



Østergaard, H. B. et al. (2022) Development and validation of a lifetime risk model for kidney failure and treatment benefit in type 2 diabetes: 10-year and lifetime risk prediction models. *Clinical Journal of the American Society of Nephrology*, (doi: 10.2215/CJN.05020422).

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Deposited on: 11 October 2022

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1 **Title page**

2 **Development and validation of a lifetime-risk model for kidney failure and estimation of**
3 **treatment benefit in type 2 diabetes**

4 **Subtitle:** *10-year and lifetime risk prediction model*

5 **Running title:** *Prediction of kidney failure in type 2 diabetes*

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7 Word count abstract: 280 words

8 Word count text: 3,369 words

9 Number of tables and figures: 5

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1 **Abstract**

2 **Background and objectives**

3 Individuals with type 2 diabetes are at higher risk of developing kidney failure. The objective
4 of this study was to develop and validate a decision support tool for estimating 10-year and
5 lifetime risk of kidney failure in individuals with type 2 diabetes as well as estimating
6 individual treatment effects of preventive medication.

7 **Design, setting, participants, and measurements**

8 The prediction algorithm was developed in 707,077 individuals with prevalent and incident
9 type 2 diabetes from the Swedish National Diabetes Register (NDR) for 2002-2019. Two Cox
10 proportional regression functions for kidney failure (first occurrence of either kidney
11 transplantation, long-term dialysis or persistent estimated glomerular filtration rate <15
12 ml/min/1.73m²) and all-cause mortality as respective endpoints were developed using
13 routinely available predictors. These functions were combined into life-tables to calculate
14 predicted survival without kidney failure, while using all-cause mortality as competing
15 outcome. The model was externally validated in 256,265 individuals with incident type 2
16 diabetes from the Scottish Care Information (SCI)-Diabetes database between 2004 and 2019.

17 **Results**

18 During a median follow-up of 6.8 years (IQR 3.2-10.6), 8,004 (1.1%) of individuals with type
19 2 diabetes in the Swedish NDR cohort developed kidney failure and 202,078 (29%) died. The
20 model performed well with a c-statistic for kidney failure of 0.891 (95%CI 0.881-0.899) for
21 internal validation and 0.741 (95%CI 0.726-0.756) for external validation. Calibration plots
22 showed good agreement in observed vs. predicted 10-year risk of kidney failure for both
23 internal and external validation.

24 **Conclusions**

1 This study derived and externally validated a prediction tool for estimating 10-year and
2 lifetime risk of kidney failure as well as life-years free of kidney failure gained with
3 preventive treatment in individuals with type 2 diabetes using easily available clinical
4 predictors.

5

6 **Introduction**

7 Worldwide, the prevalence of type 2 diabetes is rapidly increasing(1). Individuals with type 2
8 diabetes have three to five times higher risk of developing kidney failure compared with
9 individuals without type 2 diabetes(2). Treatment options to prevent or delay kidney failure in
10 individuals with type 2 diabetes include smoking cessation(3), intensive glucose- and blood
11 pressure (BP)-lowering(4, 5), treatment with angiotensin-converting enzyme-inhibitors
12 (ACEi) or Angiotensin-II Receptor Blockers (ARB)(6), sodium-glucose cotransporter-2
13 inhibitors (SGLT2i)(7) and glucagon-like peptide-1 receptor agonists (GLP1-RA)(7). The
14 absolute benefit an individual may derive in terms of kidney failure risk reduction from these
15 treatments depends on several different factors including risk factor burden, duration of
16 treatment and overall life expectancy.

17

18 Few prediction models exist for kidney failure in individuals with type 2 diabetes(8-11).
19 These models have important limitations since they predict risk over a relatively short time
20 period and often predict intermediate outcomes such as doubling of serum creatinine(8),
21 which might be less relatable to an individual than kidney failure as a hard outcome. Notably,
22 shared risk factors associated with kidney failure also contribute to a high cardiovascular
23 disease and mortality risk (12). Therefore it is crucial to take all-cause mortality into account
24 as a competing risk to avoid overestimation of kidney failure risk, since most individuals with
25 type 2 diabetes will die from other causes before developing kidney failure. These gaps

1 highlight the need to develop prediction models for long-term risk of kidney failure in
2 individuals with type 2 diabetes.

3
4 Therefore, the aim of the current study was to develop and validate a prediction model for risk
5 of kidney failure in large population-based cohorts of individuals with type 2 diabetes.
6 Further, we aimed to predict life expectancy free of kidney failure and include treatment
7 effects of preventive therapy.

8

9 **Methods**

10 Data sources and participants

11 The prediction model was developed and internally validated in the Swedish National Diabetes
12 Register (NDR) (n = 707,077), which includes individuals with both incident and prevalent
13 type 2 diabetes. Participants in NDR were included from January 1st 2002 until 25th
14 September 2019.

15 The model was externally validated in an extract of the Scottish Care Information (SCI)-
16 Diabetes database (n = 256,265), which includes individuals with incident type 2 diabetes.
17 Participants from SCI-Diabetes were included if their date of diagnosis of diabetes was between
18 January 1st 2004 and January 1st 2019. Both registers have close to complete coverage of the
19 population with a diagnosis of type 2 diabetes during the study period. Register details for both
20 cohorts have been described elsewhere(13, 14). All participants were aged >30 years at cohort
21 entry with a diagnosis of type 2 diabetes (*table S1*) without kidney failure at baseline. All use of
22 data from these registers received appropriate local data governance approvals and all studies
23 complied with the Declaration of Helsinki.

