The Effect of Dapagliflozin on Albuminuria in DECLARE-TIMI 58

Diabetes Care 2021;44:1805–1815 | https://doi.org/10.2337/dc21-0076

Ofri Mosenzon,[1,2] Stephen D. Wiviott,[3] Hiddo J.L. Heerspink,[4] Jamie P. Dwyer,[5] Avivit Cahn,[1,2] Erica L. Goodrich,[3] Aliza Rozenberg,[1,2] Meir Schechter,[1,2] Ilan Yanuv,[1,2] Sabina A. Murphy,[3] Thomas A. Zelniker,[3,6] Ingrid A.M. Gause-Nilsson,[7] Anna Maria Langkilde,[7] Martin Fredriksson,[7] Peter A. Johansson,[7] Deepak L. Bhatt,[3] Lawrence A. Leiter,[8] Darren K. McGuire,[9,10] John P.H. Wilding,[11] Marc S. Sabatine,[3] and Itamar Raz[1,2]

OBJECTIVE

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) improve albuminuria in patients with high cardiorenal risk. We report albuminuria change in the Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58) cardiovascular outcome trial, which included populations with lower cardiorenal risk.

RESEARCH DESIGN AND METHODS

DECLARE-TIMI 58 randomized 17,160 patients with type 2 diabetes, creatinine clearance >60 mL/min, and either atherosclerotic cardiovascular disease (CVD; 40.6%) or risk-factors for CVD (59.4%) to dapagliflozin or placebo. Urinary albumin-to-creatinine ratio (UACR) was tested at baseline, 6 months, 12 months, and yearly thereafter. The change in UACR over time was measured as a continuous and categorical variable (≤15, >15 to <30, ≥30 to ≤300, and >300 mg/g) by treatment arm. The composite cardiorenal outcome was a ≥40% sustained decline in the estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73 m^2, end-stage kidney disease, and cardiovascular or renal death; specific renal outcome included all except cardiovascular death.

RESULTS

Baseline UACR was available for 16,843 (98.15%) participants: 9,067 (53.83%) with ≤15 mg/g, 2,577 (15.30%) with >15 to <30 mg/g, 4,030 (23.93%) with 30–300 mg/g, and 1,169 (6.94%) with >300 mg/g. Measured as a continuous variable, UACR improved from baseline to 4.0 years with dapagliflozin, compared with placebo, across all UACR and eGFR categories (all $P < 0.0001$). Sustained confirmed ≥1 category improvement in UACR was more common in dapagliflozin versus placebo (hazard ratio 1.45 [95% CI 1.35–1.56], $P < 0.0001$). Cardiorenal outcome was reduced with dapagliflozin for subgroups of UACR ≥30 mg/g ($P < 0.0125$, $P_{interaction} = 0.033$), and the renal-specific outcome was reduced for all UACR subgroups ($P < 0.05$, $P_{interaction} = 0.480$).

CONCLUSIONS

In DECLARE-TIMI 58, dapagliflozin demonstrated a favorable effect on UACR and renal-specific outcome across baseline UACR categories, including patients with normal albumin excretion. The results suggest a role for SGLT2i also in the primary prevention of diabetic kidney disease.

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) reduce the risk for adverse renal outcomes in people with type 2 diabetes, including a reduction in deterioration of the

[1]Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Jerusalem, Israel
[2]Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel
[3]TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital and Harvard Medical School, Boston, MA
[4]University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[5]Vanderbilt University Medical Center, Nashville, TN
[6]Division of Cardiology, Medical University of Vienna, Vienna, Austria
[7]BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden
[8]Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada
[9]Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, TX
[10]Parkland Health and Hospital System, Dallas, TX
[11]Department of Cardiovascular and Metabolic Medicine, University of Liverpool, Liverpool, U.K.

Corresponding author: Ofri Mosenzon, ofrim@hadassah.org.il

Received 12 January 2021 and accepted 14 May 2021

Clinical trial reg. no. NCT01730534, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.14597772.

estimated glomerular filtration rate (eGFR) and progression to end-stage kidney disease (ESKD) (1–7). This has been demonstrated as secondary/exploratory outcomes in cardiovascular (CV) outcomes trials (CVOTs) (1–4,7) and confirmed as a primary outcome in patients with proteinuric chronic kidney disease (CKD), with or without type 2 diabetes (5,6).

Albuminuria is frequently a component of diabetic kidney disease (8,9). The presence of albuminuria in patients with or without diabetes has been associated with an increased risk for adverse renal and CV outcomes (10,11), while a reduction in albuminuria has been associated with lower rates of adverse renal and CV outcomes, both in observational studies (12) and clinical trials (13,14). The American Diabetes Association *Standards of Medical Care in Diabetes* recommends testing urinary albumin excretion annually (15) as part of the laboratory screening in patients with type 2 diabetes.

The Dapagliflozin Effect on Cardiovascular Events trial (DECLARE-TIMI 58) was a CVOT with dapagliflozin in 17,160 patients with type 2 diabetes and either multiple risk factors (MRFs) for atherosclerotic CV disease (ASCVD) (59.4%) or established ASCVD (eASCVD) (40.6%) that demonstrated a significant 17% reduction in one of its two dual primary efficacy outcomes of CV death and hospitalization for heart failure (3). The main secondary prespecified renal outcome in DECLARE-TIMI 58 was the composite cardiorenal outcome, defined as a sustained decline of at least 40% in eGFR to <60 mL/min/1.73 m^2, ESKD, or death from renal or CV causes (3). A renal-specific composite outcome was similarly predefined but excluded death from CV causes. We previously published significant reductions in both the cardiorenal and renal-specific composite outcomes (3).

In this secondary exploratory analysis, we present the effect of dapagliflozin on urinary albumin-to-creatinine ratio (UACR), both in the entire trial population and according to baseline UACR and eGFR categories. We also present the effect of dapagliflozin on the cardiorenal and renal-specific composite outcomes according to baseline UACR.

RESEARCH DESIGN AND METHODS

The DECLARE-TIMI 58 design, participants' baseline characteristics, main outcomes, and main renal results have been previously reported (3,4,16,17). Briefly, we recruited patients with type 2 diabetes and either MRFs for ASCVD (age $\geq$55 years for men or $\geq$60 years for women plus one or more of the following: dyslipidemia, hypertension, or current tobacco use), or eASCVD (age $\geq$40 years and ischemic heart disease, cerebrovascular disease, or peripheral arterial disease). Other inclusion criteria were HbA_{1c} between 6.5 and 12.0% (47.5–113.1 mmol/mol) and creatinine clearance of $\geq$60 mL/min as estimated by the Cockcroft-Gault equation (18). The institutional review board at each participating site approved the trial protocol, and all participants provided written informed consent.

Participants were randomly assigned in a double-blinded manner to once-daily dapagliflozin 10 mg or matching placebo (1:1). The primary end points of the trial, major adverse cardiovascular events (MACE), a composite of CV death, myocardial infarction, or ischemic stroke, achieved noninferiority, and a composite of CV death or hospital admission for heart failure achieved superiority (3). Since the trial met only one of its dual primary outcomes for superiority, all other analyses of additional outcomes should only be considered as hypothesis generating. The cardiorenal outcome was defined as time to first event of a composite of sustained confirmed decrease in eGFR by at least 40% (as confirmed by two tests at the central laboratory at least 4 weeks apart) to <60 mL/min/1.73 m^2, ESKD (defined as dialysis for $\geq$90 days, kidney transplantation, or sustained [i.e., two measurements at the central laboratory at least 4 weeks apart] eGFR of <15 mL/min/1.73 m^2), or CV or renal death. The renal-specific outcome included all the components of the cardiorenal outcome except CV death (3).

The serum creatinine and spot urine albumin and creatinine were measured at the central laboratories (LabCorp Clinical Trials [Covance], Singapore, Geneva, and New York) at screening, baseline, 6 months, 12 months, yearly thereafter, and at the end of the trial. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (18). Baseline values and categorization of these values were defined according to the laboratory test on the date of randomization. The change from baseline was calculated for these parameters, and time to onset of renal outcomes was calculated according to the first of the two subsequent laboratory assessments.

