Dapagliflozin and Prevention of Kidney Disease Among Patients With Type 2 Diabetes: Post Hoc Analyses From the DECLARE-TIMI 58 Trial

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OBJECTIVE
In patients with moderate to severe albuminuric kidney disease, sodium–glucose cotransporter 2 inhibitors reduce the risk of kidney disease progression. These post hoc analyses assess the effects of dapagliflozin on kidney function decline in patients with type 2 diabetes (T2D), focusing on populations with low kidney risk.

RESEARCH DESIGN AND METHODS
In the Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial, patients with T2D at high cardiovascular risk were randomly assigned to dapagliflozin versus placebo. Outcomes were analyzed by treatment arms, overall, and by Kidney Disease: Improving Global Outcomes (KDIGO) risk categories. The prespecified kidney-specific composite outcome was a sustained decline ≥40% in the estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73 m², end-stage kidney disease, and kidney-related death. Other outcomes included incidence of categorical eGFR decline of different thresholds and chronic (6 month to 4 year) or total (baseline to 4 year) eGFR slopes.

RESULTS
Most participants were in the low-moderate KDIGO risk categories (n = 15,201 [90.3%]). The hazard for the kidney-specific composite outcome was lower with dapagliflozin across all KDIGO risk categories (P-interaction = 0.97), including those at low risk (hazard ratio [HR] 0.54, 95% CI 0.38–0.77). Risks for categorical eGFR reductions [≥57% (in those with baseline eGFR ≥60 mL/min/1.73 m²), ≥50%, ≥40%, and ≥30%] were lower with dapagliflozin (HRs 0.52, 0.57, 0.55, and 0.70, respectively; P < 0.05). Slopes of eGFR decline favored dapagliflozin across KDIGO risk categories, including the low KDIGO risk (between-arm differences of 0.87 [chronic] and 0.55 [total] mL/min/1.73 m²/year; P < 0.0001).

CONCLUSIONS
Dapagliflozin mitigated kidney function decline in patients with T2D at high cardiovascular risk, including those with low KDIGO risk, suggesting a role of dapagliflozin in the early prevention of diabetic kidney disease.

Chronic kidney disease (CKD)—commonly characterized by the presence of a urine albumin-to-creatinine ratio (UACR) ≥30 mg/g and/or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m²—affects ~700 million people worldwide (1).
More than 40% of new cases of end-stage kidney disease (ESKD) are reported in patients with diabetes, making it the single leading driver of incident kidney failure in most parts of the world. The rise in prevalence of type 2 diabetes (T2D) is expected to drive an increase in the global ESKD burden in the coming decades (2,3). Thus, interventions that prevent or delay the onset and progression of CKD in patients with T2D are urgently needed (4).

Doubling serum creatinine or progression to ESKD are relatively rare, limiting their utility as a primary outcome in evaluating early intervention strategies, especially in lower-risk populations. The scientific community, in collaboration with regulatory agencies, has systematically evaluated the validity of candidate surrogate outcomes for the prevention of early-stage CKD incidence and progression (5). These efforts have led to the agreement that early changes in eGFR decline, including eGFR slope, fulfill criteria for surrogacy for kidney benefit (5).

In patients with T2D, the protective effects of sodium–glucose cotransporter 2 inhibitors (SGLT2i) on kidney function have been demonstrated either as the primary outcome (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation [CREDENCE] trial) in patients with albuminuric diabetic kidney disease or as a secondary or exploratory analysis of cardiovascular (CV) outcome trials (CVOTs; Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose [EMPA-REG OUTCOME], Canagliflozin Cardiovascular Assessment Study [CANVAS] program, Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58 [DECLARE-TIMI 58], Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes [VERTIS-CV], and Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk [SCORED]) (6–12). SGLT2i kidney protection was further proven in patients with albuminuric CKD with or without T2D (Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease [DAPA-CKD]) (13). Compared with these other randomized controlled trials, the DECLARE-TIMI 58 trial included the largest population of patients with T2D and the longest follow-up period. This trial specifically enrolled patients with creatinine clearance (CrCl) ≥60 mL/min, most of them (69.1%) within the normoalbuminuric range (14). Here, using data from DECLARE-TIMI 58, we analyzed the rate of kidney function loss and eGFR slopes for participants randomized to dapagliflozin versus placebo, focusing on subpopulations with low baseline kidney risk.

