Supplementary Material

Supplementary Table 1. Summary of survival distributions used in the analysis for each endpoint, per patient subgroup

	Full population			Established CVD			Multiple risk factors		
	Distribution	**Parameter 1**	**Parameter 2**	**Distribution**	**Parameter 1**	**Parameter 2**	**Distribution**	**Parameter 1**	**Parameter 2**
Pooled Curves: within-trial									
MI	Exponential	0.001	-	Exponential	0.002	-	Exponential	0.001	-
2nd MI	Lognormal	5.538	2.773	Lognormal	5.036	2.624	Weibull	0.720	661.631
Ischaemic stroke	Exponential	0.001	-	Exponential	0.001	-	Exponential	0.000	-
2nd Ischaemic stroke	Lognormal	7.973	3.536	Lognormal	8.598	3.894	Lognormal	7.169	3.057
HAP	Lognormal	11.212	3.426	-	-	-	-	-	-
2nd Hospitalisation for HF	Lognormal	3.855	2.267	Lognormal	3.490	2.093	Lognormal	4.984	2.766
CV mortality	Weibull	1.162	1018.424	Weibull	1.154	707.765	Weibull	1.181	1447.278
Non-CV mortality	Weibull	1.576	410.652	Weibull	1.630	338.452	Weibull	1.530	487.555
Pooled Curves: extrapolation									
MI	Exponential	0.001	-	Exponential	0.002	-	Exponential	0.001	-
2nd MI	Lognormal	5.538	2.773	Lognormal	5.036	2.624	Weibull	0.720	661.631
Ischaemic Stroke	Exponential	0.001	-	Exponential	0.001	-	Exponential	0.000	-
2nd Ischaemic stroke	Lognormal	7.973	3.536	Lognormal	8.598	3.894	Lognormal	7.169	3.057
HAP	Lognormal	11.212	3.426	-	-	-	-	-	-
2nd Hospitalisation for HF	Lognormal	3.855	2.267	Lognormal	3.490	2.093	Lognormal	4.984	2.766
CV mortality	Weibull	1.162	1018.424	Weibull	1.154	707.765	Weibull	1.181	1447.278
Non-CV mortality	Weibull	1.576	410.652	Weibull	1.630	338.452	Weibull	1.530	487.555
Dapagliflozin: Within-trial									
Hospitalisation for HF	Weibull	1.311	806.596	Log-logistic	1.303	528.587	Weibull	1.385	1126.874
End-stage kidney disease	Exponential	0.000	-	Exponential	0.000	-	Exponential	0.000	-
Dapagliflozin: Extrapolated									
Hospitalisation for HF	Lognormal	7.951	2.073	Exponential	0.001	-	Exponential	0.000	-
End-stage kidney disease	Exponential	0.000	-	Exponential	0.000	-	Exponential	0.000	-
Placebo: Within-trial									
Hospitalisation for HF	Weibull	1.093	1062.679	Exponential	0.001	-	Log-logistic	1.169	1459.078
End-stage kidney disease	Exponential	0.000	-	Exponential	0.000	-	Exponential	0.000	-
Placebo: Extrapolation									
Hospitalisation for HF	Exponential	0.001	-	Exponential	0.001	-	Exponential	0.000	-
End-stage kidney disease	Exponential	0.000	-	Exponential	0.000	-	Exponential	0.000	-

