Electronic Supplementary Material 1

Development and Internal Validation of a Discrete Event Simulation Model of Diabetic Kidney Disease Using CREDENCE Trial Data

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Table S1. Baseline Patient Characteristics, by Study Arm and Overall

		Canagliflozin Arm (N = 2,202)			Placebo Arm (N = 2,199)			Overall (N = 4,401)		
	Units	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**	**N**
Age	Years	62.88	9.17	2,202	63.16	9.23	2,199	63.02	9.20	4,401
Age at T2DM diagnosis	Years	47.33	11.06	2,202	47.14	11.12	2,199	47.24	11.09	4,401
Female	Proportion	0.35	0.48	2,202	0.33	0.47	2,199	0.34	0.47	4,401
Smoking status	Proportion	0.16	0.36	2,202	0.14	0.34	2,199	0.15	0.35	4,401
T2DM duration	Years	15.55	8.68	2,202	16.02	8.58	2,199	15.78	8.63	4,401
eGFR	mL/min/1.73 m^2	56.35	18.17	2,201[a]	56.01	18.33	2,199	56.18	18.24	4,400
ln(UACR)	mg/dL	6.77	1.02	2,202	6.81	1.01	2,199	6.79	1.02	4,401
MI Hx	Proportion	0.10	0.30	2,202	0.10	0.30	2,199	0.10	0.30	4,401
Stroke Hx	Proportion	0.10	0.30	2,202	0.11	0.31	2,199	0.10	0.31	4,401
HF Hx	Proportion	0.15	0.36	2,202	0.15	0.35	2,199	0.15	0.36	4,401

[a]One missing value

eGFR estimated glomerular filtration rate, HF heart failure, Hx history, MI myocardial infarction, T2DM type 2 diabetes mellitus, UACR urine albumin-to-creatinine ratio

Table S2. Explanatory Covariates

Variable	Dialysis	DoSCr	Nonfatal MI	Nonfatal Stroke	HHF	ACM	CV Death	ESKD
Age at diagnosis	x	x	x	x	x	x	x	x
Diabetes duration							x	
Time (weeks)								
Female	x	x	x	x	x	x	x	x
Smoking	x	x	x	x	x	x		x
MI Hx	x	x	x	x	x	x		x
MI Hx[a]						x	x	
Stroke Hx	x	x	x	x	x	x		x
Stroke Hx[a]						x	x	
HF Hx	x	x	x	x	x	x		x
HF Hx[a]						x	x	
eGFR	x	x						x
eGFR ≥60			x	x	x			
eGFR <60, ≥45			x	x	x			
eGFR <60, ≥45[a]							x	
eGFR <45, ≥30			x	x	x			
eGFR <45, ≥30[a]							x	
eGFR <30			x	x	x			
eGFR <15[a]						x		
ln(UACR)	x	x						x
UACR >300			x	x	x			
UACR >300[a]							x	
UACR ≤300			x	x	x			
Start of maintenance dialysis[a]						x	x	
First-year indicator	x	x						x
Canagliflozin							x	

[a]Time-varying

ACM all-cause mortality, CV cardiovascular, DoSCr doubling of serum creatinine, eGFR estimated glomerular filtration rate, ESKD end-stage kidney disease, HF heart failure, HHF hospitalization for heart failure, Hx history, MI myocardial infarction, UACR urine albumin:creatinine ratio

Table S3. Correlation Matrices for Baseline Patient Characteristics - Overall

Overall	Age	Female	Smoking Status	T2DM Duration	eGFR	ln(UACR)	MI Hx	Stroke Hx	HF Hx	Age at T2DM Diagnosis
Age	1.000									
Female	-0.007	1.000								
Smoking status	-0.087	-0.114	1.000							
T2DM duration	0.227	0.034	-0.060	1.000						
eGFR	-0.144	0.007	0.079	-0.131	1.000					
ln(UACR)	-0.125	0.018	0.023	0.020	-0.108	1.000				
MI Hx	0.078	-0.067	-0.005	0.020	-0.050	0.006	1.000			
Stroke Hx	0.064	0.001	0.007	0.023	-0.010	0.000	0.032	1.000		
HF Hx	0.097	0.047	-0.037	-0.040	0.018	0.021	0.125	0.049	1.000	
Age at T2DM diagnosis	0.653	-0.032	-0.025	-0.590	-0.018	-0.119	0.050	0.035	0.112	1.000

eGFR estimated glomerular filtration rate, HF heart failure, Hx history, MI myocardial infarction, UACR urine albumin:creatinine ratio

Table S4. Number of Events in CREDENCE for the Placebo Arm

Outcome	Subjects in the Placebo Arm	Number of Events
Start of dialysis	2,012	100
Doubling of serum creatinine	2,013	186
Nonfatal MI	2,199	81
Nonfatal stroke	2,199	65
HHF	2,199	129
Death	2,199	201
CV cause of death	201	140

CREDENCE Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation, HHF hospitalization for heart failure, MI myocardial infarction

Table S5. Covariance Matrix for Start of Dialysis Regression Coefficients

	Age at Diagnosis	Female	Smoking	MI Hx	Stroke Hx	HF Hx	ln(UACR)	eGFR	First-year Indicator	Intercept	Shape Parameter
Age at diagnosis	9.47E-05	-4.32E-05	2.24E-05	-7.45E-04	-3.07E-05	-5.84E-04	2.89E-04	1.34E-05	2.00E-04	-1.70E-02	2.44E-03
Female	-4.32E-05	4.99E-02	7.90E-03	1.17E-02	7.17E-03	-4.01E-03	-4.02E-03	7.46E-05	7.69E-03	-1.49E-02	6.89E-03
Smoking	2.24E-05	7.90E-03	1.62E-01	1.13E-02	7.60E-03	-1.43E-03	5.25E-03	2.14E-04	1.46E-02	-1.17E-01	1.20E-02
MI Hx	-7.45E-04	1.17E-02	1.13E-02	1.45E-01	-4.55E-03	1.17E-02	-8.04E-03	-1.05E-04	1.06E-02	1.67E-01	-2.04E-02
Stroke Hx	-3.07E-05	7.17E-03	7.60E-03	-4.55E-03	8.63E-02	2.44E-02	-3.13E-03	1.94E-04	2.35E-02	-6.54E-02	1.48E-02
HF Hx	-5.84E-04	-4.01E-03	-1.43E-03	1.17E-02	2.44E-02	8.67E-02	-4.53E-03	-3.67E-04	9.93E-03	1.67E-02	1.01E-02
ln(UACR)	2.89E-04	-4.02E-03	5.25E-03	-8.04E-03	-3.13E-03	-4.53E-03	2.33E-02	2.18E-04	-1.29E-03	-2.11E-01	2.69E-03
eGFR	1.34E-05	7.46E-05	2.14E-04	-1.05E-04	1.94E-04	-3.67E-04	2.18E-04	9.00E-05	2.36E-04	-6.89E-03	2.41E-04
First-year indicator	2.00E-04	7.69E-03	1.46E-02	1.06E-02	2.35E-02	9.93E-03	-1.29E-03	2.36E-04	5.87E-02	-1.96E-01	3.96E-02
Intercept	-1.70E-02	-1.49E-02	-1.17E-01	1.67E-01	-6.54E-02	1.67E-02	-2.11E-01	-6.89E-03	-1.96E-01	7.60E+00	-1.17E+00
Shape parameter	2.44E-03	6.89E-03	1.20E-02	-2.04E-02	1.48E-02	1.01E-02	2.69E-03	2.41E-04	3.96E-02	-1.17E+00	2.42E-01

eGFR estimated glomerular filtration rate, HF heart failure, Hx history, MI myocardial infarction, UACR urine albumin:creatinine ratio

