# A Validated Prediction Model for End-Stage Kidney Disease in Type 1 Diabetes

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## OBJECTIVE

**End-stage kidney disease (ESKD) is a life-threatening complication of diabetes that can be prevented or delayed by intervention. Hence, early detection of people at increased risk is essential.**

## RESEARCH DESIGN AND METHODS

**From a population-based cohort of 5,460 clinically diagnosed Danish adults with type 1 diabetes followed from 2001 to 2016, we developed a prediction model for ESKD accounting for the competing risk of death. Poisson regression analysis was used to estimate the model on the basis of information routinely collected from clinical examinations. The effect of including an extended set of predictors (lipids, alcohol intake, etc.) was further evaluated, and potential interactions identified in a survival tree analysis were tested. The final model was externally validated in 9,175 adults from Denmark and Scotland.**

## RESULTS

**During a median follow-up of 10.4 years (interquartile limits 5.1; 14.7), 303 (5.5%) of the participants (mean [SD] age 42.3 [16.5] years) developed ESKD, and 764 (14.0%) died without having developed ESKD. The final ESKD prediction model included age, male sex, diabetes duration, estimated glomerular filtration rate, micro- and macroalbuminuria, systolic blood pressure, hemoglobin $A_{1c}$, smoking, and previous cardiovascular disease. Discrimination was excellent for 5-year risk of an ESKD event, with a C-statistic of 0.888 (95% CI 0.849; 0.927) in the derivation cohort and confirmed at 0.865 (0.811; 0.919) and 0.961 (0.940; 0.981) in the external validation cohorts from Denmark and Scotland, respectively.**

## CONCLUSIONS

**We have derived and validated a novel, high-performing ESKD prediction model for risk stratification in the adult type 1 diabetes population. This model may improve clinical decision making and potentially guide early intervention.**


The observed incidence of end-stage kidney disease (ESKD) in people with type 1 diabetes has stabilized (1) or decreased over the past decades (2–4), probably in relation to the increased use of renin-angiotensin system (RAS) blockers. However, the decline in ESKD risk has been substantially lower compared with other common diabetes-related complications, such as cardiovascular disease (CVD) (1,5), and ESKD still remains a life-threatening complication (6) with a 10-fold increase in mortality rate in type 1 diabetes (3).

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Fortunately, ESKD can be prevented or delayed by intensive glucose- and blood pressure–lowering therapy (7), and early detection is therefore essential. ESKD often develops in people with complicated and poorly controlled type 1 diabetes (6). This group also faces a high degree of pre-ESKD death, especially in older age (3). Because death precludes the occurrence of ESKD, a person's risk of developing ESKD also depends on overall mortality risk. Not considering the "competing" risk of death is likely to overestimate the absolute risk of ESKD (8,9). Because the decision to initiate ESKD preventive treatment is often based on the absolute risk of developing ESKD, it is essential to estimate individual ESKD risk accurately.

Prediction models for ESKD in diabetes are scarce. Except for one study that used a composite outcome of end-stage renal failure, coronary heart disease, stroke, amputation, blindness, and death (10) and one study that predicted renal function decline (2), there are, to our knowledge, no ESKD risk models developed for the type 1 diabetes population. Three prediction models have been developed for cohorts of people with type 2 diabetes: one in New Zealand (11) and two in Chinese adults (12,13). Type 1 diabetes differs from type 2 diabetes in that people with type 1 diabetes are generally diagnosed at younger ages and therefore exposed to diabetes-related risk factors for ESKD, such as hyperglycemia and hypertension, for a longer time. Furthermore, while increased blood pressure, chronic kidney disease (CKD), and smoking appear to be risk factors for ESKD in both types of diabetes, obesity seems to play a larger role in type 2 diabetes (14), whereas age at diabetes diagnosis is mainly a risk factor in type 1 diabetes (3,14,15). This suggests a difference in the pathophysiology of ESKD for type 1 and type 2 diabetes, and prediction models specific to the type 1 diabetes population are needed.

