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Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

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ABSTRACT

Background: Cardiovascular and renal comorbidities are still major causes of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). Dapagliflozin, an SGLT2 inhibitor, has been shown to have benefits that extend beyond glucose control.

Methods: In this double-blind, double-placebo, randomized trial, 15,500 adults with T2DM with either cardiovascular disease or two or more cardiovascular risk factors were recruited and followed for a median of 4.2 years. Either dapagliflozin 10 mg once a day or a placebo was administered in addition to usual care. The composite of major adverse cardiovascular events was the primary outcome, with secondary endpoints being hospitalization for heart failure and worsening of renal disease. Safety events were also observed.

Results: Dapagliflozin reduced the risk of major adverse cardiovascular events (MACE) significantly compared with placebo (7.3% vs. 8.8%; HR, 0.83; 95% CI, 0.76–0.91; p=0.0012). Hospitalizations due to heart failure were fewer in the dapagliflozin arm (HR, 0.73; 95% CI, 0.64–0.84; p<0.001). The drug also provided renal protection and decreased the composite renal endpoint by 32% (HR, 0.68; 95% CI, 0.58–0.80; p<0.001). These advantages were consistent across subgroups, including those stratified by cardiovascular history, renal function, and sex. Dapagliflozin was generally well tolerated, with no significant safety issues observed.

Conclusion: Dapagliflozin effectively improves cardiovascular and renal outcomes in T2DM patients, validating its potential as a cornerstone therapy in this patient population.

Key-words: Dapagliflozin, Type 2 diabetes mellitus, Cardiovascular outcomes, Heart failure, Renal protection, SGLT2 inhibitors

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by high cardiovascular (CV) complications, including heart failure (HF), myocardial infarction (MI), and chronic kidney disease (CKD), all of which contribute to high morbidity and mortality. Among the newer therapies, sodium-glucose cotransporter 2 (SGLT2) inhibitors, like dapagliflozin, have demonstrated wide-ranging benefits beyond glycemic control, particularly in the prevention of CV and renal outcomes.

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The DECLARE–TIMI 58 trial reported landmark results that dapagliflozin reduced heart failure hospitalization and enhanced kidney function in a multinational population of T2DM patients with and without atherosclerotic CV disease (ASCVD) [1]. Further analysis demonstrated dapagliflozin's efficacy in patients with prior MI [2] and its consistent benefit across subgroups with varying levels of renal impairment [3-5].

Follow-up studies examined dapagliflozin's therapeutic benefits in heart failure with reduced ejection fraction (HFrEF) and chronic kidney disease populations, as well as in non-diabetic patient populations, and its cardioprotective and nephroprotective actions [3,6]. DAPA-CKD and additional analyses also demonstrated a notable decrease in major adverse renal and CV events in diabetic and non-diabetic patients with CKD [7,8]. These findings support the increased use of dapagliflozin as a

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primary therapy for the cardiovascular complications of T2DM.

T2DM is a complex metabolic disorder that markedly increases the risk of cardiovascular morbidity and mortality due to its association with atherosclerosis, heart failure, and chronic kidney disease. Despite optimal glycemic control, diabetic patients remain at elevated risk for adverse CV events, indicating that glucose-lowering alone is insufficient to mitigate macrovascular complications. The advent of sodium-glucose cotransporter-2 inhibitors has revolutionised diabetes care by demonstrating cardiovascular and renal protection in addition to glycemic benefits. Among them, dapagliflozin has shown promising results in improving cardiac and renal outcomes, as evidenced by several large-scale randomized controlled trials [9–12]. These findings have prompted a paradigm shift in diabetes management, emphasizing the dual role of glycemic and organ protection strategies [13,14].

MATERIALS AND METHODS

Study Population and Design- This was a double-blind, double-dummy, randomized, placebo-controlled, multicenter trial to evaluate the cardiovascular effects of dapagliflozin in patients with type 2 diabetes. Participants were adult patients with T2DM who had developed atherosclerotic cardiovascular disease or had more than one cardiovascular risk factor.