24

25 Predictor and outcome variables

1 Kidney failure was defined as chronic kidney disease (CKD) stage 5 (sustained estimated
2 glomerular filtration rate (eGFR) $<15\text{ml}/\text{min}/1.73\text{ m}^2$), long-term dialysis or kidney
3 transplantation(15), and all-cause mortality was defined as death from any cause. Linkage of
4 the NDR and SCI-Diabetes to national death registrations and hospital admission/discharge
5 registries enabled the identification of kidney failure using ICD-10 and procedure codes (*table*
6 *S2*).

7 Predictors were pre-selected based on existing risk scores for kidney failure(9-11) and their
8 availability in clinical practice. Pre-selection of variables was applied to prevent overfitting(16).
9 The predictors included age, sex (male/female), current smoking (yes/no), systolic BP, body
10 mass index (BMI), Hemoglobin A1c, eGFR(17), non-high-density lipoprotein (HDL)
11 cholesterol, albuminuria (none/moderate/severe), duration of type 2 diabetes (years since
12 diagnosis), insulin treatment (yes/no) and history of cardiovascular disease (yes/no) (*table S1*).
13 Non-HDL-cholesterol was chosen as single marker to represent lipid profile(18). Albuminuria
14 was defined as a urine-albumin/creatinine ratio (UACR) of 3-30 mg/mmol for moderate
15 albuminuria and UACR $>30\text{mg}/\text{mmol}$ for severe albuminuria. An individual's baseline was set
16 as the date of the first eGFR measurement following enrollment in NDR or diagnosis of
17 diabetes in SCI-Diabetes and the values of other predictors were defined at the first
18 measurement within 12 months after this date.

19

20 Statistical analyses

21 Baseline characteristics are described as median and interquartile range (IQR) for continuous
22 variables and as count (%) for categorical variables.

23

24 *Development of the prediction model*

1 A split-sample approach was used for development and internal validation of the prediction
2 model. A random sample of 75% of participants from NDR (n=530,308) was used as the
3 development dataset. Missing data were imputed using single imputation with predictive mean
4 matching. Details are described in the *Supplementary material, Predictors and missing data*.
5 In the derivation dataset, two Cox proportional hazards functions with left truncation and right
6 censoring were developed using age as the time-axis: one for prediction of kidney failure-events
7 (function A) and one for prediction of all-cause mortality (function B).
8 Baseline hazards for kidney failure (function A) were derived using 1-year intervals (due to the
9 low amount of kidney failure events) and thereafter smoothed and interpolated to 3-month
10 intervals. Baseline hazards for all-cause mortality (function B) were derived using 3-month
11 intervals (*figure S1*).
12 By combining the coefficients from the Cox proportional hazards functions A and B and the
13 smoothed baseline hazards, kidney failure-free survival, 10-year and lifetime risk of kidney
14 failure and all-cause mortality were calculated using previously validated life-tables(19). 10-
15 year risk of kidney failure was calculated by summation of the predicted kidney failure and all-
16 cause mortality risk, respectively, in the first 10 years and beyond from a person's age at cohort
17 entry. Similarly, lifetime risk of kidney failure was calculated by the summation of the predicted
18 kidney failure risk from an individual's age at cohort entry until the maximum age of 95 years.
19 All analyses were performed with R-statistic programming (version4.0.3,R Foundation for
20 Statistical Computing, Vienna,Austria). A detailed description of statistical methods is
21 provided in the *Supplementary material, Statistical analyses*.

22

23 *Model validation for 10-year predictions*

24 Goodness-of-fit was assessed in the remaining 25% of NDR by calibration plots. Observed risks
25 of kidney failure were calculated using cumulative incidence functions with the competing

1 event being all-cause mortality. For external validation in SCI-Diabetes, the models were
2 recalibrated based upon the incidence of kidney failure and all-cause mortality, using the
3 expected vs. observed ratios. The logarithm of the expected vs. observed ratio was subtracted
4 from the linear predictor for both outcomes. Discrimination was quantified using Harrell's c-
5 statistic for survival data(20). Our approach to model development and validation complies
6 with PROBAST guidelines(21) and TRIPOD(22).

7

8 *Prediction of treatment effects*

9 To estimate the individual treatment benefit, the linear predictor for function A was combined
10 with hazard ratios (HRs) from the most recent high quality meta-analyses describing effect sizes
11 for each intervention. For the current study, we derived estimates of the effect of glucose-
12 lowering, BP-lowering, GLP1-RA, SGLT2i, ACEi/ARB treatment and smoking cessation as
13 described in in the *Supplementary material, Relative treatment effects*. The HR of smoking
14 cessation, BP-lowering and initiation of GLP1-RA or SGLT2i for all-cause mortality were
15 added to the linear predictor for model B(5, 23-25).

16 The lifetime benefit of treatment was calculated as the difference between predicted median
17 kidney failure-free life expectancy with and without treatment. Similarly, 10-year absolute risk
18 reduction was estimated by calculating the difference between the predicted 10-year kidney
19 failure risk with and without treatment. This same approach was used for estimating lifetime
20 kidney failure risk reduction with initiation of treatment. All model assumptions are provided in
21 *table S9*.