Change in estimated glomerular filtration rate (eGFR) is a predictor of ESKD in diabetes (2), and the Kidney Disease Outcomes Quality Initiative clinical practice guidelines for diabetes and CKD suggest monitoring the rate of decline in eGFR to predict the time to onset of kidney failure (16). However, information on prior eGFR trajectory in people with type 1 diabetes requires continuous monitoring of eGFR, which is not widely feasible. Hence, the ability to assess ESKD risk in type 1 diabetes on the basis of current levels of risk factors is needed.

The aim of this study was to develop a risk prediction model for ESKD accounting for the competing risk of death, using a large population-representative cohort of adults with type 1 diabetes with an extensive range of clinical data and information on ESKD events and mortality from national registers. We externally validated the model in national and international cohorts to assess its broader generalizability.

## RESEARCH DESIGN AND METHODS

### Study Design and Participants

The study is based on a large population-based cohort of 5,506 adults with type 1 diabetes treated at the outpatient clinic at Steno Diabetes Center Copenhagen (SDCC) in the period from 1 January 2001 to 31 December 2016. In Denmark, treatment of people with type 1 diabetes is based in tertiary care, and referral to specialist care is free of charge. The type 1 diabetes population at SDCC includes the entire adult age span with both newly diagnosed and long-term diabetes, reflecting the background population with type 1 diabetes within this region. Individuals were followed from the date of their first clinical examination with a measurement of serum creatinine until first event of ESKD, death, emigration, or censor date of 31 December 2016 (date of register extraction).

To ensure exclusion of extreme values of metabolic risk factors, such as hemoglobin $A_{1c}$ ($HbA_{1c}$) and lipids often present at the time of diagnosis, clinical examinations within the 1st year of diabetes diagnosis were excluded from the analyses. We further excluded people with prevalent ESKD at their first clinical examination ($n = 46$ [0.8%]), leaving 5,460 people with type 1 diabetes with a total of 42,921 clinical examinations for analysis.

According to Danish law, ethics approval and participant consent are not required for registry-based studies. Access and use of the described data were approved by the Danish Data Protection Agency (j-No. VD-2019-197) and the Danish Patient Safety Authority (j-No. 3-3013-2959/1).

### Measurements and Definitions

Detailed clinical data of the participants were collected from the electronic health records at SDCC and linked to nationwide registries on mortality and morbidity, including ESKD (17,18), using the unique personal identification number given to all Danish residents at birth or at immigration (19). To separate type 1 from type 2 diabetes, type 1 diabetes was clinically diagnosed on the basis of phenotype and in accordance with the Danish National Diabetes Quality Database requirements (20). Participants were classified with type 1 diabetes if age at diagnosis was <30 years in combination with insulin treatment at diagnosis or if age at diagnosis was ≥30 years with randomly obtained nonfasting low C-peptide values (according to laboratory-specific reference values) or GAD65 antibody positivity, both in combination with a need for insulin to control blood glucose levels.

Electronic health data on all clinical visits with a measurement of serum creatinine were extracted together with the corresponding clinical and behavioral data. Detailed information on how measurements were obtained have been reported previously (21,22).

Albuminuria was classified from 24-h sterile urine collections (mg/24 h) or spot urine (mg/g) into normoalbuminuria (<30), microalbuminuria (30–299), or macroalbuminuria (≥300). We categorized smoking status into current smoking (yes/no), physical activity into regular physical activity defined as ≥30 min/day (yes/no), alcohol intake in three classes (0, 1–20, and >20 units/week), use of antihypertensive treatment (yes/no), lipid-lowering treatment (yes/no), and RAS-blocking treatment (yes/no). Retinopathy status was assessed from retinal photographs (no retinopathy, mild/moderate retinopathy, or severe retinopathy). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (23).