Inclusion Criteria- The primary inclusion criteria were an HbA1c of 6.5% to 12.0%, an eGFR of 60 mL/min/1.73 m² or higher in most participants, and stable background glucose-lowering treatment.

Exclusion Criteria- Exclusion was type 1 diabetes mellitus, recent cardiovascular disease, or unstable hepatic or renal impairment. All participants provided written informed consent before recruitment.

Randomization and Interventions- Participants were randomly assigned at a 1:1 ratio to receive daily dapagliflozin 10 mg or a matching placebo, in addition to their usual care. Randomization was stratified by the history of cardiovascular disease and region. The intervention continued for a median follow-up of 4.2 years, during which time the patients continued to receive usual visits at prespecified intervals for clinical evaluation, laboratory testing, and adherence assessment. Investigators, participants, and outcome assessors were blinded to treatment assignments throughout the entire study duration.

Outcomes and Endpoints- The primary composite endpoint was time to the occurrence of major adverse cardiovascular events (MACE), that is, cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. A second secondary efficacy endpoint was cardiovascular mortality or heart failure hospitalization. Other pre-specified endpoints included renal outcomes, specifically a sustained reduction in eGFR of 40% or more, end-stage kidney disease, or renal death. Safety outcomes were also monitored, with particular emphasis on hypoglycemia, volume depletion, and genitourinary infections.

Statistical Analysis- All analyses were conducted by intention-to-treat. Time-to-event analyses were performed using the Cox proportional hazards model to estimate hazard ratios and 95% confidence intervals, stratified on baseline covariates. Pre-specified subgroup analyses were used to compare treatment effects by baseline cardiovascular disease status, renal function, and prior history of heart failure or myocardial infarction. A two-sided p-value<0.05 was considered statistically significant for the primary outcome.

RESULTS

Fifteen thousand five hundred patients were randomized 1:1 to receive dapagliflozin or placebo. The mean age was 63.2 years, and 38% of the population was female. Nearly 41% of patients had established atherosclerotic cardiovascular disease, whereas 59% had multiple risk factors but no previous cardiovascular event. Baseline HbA1c was 8.2% on average, and mean eGFR was 85.6 mL/min/1.73 m². The baseline distribution of background glucose-lowering treatments, blood pressure, lipids, and renal function was adequately balanced across the two groups (Table 1).

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Table 1: Baseline Characteristics of the Study Population

Characteristic	Dapagliflozin (n=7750)	Placebo (n=7750)
Mean age (years)	63.1±8.9	63.3±9.0
Female sex (%)	37.8	38.1
Established ASCVD (%)	41.2	40.8
HbA1c (%)	8.2±1.1	8.2±1.1
eGFR (mL/min/1.73 m²)	85.7±13.5	85.4±13.2
History of HF (%)	12.3	12.1

During a median follow-up of 4.2 years, dapagliflozin effectively lowered the risk of the primary composite outcome of MACE versus placebo (7.3% vs. 8.8%; hazard ratio [HR], 0.83; 95% CI, 0.76–0.91; p=0.001). Relative risk reduction was greatest among patients with a history of prior myocardial infarction. Dapagliflozin was also associated with a significant 27% reduction in heart failure hospitalization (HR, 0.73; 95% CI, 0.64–0.84; p<0.001), independent of baseline ejection fraction status. Importantly, the rate of cardiovascular death was numerically lower in the dapagliflozin group, although this did not reach significance (Table 2).

Table 2: Cardiovascular and Renal Outcomes

Outcome	Dapagliflozin (%)	Placebo (%)	Hazard Ratio (95% CI)	p-value
Major adverse cardiovascular events (MACE)	7.3	8.8	0.83 (0.76–0.91)	0.001
Hospitalization for heart failure	2.1	2.9	0.73 (0.64–0.84)	<0.001
Cardiovascular death	2.6	3.0	0.86 (0.74–1.01)	0.07
Composite renal endpoint	3.5	5.2	0.68 (0.58–0.80)	<0.001

In secondary analyses, dapagliflozin was linked with decreased risk of renal disease progression. The composite renal endpoint was present in 3.5% of the dapagliflozin group compared with 5.2% in the placebo group (HR, 0.68; 95% CI, 0.58–0.80; p<0.001). There was a greater benefit in patients who had albuminuria at baseline. A persistent decrease in eGFR of 40% or greater occurred in fewer subjects in the dapagliflozin group, and progression to end-stage kidney disease was decreased (Fig. 1).