Participants were divided into prespecified subgroups according to their baseline eGFR (eGFR $\geq$90, $<$90 to $\geq$60, and $<$60 mL/min/1.73 m^2) and according to their baseline UACR (UACR $\leq$15, $>$15 to $<$30, $\geq$30 to $\leq$300, and $>$300 mg/g) (19). Patients with baseline urinary albumin below the laboratory's lowest detectable level were recognized as a distinct UACR category and grouped together with patients with UACR $\leq$15 mg/g. Due to a change in the assay used in the central laboratory to measure urinary albumin, the lowest detectable level of albumin was modified during the trial from urine albumin $<$3.0 mg/L since the initiation of the trial on 25 April 2013 until 30 April 2017, and then $<$7.0 mg/L until the end of the trial on 18 September 2018. For calculation of the continuous change in UACR over time and avoid bias due to the date of enrollment, all measured values of urine albumin $<$7.0 mg/L were recognized as below the detectable level and assigned a value of 7 mg/g UACR for continuous analysis. A sensitivity analysis was performed assigning below detectable measures of urinary albumin to UACR = 3.5 mg/g (the midpoint of the range). Confirmed sustained change in the categorical UACR was defined as a change in the UACR categories in two consecutive tests done according to the schedule for UACR testing at the central laboratory, as mentioned above.

Statistical Analysis

Baseline characteristics of the four predefined subgroups of baseline UACR are reported as absolute numbers and percentages for categorical variables and as mean and SD or median and interquartile range (IQR), as appropriate, for continuous variables. We used the χ^2 test to compare categorical variables and the Kruskal-Wallis test to compare continuous variables between UACR subgroups. Analyses were performed

according to the intention-to-treat principle, using data from all randomly assigned participants.

Change in the geometric mean UACR over time were analyzed using mixed models for each baseline UACR and eGFR category separately, adjusting for treatment arm, baseline ACE inhibitors (ACEi)/angiotensin II receptor blockers (ARBs) treatment, use of diuretics, baseline HbA_{1c}, visit, the interaction between treatment arm and visit, stratification factors (hematuria and eASCVD/MRF status), and the baseline value of the UACR.

UACR data were log-transformed before analysis due to their nonnormal distribution as was previously done in similar analyses (20,21). Adjusted least-square means, 95% CIs, and differences between treatments were back-transformed to the original scale.

Cox proportional hazards models were used to compare the change in categorical UACR between treatment arms, both for confirmed sustained repeated change, done according to UACR test timelines, and for a single change in UACR category. The hazard ratio (HR) and 95% CI are reported. We used Kaplan-Meier curves to demonstrate the risk of deterioration in categorical albuminuria status over time and compared between treatment arms using a log-rank test. In addition, the percentage of participants distributed within the UACR categories at baseline and 6 months, among those with readings at both time points, are presented, and a comparison between treatment arms was performed using the χ^2 test.

Cox proportional hazards models were also used to compare treatment arms for risk of cardiorenal and renal-specific composite outcomes according to baseline UACR categories. All Cox models were stratified by baseline ASCVD (i.e., established disease vs. MRFs) and hematuria (i.e., present vs. absent) at baseline.

No adjustments for multiple comparisons were made. Analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC). DECLARE-TIMI 58 is registered with ClinicalTrials.gov, clinical trial reg. no. NCT01730534.

Data and Resource Availability

Individual participant data will not be made available. However, we encourage parties interested in collaboration to contact the corresponding author directly for further discussions.

RESULTS

Of the 17,160 participants of DECLARE-TIMI 58, 16,843 (98.15%) had baseline UACR data. There were 9,067 (53.83%) participants with baseline UACR ≤15 mg/g category, of which 551 (3.30%) had albumin below detectable levels; 2,577 (15.30%) with UACR of >15 to <30 mg/g; 4,030 (23.93%) with baseline UACR ≥30 to ≤300 mg/g; and 1,169 (6.94%) with baseline UACR >300 mg/g (Table 1).

Participants with lower baseline UACR categories were more likely to be female and White, had shorter diabetes duration, and were less likely to have a history of eASCVD, heart failure, or hypertension. Patients with a higher baseline UACR had higher mean HbA_{1c}, lower eGFR, and higher systolic blood pressure. ACEi/ARBs use was common across all baseline UACR categories (80.0–85.5%) but differed with statistical significance among UACR categories ($P < 0.0001$) (Table 1).

Change in the geometric mean in UACR over time by treatment arm is presented according to the four UACR baseline subgroups ≤15, >15 to <30, ≥30 to ≤300, and >300 mg/g (Fig. 1*A–D*). At 6 months, the dapagliflozin arm had a statistically significant lower mean UACR compared with placebo in all UACR baseline subgroups ($P = 0.0033$ for UACR ≤15 mg/g and $P < 0.0001$ for all other subgroups) (Fig. 1*A–D*). Between 6 months and 4 years, UACR in the subgroup of UACR >15 mg/g was lower in the dapagliflozin arm than in the placebo arm (Fig. 1*B–D*). A separation of the curves as a marker for effect in the lowest UACR category (≤15 mg/g) was seen after 36 months ($P = 0.0140$ at 36 months, $P < 0.0001$ at 48 months) (Fig. 1*A*). In the high-risk category of patients with baseline proteinuria (UACR >300 mg/g), after a large decrease in mean UACR during the first 6 months of treatment, the mean UACR remained stable to decreased during 48 months of treatment with dapagliflozin (Fig. 1*D*). Sensitivity analyses in which below detectable levels of albumin were imputed differently (UACR = 3.5 mg/g) did not materially change outcomes.

Change in the geometric mean in UACR over time by treatment arm is presented according to the three baseline eGFR subgroups eGFR ≥90, <90–≥60, and <60 mL/min/1.73 m^2 (Fig. 1*E–G*). In all three eGFR subgroups and at all time points after baseline, the dapagliflozin arm had a statistically significant lower mean UACR compared with placebo (at 4 years $P < 0.0001$ for all three eGFR subgroups).

Analysis of confirmed sustained change in the categorical UACR from baseline to end of trial (EOT) demonstrated an improvement in UACR categories for all UACR subgroups with dapagliflozin versus placebo (Fig. 2*A*). The improvement with dapagliflozin was statistically significant for each UACR category separately as well as for the sum of patients who improved by at least one UACR category (HR 1.45 [95% CI 1.35–1.56], $P < 0.0001$) and two UACR categories (HR 1.43 [1.23–1.65], $P < 0.0001$). A statistically significant reduction in the deterioration in UACR categories from baseline to EOT was also seen with dapagliflozin in most categories (the increase to UACR >15 mg/g in those with baseline UACR ≤15 mg/g was the only category that was numerically but not statistically reduced with dapagliflozin) (Fig. 2*B*). The overall one-category and two-category deteriorations in UACR were both reduced with dapagliflozin versus placebo (HR 0.82 [0.77–0.88], $P < 0.0001$; and HR 0.79 [0.69–0.91], $P = 0.0007$, respectively).

In addition, improvement in categorical UACR on one measure from baseline to EOT was increased with dapagliflozin compared with placebo (Supplementary Fig. 1*A*), while one-time worsening in categorical UACR was greatly reduced with dapagliflozin (Supplementary Fig. 1*B*).