	Prior heart failure				No prior heart failure		
	Distribution	**Parameter 1**	**Parameter 2**	**Parameter 3**	**Distribution**	**Parameter 1**	**Parameter 2**
Pooled Curves: within-trial							
MI	Log-logistic	0.898	669.546	-	Exponential	0.001	-
2nd MI	Lognormal	5.036	2.687	-	Lognormal	5.645	2.786
Ischaemic Stroke	Exponential	0.001	-	-	Exponential	0.001	-
2nd Ischaemic stroke	Exponential	0.002	-	-	Lognormal	7.678	3.446
HAP	-	-	-	-	-	-	-
2nd Hospitalisation for HF	Lognormal	3.264	1.836	-	Lognormal	4.544	2.719
CV mortality	Exponential	0.002	-	-	Weibull	1.203	1138.347
Non-CV mortality	Weibull	1.665	271.147	-	Weibull	1.565	436.234
Pooled Curves: extrapolation							
MI	Weibull	0.878	749.996	-	Lognormal	7.952	2.402
2nd MI	Lognormal	5.036	2.687	-	Lognormal	5.645	2.786
Ischaemic Stroke	Exponential	0.001	-	-	Lognormal	9.233	2.741
2nd Ischaemic stroke	Exponential	0.002	-	-	Lognormal	7.678	3.446
HAP	-	-	-	-	-	-	-
2nd Hospitalisation for HF	Lognormal	3.264	1.836	-	Lognormal	4.544	2.719
CV mortality	Exponential	0.002	-	-	Weibull	1.203	1138.347
Non-CV mortality	Weibull	1.665	271.147	-	Weibull	1.565	436.234
Dapagliflozin: Within-trial							
Hospitalisation for HF	Log-logistic	1.203	282.721	-	Log-logistic	1.491	764.713
End-stage kidney disease	Exponential	0.000	-	-	Exponential	0.000	-
Dapagliflozin: Extrapolated							
Hospitalisation for HF	Lognormal	6.237	1.888	-	Log-logistic	1.491	764.713
End-stage kidney disease	Exponential	0.000	-	-	Exponential	0.000	-
Placebo: Within-trial							
Hospitalisation for HF	Lognormal	6.285	2.209	-	Weibull	1.291	915.487
End-stage kidney disease	Exponential	0.000	-	-	Exponential	0.000	-
Placebo: Extrapolation							
Hospitalisation for HF	Gen-gamma	6.230	1.936	0.220	Weibull	1.291	915.487
End-stage kidney disease	Exponential	0.000	-	-	Exponential	0.000	-

CV: cardiovascular; CVD: cardiovascular disease; HAP: hospitalisation for unstable angina; HF: heart failure; MI: myocardial infarction

Supplementary Table 2. Treatment effects on modifiable risk factors and incidence of adverse events and discontinuation

Variable	Control	Treatment	Source
Change in risk factor level:			
HbA1c (%)	–0.151	–0.679	Wiviott et al. 2019[1]
Weight (kg)	–0.630	–2.415	Wiviott et al. 2019[1]
SBP (mmHg)	–0.409	–2.810	Wiviott et al. 2019[1]
eGFR change (mL/min/1.73m^2/year)	–2.44	-1.78	Mosenzon et al. 2019[2]
Annual probability of event:			
Diabetic ketoacidosis	0.0003	0.0007	Wiviott et al. 2019[1]
Urinary tract infection	0.0037	0.0035	Wiviott et al. 2019[1]
Genital infection	0.0003	0.0021	Wiviott et al. 2019[1]
Kidney injury	0.0049	0.0035	Wiviott et al. 2019[1]
Fracture	0.0122	0.0126	Wiviott et al. 2019[1]
Discontinuation	0.0490	0.0000	Wiviott et al. 2019[1]

eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure
Where data required by the UKPDS 82 risk equations was unavailable, UKPDS values were applied

Supplementary Table 3. Annual cost and health-related utility inputs

Variable	Costs		Utilities	
	Cost	Source	Utility	Source
Baseline utility	-	-	0.785	UKPDS 62[3]
HAP, fatal event	£716	NHS Reference cost 2018/19[4]	-	-
HAP, non-fatal event	£716	NHS Reference cost 2018/19[4]	0.042	Sullivan et al.[5]
HAP, maintenance	£412	NICE CG181[6]	0.042	Sullivan et al.[5]
MI, fatal event	£1,674	UKPDS 84[7]	-	-
MI, non-fatal event	£8,080	UKPDS 84[7]	–0.055	UKPDS 62[3]
MI, maintenance	£2,008	UKPDS 84[7]	–0.055	UKPDS 62[3]
HF, event	£4,589	UKPDS 84[7]	–0.108	UKPDS 62[3]
HF, maintenance	£2,692	UKPDS 84[7]	–0.108	UKPDS 62[3]
Stroke, fatal event	£4,351	UKPDS 84[7]	-	-
Stroke, non-fatal event	£8,689	UKPDS 84[7]	–0.164	UKPDS 62[3]
Stroke, maintenance	£2,070	UKPDS 84[7]	–0.164	UKPDS 62[3]
Blindness, event	£3,461	UKPDS 84[7]	–0.074	Bagust et al.[8]
Blindness, maintenance	£1,311	UKPDS 84[7]	–0.074	Bagust et al.[8]
Ulcer, event	£4,701	UKPDS 84[7]	–0.17	Bagust et al.[8]
Ulcer, maintenance	£5,693	UKPDS 84[7];	–0.17	Bagust et al.[8]
CKD 1	£0	Assumption	0	Gorodetskaya et al.[9]
CKD 2	£0	Assumption	0	Gorodetskaya et al.[9]
CKD 3	£3,611#	NICE CG182[10]	–0.03	Gorodetskaya et al.[9]
CKD 4	£3,611#	NICE CG182[10]	–0.05	Gorodetskaya et al.[9]
CKD 5 (pre-dialysis)	£5,633#	NICE CG182[10]	–0.05	Gorodetskaya et al.[9]
ESKD	£38,937	Lamping et al. 2000[11]	–0.164	Wasserfallen et al.[12]
Diabetic ketoacidosis	£2,209	Dhatariya et al.[13]	0	No evidence identified
Genital infection	£39	PSSRU[14]	–0.00283	Assumed equal to UTI; Barry et al.[15]
Urinary tract infection	£39	PSSRU[14]	–0.00283	Barry et al.[15]
Acute kidney injury	£1,810	NHS Reference cost 2018/19[4]	-0.11040	Sullivan et al.[5]
Fracture	£2,211	NHS Reference cost 2018/19[4]	-0.06800	Sullivan et al.[5]
Dapagliflozin	£477	MIMS[16]		
BMI (per unit decrease)	-	-	–0.047	Lane et al.[17]
BMI (per unit increase)			0.017	Lane et al.[17]

