Supporting information

Statistical details

Let $\lambda_{ESKD}(t)$ denote the rate function for end-stage kidney disease (ESKD), such that $\lambda_{ESKD}(t).d$ for small d is the approximate conditional risk of ESKD before time $t+d$ given that the individual is alive and free of ESKD at time t.

In a similar manner, $\lambda_{death}(t)$ denotes the rate function for death, such that $\lambda_{death}(t).d$ for small d is the approximate conditional risk of dying before time $t+d$ given that the individual is alive and free of ESKD at time t.

Using the theory of survival analysis, the probability of being alive and free of ESKD at time s is then defined as:

$$S(s) = \exp\left(-\int_0^s \lambda_{ESKD}(u) + \lambda_{death}(u).du\right)$$

The risk (cumulative incidence) of developing end-stage kidney disease (ESKD) before time t, $F_{ESKD}(t)$ can then be defined as (1):

$$F_{ESKD}(t) = \int_0^t \lambda_{ESKD}(s).S(s).ds$$

Hence, cumulative incidence function for ESKD depends on both the rate function for ESKD and the rate function for the competing event of dying without ESKD.

The cause-specific rate functions $\lambda_{ESKD}(s)$ and $\lambda_{death}(s)$ are modelled with poisson regeression analysis using risk time as offset. Hence, the rate functions are constant over the follow-up time and the cumulative incidence function for ESKD is equal to:

$$F_{ESKD}(t) = \lambda_{ESKD}.\int_0^t S(s)ds = \lambda_{ESKD}.\int_0^t exp(-(\lambda_{ESKD} + \lambda_{death}).s).ds$$

1. *Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. Int J Epidemiol. 2012;41(3):861-70.*

Supplemental Table 1. Characteristics of the derivation cohort at their first clinical examination by ESKD status at end of follow-up

	No ESKD	**ESKD**	**P**
N	5157	303	
Follow-up time (years)	6 (3;10)	8 (4;15)	<0.001
Region of origin (%)			0.088
European	91.5	87.2	
Middle East	6.0	8.7	
Other	2.5	4.1	
Age (years)	41.9 (16.6)	48.4 (13.3)	<0.001
Males (%)	53.9	57.1	<0.001
Age at diabetes diagnosis (years)	21.3	16.0 (9.7;28.9)	<0.001
Diabetes duration (years)	14.8 (6.3;26.3)	28.7 (18.8;37.0)	<0.001
HbA_{1c} (mmol/mol)	68.9 (16.6)	78.5 (17.0)	<0.001
HbA_{1c} (%)	8.4 (1.5)	9.3 (1.6)	<0.001
BMI (kg/m^2)	24.6 (3.6)	25.2 (3.9)	<0.001
UACR (mg/g)	7.0 (4.0;17.0)	154.5 (12.0;876)	<0.001
Albuminuria (%)			<0.001
Normal	83.6	36.0	
Micro	12.5	22.6	
Macro	3.9	41.3	
Serum creatinine (µmol/L)	81 (68;92)	113 (91;169)	<0.001
eGFR ($mL/min/1.73m^2$)	101.1 (86.1;115.4)	64.6 (40.2;90.8)	<0.001
eGFR categories (%)			<0.001
eGFR ≥ 90	69.1	25.4	
60 ≤ eGFR < 90	26.2	27.4	
30 ≤ eGFR < 60	4.5	32.3	
15 ≤ eGFR < 30	0.3	14.9	
Hemoglobin (mmol/L)	8.7 (0.8)	8.1 (1.0)	<0.001
Potassium (mmol/L)	4.0 (0.4)	4.2 (0.5)	<0.001
Sodium (mmol/L)	138.8 (3.0)	137.8 (3.3)	0.586
TSH ($\times 10^{-3}$ IU/L)	1.5 (0.9;2.2)	1.3 (0.9;2.3)	0.281
Systolic blood pressure (mmHg)	131.5 (18.8)	143.2 (22.2)	0.045
Diastolic blood pressure (mmHg)	78 (10)	79.2 (10.6)	<0.001
Total cholesterol (mmol/L)	4.9 (1.0)	5.5 (1.3)	0.720
HDL cholesterol (mmol/L)	1.6 (0.5)	1.6 (0.6)	<0.001
LDL cholesterol (mmol/L)	2.7 (0.8)	3 (1.0)	<0.001
Triglycerides (mmol/L)	1.0 (0.7;1.5)	1.4 (1;2.1)	<0.001