Table S6. Covariance Matrix for Doubling of Serum Creatinine Regression Coefficients

	Age at Diagnosis	Female	Smoking	MI Hx	Stroke Hx	HF Hx	First-year Indicator	ln(UACR)	eGFR	Intercept	Shape Parameter
Age at diagnosis	5.67E-05	6.64E-05	4.29E-05	-3.73E-04	1.30E-04	-3.37E-04	1.17E-04	1.99E-04	3.07E-06	-1.05E-02	9.45E-04
Female	6.64E-05	2.37E-02	4.36E-03	6.99E-03	-3.02E-03	-2.97E-04	1.24E-03	-3.06E-03	-3.83E-05	3.36E-03	1.56E-03
Smoking	4.29E-05	4.36E-03	5.82E-02	7.46E-04	9.33E-04	-8.58E-04	3.39E-03	-3.70E-04	9.17E-05	-4.42E-02	4.90E-03
MI Hx	-3.73E-04	6.99E-03	7.46E-04	6.25E-02	-1.13E-03	7.98E-03	7.00E-03	-8.36E-03	2.06E-05	1.12E-01	-6.27E-03
Stroke Hx	1.30E-04	-3.02E-03	9.33E-04	-1.13E-03	7.22E-02	1.45E-03	6.46E-04	3.24E-04	7.20E-05	-4.36E-02	4.08E-03
HF Hx	-3.37E-04	-2.97E-04	-8.58E-04	7.98E-03	1.45E-03	5.03E-02	6.03E-04	-2.91E-03	1.14E-05	6.90E-02	-5.76E-03
First-year indicator	1.17E-04	1.24E-03	3.39E-03	7.00E-03	6.46E-04	6.03E-04	2.68E-02	-1.97E-03	8.51E-05	-5.39E-02	7.63E-03
ln(UACR)	1.99E-04	-3.06E-03	-3.70E-04	-8.36E-03	3.24E-04	-2.91E-03	-1.97E-03	1.38E-02	4.54E-05	-1.28E-01	1.91E-03
eGFR	3.07E-06	-3.83E-05	9.17E-05	2.06E-05	7.20E-05	1.14E-05	8.51E-05	4.54E-05	2.93E-05	-2.95E-03	1.64E-04
Intercept	-1.05E-02	3.36E-03	-4.42E-02	1.12E-01	-4.36E-02	6.90E-02	-5.39E-02	-1.28E-01	-2.95E-03	4.20E+00	-3.87E-01
Shape parameter	9.45E-04	1.56E-03	4.90E-03	-6.27E-03	4.08E-03	-5.76E-03	7.63E-03	1.91E-03	1.64E-04	-3.87E-01	4.77E-02

eGFR estimated glomerular filtration rate, HF heart failure, Hx history, MI myocardial infarction, UACR urine albumin:creatinine ratio

Table S7. Covariance Matrix for Nonfatal MI Regression Coefficients

	Age at Diagnosis	Sex (Female)	Smoking	MI Hx	Stroke Hx	HF Hx	eGFR ≥60	eGFR <60, ≥45	eGFR <45, ≥30	UACR >300	Intercept
Age at diagnosis	1.02E-04	1.39E-04	2.46E-05	-2.89E-04	-1.85E-04	-3.41E-04	3.86E-04	3.38E-04	2.86E-04	4.13E-04	-5.50E-03
Sex (female)	1.39E-04	5.68E-02	7.99E-03	6.21E-03	8.50E-04	-5.08E-03	6.69E-03	6.43E-03	8.80E-03	4.29E-03	-4.01E-02
Smoking	2.46E-05	7.99E-03	7.74E-02	5.18E-03	2.93E-03	3.37E-03	6.71E-04	6.67E-03	9.25E-03	-3.75E-03	-2.45E-02
MI Hx	-2.89E-04	6.21E-03	5.18E-03	6.36E-02	-4.59E-03	-6.19E-03	2.64E-03	7.90E-04	-1.08E-03	-3.74E-03	-3.27E-03
Stroke Hx	-1.85E-04	8.50E-04	2.93E-03	-4.59E-03	1.15E-01	-8.69E-04	1.41E-03	-2.29E-04	-4.88E-04	3.45E-03	-8.16E-03
HF Hx	-3.41E-04	-5.08E-03	3.37E-03	-6.19E-03	-8.69E-04	1.17E-01	-4.23E-03	-2.31E-03	-1.12E-03	-4.52E-03	1.13E-02
eGFR ≥60	3.86E-04	6.69E-03	6.71E-04	2.64E-03	1.41E-03	-4.23E-03	2.42E-01	2.02E-01	2.02E-01	-1.41E-03	-2.22E-01
eGFR <60, ≥45	3.38E-04	6.43E-03	6.67E-03	7.90E-04	-2.29E-04	-2.31E-03	2.02E-01	2.52E-01	2.02E-01	4.73E-04	-2.22E-01
eGFR <45, ≥30	2.86E-04	8.80E-03	9.25E-03	-1.08E-03	-4.88E-04	-1.12E-03	2.02E-01	2.02E-01	2.35E-01	-4.43E-03	-2.17E-01
UACR >300	4.13E-04	4.29E-03	-3.75E-03	-3.74E-03	3.45E-03	-4.52E-03	-1.41E-03	4.73E-04	-4.43E-03	1.42E-01	-1.45E-01
Intercept	-5.50E-03	-4.01E-02	-2.45E-02	-3.27E-03	-8.16E-03	1.13E-02	-2.22E-01	-2.22E-01	-2.17E-01	-1.45E-01	6.33E-01

eGFR estimated glomerular filtration rate, HF heart failure, Hx history, MI myocardial infarction, UACR urine albumin:creatinine ratio

