Dapagliflozin's Impact on Cardio-Renal Outcomes in Critically Ill Type 2 Diabetes Mellitus Patients

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Abstract

Background: One of the most prevalent medical conditions in the Eastern world nowadays is type 2 diabetes mellitus (T2DM). Owing to its impact on cardiovascular disease (CVD) and its significant prevalence it has been demonstrated that one in seven residents of Middle Eastern nations has diabetes.

Objectives: This work aimed to determine how sodium-glucose cotransporter 2 (SGLT 2) inhibitors affect individuals with T2DM mellitus who have chronic renal disease and CVD during critical illness.

Patients and methods: This prospective randomized, double-blind study was carried out on 142 critically ill patients with T2DM and chronic kidney disease or CVD. Patients were randomly divided into two equal groups to receive either dapagliflozin 10mg once daily during their stay in the critical care department with the standard care in the intervention group or the placebo with the standard care in the control group.

Results: Both groups' post-treatment echo parameters were comparable. On Days 3 and 4, when compared to the control group, the intervention group's eGFR and creatinine levels considerably improved ($p<0.001$). There were no appreciable differences between the groups in RBS, troponin I, total cholesterol, or triglycerides ($p >0.05$). The control group's stay in the intensive care unit was significantly longer than the intervention group.

Conclusion: Dapagliflozin significantly improved renal function. However, it has no effect on cardiovascular events in critically sick patients with type 2 diabetes. Additionally, patients treated with dapagliflozin experienced fewer hospitalizations for coronary artery disease and shorter intensive care unit stays.

Keywords: Cardiac; Renal; Dapagliflozin; Critically ill; Type 2 Diabetes Mellitus.
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Introduction

According to the International Diabetes Federation, Egypt has the ninth-highest number of people with type 2 diabetes worldwide **(Henning, 2018)**. About one in seven people in the Middle East suffer from type 2 diabetes mellitus (T2DM), which is a rapidly spreading disease **(Xu et al., 2025).**

T2DM significantly raises the risk of cardiovascular diseases (CVD), as it doubles the risk of heart failure (HF) and quadruples the incidence of CAD and stroke. The two main causes of death for these individuals are sudden cardiac death and acute myocardial infarction (AMI) **(Einarson et al., 2018).**

Renal complications are another major concern, as T2DM can progressively damage renal blood vessels, leading to chronic kidney disease (CKD). This dual burden of cardio-renal complications necessitates therapeutic interventions that address both aspects effectively **(Rossing et al., 2024).**

A possible remedy is dapagliflozin, an inhibitor of the sodium-glucose cotransporter-2 (SGLT2). SGLT2 inhibitors use the sodium gradient produced by the Na+/K+ pump to help glucose be excreted through urine **(Loh, 2025)**. Dapagliflozin has shown significant cardiovascular advantages beyond glycaemic management, which is why the American Diabetes Association (ADA) recommends medication for T2DM patients who are at high risk of cardiovascular events **(Marilly et al., 2022, Ebrahimi et al., 2025a).**

Recent large-scale, placebo-controlled trials have confirmed that dapagliflozin not only reduces the risk of major cardiovascular events but also significantly lowers the risk of renal deterioration, including end-stage renal disease and declining glomerular filtration rates **(Simes and MacGregor, 2019)**. Critically ill patients, often presenting with AMI or acute HF, benefit from these protective effects, experiencing reduced morbidity during their intensive care unit (ICU) stays **(Chang et al., 2022).**

This aimed to determine how SGLT 2 inhibitors affect individuals with T2DM mellitus who have chronic renal disease and CVD during critical illness.

Patients and methods

This prospective randomized quadruple-blind included 142 ischemic heart disease (IHD) and stent placement history, heart failure with an EF of less than 50%, an estimated glomerular filtration rate (eGFR) of 25–75 mL/min/1.73 m^2, albumin to creatinine ratio of 200–5000 mg/g, and critically ill patients with CKD or CVD and type 2 diabetes, left ventricular hypertrophy (LVH), and diabetic cardiomyopathy (DCM).