Previous CVD was defined as any previous event of ischemic heart disease, ischemic stroke, heart failure, and peripheral artery disease as previously defined (22). We defined ESKD as a composite event of CKD stage 5 (ICD-10 code DN185), dialysis (procedure code BJFD), kidney transplantation (procedure code KKAS), or an eGFR <15 mL/min/1.73 $m^2$. ESKD event data were obtained

from the Danish National Patient Register (18). Data on date and cause of death were collected from the Cause of Death Register (17). Death without having developed ESKD was defined as non-ESKD–related mortality. Data on ethnicity were obtained from the Central Person Register (19), and ethnicity in the current study was defined as geographical region of origin (Europe, Middle East, or other). The registers are nationwide and cover all Danish residents.

### Statistical Analysis

To account for the competing risk of death, cause-specific rate models for ESKD and death were estimated and then combined into a model for cumulative ESKD. We first developed a core model from commonly measured factors, including age, sex, diabetes duration, eGFR, albuminuria status, systolic and diastolic blood pressure, $HbA_{1c}$, smoking, and previous CVD, and an extended model that further included RAS-blocking treatment, other antihypertensive treatment, lipid-lowering treatment, BMI, ethnicity, retinopathy, total and HDL cholesterol, LDL cholesterol, triglycerides, hemoglobin, alcohol intake, regular exercise, height, urinary albumin-to-creatinine ratio (UACR), potassium, sodium, and thyroid-stimulating hormone (TSH). Predefined interactions between clinical measurements and treatment, as well as other interactions between predictors identified in a prior conditional survival tree analysis, were included in both models. A survival tree analysis is a hypothesis-free data-driven approach and can be used to investigate potential high-level interactions between predictors for a specific outcome (24). In a subset of 4,815 (88%) participants with at least two clinical examinations, we further tested the effect of including eGFR annual change before baseline in the core model.

The cause-specific rate models for ESKD and death were estimated separately using Poisson models, with log of risk time as offset and censoring for the other event. For each participant, the follow-up period was split into 1-year age bands to account for the nonconstant effect of age over time on risk of ESKD and mortality (25) and then additionally split at the time points of repeated clinical measurements during follow-up. At each time interval, the most recent values of the predictors were used, and age and diabetes duration were updated. Before analysis, predictors with a highly skewed distribution were $\log_2$ transformed to improve model calibration. Backward elimination was used to test the predictors and interactions. The level of statistical significance was set at 5%. Postestimation shrinkage factors for the predictors were estimated in all the cause-specific rate models (26). Finally, the cumulative incidence of ESKD within a given time period for each person was calculated using the conditional survival function (8), which is based on both the estimated rate for ESKD and the estimated rate for death (see Supplementary Material for statistical details).

The discriminatory power of the models was evaluated using the C-statistic (27), with the CI computed from the DeLong method (28). In addition, model calibration was determined with the Hosmer-Lemeshow test of goodness of fit (29) by comparing means of estimated cumulative ESKD risk with the corresponding observed incidence in deciles of estimated risk.

For most covariates, $<5\%$ of the values were missing. However, for lipids, 13–16% of data were missing, and 26% were missing for TSH. To avoid exclusion of participants with missing values on the covariates, which may infer biased results (30), analyses where performed in 50 imputed data sets using multivariate imputations by chained equations method (31) with a missing-at-random assumption. Estimates of parameters of interest were summarized across the imputation copies according to Rubin rules (32).

### Validation

The cumulative incidence functions for ESKD with the original regression coefficients in both the core and the extended models were internally validated using the first clinical examination of the derivation cohort. The cumulative incidence function for ESKD with both the original and the shrunken regression coefficients for the core model was externally validated nationally in the type 1 diabetes population of the Danish Funen Diabetes Database (FDDB) (33) and internationally in the Scottish Diabetes Research Network Type 1 Bioresource (SDRNT1BIO) (2). The validation cohorts did not have the required data available for validation of the extended model.

In FDDB, where we had access to baseline eGFR, discrimination and model calibrations for a 5- and 10-year ESKD event among participants with eGFR $\geq$60 mL/min/1.73 $m^2$ at baseline was also calculated. This subgroup constituted 91% of the FDDB study participants but accounted for only 41% and 46% of the ESKD events after 5 and 10 years of follow-up, respectively. Statistical analyses were performed using R 3.6.1 software (R Foundation for Statistical Computing, https://www.r-project.org).

