**Effect of dapagliflozin on cardiovascular outcomes in patients with type 2 diabetes according to baseline kidney function and albuminuria status: A Prespecified Secondary Analysis of a Randomized Clinical Trial**

**Short title: Cardiovascular effects of dapagliflozin by baseline kidney function in people with diabetes**

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**Counts:**

Manuscript: 3065 words (excl. References, <3200)

 32 References

1 Table, 3 Figures

Appendix: 2 Tables, 4 Figures

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# Key Points

**Question:**

What is the relative cardiovascular (CV) efficacy and safety of dapagliflozin according to baseline estimated glomerular filtration rate (eGFR) and urinary albumin to creatinine ratio (UACR) in patients with type 2 diabetes?

**Findings:**

In this secondary analysis from the DECLARE-TIMI 58 trial, the effect of dapagliflozin (versus placebo) on the relative risk of the two primary endpoints CV death and hospitalization for heart failure (HHF) and major adverse cardiovascular events was similar (p-interaction >0.24). However, the absolute risk reduction of CV death and HHF was significantly larger in dapagliflozin-treated patients who had more markers of chronic kidney disease (i.e., -0.5%, -1.0%, and -8.3% in patients who had both eGFR >60 ml/min/1.73m2 and UACR <30 mg/g, who had either ≤60 ml/min/1.73m2 or UACR ≥30 mg/g, and those who had both ≤60 ml/min/1.73m2 and UACR ≥30 mg/g, respectively; p-interaction 0.023).

**Meaning:**

The effect ofdapagliflozin on the relative risk for CV events was consistent across kidney function and albuminuria status, with the greatest absolute benefit for CV death/HHF observed in patients with both reduced eGFR and increased albuminuria.

# Abstract

**Importance:**

Sodium-glucose co-transporter 2 inhibitors (SGLT2i), which promote renal glucose excretion, reduce cardiovascular (CV) death and hospitalizations for heart failure (HHF) in patients with type 2 diabetes mellitus (T2DM).

**Objective:**

Therelative CV efficacy and safety of dapagliflozin according to baseline kidney function and albuminuria status is not known.

**Design, Setting, and Participants:**

DECLARE-TIMI 58 compared dapagliflozin vs. placebo in 17,160 patients with T2DM and a baseline creatinine clearance >60 ml/min. Patients were categorized according to baseline eGFR [<60 vs. ≥60 ml/min/1.73m2] and urinary albumin:creatinine ratio (UACR) [<30 vs. ≥30 mg/g] and categorically ranked by the number of markers (0, 1, or 2).

**Main Outcome(s) and Measure(s):**

The dual primary endpoints were CV death/HHF and MACE (MI, stroke, CV death).

**Results:**

At baseline, 1,265 (7.4%) patients had an eGFR <60 ml/min/1.73m2 and 5,198 (30.3%) had albuminuria (UACR 30-300: n=4,029; UACR>300: n=1,169). Accordingly, among patients with both readings 10,958 (65.1%) patients had an eGFR >60 ml/min/1.73m2 and UACR <30 mg/g, 5,336 (31.7%) had either an eGFR <60 ml/min/1.73m2 or albuminuria, and 548 (3.3%) patients had both. In the placebo arm, patients with more abnormal markers had higher event rates for CV death/HHF (KM event rates at 4 years: 3.9%, 8.3%, 17.4%) and MACE (7.5%, 11.6%, and 18.9%) for 0, 1, or 2 markers of CKD, respectively. The estimates for relative risk reductions for CV death/HHF and MACE were generally consistent across the subgroups (both P-interaction >0.24), though greater absolute risk reductions with more markers of CKD. The absolute risk difference for CV death/HHF was greater in patients with more markers of CKD (-0.5%, -1.0%, and -8.3%, respectively; p-interaction 0.023). The number of amputations, diabetic ketoacidosis, fractures, and major hypoglycemic events were balanced or numerically even lower with dapagliflozin as compared with placebo in patients with eGFR <60 and UACR ≥30 mg/g.

**Conclusions:**

The effect ofdapagliflozin on relative risk for CV events was consistent across eGFR/UACR groups, with the greatest absolute benefit for CVD/HHF observed in patients with both reduced eGFR and albuminuria.

**Word Count: 319 words**

# Background

Kidney dysfunction, including both reduced glomerular filtration rate (GFR) and albuminuria, is associated with increased risk for cardiovascular outcomes.1, 2 Patients with type 2 diabetes mellitus (T2DM) and kidney dysfunction, a frequent comorbidity in these patients, therefore represent a particularly vulnerable patient population.