BMI: body mass index; CKD: chronic kidney disease; ESKD: end-stage kidney disease; HAP: hospitalisation for unstable angina pectoris; HF: heart failure; MI: myocardial infarction; SGLT2i: sodium–glucose cotransporter-2 inhibitor; T2DM: type 2 diabetes

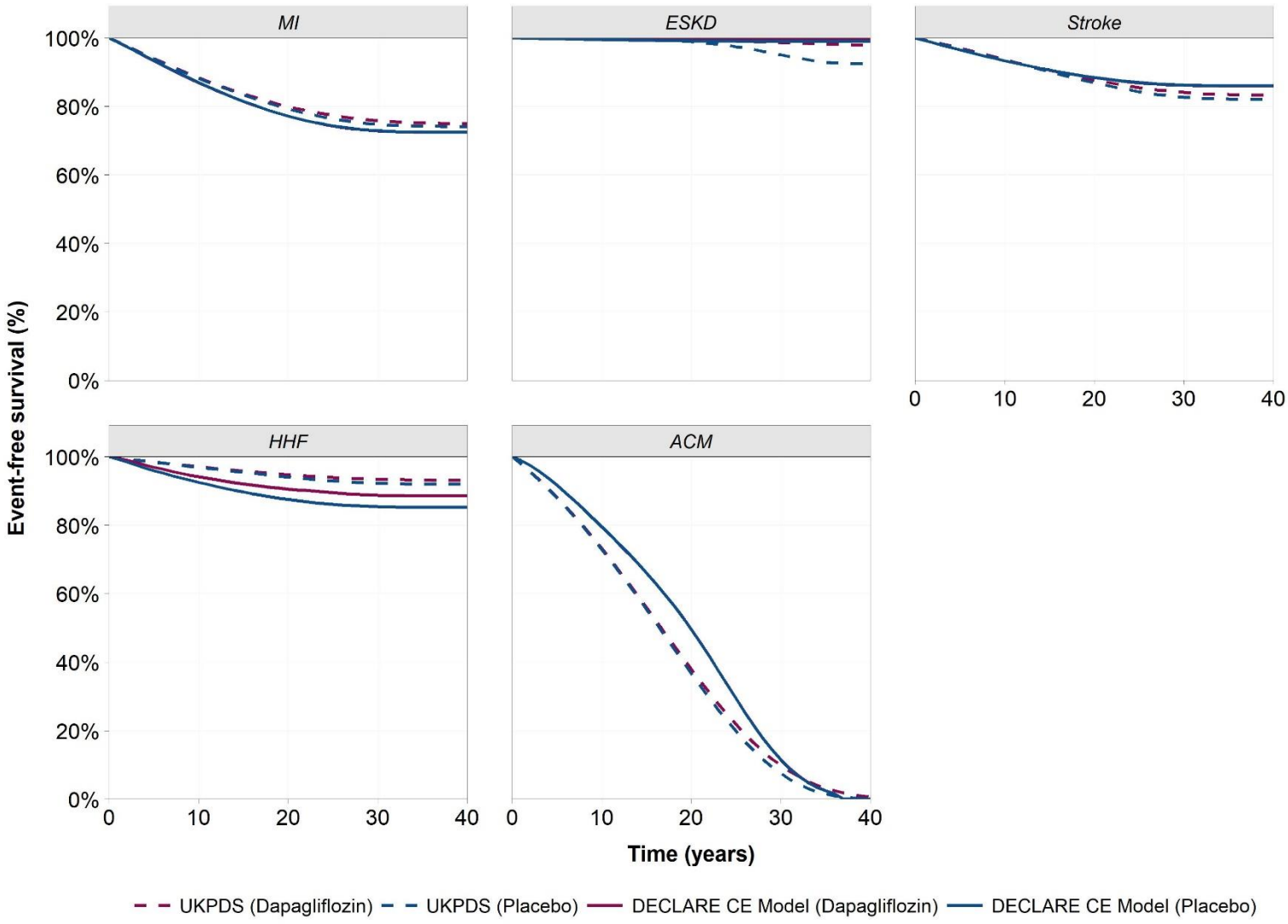
* Costs relate to primary care and diabetes medications