22

23 Sensitivity analyses

1 To incorporate the natural decline of eGFR in the predictions of kidney failure-risk several
2 sensitivity analyses were performed to incorporate functions of eGFR over time, see
3 *Supplementary materials, Sensitivity analyses.*

4

5 **Results**

6 Baseline characteristics

7 Selection of the development and the validation cohorts in NDR is illustrated in *figure S2*. For
8 NDR median(IQR) follow-up was 6.8(3.2-10.6) years with 8004 individuals(1.1%)
9 developing incident kidney failure and 202,078(29%) deaths. The cohort consisted of
10 401,433(57%) men, median(IQR) age was 65(57-74) years and median(IQR) eGFR was 85(68-
11 97) ml/min/1.73m². In SCI-Diabetes, median(IQR) follow-up was 5.9(2.6-9.6) years with
12 1653(0.7%) kidney failure-events and 45,056(18%) deaths. In this cohort, 145,753(57%) were
13 men, median(IQR) age was 61(52-70) years and median(IQR) eGFR was 83(68-96)
14 ml/min/1.73m².

15

16 Prediction model and validation

17 *Table S3* shows the HRs and 95% confidence intervals (95%CI) for functions A and B. The
18 formulae for calculating survival for 3-month intervals, including coefficients and age-specific
19 baseline hazards are included in *tables S4 and S5*.

20 Predicted 10-year risk for kidney failure and all-cause mortality showed good agreement with
21 the 10-year observed risk in the internal validation dataset(*Figure 1*). Internal model
22 performance in terms of discrimination was good, reflected in c-statistics of 0.890(95%CI
23 0.881-0.899) for kidney failure and 0.770(95%CI 0.767-0.772) for all-cause mortality.

24 Kidney failure incidence rates (IR) were higher in NDR with an IR of 1.6/1,000 person-years
25 compared to 1.0/1,000 person-years in SCI-Diabetes. Similarly, all-cause mortality also differed

1 between the cohorts: 39.5/1,000 person-years in NDR and 28.0/1,000 person-years in SCI-
2 Diabetes. For individuals with incident type 2 diabetes in NDR dataset (n = 229,635;32%),
3 event rates were similar to those observed in SCI-Diabetes (IR were 0.7/1000 person-years for
4 kidney failure and 27/1000 person-years for all-cause mortality). A table of baseline
5 characteristics stratified for incident versus prevalent type 2 diabetes in NDR is provided as
6 *table S6*. Due to the difference in event rates, the model was recalibrated according to predicted
7 vs. observed kidney failure and all-cause mortality rates. Predicted 10-year risk for kidney
8 failure and all-cause mortality showed good agreement with the 10-year observed risk in SCI-
9 Diabetes (*Figure 2*), although risk in the highest decile was overestimated. The model
10 performed well regarding discrimination with c-statistics of 0.741 (95% CI 0.726-0.756) for
11 kidney failure and 0.768 (95% CI 0.766-0.770) for all-cause mortality. A baseline table for
12 predictors stratified according to predicted kidney failure risk is provided in *table S7*.

13

14 Individual lifetime estimation of risk and treatment effects

15 An interactive user-friendly calculator is provided as *supplementary file* and will be provided at
16 www.U-Prevent.com. Individual effects from medication initiation can be modelled in terms of
17 kidney failure-free life years gained and absolute risk reduction. *Figure 3* illustrates kidney
18 failure-free life expectancy and 10-year kidney failure risk for two individual examples with
19 and without initiation of preventive medication.

20

21 Sensitivity analyses

22 When incorporating the natural decline of eGFR in the predictions of kidney failure-risk, model
23 performance did not improve for 10-year predictions (*Supplementary material, Sensitivity*
24 *analyses*).

25

1 **Discussion**

2 The current study describes the development and external validation of a prediction model for
3 estimation of 10-year and lifetime risk of kidney failure using data from almost one million
4 individuals with type 2 diabetes. Furthermore, the model allows estimation of individual benefit
5 of treatment with medication most often used for kidney protection in individuals with type 2
6 diabetes expressed as life-years gained free of kidney failure with treatment initiation. The
7 prediction tool is available as *Supplementary material* and will be provided as a calculator at
8 www.U-Prevent.com to allow use in clinical practice.

9
10 Existing kidney failure prediction models developed in individuals with type 2 diabetes are
11 based on shorter prediction horizons of up to eight years(9-11, 26-28). These shorter term
12 predictions remain relevant for use in some patient groups, i.e. those already having advanced
13 kidney damage, for intensifying follow-up and timing of kidney replacement therapy(29).
14 However, for patients with lower short-term risk, including younger patients, longer-term
15 predictions will be valuable to support decisions about preventive treatment. All models failed
16 to adjust for competing risks. This is critical to avoid overestimating predicted kidney failure
17 risks and treatment effects(30), especially in older individuals and individuals at low risk for
18 kidney failure, who are likely to die before developing kidney failure. Furthermore, only two
19 previous kidney failure risk prediction models in individuals with type 2 diabetes performed
20 external validation. Elley et al. performed external validation for 5-year risk of kidney failure in
21 5,877 individuals with type 2 diabetes arising from the same geographical region as the
22 derivation cohort with a c-statistic of 0.89 and reasonable calibration(11). Basu et al. performed
23 external validation for 10-year risk of kidney failure in 1,018 individuals with type 2 diabetes
24 with a c-statistic for kidney failure of 0.54 and did not perform calibration of this specific
25 outcome(27). In the current model, c-statistics dropped from 0.89 for internal validation to 0.74

1 for external validation. The lower discrimination ability in the external validation is likely due
2 to the categorical definitions of albuminuria used rather than continuous data that may provide a
3 better predictor, as well as the lower availability of albuminuria in the validation cohort (54%
4 missing data). Also, diabetes duration is a relevant predictor in NDR (since this was a cohort
5 with both prevalent and incident type 2 diabetes), however not in SCI-Diabetes (since this was
6 a cohort with incident type 2 diabetes).