Sodium glucose co-transporter 2 inhibitors (SGLT2i), which promote urinary glucose excretion, reduce the risk for cardiovascular death and hospitalizations for heart failure (HHF) in patients with T2DM.3 The extent of increased glucosuria and therefore the glucose-lowering efficacy of SGLT2i is attenuated in patients with worse kidney function as reflected by declining estimated GFR (eGFR).4 However, a meta-analysis of 3 SGLT2i cardiovascular outcomes trials published to date indicates that the benefit on HHF is greatest in patients with lower baseline kidney function.3 These observations support the hypothesis that glucose control per se is not the driving factor in preventing cardiovascular events with SGLT2i and underpin the paradigm shift from a glucocentric focus to broader cardiovascular risk mitigation considerations in the management of patients with T2DM. Although the exact mechanisms of CV benefits are incompletely understood, SGLT2i exert multiple favorable cardio-renal and metabolic effects including weight loss, improvement in ventricular loading by reducing pre- and afterload, reduction in inflammation and oxidative stress, increased oxygen supply by expansion of red cell mass, and lowering of intraglomerular pressure.5-9 In light of the well-known relationship between chronic kidney disease (CKD) and the risks of volume overload, mineral and bone disorders, and peripheral artery disease among others,10, 11 the safety profile of dapagliflozin is not known in this particularly susceptible and thus challenging patient cohort. The present study is a prespecified analysis from the Dapagliflozin Effect on Cardiovascular Events (DECLARE) – Thrombolysis in Myocardial Infarction (TIMI) 58 trial to examine the cardiovascular efficacy and safety of dapagliflozin according to baseline kidney function and albuminuria status.12-14 The dual primary endpoints of DECLARE-TIMI 58 were the composite of cardiovascular death and hospitalization for heart failure (HHF) and major adverse cardiovascular events (MACE), the composite of myocardial infarction, ischemic stroke, and cardiovascular death. Dapagliflozin significantly reduced the risk of cardiovascular death and HHF, driven by a reduction in HHF, and was non-inferior with respect to MACE.14

# Materials and Methods

## Study population

The design and the primary results of the DECLARE-TIMI 58 trial (NCT01730534) have been previously published.12-14 In brief, the DECLARE-TIMI 58 trial randomized 17,160 patients with T2DM and multiple risk factors (MRF) for or established atherosclerotic cardiovascular disease (ASCVD) after a 4 week run-in phase to either dapagliflozin or placebo on top of standard-of-care medical therapy. Eligible patients with established ASCVD had to be ≥40 years old and have either a history of ischemic heart disease, cerebrovascular disease, or peripheral arterial disease. Patients with MRF were men ≥55 years old and women ≥60 years old who had at least one of the following cardiovascular risk factors: dyslipidemia, hypertension or current tobacco use. Patients with a creatinine clearance below 60 ml/min at screening before entering the run-in period were excluded from the trial. The trial was approved by institutional review boards, and written consent was obtained from all participating patients.

## Outcomes of interest

The goal of the present analyses was to examine the efficacy and safety of dapagliflozin according to baseline eGFR and albuminuria status. The composites of CV death/HHF and MACE were used as the primary efficacy outcomes of interest. Additional outcomes were the individual components of the composite outcomes as well as all-cause death. Safety outcomes of interest included major hypoglycemia, amputations, diabetic ketoacidosis, and fractures.

Patients were categorized according to their baseline eGFR (<60 vs. ≥60 ml/min/1.73m2 using the CKD‑EPI formula) and baseline urinary albumin-to-creatinine ratio (UACR: <30 versus ≥30 mg/g) and categorically ranked by the number of markers (i.e., 0, 1, or 2 markers). These strata were selected based on diabetes guidelines including the recommended initiation of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients with T2DM and either eGFR <60 ml/min/1.73m2 and/or UACR >30 mg/g.15 Patients with eGFR ≥60 ml/min/1.73m2 and UACR <30 mg/g were therefore considered to have zero markers of CKD. A sensitivity analysis was done using the eGFR and albuminuria risk categories of progression of CKD from the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline (Supplemental Table 1).16 Further analyses were performed using strata of eGFR (<60, 60-<90, ≥90 ml/min/1.73 m2) and UACR (<30, 30-300, >300 mg/g).