## RESULTS

The derivation cohort was mainly (91%) of European origin. Baseline characteristics are given in Table 1. At baseline, 7% had CKD stage 3 or 4, and 37% developed ESKD during follow-up. The majority of the ESKD cases were among participants with an eGFR $\geq$60 mL/min/1.73 $m^2$ (Supplementary Table 1). This group was characterized by a high degree of micro- or macroalbuminuria (45% vs. 19% in the total cohort). Participants were followed for a median of 10.4 years (interquartile limits 5.1; 14.7), during which 303 (5.5%) developed ESKD and 764 (14.0%) died as a result of non-ESKD–related causes without having developed ESKD. The incidence rate of ESKD was 5.7 per 1,000 person-years.

The final core model for cumulative risk of ESKD included age, sex, diabetes duration, eGFR, micro- and macroalbuminuria, systolic blood pressure, $HbA_{1c}$, smoking, and previous CVD. Older age was associated with a lower rate of ESKD but with a higher rate of mortality. For the remaining predictors, more unfavorable levels were associated with higher rates of both ESKD and death (Table 2). In the extended model, increasing levels of hemoglobin and mild/moderate retinopathy were associated with a higher rate of ESKD but a lower rate of death. Higher levels of UACR were further associated with a higher risk of ESKD and death. BMI, triglycerides, regular exercise, and sodium were associated with the rate of mortality and thereby indirectly associated with the cumulative risk of ESKD (Supplementary Table 2). Overall, the results of the survival tree analyses were consistent with the difference in baseline characteristics between individuals who did and did not develop ESKD (Supplementary Table 1 and Supplementary Figs. 1–4).

**Table 1—Characteristics of the study populations at their first clinical examination in the derivation and validation cohorts**