7

8 In the current study, the event rates for both kidney failure and all-cause mortality in individuals
9 with type 2 diabetes were higher in Sweden compared to Scotland. The difference in kidney
10 failure event rates is likely explained by the use of an incident cohort from SCI-Diabetes who
11 were almost five years younger at cohort entry than the population of individuals with prevalent
12 and incident diabetes identified from NDR, despite the potential for survival bias in the NDR
13 cohort. More individuals in the NDR had severe albuminuria and a history of cardiovascular
14 disease and the prevalence of treatment with insulin was higher. Moreover, the prevalence of
15 RASi medication prescription was higher in NDR. This may be due to differences in
16 antihypertensive treatment algorithms with a more prominent role for RASi treatment in
17 Swedish guidelines as compared to Scottish guidelines(31, 32). Furthermore, since SCI-
18 Diabetes was a cohort with incident type 2 diabetes, prescription of RASi-medication is likely
19 to have increased after diagnosis(33). Future validation and recalibration of the model will be
20 valuable as data on individuals with type 2 diabetes with sufficient follow-up accrue, also to
21 account for differences in baseline risk due to changing patterns of medication use.

22

23 The current model is intended for use in clinical practice to assess kidney failure risk in
24 individuals with type 2 diabetes as well as likely benefits from preventive treatment. The model
25 is underpinned by two very large and contemporary type 2 diabetes population-based cohorts

1 with limited selection of participants. Large databases with extensive follow-up are important in
2 order to ensure sufficient power with an adequate amount of kidney failure events, since the
3 incidence of kidney failure is relatively low as compared with cardiovascular outcomes and
4 mortality in these populations. In external validation of the current model, a slight
5 overestimation of kidney failure risk for patients at highest risk of kidney failure was observed,
6 which could indicate a modest degree of overfitting in the highest risk group. However, in
7 clinical practice this is unlikely to lead to erroneous decisions regarding treatment, as the true
8 observed risk in these patients is still high and justifies intensive medical therapy. The model
9 was developed for the entire range of eGFR. Individuals with type 2 diabetes and CKD stage 3
10 or 4 are likely already managed as a high-risk group where preventive treatment is indicated.
11 However, also in these groups progression of kidney function decline may take several years
12 and the model can still act as a suitable tool to aid adherence and shared decision making in the
13 prevention of kidney failure.

14
15 The current model emphasizes lifetime benefit from treatment, which may support initiation of
16 preventive treatment if absolute benefit is deemed appropriate. Contrary, the model may support
17 not starting or postponement of preventive drug treatment if the absolute benefit is too low and
18 focus on lifestyle changes might be a more appropriate initial treatment choice. In this way
19 lifetime risk prediction informs shared decision making while lowering the risk of side effects
20 and polypharmacy. Furthermore, trials are often not powered to detect an effect on kidney
21 failure risk, and albuminuria, eGFR slopes or a combined kidney event are often used as
22 proxies for hard kidney outcomes(34). With lifetime predictions for kidney failure, a better
23 alternative for translating absolute kidney failure risk reduction with initiation of preventive
24 treatment is provided.

1 We chose to also incorporate effect on all-cause mortality of treatment initiation where there
2 was substantial evidence for this, since this leads to longer life expectancy and thus also more
3 years to develop kidney failure. However, it should be noted that kidney failure-free life years
4 gained in individuals with a low risk of kidney failure is mostly derived from the effect on all-
5 cause mortality. Treatment should always be considered and initiated according to current
6 guidelines(35, 36), and the kidney failure prediction tool can help support these decisions. It
7 should further be emphasized that preventive treatment in individuals with type 2 diabetes
8 might be initiated for other reasons than prevention or postponement of kidney failure (e.g.
9 prevention of cardiovascular outcomes or heart failure) that were not incorporated into the
10 current model. The model therefore underestimates the total benefit of treatment. Ideally, the
11 model should be combined with models predicting risk of cardiovascular disease to fully
12 capture treatment benefit(37).

13

14 The model assumes that predictors follow a natural course over time that matches the course
15 of predictors in the derivation cohort, and model predictions are based on the current predictor
16 levels of a patient. However, follow-up in the derivation cohort was not sufficient to
17 incorporate the natural course of predictors over the entire lifetime span, which might be
18 particularly important for eGFR as a strong predictor for kidney failure that is known to
19 decline with increasing age. The different methodological approaches that we used to account
20 for this general eGFR decline with age (e.g. incorporating standardized annual eGFR decline
21 and modelled decline) did not improve model performance. Furthermore, the model assumes
22 that other baseline risk factor levels follow the natural course captured in the dataset, which
23 might not always be appropriate. However, previous studies have validated methods of
24 estimating lifetime predictions for up to 17 years(19). Since all risk factors are subject to change

1 after baseline and because of the general decline of eGFR with increasing age, lifetime
2 estimations should be repeated when decisions about new treatment approaches are required.
3
4 Potential limitations of the study merit consideration. Internal and external validation was
5 performed for 10-year risk as it is not possible to perform validation over an individual's
6 lifetime. Also, diabetes duration is calculated as time since diabetes diagnosis, which is unlikely
7 to be fully accurate as some people are likely to have developed diabetes some time before a
8 clinical diagnosis is made.