Table S8. Covariance Matrix for Nonfatal Stroke Regression Coefficients

	Age at Diagnosis	Sex (Female)	Smoking	MI Hx	Stroke Hx	HF Hx	eGFR ≥60	eGFR <60, ≥45	eGFR <45, ≥30	UACR >300	Intercept
Age at diagnosis	1.24E-04	1.46E-04	7.78E-05	-1.93E-04	-1.60E-04	-5.20E-04	4.94E-04	4.99E-04	3.89E-04	4.22E-04	-6.56E-03
Sex (female)	1.46E-04	8.47E-02	9.02E-03	7.10E-03	1.39E-03	-5.01E-03	7.81E-03	8.17E-03	1.16E-02	5.13E-03	-4.27E-02
Smoking	7.78E-05	9.02E-03	2.19E-01	6.35E-03	-7.72E-05	3.35E-03	-3.16E-04	5.06E-03	7.61E-03	-2.78E-03	-2.59E-02
MI Hx	-1.93E-04	7.10E-03	6.35E-03	9.43E-02	-7.44E-03	-7.94E-03	-8.63E-04	-3.72E-03	-7.79E-03	-2.83E-03	-3.67E-03
Stroke Hx	-1.60E-04	1.39E-03	-7.72E-05	-7.44E-03	8.42E-02	-3.02E-03	-7.02E-04	-4.15E-03	-3.71E-03	2.65E-03	-1.11E-02
HF Hx	-5.20E-04	-5.01E-03	3.35E-03	-7.94E-03	-3.02E-03	9.97E-02	-4.46E-03	-4.63E-03	-1.40E-03	-2.08E-03	1.35E-02
eGFR ≥60	4.94E-04	7.81E-03	-3.16E-04	-8.63E-04	-7.02E-04	-4.46E-03	3.82E-01	3.36E-01	3.36E-01	-2.81E-03	-3.57E-01
eGFR <60, ≥45	4.99E-04	8.17E-03	5.06E-03	-3.72E-03	-4.15E-03	-4.63E-03	3.36E-01	3.82E-01	3.37E-01	-4.32E-03	-3.56E-01
eGFR <45, ≥30	3.89E-04	1.16E-02	7.61E-03	-7.79E-03	-3.71E-03	-1.40E-03	3.36E-01	3.37E-01	3.93E-01	-8.20E-03	-3.48E-01
UACR >300	4.22E-04	5.13E-03	-2.78E-03	-2.83E-03	2.65E-03	-2.08E-03	-2.81E-03	-4.32E-03	-8.20E-03	2.19E-01	-2.18E-01
Intercept	-6.56E-03	-4.27E-02	-2.59E-02	-3.67E-03	-1.11E-02	1.35E-02	-3.57E-01	-3.56E-01	-3.48E-01	-2.18E-01	8.78E-01

eGFR estimated glomerular filtration rate, HF heart failure, Hx history, MI myocardial infarction, UACR urine albumin:creatinine ratio

Table S9. Covariance Matrix for HHF Regression Coefficients

	Age at Diagnosis	Sex (Female)	Baseline Smoking	MI Hx	Stroke Hx	HF Hx	eGFR ≥60	eGFR <60, ≥45	eGFR <45, ≥30	UACR >300	Intercept	Shape Parameter
Age at diagnosis	1.05E-04	7.91E-05	1.18E-04	-1.92E-04	-1.76E-04	-2.05E-04	5.30E-04	4.10E-04	2.84E-04	1.65E-04	-1.74E-02	8.84E-04
Sex (female)	7.91E-05	3.70E-02	5.40E-03	3.32E-03	9.58E-04	-3.30E-03	2.51E-03	3.10E-03	4.53E-03	1.71E-03	-2.21E-02	6.10E-05
Smoking	1.18E-04	5.40E-03	5.85E-02	2.83E-03	1.29E-04	2.06E-03	-1.34E-03	1.12E-03	2.18E-03	-1.60E-03	-3.94E-02	1.65E-03
MI Hx	-1.92E-04	3.32E-03	2.83E-03	4.62E-02	-2.53E-03	-4.41E-03	7.88E-04	1.05E-03	-4.52E-04	-3.23E-03	1.78E-02	-1.20E-03
Stroke Hx	-1.76E-04	9.58E-04	1.29E-04	-2.53E-03	7.22E-02	-1.30E-03	-7.80E-04	-3.24E-03	-2.62E-03	3.48E-03	2.56E-02	-1.99E-03
HF Hx	-2.05E-04	-3.30E-03	2.06E-03	-4.41E-03	-1.30E-03	3.95E-02	-1.44E-03	-1.04E-03	-5.21E-04	-1.43E-03	9.18E-04	1.47E-04
eGFR ≥60	5.30E-04	2.51E-03	-1.34E-03	7.88E-04	-7.80E-04	-1.44E-03	1.93E-01	1.69E-01	1.68E-01	-2.12E-03	-2.60E-01	4.98E-03
eGFR <60, ≥45	4.10E-04	3.10E-03	1.12E-03	1.05E-03	-3.24E-03	-1.04E-03	1.69E-01	1.98E-01	1.68E-01	-2.75E-03	-2.22E-01	2.63E-03
eGFR <45, ≥30	2.84E-04	4.53E-03	2.18E-03	-4.52E-04	-2.62E-03	-5.21E-04	1.68E-01	1.68E-01	1.90E-01	-4.39E-03	-1.85E-01	4.03E-04
UACR >300	1.65E-04	1.71E-03	-1.60E-03	-3.23E-03	3.48E-03	-1.43E-03	-2.12E-03	-2.75E-03	-4.39E-03	1.53E-01	-1.31E-01	-1.34E-03
Intercept	-1.74E-02	-2.21E-02	-3.94E-02	1.78E-02	2.56E-02	9.18E-04	-2.60E-01	-2.22E-01	-1.85E-01	-1.31E-01	5.45E+00	-3.18E-01
Shape parameter	8.84E-04	6.10E-05	1.65E-03	-1.20E-03	-1.99E-03	1.47E-04	4.98E-03	2.63E-03	4.03E-04	-1.34E-03	-3.18E-01	2.05E-02

eGFR estimated glomerular filtration rate, HF heart failure, Hx history, MI myocardial infarction, UACR urine albumin:creatinine ratio