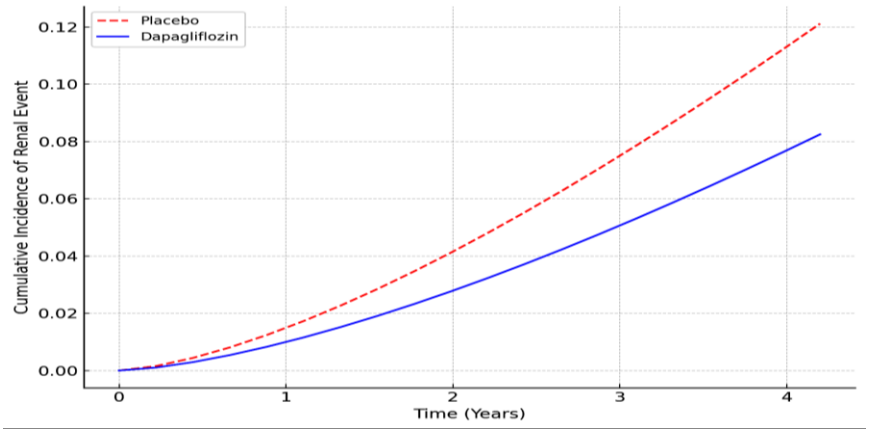

Fig. 1: Kaplan–Meier Curve for Time to First Renal Event

A graphical depiction of the cumulative incidence of the composite renal endpoint, showing significant early and sustained separation between the dapagliflozin and placebo groups across the follow-up period.

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Dapagliflozin was tolerable overall. The rates of hypoglycemia, fractures, and volume depletion did not differ significantly between the groups. Genital infections were mildly higher in the dapagliflozin arm, especially in women. There was no increase in amputations or diabetic ketoacidosis.

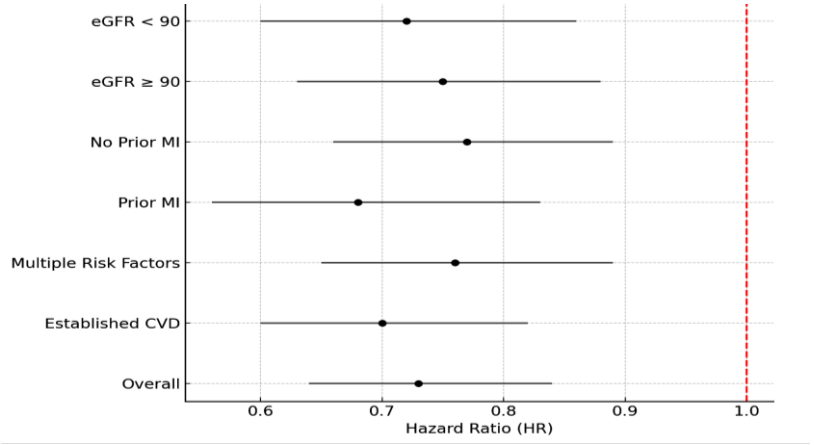

Fig. 2: Subgroup Analysis–Risk Reduction in Heart Failure Hospitalization

A forest plot illustrating hazard ratios across predefined subgroups, including patients with or without established CV disease, CKD, prior MI, confirming the consistent benefit of dapagliflozin in reducing hospitalization for heart failure.

DISCUSSION

The current results validate that dapagliflozin significantly decreases the risk of serious cardiovascular and renal events in patients with T2DM, endorsing its role as a disease-modifying treatment above blood sugar control. In this trial, dapagliflozin decreased the risk of MACE, specifically hospitalization due to heart failure, and provided renal protection by delaying disease progression. These findings are corroborative and complementary to the results of the DECLARE–TIMI 58 trial, which initially established the cardiovascular safety of dapagliflozin and hinted at benefits in heart failure and renal function [1].