9 We did not have information on ethnicity, so were not able to include this as predictor in the
10 model. It is possible that the use of ICD-10 codes to identify outcomes may have resulted in
11 misclassification, particularly underestimation of sustained eGFR $<15\text{ml}/\text{min}/1.73\text{m}^2$ in the
12 absence of long-term dialysis or transplantation as reported in a previous study(38). It is not
13 possible to validate the ICD-codes in the study populations used for this analysis or to
14 estimate the likely effect of misclassification on the estimated discrimination and calibration
15 of the risk models without knowing whether the degree of misclassification varies with
16 different levels of risk factors.

17 We performed single imputation due to computational feasibility, which might slightly
18 underestimate the true variability of outcome measures as opposed to multiple imputation.
19 However, no conclusions are drawn based on the significance of the model's coefficients. Also,
20 we chose for a split-sample approach for model development, while resampling methods would
21 have been preferred. Model development was however still performed in $>500,000$ individuals
22 with type 2 diabetes making the power of the study more than sufficient. Another assumption
23 made is full adherence to preventive treatment for the remaining lifetime. However, since lack
24 of adherence is a common problem, this current model might be used in aiding communication
25 and addressing the importance of adherence to preventive treatment. Since kidney failure is a

1 rare outcome and studies are often underpowered, treatment effects for glucose-lowering and
2 BP-lowering were estimated using the best available evidence and should be interpreted with
3 this in mind. Further research is needed to investigate to what extent the model is used in
4 clinical practice and whether its use improves outcomes.

5

6 In conclusion, 10-year and lifetime risk of kidney failure as well as kidney failure-free life
7 expectancy and life-years free of kidney failure gained with treatment initiation can be
8 estimated for individuals with type 2 diabetes using readily available characteristics.

9 Assessment of individual risk and gain from treatment facilitates personalized medicine and
10 shared-decision in the management of long-term outcomes in clinical practice.

11

12 **Acknowledgments**

13 We are grateful to Ann-Marie Svensson (recently deceased) for her keen interest and
14 consistent encouragement during this work.

15 For the Swedish National Diabetes Register, we thank all of the clinicians who were involved
16 in the care of patients with diabetes for collecting data, and staff at the Swedish National
17 Diabetes Register. We acknowledge with gratitude the contributions of people and
18 organizations involved in providing data, setting up, maintaining, and overseeing SCI-
19 Diabetes, including the Scottish Diabetes Research Network that is supported by National
20 Health Service (NHS) Research Scotland, a partnership involving Scottish NHS Boards and
21 the Chief Scientist Office of the Scottish Government.

22

23 **Author Contributions**

24 BE, SF, SW, SR and NH contributed to the design and conduct of the data acquisition. Design
25 of the paper and analysis was done by HO, SR, JW, JL and FV. All authors contributed to the

1 interpretation of the results. HO drafted the manuscript. BE, SF, SW, NS, SR, NH, JD, JW,
2 FV and JL critically revised the manuscript. All authors have reviewed and approved the final
3 manuscript.

4

5 **Data Availability Statement**

6 The data from the local registries is not compliant with publishing individual data in an open
7 access institutional repository or as supporting information files with the published paper.

8

9 **Disclosures**

10 Stefan Franzén is an employee of AstraZeneca as of October 4 2021. Dr. Eliasson reports
11 personal fees from Amgen, personal fees from AstraZeneca, personal fees from Boehringer
12 Ingelheim, personal fees from Eli Lilly, personal fees from Merck Sharp & Dohme, personal
13 fees from Mundipharma, personal fees from Navamedic, personal fees from
14 NovoNordisk, personal fees from RLS Global, grants and personal fees from Sanofi, all
15 outside the submitted work. Dr. Eliasson is supported by the "Konung Gustaf V:s och
16 Drottning Victorias Frimurarestiftelse". Dr Halbesma is supported by a British Heart
17 Foundation Intermediate Basic Science Research Fellowship (FS/16/36/32205). Dr. Sattar has
18 consulted for Amgen, Astrazeneca, Boehringer Ingelheim, Elil-Lilly, Hanmi, Novartis, Novo
19 Nordisk, Pfizer and Sanofi and received grant support from Astrazeneca, Boehringer
20 Ingelheim Novartis and Roche Diagnostics.

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1 **Table 1. Baseline characteristics of participants identified from the Swedish National**
2 **Diabetes Register and Scottish Care Information - Diabetes cohort after imputation of**
3 **missing data**

	Swedish National Diabetes Register (n = 707,077)	Scottish Care information - Diabetes cohort (n = 256,265)
Sex (male)	401,433 (57%)	145,753 (57%)
Age (years)	65 (57-74)	61 (52-70)
Current smoking	110,630 (16%)	57,702 (23%)
Duration of diabetes mellitus (years)	2 (0-7)	0 (0-0)
Incident type 2 diabetes	229,635 (32%)	256,265 (100%)
Insulin treatment	133,661 (19%)	25,227 (10%)
History of cardiovascular disease	155,806 (22%)	43,012 (17%)
eGFR (mL/min/1.73m ²)	85 (68-97)	83 (68-96)
Moderate albuminuria	104,227 (15%)	49,536 (19%)
Severe albuminuria	43,454 (6%)	5,353 (2%)
Systolic blood pressure (mmHg)	138 (126-150)	135 (124-144)
Body mass index (kg/m ²)	29 (26-33)	31 (28-36)
HbA1c (%)	6.7 (6.2-7.6)	6.9 (6.3-7.9)
HbA1c (mmol/mol)	50 (44-60)	52 (45-63)
Non HDL cholesterol (mmol/L)	3.6 (2.9-4.4)	3.3 (2.6-4.2)
Prescribed RASi medication	299,559 (42%)	38,769 (15%)