Table S10. Covariance Matrix for All-cause Mortality Regression Coefficients

	Age (at Diagnosis/at Death)	HF Hx	MI Hx	Stroke Hx	Smoking Status	Female	MI Hx[a]	HF Hx[a]	Stroke Hx[a]	eGFR <15[a]	Start of Maintenance Dialysis[a]	*Intercept*
Age (at diagnosis/at death)	4.01E-05	-7.87E-05	-4.10E-05	-3.86E-05	4.53E-05	5.95E-05	-2.77E-05	-3.39E-05	1.37E-05	-1.82E-04	4.55E-04	-2.01E-03
HF Hx	-7.87E-05	3.13E-02	-3.08E-03	-4.20E-04	2.97E-03	-3.94E-03	7.20E-04	-5.95E-03	7.39E-04	7.30E-03	-5.18E-03	-9.85E-04
MI Hx	-4.10E-05	-3.08E-03	3.79E-02	-2.34E-03	2.68E-03	2.49E-03	-3.24E-03	-3.89E-03	-1.99E-03	4.43E-03	-2.21E-03	-3.23E-03
Stroke Hx	-3.86E-05	-4.20E-04	-2.34E-03	3.93E-02	-2.72E-04	5.89E-04	7.33E-04	3.79E-03	-7.16E-03	6.25E-03	-6.66E-03	-3.69E-03
Smoking Status	4.53E-05	2.97E-03	2.68E-03	-2.72E-04	4.21E-02	3.37E-03	-4.30E-03	-6.16E-04	3.73E-03	-2.07E-03	3.82E-03	-1.04E-02
Female	5.95E-05	-3.94E-03	2.49E-03	5.89E-04	3.37E-03	2.52E-02	2.27E-04	5.18E-04	2.65E-03	-2.80E-03	6.89E-03	-1.17E-02
MI Hx[a]	-2.77E-05	7.20E-04	-3.24E-03	7.33E-04	-4.30E-03	2.27E-04	5.94E-02	-2.57E-02	4.33E-03	4.53E-03	-1.27E-02	-1.21E-03
HF Hx[a]	-3.39E-05	-5.95E-03	-3.89E-03	3.79E-03	-6.16E-04	5.18E-04	-2.57E-02	5.29E-02	-6.00E-03	-3.31E-03	-1.12E-02	-3.06E-04
Stroke Hx[a]	1.37E-05	7.39E-04	-1.99E-03	-7.16E-03	3.73E-03	2.65E-03	4.33E-03	-6.00E-03	4.89E-02	4.92E-03	-4.66E-04	-6.77E-03
eGFR <15[a]	-1.82E-04	7.30E-03	4.43E-03	6.25E-03	-2.07E-03	-2.80E-03	4.53E-03	-3.31E-03	4.92E-03	9.93E-02	-6.06E-02	3.76E-03
Start of maintenance dialysis[a]	4.55E-04	-5.18E-03	-2.21E-03	-6.66E-03	3.82E-03	6.89E-03	-1.27E-02	-1.12E-02	-4.66E-04	-6.06E-02	9.55E-02	-2.45E-02
Intercept	-2.01E-03	-9.85E-04	-3.23E-03	-3.69E-03	-1.04E-02	-1.17E-02	-1.21E-03	-3.06E-04	-6.77E-03	3.76E-03	-2.45E-02	1.14E-01

[a]Time-varying

eGFR estimated glomerular filtration rate, HF heart failure, Hx history, MI myocardial infarction, UACR urine albumin:creatinine ratio

Table S11. Covariance Matrix for Cardiovascular Cause of Death Regression Coefficients

	Age (at Diagnosis/at Death)	Sex (Female)	MI Hx[a]	HF Hx[a]	Stroke Hx[a]	eGFR <60, ≥45[a]	eGFR <45, ≥30[a]	eGFR <30[a]	UACR >300[a]	Start of Maintenance Dialysis[a]	Diabetes Duration	Intercept
Age (at diagnosis/at death)	1.15E-04	-9.30E-05	-1.20E-04	3.00E-05	-9.00E-05	-4.20E-04	-1.80E-04	1.70E-04	1.50E-04	1.70E-04	-1.15E-04	-5.47E-03
Sex (female)	-9.25E-05	6.59E-02	3.65E-03	-6.84E-03	2.54E-03	3.59E-03	-4.35E-03	-6.48E-03	2.25E-03	6.53E-03	9.77E-05	-1.87E-02
MI Hx[a]	-1.23E-04	3.66E-03	7.81E-02	-5.51E-03	-6.40E-04	-1.70E-04	-2.10E-03	2.23E-03	-1.21E-03	-3.66E-03	1.19E-04	-6.35E-03
HF Hx[a]	3.39E-05	-6.84E-03	-5.51E-03	6.80E-02	-1.23E-03	1.01E-03	4.37E-03	-5.70E-04	-2.77E-03	2.88E-03	-5.01E-05	-7.53E-03
Stroke Hx[a]	-8.69E-05	2.54E-03	-6.40E-04	-1.23E-03	8.55E-02	-1.43E-02	-9.33E-03	-1.01E-03	-1.44E-03	-5.67E-03	8.64E-05	-4.70E-03
eGFR <60, ≥45[a]	-4.24E-04	3.59E-03	-1.70E-04	1.01E-03	-1.43E-02	1.36E-01	6.50E-02	6.74E-02	-1.93E-02	-3.76E-03	4.08E-04	-1.69E-02
eGFR <45, ≥30[a]	-1.84E-04	-4.35E-03	-2.10E-03	4.37E-03	-9.33E-03	6.50E-02	1.01E-01	6.68E-02	-7.76E-03	-1.19E-02	1.71E-04	-3.65E-02
eGFR <30[a]	1.72E-04	-6.49E-03	2.23E-03	-5.70E-04	-1.01E-03	6.74E-02	6.68E-02	1.46E-01	-1.95E-02	-3.40E-02	-2.02E-04	-3.47E-02
UACR >300[a]	1.53E-04	2.25E-03	-1.21E-03	-2.77E-03	-1.44E-03	-1.93E-02	-7.76E-03	-1.95E-02	8.74E-02	-6.33E-03	-1.48E-04	-6.79E-02
Start of maintenance dialysis[a]	1.74E-04	6.53E-03	-3.66E-03	2.88E-03	-5.67E-03	-3.76E-03	-1.19E-02	-3.40E-02	-6.33E-03	1.30E-01	-1.75E-04	-8.80E-03
Diabetes duration	-1.15E-04	9.80E-05	1.20E-04	-5.00E-05	9.00E-05	4.10E-04	1.70E-04	-2.00E-04	-1.50E-04	-1.70E-04	1.15E-04	5.38E-03
Intercept	-5.47E-03	-1.87E-02	-6.35E-03	-7.53E-03	-4.70E-03	-1.69E-02	-3.65E-02	-3.47E-02	-6.79E-02	-8.80E-03	5.38E-03	4.27E-01

[a]Time-varying

eGFR estimated glomerular filtration rate, HF heart failure, Hx history, MI myocardial infarction, UACR urine albumin:creatinine ratio

Risk Prediction Equation of ESKD

A description of the results for ESKD, which was intended for assessing the robustness of the dialysis equation, is presented in Table S12 and the associated predictions of the cumulative incidence graphically compared with the study Kaplan-Meier curves are presented in Figure S1. The results are in line with those of start of maintenance dialysis with the exception of stroke, which had a statistically insignificant protective effect.

