

## SUPPLEMENTARY DATA

### **Risk Factors for Retinopathy in Type 1 Diabetes**

The Diabetes Control and Complications Trial (DCCT)-Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group\*

\*A complete list of participants in the DCCT-EDIC Research Group is presented in the Supplementary Material published online for the article in *N Engl J Med* 2015;372:1722-33.

#### **Writing Group:**

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This Appendix presents supplemental materials cited in the text of the main manuscript.

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**Supplementary Table S1. Risk factors (by block) employed in the analyses with a description of availability.**

<b>Block</b>	<b>Variable</b>	<b>Availability*</b>
<b><u>DESIGN</u></b>		
	Cohort	B
	Treatment Group	B
<b><u>DEMOGRAPHIC</u></b>		
<b>Physical</b>	Sex (male versus female)	B
	Age (yr)	B
	Adult	B
	Weight (kg)	B, C <sup>†</sup> , M <sup>†</sup>
	Weight Gain (kg)	C <sup>†</sup>
	Body mass index (kg/m <sup>2</sup> )	B, C <sup>†</sup> , M <sup>†</sup>
<b>Behavioral</b>	Current cigarette smoker	B, C <sup>†</sup>
	Occasional or regular drinker	B, C <sup>†</sup>
	Moderate or strenuous activity	B, C <sup>†</sup>
<b>Family History</b>	Family history	
	Hypertension	B
	Myocardial infarction (MI)	B
	Type 1 Diabetes	B
	Type 2 Diabetes	B
<b><u>TRADITIONAL</u></b>		
<b>Blood pressure</b>	Systolic (mm Hg)	B, C <sup>†</sup> , M <sup>†</sup>
	Diastolic (mm Hg)	B, C <sup>†</sup> , M <sup>†</sup>
	Pulse pressure (mm Hg)	B, C <sup>†</sup>
	Pulse rate (bpm)	B, C <sup>†</sup> , M <sup>†</sup>
	Hypertension (≥140/90 or medication)	B, C <sup>†</sup> , A <sup>†</sup>
<b>Medications</b>	ACE	C <sup>‡</sup>
	ARB	C <sup>‡</sup>
	Beta Blockers	C <sup>‡</sup>
	Calcium Channel Blockers	C <sup>‡</sup>
	Lipid Lowering	C <sup>‡</sup>
<b>Lipids</b>	Total cholesterol (mg/dl)	B, C <sup>§</sup> , M <sup>§</sup>
	Triglycerides (mg/dl)	B, C <sup>§</sup> , M <sup>§</sup>
	HDL cholesterol (mg/dl)	B, C <sup>§</sup> , M <sup>§</sup>
	LDL cholesterol (mg/dl)	B, C <sup>§</sup> , M <sup>§</sup>
	Hyperlipidemia (LDLc > 130 or medication)	B, C <sup>§</sup>
<b><u>DIABETES-RELATED</u></b>		
<b>History</b>	Duration of diabetes (yr)	B
	Stimulated C-peptide (nmol/L)	B
	Duration <60 months	
	Duration ≥60 months	
	Insulin dose (units/kg/day)	B, C <sup>†</sup> , M <sup>†</sup>
	eGlucose Disposal Rate	C <sup>‡</sup>
<b>Microvascular</b>	Nephropathy	B
	eGFR (mL/min per 1.73 m <sup>2</sup> )	B, C <sup>†</sup>

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	eGFR<60	C <sup>†</sup> , A <sup>†</sup>
	AER (mg/24 hr)	B, C <sup>§</sup> ,
	AER ≥40, AER≥300, Sustained	A <sup>§</sup>
	AER≥30mg/24 hr	
<b>Hypoglycemia</b>	Coma and/or seizure	B, C <sup>†</sup>
	Requiring assistance	B, C <sup>†</sup>
<b>Glycemia</b>	HbA1c (%)	B, C <sup>†</sup> , M <sup>†</sup>

\*B=Baseline Value, C=Current Value, M=Updated Mean Value, A=Cumulative Incidence (such as Any Use). Categories C, M and A enter the analyses as time dependent covariates.