## Statistical analysis

The baseline characteristics stratified by markers of kidney dysfunction are reported as means and standard deviations or medians and IQR for continuous variables and counts and proportions for categorical variables. To assess the trend across the levels of kidney dysfunction, the Jonckheere-Terpstra trend test was used for continuous and the Cochran–Armitage trend test for categorical variables.

To assess the risk of patients with CKD compared with those without within the placebo arm, Cox regression models were adjusted for age (≥ versus <65 years), sex, race (white vs non-white), median weight (≥ versus <89 kg), history of heart failure, dyslipidemia, hypertension, ischemic stroke, peripheral artery disease, duration of diabetes (≤ versus >10 years), insulin use at baseline, and smoking status. The average change in eGFR, blood pressure, and HbA1c over time and the differences between dapagliflozin and placebo during the trial were assessed using least square means and tested for interaction between subgroups at 6 months. Cox regression models with interaction testing were used to test heterogeneity of the relative treatment effect across the subgroups. All Cox models testing the treatment effect of dapagliflozin versus placebo were stratified according to presence or absence of known ASCVD and hematuria at baseline and analyzed using an intention-to-treat approach. The proportional hazards assumption was confirmed using statistical tests.17 P-values for heterogeneity are reported for the difference in magnitude of the absolute risk difference across subgroups.18

Statistical significance was assessed at a nominal alpha level of 0.05. All reported p values are two-sided with no adjustments for multiple testing. Statistical analyses were carried out using R (version 3.6.0) and SAS software, Version 9.4.

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. However, we encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions.

# Results

## Study population

The number of participants randomized and constituting follow-up have been published previously14 and are shown in Supplemental Figure 1. The mean eGFR was 85 (±17) ml/min/1.73m2 and the median UACR was 15 mg/g (interquartile range 6 - 55) g/mg in the overall population. Overall, 1,265 (7.4%) patients had an eGFR <60 ml/min/1.73m2 and 5,198 (30.3%) had albuminuria (UACR 30-300: n=4,029; UACR>300: n=1,169). Among patients who had both eGFR and UACR readings, 1,234 (7.3%) had an eGFR <60 ml/min/1.73m2 and 5,199 (31.9%) patients had albuminuria (UACR 30-300: n=4030; UACR >300: n=1169) atrandomization. Accordingly, 10,958 (65.1%) patients had no markers of >stage 2 CKD, while 5,336 (31.7%) had 1 marker of CKD (either an eGFR <60 ml/min/1.73m2 [n=686] or albuminuria ≥30 mg/g [n=4,650]), and 548 (3.3%) patients had both (Table 1). These categories are similar to the KDIGO low, mild, and moderate or high risk of CKD progression categories (Supplemental Tables 1 and 2).Patients with more markers of CKD were more likely to be older, male and have ASCVD and HF, and were well-treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (87.6%) and statins (81.4%) (Table 1).

## Cardiovascular outcomes by markers of chronic kidney disease in the placebo arm

Within the placebo arm, patients with more markers of kidney disease had higher risk for CV death/HHF (KM event incidence at 4 years: 3.9%, 8.3%, 17.4% for 0, 1, or 2 markers of CKD, respectively) and MACE (KM event incidence at 4 years: 7.5%, 11.6%, and 18.9% for 0, 1, or 2 markers of CKD, respectively; Figure 1, Panel A). Patients with only 1 marker of CKD had comparably increased event rates irrespective whether it was eGFR <60 ml/min/1.73 m2 (4-year KM incidence: 7.2% for CV Death/HHF and 12.1% for MACE) or UACR ≥30 mg/g (4-year KM incidence: 8.5% for CV Death/HHF and 11.6% for MACE).

This gradient, with a stepwise increase of risk for patients with more markers of CKD, remained apparent after multivariable adjustment for both CV death/HHF (Adjusted (Adj.) hazard ratio (HR) with no markers of CKD as reference: Adj. HR 1.84, 95% CI 1.52 to 2.97 for 1 marker; Adj. HR 2.97, 95% CI 2.17 to 4.07 for 2 markers of CKD; both P <0.001) as well as MACE (Adj. HR 1.38, 95% CI 1.19 to 1.61 for 1 marker of CKD; Adj. HR 2.00, 95% CI 1.51 to 2.65 for 2 markers of CKD; both P <0.001).

