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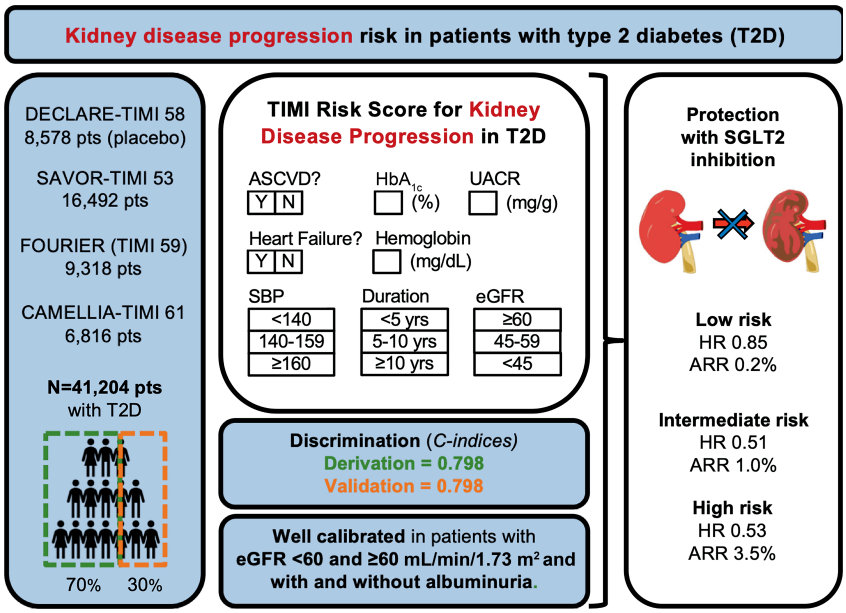

ARR, absolute risk reduction; ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SGLT2, sodium–glucose cotransporter 2; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio

ARTICLE HIGHLIGHTS

- A novel risk model for kidney disease progression (defined as a sustained ≥40% decrease in estimated glomerular filtration rate, end-stage kidney disease, or kidney death) was developed and applied to stratify risk in patients with type 2 diabetes.
- The model performs well in patients with an estimated glomerular filtration rate of <60 and ≥60 mL/min/1.73 m^2 and with and without albuminuria.
- Patients with type 2 diabetes with a higher baseline risk of kidney disease progression experience a greater magnitude of benefit from sodium–glucose cotransporter 2 inhibition.

Risk Assessment of Kidney Disease Progression and Efficacy of SGLT2 Inhibition in Patients With Type 2 Diabetes

Filipe A. Moura,[1] David D. Berg,[1] Andrea Bellavia,[1] Jamie P. Dwyer,[2] Ofri Mosenzon,[3,4] Benjamin M. Scirica,[1] Stephen D. Wiviott,[1] Deepak L. Bhatt,[5] Itamar Raz,[3,4] Mark W. Feinberg,[6] Eugene Braunwald,[1] David A. Morrow,[1] and Marc S. Sabatine[1]

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OBJECTIVE

To develop a risk assessment tool to identify patients with type 2 diabetes (T2D) at higher risk for kidney disease progression and who might benefit more from sodium–glucose cotransporter 2 (SGLT2) inhibition.

RESEARCH DESIGN AND METHODS

A total of 41,204 patients with T2D from four Thrombolysis In Myocardial Infarction (TIMI) clinical trials were divided into derivation (70%) and validation cohorts (30%). Candidate predictors of kidney disease progression (composite of sustained ≥40% decline in estimated glomerular filtration rate [eGFR], end-stage kidney disease, or kidney death) were selected with multivariable Cox regression. Efficacy of dapagliflozin was assessed by risk categories (low: <0.5%; intermediate: 0.5 to <2%; high: ≥2%) in Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58.

RESULTS

There were 695 events over a median follow-up of 2.4 years. The final model comprised eight independent predictors of kidney disease progression: atherosclerotic cardiovascular disease, heart failure, systolic blood pressure, T2D duration, glycated hemoglobin, eGFR, urine albumin-to-creatinine ratio, and hemoglobin. The c-indices were 0.798 (95% CI, 0.774–0.821) and 0.798 (95% CI, 0.765–0.831) in the derivation and validation cohort, respectively. The calibration plot slope (deciles of predicted vs. observed risk) was 0.98 (95% CI, 0.93–1.04) in the validation cohort. Whereas relative risk reductions with dapagliflozin did not differ across risk categories, there was greater absolute risk reduction in patients with higher baseline risk, with a 3.5% absolute risk reduction in kidney disease progression at 4 years in the highest risk group (≥1%/year). Results were similar with the 2022 Chronic Kidney Disease Prognosis Consortium risk prediction model.

CONCLUSIONS

Risk models for kidney disease progression can be applied in patients with T2D to stratify risk and identify those who experience a greater magnitude of benefit from SGLT2 inhibition.