<sup>†</sup>Collected annually during DCCT and EDIC;

<sup>‡</sup> Collected Annually in EDIC, not collected in DCCT;

<sup>§</sup> Collected annually in DCCT, every two years in EDIC

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**Supplementary Table S2.** Baseline Characteristics of DCCT/EDIC Participants According to the Presence or Absence of CSME over the Course of the DCCT/EDIC Study

	Overall	Any CSME		HR	95% CI	p-value
		No	Yes			
N	1440	1009	431			
Treatment group (% conventional)	51	46	61	1.763	(1.453, 2.14)	<b>&lt;0.0001</b>
Cohort (% secondary)	50	45	60	1.652	(1.361, 2.005)	<b>&lt;0.0001</b>
Sex (% males)	53	51	58	1.331	(1.099, 1.612)	<b>0.0034</b>
Age (yr)	27 (22,32)	27 (22,32)	28 (22,33)	1.017	(1.004, 1.031)	<b>0.0129</b>
Adult vs. adolescent	86	87	86	1.041	(0.791, 1.371)	0.7736
Weight Males (kg)	75 (68,82)	74 (68,82)	76 (67,83)	1.009	(0.997, 1.021)	0.1245
Weight Females (kg)	62 (56,69)	61 (56,68)	64 (58,70)	1.023	(1.007, 1.039)	<b>0.0042</b>
BMI Males (kg/m <sup>2</sup> )	24 (22,25)	23 (22,25)	24 (22,26)	1.077	(1.028, 1.129)	<b>0.0019</b>
BMI Females (kg/m <sup>2</sup> )	23 (21,25)	23 (21,25)	24 (22,26)	1.089	(1.036, 1.145)	<b>0.0009</b>
Smoking (%)	18	18	19	1.096	(0.861, 1.396)	0.4573
Drinking (% occasional or	29	28	32	1.225	(1.001, 1.498)	<b>0.0488</b>

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regular)						
Exercise (% moderate or strenuous)	82	82	81	0.924	(0.728, 1.172)	0.5131
Family history of HT (%)	56	55	58	1.124	(0.928, 1.361)	0.2315
Family history of MI (%)	49	48	50	1.022	(0.846, 1.235)	0.8205
Family history of T1D (%)	14	13	17	1.326	(1.034, 1.701)	<b>0.0264</b>
Family history of T2D (%)	9	9	10	1.187	(0.869, 1.622)	0.2803
Systolic BP (mm Hg)	114 (108,122)	112 (106,122)	116 (110,124)	1.014	(1.005, 1.022)	<b>0.0016</b>
Diastolic BP (mm Hg)	72 (68,80)	72 (68,78)	74 (70,81)	1.027	(1.015, 1.039)	<b>&lt;0.0001</b>
Pulse pressure (mm Hg)	40 (36,48)	40 (36,48)	40 (36,48)	0.999	(0.989, 1.009)	0.8022
Pulse (bpm)	76 (68,84)	76 (68,82)	76 (68,84)	1.014	(1.006, 1.023)	<b>0.0007</b>
Hypertension (%)	3	2	3	1.443	(0.831, 2.506)	0.1930
Total cholesterol (mg/dl)	174 (153,196)	172 (152,194)	177 (155,204)	1.006	(1.003, 1.009)	<b>&lt;0.0001</b>
Triglycerides	73 (55,93)	71 (53,91)	79 (60,98)	1.67	(1.361, 2.048)	<b>&lt;0.0001</b>

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(mg/dl)						
HDLc (mg/dl)	49 (42,57)	50 (42,58)	48 (42,57)	0.997	(0.989, 1.004)	0.3952
LDLc (mg/dl)	107 (91,127)	105 (89,125)	110 (94,130)	1.006	(1.003, 1.01)	<b>0.0001</b>
Duration of Diabetes (years)	4.3 (2.3,9.1)	3.9 (2.2, 8.7)	5.2 (2.9, 10)	1.061	(1.036, 1087)	<b>&lt;0.0001</b>
100*C-peptide duration<5yrs (nmol/L)	13 (4,25)	13 (4,25)	11 (4,26)	0.998	(0.988, 1.009)	0.7300
100*C-peptide duration>5yrs (nmol/L)	3 (3,4)	3 (3,4)	3 (3,4)	0.998	(0.963, 1.034)	0.9037
Log AER (mg/24 hr)	2.4 (2.0,2.9)	2.3 (1.8,2.8)	2.6 (2.0,3.1)	1.307	(1.164, 1.468)	<b>&lt;0.0001</b>
HbA1c (%)	8.7 (7.8,9.9)	8.5 (7.6,9.6)	9.2 (8.1,10.4)	1.244	(1.178, 1.314)	<b>&lt;0.0001</b>

Included in this table are 1440 patients who had at least 2 fundus photographs.