Looking specifically at the change in the distribution of UACR categories from randomization to 6 months according to treatment arms, there were statistically significant differences between patients treated with dapagliflozin versus placebo. While at baseline the UACR categories distribution was equal between treatment arms ($P = 0.99$), at 6 months there was a higher percentage of patients treated with dapagliflozin than placebo in the UACR ≤15 mg/g category, at 56% vs. 52%. The opposite was true for the ≥30 to ≤300 mg/g category, at 23% vs. 25%, and for the >300 mg/g category, at 5% vs. 7%, in the dapagliflozin and

Table 1—Patients' baseline characteristics in DECLARE-TIMI 58 according to four baseline UACR categories: UACR ≤15, >15 to <30, ≥30 to ≤300, and >300 mg/g

	UACR ≤15 mg/g (*n* = 9,067)	UACR >15 to <30 mg/g (*n* = 2,577)	UACR ≥30 to ≤300 mg/g (*n* = 4,030)	UACR >300 mg/g (*n* = 1,169)	*P*
Demographic characteristics					
Female sex	3,583 (39.5)	1,083 (42.0)	1,292 (32.1)	339 (29.0)	<0.0001
Age, years, mean (SD)	63.8 (6.6)	64.4 (7.0)	64 (7.1)	63.5 (6.9)	0.0008
BMI, kg/m^2	31.2 (27.7–35.2)	31.2 (27.7–35.4)	31.5 (28.0–35.5)	32.0 (28.1–36.3)	0.0002
BMI, kg/m^2, mean (SD)	31.9 (5.9)	32.0 (6.1)	32.1 (6.0)	32.7 (6.2)	0.0002
Race					
White	7,441 (82.1)	2,000 (77.6)	3,079 (76.4)	860 (73.6)	
Asian	1,015 (11.2)	402 (15.6)	674 (16.7)	190 (16.3)	<0.0001
Black	319 (3.5)	81 (3.1)	139 (3.4)	49 (4.2)	
Other	292 (3.2)	94 (3.6)	138 (3.4)	70 (6.0)	
Medical history					
Diabetes duration					
≤5 years	2,303 (25.4)	555 (21.5)	750 (18.6)	145 (12.4)	<0.0001
>5 to ≤15 years	4,647 (51.3)	1,325 (51.4)	1,997 (49.6)	567 (48.5)	
>15 years	2,117 (23.3)	697 (27)	1,283 (31.8)	457 (39.1)	
eASCVD	3,415 (37.7)	1,037 (40.2)	1,786 (44.3)	578 (49.4)	<0.0001
History of congestive heart failure	811 (8.9)	274 (10.6)	437 (10.8)	169 (14.5)	<0.0001
Hypertension	8,025 (88.5)	2,333 (90.5)	3,690 (91.6)	1,096 (93.8)	<0.0001
Hyperlipidemia	7,319 (80.7)	2,071 (80.4)	3,217 (79.8)	930 (79.6)	0.5815
CV and glucose-lowering drug used					
ACEi/ARB	7,257 (80.0)	2,115 (82.1)	3,316 (82.3)	1,000 (85.5)	<0.0001
MRAs	413 (4.6)	93 (3.6)	182 (4.5)	59 (5.0)	0.1355
Diuretic	3,561 (39.3)	1,051 (40.8)	1,708 (42.4)	517 (44.2)	0.0004
Metformin	7,482 (82.5)	2,119 (82.2)	3,308 (82.1)	919 (78.6)	0.013
Insulin	3,248 (35.8)	1,073 (41.6)	1,897 (47.1)	656 (56.1)	<0.0001
Sulfonylurea	3,896 (43.0)	1,137 (44.1)	1,680 (41.7)	489 (41.8)	0.2196
DPP-4 inhibitors	1,562 (17.2)	453 (17.6)	646 (16.0)	185 (15.8)	0.1975
GLP-1 receptor agonist	383 (4.2)	115 (4.5)	181 (4.5)	50 (4.3)	0.8928
Laboratory and clinical measurements					
HbA_{1c}, %	7.9 (7.3–8.8)	8.1 (7.5–9.1)	8.3 (7.5–9.3)	8.4 (7.6–9.6)	<0.0001
HbA_{1c}, %, mean (SD)	8.1 (1.1)	8.4 (1.2)	8.5 (1.3)	8.6 (1.3)	<0.0001
eGFR, mL/min/1.73 m^2, mean (SD)	85.9 (15.0)	86.2 (15.7)	84.6 (17.0)	80.7 (18.3)	<0.0001
eGFR (CKD-EPI) categories					
<60 mL/min/1.73 m^2	508 (5.6)	178 (6.9)	381 (9.5)	167 (14.3)	<0.0001
60 to <90 mL/min/1.73 m^2	4,156 (45.8)	1,111 (43.1)	1,761 (43.7)	554 (47.4)	
≥90 mL/min/1.73 m^2	4,403 (48.6)	1,288 (50.0)	1,887 (46.8)	448 (38.3)	
Blood pressure					
Systolic, mmHg	132.5 (122.5–142.5)	135 (125.0–145.0)	137.5 (127.0–147.5)	142 (132.0–154.0)	<0.0001
Systolic, mmHg, mean (SD)	132.9 (14.8)	135.4 (15.2)	137.3 (15.6)	142.7 (16.1)	<0.0001
Diastolic, mmHg	78 (71.0–83.5)	79 (71.5–84.5)	79 (71.5–85.0)	80 (74.0–86.5)	<0.0001
Diastolic, mmHg, mean (SD)	77.6 (9.0)	78.2 (9.1)	78.2 (9.2)	79.9 (9.3)	<0.0001
Total cholesterol, mg/dL	163 (138.0–194.0)	163 (138.0–195.0)	162 (137.0–193.0)	171 (142.0–206.0)	<0.0001
Total cholesterol, mg/dL, mean (SD)	168.7 (43.2)	168.6 (42.6)	168.7 (45.1)	178.2 (53.3)	<0.0001
Fasting triglycerides, mg/dL	141 (104.0–197.0)	149 (107.0–208.0)	155 (112.0–224.0)	160.5 (114.0–238.0)	<0.0001
Fasting triglycerides, mg/dL, mean (SD)	168.4 (120.9)	175.7 (112.9)	192.6 (153.2)	211.1 (191.3)	<0.0001

Categorical data are shown as *n* (%) and continuous data as median (IQR) or as indicated otherwise. The *P* value between UACR subgroups was calculated using the χ^2 test to compare categorical variables and the Kruskal-Wallis test to compare continuous variables. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; MRAs, mineralocorticoid receptor antagonists.

