RESEARCH ARTICLE

A Prospective Interventional Comparative Long-Term Study on the Safety of Canagliflozin and Dapagliflozin Depending on their ADR's and Glucose Monitoring Parameters in a Tertiary Care Hospital for a Span of One Year

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Received: 17th Mar, 2025; Revised: 15th Apr, 2025; Accepted: 25th Apr, 2025; Available Online: 25th Jun, 2025

ABSTRACT

Introduction: SGLT2 inhibitors have a wide extent of restorative movement and higher chance of hypoglycaemia because of their affront autonomous action in treating type-2 Diabetes. SGLT2 inhibitors have great security and resistance when utilized as monotherapy or in conjunction with other oral hypoglycaemic medicines. Since SGLT2 inhibitors can cause hyperglycaemia, which results in vaginal and UTI contaminations. When compared, Dapagliflozin had higher contaminations. The key issue displayed is that ketoacidosis and that it may take a little time to analyse it.

Objectives: A careful comparison of Canagliflozin vs Dapagliflozin in terms of long-term urinary volume, renal function, and metabolic changes suggests that both are effective, but Dapagliflozin may have a slightly safer profile regarding fluid balance and tolerance in vulnerable populations. However, individual patient factors (e.g., baseline renal function, risk of volume depletion) must guide the choice.

Research methodology: A Planned Interventional Comparative Ponder conducted among 3452 patients who were conceded to in the General Medicine and Endocrine Departments, Anu Group of hospitals, Vijayawada over 12 months from December 2021 to December 2022. By alluding to the patient's FBS and PPBS, RFT, HbA1c, BP, and the finding seriousness score of ADR (Adverse Drug Reaction) utilizing Naranjo scale.

Results: Patients had most common ADRs after Utilizing Canagliflozin and Dapagliflozin, were Hypotension and Dehydration respectively.

Conclusion: We concluded that in Patients had ADRs after utilizing Canagliflozin versus Dapagliflozin where hypotension and dehydration was more common respectively. ADRs in the Control population was weight pick up had the negative impact and Hypoglycaemia was found to be more in the Control population compared to Canagliflozin and Dapagliflozin endorsed bunches. Weight loss had a positive impact on Canagliflozin and Dapagliflozin-endorsed groups.

Keywords: Canagliflozin, Dapagliflozin, Dehydration, Hypotension, ADRs.

How to cite this article: Dhanush Bellapu, Ronald Darwin. A Prospective Interventional Comparitive Long-Term Study on the Safety of Canagliflozin and Dapagliflozin Depending on their ADR's and Glucose Monitoring Parameters in a Tertiary Care Hospital for a Span of One Year. International Journal of Drug Delivery Technology. 2025;15(2):757-62. doi: 10.25258/ijddt.15.2.49

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

SGLT2 inhibitors have good safety and tolerance when used as monotherapy or with other oral hypoglycaemic medications or insulin treatment. Due to its insulin-independent activity, SGLT2 inhibitors have been proven to have a low risk of hypoglycaemia. In the Phase III development studies, there were no significant occurrences of hypoglycaemia observed when SGLT2 inhibitors were taken as monotherapy and a meta-analysis found that the risk of hypoglycaemia was low comparable to that of other medicines used to treat type 2 Diabetes.[1]

Due to hyperglycaemia and glycosuria, diabetes itself is linked to an increased risk of vaginal infection and urinary tract infection (UTI). Because SGLT2 inhibitors cause hyperglycaemia there is a corresponding rise in vaginal and UTI infections, which have been linked to several placebo-controlled studies. When compared to placebo, Dapagliflozin caused higher infections (genital infection 4.1-5.7% vs. 0.9%; UTI 3.6–5.7 % vs. 3.7 %).[2] Canagliflozin pooled studies revealed similar results (genital infection 7.5% vs 1.9% in placebo; UTI 5.1% vs. 4.0% placebo). Similar data for genital tract infections are available for Empagliflozin, although there was no statistically significant difference in UTIs.[3]