HT=hypertension; T1D=type 1 diabetes; T2D=type 2 diabetes; BP=blood pressure; ACE=angiotensin converting enzyme inhibitors; ARB=angiotensin receptor blockers; HDL=high-density lipoprotein; LDL=low-density lipoprotein; eGDR=estimated glucose disposal rate; eGFR=estimated glomerular filtration rate; AER=albumin excretion rate; HR=hazard ratio; CI=confidence interval.

Data are medians (first quartile, third quartile) or %. Hazard ratios (HR) and p-values are generated using a Cox Proportional hazards model.

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**Supplementary Table S3.** Baseline Characteristics of DCCT/EDIC Participants According to the Presence or Absence of Ocular Surgery over the Course of the DCCT/EDIC Study

	Any Ocular Surgery			HR	95% CI	p-value
	Overall	No	Yes			
N	1439	1158	281			
Treatment group (%conventional)	51	48	60	1.654	(1.302, 2.1)	<b>&lt;0.0001</b>
Cohort (% secondary)	50	46	63	1.608	(1.26, 2.053)	<b>0.0001</b>
Sex (% males)	53	54	47	0.817	(0.646, 1.033)	0.0917
Age (yr)	27 (22,32)	27 (22,32)	30 (24,34)	1.048	(1.03, 1.067)	<b>&lt;0.0001</b>
Adult vs. adolescent	86	86	87	1.149	(0.811, 1.628)	0.4341
Weight Males (kg)	75 (68,82)	74 (67,82)	76 (70,85)	1.016	(1.000, 1.031)	<b>0.0498</b>
Weight Females (kg)	62 (56,69)	61 (56,68)	64 (58,70)	1.025	(1.007, 1.042)	<b>0.0048</b>
BMI Males (kg/m <sup>2</sup> )	24 (22,25)	23 (22,25)	24 (22,26)	1.078	(1.013, 1.147)	<b>0.0179</b>
BMI Females (kg/m <sup>2</sup> )	23 (21,25)	23 (21,25)	24 (22,25)	1.078	(1.022, 1.137)	<b>0.0061</b>
Smoking (%)	18	17	22	1.426	(1.077, 1.889)	<b>0.0131</b>
Drinking (% occasional or regular)	29	29	30	1.073	(0.831, 1.384)	0.5888
Exercise (% moderate or strenuous)	82	82	79	0.825	(0.619, 1.099)	0.1891
Family history of HT (%)	56	55	60	1.209	(0.952, 1.536)	0.1191
Family history of MI (%)	49	48	51	1.077	(0.852, 1.362)	0.5341
Family history of T1D (%)	14	13	17	1.302	(0.957, 1.772)	0.0934
Family history of T2D (%)	9	8	12	1.419	(0.987, 2.041)	0.0590

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Systolic BP (mm Hg)	114 (108,122)	114 (108,122)	114 (108,122)	1.003	(0.993, 1.013)	0.5885
Diastolic BP (mm Hg)	72 (68,80)	72 (68,80)	74 (68,80)	1.011	(0.997, 1.025)	0.1211
Pulse pressure (mm Hg)	40 (36,48)	40 (36,48)	40 (36,46)	0.995	(0.983, 1.008)	0.4628
Pulse (bpm)	76 (68,84)	76 (68,82)	80 (72,84)	1.019	(1.009, 1.029)	<b>0.0002</b>
Hypertension (%)	3	2	4	1.443	(0.767, 2.713)	0.2554
Total cholesterol (mg/dl)	174 (153,196)	173 (152,196)	176 (156,200)	1.003	(1.000, 1.007)	0.0894
Triglycerides (mg/dl)	73 (55,93)	72 (54,92)	77 (58,100)	1.376	(1.065, 1.777)	<b>0.0145</b>
HDLc (mg/dl)	49 (42,58)	49 (42,57)	48 (42,58)	1.002	(0.993, 1.012)	0.6412
LDLc (mg/dl)	107 (91,127)	106 (90,127)	110 (94,127)	1.003	(0.999, 1.007)	0.2098
Duration of Diabetes (years)	4.3 (2.3,9.1)	4 (2.3, 8.7)	6.3 (3.3,10.9)	1.061	(1.036, 1.100)	<b>&lt;0.0001</b>
100*C-peptide duration<5yrs (nmol/L)	12 (4,25)	13 (4,25)	10 (4,24)	0.992	(0.979, 1.006)	0.2662
100*C-peptide duration>5yrs (nmol/L)	3 (3,4)	3 (3,4)	3 (3,3)	0.985	(0.941, 1.031)	0.5038
Log AER (mg/24 hr)	2.4 (2.0,2.9)	2.4 (2.0,2.8)	2.4 (2.0,3.0)	1.108	(0.958, 1.283)	0.1675
HbA1c (%)	8.7 (7.8,9.9)	8.5 (7.7,9.7)	9.2 (8.2,10.2)	1.228	(1.147, 1.314)	<b>&lt;0.0001</b>