## Effects of dapagliflozin on cardiovascular risk factors according to baseline kidney function

At 6 months, the extent of HbA1c reduction with dapagliflozin was significantly smaller in patients with lower baseline eGFR as compared with those with more preserved kidney function (least-squares mean absolute difference at 6 months: -0.39 [95% CI -0.52 to -0.27], -0.47 [95% CI -0.51to -0. 42], and -0.70 [95% CI -0.75 to -0.65] for eGFR <60, 60-90, and ≥90 ml/min/1.73 m2, respectively; p for interaction <0.001; Supplemental Figure 2). Conversely, the magnitude of effect of dapagliflozin compared with placebo (average least-squares mean absolute difference at 6 months) across baseline kidney function (eGFR ≥90, 60-90, and <60 ml/min/1.73 m2) was similar for systolic blood pressure (-3.0, -3.2, and -3.6 mmHg, respectively; p for interaction 0.25), diastolic blood pressure (-1.2, -1.1, and -1.6 mmHg, respectively; p for interaction 0.50), and body mass index (-0.6, -0.6, and -0.5 kg/m2, respectively; p for interaction 0.063) (Supplemental Figure 1).

## Clinical efficacy and safety of dapagliflozin versus placebo according to baseline kidney function

The relative risk reduction for CV death/HHF for dapagliflozin versus placebo was consistent across the kidney function subgroups (P-interaction 0.24), though numerically greatest (42%) in patients with both reduced eGFR and albuminuria (No CKD: HR 0.87, 95% CI 0.72 to 1.06; 1 marker of CKD: HR 0.87, 95% CI 0.72 to 1.05; 2 markers of CKD: HR 0.58, 95% CI 0.36 to 0.94; Figure 2). Moreover, no effect modification for the magnitude of the relative risk reduction was observed when eGFR (p-interaction 0.54) and UACR (p-interaction 0.24) were fitted as continuous log-transformed variables using natural splines with 4 knots. However, given their higher baseline risk, the magnitude of the absolute risk difference was significantly larger in patients with more markers of CKD (-0.5%, -1.0%, and -8.3% for 0, 1, or 2 markers of CKD, respectively; p-interaction for absolute risk difference 0.023). These findings suggest that 13 patients with both eGFR <60 ml/min/1.73m2 and UACR ≥30mg/g need to be treated over a duration of 4 years to prevent 1 event of CV death/HHF. An analogous pattern was seen for MACE, with similar relative risk reductions across the subgroups (p-interaction 0.65), but with the absolute risk difference being numerically greatest in patients with more markers of CKD (-0.3%, -0.3%, -5.3% for 0, 1, or 2 markers of CKD, respectively; p-interaction for absolute risk difference 0.31). In patients with 1 marker of CKD, the results were consistent and qualitatively similar irrespective whether eGFR was below 60 ml/min or UACR ≥30 mg/g (Supplemental Figure 2).

Examining the individual components of CVD/HHF, eGFR appeared to have a greater association with the magnitude of risk reduction with dapagliflozin on HHF whereas UACR appeared to have a greater association with the magnitude of risk reduction for CV death (Supplemental Figure 3A and Supplemental Figure 3B, respectively). Moreover, an interaction (p-interaction 0.036) was observed for effects of dapagliflozin versus placebo on all-cause mortality indicating a relative greater treatment benefit in patients with more markers of CKD (1 marker of CKD: HR 0.82, 95% CI 0.68 to 0.98; 2 marker: HR 0.75, 95% CI 0.47to 1.18), while no effect was seen for patients with 0 markers (HR 1.11, 95% CI 0.93 to 1.32). This effect modification appeared to be driven by UACR (p-interaction 0.007) and not by eGFR (p-interaction 0.61). In particular, patients with greater UACR tended to derive a greater reduction in all-cause mortality (UACR <30 mg/g HR 1.11, 95% CI 0.94 to 1.30; UACR 30-300 mg/g HR 0.77, 95% CI 0.62 to 0.95; UACR ≥300 mg/g HR 0.73, 95% 0.53 to 1.01; p-interaction 0.007).

Similar results were found when examining patients categorized according to the KDIGO risk grouping (Supplemental Figure 5). Moreover, applying the inclusion criteria of the CREDENCE trial4 (i.e., eGFR between ≥30 to <90 ml/min/1.73 m2 and UACR >300 mg/g; 718 subjects) identified a subgroup that demonstrated a 32% relative risk reduction (HR 0.68, 95% CI 0.46 to 1.00) for CV death/HHF and a 17% relative risk reduction (HR 0.83, 95% CI 0.58 to 1.18) for MACE. The observed point estimates were thus similar to those observed in the CREDENCE trial (CV death/HHF HR 0.69, 95% CI 0.57 to 0.83, MACE HR 0.80, 95% CI 0.67 to 0.95).4

The safety profile of dapagliflozin was similar across all tested subgroups (Figure 3). Most notably, the number of amputations, diabetic ketoacidosis, fractures, and major hypoglycemic events were balanced or numerically even lower with dapagliflozin as compared with placebo in patients with eGFR <60 and UACR ≥30 mg/g.

