT2 inhibition, which would be expected to shift metabolism toward increased ketone body production. While this is benign and may contribute to cardiorenal benefits, it underscores the importance of monitoring for euglycemic diabetic ketoacidosis in at-risk patients.

7. Comparison with Published Real-World Evidence
The glycemic improvements observed in our study align closely with recently published real-world evidence. A 2024 prospective observational study from India involving 278 patients with type 2 diabetes reported the following changes with dapagliflozin-based therapy:

HbA1c reduction: from 8.7% to 7.2% in 6 months (1.5% reduction)

FBS reduction: from 176 mg/dL to 132 mg/dL (44 mg/dL reduction)

PPBS reduction: from 254 mg/dL to 208 mg/dL (46 mg/dL reduction)

These findings are remarkably similar to our study's results, validating the effectiveness of dapagliflozin in real-world clinical settings outside of tightly controlled clinical trials. The consistency between our findings and published real-world evidence strengthens the generalizability of our conclusions.

Drug Interaction Chart in the Context of Dapagliflozin and Cardiovascular/Metabolic Polypharmacy

Table No. 11 presents nine identified drug-drug interactions (DDIs) observed in the study population, involving combinations of cardiovascular drugs (aspirin, bisoprolol, ticagrelor, enalapril, digoxin, rosuvastatin), antidiabetic agents (dapagliflozin, glimepiride, metformin, insulin aspart), an antibiotic (ofloxacin), a proton pump inhibitor (pantoprazole), and a thyroid hormone (levothyroxine). The interactions are classified as Mild (n=2), Moderate (n=6), and Minor (n=1), with corresponding management recommendations ranging from "use caution/monitor" to "avoid/use alternate drug." This polypharmacy profile is highly characteristic of patients with type 2 diabetes and cardiovascular comorbidities, and the identified interactions warrant detailed discussion in the context of current literature.

1. Dapagliflozin-Related Interactions: Hypoglycemia Risk

Two interactions in the chart directly involve dapagliflozin: Glimepiride + Dapagliflozin (Moderate, modify therapy/monitor closely) and Dapagliflozin + Insulin Aspart (Moderate, use caution/monitor). Both interactions share a common mechanistic basis and are well-documented in the literature.

Glimepiride (Sulfonylurea) + Dapagliflozin

The combination of dapagliflozin with glimepiride, a sulfonylurea insulin secretagogue, is classified as a moderate interaction requiring dosage adjustment and close monitoring. The primary concern is potentiation of hypoglycemia risk. Sulfonylureas stimulate endogenous insulin secretion regardless of blood glucose levels, while SGLT2 inhibitors increase urinary glucose excretion. When used together, the glucose-lowering effects are additive, increasing the likelihood of hypoglycemic events.

The management recommendation in our chart “modify therapy/monitor closely"—aligns precisely with evidence-based guidance. According to drug interaction databases, a lower dosage of the insulin secretagogue (glimepiride) may be required when used in combination with an SGLT-2 inhibitor. This is particularly important because sulfonylureas have a well-established risk of causing hypoglycemia as monotherapy, and this risk is amplified by the addition of dapagliflozin.

A recent real-world study (2025) evaluating a fixed-dose combination of dapagliflozin, glimepiride, and metformin in 78 patients with type 2 diabetes reported significant glycemic improvements (HbA1c reduction of 1.2%, $p < 0.0001$). Importantly, the study noted that there were no clinically relevant episodes of hypoglycemia. This finding suggests that with appropriate monitoring and dose adjustment, the combination can be used safely. However, the study population was carefully selected, and the authors emphasized the importance of balancing efficacy with safety, particularly regarding hypoglycemia risk. The absence of hypoglycemia in that study may reflect vigilant monitoring and appropriate dose titration, underscoring the importance of the "monitor closely" recommendation in our chart.

Dapagliflozin + Insulin Aspart

The combination of dapagliflozin with insulin aspart (a rapid-acting insulin) is similarly classified as a moderate interaction requiring caution and monitoring. The mechanism is analogous to the sulfonylurea interaction: both drugs lower blood glucose, and their effects are additive. Insulin stimulates cellular glucose uptake and suppresses hepatic glucose production, while dapagliflozin increases urinary glucose excretion.

The management recommendation from authoritative sources advises that a lower dosage of insulin may be required when used in combination with an SGLT-2 inhibitor to reduce the risk of hypoglycemia. This is particularly relevant for patients with type 2 diabetes who require insulin therapy, as the addition of dapagliflozin can improve glycemic control sufficiently to necessitate downward insulin titration.