Chronic kidney disease (CKD) affects approximately one-third of patients with type 2 diabetes (T2D), and its prevalence has remained high worldwide (1,2). The rate of decline in kidney function, as measured by the estimated glomerular filtration rate (eGFR), and the risk of progression to advanced kidney disease are highly variable in

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patients with T2D (3,4). Early identification of patients with T2D that are at higher risk of kidney disease progression can help inform patient-provider communication, timing of referral to nephrology, and selection of optimal medical management. This is particularly helpful at a time of availability of several pharmacotherapeutic strategies that can modify the course of CKD, such as renin-angiotensin system inhibitors (5,6), sodium–glucose cotransporter 2 (SGLT2) inhibitors (7–10), selective mineralocorticoid receptor antagonists (11), and glucagon-like peptide 1 receptor agonists (12).

Although other kidney risk scores have been developed, they were developed using a general population without a specific attention to T2D, focused on predicting an eGFR $<$60 mL/min/1.73 m^2, which is applicable only to patients with preserved renal function, or were generated to predict kidney failure, a late and less common outcome in patients without advanced CKD (13–16). Given limitations in these singular outcomes, the U.S. Food and Drug Administration and the European Medicines Agency have embraced a composite kidney disease progression outcome of sustained $\geq$40–50% decline in eGFR, development of end-stage kidney disease (ESKD), or kidney death (17). This was recently adopted by the CKD Prognosis Consortium in their development and validation of a robust prediction model for the composite of $\geq$40% eGFR decline or kidney failure in patients with and without T2D (18).

Thus, we leveraged data from multiple cardiovascular clinical trials enrolling patients with T2D to develop and validate a clinical risk model for predicting the risk of kidney disease progression as defined by the composite outcome advocated by regulatory authorities.

RESEARCH DESIGN AND METHODS

Study Population

This study consisted of patients with T2D from a pooled cohort of four multinational, randomized, placebo-controlled, cardiovascular clinical trials: Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 (19), Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 (20), Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) (TIMI 59) (21), and Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients (CAMELLIA)-TIMI 61 (22). SAVOR-TIMI 53 was a randomized, placebo-controlled outcomes trial that evaluated the dipeptidyl peptidase 4 inhibitor saxagliptin in 16,492 patients with T2D with multiple risk factors for or established atherosclerotic cardiovascular disease (ASCVD) followed for a median of 2.1 years. DECLARE-TIMI 58 was a randomized, placebo-controlled, outcomes trial that evaluated the SGLT2 inhibitor dapagliflozin in 17,160 patients with T2D with multiple risk factors for or established ASCVD followed for a median of 4.2 years. Only the placebo arm (n = 8,578) was used for the purposes of clinical risk score development given the known effect of dapagliflozin on kidney outcomes. FOURIER (TIMI 59) was a randomized, placebo-controlled, outcomes trial of the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor evolocumab in 27,564 patients with stable ASCVD on statin therapy followed for a median of 2.2 years, of whom 9,318 were available for this analysis and had T2D. Lastly, CAMELLIA-TIMI 61 was a randomized, placebo-controlled, outcomes trial of the selective serotonin 2C receptor agonist lorcaserin in 12,000 patients with overweight or obesity with multiple risk factors for or established ASCVD followed for a median of 3.3 years, of whom 6,816 had T2D.

The derivation cohort consisted of 70% of patients (n = 28,842) selected at random from the pooled cohort. The validation cohort consisted of the remaining 30% of patients (n = 12,362) from the pooled cohort. The ethics committees from participating study centers approved the protocols for each of the trials. Written informed consent was obtained from all patients prior to enrollment.

Clinical Outcome

The primary outcome for this analysis was kidney disease progression, defined as the composite of sustained $\geq$40% decline in eGFR, ESKD (defined as dialysis for $\geq$90 days, kidney transplantation, or sustained eGFR $<$15 mL/min/1.73 m^2), or kidney death. eGFR was estimated with the Chronic Kidney Disease Epidemiology Collaboration equation using serum creatinine (23). This outcome was selected given current clinical trial and drug development standards following discussions between the National Kidney Foundation and U.S. Food and Drug Administration, in which a confirmed and sustained $\geq$40% decline in eGFR was deemed to be an acceptable surrogate end point for the subsequent development of kidney failure (17). ESKD and kidney death were prospectively collected and centrally adjudicated by the TIMI Clinical Events Committee using standard definitions in SAVOR-TIMI 53, DECLARE-TIMI 58, and CAMELLIA-TIMI 61. In FOURIER (TIMI 59), ESKD was identified by search of the adverse event reporting safety clinical trial database using the Medical Dictionary of Regulatory Affairs (MedDRA) preferred terms ("end stage renal disease" and "diabetic end stage renal disease"). In DECLARE-TIMI 58, we also assessed chronic eGFR slope (6 months to 48 months) using previously published methodology (24).