Included in this table are 1439 patients who had at least 2 visual acuity evaluations.

HT=hypertension; T1D=type 1 diabetes; T2D=type 2 diabetes; BP=blood pressure; ACE=angiotensin converting enzyme inhibitors; ARB=angiotensin receptor blockers; HDL=high-density lipoprotein; LDL=low-density lipoprotein; eGDR=estimated glucose disposal rate; eGFR=estimated glomerular filtration rate; AER=albumin excretion rate; HR=hazard ratio; CI=confidence interval.

Data are medians (first quartile, third quartile) or %. Hazard ratios (HR) and p-values are generated using a Cox Proportional hazards model



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**Supplementary Table S4.** Hazard ratios for PDR per unit change in each time-dependent covariate with no adjustment, adjusted for age and adjusted for age and mean HbA1c

	Unadjusted				Adjusted for Age				Adjusted for Age and mean HbA1c			
	HR	LL	UL	p-value	HR	LL	UL	p-value	HR	LL	UL	p-value
Treatment group	2.1509	1.7413	2.6570	<0.0001	2.1385	1.7306	2.6427	<0.0001	0.8794	0.6953	1.1122	0.2837
Cohort	2.1576	1.7428	2.6712	<0.0001	2.1850	1.7641	2.7065	<0.0001	2.7107	2.1848	3.3631	<0.0001
Sex	1.1034	0.9014	1.3506	0.3401	1.1148	0.9102	1.3653	0.2933	1.1092	0.9050	1.3593	0.3178
Age	0.9904	0.9765	1.0045	0.1825	-	-	-	-	-	-	-	-
Adult vs. adolescent	0.8210	0.6246	1.0793	0.1577	0.8820	0.6025	1.2910	0.5184	1.5370	1.0427	2.2656	<b>0.0299</b>
Weight	0.9942	0.9876	1.0009	0.0947	0.9946	0.9880	1.0014	0.1214	0.9974	0.9906	1.0042	0.4551
BMI	0.9833	0.9601	1.0071	0.1681	0.9839	0.9607	1.0076	0.1832	0.9980	0.9747	1.0219	0.8723
Mean weight	0.9977	0.9900	1.0055	0.5752	0.9985	0.9907	1.0064	0.7251	1.0004	0.9924	1.0084	0.9204
Mean BMI	1.0029	0.9733	1.0333	0.8489	1.0046	0.9749	1.0352	0.7609	1.0161	0.9860	1.0472	0.2961
Weight gain males	0.9788	0.9647	0.9932	<b>0.0041</b>	0.9756	0.9610	0.9904	<b>0.0013</b>	0.9899	0.9761	1.0038	0.1539
Weight gain females	0.9733	0.9572	0.9896	<b>0.0014</b>	0.9726	0.9567	0.9888	<b>0.0010</b>	0.9799	0.9649	0.9951	<b>0.0098</b>
Smoking status	1.4901	1.1688	1.8997	<b>0.0012</b>	1.4960	1.1734	1.9072	<b>0.0011</b>	1.0137	0.7919	1.2976	0.9137
Drinking status	0.9963	0.8103	1.2250	0.9720	1.0012	0.8141	1.2311	0.9908	1.0972	0.8916	1.3504	0.3805
Exercise	1.1954	0.9620	1.4856	0.1071	1.1854	0.9535	1.4737	0.1256	1.1168	0.8971	1.3902	0.3226
Family history of HT	1.1568	0.9422	1.4203	0.1640	1.1505	0.9369	1.4128	0.1808	1.0278	0.8359	1.2639	0.7942
Family history of MI	0.9856	0.8058	1.2056	0.8881	0.9901	0.8093	1.2112	0.9232	1.0276	0.8396	1.2576	0.7914
Family history of T1D	1.2447	0.9496	1.6314	0.1127	1.2728	0.9695	1.6710	0.0822	1.1310	0.8599	1.4875	0.3784
Family history of T2D	0.9690	0.6779	1.3850	0.8628	1.0025	0.6987	1.4383	0.9890	1.0205	0.7125	1.4615	0.9116
Systolic BP (SBP)	1.0211	1.0137	1.0286	<0.0001	1.0229	1.0153	1.0306	<0.0001	1.0162	1.0087	1.0239	<0.0001
Diastolic BP (DBP)	1.0351	1.0232	1.0470	<0.0001	1.0351	1.0233	1.0471	<0.0001	1.0319	1.0201	1.0439	<0.0001
Pulse	1.0423	1.0336	1.0512	<0.0001	1.0421	1.0333	1.0510	<0.0001	1.0197	1.0107	1.0289	<0.0001
Mean SBP	1.0289	1.0167	1.0412	<0.0001	1.0325	1.0199	1.0454	<0.0001	1.0279	1.0151	1.0408	<0.0001