Both dapagliflozin-related interactions in our chart highlight a critical theme in diabetes management: intensification of therapy with SGLT2 inhibitors requires concomitant de-intensification of other glucose-lowering agents to maintain safety while achieving glycemic targets.

2. Dapagliflozin and Rosuvastatin: Emerging Evidence of Rhabdomyolysis Risk

While not listed as a direct interaction in our chart, the combination of dapagliflozin with rosuvastatin appears in the context of patient medication lists, and recent literature has identified a potentially serious interaction between these agents. A 2024 case report published in the Indian Journal of Nephrology described a 57-year-old man with normal renal function who developed severe rhabdomyolysis within three days of adding dapagliflozin to pre-existent rosuvastatin therapy.

The patient presented with fatigue and oliguria, and investigations revealed severe acute kidney injury (AKI) with elevated serum creatine-phosphokinase (CPK) and myoglobinuria. Renal biopsy demonstrated severe acute tubular necrosis with interstitial nephritis and myoglobin casts, confirming the diagnosis of rhabdomyolysis. Both drugs were discontinued, and the patient required hemodialysis and oral steroids, with recovery occurring over several weeks. Importantly, rosuvastatin was rechallenged after two months, and renal functions and CPK levels remained normal, suggesting that dapagliflozin played a causative role in the interaction.

This case report adds to a growing literature on potential myotoxicity with SGLT2 inhibitor-statin combinations. While the interaction is not listed in standard drug interaction databases, the temporal relationship and positive de challenge/rechallenge pattern suggest a clinically significant interaction that warrants awareness. The mechanism may involve SGLT2 inhibitors affecting drug transporters or metabolic pathways involved in statin disposition.

In our study, if any patient were taking both dapagliflozin and rosuvastatin, this emerging safety signal would merit consideration, particularly if patients developed unexplained muscle pain, weakness, or dark urine.

Adverse Drug Reaction Distribution in the Context of Dapagliflozin's Safety Profile
Table No. 12 presents the adverse drug reactions (ADRs) reported among patients receiving dapagliflozin therapy. A total of 11 ADRs were documented across three categories: Urinary Tract Infection (UTI) was the most frequent (n=6, 54.54%), followed by Burning Sensation in the Genital Area (n=4, 36.36%), and Hypoglycemia (n=1, 9.08%). This distribution is highly consistent with the established safety profile of SGLT2 inhibitors and warrants detailed discussion in the context of current literature on dapagliflozin's drug-related problems.

1. Urinary Tract Infections: The Most Prevalent ADR
The finding that UTIs accounts for the majority (54.54%) of reported ADRs aligns with the well-documented association between SGLT2 inhibitors and genitourinary infections. However, as noted in previous discussions, the relationship between dapagliflozin and UTIs requires nuanced interpretation.

Incidence Compared to Literature

A comprehensive 2023 meta-analysis of forty-two randomized controlled trials involving over 35,000 patients with type 2 diabetes mellitus confirmed that dapagliflozin is associated with a statistically significant increased risk of UTIs (odds ratio 1.17). This risk was found to be higher with the standard 10 mg dose and with treatment durations exceeding 24 weeks. The fact that UTIs represent the majority of ADRs in our study (54.54%) is consistent with dapagliflozin being a significant contributor to UTI risk, though absolute incidence cannot be determined without denominator data.

Mechanistic Basis

The mechanism underlying increased UTI risk is straightforward: dapagliflozin promotes glucosuria by inhibiting SGLT2 in the proximal renal tubule, resulting in urinary glucose concentrations that may exceed 50-80 g/day. This glucose-rich urine provides a favorable environment for bacterial growth and colonization of the urinary tract. The effect is dose-dependent, with higher doses producing greater glucosuria and potentially higher infection risk.

Gender Considerations

Critically, the literature consistently demonstrates that the risk of UTIs with SGLT2 inhibitors is not evenly distributed across genders. Women are at significantly higher baseline risk for UTIs due to anatomical factors (shorter urethra, proximity to anus), and this risk is amplified by SGLT2 inhibitor therapy. The FDA-approved prescribing information notes that UTIs were reported more frequently in female patients.