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5 Variables are displayed as median (IQR) for continuous variables and counts (%) for
6 categorical variables. Abbreviations: eGFR = estimated glomerular filtration rate, HbA1c =
7 hemoglobin A1c, HDL = high-density-lipoprotein, RASi = Renin-angiotensin-system
8 inhibition medication

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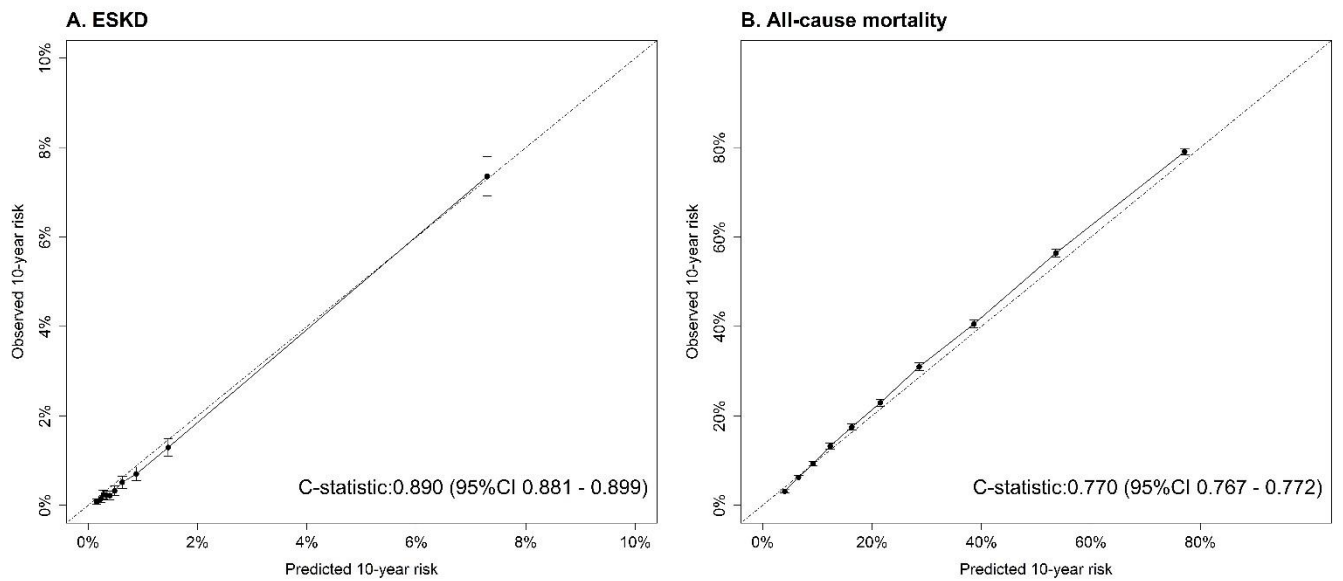
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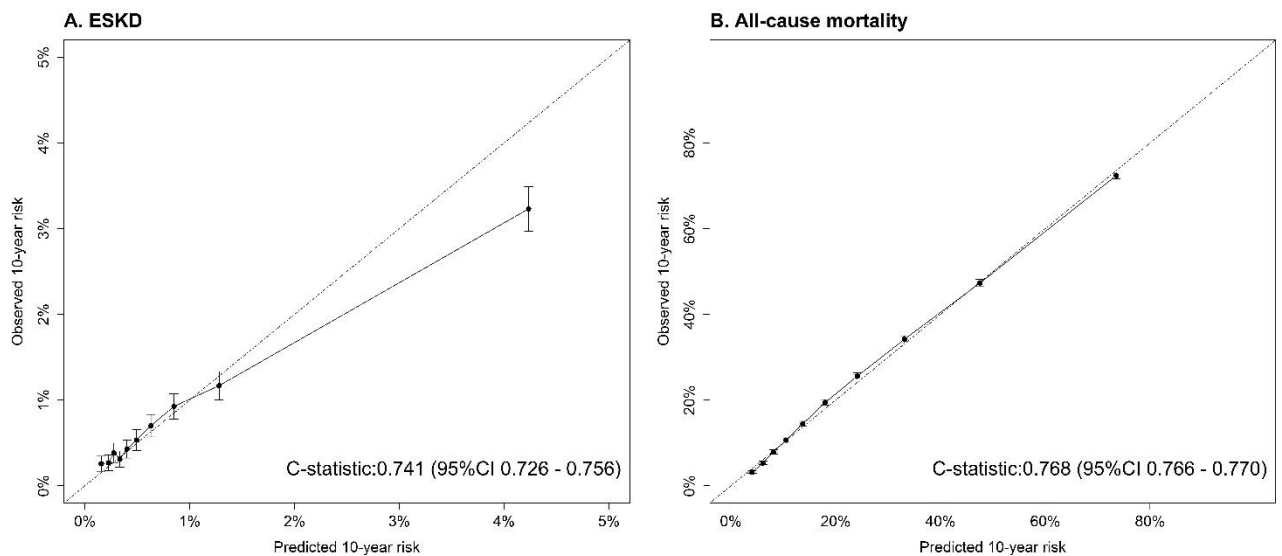
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1 **Figure 1. Calibration plots for internal validation in a random sample of 25% from the**
 2 **Swedish National Diabetes Register (n = 170,114)**