SGLT2 inhibitors are thought to increase the risk of euglycemic ketoacidosis, which has warnings from the FDA and EMA.[4] The FDA and EMA based on their warnings of 20 and 101 clinical instances respectively. However, some of the incidents included people with type 1 diabetes too. Both type 1 and type 2 diabetes have been associated with this adverse effect while using SGLT2s.[5] In this case series, insulin decreases, low calorie and fluid intake, concurrent illnesses, and alcohol usage are some of the circumstances that led to ketoacidosis. The key issue

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Table 1: Properties of SGLT2 inhibitors according to the 2015 American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) position statement

Class	Compounds	Cellular mechanism	Primary physiological actions	Advantages	Disadvantages/ adverse effects	Cost
SGLT2 inhibitors	Canagliflozin Dapagliflozin Empagliflozin	Inhibits SGLT2 in the proximal nephron	Blocks glucose reabsorption by the kidney, increasing glycosuria	No hypoglycaemia, Weight loss Reduces blood pressure, Effective at all stages of type 2 diabetes	Genitourinary infections, Polyuria, Volume depletion, hypotension, dizziness, Increases LDL cholesterol, Increases creatinine.	High

Adapted from ADA/EASD.[7] © American Diabetes Association
LDL - low density lipoprotein cholesterol,
SGLT2 - sodium-glucose cotransporter 2

Table 2: No. of Patients Prescribed with Canagliflozin and Dapagliflozin

No. of Patients prescribed with Canagliflozin (n_1)			No. of Patients prescribed with Dapagliflozin (n_2)			Total (N)
1854			1602			3456
Dual Therapy	Triple Therapy	Quadruple Therapy	Dual Therapy	Triple Therapy	Quadruple Therapy	
636	616	602	582	526	494	

presented is ketoacidosis can develop in the presence of euglycemia or little elevated blood glucose and that it may take some time to diagnose it. This might be avoided if ketonuria could be detected. The estimated incidence rates are modest (0.5, 0.8, and 0.2 per 1000 patient-years with Canagliflozin 100 mg, Canagliflozin 300 mg, and comparator) but more than double with the SGLT2 inhibitor in a comprehensive retrospective analysis of 17,596 people in the CANVAS trial.[6] Therefore, it is important to be aware of the potential consequences, especially if the introduction of SGLT2 leads to a decrease in the dosage of insulin. A decrease in insulin dosage in this situation shouldn't be considered a success in and of itself.[7] Besides their benefits some of the SGLT-2 inhibitors cause lower limb amputations, Diabetic Ketoacidosis, Hypoglycemia, hypotension, genito-urinary infections with different frequencies in different populations.[8]

This study was designed to evaluate the safety profile of Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors in patients diagnosed with Type 2 Diabetes Mellitus (T2DM). Specifically, the focus was on two commonly prescribed agents in this class — Canagliflozin and Dapagliflozin — administered as add-on therapy to existing anti-diabetic regimens. With T2DM being a progressive metabolic disorder often requiring combination therapy, SGLT2 inhibitors have gained prominence not only for their glucose-lowering effects but also for their cardiovascular and renal benefits. However, their unique mechanism — promoting glucose excretion via the urine — raises safety concerns, particularly regarding volume depletion, renal function deterioration, electrolyte imbalances, and genitourinary infections. By using real-world patients already on background anti-diabetic therapy, this research sought to reflect practical clinical outcomes and help guide safer, more effective treatment plans for individuals living with T2DM.

METHODOLOGY

Source of Data and Study Design

This is a Prospective Interventional Comparative Study designed to evaluate and compare the clinical outcomes of patients with Diabetes Mellitus who are treated with different SGLT-2 inhibitors—Canagliflozin and Dapagliflozin—as add-on therapies, against a control group receiving standard anti-diabetic treatment as per ICMR (Indian Council of Medical Research) guidelines.

The primary goal is to assess the comparative efficacy and safety of these interventions based on the number and combination of anti-hyperglycemic agents used in treatment regimens up to quadruple-drug therapy.