RAS blockers (%)	19.9	50.8	<0.001
Other antihypertensive treatment (%)	24.8	64.0	<0.001
Lipid-lowering medication (%)	9.8	20.8	<0.001
Retinopathy status (%)			<0.001
No apparent retinopathy	48.2	16.3	
Mild/moderate	22.4	16.7	
Severe	29.4	67.0	
Current smoking (%)	50.9	65.9	0.631
Alcohol intake (%)[#]			0.247
0 units/week	14.5	16.5	
1-20 units/week	80.8	74.7	
> 20 units/week	4.7	8.9	
Regular exercise (%)†	69.4	60.3	0.134
Previous CVD (%)	8.2	20.5	0.029

Data are means (SD), medians (interquartile limits), or percentages.

BMI: body mass index; eGFR: estimated glomerular filtration rate calculated using the Chronic Kidney Disease (CKD) Epidemiology Collaboration standard equation.; HbA_{1c}: hemoglobin A1c; UACR: urinary albumin-to-creatinine ratio; TSH: thyroid-stimulating hormone; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CVD: Cardiovascular disease; #A unit alcohol: 12 g of pure alcohol. †Regular exercise: ≥ 30 minutes per day

Supplemental Table 2. Incidence Rate Ratios (IRR) With 95% confidence intervals for predictors of ESKD and death - *extended model*.

	ESKD		Non-ESKD death	
	RR (95%CI)	**P value**	**RR (95%CI)**	**P value**
Age (10 years)	0.81 (0.73;0.9)	<0.001	2.02 (1.89;2.15)	<0.001
Male sex (vs female sex)	1.46 (1.14;1.87)	0.003	1.50 (1.28;1.77)	<0.001
Diabetes duration (10 years)	1.15 (1.04;1.28)	0.007	1.06 (1.01;1.11)	0.027
eGFR (halving)	6.94 (5.75;8.39)	<0.001	-	
Microalbuminuria (vs normoalbuminuria)	0.47 (0.28;0.76)	0.002	-	
Macroalbuminuria (vs normoalbuminuria)	0.34 (0.15;0.76)	0.008	-	
Systolic blood pressure (10 mmHg)	1.07 (1.01;1.13)	0.030	0.93 (0.89;0.96)	<0.001
HbA_{1c} (10 mmol/mol)	1.11 (1.02;1.19)	0.010	-	
Smoking (vs no smoking)	-		1.65 (1.40;1.95)	<0.001
Previous CVD event (vs no)	0.83 (0.72;0.96)	0.012	1.71 (1.46;2.00)	<0.001
Hemoglobin (mmol/L)	1.33 (1.03;1.72)	0.027	0.79 (0.71;0.88)	<0.001
Mild/moderate retinopathy (vs no)	1.66 (1.16;2.39)	0.006	0.80 (0.66;0.98)	0.031
Severe retinopathy (vs no)	1.05 (0.79;1.41)	0.734	1.13 (0.95;1.35)	0.163
UACR (doubling)	1.28 (1.15;1.43)	<0.001	1.10 (1.07;1.14)	<0.001
BMI (kg/m^2)	-		0.94 (0.90;0.97)	0.002
Triglycerides (doubling)	-		1.21 (1.07;1.38)	0.003
Regular exercise (vs no)	-		0.52 (0.44;0.62)	<0.001
Sodium (mmol/L)	-		0.95 (0.93;0.97)	<0.001

ESKD: end-stage kidney disease; CVD: Cardiovascular disease; UACR: urinary albumin-to-creatinine ratio; †Regular exercise: ≥ 30 minutes per day. IRR (95%CI): incidence rate ratios with 95% confidence intervals