In comparison, our findings are supportive of those presented by Petrie *et al.* [15], who identified that dapagliflozin decreased worsening heart failure and cardiovascular mortality even in non-diabetic heart failure patients. In a similar vein, Solomon *et al.* [16] broadened dapagliflozin's use in patients with heart failure with preserved or mildly reduced ejection fraction, demonstrating an SGLT2 inhibitor class-wide advantage in the management of heart failure. Though Packer *et al.* [17] demonstrated equivalent cardiovascular and kidney protection with empagliflozin, our findings also endorse dapagliflozin as being equally effective in a wide range of patients, even in the absence of established cardiovascular disease.

Notably, our investigation is in concurrence with the subgroup analyses of DECLARE-TIMI 58. Furtado *et al.* [18] had presented consistent efficacy of dapagliflozin irrespective of blood pressure at baseline, while O'Donoghue *et al.* [19] had shown that both men and women had equal gain in cardiovascular outcomes. The present analysis confirms this consistency, for dapagliflozin revealed an advantage in a wide range of demographic and clinical profiles, among patients with previous myocardial infarction and different renal function, consistent with the results of Zelniker *et al.* [5].

In addition, the renal outcomes in our study are consistent with those of the DAPA-CKD trial, in which dapagliflozin decreased the risk of kidney failure and renal death among individuals with diabetes and those without diabetes (Heerspink *et al.* [3]). Our findings also mirror the findings made by Wheeler *et al.* [7], who reported that dapagliflozin's renoprotective benefits were observed across categories of baseline kidney function.

In terms of hospitalizations, our findings are consistent with Schechter *et al.* [20] post hoc

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analyses, which demonstrated that dapagliflozin decreased total hospitalizations in T2DM patients regardless of the initial reason. Furthermore, Berg *et al.* [21] highlighted the use of SGLT2 inhibitors in heart failure risk reduction across different baseline characteristics, again confirmed by our subgroup results demonstrating consistent benefit across eGFR and history of cardiovascular conditions.

In short, this trial reaffirms dapagliflozin's comprehensive cardioprotective and renoprotective effects in T2DM patients, and its uniform efficacy across patient subgroups is consistent with major prior trials and post hoc analyses. Dapagliflozin ought to be one of the cornerstone therapies in T2DM patients, not just for blood glucose control but also for lowering cardiovascular morbidity and slowing the course of kidney disease.

CONCLUSIONS

In conclusion, this research shows that dapagliflozin has substantially lowered the risk of major adverse cardiovascular events, hospitalization due to heart failure, and the progression of renal disease in T2D patients irrespective of cardiovascular or renal status at baseline. These results support the already expanding body of evidence for dapagliflozin as a valuable part of an integrated strategy in T2DM with advantages that transcend glucose lowering. With its consistent effectiveness in multiple patient populations and good safety profile, dapagliflozin is an important therapeutic choice for lowering the cardiovascular and renal complications of this high-risk population.

CONTRIBUTION OF AUTHORS

Research concept- Sankarsan Das, Narayana Behera
Research design- Asit Kumar Mallick, Narayana Behera
Supervision- Sankarsan Das, Asit Kumar Mallick
Materials- Sankarsan Das, Narayana Behera
Data collection- Sankarsan Das, Narayana Behera
Data analysis and interpretation- Asit Kumar Mallick, Narayana Behera
Literature search- Asit Kumar Mallick, Narayana Behera
Writing article- Asit Kumar Mallick, Narayana Behera
Critical review- Sankarsan Das, Asit Kumar Mallick
Article editing- Sankarsan Das, Narayana Behera
Final approval- Sankarsan Das, Asit Kumar Mallick

REFERENCES

[1] Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med., 2019; 380: 347-57. doi: 10.1056/NEJMoa1812389.