| | Derivation cohort | Validation cohorts | |
|---|---|---|---|
| | SDCC | FDDB | SDRNT1BIO |
| Participants, *n* | 5,460 | 3,150 | 6,025 |
| Follow-up time (years) | 10.4 (5.1; 14.7) | 10.7 (5.8; 13.6) | 6.9 (6.2; 7.4) |
| Region of origin | | | |
| Europe | 91.3 | — | — |
| Middle East | 6.1 | — | — |
| Other | 2.6 | — | — |
| Age (years) | 42.3 (16.5) | 42.8 (16.7) | 45.1 (15.0) |
| Male | 54.1 | 57.8 | 56.1 |
| Age at diabetes diagnosis (years) | 21.0 (12.2; 33.8) | 26.1 (14.3; 40.4) | 21.6 (12.1; 32.2) |
| Diabetes duration (years) | 15.6 (6.6; 27.4) | 10.9 (2.5; 21.9) | 20.3 (11.0; 30.9) |
| $HbA_{1c}$ (mmol/mol) | 69.4 (16.7) | 67.0 (18.8) | 71.1 (17.0) |
| $HbA_{1c}$ (%) | 8.5 (1.5) | 8.3 (1.7) | 8.7 (2.0) |
| BMI (kg/m$^2$) | 24.7 (3.7) | 25.2 (4.3) | 27.1 (5.0) |
| UACR (mg/g) | 8.0 (4.0; 19.0) | 10.6 (4.5; 26.8) | 8.8 (5.1; 25.7) |
| Albuminuria | | | |
| Normal | 81.0 | 76.8 | 83.1 |
| Micro | 13.0 | 19.9 | 12.6 |
| Macro | 6.0 | 3.4 | 4.3 |
| Serum creatinine (μmol/L) | 82.0 (69.0; 93.0) | — | — |
| eGFR (mL/min/1.73 m$^2$) | 99.8 (84.3; 114.6) | 89.5 (75.1; 104.2) | 100.0 (84.3; 111.4) |
| eGFR categories (mL/min/1.73 m$^2$) | | | |
| eGFR ≥90 | 66.6 | 49.3 | — |
| 60 ≤ eGFR < 90 | 26.3 | 41.8 | — |
| 30 ≤ eGFR < 60 | 6.0 | 8.1 | — |
| 15 ≤ eGFR < 30 | 1.1 | 0.8 | — |
| Hemoglobin (mmol/L) | 8.7 (0.8) | — | — |
| Potassium (mmol/L) | 4.0 (0.4) | — | — |
| Sodium (mmol/L) | 138.8 (3.0) | — | — |
| TSH ($\times 10^{-3}$ IU/L) | 1.5 (0.9; 2.2) | — | — |
| Systolic blood pressure (mmHg) | 132.1 (19.2) | 130.9 (18.3) | 130.8 (16.0) |
| Diastolic blood pressure (mmHg) | 78.0 (10.0) | 77.7 (10.5) | 75.4 (10.0) |
| Total cholesterol (mmol/L) | 4.9 (1.0) | 4.9 (1.0) | — |
| HDL cholesterol (mmol/L) | 1.6 (0.5) | 1.7 (0.5) | 1.5 (0.5) |
| LDL cholesterol (mmol/L) | 2.7 (0.9) | 2.7 (0.9) | 2.5 (1.0) |
| Triglycerides (mmol/L) | 1.0 (0.7; 1.5) | 1.0 (0.7; 1.5) | 1.1 (0.8; 1.7) |
| RAS blockers | 21.6 | 8.9 | 37.3 |
| Other antihypertensive treatment | 26.9 | 7.1 | 28.1 |
| Lipid-lowering medication | 10.4 | 9.3 | 52.1 |
| Retinopathy status | | | |
| None apparent | 46.3 | 50.1 | 38.5 |
| Mild/moderate | 22.0 | 32.5 | 34.9 |
| Severe | 31.7 | 17.5 | 26.6 |
| Current smoking | 51.3 | 27.1 | 21.9 |
| Alcohol intake# | | | |
| 0 units/week | 14.5 | — | 15.2 |
| 1–20 units/week | 80.6 | — | 71.9 |
| >20 units/week | 4.8 | — | 12.8 |
| Regular exercise† | 69.1 | 56.7 | 40.0 |
| Previous CVD | 8.9 | 9.4 | 6.8 |

Data are mean (SD), median (interquartile limits), or % unless otherwise indicated. #One unit alcohol = 12 g of pure alcohol. †Regular exercise: ≥30 min/day.

The estimated impact of calendar time was small (<2% difference in incidence rate per calendar year) and was not statistically significant ($P \geq 0.241$ for ESKD, $P \geq 0.066$ for death). Hence, calendar time was not included.

The core model showed excellent and robust discrimination, with C-statistics of ≥0.872 over the 10 years of follow-up in the derivation data. Model calibration was good for up to 5 years. The extended model had slightly better performance, with C-statistics of ≥0.883 and good calibration for up to 6 years (Fig. 1 and Supplementary Table 3). Details on the estimated model parameters with and without postestimation shrinkage and how to apply them in the cumulative risk model are given in Supplementary Tables 4 and 5.

In the sensitivity analysis, prebaseline change in eGFR in the core model had little effect, with an incidence rate ratio <1% for a 10-unit difference in eGFR change ($P = 0.078$). Also, discrimination for a 5- and 10-year ESKD event was not improved ($P \geq 0.290$), and model calibration was unchanged.