Candidate Risk Variables

Based on clinical relevance and availability in the clinical trial record of participants treated in the cohort, 23 baseline candidate risk variables were considered for inclusion in the risk model. The candidates included age, sex, coronary artery disease, ASCVD (defined as prior myocardial infarction, prior ischemic stroke, and peripheral artery disease), percutaneous coronary intervention, coronary artery bypass grafting, history of heart failure, atrial fibrillation, hypertension, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, current smoker status, duration of T2D, baseline insulin use, eGFR, urine albumin-to-creatinine ratio (UACR), BMI, waist circumference, glycated hemoglobin (HbA_{1c}), HDL-cholesterol (-C), LDL-C, and hemoglobin. Race was not included as a candidate variable to align with the broader initiative of removing race from clinical algorithms.

Variable Selection

Kidney disease progression was evaluated as a time-to-event end point using multivariable Cox regression. Schoenfeld residuals were used to test the proportional hazards assumption, which was met for all evaluated variables. Clinical predictors of kidney disease progression were selected using backward selection, with a threshold of $P < 0.001$ so that only highly significant variables were included in the final model. Prior to the selection

procedure, potential nonlinearities in the association between candidate continuous predictors and composite kidney end points were assessed with spline curves. If the linearity assumption was not met, categorization based on graphically determined thresholds was considered. Accordingly, age, DBP, heart rate, HbA_{1c}, UACR, waist circumference, HDL-C, LDL-C, and hemoglobin were modeled continuously, whereas SBP, duration of T2D, eGFR, and BMI were modeled categorically.

Discrimination and Calibration

The discriminatory performance of the final risk model was assessed in both the derivation and validation sets using the Harrell c-index. In addition, the cumulative incidence of kidney disease progression was assessed according to categories of predicted risk. Extrapolating from a 10-year risk framework, with $<$2.5%, 2.5 to $<$10%, and $\geq$10% 10-year risk of kidney disease progression corresponding to low-, intermediate-, and high-risk, respectively, 2-year risk bins were defined: $<$0.5% (low), 0.5 to $<$2% (intermediate), and $\geq$2% (high). Calibration was assessed graphically in the validation cohort by calculating the slope with 95% CI of the comparison between the predicted 2-year risk (*x*-axis) and observed Kaplan-Meier cumulative incidence at 2 years (*y*-axis).

The performance of the final risk model was assessed separately in patients with and without eGFR $<$60 mL/min/1.73 m^2 as well as in patients with and without albuminuria (UACR $<$30 mg/g). In addition, discrimination for the individual components of the composite end point was assessed. We also assed the discriminatory performance of previous risk models including the kidney failure risk equation (14), the CKD Prognosis Consortium risk equation for incident CKD (13), and the CKD Prognosis Consortium risk model for decline in kidney function (18). We assessed the Harrell c-index for each of the models in the validation cohort using the published coefficients in each of the original manuscripts as well as coefficients resulting from refitting the models of the existing scores in our derivation cohort.

Assessment of Treatment Benefit From SGLT2 Inhibition According to Risk Assessment

We assessed for heterogeneity in the relative and absolute treatment effect of dapagliflozin versus placebo on kidney end points in DECLARE-TIMI 58 according to baseline predicted risk. To test for heterogeneity in the hazard of the event, the interaction between treatment and the predicted risk was included in the Cox regression model. To compare absolute differences in the treatment effect of dapagliflozin versus placebo on absolute risk reduction (ARR) in kidney disease progression, the 4-year Kaplan-Meier cumulative incidence in patients randomly assigned to dapagliflozin was subtracted from that of patients randomly assigned to placebo across each risk category. To assess the trend of ARR in kidney disease progression with dapagliflozin by baseline risk category, we used an inverse-variance weighted least squares model, regressing ARR on risk category. Hence, the *P*-interaction was calculated as an ARR trend over the risk groups. In addition, we also assessed for heterogeneity of treatment effect in the herein described manner according to baseline predicted risk using the CKD Prognosis Consortium risk model for decline in kidney function (18). Finally, to assess the treatment effect of dapagliflozin on chronic eGFR slope, we assessed differences in least squares means eGFR between dapagliflozin and placebo from a mixed model as well as differences in chronic eGFR slope (generated from linear regression using measured values at months 6, 12, 24, 36, and 48) according to baseline predicted risk (24).

All statistical analyses were performed in R 4.2.2 software. All *P* values are two-sided, unless otherwise specified.

Data Resource and Availability

We encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions.

RESULTS

Study Population Characteristics

The baseline characteristics of the study population are summarized in Table 1. In the derivation cohort (*n* = 28,842), the median age was 64 years (interquartile range [IQR] 59–70), 34% were women, and 21% were non-White. The median duration of diabetes was 9.2 years (IQR 4.1–15), and median HbA_{1c} was 7.5% (IQR 6.7–8.5; 58 mmol/mol [IQR 50-69]); 35.6% of patients were receiving insulin therapy at baseline. The median eGFR at baseline was 76 mL/min/1.73 m^2 (IQR 62–91), with 77.6% of patients having preserved kidney function (eGFR $\geq$60 mL/min/1.73 m^2). The median UACR was 13.3 mg/g (IQR 5.1–49), with 67% of patients having normal or mildly increased albuminuria (UACR $<$30 mg/g). During a median follow-up of 2.4 years, kidney disease progression occurred in 481 patients (Supplementary Table 1).