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Mean DBP	1.0701	1.0509	1.0897	<b>&lt;0.0001</b>	1.0730	1.0536	1.0928	<b>&lt;0.0001</b>	1.0605	1.0413	1.0801	<b>&lt;0.0001</b>
Mean Pulse	1.0717	1.0568	1.0868	<b>&lt;0.0001</b>	1.0715	1.0565	1.0866	<b>&lt;0.0001</b>	1.0323	1.0170	1.0479	<b>&lt;0.0001</b>
Pulse pressure	1.0090	0.9998	1.0184	0.0544	1.0109	1.0014	1.0204	<b>0.0237</b>	1.0036	0.9941	1.0132	0.4518
Hypertension	1.5944	1.2575	2.0215	<b>0.0001</b>	1.6655	1.3089	2.1194	<b>&lt;0.0001</b>	1.4137	1.1115	1.7981	<b>0.0047</b>
History of Hypertension	1.5201	1.2174	1.8981	<b>0.0002</b>	1.5504	1.2407	1.9373	<b>0.0001</b>	1.2427	0.9893	1.5611	0.0617
Any ACE	1.2857	0.9813	1.6845	0.0682	1.3262	1.0093	1.7426	<b>0.0426</b>	1.1983	0.9151	1.5691	0.1882
Any ARB	0.9325	0.5569	1.5616	0.7907	0.9579	0.5711	1.6067	0.8707	0.8732	0.5210	1.4636	0.6069
Any beta blockers	1.3328	0.7186	2.4719	0.3619	1.3867	0.7454	2.5795	0.3018	0.8779	0.4738	1.6266	0.6790
Lipid lowering	0.7637	0.5602	1.0412	0.0882	0.7887	0.5747	1.0824	0.1416	0.7610	0.5543	1.0448	0.0912
Calcium channel blockers	1.1400	0.6199	2.0965	0.6732	1.1943	0.6470	2.2046	0.5701	1.0262	0.5565	1.8922	0.9339
Total cholesterol (CHL)	1.0078	1.0051	1.0105	<b>&lt;0.0001</b>	1.0081	1.0054	1.0108	<b>&lt;0.0001</b>	1.0034	1.0007	1.0061	<b>0.0121</b>
Triglycerides (log)	1.9292	1.6175	2.3009	<b>&lt;0.0001</b>	1.9236	1.6134	2.2934	<b>&lt;0.0001</b>	1.4359	1.1907	1.7315	<b>0.0001</b>
LDL cholesterol	1.0087	1.0055	1.0119	<b>&lt;0.0001</b>	1.0090	1.0058	1.0122	<b>&lt;0.0001</b>	1.0038	1.0007	1.0070	<b>0.0162</b>
HDL cholesterol	0.9892	0.9821	0.9963	<b>0.0030</b>	0.9895	0.9824	0.9967	<b>0.0042</b>	0.9915	0.9843	0.9987	<b>0.0217</b>
Mean CHL	1.0110	1.0075	1.0146	<b>&lt;0.0001</b>	1.0118	1.0082	1.0154	<b>&lt;0.0001</b>	1.0030	0.9993	1.0067	0.1029
Mean TRG (log)	2.6945	2.1576	3.3649	<b>&lt;0.0001</b>	2.6794	2.1445	3.3476	<b>&lt;0.0001</b>	1.6398	1.2919	2.0813	<b>&lt;0.0001</b>
Mean LDLc	1.0110	1.0070	1.0151	<b>&lt;0.0001</b>	1.0119	1.0078	1.0160	<b>&lt;0.0001</b>	1.0029	0.9988	1.0070	0.1633
Mean HDLc	0.9894	0.9808	0.9980	<b>0.0168</b>	0.9899	0.9813	0.9986	<b>0.0236</b>	0.9917	0.9829	1.0005	0.0666
Duration (years)	1.0834	1.0591	1.1082	<b>&lt;0.0001</b>	1.0847	1.0604	1.1108	<b>&lt;0.0001</b>	1.1511	1.1241	1.1801	<b>&lt;0.0001</b>
Stimulated C-peptide (< 5yr)	0.4099	0.1202	1.3977	0.1541	0.4087	0.1183	1.4113	0.1570	0.2573	0.0698	0.9473	<b>0.0412</b>
Stimulated C-peptide (> 5)	0.1578	<b>0.0029</b>	8.5301	0.3644	0.2303	<b>0.0042</b>	12.3472	0.4698	0.5395	<b>0.0084</b>	34.6174	0.7713
Insulin dose (per kg)	1.7123	1.2273	2.3890	<b>0.0015</b>	1.6767	1.1920	2.3586	<b>0.0029</b>	1.0199	0.6794	1.5312	0.9240
Mean insulin dose	2.5244	1.5635	4.0758	<b>&lt;0.0001</b>	2.5498	1.5124	4.2986	<b>&lt;0.0001</b>	1.3225	0.7753	2.2556	0.3048
Estimated GFR	1.0124	1.0047	1.0202	<b>0.0014</b>	1.0134	1.0043	1.0227	<b>0.0038</b>	1.0041	0.9962	1.0121	0.2996
Any eGFR < 60	2.4287	1.2799	4.6086	<b>0.0066</b>	2.6054	1.3649	4.9734	<b>0.0036</b>	1.7484	0.9150	3.3410	0.0907
AER	1.0003	1.0002	1.0005	<b>&lt;0.0001</b>	1.0003	1.0002	1.0005	<b>&lt;0.0001</b>	1.0002	1.0000	1.0003	<b>0.0024</b>