The research was conducted between June 2022 and June 2024, following the approval from the Armed Forces College of Medicine Ethical Committee. The patients provided informed written consent.

Exclusion criteria included individuals with type 1 diabetes, polycystic kidney disease, vasculitis or lupus nephritis, recent use of immunosuppressive/cytotoxic medications for kidney disease, organ transplant recipients who started SGLT2 inhibitors within eight weeks, mechanically ventilated patients, and those who had experienced cardiac arrest.

All patients were assessed before receiving the treatment and throughout their stay in the critical care unit to monitor any improvements or deterioration in their condition, allowing for evaluating the drug's efficacy. They received the standard healthcare along with either the drug or a placebo.

Randomization and blinding

To maintain the integrity of the study, a random allocation process was utilized, employing computer-generated numbers (https://www.randomizer.org/). Each participant's code was placed in an opaque, sealed envelope to preserve blinding. The patients were randomly assigned in a

parallel manner into two groups (1:1 ratio) to receive either dapagliflozin 10mg once daily during their stay in the critical care department with the standard care in the intervention group or receive the placebo with the standard care in the control group. To maintain the blinding, the participant, care provider, investigator, and outcome assessors were blind to the group allocation.

Data collection involved gathering essential information about each patient, including age, sex, systolic and diastolic blood pressure, smoking history, pre-existing comorbidities, any medical conditions, and medication history. The length of the ICU stay was also recorded.

For laboratory investigations, blood samples were obtained daily to assess renal function. The tests performed included serum urea, serum creatinine, serum sodium (Na+), serum potassium (K+), and GFR. Oxygenation and hemodynamic stability were monitored every 12 hours, with arterial and central venous blood gases and serum lactate levels being checked. Random blood glucose levels were measured every 4 hours to monitor diabetes, and glycated hemoglobin (HbA1c) was measured on admission. A lipid profile was conducted on day 1 and before discharge to assess the state of atherosclerosis and cardiovascular health.

Cardiac monitoring involves daily ECG assessments for arrhythmias or ischemic changes. Baseline and follow-up echocardiographies were performed using the GE Healthcare Vivid E95, and two echocardiographers followed the guidelines set by the European Association of Cardiovascular Imaging. Parameters such as left ventricular dimensions, end-systolic volume (LVESVi), end-diastolic volume (LVEDVi), and left ventricular ejection fraction (LVEF) were measured. Troponin levels were analyzed using a Siemens Dimension EXL analyzer.

According to the inclusion criteria, patients with renal or cardiac diseases related to T2DM were administered dapagliflozin with a dose of 10 mg once daily during the patients' stay in the critical care department. The duration of treatment aligned with their time in the intensive care unit. Their cardiac and renal conditions were continuously monitored through blood samples, ECGs, and echocardiography to track any improvement or deterioration, ensuring the efficacy of the SGLT2 inhibitors **(Ebrahimi et al., 2025b)**.

Evaluating dapagliflozin's safety and efficacy in enhancing the prognosis of cardiovascular and renal disorders in critically sick type 2 diabetic patients was the main objective of the research.

Additionally, the study sought to understand how dapagliflozin affects cardiovascular events like ischemia and HF and to determine its impact on renal function in critically ill patients. The length of ICU stays was also assessed as a potential outcome of dapagliflozin treatment.

Sample size calculation

G*Power 3.1.9.2 was used to determine the sample size (Universitat Kiel, Germany). According to **(Perkovic et al., 2019)**, a minimum of 64 individuals per group were needed to detect a hazard ratio (HR) of 0.68 with 80% power and a 5% significance error. The final sample size was 142 individuals, with 71 in the intervention group and 71 in the control group, after adjusting for a 10% dropout rate.