Table S12. Risk Equations: ESKD

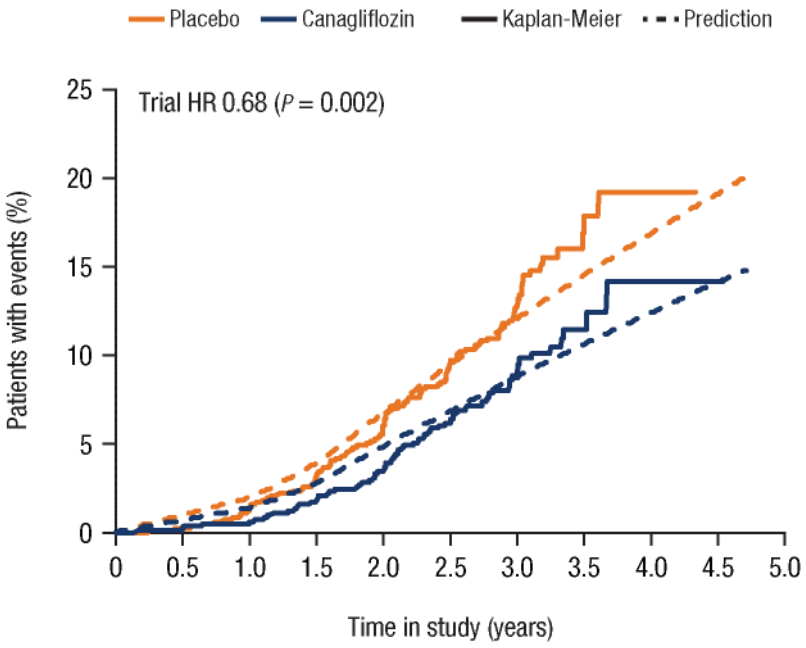
	ESKD Weibull N = 2,012 100 Events	
Parameter	HR (SE)	*P*
Intercept	4.16E-04 (8.67E-04)	<0.001
P[a]	0.438 (0.138)	<0.001
Age at T2DM diagnosis	0.973 (0.007)	<0.001
Female	0.931 (0.150)	0.657
Smoking	0.633 (0.162)	0.073
MI Hx	0.853 (0.214)	0.527
Stroke Hx	0.911 (0.238)	0.721
HF Hx	0.921 (0.197)	0.7
eGFR	0.939 (0.006)	<0.001
ln(UACR)	3.496 (0.413)	<0.001
First-year indicator	0.245 (0.042)	<0.001
AIC	165.315	
C statistic		
Placebo	0.865	
Canagliflozin	0.856	
Calibration		
Placebo	0.998	
Canagliflozin[b]	1.089	

[a]Time-varying

[b]After adjusting for the trial-reported HR for canagliflozin.

AIC Akaike information criterion, CV cardiovascular, eGFR estimated glomerular filtration rate, ESKD end-stage kidney disease, HF heart failure, HR hazard ratio, Hx history, MI myocardial infarction, SE standard error, UACR urine albumin:creatinine ratio

Figure S1. Predicted cumulative incidence of ESKD vs. study Kaplan-Meier, by study arm.



ESKD end-stage kidney disease, HR hazard ratio

Table S13. Stress-testing Overview

Scenario		Description	BC Value	Test value	Expected Outcomes	Results
Base Case	**BC**	--	--	--	(1) CV event rates should be lower in the intervention arm (2) Rates for dialysis and transplant should be lower in the intervention arm (3) CKD should progress over time with no regression of CKD (4) AE rates should be 0 in the comparator arm (5) CV mortality should be lower in the intervention arm (6) Procedural mortality should be lower in the intervention arm (7) Other cause mortality should be lower in the intervention arm (8) SoC costs should equal 100 X LY in the intervention arm	
transplant stage 5 pre-RRT	**T1**	Set an extremely high risk of transplant in stage 5 pre-RRT	Start eGFR: 55 Event rate pre-RRT: 0.1 Event rate post-RRT: 0.1	Start eGFR: 15 Event rate pre-RRT: 10000 Event rate post-RRT: 0	Everyone reaching the stage receives transplant, no-one progresses to dialysis, no costs for dialysis	Everyone reaching the stage receives transplant, no-one progresses to dialysis, no costs for dialysis
transplant stage 5 post-RRT	**T2**	Set an extremely high risk of transplant in stage 5 post-RRT, others to 0	Start eGFR: 55 Event rate pre-RRT: 0.1 Event rate post-RRT: 0.1	Start eGFR: 15 Event rate pre-RRT: 0 Event rate post-RRT: 10000 HR for dialysis set to 1000	Everyone reaching the stage receives transplant, no-one progresses to dialysis, no costs for dialysis	Everyone reaching the stage receives transplant, no-one progresses to dialysis, no costs for dialysis
transplant stage 5 pre-RRT	**T3**	Set low risk of transplant in stage 5 pre-RRT	Start eGFR: 55 Event rate pre-RRT: 0.1 Event rate post-RRT: 0.1	Start eGFR: 15 Event rate pre-RRT: 0 Event rate post-RRT: 0	No incidence of transplant, no costs for transplant	Extremely small event rates, cost indicate 1,47 events.
Minimum eGFR for transplant	**T4**	Minimum level set at 200	eGFR threshold: 10	eGFR threshold: 200 probability of transplant: 100%	Everyone receives transplant at simulation start, no start of dialysis	Everyone receives transplant at simulation start, no start of dialysis
Minimum eGFR for dialysis	**T5**	Minimum level set at 200	eGFR threshold: 10	eGFR threshold: 200 probability of transplant: 0%	Everyone receives dialysis at simulation start	Large amounts of dialysis at start