SUPPLEMENTARY DATA

Any Macroalbuminuria	3.9160	2.8596	5.3627	<b>&lt;0.0001</b>	3.8802	2.8321	5.3161	<b>&lt;0.0001</b>	1.8899	1.3716	2.6040	<b>&lt;0.0001</b>
Coma/Seizure	0.9540	0.8148	1.1169	0.5585	0.9533	0.8144	1.1159	0.5524	0.9812	0.8421	1.1432	0.8079
Required Assistance	0.9368	0.8573	1.0236	0.1492	0.9355	0.8560	1.0225	0.1418	0.9756	0.8971	1.0610	0.5649
HbA1C at baseline	1.3618	1.2907	1.4368	<b>&lt;0.0001</b>	1.3608	1.2892	1.4364	<b>&lt;0.0001</b>	1.0843	1.0189	1.1539	<b>0.0107</b>
HbA1c	1.6482	1.5564	1.7454	<b>&lt;0.0001</b>	1.6477	1.5553	1.7456	<b>&lt;0.0001</b>	1.0386	0.9478	1.1381	0.4163
Mean HbA1C	2.2386	2.0765	2.4133	<b>&lt;0.0001</b>	2.2673	2.1005	2.4475	<b>&lt;0.0001</b>	-	-	-	-

SUPPLEMENTARY DATA

**Supplementary Table S5.** Hazard ratios for CSME per unit change in each time-dependent covariate with no adjustment, adjusted for age and adjusted for age and mean HbA1c