Statistical analysis

SPSS programming adaptation 26 (IBM Inc., Chicago, IL, USA) was utilized for factual investigation. The unpaired t-test was utilized to analyze gatherings, and quantitative parametric information were displayed as means and standard deviations. Frequencies (%) were utilized to show the subjective information, and the chi-square test or Fisher exact test, as material, were utilized to look at gatherings. A p-value below 0.05 was used to decide the significance level.

Results

Age, sex, BMI, comorbidities, and medication distributions were comparable between groups, (**Table.1**).

Table 1. Demographic data of the studied groups

Variables		Intervention (n=71)	Control (n=71)	P
Age (years)		68.41 ± 8.72	67.55 ± 8.14	.545
Sex	**Male**	39 (54.9%)	40 (56.3%)	.866
	Female	32 (45.1%)	31 (43.7%)	
Body mass index (kg/m^2)		27.98 ± 4.28	28.57 ± 4.68	.434
Comorbidities	**Hypertension**	34 (47.9%)	31 (43.7%)	.613
	Dyslipidemia	30 (42.3%)	25 (35.2%)	.389
	Heart failure	12 (16.9%)	9 (12.7%)	.478
	Ischemic heart disease	21 (29.6%)	15 (21.1%)	.248
	Diabetic retinopathy	11 (15.5%)	8 (11.3%)	.460
	Diabetic neuropathy	9 (12.7%)	7 (9.9%)	.596
	Peripheral artery disease	5 (7.1%)	8 (11.3%)	.383
Medications	**Aspirin**	26 (36.6%)	30 (42.3%)	.492
	Clopidogrel	18 (25.4%)	19 (26.8%)	.848
	Statins	51 (71.8%)	49 (69%)	.713
	ACEi or ARBs	41 (57.7%)	39 (54.9%)	.735
	β-blockers	20 (28.2%)	14 (19.7%)	.239
	Diuretics	16 (22.5%)	18 (25.4%)	.694
	CCB	25 (35.2%)	23 (32.4%)	.723

Data are presented as mean ± SD or frequency (%). ACEi: Angiotensin-converting enzyme inhibitors. ARBs: Angiotensin 2 receptor blockers. CCB: calcium channel blockers.

Baseline clinical data (vital signs and laboratory and echo parameters) were comparable between groups. (**Table .2).**

Both groups' post-treatment echo parameters were comparable. (**Table.3).**

Table 2. Baseline clinical data of the studied groups

Variables		Intervention (n=71)	Control (n=71)	P
Vital signs	**HR (beat/min)**	81.25 ± 9.17	79.72 ± 8.42	.302
	SBP (mmHg)	128.5 ± 7.63	125.9 ± 8.75	.061
	DPB (mmHg)	82.1 ± 5.64	80.7 ± 4.32	.099
Laboratory	**TC (mg/dl)**	184.22 ± 36.19	182.46 ± 30.12	0.753
	Triglycerides (mg/dl)	163.84 ± 25.36	161.79 ± 23.65	0.619
	LDL (mg/dl)	113.65 ± 14.23	114.75 ± 13.92	0.642
	HDL (mg/dl)	48.61 ± 7.95	46.9 ± 6.43	0.161
	RBS (mg/dl)	176.33 ± 24.45	179.42 ± 26.88	0.475
	Creatinine (mg/dl)	1.36 ± 0.467	1.27 ± 0.519	0.279
	Urea (mg/dl)	56.12 ± 12.79	53.97 ± 14.86	0.357
	eGFR (mL/min/1.73m^2)	61.39 ± 15.71	62.17 ± 17.58	0.781
	ALT (U/L)	28.97 ± 6.07	28.37 ± 5.76	0.547
	AST (U/L)	28.48 ± 7.34	27.65 ± 6.33	0.472
	Albumin (g/dl)	3.89 ± 0.452	3.96 ± 0.508	0.387