**RESEARCH DESIGN AND METHODS**

The DECLARE-TIMI 58 Trial

The DECLARE-TIMI 58 trial enrolled 17,160 patients with T2D and either established atherosclerotic CV disease (ASCVD; age ≥40 years and ischemic heart disease, cerebrovascular disease, or peripheral arterial disease; 40.6%), or patients with multiple risk factors for ASCVD (≥60 years for women or ≥55 years for men plus one or more of the following: dyslipidemia, hypertension, or current tobacco use; 59.4%) (15). At screening, eligible patients had HbA1c 6.5–12% and CrCl (estimated by the Cockcroft-Gault equation) (16) ≥60 mL/min. Patients were randomly assigned in a double-blinded fashion to receive dapagliflozin 10 mg/day or matching placebo (1:1), on top of standard-of-care therapy for other comorbidities. Patients were followed for a median of 4.2 years (interquartile range 3.9–4.4). The trial’s prespecified dual primary outcomes were major adverse CV event (MACE) (the composite of CV death, myocardial infarction, or ischemic stroke) demonstrating noninferiority for dapagliflozin versus placebo, and the composite of CV death or hospitalization for heart failure, which achieved superiority of dapagliflozin over placebo. The prespecified primary composite kidney outcome, a cardio renal outcome, was defined as time to first event of a sustained confirmed (two tests at a central laboratory at least 4 weeks apart) decrease by at least 40% of eGFR (calculated by Chronic Kidney Disease Epidemiology Collaboration equation [CKD-EPI] (17)) to eGFR <60 mL/min/1.73 m², ESKD (defined as dialysis for ≥90 days, kidney transplantation, or sustained eGFR of <15 mL/min/1.73 m²), and/or CV or kidney-related death. The primary kidney outcome demonstrated superiority of dapagliflozin versus placebo (hazard ratio [HR] 0.76 [95% CI 0.67–0.87]). The secondary composite kidney outcome, a kidney-specific outcome, was the same as the primary composite kidney outcome, but without CV death, and also achieved superiority of dapagliflozin versus placebo (HR 0.53 [95% CI 0.43–0.66]). Dapagliflozin also reduced the risk for acute kidney injury (HR 0.69 [95% CI 0.55–0.87]) (15). However, since the trial met only one of its dual primary outcomes for superiority, all analyses of additional outcomes should be considered hypothesis-generating.

At each participating site, the trial’s protocol was approved by the Institutional Review Board and all participants provided written informed consent. The trial was registered at clinicaltrials.gov NCT01730534.

**Kidney Data Collection and Calculation**

Serum creatinine values were collected and analyzed in the central laboratory (Covance Central Laboratories Services) at screening, baseline, 6 and 12 months, once a year thereafter, and at the end-of-treatment visit. Unscheduled creatinine tests were done in the following scenarios: doubling from baseline of serum creatinine, a serum creatinine >6.0 mg/dL (530 µmol/L), or a decrease in eGFR of ≥30% from baseline to eGFR <60 mL/min/1.73 m² or an eGFR value of <15 mL/min/1.73 m². If at any time the patient’s eGFR fell <30 mL/min/1.73 m² and was confirmed at a repeated central laboratory measurement, the patient was discontinued from the study drug. Baseline values of each laboratory test were the last assessment before the randomization date, inclusive. Time to onset of a composite kidney outcome was calculated according to the first of the two subsequent laboratory assessments needed according to the outcome definition.

eGFR slope was calculated based on creatinine measurement using CKD-EPI formulation (17). Three different time periods were defined: acute slope (baseline to 6 months), chronic slope (6 months to 4 years), and total slope (baseline to 4 years). Chronic and total slopes are presented annually, while the acute slope is presented per 6 months.