Scenario		Description	BC Value	Test value	Expected Outcomes	Results
Minimum eGFR for transplant	**T6**	Minimum level set at 0	eGFR threshold: 10	eGFR threshold: 0 probability of transplant: 100%	No start of transplant at simulation start	No start of transplant at simulation start
Minimum eGFR for dialysis	**T7**	Minimum level set at 0	eGFR threshold: 10	eGFR threshold: 0 probability of transplant: 0%	No start of dialysis at simulation start	No start of dialysis at simulation start
Minimum eGFR for death	**T8**	Minimum level set at 200	eGFR threshold: 5	eGFR threshold: 200	Everyone dies at simulation start	Everyone dies at simulation start
Minimum eGFR for death	**T9**	Minimum level set at 0	eGFR threshold: 5	eGFR threshold: 0	Results in line with BC	Results in line with BC
Extreme first year HRs mortality	**T10**	First year HR set to 0,000001	0.5	0.000001	Minimum amount of mortality in first year for intervention arm, PBO arm should be unaffected	Minimum amount of mortality in first year for intervention arm, PBO arm should be unaffected
Extreme first year HRs for mortality	**T11**	First year HR set to 100	0.5	100.0	High amount of mortality in first year for intervention arm, PBO arm should be unaffected	High amount of mortality in first year for intervention arm, PBO arm should be unaffected
Extreme first year HRs for other complications	**T12**	First year HR set to 0,000001	0.5	0.000001	Minimum number of events in first year, PBO arm should be unaffected	Minimum number of events in first year, PBO arm should be unaffected
Extreme first year HRs for other complications	**T13**	First year HR set to 100	0.5	100.0	Extreme number of events for intervention arm in first year, PBO arm should be unaffected	Extreme number of events for intervention arm in first year, PBO arm should be unaffected
No treatment effect in first year	**T14**	First year HR set to 1	0.5	1.0	Intervention arm follows comparator arm, PBO arm should be unaffected	Intervention arm follows comparator arm, PBO arm unaffected
Immediate cessation during simulation time	**T15**	Immediate secession set after year 1 and before simulation end	Inactive	Cessation after year 1	Event rates should be in line with PBO arm, Higher event rates than BC for intervention arm, PBO arm should be unaffected	Lower events in intervention arm in first year and then diminish difference between arms
Immediate cessation after simulation time	**T16**	Immediate secession set after year 100 and before simulation end	Inactive	Cessation after year 100	Same as BC	Same as BC
Fade-out during simulation	**T17**	Fade out effect at year 2 with a fade-	Inactive	Cessation after year 2 with fade-off set to 2 years	Lower event rates for intervention arm than in BC, PBO arm should be unaffected	Lower event rates for intervention arm than in BC, PBO arm should be unaffected

Scenario		Description	BC Value	Test value	Expected Outcomes	Results
		duration of 2 years				
Fade-out beyond simulation	**T18**	Fade out effect at year 2 with a fade-duration of 1000 years	Inactive	Cessation after year 2 with fade-off set to 1000 years	Results for intervention arm almost identical to those in BC and more favorable than results of Verification Test TX, PBO arm should be unaffected	Results for intervention arm almost identical to those in BC and more favorable than results of Verification Test TX, PBO arm should be unaffected
Fade-out after simulation	**T19**	Fade out effect starts after simulation ends	Inactive	Cessation after year 2 with fade-off set to 11 years	Same as BC	Same as BC
Intervention same as SoC	**T20**	Set intervention HR to 1	0.5	1.0	The results should be the same in both for both arms	Events same as Placebo
Active comparator	**T21**	Set active comparator effects to HR 1 and Intervention effects to HR 0.5	Intervention only	HR active comparator: 1.0 HR intervention: 0.5	The results should be the same as the BC for the intervention arm and the comparator arm	The results should be the same as the BC for the intervention arm and the comparator arm
Zero Values						
Progression	**T22**	Set progression to 0	As in CREDENCE	deactivated risk equations	No new events should occur	No events occurring
Pre-existing CV comorbidities	**T23**	Set pre-existing CV comorbidities to 0	CV history: 10%	CV history: 0%	State costs and disutility for CV events should be 0 in year one leading to less costs and QALYs CV compared to the BC in both arms	Less QALYs of CV compared to BC in both arms
Mortality	**T24**	Set mortality to 0	As in CREDENCE	Deactivated mortality	100% survival in both arms	Almost 100% survival, believe to be settings related
State and event costs	**T25**	Set all state and event costs to 0	Costs applied for events	No costs applied for events	Event and state costs should be 0	Event and state costs should be 0
Treatment costs	**T26**	Set treatment costs to 0	Treatment costs for intervention: 1 000	Treatment costs for intervention: 0	Treatment costs should be 0 in the intervention arm	Treatment costs should be 0 in the intervention arm
Treatment effects	**T27**	Set all HRs for the intervention	HR for intervention arm: 0.5	HR for intervention arm: 0.000001	In the Intervention arm: (1) almost 0 events should occur; (2) almost 0 event costs. In comparator arm: similar results as BC	As Expected,

Scenario		Description	BC Value	Test value	Expected Outcomes	Results
		arm to 0.000001				
Doubling of inputs		--				
Event rates	**T28**	Double all event rates	As in CREDENCE	Double the risk of events	Predicted events rates for HHF, MI, and stroke are doubled compared to BC	HHF & stroke doubled; MI substantially higher
Mortality	**T29**	Double mortality rate	As in CREDENCE	Double the risk of mortality	All-cause death is doubled compare to BC	All-cause death more than doubled compared to BC
State and event costs	**T30**	Double all state and event costs	Costs applied for events	Double costs applied for events	Event and state costs for CKD and CV should be doubled compared to BC	Event and state costs for CKD and CV doubled compared to BC
Treatment costs	**T31**	Double the treatment cost for intervention	Treatment costs for intervention/comparator: 1000	Treatment costs for intervention/comparator: 2000	Treatment cost for intervention doubled compared to BC	Treatment cost for intervention doubled compared to BC
Treatment effects	**T32**	Set all HRs for the intervention arm to 2	HR for intervention arm: 1.0	HR for intervention arm: 2.0	In intervention arm: (1) Even and CV/CKD mortality rates should be higher in the intervention arm; (2) Cost should be higher in the intervention arm; In comparator arm: similar results as BC	In intervention arm: (1) Even and CV/CKD mortality rates should be higher in the intervention arm; (2) Cost should be higher in the intervention arm; In comparator arm: similar results as BC
Baseline						
Age	**T33**	Set a low starting age	Starting age: 60(10)	Starting age: 40	(1) LY should be higher than BC	Higher LY than BC.
Age	**T34**	Set a high starting age	Starting age: 60(10)	Starting age: 80	(1) LY should be lower than BC	LY lower than BC.
Sex	**T35**	Set all patients to male	50% male/females	100% males	(1) LY should be lower vs BC	(1) LY lower vs BC
Sex	**T36**	Set all patients to female	50% male/females	100% females	(1) LY should higher vs BV	(1) LY higher vs BC
Smoking	**T37**	Set smoking status to 0%	10% Smokers	0% Smokers	(1) Lower LY vs BC	(1) Lower LY vs BC
Smoking	**T38**	Set smoking status to 100%	10% Smokers	100% Smokers	(1) Higher LY vs BC	Slightly lower LY vs BC
Diabetes Duration	**T39**	No diabetes duration	Diabetes duration 10(5)	Diabetes duration 0	(1) LY should be lower vs. BC (2) eGFR should decline more than BC	(1) LY lower vs. BC (2) very similar eGFR decline compared to BC