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 4 *Calibration slope for kidney failure as outcome 1.02, slope for all-cause mortality as outcome*
 5 *1.04.*

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 7 **Figure 2. Calibration plots for external validation in SCI-Diabetes cohort (n = 256,265)**

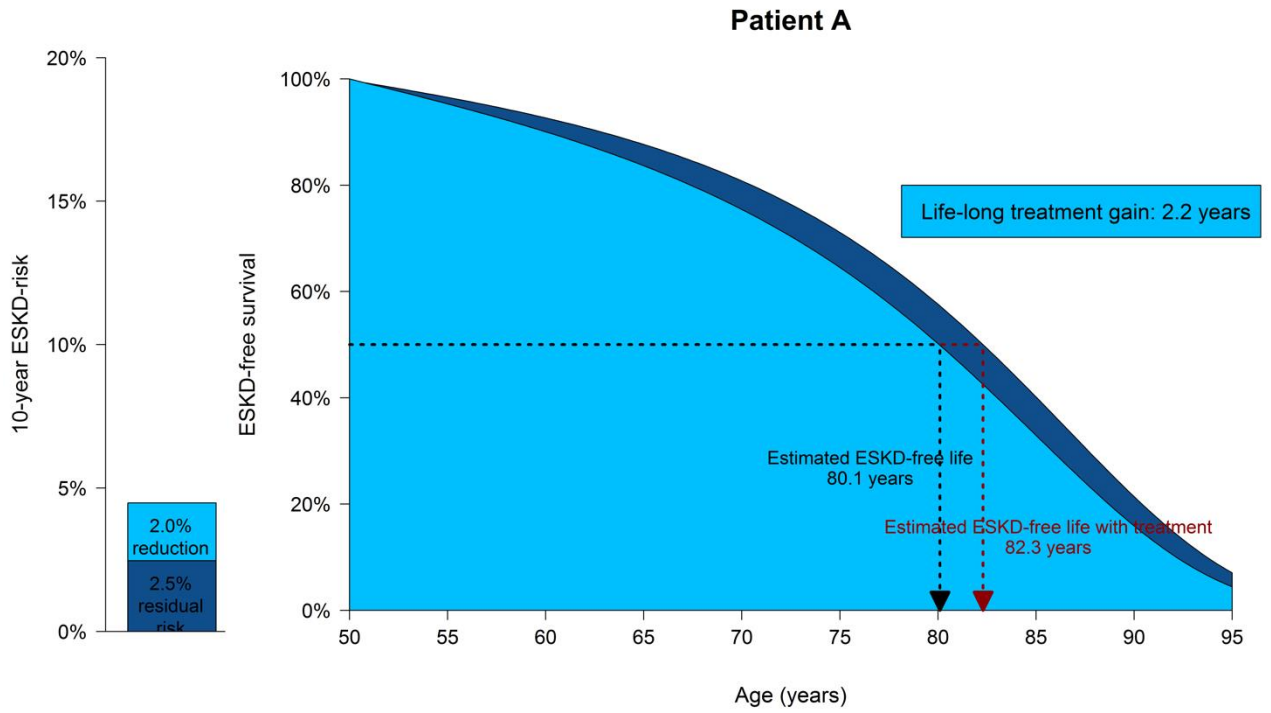


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 9 *Calibration slope for kidney failure as outcome 0.73, slope for all-cause mortality as outcome*
 10 *0.99 after recalibration.*

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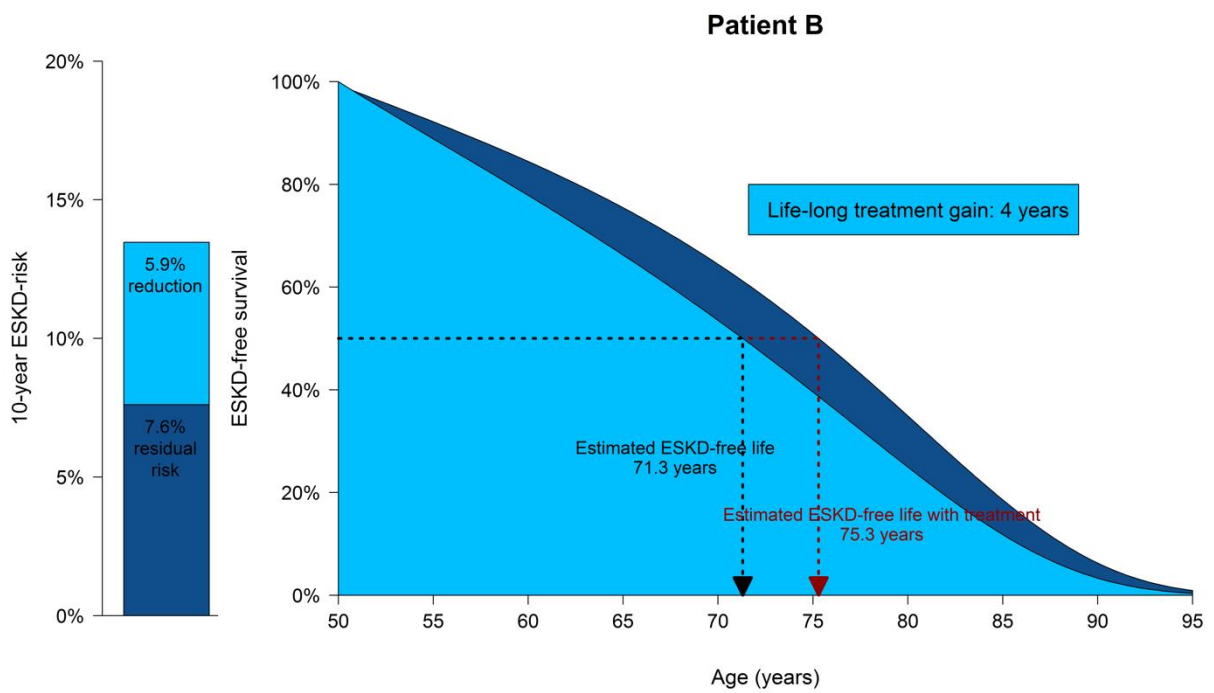
2 **Figure 3. Example of 10-year kidney failure risk, life-years free of kidney failure and**