In our study population, females constituted only 27% of the total (5 of 19 patients), yet they would be expected to account for a disproportionate share of UTI events. If the 6 UTI events occurred in female patients, this would represent a remarkably high incidence in that subgroup—potentially approaching 100% if all five females experienced UTIs and one male also reported UTI. Alternatively, if UTIs were distributed more evenly, it would suggest an unusually high rate in male patients. Without gender-stratified ADR data, the precise risk profile cannot be determined, but the predominance of UTIs in the ADR list is consistent with the known pharmacology of dapagliflozin.

Comparison with Other SGLT2 Inhibitors

It is worth noting that dapagliflozin may have a slightly different UTI risk profile compared to other agents in its class. The 2023 meta-analysis identified dapagliflozin specifically as being associated with increased UTI risk, whereas the class effect for SGLT2 inhibitors does not consistently show elevated UTI risk. This finding suggests potential differences among individual agents, though the mechanism for such differences remains unclear.

2. Burning Sensation in Genital Area: Genital Mycotic Infections
The second most frequent ADR, reported in four patients (36.36%), is described as "burning sensation in genital area." Based on the literature, this symptom is highly characteristic of genital mycotic infections (fungal infections), which represent the most common adverse effect of SGLT2 inhibitor therapy.

Incidence and Risk

Genital mycotic infections are considered a class effect of SGLT2 inhibitors and are the most consistently reported ADR in clinical trials and real-world studies. Meta-analyses have shown that SGLT2 inhibitors increase the risk of genital infections by three to five times compared to placebo. A 2025 prospective observational study found that among patients on SGLT2 inhibitors (98.5% on dapagliflozin), the incidence of genital infections was 36.25% in females and 30.8% in males.

Clinical Presentation

The burning sensation reported by patients in our study represents the typical symptoms of vulvovaginal candidiasis in females or balanitis/candidal urethritis in males. Common symptoms include:

Genital itching or pruritus

Burning sensation, particularly during urination

Erythema and swelling of genital tissues.

Thick, white discharge (in females)

Foul odor

The fact that four patients (36.36% of ADRs) reported this symptom suggests that genital mycotic infections are a significant clinical problem in this population, consistent with the literature.

Gender Distribution

As discussed in the context of Table No. 2, females are at higher risk for genital mycotic infections due to anatomical and physiological factors. The FDA-approved prescribing information explicitly states that genital mycotic infections were "more frequently reported in females than in males." In our study, with only five female participants (27%), the four burning sensation reports could represent:

All four occurring in females (80% of female patients affected)

A mix of male and female patients, with females still disproportionately affected.

Male patients, which would be unusual but possible.

The literature suggests that while males are at lower absolute risk, they still experience genital infections at clinically meaningful rates (approximately 30% in the 2025 study). Without gender-specific ADR data, the precise distribution cannot be determined.

Management Strategies

The literature supports several management strategies for genital mycotic infections associated with SGLT2 inhibitor therapy:

Patient education about genital hygiene, including keeping the area clean and dry.

Over-the-counter antifungal preparations (clotrimazole, miconazole) for mild cases

Prescription antifungal therapy (fluconazole, topical prescriptions) for persistent or severe cases

Temporary discontinuation of dapagliflozin in refractory cases, with rechallenge after resolution.

Consideration of alternative SGLT2 inhibitor if infections are recurrent, though this is a class effect.

Importantly, the literature indicates that genital infections are mild to moderate in severity, respond well to standard antifungal therapy, and rarely require discontinuation of dapagliflozin. Patient education about recognizing early symptoms and seeking prompt treatment can minimize discomfort and prevent complications.

3. Hypoglycemia: A Single Reported Case
The finding of one case of hypoglycemia (9.08% of ADRs) is consistent with the known safety profile of dapagliflozin and warrants careful interpretation.

Intrinsic Hypoglycemia Risk

As an SGLT2 inhibitor, dapagliflozin has a low intrinsic risk of causing hypoglycemia when used as monotherapy. This is because its mechanism of action—increasing urinary glucose excretion—does not depend on insulin secretion and does not cause hypoglycemia in the absence of excess insulin or insulin secretagogues. The glucose-lowering effect is self-limiting, as glucosuria ceases when plasma glucose concentrations fall below the renal threshold for glucose reabsorption (approximately 180 mg/dL in healthy kidneys).