Scenario		Description	BC Value	Test value	Expected Outcomes	Results
Diabetes Duration	**T40**	Long diabetes duration	Diabetes duration 10(5)	Diabetes duration 20	(1) LY should be higher vs. BC (2) eGFR should decline less than BC	(1) LY higher vs. BC (2) very similar eGFR decline compared to BC
eGFR	**T41**	Set a low eGFR	Baseline eGFR: 55	Baseline eGFR: 30	(1) LY should be lower vs. BC (2) CV and CKD event should be higher vs. BC	LY lower than BC. CV and CKD event higher than BC
eGFR	**T42**	Set a high eGFR	Baseline eGFR: 55	Baseline eGFR: 90	(1) LY should be higher vs. BC (2) CV and CKD event should be lower vs. BC	(1) LY higher vs. BC (2) CV and CKD event lower vs. BC
log (UACR)	**T43**	Set a low log (UACR)	Baseline log (UACR): 6.5	Baseline log (UACR): 3	(1) LY should be higher vs. BC (2) DoSCR should be lower vs BC (3) Lower rates of CKD and CV event	(1) LY higher vs. BC (2) Lower rates of CKD and CV event. (3) DoSCr lower than BC
log (UACR)	**T44**	Set a high log (UACR)	Baseline log (UACR): 6.5	Baseline log (UACR): 9	(1) Lower LY vs BC (2) DoSCr rates should be higher vs BC (3) Higher rates of CV and CKD events	(1) Lower LY than BC. (2) DOSCr higher than BC. (3) higher event rates
Pre-existing CV comorbidities	**T45**	Set pre-existing CV complications to 100%	CV history: 10%	CV history: 100%	(1) LY should be lower vs BC (2) Costs should be greater vs. BC	(1) lower LY than BC (2) CV costs greater than BC, Higher costs in BC from treatment costs
Other logic tests						
State costs	**T46**	Set pre-existing CV complications to 100%, event and mortality rate to 0	CV history: 10% Risk: As in CREDENCE	CV history: 100% Mortality Intercept - 10,000	CV State costs should equal state costs for CV history times LY, should equal time horizon => (MI+stroke+HF) X LY => (500+500+500) X 10 =15,000	Approx. 15,000 (15,882)
Mortality	**T47**	Set mortality risk high	As in CREDENCE	Mortality intercept: 10,000	All-cause mortality should be almost 100% in year 1	Mortality at 100% at year 1
Slope effect eGFR	**T48**	Set slope to 0 for the intervention	Slope: 2.0	Slope: 0.0	(1) 100% of patients should be in Stage 5 at simulation start, (2) no progression should occur, (3) All patients should regress over time	100% of patients in Stage 5, patients regress over time
Slope effect eGFR	**T49**	Set slope to 100 for the intervention	Slope: 2.0	Slope: 100	Intervention group regress to Stage 1	Intervention group regress to Stage 1
Baseline CKD stage						
100% in stage 1	**T50**	Set baseline CKD stage to 100% in stage 1	Distribution between all CKD stages	eGFR 100	100% of patients should be in stage 1 at baseline, progression should occur over time	100% of patients should be in stage 1 at baseline, progression should occur over time

Scenario		Description	BC Value	Test value	Expected Outcomes	Results
100% in stage 2	**T51**	Set baseline CKD stage to 100% in stage 2	Distribution between all CKD stages	eGFR 75	100% of patients should be in stage 2 at baseline, progression should occur over time	100% of patients should be in stage 2 at baseline, progression should occur over time
100% in stage 3a	**T52**	Set baseline CKD stage to 100% in stage 3a	Distribution between all CKD stages	eGFR 52.5	100% of patients should be in stage 3a at baseline, progression should occur over time	100% of patients should be in stage 3a at baseline, progression should occur over time
100% in stage 3b	**T53**	Set baseline CKD stage to 100% in stage 3b	Distribution between all CKD stages	eGFR 37.5	100% of patients should be in stage 3b at baseline, progression should occur over time	100% of patients should be in stage 3b at baseline, progression should occur over time
100% in stage 4	**T54**	Set baseline CKD stage to 100% in stage 4	Distribution between all CKD stages	eGFR 22.5	100% of patients should be in stage 4 at baseline, progression should occur over time	100% of patients should be in stage 4 at baseline, progression should occur over time
100% in stage 5	**T55**	Set baseline CKD stage to 100% in stage 5	Distribution between all CKD stages	eGFR 5	100% of patients should be in stage 5 at baseline	100% of patients should be in stage 5 at baseline
Adverse events						
Once	**T56**	Set the occurrence for AE to Once	Recurrent AE	AE can only occur once	Less AE events/costs compared to BC in the intervention arm	Less AE events/costs compared to BC in the intervention arm
Permanent	**T57**	Set the occurrence for AE to permanent	Recurrent AE	AE are permanent	Less events but more costs related to AE compared to BC in the intervention arm	Less events but more costs related to AE compared to BC in the intervention arm
Stop treatment for AE A	**T58**	Set AE event rate for event A to 10 000, activate stop treatment for event A	Rate: 0.1 Stop treatment: No	Rate: 10 000 Stop treatment: Yes	(1) Intervention should be stopped almost immediately (2) The results should be the same in both treatment arms with the exception of AE-related results	No time on treatment, results similar. More transplants in intervention arm
Stop treatment for AE B	**T59**	Set AE event rate for event B to 10 000, activate stop treatment for event B	Rate: 0.1 Stop treatment: No	Rate: 10 000 Stop treatment: Yes	(1) Intervention should be stopped almost immediately (2) The results should be the same in both treatment arms with the exception of AE-related results	No time on treatment, results similar. More transplants in intervention arm