Supplemental Table 3. Discrimination and calibration by years of follow-up

Years of Follow-up	Cumulative no. of ESKD events	Core model		Extended model	
		C-statistic (95%CI)	P_{HL}	C-statistic (95%CI)	P_{HL}
Derivation data (SDCC)					
2	48	0.914 (0.853; 0.974)	0.408	0.928 (0.878; 0.977)	0.701
3	69	0.894 (0.841; 0.947)	0.416	0.911 (0.867; 0.954)	0.848
4	97	0.892 (0.849; 0.935)	0.397	0.904 (0.867; 0.941)	0.526
5	122	0.888 (0.849; 0.927)	0.100	0.897 (0.863; 0.931)	0.166
6	140	0.890 (0.854;0.926)	0.033	0.898 (0.866;0.930)	0.138
7	161	0.887 (0.852;0.921)	0.001	0.896 (0.865;0.926)	0.034
8	179	0.882 (0.850;0.914)	0.001	0.891 (0.862;0.919)	0.025
9	200	0.882 (0.852;0.912)	<0.001	0.891 (0.865;0.917)	0.002
10	221	0.872 (0.843; 0.902)	<0.001	0.883 (0.857; 0.909)	<0.001
Validation data (FDD)					
2	21	0.847 (0.740;0.954)	0.774	-	
3	36	0.828 (0.746;0.911)	0.381	-	
4	47	0.845 (0.777;0.914)	0.314	-	
5	63	0.865 (0.811;0.919)	0.043	-	
6	73	0.863 (0.813;0.913)	0.060	-	
7	82	0.859 (0.812;0.907)	0.036	-	
8	93	0.867 (0.825;0.910)	0.016	-	
9	104	0.867 (0.827;0.907)	0.003	-	
10	116	0.863 (0.826;0.900)	0.002	-	
Validation data (SDRNT1BIO)					
2	14	0.996 (0.991;1.000)	0.044	-	
3	35	0.993 (0.986;0.999)	0.039	-	
4	54	0.972 (0.951;0.992)	0.044	-	
5	67	0.961 (0.940;0.981)	0.029	-	
6	83	0.955 (0.935;0.974)	0.013	-	
7	93	0.952 (0.931;0.974)	0.002	-	
8	95	0.952 (0.931;0.973)	<0.001	-	

P_{HL}: Hosmer-Lemeshow test of goodness of fit. $P_{HL} \geq 0.05$ indicate good model fit

FDDB: the Funen Diabetes Database. SDRNT1BIO: the Scottish Diabetes Research Network Type 1 Bioresource

Supplemental Table 4. Parameter estimates for the predictors included in the *core model*

			ESKD			Non-ESKD death	
			Original	**PES**		**Original**	**PES**
Intercept		α =	5.748317	4.783935	σ =	-8.18017	-10.193500
Age	(years)	β_1 =	-0.018850	-0.015820			
Male sex	(1 for yes, 0 for no)	β_2 =	0.337922	0.229484	γ_1 =	1.699476	1.746154
Diabetes duration	(years)	β_3 =	0.011857	0.009617	γ_2 =	0.010190	0.008748
eGFR	(mL/min/1.73m^2)	β_4 =	-2.097550	-1.975550	γ_3 =	-0.248760	-0.044020
Microalbuminuria	(1 for yes, 0 for no)	β_5 =	0.083593	0.063436	γ_4 =	0.496541	0.380168
Macroalbuminuria	(1 for yes, 0 for no)	β_6 =	0.635484	0.482441	γ_5 =	0.870400	0.666386
Systolic blood pressure	(mmHg)	β_7 =	0.007988	0.006247	γ_6 =	-0.010820	-0.011110
HbA_{1c}	(mmol/mol)	β_8 =	0.010978	0.006987	γ_7 =	0.009208	0.007618
Current smoking	(1 for yes, 0 for no)	β_9 =	0.242820	0.265174	γ_8 =	0.632938	0.679023
Previous CVD event	(1 for yes, 0 for no)	β_{10} =	0.301880	0.243471	γ_9 =	0.655959	0.601755
Age for women	(years)				γ_{10} =	0.086434	0.091864
Age for men	(years)				γ_{11} =	0.065228	0.069326

PES: post estimation shrinkage; eGFR: estimated glomerular filtration rate; CVD: cardiovascular disease