Fast or severe eGFR declines were defined post hoc as a eGFR decline of ≥3 or ≥5 mL/min/1.73 m²/year, respectively, using previously published thresholds (18–20). These definitions were used either from baseline to 4 years or from 6 months to 4 years.
Predefined eGFR subgroups were ≥ 90 ml/min/1.73 m², 60 to < 90 ml/min/1.73 m², and < 60 ml/min/1.73 m². While CrCl ≥ 60 ml/min at the screening visit was an inclusion criterion, eGFR was assessed again at randomization visit; hence, some patients had eGFR < 60 ml/min/1.73 m² at baseline (8). The UACR subgroups were UACR = 15, > 15 to < 30, ≥ 30 to < 300, and > 300 mg/g. Kidney risk categories, which combine eGFR and UACR according to the Kidney Disease: Improving Global Outcomes in Chronic Kidney Disease (KDIGO CKD), were also used (21). Low KDIGO risk is defined as eGFR ≥ 60 ml/min/1.73 m² and UACR < 30 mg/g; moderate KDIGO risk is defined as eGFR 45 to < 60 ml/min/1.73 m² and UACR < 30 mg/g, or as eGFR ≥ 60 ml/min/1.73 m² and UACR 30–300 mg/g; high KDIGO risk is defined as eGFR 30 to < 45 ml/min/1.73 m² and UACR < 30 mg/g, or as eGFR 45 to < 60 ml/min/1.73 m² and UACR 30–300 mg/g, or as eGFR ≥ 60 ml/min/1.73 m² and UACR > 300 mg/g; very high KDIGO risk covers the rest of the eGFR and UACR categories (Supplementary Table 1A–C) (21). For the slope and proportion of fast decline analysis, the high and very high KDIGO risk categories were combined due to the small number of participants in these subgroups.

Statistical Analysis
Baseline characteristics are reported as absolute numbers and percentages for categorical variables and as mean and SD or median and interquartile range for continuous variables. KDIGO risk categories were compared using the χ² test for categorical variables and Kruskal-Wallis test for continuous variables. Analyses were performed according to the intention-to-treat principle. Event rates were reported as n/N and 4 year Kaplan-Meier estimates. Number of patients needed to treat (NNT) to prevent one event during the study follow up was calculated based on the absolute risk reduction observed in the Kaplan-Meier estimates. HRs and 95% CIs were calculated using the Cox proportional hazard model for the primary and secondary composite kidney outcomes and to a list of other dichotomous changes in eGFR outcomes. Mean eGFR slope was calculated for the entire population and by subgroups using a random-effects model analysis including the following covariates: baseline measurements and stratification factors of baseline ASCVD category (established ASCVD or multiple risk factors for ASCVD) and the presence or absence of hematuria at baseline (15), treatment arm, visit, and interaction terms of treatment and visit. eGFR slopes were calculated separately for each time-period definition (acute, chronic, and total, as above). The eGFR slopes are presented as least square mean estimators, SE, and 95% CI 0.38–0.77, P < 0.001 (Fig. 1). The calculated NNT to prevent one kidney-specific event during the study follow-up ranged from 177 to 13 in the low to very high KDIGO risk, respectively (Fig. 1). The lower risk for the kidney-specific outcome with dapagliflozin compared with placebo was 0.54 (95% CI 0.38–0.77, P < 0.001) (Fig. 1). The calculated NNT to prevent one kidney-specific event during the study follow-up ranged from 177 to 13 in the low to very high KDIGO risk, respectively (Fig. 1).