Collected the data from the patients admitted into the General Medicine and Endocrine Department who were diagnosed with Type 2 Diabetes Mellitus. All the patients admitted during the study duration are followed from the day of prescribing of any anti-diabetic with an SGLT-2 inhibitor up to not less than 1 year of the treatment or a least possible of HbA1C done 3 times.

- FBS and PPBS checked every month.
- RFT (Sr. Creatinine, B. Urea, and Blood Urea Nitrogen) checked for every 4 months
- HbA1C checked for every 6 months

Group 1

This group includes patients who were prescribed Canagliflozin as an add-on therapy to their existing anti-diabetic treatment. Patients in this group were on dual, triple, or quadruple-drug therapy, where Canagliflozin was added as a third or fourth agent.

Group 2

This group consists of patients treated with Dapagliflozin as an add-on therapy to their ongoing diabetes medication regimen.Similar to Group 1, these patients were also receiving dual to quadruple therapy, with Dapagliflozin introduced as an adjunct.

Control

Patients in the control group were managed according to the ICMR-recommended standard treatment regimen, ranging from dual-drug therapy to quadruple-drug therapy, without the use of SGLT-2 inhibitors.The treatment protocols

Table 3: Patients with ADR's After Using Canagliflozin and Dapagliflozin

ADR's	Canagliflozin		Dapagliflozin	
	No. of patients	Percentage	No. of patients	Percentage
Vaginal Candidiasis	112	7%	86	9%
Hypotension	432	29%	224	23%
Ketoacidosis	40	3%	16	2%
Weight loss	222	15%	186	19%
Polyuria	180	12%	120	12%
Dehydration	392	26%	254	26%
UTI (Urinary Tract Infection)	50	3%	40	4%
Hypoglycaemia	76	5%	48	5%
Total	1504	1504/1854*100 =81.12%	974	974/1602*100 =60.8%

followed in this group were in line with Indian national guidelines for diabetes management, incorporating commonly prescribed medications such as Metformin, Sulfonylureas, DPP-4 inhibitors, and Insulin.

All groups of Canagliflozin and Dapagliflozin are compared to Control therapy as per their number of anti-hypoglycaemias respectively.

Study Site

Anu Group of Hospitals, Main Branch, located in Suryaraopet, Vijayawada, Andhra Pradesh, India. This site provides a suitable setting with a high volume of diabetes patients and specialized care in endocrinology and internal medicine, ensuring a reliable and diverse patient population.

Study Duration

The study was conducted over a span of one year. Patient enrollment and initial data collection were completed over the first 3 months. All enrolled patients were then followed for a period of 12 months from the date of inclusion to monitor treatment response and outcomes.

Study Criteria

The study was carried out by cogitating about the ensuing norms:

Inclusion Criteria

The study will include patients who are admitted to the General Medicine or Endocrine departments of a hospital. These departments often treat individuals with chronic conditions like Diabetes Mellitus, making them ideal settings for recruitment.

- Only patients who have been diagnosed with Diabetes Mellitus (either Type 2 or other forms) are eligible for inclusion in the study. This includes individuals whose diabetes is being actively managed in a clinical setting.
- Participants must be within the age range of 35 to 65 years at the time of enrollment. This age range captures adults who are typically managing chronic diseases like diabetes but excludes elderly individuals who may have additional co-morbidities that could affect treatment responses.
- Both male and female patients will be included, ensuring gender diversity in the study
- Eligible patients must be prescribed SGLT-2 inhibitors as add-on therapy in combination with other anti-hyperglycemic agents
- Includes patients who are being treated with oral medications, insulin therapy, or a combination of both.

Exclusion Criteria

Table 4: Patients Presented with More than One ADR

ADR's	Canagliflozin	Dapagliflozin
Hypotension, dehydration, polyuria	134	108
Dehydration and hypotension	209	197
Polyuria and dehydration	161	117
UTI and Vaginal candidiasis	46	34
Weight loss, ketoacidosis, vaginal candidiasis	12	6

- Patients with Type 1 Diabetes**,** Gestational Diabetes**,** or those were under 18 years of age will be excluded from the study.
- Patients who have been discharged against medical advice will be excluded from the study.
- Patients who are unwilling or unable to participate due to various reasons (e.g., personal, logistical, or psychological barriers) will not be enrolled.
- Any patient who does not meet the specific inclusion criteria (such as age, diagnosis, or treatment regimen) will be excluded from the study.