The baseline characteristics of the validation cohort (*n* = 12,362) were very similar (Table 1). The median duration of diabetes was 9.0 years, with 77.4% of patients having preserved kidney function and 66% of patients having normal or mildly increased albuminuria. Kidney disease progression occurred in 214 patients during a median follow-up of 2.4 years (Supplementary Table 1).

Clinical Risk Model Development and Performance

From the 23 candidate variables, 8 independent predictors of kidney disease progression were selected for inclusion in the final clinical risk model, which is presented in Table 2. The model had very good discrimination in both the derivation and validation cohorts, with Harrell c-indices of 0.798 (95% CI, 0.774–0.821) and 0.798 (95% CI, 0.765–0.831), respectively. Discrimination for the individual components of the kidney disease progression composite was also very good, with Harrell c-indices of 0.799 for sustained $\geq$40% eGFR decline, 0.894 for ESKD or kidney death, 0.891 for ESKD, and 0.867 for kidney death in the validation cohort (Supplementary Table 2). Finally, the model predicted kidney disease progression in the validation cohort both in patients with and without baseline eGFR $<$60 mL/min/1.73 m^2 (c-indices of 0.845 and 0.763, respectively) (Supplementary Table 3) as well as patients with and without baseline albuminuria (c-indices of 0.729 and 0.803, respectively) (Supplementary Table 3).

As shown in Fig. 1*A*, the model identified strong gradients of risk for kidney disease progression in both the derivation and validation cohorts. Moreover, the 2-year cumulative incidence fell within the appropriate predefined 2-year risk categories, indicating appropriate calibration of the risk model as well. Further supporting the risk model's calibration, observed Kaplan-Meier cumulative incidence of kidney disease progression closely corresponded to predicted risk (across risk deciles), resulting in a calibration slope

Table 1—Clinical characteristics of patients in the derivation and validation cohorts

Variable	Derivation cohort (*n* = 28,842)	Validation cohort (*n* = 12,362)
Age, years	64 (59–70)	64 (59–70)
Male sex	66.0	66.2
White race	79.3	79.5
BMI, kg/m^2	32 (28–36)	31 (28–36)
BMI ≥30 kg/m^2	61.0	59.9
Waist circumference, cm	110 (99–120)	110 (98–120)
Duration of type 2 diabetes, years	9.2 (4.1–15.0)	9.0 (4.1–15.0)
5–10	26.3	26.9
>10	44.8	44.1
HbA_{1c}, %	7.5 (6.7–8.5)	7.4 (6.7–8.5)
Baseline insulin use	35.6	34.5
Current tobacco use	14.4	14.6
Established ASCVD	57.6	57.0
Coronary artery disease	59.4	59.1
Prior myocardial infarction	42.3	41.4
Peripheral artery disease	10.3	10.6
Prior ischemic stroke	12.5	12.2
Congestive heart failure	14.7	15.0
Heart rate, bpm	70 (63–78)	70 (64–78)
SBP, mmHg	130 (120–150)	130 (120–150)
140–159	31.0	31.5
≥160	7.0	7.5
DBP, mmHg	79 (71–85)	79 (71–85)
eGFR, mL/min/1.73 m^2	76 (62–91)	76 (62–91)
eGFR 45–59	15.0	15.1
eGFR <45	7.6	7.2
UACR, mg/g	13.0 (5.2–51.0)	13.0 (5.0–48.0)
<30	67	66
30–299	25	25
≥300	8	9
LDL-C, mg/dL	85 (68–110)	85 (68–110)
HDL-C, mg/dL	42 (35–50)	42 (36–51)
Hemoglobin, g/dL	14 (13–15)	14 (13–15)

Categorical variables are shown as percentages; continuous variables are shown as medians (interquartile range). bpm, beats per minute.

of 0.98 (95% CI, 0.93–1.04) in the validation cohort (Fig. 1*B*).

In terms of comparative discriminatory performance, our final risk model in general compared favorably to the kidney failure risk equation (14), the CKD Prognosis Consortium risk equation for incident CKD (13), and the CKD Prognosis Consortium risk model for decline in kidney function (18) when using both the published formulas and refit models (Supplementary Tables 4 and 5). Supplementary Table 6 demonstrates the kidney failure risk equation (14) is well calibrated in our cohort of clinical trials, while the CKD Prognosis Consortium risk model for decline in kidney function (18) tends to slightly overestimate risk and the CKD Prognosis Consortium risk equation for incident CKD (13) strongly underestimates risk.