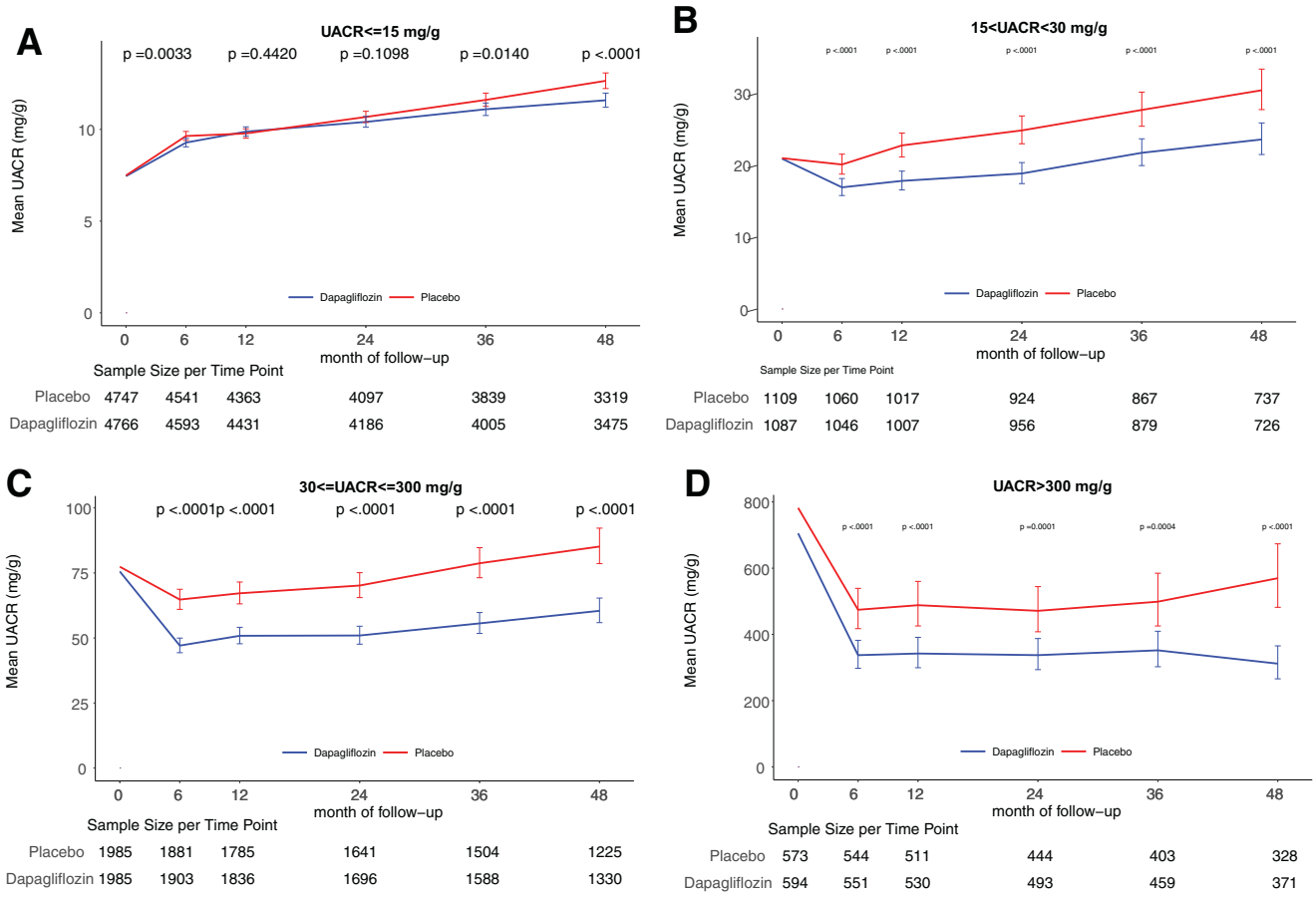

Figure 1—Change in UACR over time by treatment arm at baseline, 6 months, and 1, 2, 3, and 4 years in the group of patients with baseline UACR ≤15 mg/g (*A*), baseline UACR >15 to <30 mg/g (*B*), baseline UACR ≥30 to ≤300 mg/g (*C*) and baseline UACR >300 mg/g (*D*), and in the group of patients with baseline eGFR ≥90 mL/min/1.73 m^2 (*E*), baseline eGFR <90 to ≥60 mL/min/1.73 m^2 (*F*), and baseline eGFR <60 mL/min/1.73 m^2 (*G*). Shown are point estimates and 95% confidence intervals of geometric mean back-transformed to the original scale.

placebo arm, respectively ($P < 0.0001$) (Supplementary Table 1).

Kaplan-Meier curves for new onset of UACR >15 mg/g in patients with a baseline UACR ≤15 mg/g did not achieve statistical significance (log-rank $P = 0.0536$) (Supplementary Fig. 2*A*). Kaplan-Meier curves for new onset of UACR ≥30 mg/g in patients with a baseline UACR <30 mg/g (Supplementary Fig. 2*B*) and new onset of UACR ≥300 mg/g in patients with a baseline UACR <300 mg/g (Supplementary Fig. 2*C*) demonstrated an improvement with dapagliflozin compared with placebo (log-rank $P < 0.0001$ for both).

The cardiorenal event rates in the placebo arm in participants with UACR ≤15 mg/g versus those with UACR >15 to <30 mg/g were 3.1% and 4.9% ($P < 0.0001$), and the renal-specific event rates in the placebo arm were 1.3% and 2.4% ($P < 0.0001$) for the UACR ≤15 mg/g versus those with UACR >15 to <30 mg/g, respectively. Together these findings demonstrate an increased risk for both outcomes with higher baseline UACR categories, even in the normoalbuminuria range. The cardiorenal outcome was reduced with dapagliflozin for all UACR ≥30 mg/g subgroups ($P < 0.0125$, $P_{interaction} = 0.0327$) while the renal-specific outcome was reduced with dapagliflozin versus placebo for all UACR subgroups ($P < 0.05$, $P_{interaction} = 0.480$) (Fig. 3).

CONCLUSIONS

In this exploratory analysis of the results from DECLARE-TIMI 58, dapagliflozin reduced the deterioration of UACR, regardless of baseline eGFR and UACR, even in the category of UACR ≤15 mg/g. Dapagliflozin increased the likelihood of categorical improvement in UACR and decreased the risk for categorical UACR deterioration. This improvement was already demonstrated in the first postrandomization UACR test at 6 months. We also demonstrated a decreased risk for cardiorenal outcome with dapagliflozin for those with baseline UACR ≥30 mg/g. In addition, a decreased risk for renal-specific outcomes with dapagliflozin was demonstrated for all baseline UACR categories.

SGLT2i have been previously demonstrated to reduce albuminuria by 30–40% (22–24), and various mechanisms have been proposed to explain this effect. These include an increase in natriuresis, a contraction in plasma volume, and a reduction in single nephron hyperfiltration (25). Reduction in hyperfiltration has been suggested to result from sodium delivery to the macula densa, thereby restoring glomerular pressure to physiological levels (26,27). The decrease in nephron perfusion back to normal levels may cause reduced wall tension and shear stress (28), leading to the deactivation of proinflammatory cytokines and a possible reduction in renal fibrosis (29). Moreover, SGLT2i have been shown to decrease renal cortical hypoxia

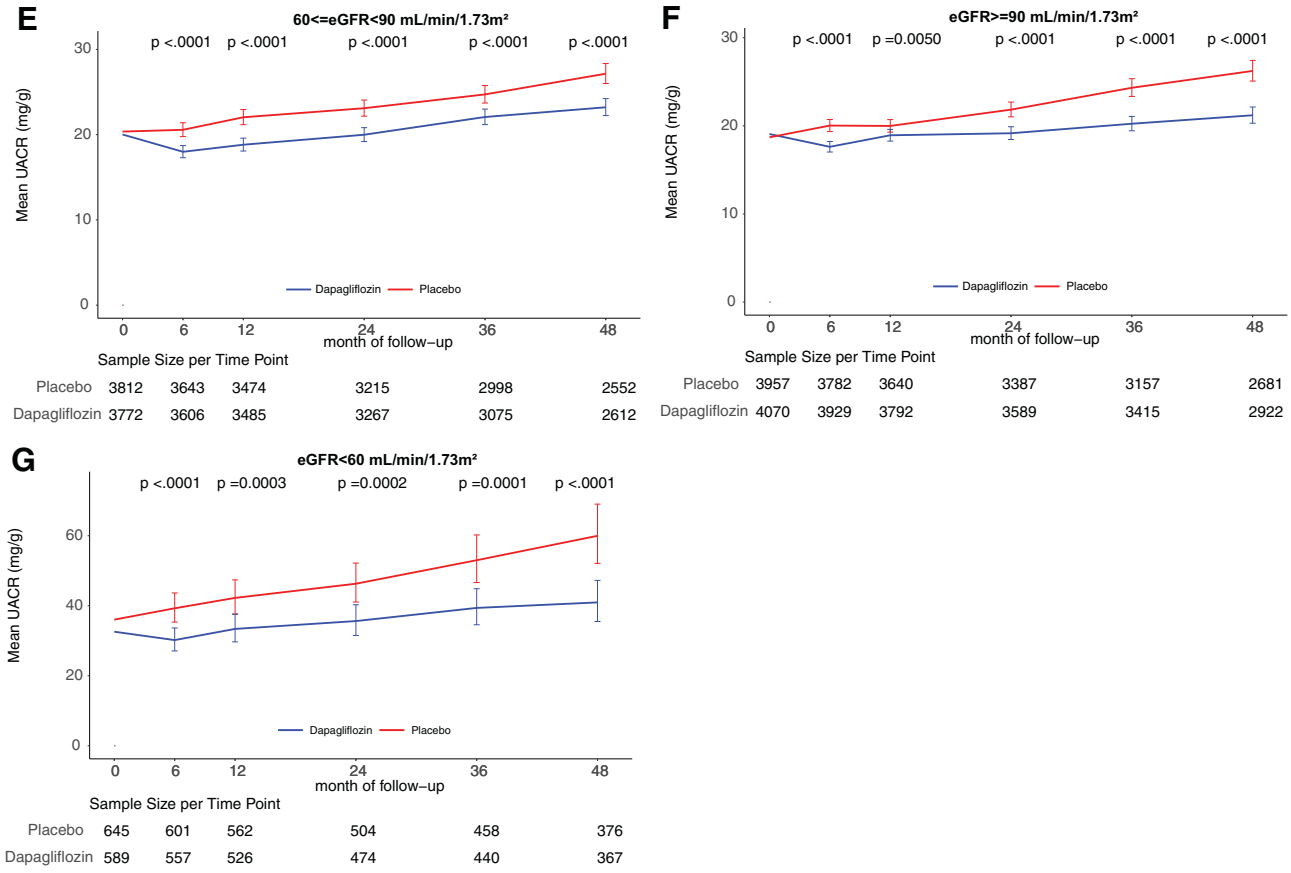

Figure 1—Continued.

due to a reduction in the energy requirement of proximal tubular cells (30) and in contrary to increased renal medullary hypoxia causing an increase in the expression of hypoxia-inducible factors and erythropoietin (31).