	Troponin I (ng/mL)	1.07 ± 0.812	0.863 ± 0.634	0.096
Echo	**EF (%)**	45.79 ± 5.67	46.13 ± 6.22	0.734
	FS (%)	28.38 ± 5.27	28.14 ± 5.41	0.789
	LVEDd (mm)	46.78 ± 5.82	48.27 ± 6.29	0.145
	LVESd (mm)	31.37 ± 5.01	29.84 ± 6.42	0.116
	E velocity (m/s)	0.703 ± 0.157	0.716 ± 0.164	0.631
	E/A ratio	1.14 ± 0.351	1.07 ± 0.243	0.169

Data are presented as mean ± SD. HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TC: Total cholesterol, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, RBS: Random blood sugar, Creatinine: Creatinine, Urea: Urea, eGFR: Estimated glomerular filtration rate, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, Albumin: Albumin, Troponin I: Troponin I, EF: Ejection fraction, FS: Fractional shortening, LVEDd: Left ventricular end-diastolic diameter, LVESd: Left ventricular end-systolic diameter, E velocity: Early diastolic velocity, E/A ratio: Early to late diastolic filling velocity ratio.

Table 3. Post-treatment Echo parameters of the studied groups

Variables	Intervention (n=71)	Control (n=71)	P
EF (%)	48.81 ± 6.42	46.52 ± 6.71	0.060
FS (%)	30.21 ± 6.13	28.39 ± 5.65	0.068
LVEDd (mm)	48.35 ± 6.22	47.89 ± 6.09	0.657
LVESd (mm)	32.17 ± 5.69	30.87 ± 6.63	0.212
E velocity (m/s)	0.766 ± 0.203	0.723 ± 0.186	0.190
E/A ratio	1.12 ± 0.367	1.09 ± 0.239	0.655

Data are presented as mean ± SD. EF: Ejection fraction, FS: Fractional shortening, LVEDd: Left ventricular end-diastolic diameter, LVESd: Left ventricular end-systolic diameter, E velocity: Early diastolic velocity, E/A ratio: Early to late diastolic filling velocity ratio.

On Days 3 and 4, the Intervention group's eGFR and creatinine levels significantly improved compared to the control group (p-values <0.001). However, no significant changes were seen between the groups for RBS, troponin I, TC, or triglycerides, (**Table.4**).

Table 4. Estimated glomerular filtration rate, creatinine, random blood sugar, troponin I, total cholesterol, and triglyceride levels at follow-up

Variables		Intervention (n=71)	Control (n=71)	P
eGFR (mL/min/1.73m^2)	**Day 1**	50.76 ± 10.76	51.68 ± 11.57	0.843
	Day 2	48.38 ± 15.56	47.46 ± 13.29	0.958
	Day 3	55.23 ± 17.7	46.48 ± 15.13	0.002
	Day 4	59.19 ± 21.6	46.23 ± 20.42	<0.001
Creatinine (mg/dl)	**Day 1**	2.05 ± 0.739	1.85 ± 0.673	0.094
	Day 2	2.43 ± 0.512	2.07 ± 0.592	0.145
	Day 3	1.74 ± 0.512	2.019 ± 0.592	0.002
	Day 4	1.45 ± 0.478	2.30 ± 0.563	<0.001
RBS (mg/dl)	**Day 1**	175.63 ± 41.98	173.39 ± 40.49	0.747
	Day 2	135.27 ± 7.1	139.4 ± 7.36	<0.001
	Day 3	141.54 ± 12.42	150.9 ± 11.89	<0.001
	Day 4	129.42 ± 9.87	138.2 ± 10.61	<0.001
Troponin I (ng/mL)	**Day 1**	1.07 ± 0.812	0.863 ± 0.634	0.096
	Day 2	1.1 ± 1.22	1.08 ± 1.28	0.924
	Day 3	1.02 ± 1.07	1.1 ± 1.31	0.691

TC (mg/dl)	**Day 1**	165.56 ± 38.95	163.44 ± 39.91	0.749
	Day 2	167.46 ± 25.42	166.8 ± 26.33	0.879
	Day 3	156.17 ± 24.51	160.25 ± 26.44	0.342
Triglyceride (mg/dl)	**Day 1**	147.86 ± 55.1	156.1 ± 52.58	0.364
	Day 2	157.13 ± 19.59	158.6 ± 22.63	0.679
	Day 3	127.49 ± 17.81	132.45 ± 20.58	0.127

Data are presented as mean ± SD. eGFR: Estimated glomerular filtration rate. RBS: Random blood sugar, TC: Total cholesterol.