Treatment Benefit of SGLT2 Inhibition in DECLARE-TIMI 58

Figure 2 demonstrates the relative and absolute reductions in the risk of kidney disease progression with dapagliflozin according to predicted 4-year risk of <1%, 1 to <4%, and ≥4% (corresponding to 2-year risk categories of <0.5%, 0.5 to <2%, and ≥2%). The relative rate reductions with dapagliflozin were generally consistent across risk categories (15%, 49%, and 47%, respectively; *P*-interaction = 0.70), but the ARRs were greater across increasing risk categories (0.2%, 1.0%, and 3.5%, respectively; *P*-interaction = 0.01). The balanced numbers of patients in the dapagliflozin and placebo arms in each risk category are reflective of the 1:1 randomization in DECLARE-TIMI 58. Similarly, Supplementary Fig. 1 demonstrates the same pattern of consistent relative rate reduction and greater ARRs across increasing previously suggested 3-year kidney risk categories adapted to the ∼4-year follow-up of DECLARE-TIMI 58 patients (4.2 year median) (25). Supplementary Fig. 2 demonstrates that using the CKD Consortium risk model for decline in kidney function, the relative rate reductions with dapagliflozin were also consistent across risk categories (53%, 42%, and 48%, respectively; *P*-interaction = 0.58), but the ARRs were greater across increasing risk categories (0.5%, 0.8%, and 3.7%, respectively; *P*-interaction < 0.001).

Assessment of Chronic eGFR Slope and Treatment Effect of SGLT2 Inhibition According to Baseline Predicted Risk in DECLARE-TIMI 58

Supplementary Fig. 3 presents mean eGFR decline over the span of 4 years in the placebo group from DECLARE-TIMI 58 according to predicted risk of kidney disease progression. The mean chronic eGFR slope was steeper in higher-risk compared with lower-risk groups (−3.97 vs. −2.48 vs. −2.13 mL/min/1.73 m^2/year in the high-, intermediate-, and low-risk groups, respectively; $P < 0.001$ for each pairwise comparison). There was a slower decline in eGFR in patients treated with dapagliflozin versus placebo within every stratum of predicted baseline risk (Supplementary Fig. 4). The improvement in eGFR slope with dapagliflozin was +0.65, +0.43, and +0.33 mL/min/1.73 m^2/year in the high-, intermediate-, and low-risk groups, respectively.

CONCLUSIONS

We derived and validated a clinical risk model that predicts kidney disease

Table 2—TIMI risk score for kidney disease progression in type 2 diabetes

Domain	Risk indicator	Adjusted HR (95% CI)	*P* value
Cardiovascular disease	ASCVD (MI, stroke, or PAD)	1.62 (1.32–1.98)	<0.001
	Heart failure	1.68 (1.33–2.12)	<0.001
	SBP 140–159 mmHg	1.26 (1.02–1.56)	0.036
	SBP ≥160 mmHg	2.42 (1.85–3.17)	<0.001
Diabetes	Duration 5–10 years	1.16 (0.83–1.63)	0.383
	Duration >10 years	1.80 (1.35–2.42)	<0.001
	HbA_{1c} (per 1% higher)	1.10 (1.03–1.18)	0.004
Renal	eGFR 45–59 mL/min/1.73 m^2	1.43 (1.10–1.85)	0.007
	eGFR <45 mL/min/1.73 m^2	2.15 (1.64–2.81)	<0.001
	UACR (per 100 mg/g higher)	1.04 (1.04–1.04)	<0.001
	Hemoglobin (per 1 g/dL lower)	1.03 (1.03–1.04)	<0.001

HR, hazard ratio; MI, myocardial infarction; PAD, peripheral artery disease.

progression, defined as sustained ≥40% decline in eGFR, ESKD, or kidney death, in a large cohort of patients with T2D with a broad spectrum of kidney function across four contemporary clinical trials. The TIMI Risk Score for Kidney Disease Progression in Type 2 Diabetes (https://timi.org/timi-calculators/) had very good discrimination and calibration in the validation cohort and performed well in important subgroups, including those with and without eGFR <60 mL/min/1.73 m^2 as well as with and without albuminuria. The CKD Prognosis Consortium risk model for decline in kidney function also discriminates kidney disease progression in our clinical trial cohort population quite well. Uniquely, we also showed how risk prediction with these tools enabled identifying the magnitude of absolute clinical benefit from SGLT2 inhibition with dapagliflozin in patients with T2D.

The risk model leverages eight variables that are routinely used in the care of patients with T2D. Naturally, indicators related to kidney disease were relevant variables, including baseline eGFR and UACR, both of which are established strong indicators for kidney disease, and hemoglobin, likely reflecting the severity of baseline CKD. Baseline glycemia measured by HbA_{1c} and duration of diabetes were both independently associated with progression of kidney disease, likely representing the negative effects of longstanding diabetes on renal function. Notably, SBP ≥160 mmHg stood out as having one of the strongest associations with kidney disease progression. Lastly, the presence of vascular disease and heart failure were also independent predictors, reflecting the interdependence of these organ systems.