Contextual Risk Factors

When hypoglycemia occurs with dapagliflozin, it is always in the context of concomitant use of other glucose-lowering medications that have intrinsic hypoglycemia risk, particularly:

Insulin

Sulfonylureas (e.g., glimepiride)

Meglitinides

The single hypoglycemia case in our study reflects this phenomenon. As documented in Table No. 11 (Drug Interaction Chart), two interactions involving dapagliflozin were identified:

Glimepiride + Dapagliflozin (Moderate, modify therapy/monitor closely)

Dapagliflozin + Insulin Aspart (Moderate, use caution/monitor)

Both combinations increase hypoglycemia risk, and the patient experiencing hypoglycemia was likely on one of these regimens. The significant glycemic improvements documented in Table No. 9 (HbA1c reduction 1.32%, FBS reduction 49.6 mg/dL) suggest that dapagliflozin was effective, and in patients on sulfonylureas or insulin, this efficacy would be expected to increase hypoglycemia risk unless concomitant medications were appropriately dose-reduced.

Incidence Comparison with Literature

The rate of hypoglycemia observed in our study (1 event, representing 9.08% of ADRs) appears low, particularly given the prevalence of sulfonylurea and insulin use suggested by the interaction chart. This could reflect:

Appropriate initiative-taking dose reduction of sulfonylureas/insulin at dapagliflozin initiation

Effective patient education about hypoglycemia recognition and prevention

Underreporting of mild hypoglycemic events

The small sample size

Large clinical trials report variable rates of hypoglycemia with dapagliflozin depending on background therapy. In the DECLARE-TIMI 58 trial, severe hypoglycemia occurred in 0.7% of dapagliflozin-treated patients versus 0.8% of placebo-treated patients, with no significant difference. However, in trials where dapagliflozin was added to sulfonylureas or insulin, hypoglycemia rates were higher, emphasizing the importance of dose adjustment.

4. Comparison with Known ADR Profile of Dapagliflozin

The ADR distribution in our study aligns well with the established safety profile of dapagliflozin, but it is important to note what is not present in the ADR list. Several well-documented adverse effects of dapagliflozin were not reported in our study:

Genital Infections (vs. Burning Sensation)

The burning sensation reported represents genital mycotic infections, which are the most common ADR. The absence of separate reporting for male-specific genital infections (balanitis, candidal urethritis) is consistent with the symptom-based description.

Volume Depletion/Hypotension

As discussed in the context of Table No. 4 (Blood Pressure), dapagliflozin can cause volume depletion and hypotension, particularly in elderly patients and those on diuretics. The absence of these ADRs in our list may reflect:

Low prevalence of at-risk patients

Adequate hydration and monitoring

Underreporting of milder symptoms (dizziness, lightheadedness)

Small sample size

Euglycemic Diabetic Ketoacidosis (DKA)

This rare but serious ADR was not reported, which is expected given its low incidence (0.3% in DECLARE-TIMI 58). The absence of DKA cases is reassuring.

Renal Adverse Events

Acute kidney injury or significant eGFR decline was not reported, consistent with the overall renal safety profile of dapagliflozin when used in appropriate patients with adequate baseline renal function.

Fournier's Gangrene
This rare but serious necrotizing infection was not reported, consistent with its incredibly low incidence (<0.01%).

5. Clinical Implications and Management Strategies
The ADR profile observed in our study has several important clinical implications:

Patient Education Priorities
The predominance of genitourinary ADRs (UTI and burning sensation, together accounting for 90.9% of all ADRs) underscores the critical importance of pre-treatment patient education. Patients should be counseled about:

The mechanism of glucosuria and its relationship to infection risk

Symptoms of UTI (dysuria, frequency, urgency, suprapubic discomfort)

Symptoms of genital mycotic infections (itching, burning, discharge, erythema)

Importance of genital hygiene (keeping area clean and dry, wearing breathable underwear)

Prompt reporting of symptoms for initial treatment.

Over-the-counter antifungal options for mild genital symptoms

Monitoring Recommendations
Based on the observed ADR pattern, monitoring should focus on:

Regular inquiry about genitourinary symptoms at follow-up visits

Urinalysis if UTI symptoms develop.

Clinical examination whether genital symptoms persist or worsen.

Blood glucose monitoring, particularly in patients on sulfonylureas or insulin

Hypoglycemia assessment in high-risk patients

Management Protocols
For patients developing genitourinary ADRs:

UTI: Obtain urinalysis and culture if indicated; treat appropriate antibiotics based on susceptibility; ensure adequate hydration

Genital mycotic infection: Recommend over-the-counter antifungal cream (clotrimazole, miconazole); if persistent, consider prescription antifungal (fluconazole 150 mg single dose); if recurrent, evaluate for other risk factors (poor glycemic control, antibiotic use, immunosuppression)

Hypoglycemia: Review concomitant medications; consider reduction of sulfonylureas or insulin; reinforce hypoglycemia education; consider blood glucose monitoring adjustments

6. Strengths and Limitations of ADR Reporting
The ADR data presented has several strengths:

Real-world evidence: Reflects actual clinical practice rather than controlled trial conditions.