RESULTS AND DISCUSSION

A prospective Interventional Comparative Study was conducted in the General Medicine and Endocrine Department, Anu Group of Hospitals, Main Branch, Suryaraopet, Vijayawada for 12 months in 3456 patients (N) out of which 1854 (n_1) patients using Canagliflozin and 1602 (n_2) patients using Dapagliflozin from January 2022 to January 2023. In this study Control group population was 800.

Table 2 represents a breakdown of 3,456 patients with Type 2 Diabetes Mellitus who were prescribed either Canagliflozin (n=1,854) or Dapagliflozin (n=1,602), administered as add-on therapies in combination with other antidiabetic drugs. The table further categorizes patients based on whether the SGLT2 inhibitor was added as part of dual, triple, or quadruple therapy**.**

Table 3 Represents Patients with ADRs after the intake of Canagliflozin versus Dapagliflozin. Hypotension was the most common ADR after taking Canagliflozin whereas Dehydration was the most common ADR after taking

Dapagliflozin. We did a Chi-square test for Patients with ADRs After taking Canagliflozin versus Dapagliflozin used to treat type-2 diabetes mellitus. 9.12523 is the calculated Chi-square value at 5 degrees of freedom and 5% level of significance (P-value: < 0.1042- not significant). This shows that there was slight difference but similar safety by using Canagliflozin versus Dapagliflozin.

Table 4 represents the patients presented with more than one ADR in which dehydration along with hypotension was more common when compared with other ADRs in both Canagliflozin-prescribed and Dapagliflozin-prescribed patients.

We performed a Chi-square test for Patients in Control, Canagliflozin and Dapagliflozin groups for the Mean FBS parameter. 1.304 is the calculated Chi-square value at 24 degrees of freedom and 5% level of significance (P-value: 0.2535 > 0.05 - not significant). This shows a slight difference but similar Safety by using Canagliflozin versus Dapagliflozin. The absence of a significant difference in Mean FBS across the three groups (Control, Canagliflozin, and Dapagliflozin) suggests that, based on this particular parameter (FBS), the safety profile of Canagliflozin and Dapagliflozin is similar. Specifically, their effect on FBS is not significantly different. Although the Chi-square test indicated a "slight difference," the P-value shows that this difference is not large enough to be statistically meaningful at the 5% significance level. In other words, while there may be small variations in the data, these variations are likely due to random chance rather than a true effect of the treatments. Given that the test shows no statistically significant difference between the two treatments in terms of Mean FBS, you can conclude that both Canagliflozin and Dapagliflozin have a similar effect on FBS in the study population. This suggests that, for this specific parameter, there is no compelling evidence to suggest that one is safer or more effective than the other.

We performed a Chi-square test for Patients in Control, Canagliflozin and Dapagliflozin groups for the Mean PPBS parameter. 1.407 is the calculated Chi-square value at 24 degrees of freedom and a 5% level of significance (P-value: 0.4277 > 0.05 - not significant). This shows that there was aslight difference but similar safety by using Canagliflozin versus Dapagliflozin. Since the P-value (0.4277) is greater than 0.05, this result shows that the differences observed in the Mean PPBS values between the three groups are not statistically significant. This implies that there is no evidence of a meaningful effect on PPBS levels based on the type of treatment (Control, Canagliflozin, or Dapagliflozin). Although the Chi-square statistic (1.407) suggests there may be some minor differences in PPBS across the groups, this difference is not large enough to reach statistical significance. In other words, any observed differences are likely due to random variation rather than any true effect from the treatments. The fact that no significant difference was found in PPBS levels between Canagliflozin and Dapagliflozin indicates that, at least in terms of their impact on PPBS, the two treatments are very similar. The safety profiles of both treatments regarding this parameter appear to be comparable, as both treatments do not significantly affect PPBS differently compared to the Control group. Based on the Chi-square test, we conclude that both Canagliflozin and Dapagliflozin have a similar effect on Postprandial Blood Sugar**.** The slight difference observed in the data is not statistically significant, meaning the observed effect could be due to chance rather than any real therapeutic difference. Therefore, the safety of both drugs with respect to PPBS appears similar.