# Discussion

The results from the present analyses of the DECLARE-TIMI 58 trial showed largely consistent relative risk reductions with dapagliflozin in cardiovascular events irrespective of baseline eGFR and albuminuria status in a broad population of patients with T2DM who had or were at risk for ASCVD. However, patients with more markers of CKD derived significantly greater absolute risk reduction for the composite of CV death and HHF reflecting a consistent effect in the context of their higher baseline risk, and with a clear disconnect between CV efficacy and measures of glucose control. Consistent with the results in the overall patient population, these favorable effects were not counterbalanced by adverse events as there was no difference in major hypoglycemic events, amputations, or fractures by treatment group in patients with more markers of CKD. Baseline kidney function also did not modify the risk of diabetic ketoacidosis.

Initial concerns about the glucose-lowering efficacy of dapagliflozin in patients with lower eGFR, led to requested modifications of the DECLARE-TIMI 58 study protocol by the US Food and Drug Administration to exclude patients with a creatinine clearance below 60 ml/minat screening. The timing (enrollment before entering the run-in period versus randomization) as well as the use of the CKD-EPI equation that tends to yield eGFR values lower than corresponding CrCl estimates explains why a small proportion of patients with an estimated creatinine clearance >60 ml/min at enrollment had eGFR levels below 60 ml/min/1.73 m2 at randomization. Treatment with dapagliflozin is not recommended by the US Food and Drug Administration for glycemic control in patients with an eGFR <45 ml/min/1.73 m2,andiscontraindicated for glycemic control in patients with an eGFR <30 ml/min/1.73 m2 without established cardiovascular disease or cardiovascular risk factors. However, these regulations were established because of an attenuated urinary glucosuria and thus lower efficacy in HbA1c reductions in these patients and not because of safety concerns. In DECLARE-TIMI 58, we observed lower, albeit still significant, reductions in HbA1c in patients with lower baseline eGFR as compared with patients who had more preserved baseline kidney function, whereas the magnitude in blood pressure and body mass index reductions were consistent irrespective of baseline kidney function, suggesting that these effects are mediated through non-diuretic mechanisms.

While no difference was appreciated in secondary analyses of the individual trials by baseline kidney function,19, 20 meta-analyses of the three completed SGLT2i cardiovascular outcomes trials indicated even greater protection from HHF in patients with worse baseline kidney function.3 In addition to the favorable cardiovascular outcomes across the different stages of chronic kidney disease, SGLT2i preserved the effect on risk reduction of renal events in patients with worse baseline kidney function. The prognostic importance of the cardiorenal interaction and its bidirectional nature has been well established.1, 21, 22 Both acute and chronic disorders of the heart and kidneys can cause acute or chronic disorders in the other.1, 21 SGLT2i have multiple favorable effects that may interrupt this vicious circle by reducing the risk of hospitalization for heart failure, prevention of deterioration of kidney function and reduction in progression of albuminuria.23-27 The exact mechanisms of action remain incompletely understood and are subject to current research are believed to include lowering of blood pressure, reduction in volume overload, changes in myocardial energetics, reducing the intraglomerular pressure, inflammation, and oxidant stress.5, 9, 28

The first dedicated SGLT2i kidney outcomes trial, the *Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation* (CREDENCE) trial lends further support for the use of SGLT2i in patients with kidney dysfunction. The CREDENCE trial, which included 4401 patients with diabetes and an eGFR between 30 and 90 ml/min/1.73 m2 and concomitant macroalbuminuria (UACR >300 mg/g to ≤5000 mg/g) was terminated early for overwhelming efficacy.4 As compared with placebo, canagliflozin reduced the risk of the primary endpoint, a composite of end-stage kidney disease, doubling of serum creatinine, or renal or cardiovascular death by 30%. In addition, significant reductions for cardiovascular outcomes including the composite of hospitalization for heart failure and cardiovascular death (31%) and the composite of myocardial infarction, stroke, or cardiovascular death (20%) were observed.4, 29 As compared with CREDENCE4 (and the 2 other SGLT2i cardiovascular outcomes trials30, 31), patients in DECLARE-TIMI 58 had more preserved baseline kidney function. Even though only a small proportion of the DECLARE-TIMI 58 patient population would have met the inclusion criteria of CREDENCE (and thus the confidence intervals are wide), it is noteworthy that the point estimates of cardiovascular efficacy from analyses of this small subset in the DECLARE-TIMI 58 trial yielded nearly identical relative risk reductions as observed in CREDENCE for CV death/HHF (32% vs 31%) and MACE (17% vs. 20%).