CKD care, comprising inpatient stays, nephrology outpatient visits, antihypertensive drugs, and GP visits

Supplementary Table 4. National level estimates based on overall DECLARE-TIMI 58 population; number of individuals and health economic estimates reported in millions

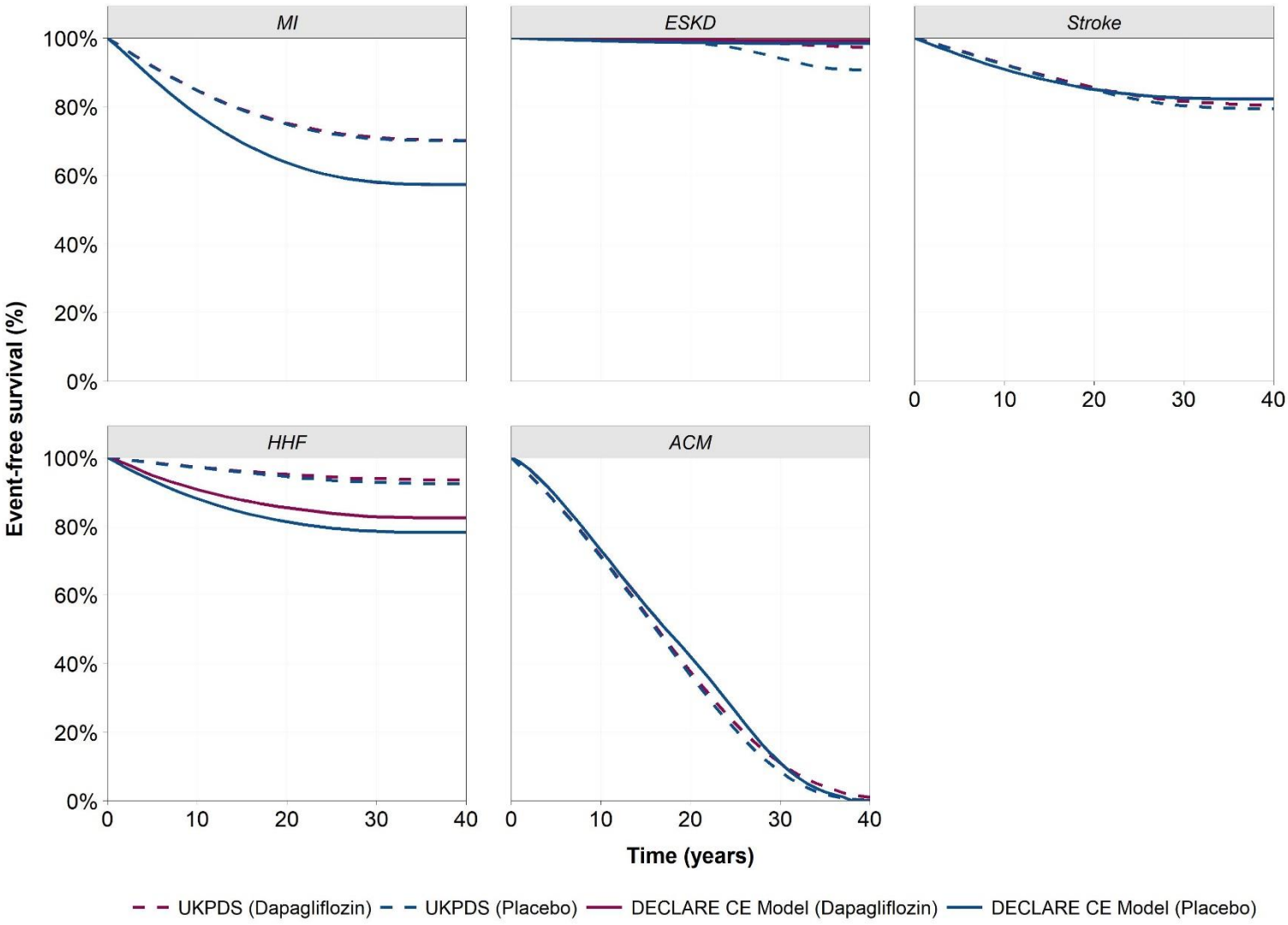
Parameter		UK
Number of people:	(millions)	
with diabetes		3.9
with T2DM (90%)		3.5
represented by DECLARE	percentage	59%[18]
represented by DECLARE	number of people	2.1
Health economic impact of dapagliflozin:		
Total cost difference		-£5,311
Total life years gained		0.0
Total QALYs gained		0.1
Incremental NMB		£7,616