Compared with placebo, dapagliflozin treatment reduced UACR across all baseline eGFR and UACR categories, including those with UACR ≤15 mg/g and those with eGFR ≥90 mL/min/1.73 m^2, during ∼4 years of follow-up. The results indicate a beneficial effect for dapagliflozin on UACR as early as 6 months following treatment initiation. Dapagliflozin decreased UACR compared with placebo after 6 months for most baseline eGFR and UACR categories, except for the UACR ≤15 mg/g subgroups. In the placebo arm at 6 months, UACR values in the subgroups of UACR >15 mg/g seemed lower compared with baseline, a phenomenon that may be partially explained by regression to the mean, placebo-effect, or adjustment of background medications. Nonetheless, in all these subgroups, the reduction in UACR in the dapagliflozin arm was significantly larger, which testifies to the effect of the drug. Analysis of the distribution between subgroups of UACR after 6 months of treatment compared with baseline demonstrated an increase in the percentage of patients with UACR ≤15 mg/g in the dapagliflozin treatment arm, while the percentage of patients with UACR ≥30 mg/g was increased in the placebo arm. These findings add important information to the findings from the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial and the Canagliflozin Cardiovascular Assessment Study (CANVAS) program, which had smaller populations with normoalbuminuria and did not divide this group category into two subgroups (1,2,20,21). The population in DECLARE-TIMI 58 was larger than previous trials and included a higher percentage of participants both without eASCVD and with normal kidney function and UACR at baseline (3). The length of follow-up in the trial was also longer, with a median follow-up of 4.2 (IQR 3.9–4.4) years compared with 3.1 (IQR 2.2–3.6) years of follow-up and 2.6 years (IQR 2.0–3.4) of treatment duration in the EMPA REG and 188 (SD 106) weeks in CANVAS and 108 (SD 20) weeks in Canagliflozin Cardiovascular Assessment Study-Renal (CANVAS-R) (1–3). Similar to previous trials, the effect of dapagliflozin on UACR was in addition to widespread treatment with ACEi/ARBs (81.3% of participants) (3).

Unlike previous trials, we grouped our population into four categories of baseline UACR, dividing the large group of patients with normal albuminuria at baseline (11,644 patients, 69.1% of patients with baseline UACR measurements) into those with UACR ≤15 versus those with UACR >15 to <30 mg/g. The greater representation of patients with normal albumin excretion compared with previous trials allowed us to better define subtle changes within this important group of patients, which according to prior publications represent

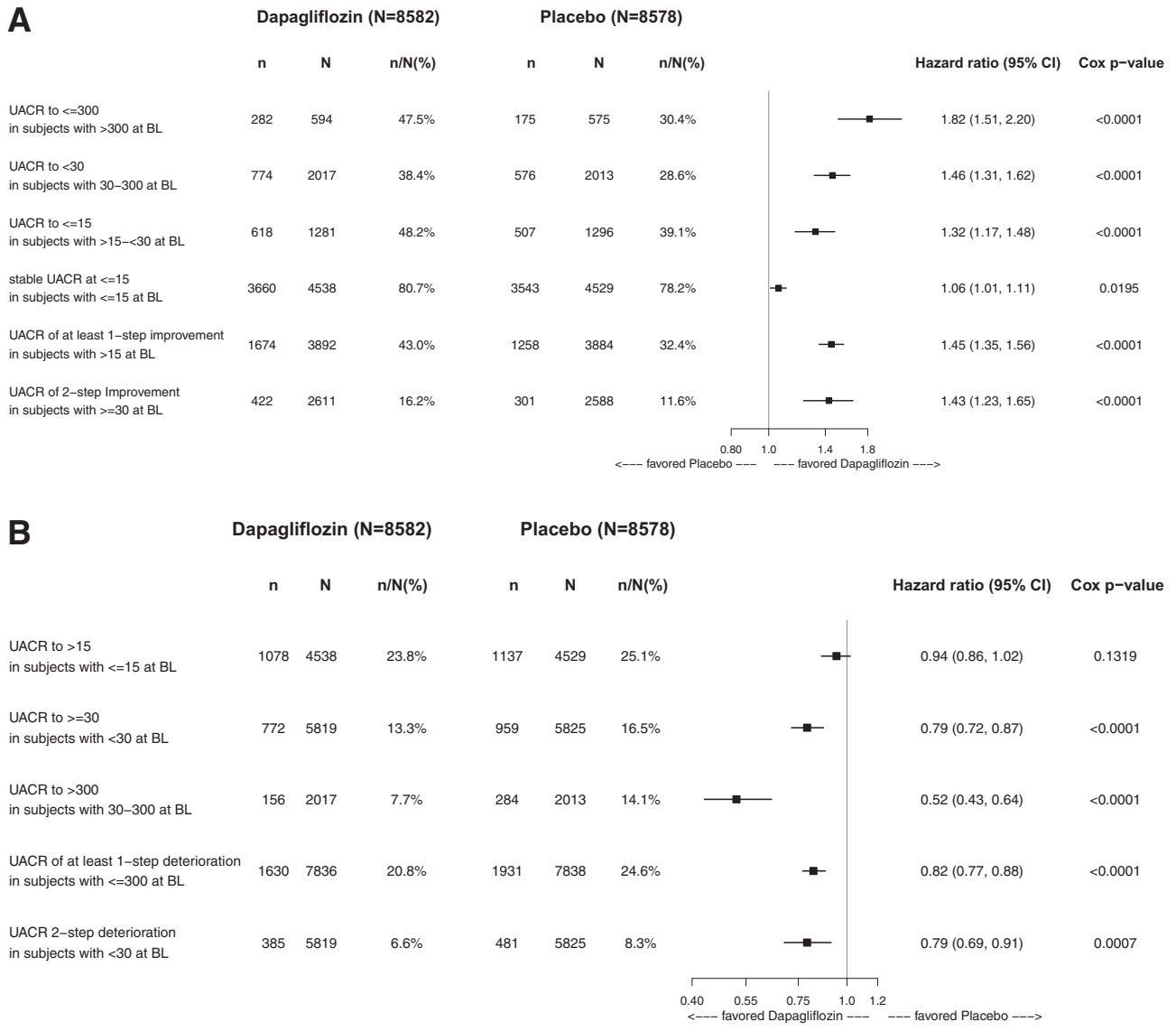

Figure 2—Change in confirmed sustained categorical UACR (mg/g) from baseline (BL) to EOT in dapagliflozin vs. placebo arm. *A*: Improvement in UACR categories. *B*: Deterioration in UACR categories.

50–70% of the general population of patients with type 2 diabetes (32–34). We were able to demonstrate an improvement in UACR deterioration even in this group of patients with UACR ≤15 mg/g. The division into four categories also conforms to the current knowledge that both increased renal and CV risk do not begin at UACR ≥30 mg/g, but rather at much lower levels of UACR (35–37), and to the current Kidney Disease: Improving Global Outcomes (KDIGO) recommendation to divide the range of normoalbuminuria into two separate groups (19). The data presented here further emphasize the association between higher levels of UACR within the normoalbuminuria range and increased risk for adverse renal events.