Kidney outcomes in the DECLARE‑TIMI 58 trial according to baseline kidney function have been recently reported showing a consistent favorable effect supporting the use of SGLT2i in patients with CKD.32 Dedicated kidney outcome trials studying the role of SGLT2i in in patients with and without T2DM are currently ongoing. Recently, a press release has been issued stating that the *Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease* (DAPA-CKD) trial, a kidney outcomes trial comparing dapagliflozin with placebo in 4,245 patients with chronic kidney irrespective of the presence of diabetes has been stopped early for overwhelming efficacy.

These data with their favorable safety profile across the different subgroups of CKD support the use of dapagliflozin in this patient population and further investigation of patients with more severe stages of CKD despite its lower glucose lowering effectiveness in this condition.

**Limitations**

These analyses are subject to the known limitations of subgroup analyses including their exploratory nature and limited statistical power. Also, no adjustment for multiple testing was done. Furthermore, as aforementioned, owing to the inclusion criteria of the DECLARE-TIMI 58 trial, the majority of the patients had an eGFR ≥60ml/min/1.73 m2 constraining the generalizability to patients with lower eGFR.

# Conclusions

Patients with more markers of kidney dysfunction had higher rates of adverse CV outcomes.Dapagliflozin had generally consistent relative risk reductions but greater absolute risk reductions of CVD/HHF in patients with more severe kidney disease (evidenced by both reduced eGFR and albuminuria), reflecting their increased baseline risk.

# Funding

The DECLARE TIMI-58 trial was funded by a grant from Astra Zeneca to Brigham and Women’s Hospital. TAZ was supported by the German Science Foundation (ZE 1109/1-1 to TAZ) and the Austrian Science Funds (KLI 876-B).

# Role of the Funder:

The trial was designed as a collaboration among the TIMI Study Group, the Hadassah Medical Center, the executive and steering committees, and AstraZeneca. The TIMI Study Group, Hadassah Medical Center, and AstraZeneca were responsible for the design and conduct of the trial; and collection and management of the data. The TIMI Study Group is responsible for the current analysis, interpretation of the data; preparation, review, and approval of the manuscript; and decision to submit the manuscript for publication.

# Access to Data and Data Analysis:

Dr. Wiviott had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

# Author Contributions:

*Study concept and design:* Zelniker, Raz, Mosenzon, Dwyer, Heerspink, Cahn, Bhatt, Leiter, McGuire, Wilding, Gause-Nilsson, Langkilde, Sabatine, Wiviott

*Acquisition, analysis, or interpretation of data:*

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*Drafting of the manuscript:*