Kidney Outcomes by KDIGO and Other Kidney Risk Classification
The risk reduction with dapagliflozin compared with placebo for both the cardiorenal and kidney-specific outcomes was consistent across KDIGO risk categories (P-interaction = 0.151 and 0.968, respectively). Specifically, in the low KDIGO risk category, the HR of the kidney-specific outcome with dapagliflozin compared with placebo was 0.54 (95% CI 0.38–0.77, P < 0.001) (Fig. 1). The calculated NNT to prevent one kidney-specific event during the study follow-up ranged from 177 to 13 in the low to very high KDIGO risk, respectively (Fig. 1). The lower risk for the kidney-specific outcome with dapagliflozin compared with placebo was consistent in other commonly used subgroups of patients at high kidney risk (eGFR < 60 and/or UACR > 30, eGFR > 60 and UACR ≥ 30, and UACR > 30) (Supplementary Table 3). There was no observed heterogeneity in respect to dapagliflozin effects on the risk of acute kidney injury (P-interaction = 0.545) or CV death (P-interaction = 0.129) by baseline KDIGO subgroups (Supplementary Table 4).

Dapagliflozin reduced the risk for confirmed reduction in eGFR by ≥ 30%, ≥ 40%, or ≥ 50%, with and without reduction of eGFR to < 60 ml/min/1.73 m². In addition, in those with a baseline eGFR ≥ 60 ml/min/1.73 m², dapagliflozin mitigated the risk for reduction of ≥ 57% in eGFR (considered equivalent to doubling of serum creatinine) (Fig. 2). Likewise, in patients with baseline eGFR > 70 ml/min/1.73 m², dapagliflozin reduced the risk for confirmed eGFR reduction to
Data were consistent in terms of dapagliflozin tending to prevent declines to even lower eGFR thresholds of <45 and <30 mL/min/1.73 m² (Fig. 2). Analyzing the same outcomes, but without the requirement for a confirming value (i.e., at least one measurement), yielded similar results (Supplementary Fig. 1).

Acute, Chronic, and Total eGFR Slopes

The mean acute slope of eGFR was steeper in patients treated with dapagliflozin versus placebo (−2.99 vs. −1.15 mL/min/1.73 m²/6 months) (Fig. 3A and Supplementary Fig. 2). In contrast, the mean chronic slope (−1.54 vs. −2.55 mL/min/1.73 m²/year) and the mean total slope (−1.78 vs. −2.44 mL/min/1.73 m²/year) demonstrated a slower reduction in eGFR in patients treated with dapagliflozin versus placebo (all P < 0.0001) (Fig. 3B and A, respectively). The between-arms difference in eGFR slopes was 1.01 mL/min/1.73 m²/year (95% CI 0.90–1.12) for the chronic slope and 0.66 mL/min/1.73 m²/year (95% CI 0.59–0.73) for the total slope in favor of dapagliflozin.

Figure 2—Confirmed categorical eGFR declines with dapagliflozin compared with placebo. HRs and 95% CIs were calculated using Cox proportional hazard regression models. eGFR was calculated by the CKD-EPI equation. All eGFR values are presented in mL/min/1.73 m². KM, Kaplan-Meier.
Similarly, participants in the dapagliflozin arm, compared with placebo, had steeper acute slopes and improved chronic totals slope across tested subgroups, including demographic variables and medical background (Supplementary Fig. 3A and B). These differences in favor of dapagliflozin were also observed in all low kidney risk subgroups (low KDIGO risk, eGFR >90 mL/min/1.73 m² or UACR ≤15 mg/g). In a subgroup of patients with very low kidney risk (those having both eGFR >90 mL/min/1.73 m² and UACR ≤15 mg/g), significant between-group differences were observed for the total and the chronic slopes in favor of dapagliflozin (0.39 mL/min/1.73 m²/year [95% CI 0.29–0.50] and 0.62 mL/min/1.73 m²/year [95% CI 0.44–0.81], respectively). However, the differences were most pronounced in the subgroups with UACR >300 mg/g or high to very high KDIGO risk (Fig. 3A and B, respectively).