### Validation

The Danish FDDB cohort of 3,150 adults was followed between 1 January 2003 and 31 December 2016 and was representative of the type 1 diabetes population in that region. The participants were, on average, 5 years older at diabetes diagnosis; macroalbuminuria and severe retinopathy were less frequent; and current smoking was around one-half of that in the derivation cohort (Table 1). Median (interquartile limits) years of follow-up were 10.7 (5.8; 13.6), during which 147 (4.7%) participants developed ESKD and 422 (13.3%) died as a result of non-ESKD causes, corresponding to an incidence rate of ESKD of 4.9 per 1,000 person-years. The core model without shrinkage of the parameters performed best. Discrimination was excellent and robust over time, with a C-statistic of 0.871 for an ESKD event within 5 years and 0.866 for an event within 10 years. Model calibration was good for up to 5–6 years of follow-up (Fig. 1 and Supplementary Table 3). In the subgroup with baseline eGFR ≥60 mL/min/1.73 m$^2$, the C-statistics were 0.744 (95% CI 0.641; 0.847) and 0.775 (0.711; 0.840) for a 5- and 10-year ESKD event, respectively. Model calibration was adequate ($P \geq 0.097$).

The SDRNT1BIO cohort of 6,025 adults was followed between 1 January 2011 and 31 December 2018 and was representative of the type 1 diabetes population in Scotland. The SDRNT1BIO population was slighter older and with ~5 years longer diabetes duration at baseline. The majority (89%) was of White

**Table 2—Incidence rate ratios (IRR) for predictors of ESKD and death: core model**

| | ESKD | | Non-ESKD death | |
|---|---|---|---|---|
| | IRR (95% CI) | *P* value | IRR (95% CI) | *P* value |
| Age (10 years) | 0.83 (0.75; 0.92) | <0.001 | — | |
| Male sex (vs. female sex) | 1.40 (1.11; 1.78) | 0.005 | 5.47 (2.58; 11.61) | <0.001 |
| Diabetes duration (10 years) | 1.13 (1.02; 1.25) | 0.022 | 1.11 (1.05; 1.16) | <0.001 |
| eGFR (halving) | 8.15 (6.88; 9.65) | <0.001 | 1.28 (1.11; 1.49) | <0.001 |
| Microalbuminuria (vs. normoalbuminuria) | 1.09 (0.76; 1.55) | 0.643 | 1.64 (1.39; 1.94) | <0.001 |
| Macroalbuminuria (vs. normoalbuminuria) | 1.89 (1.32; 2.70) | <0.001 | 2.39 (1.88; 3.02) | <0.001 |
| Systolic blood pressure (10 mmHg) | 1.08 (1.03; 1.14) | 0.004 | 0.90 (0.86; 0.93) | <0.001 |
| $HbA_{1c}$ (10 mmol/mol) | 1.12 (1.03; 1.20) | 0.005 | 1.10 (1.04; 1.15) | <0.001 |
| Smoking (vs. no smoking) | 1.27 (1.00; 1.62) | 0.048 | 1.88 (1.63; 2.18) | <0.001 |
| Previous CVD event (vs. no) | 1.35 (1.05; 1.74) | 0.019 | 1.93 (1.65; 2.25) | <0.001 |
| Age (10 years), women | — | | 2.37 (2.18; 2.59) | <0.001 |
| Age (10 years), men | — | | 1.92 (1.78; 2.07) | <0.001 |

ethnicity. Like the FDDB population, this cohort had less macroalbuminuria and severe retinopathy, and the prevalence of current smoking was around one-half of that in the derivation cohort. The SDRNT1BIO population had almost twice as many using RAS-blocking agents and five times as many using lipid-lowering medications (Table 1). Median (interquartile limits) follow-up was 6.9 (6.2; 7.4) years, during which 95 (1.6%) participants developed ESKD and 321 (5.3%) died as a result of non-ESKD causes, corresponding to an incidence rate of ESKD of 2.4 per 1,000 person-years (Table 1). The performance of the core model was similar with and without shrinkage of the parameters. For the model without shrinkage, discrimination was excellent and robust, with a C-statistic of 0.961 for an ESKD event within 5 years and 0.952 for an event within 8 years (the maximum follow-up time). Calibration was only borderline acceptable in the first 4–5 years for the core model (Fig. 1 and Supplementary Table 3).