3 **benefit from preventive treatment in two patient scenarios**



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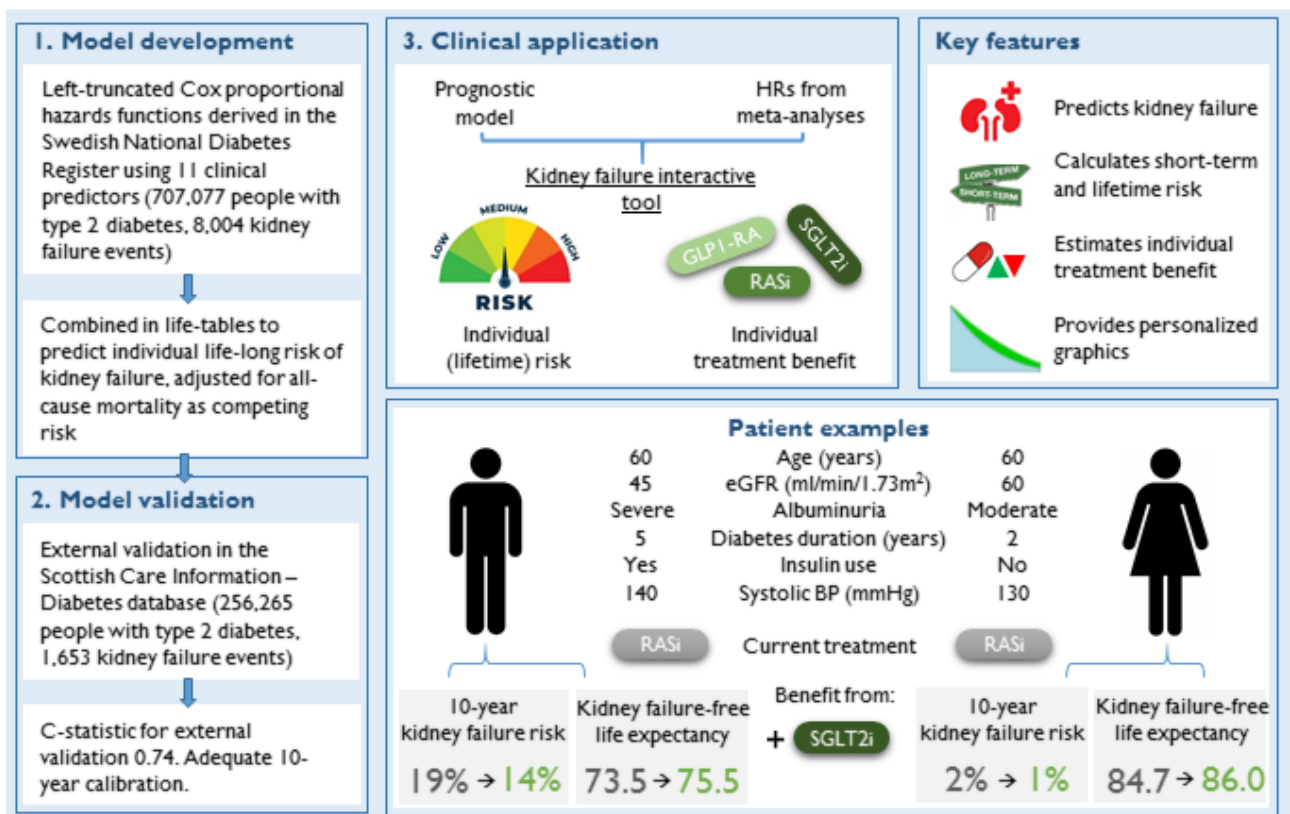
Effect of initiation of RAS-inhibitor and SGLT2i on kidney failure-free lifetime expectancy for two patient examples

Patient A; a 50-year old male, non-smoker, 5 years diabetes duration, no history of cardiovascular disease, no insulin use, systolic blood pressure 140 mmHg, BMI 33 kg/m², eGFR 60 ml/min/1.73m², moderate albuminuria, non HDL cholesterol 3.0 mmol/L, HbA1c 8.1% (65 mmol/mol).

Patient B; a 65-year old female, non-smoker, 2 years diabetes duration, history of cardiovascular disease, no insulin use, systolic blood pressure 150 mmHg, BMI 25 kg/m², eGFR 50 ml/min/1.73m², severe albuminuria, non HDL cholesterol 4.0 mmol/L, HbA1c 7.5% (58 mmol/mol).

Take home figure

Lifetime risk of kidney failure and treatment benefit



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1 *GLP-1 RA = glucagon-like peptide-1 receptor agonist, RASi = Renin-Angiotensin-System*
2 *inhibitor, SGLT2i = sodium–glucose co-transporter-2 inhibitor, HRs = hazard ratios, eGFR*
3 *= estimated glomerular filtration rate, BP = blood pressure.*

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