CVOT: cardiovascular outcome trial; NMB: net monetary benefit; QALYs: quality-adjusted life years; SGLT2i: sodium–glucose cotransporter-2 inhibitor; T2DM: type 2 diabetes mellitus



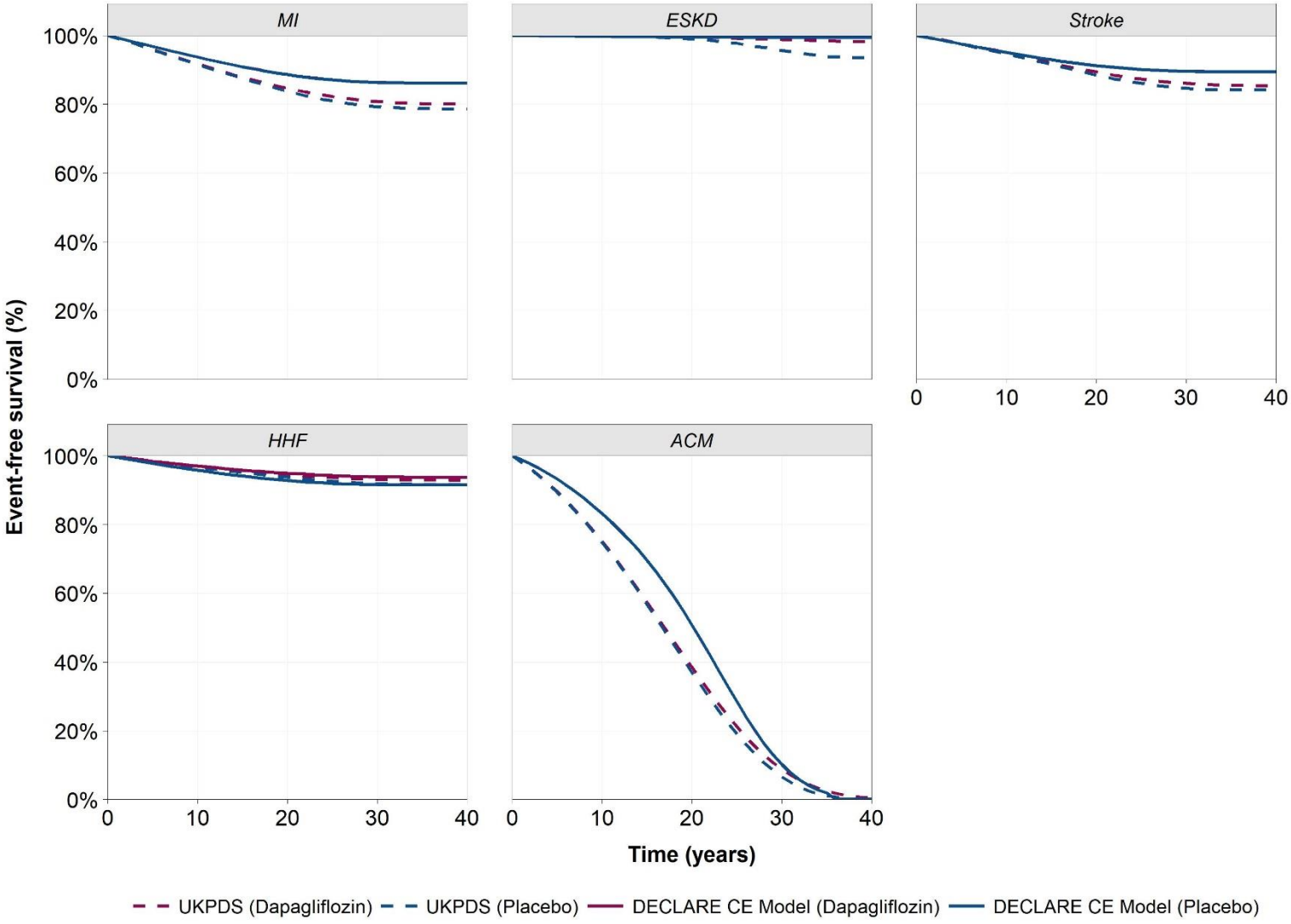
Supplementary Figure 1. Outcomes predicted for the overall DECLARE population using the DECLARE CE Model, validated to UKPDS 82 equations