Studying the categorical changes in UACR, we found that patients treated with dapagliflozin were more likely to experience a categorical improvement and were less likely to experience deterioration. The observation was consistent when defined as at least one categorical shift, or at least two shifts, and remained stable when calculated as a single measurement change or as sustained change. Although albuminuria-based end points are limited by high day-to-day variability, recent analyses indicated that similar drug effects are achieved when comparing single and confirmed measurements (38). The single measurement analysis may suffer from increased "noise" but benefits from a higher number of events, resulting in a possible increase in statistical power (39). Time wise, dapagliflozin reduced the rate of new onset micro- or macroalbuminuria relatively early during the trial, and the separation between the populations was maintained throughout (Supplementary Fig. 2*B* and *C*). Considering these findings, the analyses of the change in UACR both as a continuous and categorical variable provide a comprehensive picture, emphasizing the beneficial effect for dapagliflozin on urinary albumin excretion across all baseline UACR and eGFR categories.

Albumin excretion rate is a clinically useful surrogate marker for severity of

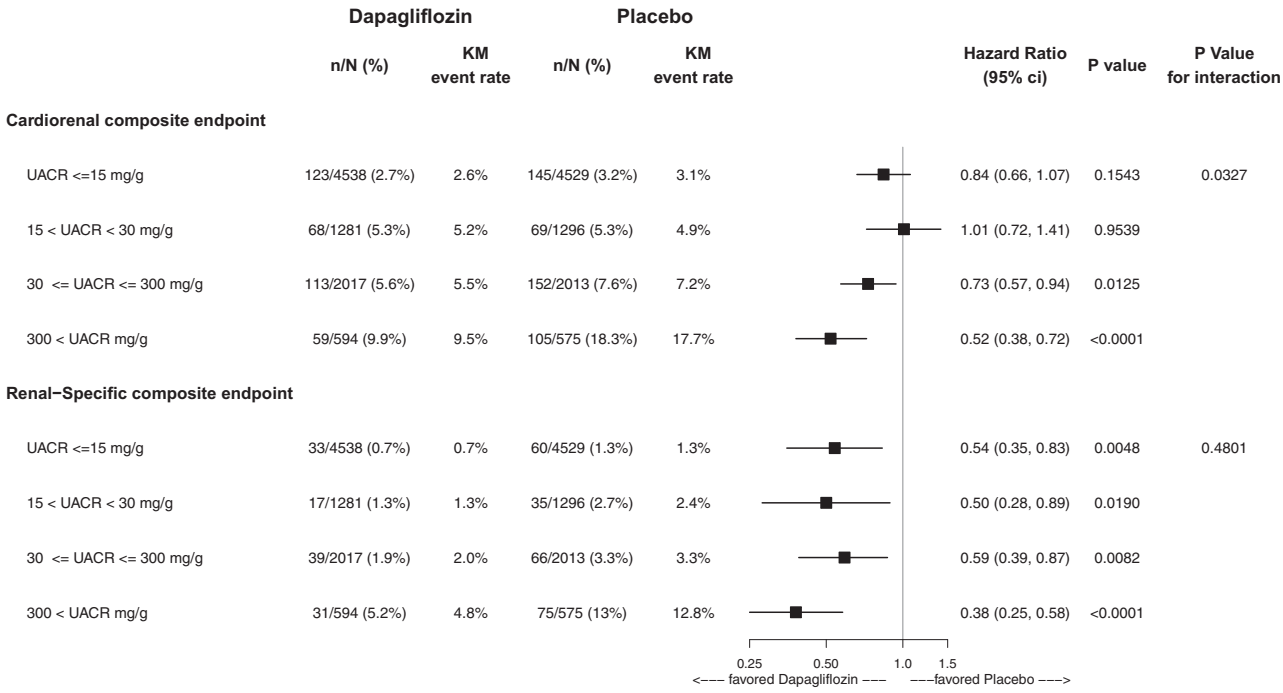

Figure 3—Treatment effect of dapagliflozin vs. placebo on composite cardiorenal and renal-specific outcomes according to baseline UACR categories of ≤15, >15 to <30, ≥30 to ≤300, and >300 mg/g. Cox model with stratification factor (baseline hematuria status and eASCVD or MRF status). KM, Kaplan-Meier.

kidney disease. Treatments that improve albuminuria status are associated with a reduction in the progression of CKD (13). Clinically, improvement in albuminuria status serves as a positive prognostic factor for adverse CV and renal outcomes, while increased albumin excretion serves as a warning sign (14). We previously reported a 24% decrease in the composite cardiorenal outcome of the trial (40% sustained decrease in eGFR, ESKD, and renal or CV death) (3,4). Here we demonstrated that the improvement was most pronounced in those patients with higher albuminuria at baseline ($P_{interaction}$ = 0.0327), however this analysis was not adjusted for the differences in the subgroups population. This stands in contrast to the renal-specific composite outcome (defined as all of the above but without CV death), in which the improvement with dapagliflozin was independent of baseline UACR ($P_{interaction}$ = 0.4801). These results emphasize that dapagliflozin improved renal outcomes in all patients, but improvement of composite cardiorenal outcomes was achieved in patients who already had renal damage, as evidenced by an increased UACR. This finding widens the newer findings from the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) (5) and Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) (6) trials, both of which demonstrated a lower rate of both renal and cardiorenal outcomes in different populations of patients with CKD, with (5,6) and without (6) type 2 diabetes.

While treatment with dapagliflozin may improve prognosis even when initiated in patients with kidney markers in the normal-healthy range, the low rate of adverse renal events in this population may require longer duration of treatment to demonstrate dapagliflozin's full effect. These results, along with the improvement demonstrated in the renal-specific outcome for all UACR subgroups, emphasize the way in which DECLARE-TIMI 58 was able to add supporting information to the renal-specific outcomes trials (CREDENCE, DAPA-CKD, EMPA-KIDNEY and others) (4–6,40) regarding the effect of SGLT2i in the healthier population of patients with type 2 diabetes that is a large part of the population with type 2 diabetes in our daily practice but not well represented in renal outcomes trials.

These analyses must be viewed as hypothesis generating, since one of the dual primary efficacy outcomes (MACE) was not achieved and because DECLARE-TIMI 58 was a CV outcome trial rather than a renal outcome trial. Though African American and Hispanic patients are at high risk for CKD, the limited number of subjects enrolled from these categories precludes a definitive understanding of any race- or ethnicity-based differences in outcomes or treatment effects (41). Another limitation of our trial was that we tested UACR only as a single sample, rather than an average of two to three samples, and only 6 months from baseline and thereafter once yearly. The eGFR dynamics in DECLARE-TIMI 58, including the early drop following dapagliflozin initiation, are not included in this analysis. An additional limitation is the relatively low number of patients in the highest risk category of albuminuria (1,169 patients with UACR >300 mg/g at baseline, <7% of the entire trial population), reflected in the relatively small number of renal events. However, this can also be seen as a possible strength of the trial, as this is more representative of the general population of patients with type 2 diabetes worldwide (32–34).

In conclusion, in the large population of patients with type 2 diabetes and low renal risk in DECLARE-TIMI 58, we

were able to demonstrate a significant positive long-term effect of dapagliflozin on UACR, irrespective of baseline eGFR and UACR, and even in patients with normoalbuminuria at baseline. We also demonstrated a reduction in renal-specific outcomes across all baseline UACR categories. This reduction in UACR and renal outcomes with dapagliflozin was achieved on top of >80% use of ACEi/ARBs. The possible association between the positive effect of dapagliflozin on albuminuria and its positive effect on the cardiorenal and renal-specific outcomes in DECLARE-TIMI 58 remain to be further analyzed.