The Proportions of Patients With Fast eGFR Decline by Treatment Arm
Of patients with calculated change in eGFR value (n = 16,108), 5,685 (35.3%) had fast eGFR decline, and 2,974 (18.5%) had severe decline (i.e., mean eGFR decline ≥3 and ≥5 mL/min/1.73 m²/year, respectively) from baseline to 4 years. The dapagliflozin arm had lower proportion of patients with fast decline (33.7 vs. 37.0%; P < 0.0001) and severe decline (16.8% vs. 20.2%; P < 0.0001) compared with the placebo arm (Table 1 and Supplementary Fig. 2). These findings were more pronounced in the 6-month to 4-year period (26.8% vs. 37.1% in the dapagliflozin and placebo arm, respectively; P < 0.0001) (Table 1).
in the dapagliflozin compared with placebo arms across all tested baseline categories in the 6-month to 4-year period and in most categories for the baseline to 4-year period (Table 1). This finding was observed also in the low kidney risk categories: low KDIGO risk category, baseline eGFR $90 \text{ mL/min/1.73 m}^2$, a
dd UACR $< 15 \text{ mg/g}$.

Finally, we present the total eGFR slopes and proportion of patients with fast and severe eGFR decline (baseline to 4 years) per treatment arm, overall and by baseline kidney markers (Supplementary Fig. 2). Higher baseline UACR was associated with a higher rate of eGFR loss, even when comparing those with baseline UACR 15 to $< 30 \text{ mg/g}$ versus UACR $< 15 \text{ mg/g}$ ($P < 0.001$). A gap between dapagliflozin and placebo was observed across all of the tested baseline kidney subgroups and was most pronounced in the UACR $> 300 \text{ mg/g}$ category (Supplementary Fig. 2).

CONCLUSIONS

The DECLARE-TIMI 58 trial included patients with T2D and mostly low-moderate KDIGO kidney risk at baseline ($n = 15,201 \text{ [90.3%]}$). In this post hoc analysis, the reduction in the kidney-specific outcome was significant and consistent across all KDIGO risk categories, including a 46% (95% CI 23–62) risk reduction in those with low baseline KDIGO risk. A significant improvement with dapagliflozin compared with placebo was observed in eGFR categorical outcomes ($\geq 30\%$, $\geq 40\%$, $\geq 50\%$, or $\geq 57\%$ reductions), also in those with eGFR $> 60$ or 70 mL/min/1.73 m$^2$ at baseline. Chronic and total eGFR slopes were mitigated with dapagliflozin in the overall population and across all tested subgroups, including patients with low baseline kidney risk. The
proportion of patients experiencing fast or severe eGFR decline (≥3 or ≥5 mL/min/1.73 m² annual eGFR loss, respectively) was lower with dapagliflozin.

The results of the analyses presented here add to the accumulated data demonstrating that clinically meaningful kidney outcomes in patients with T2D can be favorably affected with SGLT2i, extending those observations to patients with low baseline kidney risk. These observations add to data from other CVOTs demonstrating that clinically meaningful kidney outcomes in patients with T2D can be favorably affected with SGLT2i, extending those observations to patients with low baseline kidney risk, all consistent with results of the present analyses, along with findings from other SGLT2i CVOTs, consolidating the role of SGLT2i as a class of medications that prevents and slows