(**Table.5**) shows that the control group's length of ICU stay was noticeably more prolonged than that of the intervention group.

Table 5. Length of intensive care unit stay of the studied groups

Variables	Intervention (n=71)	Control (n=71)	P
Intensive care unit stay (Days)	6.29 ± 1.57	7.1 ± 1.69	0.004

Data is presented as mean ± SD.

Discussion

Two kidney diseases significantly increase the risk of CV outcomes are reduced GFR and albuminuria **(Rangaswami et al., 2019)**. Individuals with T2DM often have both conditions, making them particularly vulnerable to CV complications.

A meta-analysis of three significant SGLT2i cardiovascular trials found that patients with lower baseline renal function was benefit most from SGLT2i treatment **(Zelniker et al., 2019)** but that the effectiveness of SGLT2i in lowering glucose and reducing glycosuria in patients with impaired renal function diminishes with a lower eGFR **(Perkovic et al., 2019)**. SGLT2i, which improves urine glucose excretion, has demonstrated promise in lowering the risk of CV death and HF hospitalization in T2DM patients **(Scirica et al., 2018).**

These findings support the idea that glucose control alone is insufficient to prevent CV events and emphasize the need to shift from a purely glucocentric approach to one considering broader CV risk reduction factors.

Several potential mechanisms have been proposed to explain the cardiovascular benefits of SGLT2i therapy, but the exact mechanisms behind these benefits remain unclear. This strategy has several advantages, such as lowering intraglomerular pressure, improving heart function by reducing preload and afterload, reducing oxidative stress and inflammation, enhancing oxygen supply by increasing red blood cell mass, and promoting weight reduction **(Zelniker and Braunwald, 2018)**. Although the connection between CKD, peripheral artery disease, anomalies of the bones and minerals, and fluid overload **(Webster et al., 2017)** is well documented, yet the safety profile of dapagliflozin in this vulnerable and hard-to- is well established, it is still unclear how safe dapagliflozin is for this susceptible and challenging patient population. The results of the DECLARE-TIMI 58 research, which examined major adverse cardiovascular events (MACE) and a composite of cardiovascular death or hospitalization for heart failure, showed that dapagliflozin significantly decreased mortality and myocardial infarction risk **(Wiviott et al., 2019)**.

The study's findings showed no substantial variations in age, sex, body mass index (BMI), or co-existing medical conditions between the two groups being examined. There were no notable disparities in medication usage, heart rate, or systolic and diastolic blood pressure readings (SBP, DBP). The study's results were consistent with those of **(Nicholson et al., 2021)**, who found that the dapagliflozin group outperformed the placebo group in terms of MACE

(ischaemic stroke, myocardial infarction, and cardiovascular mortality), as well as the combined incidence of heart failure hospitalizations and cardiovascular death. With a hazard ratio of 0.83 (4.9% vs. 5.8%), the combined outcome of cardiovascular mortality and heart failure hospitalization happened less frequently in the dapagliflozin group than in the other group. Notably, heart failure hospitalizations were less prevalent in this group, with a hazard ratio of 0.73 (95% confidence interval 0.61 to 0.88). However, rates of cardiovascular mortality were not substantially different between the two groups.