Currently, comprehensive care of patients with T2D at risk for CKD involves adequate control of glycemia, blood pressure, lipids, smoking cessation, promoting healthy lifestyle choices, appropriate referrals to kidney specialists, and initiation of medications that have consistently been shown to slow kidney disease progression such as SGLT2 inhibitors. Delivery of risk-based and personalized care requires both accurate risk prediction models and relevant absolute risk thresholds for clinical decision making. This is particularly important in an era where there is a sizeable and growing set of pharmacotherapeutic options to combat kidney disease, especially in patients with T2D, in whom there is high interpersonal variability in kidney disease risk (26).

Other kidney risk assessment tools have been published (13,14,18). However, there are a few key differences worth highlighting. First, our risk model was developed in a population of patients with T2D with less advanced kidney disease compared with other model derivation cohorts (27). Historically, eGFR and albuminuria have been regarded as the most important indicators of kidney disease progression. However, in a population without advanced kidney disease, as in the case of our own cohort where <10% of patients had UACR ≥300 mg/g or eGFR <45 mL/min/1.73 m^2, the discrimination of eGFR and albuminuria is reduced. More established risk models, such as the CKD Prognosis Consortium risk equation for incident CKD developed by Nelson et al. (13), although with potential for use in the general population, were developed to predict new-onset CKD (eGFR <60 mL/min/1.73 m^2) in patients with preserved renal function, a strategy that has limited applicability for risk stratification and therapy selection for patients with CKD or eGFR that approximates the eGFR threshold of 60 mL/min/1.73 m^2. This was demonstrated by the score's tendency to underestimate risk in our clinical trial population. Other risk models that have been more widely validated, such as the kidney failure risk equation (14), have focused on predicting kidney failure in patients with established CKD, which is a late and less common short- and intermediate-term outcome in patients without advanced CKD. Despite performing well in predicting kidney end points in our own cohort, these risk scores were not superior to the TIMI Risk Score for Kidney Disease Progression in Type 2 Diabetes. This is not surprising, considering that the kidney failure risk equation (14) and CKD Prognosis Consortium model for new-onset CKD (eGFR <60 mL/min/1.73 m^2) (13) were each developed to predict different end points (i.e., kidney failure and new-onset CKD, respectively) than our own model. However, the comparison was made in context of their wide recognition and the shift of focus to include changes in eGFR in defining kidney disease progression. Moreover, we found that the CKD Prognosis Consortium model for new-onset CKD also did well predicting ESKD.

Lastly, our focus on predicting broad and earlier outcomes is in line with the recent shift toward use of a sustained ≥40% eGFR decline as an accepted major surrogate end point of progression to kidney failure (17,20,28,29), allowing earlier recognition of risk and greater opportunity to slow the progression of kidney disease. The CKD Prognosis Consortium has recently developed and validated