ACM: all-cause mortality; ESKD: end-stage kidney disease; HHF: hospitalisation for heart failure; MI: myocardial infarction



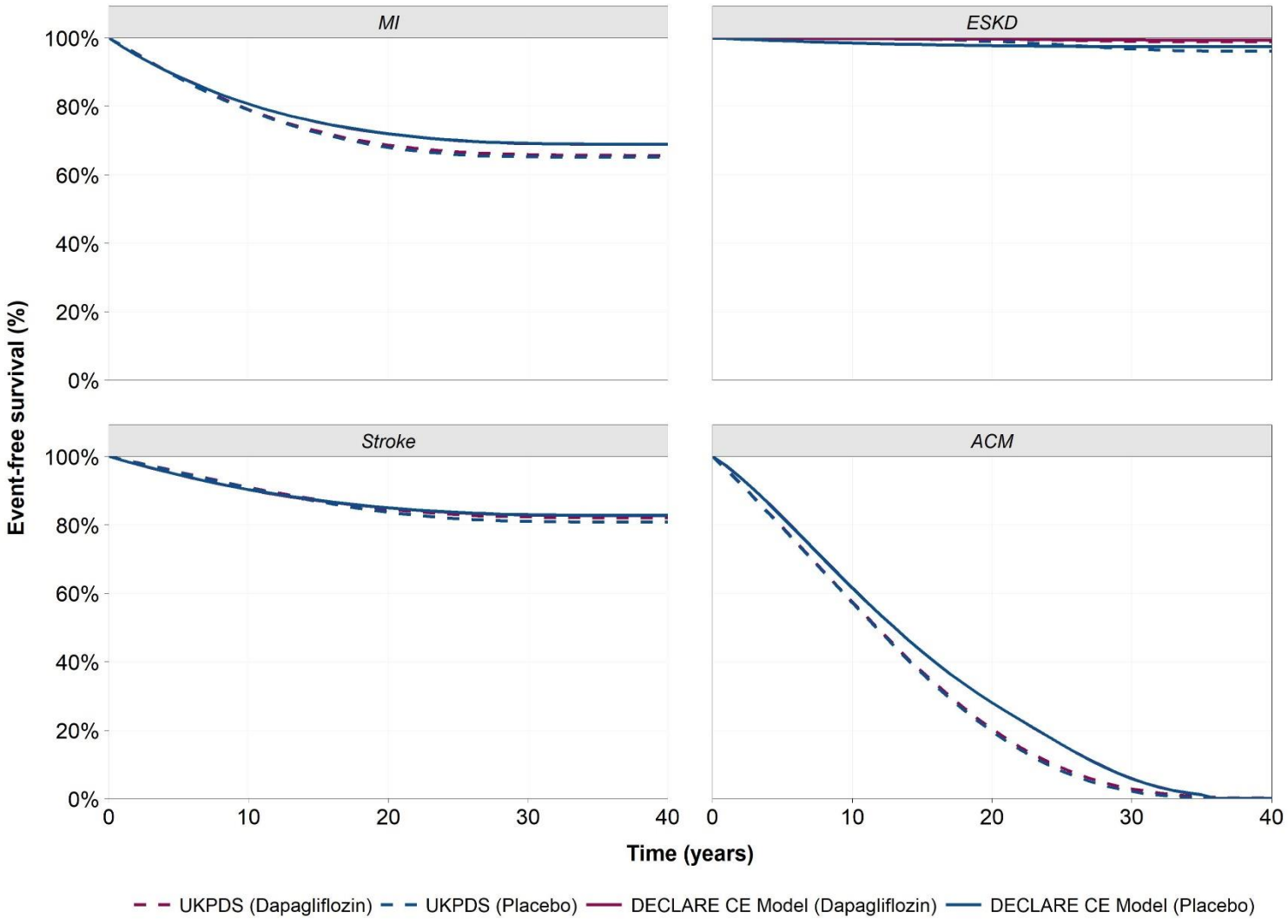
Supplementary Figure 2. Outcomes predicted for the eCVD DECLARE population using the DECLARE CE Model, validated to UKPDS 82 equations

ACM: all-cause mortality; eCVD: established cardiovascular disease; ESKD: end-stage kidney disease; HHF: hospitalisation for heart failure; MI: myocardial infarction