**Table 1—Proportions of patients with fast eGFR decline (mean annual decrease of eGFR ≥3 mL/min/1.73 m²/year), by treatment arm**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Baseline to 4 years</th>
<th>6 months to 4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dapagliflozin</td>
<td>Placebo</td>
</tr>
<tr>
<td>Overall</td>
<td>2,724/8,096 (33.7)</td>
<td>2,961/8,012 (37.0)</td>
</tr>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, &lt;65 years</td>
<td>1,436/4,380 (32.8)</td>
<td>1,560/4,355 (35.8)</td>
</tr>
<tr>
<td>Age, ≥65 years</td>
<td>1,288/3,716 (34.7)</td>
<td>1,401/3,657 (38.3)</td>
</tr>
<tr>
<td>Medical History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>1,298/4,030 (32.2)</td>
<td>1,441/4,053 (35.6)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>1,426/4,066 (35.0)</td>
<td>1,520/3,958 (38.4)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2,509/7,327 (34.2)</td>
<td>2,693/7,150 (37.7)</td>
</tr>
<tr>
<td>No</td>
<td>215/769 (28.0)</td>
<td>268/862 (31.1)</td>
</tr>
<tr>
<td>Laboratory and clinical measurements</td>
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<tr>
<td>Baseline HbA1c</td>
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<tr>
<td>&lt;9%/75 mmol/mol</td>
<td>1,877/5,940 (31.6)</td>
<td>2,128/5,994 (35.5)</td>
</tr>
<tr>
<td>≥9%/75 mmol/mol</td>
<td>847/2,154 (39.3)</td>
<td>833/2,014 (41.4)</td>
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<tr>
<td>Baseline eGFR (mL/min/1.73m²)</td>
<td></td>
<td></td>
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<tr>
<td>&lt;60</td>
<td>144/555 (26.0)</td>
<td>162/592 (27.4)</td>
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<tr>
<td>60 to &lt;90</td>
<td>1,345/3,614 (37.2)</td>
<td>1,472/3,636 (40.5)</td>
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<tr>
<td>≥90</td>
<td>1,235/3,927 (31.5)</td>
<td>1,327/3,784 (35.0)</td>
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<tr>
<td>Baseline UACR (mg/g)</td>
<td></td>
<td></td>
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<tr>
<td>Below detectable to &lt;15</td>
<td>1,207/4,298 (28.1)</td>
<td>1,316/4,261 (30.9)</td>
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<tr>
<td>15 to &lt;30</td>
<td>416/1,212 (34.3)</td>
<td>446/1,209 (36.9)</td>
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<td>≥30 to ≤300</td>
<td>757/1,898 (39.9)</td>
<td>800/1,864 (42.9)</td>
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<td>&gt;300</td>
<td>294/548 (53.7)</td>
<td>345/528 (65.2)</td>
</tr>
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<td>KDIGO risk categories</td>
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<tr>
<td>Low risk</td>
<td>1,562/5,204 (30.0)</td>
<td>1,703/5,150 (33.1)</td>
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<tr>
<td>Moderate risk</td>
<td>769/2,001 (38.4)</td>
<td>803/1,965 (40.9)</td>
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<tr>
<td>High/very high risk</td>
<td>343/751 (45.7)</td>
<td>401/747 (85.7)</td>
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<tr>
<td>Cardiovascular drugs—ACEi/ARB</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2,244/6,579 (34.1)</td>
<td>2,475/6,529 (37.9)</td>
</tr>
<tr>
<td>No</td>
<td>480/1,517 (31.6)</td>
<td>486/1,483 (32.8)</td>
</tr>
</tbody>
</table>

endorsed reliance on surrogate markers to prove kidney disease prevention in specific populations (5). A meta-analysis including >1.4 million participants has demonstrated that even a 30% eGFR decline over 2 years is associated with a higher risk of ESKD and mortality (30). Results from the present analyses showed lower risks for ≥30%, ≥40%, ≥50%, or ≥57% reductions in eGFR with dapagliflozin, when analyzed as a single measurement or as repeated consecutive measurements. A recent meta-analysis of four CVOTs with SGLT2i demonstrated a large, significant, and highly consistent reduction in the composite kidney outcome: ≥40% reduction in eGFR and ESKD or kidney-related death (31). Thus, results of the present analyses, along with findings from other SGLT2i CVOTs, consolidate the role of SGLT2i as a class of medications that prevents and slows
diabetic kidney disease progression in patients with T2D.

Results from previous modeling analysis inferred that affecting a eGFR slope reduction by 0.5 to 1.0 mL/min/1.73 m²/year has a >98% predictive value for benefit on clinical kidney outcomes of doubling of serum creatinine or ESKD (32). In the DECLARE-TIMI 58 trial, the between-arms difference in eGFR slopes favored dapagliflozin by 1.01 (0.9–1.12) mL/min/1.73 m²/year for the chronic slope and by 0.66 (0.59–0.73) for the total slope (P < 0.0001 for both). Thus, dapagliflozin meets slope criteria for the prediction of clinical kidney benefits.