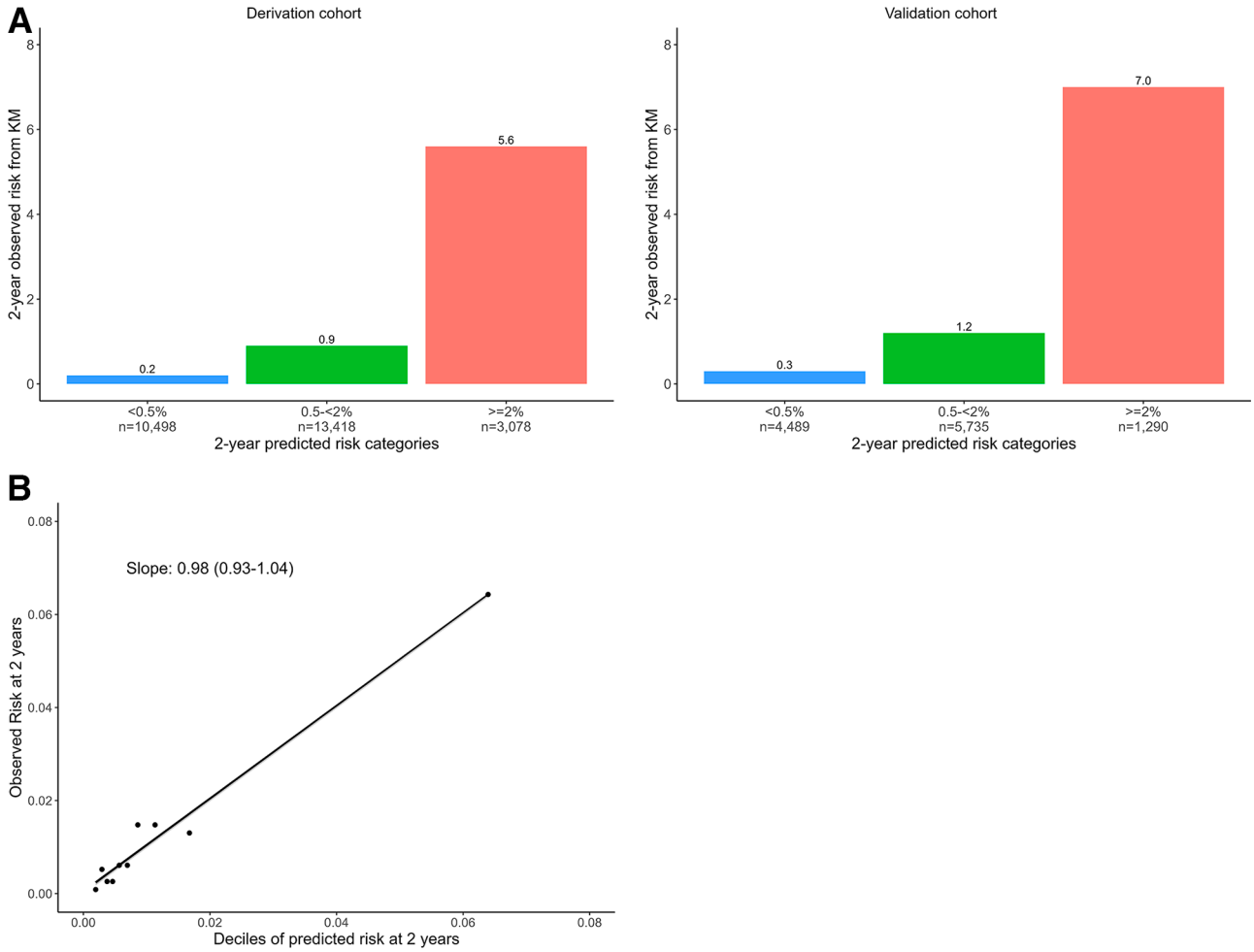

Figure 1—*A*: Cumulative incidence of kidney disease progression according to predicted 2-year risk categories. Risk categories displayed on the *x*-axis reflect TIMI Risk Score for Kidney Disease Progression in Type 2 Diabetes annual risk categories of <0.25%, 0.25% to <1%, and ≥1%, which when extended over 2 years are equivalent to <0.5%, 0.5% to <2%, and ≥2% 2-year predicted risk categories. The *y*-axis displays 2-year incidence of kidney disease progression events. Overall, the observed cumulative incidence fell within the appropriate predefined 2-year risk categories, indicating appropriate calibration of the risk model. KM, Kaplan-Meier. *B*: Calibration plot of observed vs. predicted risk of kidney disease progression in the validation cohort. Calibration was assessed in the validation cohort by comparing predicted 2-year risk with observed 2-year Kaplan-Meier cumulative incidence of kidney disease progression. The data points in the plot represent the observed risk for deciles of predicted risk. The dark line represents the least squares regression line through these 10 data points. The slope of the line with 95% CI reflects calibration of the model. The slope of 0.98 (95% CI, 0.93–1.04) indicates appropriate model calibration.

a prediction model for the composite of ≥40% eGFR decline or kidney failure (defined as kidney replacement therapy) in patients with and without T2D and stratified by presence of CKD (18). We add to this by requiring events of eGFR decline to be confirmed, which is a relevant distinction when using the risk score for tailoring drug therapies such as SGLT2 inhibitors and renin-angiotensin system inhibitors, which are known to cause transient declines in eGFR due to intraglomerular hemodynamic changes. Nonetheless, we further add to the literature by showing that the CKD Prognosis Consortium risk model (18) not only validates well as a risk stratification tool for a composite kidney end point that includes eGFR reduction of ≥40% that is sustained but also discriminates treatment heterogeneity with dapagliflozin. Overall, these data support the ability of risk prediction models for kidney disease progression to discriminate risk and the magnitude of treatment benefit.

As contemplated in existing guidelines and expert consensus pathways, particularly in T2D, there is ample room for tailoring kidney disease-modifying therapy, but these efforts are often guided by abnormalities of single parameters such as eGFR or albuminuria (30,31). Consequently, there may be a proportion of patients with higher risk but without overt abnormalities in these two indicators who may be identified with a multivariable risk stratification tool. Using the TIMI Risk Score for Kidney Disease Progression in Type 2 Diabetes, we demonstrate that there is a clear gradient of absolute risk reduction in progression of kidney disease with SGLT2 inhibition as a function of being able to detect those that have higher baseline risk. In addition, despite experiencing the greatest decline in eGFR over time in DECLARE, patients at the higher predicted risk category also experienced the greatest numerical attenuation of decline in eGFR slope with dapagliflozin. This is particularly helpful in addressing potential prescriber hesitancy in patients with more advanced CKD given clinicians' concern for acute reduction in eGFR with initiation of dapagliflozin, which is now