Funding and Duality of Interest. T.A.Z. reports a research grant from Deutsche Forschungsgemeinschaft (ZE 1109/1-1). J.P.D. reports support from U.S. Food and Drug Administration. DECLARE-TIMI 58 was initially funded by AstraZeneca and Bristol-Myers Squibb; by the time of publication AstraZeneca was the sole funder (NCT01730534). O.M. declares advisory board membership from AstraZeneca, Novo Nordisk, Eli Lilly, Sanofi, Merck Sharp & Dohme, Boehringer Ingelheim, and BOL Pharma; speakers bureau honorarium from AstraZeneca, Novo Nordisk, Eli Lilly, Sanofi, Merck Sharp & Dohme, Boehringer Ingelheim, and Jansen; and research grants from Novo Nordisk and AstraZeneca. S.D.W. reports grants from AstraZeneca during the conduct of the study, grants from Amgen and Sanofi, grants and personal fees from Arena, AstraZeneca, Bristol-Myers Squibb, Daiichi Sankyo, Eisai, Eli Lilly, and Janssen; grants, personal fees, and other from Merck; personal fees from Aegerion, Allergan, AngelMed, Boehringer Ingelheim, Boston Clinical Research Institute, Icon Clinical, Lexicon, Servier, St. Jude Medical, and XOMA, outside the submitted work; 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, Anthos Therapeutics, Aralez, AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., Daiichi Sankyo, Eisai, Intarcia, MedImmune, Merck, Novartis, Pfizer, Quark Pharmaceuticals, Regeneron Pharmaceuticals, Inc., Roche, Siemens Healthcare Diagnostics, Inc., Takeda, The Medicines Company, and Zora Biosciences. H.J.L.H. reports grants and other from AstraZeneca, AbbVie, and Boehringer Ingelheim, and other from CSL Behring, Bayer, Chinook, Gilead, Merck, Novo Nordisk, Janssen, Mitsubishi Tanabe, and Retrophin. J.P.D. reports personal fees from AstraZeneca during the conduct of the study; personal fees from Sanofi, Bayer, CSL Behring, Novo Nordisk/ICON Clinical Research, Amgen, and Ironwood Pharmaceuticals; other from Collaborative Study Group, and personal fees from Boehringer-Ingelheim. A.C. reports grants from Novo Nordisk and AstraZeneca, and personal fees from Novo Nordisk, AstraZeneca, Abbot, Eli Lilly, Sanofi, Boehringer Ingelheim, Merck Sharp & Dohme, GlucoMe, and Medial Early Sign. E.L.G. and S.A.M. report grants from AstraZeneca during the conduct of the study and are members of the TIMI Study Group, which has received institutional research grant support through Brigham and Women's Hospital from Abbott, Amgen, Anthos Therapeutics, Aralez, AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., Daiichi Sankyo, Eisai, Intarcia, MedImmune, Merck, Novartis, Pfizer, Quark Pharmaceuticals, Regeneron Pharmaceuticals, Inc., Roche, Siemens Healthcare Diagnostics, Inc., Takeda, The Medicines Company, and Zora Biosciences. A.R. and I.Y. report consultation fees from AstraZeneca and Novo Nordisk. T.A.Z. T.A.Z reports research grants from the Austrian Science Funds and the German Research Foundation, honoraria for serving on advisory boards from Boehringer Ingelheim, personal fees from AstraZeneca, Boehringer Ingelheim, and Sun Pharmaceutical Industries, and educational grants from Eli Lilly and Company. I.A.M.G.-N., A.M.L., M.F., and P.A.J. are employees at BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden. D.L.B. discloses advisory board: Cardax, CellProthera, Cereno Scientific, Elsevier PracticeUpdate Cardiology, Level Ex, Medscape Cardiology, MyoKardia, PhaseBio, PLx Pharma, and Regado Biosciences; board of directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, and TobeSoft; chair: American Heart Association Quality Oversight Committee; data monitoring committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the CENTERA THV System in Intermediate Risk Patients Who Have Symptomatic, Severe, Calcific, Aortic Stenosis Requiring Aortic Valve Replacement [ExCEED] trial, funded by Edwards), Contego Medical (chair, Protection Against Emboli During Carotid Artery Stenting Using the Neuroguard IEP System [PERFORMANCE 2]), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the Edoxaban Compared to Standard Care After Heart Valve Replacement [ENVISAGE] trial, funded by Daiichi Sankyo), and Population Health Research Institute; honoraria: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention [RE-DUAL PCI] clinical trial steering committee funded by Boehringer Ingelheim; Study to Investigate CSL112 in Subjects With Acute Coronary Syndrome [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 Prostate Cancer and Cardiovascular Disease [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 (Continuing Medical Education [CME] steering committees), MJH Life Sciences, Population Health Research Institute (for the Cardiovascular Outcomes for People Using Anticoagulation Strategies [COMPASS] operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), and WebMD (CME steering committees); other: *Clinical Cardiology* (deputy editor), National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network (NCDR-ACTION) Registry Steering Committee (chair), and Veterans Administration Clinical Assessment, Reporting and Tracking System for Cath Labs (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, Eli Lilly, Medtronic, MyoKardia, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi, Synaptic, and 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), and Svelte; trustee: American College of Cardiology; and unfunded research: FlowCo, Merck, Novo Nordisk, and Takeda. L.A.L. has received research funding from, has provided CME on behalf of, and/or has acted as an advisor to AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, GSK, Janssen, Lexicon, Merck, Novo Nordisk, Sanofi, and Servier. D.K.M. has received personal fees from AstraZeneca, Boehringer Ingelheim, Janssen, Lexicon, Merck & Company, Merck Sharp & Dohme, Novo Nordisk, Sanofi, Eisai, Esperion, GlaxoSmithKline, Eli Lilly USA, Pfizer, Metavant, Applied Therapeutics, Afimmune, and CSL Behring. J.P.H.W. reports grants, personal fees, and other from AstraZeneca and Novo Nordisk; other from Astellas, Janssen, Sanofi, Rhythm Pharmaceuticals, Wilmington Healthcare, and Eli Lilly; personal fees and other from Boehringer Ingelheim, Napp, and Mundipharma; and grants and personal fees from Takeda. M.S.S. reports grants and personal fees from Amgen, Anthos Therapeutics, AstraZeneca, Intarcia The Medicines Company, MedImmune, and Merck; personal fees from Althera, Bristol-Myers Squibb, CVS Caremark, DalCor, Dr. Reddy's Laboratories, Dyrnamix, and IFM Therapeutics; and grants from Bayer, Daiichi-Sankyo, Eisai, Novartis, Pfizer and Quark Pharmaceuticals, 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, Regeneron, Roche, and Zora Biosciences. I.R. declares advisory board membership from AstraZeneca, Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk, Inc., and Sanofi; consultant fees from AstraZeneca, Insuline Medical, Medial EarlySign Ltd., CamerEyes Ltd., Exscopia, Orgenesis Ltd., BOL Pharma, Glucome Ltd., DarioHealth, Diabot, Concenter BioPharma, and CuraLife Ltd.; speakers bureau honorarium from AstraZeneca, Eli Lilly and Company, Merck

Sharp & Dohme, Novo Nordisk, Inc., and Sanofi; and stock/shareholder interests from Glucome Ltd., Orgenesis Ltd., DarioHealth, CamerEyes Ltd., Diabot, and BOL Pharma. D.L.B. received honoraria from American College of Cardiology (ACC) (senior associate editor, Clinical Trials and News, ACC.org; vice-chair, ACC Accreditation Committee), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Society of Cardiovascular Patient Care (secretary/treasurer), National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network (NCDR-ACTION) Registry Steering Committee (chair), and Veterans Administration Clinical Assessment, Reporting and Tracking System for Cath Labs (VA CART) Research and Publications Committee (chair). No other potential conflicts of interest relevant to this article were reported.