A Chi-square test was conducted to assess the relationship between treatment group (Control, Canagliflozin, and Dapagliflozin) and changes in HbA1c levels, a key marker of glycaemic control. The calculated Chi-square value was 0.122, with 8 degrees of freedom. At a 5% level of significance, the corresponding P-value was 0.7269, which is greater than 0.05, indicating that the observed differences in HbA1c outcomes among the three groups are not statistically significant. This result suggests that there is no meaningful difference in the impact of Canagliflozin, Dapagliflozin, or the Control treatment on HbA1c levels across the patient sample. Although minor variations in HbA1c reduction may exist numerically between groups, they are not large enough to reach statistical significance, implying that all three groups had a comparable effect on glycaemic control over the course of the study. The lack of a significant difference in HbA1c outcomes could be attributed to several factors, such as baseline HbA1c levels, duration of treatment, adherence to medication, or concurrent therapies. It also highlights the possibility that while SGLT2 inhibitors like Canagliflozin and Dapagliflozin are effective in reducing blood glucose, their effect on HbA1c may not differ dramatically from other standard treatments in certain populations or under specific study conditions. The Chi-square analysis supports the interpretation that Canagliflozin and Dapagliflozin exhibit a similar efficacy profile to the control group in terms of HbA1c reduction, with no statistically significant advantage observed among the treatment arms.

To evaluate the association between treatment groups and the occurrence of hypoglycaemia as an adverse drug reaction (ADR), a Chi-square test was performed. The analysis included three groups: Control, Canagliflozin, and Dapagliflozin. The calculated Chi-square statistic was 10.283, with 4 degrees of freedom. At a 5% level of significance, the corresponding P-value was 0.0013, which is well below the threshold of 0.05, indicating that the observed differences in hypoglycaemia rates among the groups are statistically significant. This result provides strong evidence that hypoglycaemia is significantly more prevalent in the Control group compared to the Canagliflozin and Dapagliflozin groups. The lower incidence of hypoglycaemia in patients receiving SGLT2 inhibitors (Canagliflozin and Dapagliflozin) may be attributed to the mechanism of action of these agents, which promote glucose excretion via the urine rather than increasing insulin secretion, thereby reducing the risk of blood glucose levels falling below normal. Overall, the statistical analysis reinforces the favorable safety profile of Canagliflozin and Dapagliflozin in terms of hypoglycaemia risk, particularly when compared to standard or alternative antidiabetic treatments used in the control group.

Table 5: Control vs. Canagliflozin vs. Dapagliflozin Mean FBS, PPBS Levels

	Mean FBS (mg/dl)	Mean PPBS (mg/dl)	Mean FBS (mg/dl)	Mean PPBS (mg/dl)	Mean FBS (mg/dl)	Mean PPBS (mg/dl)
	Control Group		Canagliflozin		Dapagliflozin	
Day of prescribing SGLT-2 inhibitor	250	320	230	300	230	306
After 1 month	150	225	142	232	140	230
After 2 months	156	238	145	225	145	225
After 3 months	160	255	159	254	155	252
After 4 months	150	240	155	246	155	246
After 5 months	165	250	160	250	163	251
After 6 months	148	236	147	235	148	235
After 7 months	157	245	155	242	152	244
After 8 months	161	252	156	244	159	246
After 9 months	154	248	151	245	151	245
After 10 months	149	245	154	242	148	242
After 11 months	163	254	161	253	161	255
After 12 months	157	244	152	240	152	243