The annual incidence rate of ESKD and death in the *base model* can be calculated from the parameters in Supplemental Table S4 as:

$$\lambda_{ESKD} = exp\begin{pmatrix} \alpha + \beta_1.age + \beta_2.male + \beta_3.DM\ duration + \beta_4.log2(eGFR) \\ +\beta_5.microalbuminuria + \beta_6.macroalbuminuria \\ +\beta_7.systolic\ BP + \beta_8.HbA_{1c} + \beta_9.smoking + \beta_{10}.previous\ CVD \end{pmatrix}$$

$$\lambda_{death} = exp\begin{pmatrix} \sigma + \gamma_1.male + \gamma_2.DM\ duration + \gamma_3.log2(eGFR) \\ +\gamma_4.microalbuminuria + \gamma_5.macroalbuminuria \\ +\gamma_6.systolic\ BP + \gamma_7.HbA_{1c} + \gamma_8.smoking + \gamma_9.previous\ CVD \\ +\gamma_{10}.age.1_{(women)} + \gamma_{11}.age.1_{(men)} \end{pmatrix}$$

A corresponding free and interactive web-based risk engine for the calculation of ESKD risk is available online from http://www.sdcc.dk/T1RiskEngine.

Supplemental Table 5. Parameter estimates for the predictors included in the *extended model*

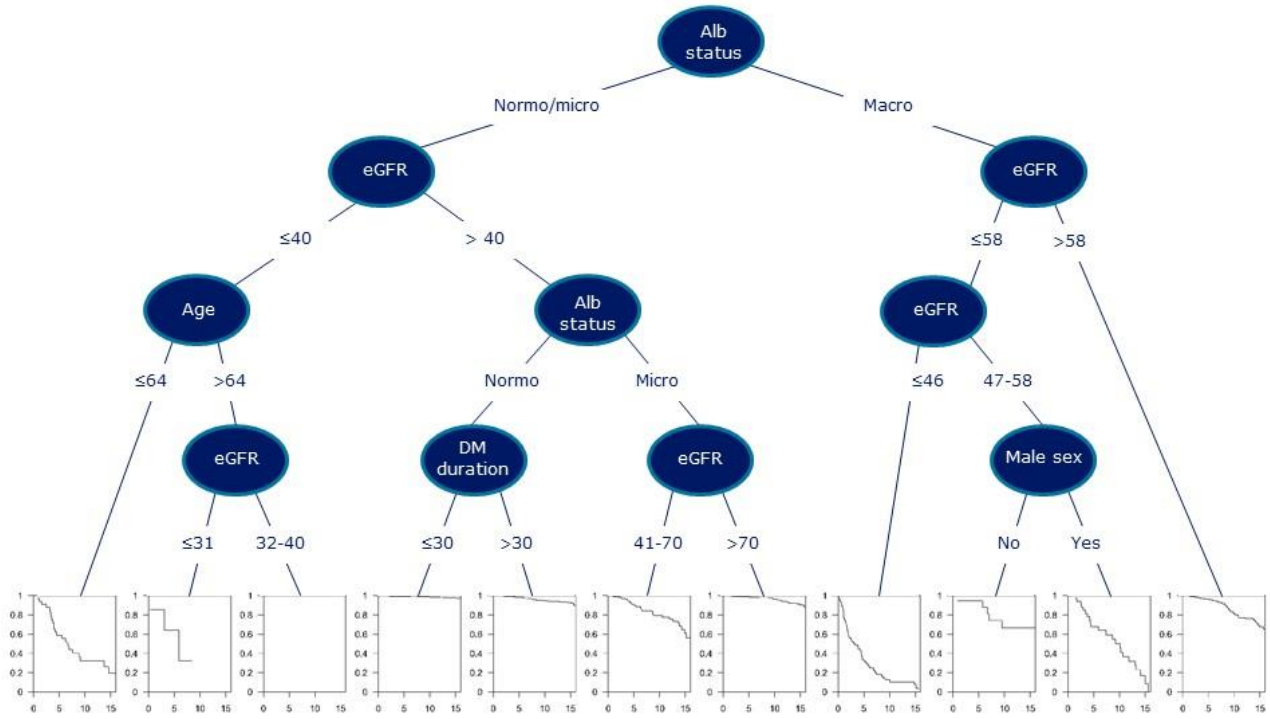
			ESKD			Non-ESKD death	
			Original	**PES**		**Original**	**PES**
Intercept		α =	5.761254	4.483810	σ =	3.061301	0.413924
Age	(years)	β_1 =	-0.020530	-0.017250	γ_1 =	0.070157	0.072779
Male sex	(1 for yes, 0 for no)	β_2 =	0.378421	0.242121	γ_2 =	0.407216	0.326529
Diabetes duration	(years)	β_3 =	0.014153	0.011952	γ_3 =	0.005618	0.004141
eGFR	(mL/min/1.73m^2)	β_4 =	-1.937920	-1.879950			
Microalbuminuria	(1 for yes, 0 for no)	β_5 =	-0.763170	-0.694890			
Macroalbuminuria	(1 for yes, 0 for no)	β_6 =	-1.076780	-0.980110			
Systolic blood pressure	(mmHg)	β_7 =	0.006319	0.004773	γ_4 =	-0.007370	-0.007620
HbA_{1c}	(mmol/mol)	β_8 =	0.009988	0.006943			
Current smoking	(1 for yes, 0 for no)				γ_5 =	0.503585	0.561868
Previous CVD event	(1 for yes, 0 for no)	β_9 =	0.288113	0.234314	γ_6 =	0.537592	0.486676
Hemoglobin	(mmol/L)	β_{10} =	-0.182160	-0.094450	γ_7 =	-0.067160	-0.068300
Mild/moderate retinopathy	(1 for yes, 0 for no)	β_{11} =	0.508559	0.566275	γ_8 =	-0.239990	-0.136980
Severe retinopathy	(1 for yes, 0 for no)	β_{12} =	0.050643	0.056184	γ_9 =	0.193691	0.157479
UACR	(mg/g)	β_{13} =	0.249721	0.211375	γ_{10} =	-0.218460	-0.176130
BMI	(mmol/L)				γ_{11} =	0.124892	0.100726
Triglycerides	(mmol/L)				γ_{12} =	-0.649950	-0.643150
Regular exercise	(1 for yes, 0 for no)				γ_{13} =	0.096787	0.066421
Sodium	(mmol/L)				γ_{14} =	-0.055160	-0.046110