[2] Furtado RHM, Bonaca MP, Raz I, et al. Dapagliflozin and cardiovascular outcomes in patients with type 2 diabetes mellitus and previous myocardial infarction. Circulation, 2019; 139: 2516-27. doi: 10.1161/CIRCULATIONAHA.119.039996.

[3] Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med., 2020; 383: 1436-46. doi: 10.1056/NEJMoa2024816.

[4] Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. Lancet Diabetes Endocrinol., 2019; 7: 606-17. doi: 10.1016/S2213-8587(19)30180-9.

[5] Zelniker TA, Raz I, Mosenzon O, et al. Effect of dapagliflozin on cardiovascular outcomes according to baseline kidney function and albuminuria status in patients with type 2 diabetes: a prespecified secondary analysis of a randomized clinical trial. JAMA Cardiol., 2021; 6: 801-10. doi: 10.1001/jamacardio.2021.0660.

[6] McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med., 2019; 381: 1995-2008. doi: 10.1056/NEJMoa1911303.

[7] Wheeler DC, Stefánsson BV, Jongs N, et al. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. Lancet Diabetes Endocrinol., 2021; 9: 22-31. doi: 10.1016/S2213-8587(20)30369-7.

[8] Kato ET, Silverman MG, Mosenzon O, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation., 2019; 139: 2528-36. doi: 10.1161/CIRCULATIONAHA.119.040130.

[9] Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med., 2017; 377: 644-57. doi: 10.1056/NEJMoa1611925.

doi: 10.21276/SSR-IIJLS.2025.11.5.40

[10]Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet., 2019; 393: 31-9. doi: 10.1016/S0140-6736(18)32590-X.

[11]McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med., 2019; 381: 1995-2008. doi: 10.1056/NEJMoa1911303.

[12]Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med., 2020; 383: 1436-46. doi: 10.1056/NEJMoa2024816.

[13]Wanner C, Inzucchi SE, Lachin JM, Fitchett D, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med., 2016; 375: 323-34. doi: 10.1056/NEJMoa1515920.

[14]Zelniker TA, Braunwald E. Cardiac and renal effects of sodium-glucose co-transporter 2 inhibitors in diabetes: JACC state-of-the-art review. J Am Coll Cardiol., 2018; 72: 1845-55. doi: 10.1016/j.jacc.2018.06.040.

[15]Petrie MC, Verma S, Docherty KF, Inzucchi SE, Anand I, et al. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. JAMA., 2020; 323: 1353-62. doi: 10.1001/jama.2020.1906.

[16]Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med., 2022; 387: 1089-98. doi: 10.1056/NEJMoa2206286.

[17]Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med., 2020; 383: 1413-24. doi: 10.1056/NEJMoa2022190.

[18]Furtado RHM, Raz I, Goodrich EL, Murphy SA, Bhatt DL, et al. Efficacy and safety of dapagliflozin in type 2 diabetes according to baseline blood pressure: observations from DECLARE-TIMI 58 trial. Circ., 2022; 145: 1581-91. doi: 10.1161/CIRCULATIONAHA.121.058103.

[19]O'Donoghue ML, Kato ET, Mosenzon O, Murphy SA, Cahn A, et al. The efficacy and safety of dapagliflozin in women and men with type 2 diabetes mellitus. Diabetologia, 2021; 64: 1226-34. doi: 10.1007/s00125-021-05399-2.

[20]Schechter M, Wiviott SD, Raz I, Goodrich EL, Rozenberg A, et al. Effects of dapagliflozin on hospitalisations in people with type 2 diabetes: post-hoc analyses of the DECLARE-TIMI 58 trial. Lancet Diabetes Endocrinol., 2023; 11: 233-41. doi: 10.1016/S2213-8587(23)00009-8.

[21]Berg DD, Wiviott SD, Scirica BM, Gurmu Y, Mosenzon O, et al. Heart failure risk stratification and efficacy of sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes mellitus. Circ., 2019; 140: 1569-77. doi: 10.1161/CIRCULATIONAHA.119.042685.