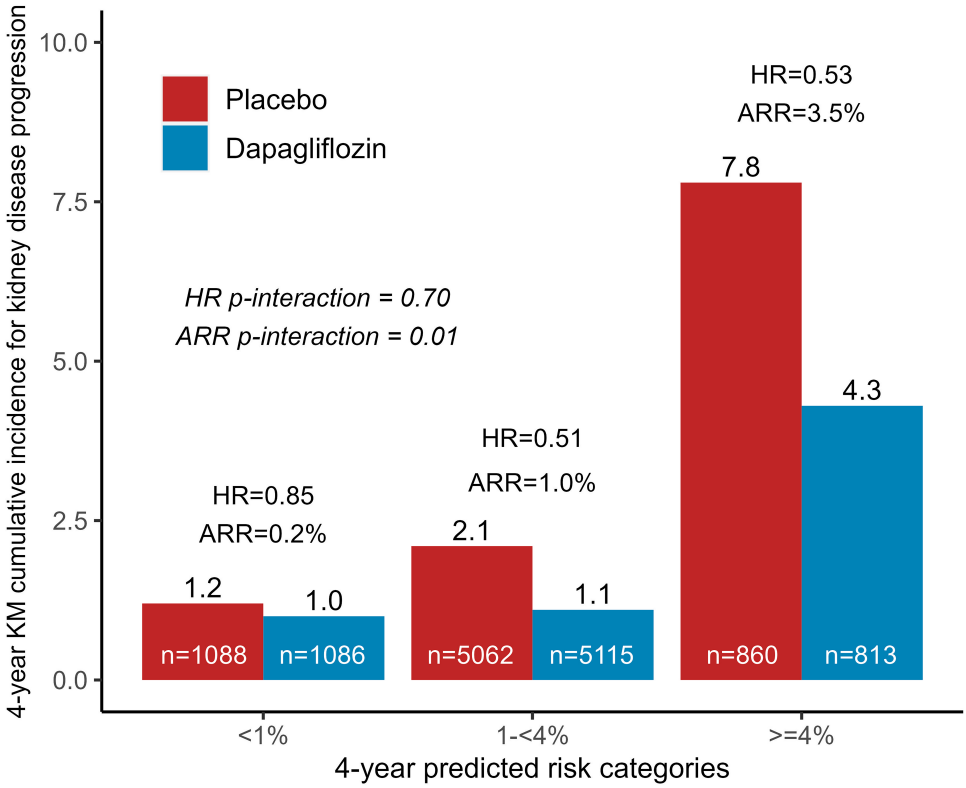

Figure 2—Treatment benefit of dapagliflozin by baseline risk of kidney disease progression. Risk categories displayed in the *x*-axis reflect TIMI Risk Score for Kidney Disease Progression in Type 2 Diabetes annual risk categories of <0.25%, 0.25% to <1%, and ≥1%, which when extended over 4 years are equivalent to <1%, 1% to <4%, and ≥4% 4-year predicted risk categories. To test for relative differences in the treatment effect of dapagliflozin vs. placebo in DECLARE-TIMI 58 according to baseline predicted risk, a randomized treatment-by-risk score interaction term was included as a covariate in the Cox model. ARR was calculated by subtracting the 4-year Kaplan-Meier (KM) event rates for kidney disease progression in patients treated with dapagliflozin from the 4-year Kaplan-Meier event rates in patients treated with placebo across risk categories. The ARR *P*-interaction was calculated as an ARR trend over the risk groups. There was greater absolute reduction in risk of kidney disease progression in patients with higher baseline predicted risk. HR, hazard ratio.

known to be related to acute glomerular hemodynamic changes rather than a true decline in kidney function (32).

There are limitations to this study. First, there are other known established biomarkers of kidney disease progression that were not measured, such as phosphate levels, cystatin C, and fibroblast growth factor 23. However, the objective of this study was to generate a clinical stratification tool that would be more widely implemented and thus based on readily accessible clinical markers used in routine management of patients with T2D.

Second, our risk model was developed in clinical trial patients, which may impact generalizability to nontrial cohorts. Nevertheless, the patients in these trials were chosen for their overall cardiovascular risk rather than their CKD risk, and, in fact, in comparison with other existing clinical trials, there is ample representation of patients with normal eGFR and normal or mildly increased albuminuria. Therefore, in cardiovascular trials in which albuminuria is traditionally used as an enrichment factor for cardiovascular outcomes, future use of the TIMI Risk Score for Kidney Disease Progression in Type 2 Diabetes would allow simultaneous enrichment for kidney outcomes in trials not traditionally designed to do so. An additional strength of developing this score in a clinical trial cohort is the protocol-driven measurement and confirmation of eGFR changes, which add to the fidelity of the end point of eGFR change.

Lastly, because the median follow-up time across the four trial cohorts was only 2.4 years and the decline in eGFR required confirmation with a subsequent scheduled blood draw, the primary time horizon for risk prediction was limited to 2 years. Nevertheless, the large number of events supported the development of a robust model, and the model performed very well when applied to 4-year risk prediction in DECLARE-TIMI 58.

Conclusion

Management of patients with T2D aimed at modifying kidney complications will benefit from accurate risk prediction and can align risk and therapeutic decision making while personalizing the care of these patients. Such an approach is highly appealing with the availability of established and a growing number of disease-modifying options to reduce the risk of kidney disease progression. Clinical risk models that help identify individuals at high risk of kidney disease progression might be used to tailor effective intervention to those who could benefit most.

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