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*Study supervision:*

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# Conflicts of interest

**TAZ** reports a research grant from Deutsche Forschungsgemeinschaft (ZE 1109/1-1) and lecture fees from AstraZeneca. **IR** reports reports personal fees from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Concenter BioPharma and Silkim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Orgenesis, Pfizer, Sanofi, SmartZyme Innovation, Panaxia, FuturRx, Insuline Medical, Medial EarlySign, CameraEyes, Exscopia, Dermal Biomics, Johnson & Johnson, Novartis, Teva, GlucoMe, and DarioHealth. **OM** reports grants and personal fees from AstraZeneca, Bristol-Myers Squibb, and Novo Nordisk and personal fees from Eli Lilly, Sanofi, Merck Sharp & Dohme, Boehringer Ingelheim, Johnson & Johnson, and Novartis. **EG** and **KI**  are members of the TIMI Study Group, which has received institutional research grant support through Brigham and Women’s Hospital from: Abbott, Amgen, Aralez, AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., BRAHMS, Daiichi-Sankyo, Eisai, GlaxoSmithKline, Intarcia, Janssen, MedImmune, Merck, Novartis, Pfizer, Poxel, Quark Pharmaceuticals, Roche, Takeda, The Medicines Company, Zora Biosciences. **DLB** discloses the following relationships - Advisory Board: Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Level Ex, Medscape Cardiology, PhaseBio, PLx Pharma, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today’s Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald’s Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, Takeda. **DKG** has provided clinical trial leadership for AstraZeneca, Sanofi Aventis, Janssen, Boehringer Ingelheim, Merck & Co, Pfizer, Lilly US, Novo Nordisk, Lexicon, Eisai, GlaxoSmithKline, and Esperion, and consultancy for AstraZeneca, Sanofi Aventis, Lilly US, Boehringer Ingelheim, Merck & Co, Novo Nordisk, Applied Therapeutics, Afimmune, Metavant and Merck Sharp & Dohme. **JPHW** reports grants, consultancy fees (paid to his institution), and personal fees for lectures and trial steering committee participation from AstraZeneca; grants, consultancy fees (paid to his institution), and personal fees for lectures from Novo Nordisk; consultancy fees (paid to his institution) and personal fees for lectures from Boehringer Ingelheim, Janssen, Napp, Mundipharma, Lilly, Takeda, and Sanofi; and consultancy fees (paid to his institution) from Wilmington Healthcare. **IGN** and **AML** are employees of AstraZeneca. **MSS** reports reports grants from AstraZeneca during the conduct of the study; grants and personal fees from Amgen, personal fees from Anthos Therapeutics, grants and personal fees from AstraZeneca, grants from Bayer, personal fees from Bristol-Myers Squibb, personal fees from CVS Caremark, grants from Daiichi-Sankyo, personal fees from DalCor, personal fees from Dyrnamix, grants from Eisai, personal fees from Esperion, grants from GlaxoSmithKline, personal fees from IFM Therapeutics, grants and personal fees from Intarcia, personal fees from Ionis, grants and personal fees from Janssen Research and Development, grants and personal fees from Medicines Company, grants and personal fees from MedImmune, grants and personal fees from Merck, grants and personal fees from Novartis, grants from Pfizer, grants from Poxel, grants from Quark Pharmaceuticals, grants from Takeda, outside the submitted work; and is a member of the TIMI Study Group, which has also received institutional research grant support through Brigham and Women’s Hospital from: Abbott, Aralez, Roche, and Zora Biosciences. **SDW** reports Dr. Wiviott reports grants from Amgen, Arena, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Eisai, Eli Lilly, Janssen, Merck and Sanofi-Aventis, consulting fees from ARENA, AstraZeneca, Aegerion, Allergan, Angelmed, Boehringer-Ingelheim, Boston Clinical Research Institute, Bristol Myers Squibb, Daiichi Sankyo, Eisai, Eli Lilly, Icon Clinical, Janssen, Lexicon, Merck, Servier, St Jude Medical, Xoma; his spouse, Dr. Caroline Fox is an employee of Merck; and is a member of the TIMI Study Group, which has received institutional research grant support through Brigham and Women’s Hospital from: Abbott, Amgen, Aralez, AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., BRAHMS, Daiichi-Sankyo, Eisai, GlaxoSmithKline, Intarcia, Janssen, MedImmune, Merck, Novartis, Pfizer, Poxel, Quark Pharmaceuticals, Roche, Takeda, The Medicines Company, Zora Biosciences.

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## Table 1: Baseline characteristics according to baseline kidney function and urinary albumin status