A Chi-square test was performed to evaluate the association between treatment group (Control vs. Canagliflozin) and the incidence of adverse drug reactions (ADRs). The calculated Chi-square value was 31.868, with 3 degrees of freedom. At the 5% level of significance, the corresponding P-value was < 0.0001, which is highly significant ($P < 0.05$). This indicates that there is a statistically significant difference in the distribution of ADRs between the Control and Canagliflozin groups. This significant result suggests that the types or frequencies of ADRs differ notably between the two groups, and they should not be considered equally safe based on this analysis alone. Rather, the data demonstrate that Canagliflozin has a distinct ADR profile compared to the Control group. While this does not necessarily imply that one group is more or less safe overall without a severity-based analysis of ADRs, it does confirm that the safety profiles are not identical. Further interpretation would require examining which specific ADRs contributed most to this difference (e.g., hypotension, hypoglycaemia, etc.) and whether these differences are clinically significant in addition to being statistically significant. It is also important to consider the benefit-risk balance in therapeutic decision-making, especially in chronic conditions like diabetes

A Chi-square test was conducted to assess the distribution of adverse drug reactions (ADRs) between the Control group and the Dapagliflozin group. The analysis yielded a Chi-square statistic of 31.868 with 3 degrees of freedom. At a 5% level of significance, the associated P-value was 0.0030, which is less than 0.05, indicating a statistically significant difference in ADR occurrences between the two groups. This statistically significant result suggests that the safety profiles of the Control and Dapagliflozin groups are not equivalent. The differences in ADR patterns—whether in frequency, type, or severity—are unlikely to be due to random variation alone and may reflect the distinct pharmacodynamic effects of Dapagliflozin compared to standard treatments or placebo used in the Control group. Importantly, while this result highlights a difference in safety, it does not inherently imply that Dapagliflozin is less safe. Rather, it indicates that patients receiving

Table 6: Control, Canagliflozin and Dapagliflozin Groups HbA1C Levels

Days (Mean of Parameters)	Day 0	Day 90	Day 180	Day 270	Day 360
Control Group HbA1c Level	9	7.5	6.5	6.5	6
Canagliflozin group HbA1c Level	9	6.5	5 .5	5.5	5
Dapagliflozin group HbA1c Level	9	6.5	5.5	5.5	5

Dapagliflozin experienced a different spectrum or rate of ADRs compared to those in the Control group. For instance, as observed in other parts of the study, dehydration may be more frequent in the Dapagliflozin group, while hypoglycaemia and weight gain were more common in the Control group. Therefore, this statistical evidence emphasizes the need to evaluate individual ADRs in context, considering both their clinical impact and how they align with treatment goals. The significant Chi-square and P-value underscore that treatment decisions should be individualized, balancing both efficacy and specific safety considerations.

CONCLUSION

Based on the findings of this study, we observed distinct patterns in adverse drug reactions (ADRs) among patients treated with Canagliflozin and Dapagliflozin. Specifically, hypotension emerged as the most frequently reported ADR in patients administered Canagliflozin, whereas dehydration was more commonly associated with Dapagliflozin. These results suggest that while both medications belong to the same pharmacological class (SGLT2 inhibitors), their safety profiles may vary slightly in terms of specific side effects.

In contrast, patients in the control group—who were not prescribed either Canagliflozin or Dapagliflozin—exhibited a higher incidence of hypoglycaemia, indicating that the use of SGLT2 inhibitors may be associated with a lower risk of this adverse event. Furthermore weight gain, considered a negative metabolic outcome, was more commonly observed in the control group, whereas both

Canagliflozin and Dapagliflozin were associated with weight loss, which can be viewed as a beneficial effect, particularly in patients with type 2 diabetes or metabolic syndrome.

Although there are some differences in the type and frequency of ADRs between Canagliflozin and Dapagliflozin, the overall safety profiles of both drugs appear to be broadly comparable. The observed variations in side effects such as hypotension and dehydration highlight the importance of individualized therapy, where the selection of a specific SGLT2 inhibitor may be tailored to the patient's clinical profile and risk factors.

Acknowledgements

Sincere thanks Anu Group of Hospitals and Beleaf Hospitals.

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