Supplementary Figure 3. Outcomes predicted for the MRF DECLARE population using the DECLARE CE Model, validated to UKPDS 82 equations

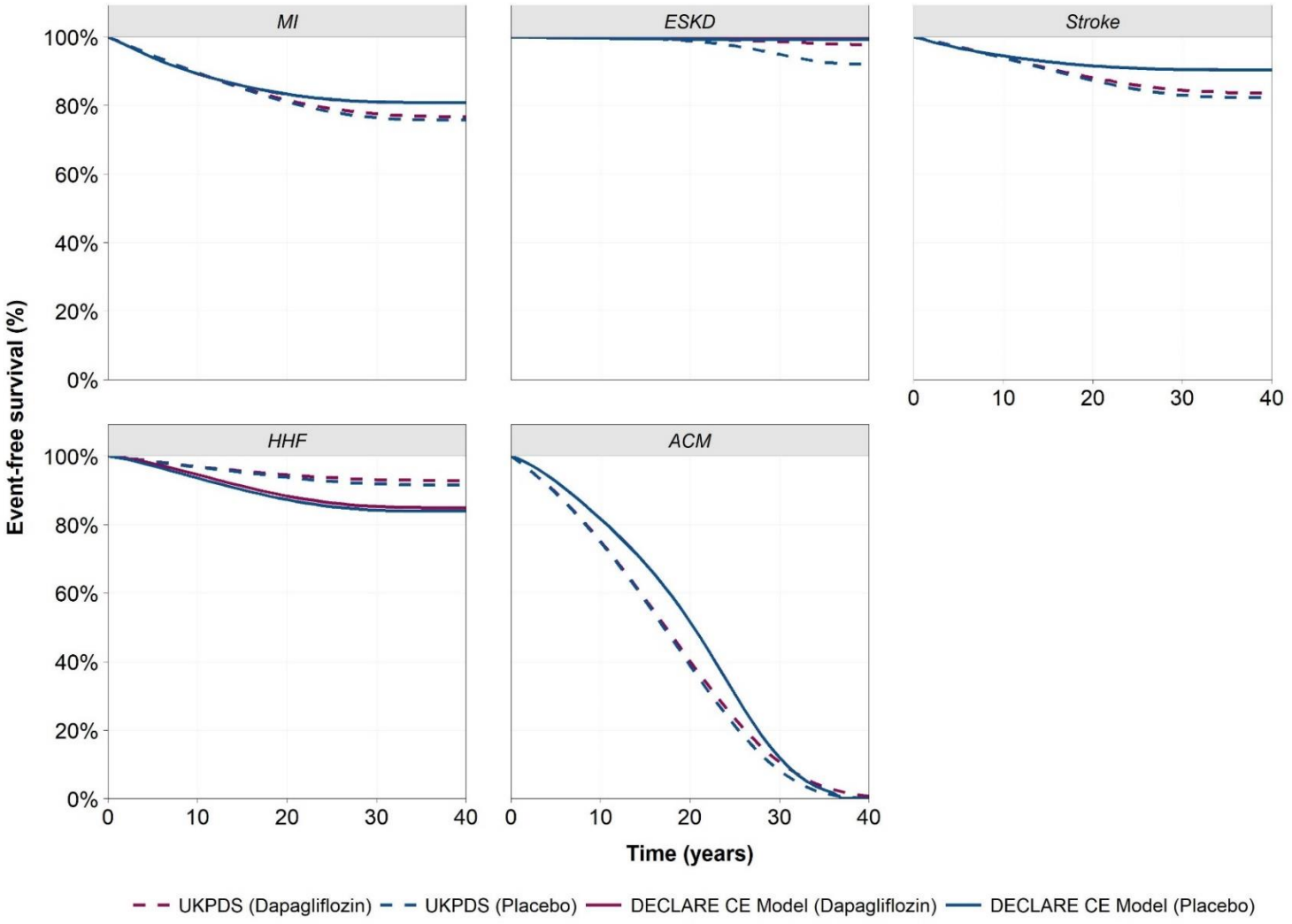
ACM: all-cause mortality; ESKD: end-stage kidney disease; HHF: hospitalisation for heart failure; MI: myocardial infarction; MRF: multiple risk factor



Supplementary Figure 4. Outcomes predicted for the prior HF DECLARE population using the DECLARE CE Model, validated to UKPDS 82 equations