Author Contributions. O.M., S.D.W., H.J.L.H, J.P.D., A.C., A.R., M.S., I.Y., T.A.Z., I.A.M.G.-N., A.M.L., M.F., D.L.B., L.A.L., D.K.M., J.P.H.W., M.S.S., and I.R. contributed to data interpretation. O.M., S.D.W., H.J.L.H, J.P.D., A.C., A.R., M.S., I.Y., T.A.Z., I.A.M.G.-N., A.M.L., M.F., D.L.B., L.A.L., D.K.M., J.P.H.W., M.S.S., and I.R. contributed to the writing of the report. O.M., S.D.W., H.J.L.H, J.P.D., I.A.M.G.-N., A.M.L., M.F., M.S.S., and I.R. contributed to the study design. O.M., S.D.W., A.C., E.L.G., A.R., M.S., I.Y., S.A.M., I.A.M.G.-N., A.M.L., M.F., P.A.J., D.L.B., L.A.L., D.K.M., J.P.H.W., M.S.S., and I.R. contributed to data analysis. O.M., S.D.W., E.L.G., A.R., M.S., I.Y., S.A.M., I.A.M.G.-N., A.M.L., M.S.S., and I.R. designed the figures. O.M., S.D.W., M.S., I.A.M.G.-N., A.M.L., M.S.S., and I.R. did the literature search. O.M., S.D.W., I.A.M.G.-N., A.M.L., M.F., M.S.S., and I.R. contributed to data collection. O.M. and I.R. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 79th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 7–11 June 2019.

References

1. Wanner C, Inzucchi SE, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323–334
2. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–657
3. Wiviott SD, Raz I, Bonaca MP, et al.; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347–357
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;7:606–617
5. Perkovic V, Jardine MJ, Neal B, et al.; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295–2306
6. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al.; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436–1446
7. Cannon CP, Pratley R, Dagogo-Jack S, et al.; VERTIS CV Investigators. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med 2020;383:1425–1435
8. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care 2014;37:2864–2883
9. Yamanouchi M, Furuichi K, Hoshino J, et al.; Research Group of Diabetic Nephropathy, the Ministry of Health, Labour and Welfare, and the Japan Agency for Medical Research and Development. Nonproteinuric versus proteinuric phenotypes in diabetic kidney disease: a propensity score-matched analysis of a nationwide, biopsy-based cohort study. Diabetes Care 2019;42:891–902
10. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010;375:2073–2081
11. van der Velde M, Matsushita K, Coresh J, et al.; Chronic Kidney Disease Prognosis Consortium. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int 2011;79:1341–1352
12. Coresh J, Heerspink HJL, Sang Y, et al.; Chronic Kidney Disease Prognosis Consortium and Chronic Kidney Disease Epidemiology Collaboration. Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies. Lancet Diabetes Endocrinol 2019;7:115–127
13. Heerspink HJL, Greene T, Tighiouart H, et al.; Chronic Kidney Disease Epidemiology Collaboration. Change in albuminuria as a surrogate endpoint for progression of kidney disease: a meta-analysis of treatment effects in randomised clinical trials. Lancet Diabetes Endocrinol 2019;7:128–139
14. Schmieder RE, Mann JFE, Schumacher H, et al.; ONTARGET Investigators. Changes in albuminuria predict mortality and morbidity in patients with vascular disease. J Am Soc Nephrol 2011;22:1353–1364
15. American Diabetes Association. 11. Microvascular complications and foot care: *Standards of Medical Care in Diabetes—2021*. Diabetes Care 2021;44(Suppl. 1):S151–S167
16. Wiviott SD, Raz I, Bonaca MP, et al. The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 Trial. Am Heart J 2018;200:83–89
17. Raz I, Mosenzon O, Bonaca MP, et al. DECLARE-TIMI 58: participants' baseline characteristics. Diabetes Obes Metab 2018;20:1102–1110
18. Schwandt A, Denkinger M, Fasching P, et al. Comparison of MDRD, CKD-EPI, and Cockcroft-Gault equation in relation to measured glomerular filtration rate among a large cohort with diabetes. J Diabetes Complications 2017;31:1376–1383
19. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int 2011;80:17–28
20. Cherney DZI, Zinman B, Inzucchi SE, et al. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2017;5:610–621
21. Perkovic V, de Zeeuw D, Mahaffey KW, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. Lancet Diabetes Endocrinol 2018;6:691–704
22. Heerspink HJL, Johnsson E, Gause-Nilsson I, Cain VA, Sjöström CD. Dapagliflozin reduces albuminuria in patients with diabetes and hypertension receiving renin-angiotensin blockers. Diabetes Obes Metab 2016;18:590–597
23. Fioretto P, Stefansson BV, Johnsson E, Cain VA, Sjöström CD. Dapagliflozin reduces albuminuria over 2 years in patients with type 2 diabetes mellitus and renal impairment. Diabetologia 2016;59:2036–2039
24. Cherney D, Lund SS, Perkins BA, et al. The effect of sodium glucose cotransporter 2 inhibition with empagliflozin on microalbuminuria and macroalbuminuria in patients with type 2 diabetes. Diabetologia 2016;59:1860–1870
25. Heerspink HJL, Perkins BA, Fitchett DH, Husain M, Cherney DZI. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. Circulation 2016;134:752–772
26. Tonneijck L, Muskiet MHA, Smits MM, et al. Glomerular hyperfiltration in diabetes: mechanisms, clinical significance, and treatment. J Am Soc Nephrol 2017;28:1023–1039
27. van Bommel EJM, Muskiet MHA, van Baar MJB, et al. The renal hemodynamic effects of the SGLT2 inhibitor dapagliflozin are caused by post-glomerular vasodilatation rather than pre-glomerular vasoconstriction in metformin-treated patients with type 2 diabetes in the randomized, double-blind RED trial. Kidney Int 2020;97:202–212
28. Lytvyn Y, Bjornstad P, van Raalte DH, Heerspink HL, Cherney DZI. The new biology of diabetic kidney disease—mechanisms and therapeutic implications. Endocr Rev 2020;41:202–231
29. Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. Diabetologia 2017;60:215–225
30. Tsimihodimos V, Filippatos TD, Elisaf MS. SGLT2 inhibitors and the kidney: effects and mechanisms. Diabetes Metab Syndr 2018;12:1117–1123
31. O'Neill J, Fasching A, Pihl L, Patinha D, Franzén S, Palm F. Acute SGLT inhibition normalizes O2 tension in the renal cortex but causes hypoxia in the renal medulla in anaesthetized control and diabetic rats. Am J Physiol Renal Physiol 2015;309:F227–F234
32. Parving HH, Lewis JB, Ravid M, Remuzzi G; DEMAND investigators. Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: a global perspective. Kidney Int 2006;69:2057–2063
33. Young BA, Katon WJ, Von Korff M, et al. Racial and ethnic differences in microalbuminuria prevalence in a diabetes population: the pathways study. J Am Soc Nephrol 2005;16:219–228

34. Newman DJ, Mattock MB, Dawnay ABS, et al. Systematic review on urine albumin testing for early detection of diabetic complications. Health Technol Assess 2005;9:iii–vi, xiii-163
35. Scirica BM, Mosenzon O, Bhatt DL, et al. Cardiovascular outcomes according to urinary albumin and kidney disease in patients with type 2 diabetes at high cardiovascular risk: observations from the SAVOR-TIMI 53 Trial. JAMA Cardiol 2018;3:155–163
36. Blecker S, Matsushita K, Köttgen A, et al. High-normal albuminuria and risk of heart failure in the community. Am J Kidney Dis 2011;58:47–55
37. Astor BC, Matsushita K, Gansevoort RT, et al.; Chronic Kidney Disease Prognosis Consortium. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. Kidney Int 2011;79:1331–1340
38. Kröpelin TF, de Zeeuw D, Andress DL, et al. Number and frequency of albuminuria measurements in clinical trials in diabetic nephropathy. Clin J Am Soc Nephrol 2015;10:410–416
39. Kröpelin TF, de Zeeuw D, Remuzzi G, Bilous R, Parving H-H, Heerspink HJL. Determining the optimal protocol for measuring an albuminuria class transition in clinical trials in diabetic kidney disease. J Am Soc Nephrol 2016;27:3405–3412
40. EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin). ClinicalTrials.gov. Accessed 9 May 2020. Available from https://clinicaltrials.gov/ct2/show/NCT03594110
41. Vart P, Powe NR, McCulloch CE, et al.; Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. National trends in the prevalence of chronic kidney disease among racial/ethnic and socioeconomic status groups, 1988-2016. JAMA Netw Open 2020;3:e207932