Patient-reported symptoms: Captures the patient experience of ADRs.

Clinically meaningful categories: The ADRs identified are clinically relevant and actionable.

However, several limitations warrant acknowledgment:

No denominator for incidence rates: The frequency column shows number of ADRs, not number of patients experiencing ADRs. A single patient could have experienced multiple ADRs, or each ADR could represent a different patient. Incidence rates cannot be calculated without knowing how many patients experienced each ADR.

No severity grading: The table does not indicate whether ADRs were mild, moderate, or severe, nor whether they required treatment discontinuation.

No temporal information: The timing of ADR onset relative to dapagliflozin initiation is not provided, which is important for establishing causality.

No management outcomes: It is unclear whether ADRs resolved with treatment, required dose adjustment, or led to drug discontinuation.

Potential underreporting: Mild or transient ADRs may not have been reported by patients or captured in the study.

Small sample size: With only nineteen patients, the ADR profile may not be generalizable to larger populations.

7. Causality Assessment
While the table does not include causality assessment, the pattern of ADRs is highly consistent with dapagliflozin's known adverse effect profile. The World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality categories that would apply include:

UTI and burning sensation: Probable/Certain — well-established association, plausible mechanism, consistent with literature.

Hypoglycemia: Possible/Probable — depends on concomitant medications, but plausible given dapagliflozin's glycemic efficacy

8. Comparison with Published ADR Data
The ADR distribution in our study can be compared with published pharmacovigilance data. An analysis of the FDA Adverse Event Reporting System (FAERS) from 2013 to 2024 confirmed known signals for genital and urinary tract infections with dapagliflozin. Importantly, that analysis also identified potentially overlooked ADRs including bladder cancer, cholangiocarcinoma, and thrombotic stroke, which were not observed for canagliflozin. While these serious ADRs were not reported in our small study, they underscore the importance of ongoing post-marketing surveillance.

A 2024 systematic review of real-world evidence on SGLT2 inhibitor safety in Asian populations found that genitourinary infections were the most reported ADRs, with rates ranging from 5-15% depending on the population and follow-up duration. The proportion of ADRs in our study (UTI 54.5%, genital symptoms 36.4%) suggests that genitourinary ADRs may be overrepresented relative to other potential ADRs, but this could reflect the specific population, duration of follow-up, or reporting patterns.

Side Effect Distribution in the Context of Dapagliflozin's Safety Profile
Table No. 9 presents the distribution of side effects reported among patients receiving dapagliflozin therapy, stratified by gender. A total of 15 side effects were documented across four categories: hypoglycemia (n=5, 33.3% of side effects), dehydration (n=4, 26.7%), hypotension (n=3, 20%), and weight loss (n=3, 20%). The gender distribution shows notable differences: females reported more hypoglycemia (3 vs. 2) and hypotension (2 vs. 1), while males reported more dehydration (3 vs. 1). This distribution aligns with the established safety profile of SGLT2 inhibitors but reveals important gender-specific patterns that warrant detailed discussion in the context of current literature.

1. Hypoglycemia: Gender Distribution and Contextual Risk
Hypoglycemia was the most frequently reported side effect overall (n=5, 33.3%), with a higher frequency in females (3 reports, 20% of female patients) compared to males (2 reports, 13.3% of male patients). This finding requires careful interpretation considering dapagliflozin's pharmacological profile.

Intrinsic Hypoglycemia Risk

As discussed previously, dapagliflozin has a low intrinsic risk of causing hypoglycemia when used as monotherapy. The mechanism of action—increasing urinary glucose excretion—does not depend on insulin secretion and does not cause hypoglycemia in the absence of excess insulin or insulin secretagogues. The glucose-lowering effect is self-limiting, as glucosuria ceases when plasma glucose concentrations fall below the renal threshold for glucose reabsorption.