Slope analyses of eGFR have been reported from other CVOTs of SGLT2i in patients with T2D (EMPA-REG OUTCOME [33], CANVAS program [7], and VERTIS-CV [9,34]). Results from the present analyses both strengthen and add to these previous observations. The improvements in eGFR slopes are demonstrated in a larger and more diverse population of patients, including patients with lower CV and kidney risk and with longer follow-up. The comprehensive analysis of all slope components, including acute, chronic, and total slopes, is reassuring for health care providers that may be concerned about the clinical significance of the initial drop in eGFR. The present results demonstrate a slower loss of kidney function with dapagliflozin compared with placebo even in patients with low KDIGO risk without established CV disease or those with very low kidney risk (UACR ≥15 mg/g and eGFR ≥90 mL/min/1.73 m²; P < 0.0001). These findings highlight the role of SGLT2i for primary CKD prevention, even in patients with normal kidney markers without evidence of CV disease, and are clinically relevant to a large portion of the T2D population worldwide.

On the other side of the scale, patients with macroalbuminuria at baseline (UACR >300 mg/g) had the largest numerical eGFR slope reduction with dapagliflozin compared with placebo. This might reflect both the higher risk for kidney function deterioration in patients with macroalbuminuria as well as the known benefits of dapagliflozin and other SGLT2i on albuminuria risk and progression (8). These results are in line with findings from the DAPA-CKD trial (13,35) that dapagliflozin’s improvement of eGFR slope is more pronounced in patients with a higher baseline UACR (36).

A rapid decline in eGFR is often defined as a mean sustained yearly reduction in eGFR of >3 mL/min/1.73 m² or >5 mL/min/1.73 m² (18–20,37). Fast eGFR decline was found associated with both worse kidney (30,37–40) and CV outcomes, including CV-related and all-cause mortality (30,41–43). In our current analysis, dapagliflozin reduced the proportion of patients with fast eGFR decline. The results were apparent in various definitions of fast decline (≥3, ≥5 mL/min/1.73 m²/year) and for different period definitions (baseline/6 months to 4 years). A recent study reported a slow and consistent >0.7% annual eGFR loss over 13 years of follow-up in most patients with T2D, and only ~10% of patients had progressive or accelerated eGFR decline (7.2% or 14.3% median annual eGFR loss, respectively) (44). Slope analyses assume linear eGFR loss and do not consider these variations between patients. In addition, while a slower eGFR slope of 0.5–1.0 mL/min/1.73 m²/year meets surrogacy criteria, as above, some might argue that these are clinically small effects. Thus, the lower risk for fast and severe eGFR decline associated with dapagliflozin use, across baseline subgroups, completes the overall view obtained in this slope analysis, highlighting the potential clinical significance of the findings.

The present analyses have notable limitations. First, these are post hoc analyses from a randomized controlled trial, and therefore, their results can only be viewed as hypothesis-generating. Moreover, the DECLARE-TIMI 58 trial was a CV outcome trial and not a kidney outcome trial (like the CREDENCE and the DAPA-CKD trials [12,13]). Therefore, creatinine and UACR were only collected at randomization, 6 months, 12 months, and yearly thereafter. These infrequent measurements made both the analysis of the acute phase and any acute changes during the entire trial more difficult to detect, especially as sustained changes in eGFR are key outcomes and were sometimes achieved only a year later. No adjustment was done for multiple comparisons. Unlike in some other trials with SGLT2i, no repeated measurements of kidney markers were collected after the end of study drug use, limiting the ability to analyze the full effect of dapagliflozin.

Conclusion

In patients with T2D at high CV risk, dapagliflozin improved kidney outcomes, including categorical changes in eGFR, eGFR slopes, and rate of fast eGFR decline, highlighting its kidney protective role. This analysis of DECLARE-TIMI 58 trial, relying on its large number of participants with low kidney risk and long follow-up, suggests that dapagliflozin meets accepted outcomes to demonstrate primary CKD prevention in patients with T2D at high CV risk and low kidney risk.

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