## CONCLUSIONS

We have derived and validated a high-performing model for predicting individual risk of ESKD in the adult type 1 diabetes population on the basis of predictors routinely collected in the clinic. An extension of the model to include less frequently measured factors did not substantially improve prediction, suggesting that the more parsimonious core model, which is more feasible in a clinical setting, is preferable for assessing individual 5-year ESKD risk in people with type 1 diabetes.

The ESKD cumulative incidence rates in the Danish derivation and validation cohorts were twice that of the validation cohort from Scotland and considerably higher than previously reported in Sweden and Finland (3,34). The annual incidence rates in the derivation cohort only decreased slightly over the 2001–2016 follow-up period. The referral criteria for people with type 1 diabetes are comparable in Denmark and Scotland, and the selection criteria for the cohorts were similar, except the Scottish cohort did not include people diagnosed with type 1 diabetes after age 50 years. A possible explanation for the difference in ESKD risk could be the more aggressive treatment with RAS blockers and a lower prevalence of smoking in Scotland.

The predictors included in the core model have previously been found to be associated with ESKD (2–4,15). However, no studies have combined them into a model for predicting individual risk of ESKD in type 1 diabetes. Only one model for ESKD has been developed in a population-representative type 2 diabetes cohort of mainly White ethnicity (11). When applied to our type 1 diabetes population, we found discrimination to be adequate for a 5-year ESKD event (C-statistic 0.790 [95% CI 0.688; 0.893]), but calibration was poor ($P < 0.001$).

Male sex was associated with an increased risk of ESKD in our model, which is in line with previous studies (3,15). A study from New Zealand found male sex to be associated with a decreased risk of ESKD but not when including eGFR in the model (11). The finding in a Swedish study of no risk difference in men and women diagnosed before puberty (34) was not supported by the survival tree analysis in our study, where no interaction between sex and age and diabetes duration was found.

Although, ESKD is more frequent in old age (4,15), the rate of ESKD decreased with age in our model. This is likely due to a healthy survivor effect driven by the strong association between age and mortality. In other words, old age seems to be a protective factor in ESKD because older people die before they develop ESKD. This finding is in line with another competing risk analysis of ESKD risk in people with type 1 diabetes who have macroalbuminuria and CKD stages 1–3 (15).

RAS-blocking agents and other antihypertensive treatment did not improve the models, which may be because of the association being mediated through an improvement in albuminuria and blood pressure. A similar result was found in 1,000 people with type 1 diabetes followed for 25 years in the U.S. where the association of antihypertensive medication with ESKD was lost when eGFR was included in the model (4). The same was found in a Caucasian type 1 diabetes population with macroalbuminuria and CKD stages 1–3 (15).

Some studies have shown a decline in ESKD incidence over time (3,4). However, calendar time was not associated with ESKD in our model, indicating that any observed decline in ESKD over the years is reflected in the change in risk factor