Scenario		Description	BC Value	Test value	Expected Outcomes	Results
Stop treatment for AE C	**T60**	Set AE event rate for event C to 10 000, activate stop treatment for event C	Rate: 0.1 Stop treatment: No	Rate: 10 000 Stop treatment: Yes	(1) Intervention should be stopped almost immediately (2) The results should be the same in both treatment arms with the exception of AE-related results	No time on treatment, results similar. More transplants in intervention arm
Stop treatment for AE D	**T61**	Set AE event rate for event D to 10 000, activate stop treatment for event D	Rate: 0.1 Stop treatment: No	Rate: 10 000 Stop treatment: Yes	(1) Intervention should be stopped almost immediately (2) The results should be the same in both treatment arms with the exception of AE-related results	No time on treatment, results similar. More transplants in intervention arm
Stop treatment for AE E	**T62**	Set AE event rate for event E to 10 000, activate stop treatment for event E	Rate: 0.1 Stop treatment: No	Rate: 10 000 Stop treatment: Yes	(1) Intervention should be stopped almost immediately (2) The results should be the same in both treatment arms with the exception of AE-related results	No time on treatment, results similar. More transplants in intervention arm
Discount rate	**T63**	Set discount rate to 10%	Discount rate: 0.0%	Discount rate: 10%	All costs should be less compared to the BC	All costs less compared to the BC
Time horizon 1 years	**T64**	Set time horizon to 1 years	Time horizon: 10 yrs.	Time horizon: 1 yr.	(1) Event/mortality rates should be lower than BC (2) LY should be less than 1 (3) costs should be less vs. BC	1) Events & Mortality lower than BC 2) LY less than 1. 3) Costs lower than BC.
Time horizon 5 years	**T65**	Set time horizon to 5 years	Time horizon: 10 yrs.	Time horizon: 5 yrs.	(1) Event rates should be similar to the BC (2) LY should be less than 5 (3) costs should be less vs. BC	Event rates similar to BC, LY < 5, costs lower than BC
Time horizon 20 years	**T66**	Set time horizon to 20 years	Time horizon: 10 yrs.	Time horizon: 20 yrs.	(1) Event rates should be similar to the BC (2) LY should be less than 20 (3) costs should be higher vs. BC	Approx. Similar event rates to BC, LY lower than 20, costs higher than BC
Costs						
Event costs	**T67**	Test Event Costs and Cum Incidence Match	BC Costs	Set all costs to 0. Then set event costs to1 for MI, HF, stroke, dialysis, and CV death. No discounting.	(1) Costs should match cumulative incidence for each of the selected outcomes	Cost matches

AE adverse event, BC base case, CKD chronic kidney disease, CREDENCE Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation, CV cardiovascular, DKD diabetic kidney disease, DoSCr doubling of serum creatinine, eGFR estimated glomerular filtration rate, HF heart failure, HHF hospitalization for heart failure, HR hazard ratio, LY life-year, MI myocardial infarction, PBO placebo, SoC standard of card, UACR urine albumin:creatinine ratio

Table S14. Baseline Patient Characteristics for the CANVAS Program Subgroup

	CANVAS Program Subgroup N = 567		CREDENCE N = 4,401	
	Mean	**SD**	**Mean**	**SD**
Age	64.500	7.940	63.019	9.199
Females (proportion)	0.302	0.459	0.339	0.474
Smokers (proportion)	0.164	0.371	0.145	0.352
Diabetes duration	16.200	7.940	15.783	8.629
eGFR	59.000	16.300	56.178	18.244
ln(UACR)	7.053	7.085	6.791	1.019
MI (proportion)	0.277	0.448	0.100	0.301
Stroke (proportion)	0.162	0.369	0.104	0.305
HF (proportion)	0.164	0.371	0.148	0.355

CANVAS CANagliflozin cardioVascular Assessment Study, CREDENCE Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation, eGFR estimated glomerular filtration rate, HF heart failure, MI myocardial infarction, SD standard deviation, UACR urine albumin:creatinine ratio

Table S15. HRs in the CANVAS Program Subgroup

	CANAVS Program Subgroup
Outcomes	**HR**
1st in trial nonfatal MI	0.500
1st in trial nonfatal stroke	1.263
HHF	0.689
All-cause mortality	0.764
CV death	0.892
Doubling of serum creatinine	0.600
Dialysis	N/A

CANVAS CANagliflozin cardioVascular Assessment Study, CV cardiovascular, HHF hospitalization for heart failure, HR hazard ratio, MI myocardial infarction, N/A not applicable

Numerical Examples for Programmers

To ensure reproducibility, we present sample calculations of one-year (365.25 day) risk for nonfatal MI which uses the Exponential parametric form and HHF which uses the Weibull parametric form. As typical of DES models, the formula is based on the cumulative hazard $\widehat{H}(t)$ and the probability $\hat{P}(t_0, t_1)$ of an event occurring in the interval (t_0, t_1) is calculated as $\hat{P}(t_0, t_1) = 1 - \exp(\widehat{H}(t_1) - \widehat{H}(t_0))$.

For the exponential model, the cumulative hazard was defined as $\widehat{H}_{exp}(t) = t \prod {\beta_i}^{X_i}$, where β_i are the coefficients (including intercept) and X_i are the covariates. For the Weibull model, the cumulative hazard was defined as $\widehat{H}_{Weib}(t) = t^{\rho} \prod {\beta_i}^{X_i}$, where ρ is the shape parameter. For covariates that vary during the interval, the cumulative hazard is calculated piecewise across sub-intervals.

We illustrate numerically assuming the risk corresponds to a female with the following characteristics evaluated at the simulation baseline: diagnosed with diabetes at age 50 years, diabetes duration of 5 years at baseline, smoker at baseline, history of myocardial infarction (MI), history of stroke, history of heart failure (HF), estimated glomerular filtration rate (eGFR) between 45 and 60 mL/min/1.73 m^2 at baseline, and urinary albumin:creatinine ratio (UACR) above 300 mg/g at baseline.

Estimated probability of nonfatal MI in the year is calculated as follows:

$$\widehat{H}_{MI}(t_0) = 365.25 \times 5 \times 2.97 \times 10^{-5} \times 1.003^{50} \times 1.276 \times 1.932 \times 3.584 \times 1.124 \times 0.732 \times 0.564 \times 1.213 \approx 0.313$$

$$\widehat{H}_{MI}(t_1) = 365.25 \times (5+1) \times 2.97 \times 10^{-5} \times 1.003^{50} \times 1.276 \times 1.932 \times 3.584 \times 1.124 \times 0.732 \times 0.564 \times 1.213 \approx 0.376$$

$$\hat{P}_{MI}(t_0, t_1) = 1 - \exp\left(\widehat{H}_{MI}(t_1) - \widehat{H}_{MI}(t_0)\right) \approx 1 - \exp(0.376 - 0.313) \approx 0.0607$$

Estimated probability of hospitalization for heart failure (HHF) in the year is calculated as follows:

$$\widehat{H}_{HHF}(t_0) = 365.25 \times 5 \times 1.45 \times 10^{-7} \times 1.023^{50} \times 0.996 \times 1.416 \times 2.161 \times 1.064 \times 2.253 \times 0.799 \times 2.347 \approx 0.273$$

$$\widehat{H}_{HHF}(t_1) = 365.25 \times (5+1) \times 1.45 \times 10^{-7} \times 1.023^{50} \times 0.996 \times 1.416 \times 2.161 \times 1.064 \times 2.253 \times 0.799 \times 2.347 \approx 0.354$$

$$\hat{P}_{HHF}(t_0, t_1) = 1 - \exp\left(\widehat{H}_{HHF}(t_1) - \widehat{H}_{HHF}(t_0)\right) \approx 1 - \exp(0.354 - 0.273) \approx 0.0778$$