PES: post estimation shrinkage; eGFR: estimated glomerular filtration rate; CVD: cardiovascular disease; UACR: urinary albumin-to-creatinine ratio; †Regular exercise: ≥ 30 minutes per day

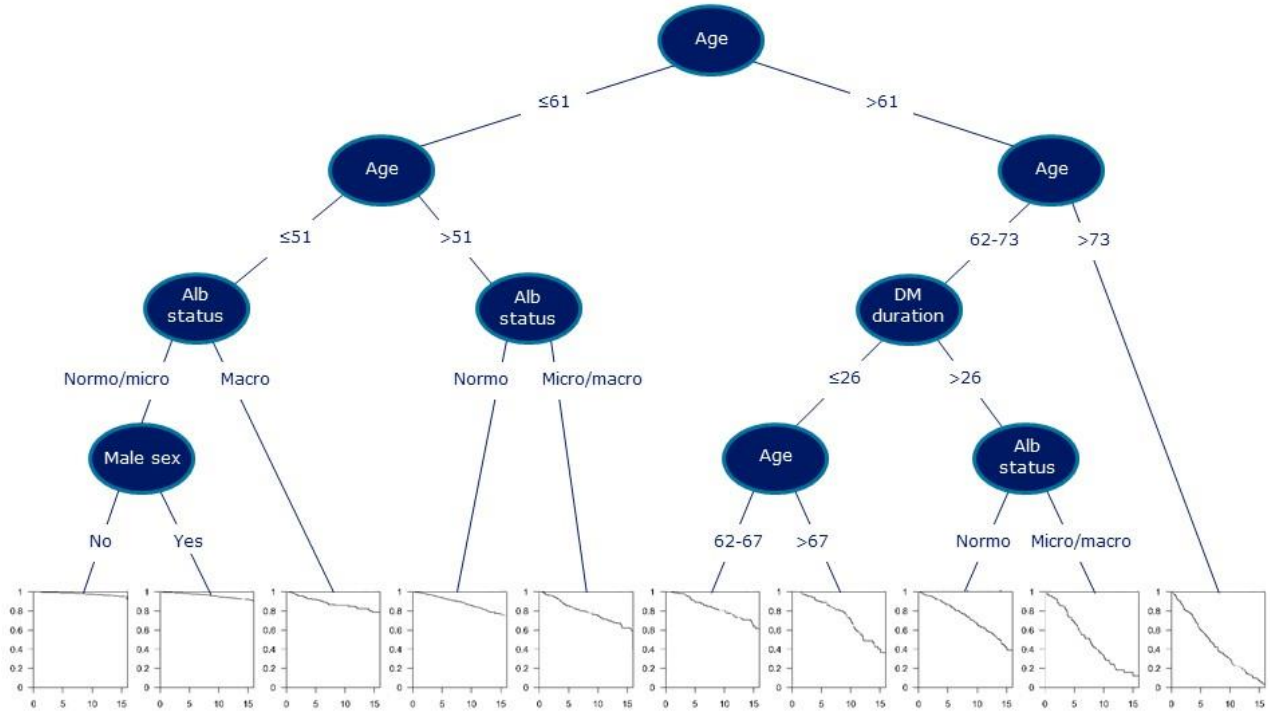
The annual incidence rate of ESKD and death in the *extended model* can be calculated from the parameters in Supplemental Table S5 as:

$$\lambda_{ESKD} = exp\begin{pmatrix} \alpha + \beta_1.age + \beta_2.male + \beta_3.DM\ duration + \beta_4.log2(eGFR) \\ +\beta_5.microalbuminuria + \beta_6.macroalbuminuria \\ +\beta_7.systolic\ BP + \beta_8.HbA_{1c} + \beta_9.previous\ CVD + \beta_{10}.haemoglobin \\ +\beta_{11}.mild/moderate\ retinopathy + \beta_{12}.severe\ retinopathy + \beta_{13}.Log2(UACR) \end{pmatrix}$$

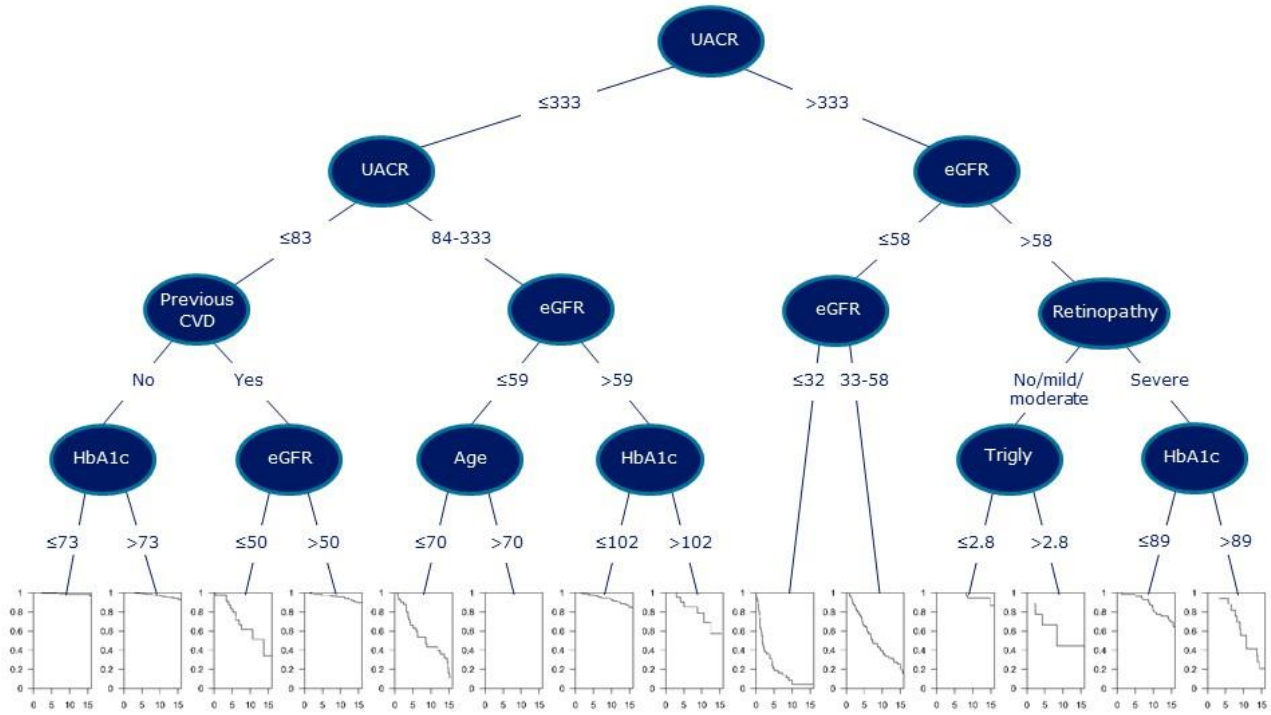
$$\lambda_{death} = exp\begin{pmatrix} \sigma + \gamma_1.age + \gamma_2.male + \gamma_3.DM\ duration \\ +\gamma_4.systolic\ BP + \gamma_5.smoking + \gamma_6.previous\ CVD + \gamma_7.haemoglobin \\ +\gamma_8.mild/moderate\ retinopathy + \gamma_9.severe\ retinopathy + \gamma_{10}.Log2(UACR) \\ +\gamma_{11}.BMI + \gamma_{12}.Log2(triglycerides) + \gamma_{13}.regular\ exercise + \gamma_{14}.sodium \end{pmatrix}$$