	Unadjusted				Adjusted for Age				Adjusted for Age and mean HbA1c			
	HR	LL	UL	p-value	HR	LL	UL	p-value	HR	LL	UL	p-value
Treatment group	1.7631	1.4527	2.1398	<0.0001	1.7961	1.4793	2.1808	<0.0001	0.8552	0.6869	1.0646	0.1616
Cohort	1.6517	1.3610	2.0045	<0.0001	1.6383	1.3498	1.9885	<0.0001	1.8580	1.5291	2.2578	<0.0001
Sex	1.3309	1.0991	1.6116	<b>0.0034</b>	1.3089	1.0804	1.5857	<b>0.0059</b>	1.3358	1.1019	1.6195	<b>0.0031</b>
Age	1.0173	1.0036	1.0312	<b>0.0128</b>	-	-	-	-	-	-	-	-
Adult vs. adolescent	1.0412	0.7907	1.3710	0.7736	0.6978	0.4774	1.0200	0.0632	1.0395	0.7075	1.5273	0.8434
Weight	1.0065	1.0004	1.0126	<b>0.0357</b>	1.0058	0.9997	1.0120	0.0600	1.0074	1.0013	1.0135	<b>0.0161</b>
BMI	1.0147	0.9936	1.0364	0.1725	1.0139	0.9928	1.0355	0.1953	1.0214	0.9999	1.0433	0.0501
Mean weight	1.0090	1.0020	1.0162	<b>0.0114</b>	1.0078	1.0007	1.0150	<b>0.0309</b>	1.0088	1.0017	1.0160	<b>0.0147</b>
Mean BMI	1.0295	1.0014	1.0585	<b>0.0391</b>	1.0269	0.9988	1.0559	0.0602	1.0316	1.0029	1.0611	<b>0.0304</b>
Weight gain males	0.9942	0.9814	1.0071	0.3788	0.9956	0.9823	1.0092	0.5290	1.0044	0.9916	1.0173	0.4978
Weight gain females	0.9851	0.9696	1.0008	0.0627	0.9864	0.9707	1.0024	0.0970	0.9926	0.9772	1.0082	0.3523
Smoking status	1.2666	1.0000	1.6043	<b>0.0499</b>	1.2487	0.9855	1.5823	0.0658	0.8907	0.6997	1.1339	0.3475
Drinking status	1.1236	0.9270	1.3618	0.2347	1.1104	0.9160	1.3460	0.2861	1.2150	1.0017	1.4736	<b>0.0479</b>
Exercise	0.9235	0.7276	1.1721	0.5130	0.9495	0.7474	1.2062	0.6714	0.9043	0.7116	1.1491	0.4105
Family history of HT	1.1240	0.9280	1.3614	0.2315	1.1349	0.9369	1.3748	0.1956	1.0751	0.8872	1.3030	0.4596
Family history of MI	1.0221	0.8462	1.2345	0.8204	1.0131	0.8386	1.2238	0.8925	1.0506	0.8695	1.2694	0.6086
Family history of T1D	1.3260	1.0336	1.7010	<b>0.0263</b>	1.2877	1.0026	1.6538	<b>0.0476</b>	1.1738	0.9130	1.5092	0.2111
Family history of T2D	1.1874	0.8692	1.6219	0.2803	1.1239	0.8203	1.5397	0.4670	1.1187	0.8177	1.5306	0.4828
Systolic BP (SBP)	1.0193	1.0122	1.0266	<0.0001	1.0183	1.0110	1.0256	<0.0001	1.0129	1.0057	1.0201	<b>0.0003</b>
Diastolic BP (DBP)	1.0345	1.0234	1.0457	<0.0001	1.0345	1.0234	1.0457	<0.0001	1.0300	1.0190	1.0411	<0.0001
Pulse	1.0275	1.0190	1.0360	<0.0001	1.0281	1.0197	1.0366	<0.0001	1.0123	1.0036	1.0210	<b>0.0050</b>
Mean SBP	1.0316	1.0201	1.0431	<0.0001	1.0297	1.0181	1.0415	<0.0001	1.0272	1.0154	1.0390	<0.0001