Therefore, the high frequency of hypoglycemia reports (5 events) in this study strongly suggests that affected patients were likely on concomitant therapy with insulin or sulfonylureas. This hypothesis is supported by the drug interaction data in Table No. 11, which identified two dapagliflozin-related interactions:

Glimepiride + Dapagliflozin (Moderate, requiring close monitoring)

Dapagliflozin + Insulin Aspart (Moderate, requiring caution/monitoring)

Gender Differences in Hypoglycemia Risk

The finding that females reported more hypoglycemia events (3 vs. 2) than males is consistent with emerging literature on gender differences in diabetes outcomes. A 2024 systematic review and meta-analysis examining gender differences in the efficacy and safety of SGLT2 inhibitors in type 2 diabetes found that women achieved greater HbA1c reductions compared to men with SGLT2 inhibitor therapy. This enhanced glycemic response in women could potentially translate into a higher risk of hypoglycemia, particularly when SGLT2 inhibitors are combined with sulfonylureas or insulin.

The review also noted that SGLT2 inhibitors were associated with greater reductions in body weight, BMI, and waist circumference in women compared to men. While this weight loss effect is beneficial, it may reflect greater metabolic responsiveness that could also increase hypoglycemia susceptibility.

STUDY IMPLICATIONS

1. Clinical Practice Implications

Gender-sensitive prescribing: Women require closer monitoring for hypoglycemia, hypotension, and excessive weight loss; men need specific attention to hydration status and dehydration prevention.

Age-tailored monitoring: Patients >60 years need regular renal function assessment, volume status checks, and falls risk evaluation; those >80 years warrant enhanced vigilance and more frequent follow-up.

Pre-treatment assessment: Mandatory medication reconciliation (especially for sulfonylureas, insulin, diuretics, digoxin), baseline vital signs, renal function, and genitourinary symptom inquiry.

Structured patient education: Focus on genitourinary hygiene, symptom recognition (UTI, fungal infections, dehydration, hypoglycemia), and clear action plans including "sick day" protocols.

Initiative-taking medication management: Reduce sulfonylurea doses by 25-50% and insulin by 10-20% at initiation; consider diuretic dose reduction; increase blood glucose monitoring frequency.

2. Patient Safety Implications

Genitourinary infections (90.9% of ADRs) are the primary safety concern—implement prevention protocols and empower patient self-management.

Volume depletion (dehydration 26.7%, hypotension 20%) requires "sick day" protocols, patient education on early recognition, and temporary drug holds during illness.

Hypoglycemia (33.3% of side effects) is preventable through appropriate dose adjustment of concomitant insulin/sulfonylureas and enhanced monitoring.

3. Health Policy Implications
Mandate adequate female representation in clinical trials to elucidate gender-specific safety profiles.

Invest in real-world evidence infrastructure to complement clinical trial data.

Support pharmacist-led medication reconciliation and team-based care for complex patients with polypharmacy.

4. Research Implications
Investigate mechanisms underlying gender differences in SGLT2 inhibitor response and safety.

Conduct dedicated studies in frail older adults and those >80 years.

Evaluate clinically significant drug interactions (particularly statins, PPIs).

Establish long-term safety surveillance for rare but serious events.

5. Educational Implications
Enhance provider education on SGLT2 inhibitor safety, drug interactions, and adverse effect management.

Develop accessible, multilingual patient education materials with visual aids and teach-back methods.

Engage caregivers in education, especially for older adult patients.

CONCLUSION

SGLT2 inhibitors represents an effective and well tolerated option for patients with type2diabetes mellitus`. By selectively inhibiting sodium- glucose cotransport-2[SGLT2], it improves glycemic control through an insulin independent mechanism, contributing to reduction in HbA1c.comprehensive detection and assessment contributes to good clinical decision making improve long term patient outcome in type 2 diabetes population. evaluation frameworks incorporating drug interaction, nonadherence, contraindication, therapeutic ineffectiveness, side effects, ADR, etc. the detection and assessment of sglt2 inhibitors in diabetes mellitus patient are essential components of safe and effective diabetes management. according to population, males are more prior to diabetic. Most middle aged to elderly are affected more. FBS level varies according to the patient, mostly ranging from less than 250mg/dl. sglt2 inhibitors enhances blood pressure, pulse rate, respiration rate. According to the study, urinary tract infections are most common side effects, burning sensation in genital areas and hypoglycemia also seen. Side effects are minimal but it chances are more often. careful monitoring and appropriate management can reduce the risk of adverse effects. While further long-term studies are ongoing, current study suggests SGLT2 inhibitors could be a standard option for treatment of type 2 diabetes mellitus, improving quality of life and clinical outcomes.

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