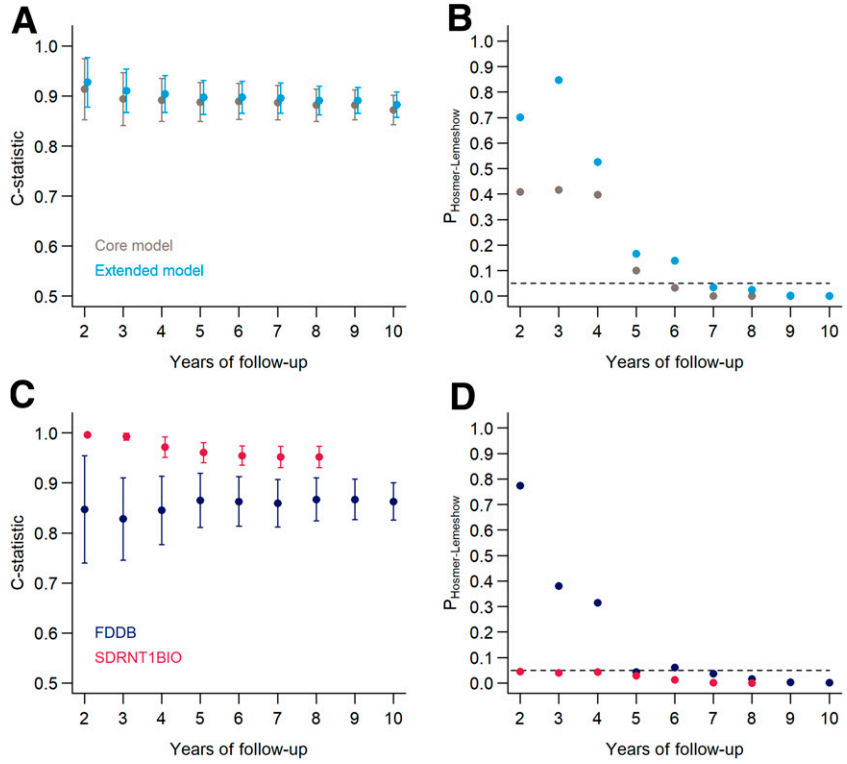


**Figure 1**—C-statistics for an ESKD event within years of follow-up time in the derivation (*A*) and validation (*C*) cohorts and *P* values for test of adequate model fit in the derivation (*B*) and validation (*D*) cohorts. The dotted lines in *B* and *C* denote the threshold for acceptable model calibration (acceptable above the dotted line).

levels (35). This is supported by the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) from the U.S. where an observed decline in incidence of ESKD over time was explained by improvements in glycemic and blood pressure control (4).

Our core model is adequate for assessing 5-year risk of ESKD, but predictions beyond this are questionable. Previous models have also been primarily assessed for 5-year risk of ESKD (11,13), although one model in type 2 diabetes was well calibrated up to 8 years of follow-up (12).

### Strengths and Limitations

We had access to detailed data from repeated clinical examinations for the study participants, which allowed us to update the values of the predictors during follow-up to give a more correct estimate of the associations between the predictors and the event. In addition, missing data were imputed, thereby removing selection bias.

The derivation cohort was mainly of White ethnicity, which may explain why ethnicity was not predictive in the models, and further validation in populations of non-White ethnicity is needed. Our models were developed on the basis of data collected at a single clinical examination. Although recent studies have found historical measures of eGFR to improve prediction of future eGFR levels in type 1 diabetes (2) and ESKD in the general population (36), prebaseline change in eGFR in addition to baseline eGFR level did not improve prediction of future ESKD in our study.

In the future, prediction models for ESKD may also benefit from the inclusion of novel biomarkers or various omics data. However, such biomarkers, which are not used or collected routinely in clinical practice (37), have yet to prove predictive beyond that of clinical data (38).

### Clinical Perspective

Although age-specific prevalence and incidence of ESKD have been stable since 2006 in Denmark (1), the actual number of people with type 1 diabetes who develop ESKD is increasing because of the general aging of the population. Mortality is still 70% higher in type 1 compared with type 2 diabetes (39), and quality measures of diabetes care in Denmark indicate a less aggressive approach to managing cardiovascular risk factors in type 1 diabetes (40). Early treatment could prevent or at least postpone the development of ESKD and thereby reduce treatment expenses and increase quality of life.

Our prediction model was developed for the entire range of eGFR not within the ESKD diagnostic range. Although people with CKD stage 3 and 4 are likely already managed as a high-risk group, not all will develop ESKD. In contrast, the majority of the ESKD events occur among people considered at low risk with a baseline eGFR $\geq$60 mL/min/1.73 m$^2$. Our model also performed well in this subpopulation, and we believe that ESKD risk assessment is relevant at all levels of eGFR.

In conclusion, we have derived and validated a novel, high-performing ESKD prediction model for risk stratification in the adult type 1 diabetes population. This model may improve clinical decision making and potentially guide early intervention.

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**Author Contributions**. D.V. and G.S.A. analyzed the data. D.V., F.P., P.R., and M.E.J. conceived of the study concept and design. All authors took part in the interpretation of the results, commented on the manuscript, and had final responsibility for the decision to submit for publication. D.V. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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