Dapagliflozin was shown to significantly lower cardiovascular mortality and heart failure hospitalizations when compared to a placebo; however, it did not significantly lower the risk of serious adverse cardiovascular events. The study found that the incidence of the renal composite endpoint was 4.3% for dapagliflozin-treated individuals and 5.6% for placebo-treated participants, with a hazard ratio of 0.76 and a 95% CI between 0.67 and 0.87. The all-cause death rates for individuals receiving dapagliflozin and those receiving a placebo were 6.2% and 6.6%, respectively, with no discernible differences between the two groups. The hazard ratio was 0.93, and the 95% CI ranged from 0.82 to 1.04 **(Solomon et al., 2022)**. The study also found no significant variance in baseline laboratory measures (e.g., hemoglobin, LDL, HDL, random blood sugar, creatinine, eGFR, albumin, triglycerides, urea, total cholesterol, and troponin I) between the two groups.

(Zelniker et al., 2021) similarly observed that patients with less preserved kidney function (eGFR < 60 mL/min/1.73 m²) had a smaller reduction in glycemic levels with dapagliflozin and a significant interaction was found between the effects of placebo and dapagliflozin on overall mortality. The results indicated that patients with more CKD markers benefited more from treatment. This impact modification was more pronounced in patients with a urine albumin-to-creatinine ratio (UACR) of 300 mg/g (P = 0.007 for interaction) than in those with impaired eGFR (P = 0.61 for interaction). Moreover, patients with higher CKD markers exhibited a greater reduction in mortality from all causes (HR 0.75 [95% CI: 0.47 to 1.18] for two markers).

The study's findings also showed that there was a significant difference in eGFR between the two groups on Days 3 and 4. Following dapagliflozin administration, the intervention group experienced a decrease in eGFR followed by a sharp increase, while the control group's eGFR remained relatively unchanged. These results are comparable with **(Solomon et al., 2022),** who observed a mean eGFR of 85 mL/min/1.73 m² in their research, with a large number of patients demonstrating decreased renal function (7.3% with eGFR < 60 mL/min/1.73 m²). The study also indicated notable changes in creatinine levels between the groups, with a more significant improvement in the intervention group.

Both study groups showed significant improvements in RBS following treatment, with a statistically significant difference between the two groups. This discovery aligns with the observations of **(Ata et al., 2021)**, who found a substantial decrease in RBS in patients with diabetic ketoacidosis (DKA). The study found no noticeable difference in the levels of total cholesterol and triglycerides between the two groups, but both groups did see a significant decrease in these parameters after receiving treatment. The intervention group experienced a significantly shorter intensive care unit (ICU) stay and a lower rate of composite renal events as well as composite heart failure and renal events compared to the control group. When compared to the control group, the intervention group's overall mortality rate was reduced. These findings are in line

with those of **(Nicholson et al., 2021)**, who found that the dapagliflozin group had a lower risk of both cardiovascular death and heart failure hospitalization. Their hazard ratio was 0.83, indicating a difference of 4.9% vs. 5.8%, and they attributed the lower cardiovascular death rate to the lower heart failure hospitalization rate. The results of this study are in line with those of the EMPA-REG OUTCOME trial, which shown that empagliflozin significantly decreased the risk of cardiovascular and overall mortality in people with type 2 diabetes **(Zinman et al., 2015)**.

Future research should utilize well-designed randomized controlled trials or substantial, comparative observational studies to corroborate the findings of this study. Including a diverse group of patients of similar age, gender, and disease severity is essential for increasing the applicability of the study outcomes. Accurate long-term outcomes should be ensured by collecting data with standardized tools and protocols at regular intervals and performing follow-up checks. Future studies should have a sufficiently large sample size to ensure that their conclusions are meaningful and to mitigate the influence of confounding factors effectively. It is suggested that extended follow-up periods be utilized to evaluate the long-term advantages of SGLT2i medications, and multi-center studies would assist in verifying the results across diverse populations.

Conclusion

The SGLT2 family of medications, which includes dapagliflozin significantly improved renal function. However, it has no effect on cardiovascular events in critically sick patients with type 2 diabetes. Additionally, patients treated with dapagliflozin experienced fewer hospitalizations for CAD and shorter ICU stays.

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