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Characteristics: | **No markers of CKD**eGFR >60 ml/min/1.73 m2 and UACR <30 mg/g**(N = 10958)** | **1 marker of CKD**eGFR <60 ml/min/1.73 m2 or UACR ≥30 mg/g**(N = 5336)** | **2 markers of CKD**eGFR <60 ml/min/1.73 m2 and UACR ≥30 mg/g**(N = 548)** | **P-trend** |
| Age, Mean (SD) | 63.7 (6.7) | 64.1 (7.1) | 66.8 (6.9) | <0.001 |
| Female Sex, N (%) | 4392 (40.1) | 1738 (32.6) | 167 (30.5) | <0.001 |
| Race (Black/African-American), N (%) | 371 (3.4) | 189 (3.5) | 28 (5.1) | 0.12 |
| BMI (kg/m2), Mean (SD) | 31.8 (5.9) | 32.3 (6.1) | 34.8 (6.1) | <0.001 |
| HbA1c (%), Mean (SD) | 8.2 (1.2) | 8.5 (1.3) | 8.4 (1.2) | <0.001 |
| LDL-C (mg/dL), Mean (SD) | 87.8 (34.7) | 87.3 (36.8) | 84.3 (36.7) | 0.007 |
| Diabetes duration, Median (IQR) | 10.0 (6.0, 15.0) | 12.0 (7.0, 18.0) | 15.0 (10.0, 20.0) | <0.001 |
| ASCVD, N (%) | 4123 (37.6) | 2396 (44.9) | 297 (54.2) | <0.001 |
| Ischemic Heart Disease, N (%) | 3367 (30.7) | 1921 (36.0) | 252 (46.0) | <0.001 |
| Prior Ischemic Stroke, N (%) | 611 (5.6) | 399 (7.5) | 63 (11.5) | <0.001 |
| PAD, N (%) | 508 (4.6) | 423 (7.9) | 62 (11.3) | <0.001 |
| Prior HF, N (%) | 970 (8.9) | 615 (11.5) | 106 (19.3) | <0.001 |
| Prior amputation, N (%) | 30 (0.3) | 62 (1.2) | 11 (2.0) | <0.001 |
| Smoker, N (%) | 1548 (14.1) | 833 (15.6) | 54 (9.9) | 0.66 |
| Insulin, N (%) | 3972 (36.2) | 2559 (48.0) | 343 (62.6) | <0.001 |
| Metformin, N (%) | 9121 (83.2) | 4359 (81.7) | 347 (63.3) | <0.001 |
| Sulfonylurea, N (%) | 4782 (43.6) | 2236 (41.9) | 183 (33.4) | <0.001 |
| ACE-I/ARB, N (%) | 8782 (80.1) | 4425 (82.9) | 480 (87.6) | <0.001 |
| Any diuretic, N (%) | 4204 (38.4) | 2291 (42.9) | 342 (62.4) | <0.001 |
| Antiplatelet Therapy, N (%) | 6526 (59.6) | 3370 (63.2) | 389 (71.0) | <0.001 |
| Statin, N (%) | 8090 (73.8) | 3988 (74.7) | 446 (81.4) | 0.0018 |
| eGFR (ml/min/1.73 m2 CKD-EPI), Mean (SD) | 88.1 (12.7) | 83.0 (17.7) | 50.7 (7.2) | n/a |
| UACR (mg/g), Median (IQR) | 7.9 (4.7, 13.8) | 73.6 (38.7, 205.8) | 118.9 (58.5, 422.3) | m/a |
| UACR <30 mg/g, N (%) | 10958 (100.0) | 686 (12.9) | 0 (0.0) | n/a |
| UACR 30-300 mg/g, N (%) | 0 (0.0) | 3648 (68.4) | 381 (69.5) | n/a |
| UACR ≥300 mg/g, N (%) | 0 (0.0) | 1002 (18.8) | 167 (30.5) | n/a |

Legend: ACE-I = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, ASCVD = atherosclerotic cardiovascular disease, BMI = body mass index, eGFR = estimated glomerular filtration rate, HbA1c = glycated hemoglobin A1c, HF = heart failure, LDL-C = low-density lipoprotein cholesterol, n/a = not applicable, PAD = peripheral artery disease, UACR = urinary albumin to creatinine ratio

# Figures:

Figure 1:

Panel A: Kaplan Meier curves for the composite of CV death and hospitalization for heart failure (HHF) stratified by treatment and the number of markers of chronic kidney disease .

Panel B: Kaplan Meier curves the composite of CV death and hospitalization for heart failure (HHF) [top panel] and for major adverse cardiovascular events (MACE), the composite of myocardial infarction, ischemic stroke, and cardiovascular (CV) death [bottom panel] according to the number of markers of chronic kidney disease within the *dapagliflozin* arm.

Panel B: Kaplan Meier curves for major adverse cardiovascular events (MACE), the composite of myocardial infarction, ischemic stroke, and cardiovascular death stratified by treatment and the number of markers of chronic kidney disease . The solid and dashed lines indicate treatment with placebo and dapagliflozin, respectively.

Figure 2: Relative effect and absolute risk difference of dapagliflozin versus placebo on cardiovascular events by number of markers of chronic kidney disease.

Legend: ACM = all-cause mortality, Adj. = adjusted, CI = confidence interval, CKD = chronic kidney disease, CV = cardiovascular, eGFR = estimated glomerular filtration rate, HHF = hospitalization for heart failure, HR = hazard ratio, MACE = major adverse cardiovascular events, MI = myocardial infarction, UACR = urinary albumin to creatinine ratio

## Figure 3: Safety outcomes of dapagliflozin versus placebo by number of markers of chronic kidney disease.

## Figure 1, Panel A: CV death/HHF



## Figure 1, Panel B: MACE



## Figure 2



## Figure 3