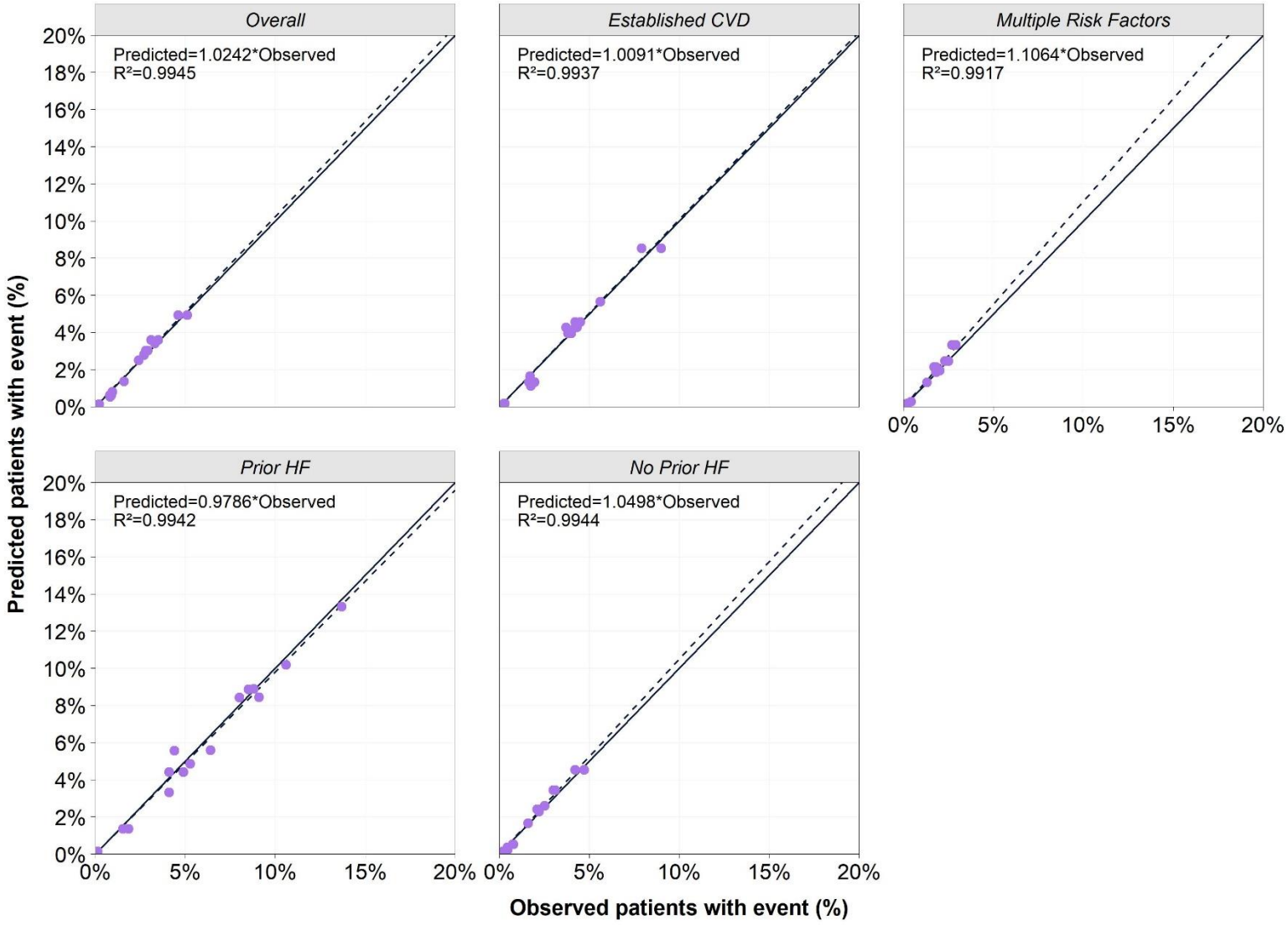
ACM: all-cause mortality; CHF: congestive heart failure; ESKD: end-stage kidney disease; HF: heart failure; HHF: hospitalisation for heart failure; MI: myocardial infarction

Note: HHF not included as an event as UKPDS equations do not model CHF for those with a prior history of HF.



Supplementary Figure 5. Outcomes predicted for the no prior HF DECLARE population using the DECLARE CE Model, validated to UKPDS 82 equations

ACM: all-cause mortality; ESKD: end-stage kidney disease; HHF: hospitalisation for heart failure; MI: myocardial infarction



Supplementary Figure 6. Outcomes from the DECLARE CE model over a 4.2 year time horizon, validated against DECLARE-TIMI 58 trial results

CVD: cardiovascular disease; HF: heart failure

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