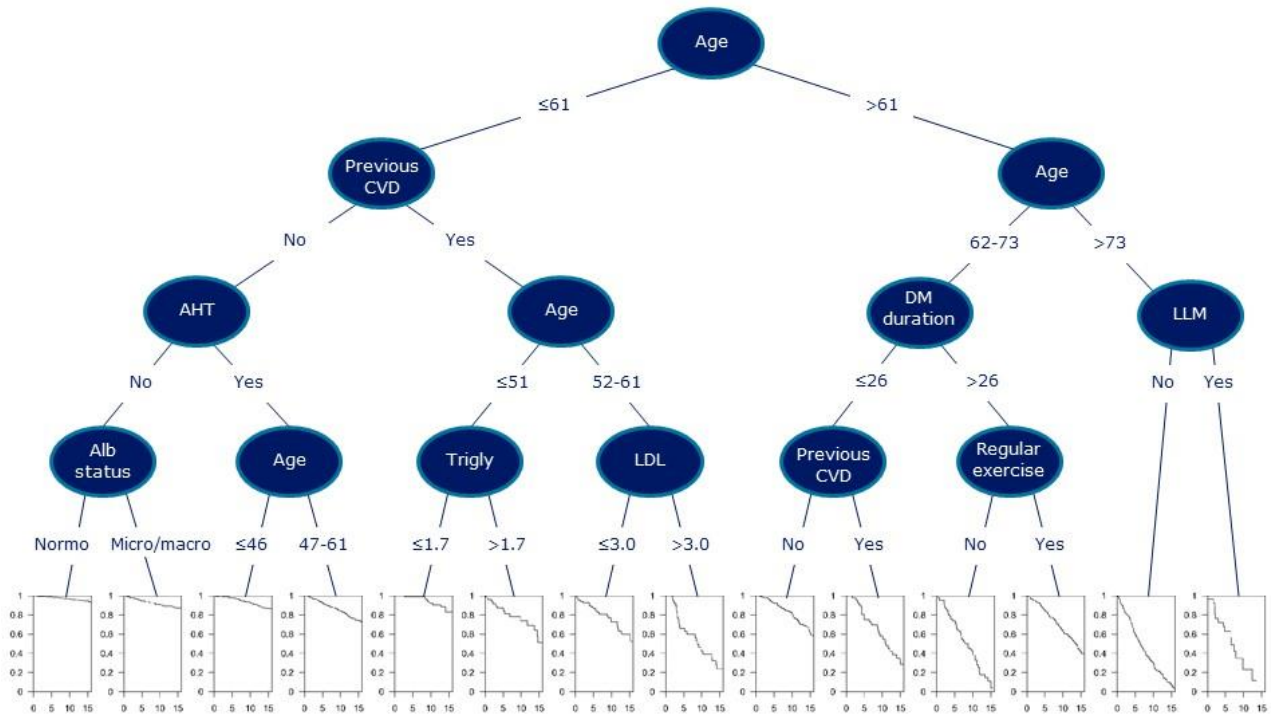
Supplemental Figure 1. Survival tree for <u>end-stage kidney disease</u> with depth 4 generated from the predictors of the *core model* using the ctree function from the party package in R



Supplemental Figure 2. Survival tree for <u>non-ESKD death</u> with depth 4 generated from the predictors of the *core model* using the ctree function from the party package in R



Supplemental Figure 3. Survival tree for <u>end-stage kidney disease</u> with depth 4 generated from the predictors of the *extended model* using the ctree function from the party package in R



Supplemental Figure 4. Survival tree for <u>non-ESKD death</u> with depth 4 generated from the predictors of the *extended model* using the ctree function from the party package in R