SUPPLEMENTARY DATA

Mean DBP	1.0610	1.0432	1.0792	<b>&lt;0.0001</b>	1.0593	1.0413	1.0775	<b>&lt;0.0001</b>	1.0524	1.0344	1.0706	<b>&lt;0.0001</b>
Mean Pulse	1.0390	1.0259	1.0522	<b>&lt;0.0001</b>	1.0409	1.0278	1.0542	<b>&lt;0.0001</b>	1.0144	1.0012	1.0279	<b>0.0324</b>
Pulse pressure	1.0057	0.9967	1.0147	0.2136	1.0036	0.9945	1.0129	0.4317	0.9990	0.9899	1.0081	0.8343
Hypertension	1.4116	1.1207	1.7779	<b>0.0034</b>	1.3594	1.0761	1.7172	<b>0.0100</b>	1.2018	0.9526	1.5163	0.1209
History of Hypertension	1.3913	1.1271	1.7174	<b>0.0021</b>	1.3606	1.1006	1.6819	<b>0.0044</b>	1.1741	0.9459	1.4572	0.1453
Any ACE	1.0385	0.7922	1.3613	0.7840	0.9955	0.7580	1.3076	0.9746	0.9583	0.7318	1.2547	0.7567
Any ARB	1.1844	0.7651	1.8336	0.4477	1.1286	0.7279	1.7500	0.5885	1.0956	0.7072	1.6975	0.6824
Any beta blockers	0.7923	0.3720	1.6875	0.5462	0.7448	0.3492	1.5884	0.4457	0.6066	0.2850	1.2912	0.1946
Lipid lowering	0.7332	0.5429	0.9901	<b>0.0429</b>	0.6757	0.4981	0.9165	<b>0.0117</b>	0.6565	0.4851	0.8884	<b>0.0064</b>
Calcium channel blockers	1.1925	0.6514	2.1830	0.5681	1.1320	0.6174	2.0753	0.6884	1.0180	0.5557	1.8649	0.9537
Total cholesterol (CHL)	1.0095	1.0071	1.0118	<b>&lt;0.0001</b>	1.0093	1.0069	1.0117	<b>&lt;0.0001</b>	1.0052	1.0027	1.0077	<b>&lt;0.0001</b>
Triglycerides (log)	2.0219	1.7186	2.3787	<b>&lt;0.0001</b>	2.0500	1.7401	2.4150	<b>&lt;0.0001</b>	1.6188	1.3634	1.9220	<b>&lt;0.0001</b>
LDL cholesterol	1.0106	1.0077	1.0135	<b>&lt;0.0001</b>	1.0104	1.0074	1.0133	<b>&lt;0.0001</b>	1.0058	1.0028	1.0088	<b>0.0001</b>
HDL cholesterol	0.9936	0.9871	1.0001	0.0553	0.9927	0.9862	0.9992	<b>0.0298</b>	0.9932	0.9866	0.9998	<b>0.0450</b>
Mean CHL	1.0129	1.0096	1.0162	<b>&lt;0.0001</b>	1.0126	1.0093	1.0159	<b>&lt;0.0001</b>	1.0054	1.0020	1.0089	<b>0.0017</b>
Mean TRG (log)	2.4469	1.9863	3.0143	<b>&lt;0.0001</b>	2.5056	2.0339	3.0867	<b>&lt;0.0001</b>	1.7128	1.3746	2.1343	<b>&lt;0.0001</b>
Mean LDLc	1.0131	1.0094	1.0168	<b>&lt;0.0001</b>	1.0126	1.0089	1.0164	<b>&lt;0.0001</b>	1.0053	1.0015	1.0092	<b>0.0060</b>
Mean HDLc	0.9942	0.9864	1.0021	0.1507	0.9931	0.9853	1.0009	0.0865	0.9939	0.9859	1.0018	0.1342
Duration (years)	1.0604	1.0378	1.0834	<b>&lt;0.0001</b>	1.0591	1.0366	1.0821	<b>&lt;0.0001</b>	1.0977	1.0731	1.1228	<b>&lt;0.0001</b>
Stimulated C-peptide (< 5yr)	0.8315	0.2916	2.3708	0.7299	0.6999	0.2421	2.0231	0.5100	0.7517	0.2516	2.2459	0.6093
Stimulated C-peptide (> 5yr)	0.8017	<b>0.0223</b>	28.750 2	0.9036	0.6409	<b>0.0173</b>	23.6486	0.8090	1.1645	<b>0.0309</b>	43.776 5	0.9343
Insulin dose (per kg)	1.7154	1.2281	2.3959	<b>0.0015</b>	1.8595	1.3442	2.5723	<b>0.0001</b>	1.3928	0.9740	1.9915	0.0693
Mean insulin dose	1.5964	1.0037	2.5390	<b>0.0481</b>	2.2658	1.3749	3.7339	<b>0.0013</b>	1.5845	0.9615	2.6112	0.0708
Estimated GFR	1.0073	1.0002	1.0145	<b>0.0423</b>	1.0163	1.0076	1.0251	<b>0.0002</b>	1.0105	1.0026	1.0184	<b>0.0084</b>
Any eGFR < 60	1.4415	0.6784	3.0629	0.3415	1.3547	0.6364	2.8835	0.4308	0.9510	0.4471	2.0230	0.8963
AER	1.0003	1.0001	1.0005	<b>&lt;0.0001</b>	1.0003	1.0002	1.0005	<b>&lt;0.0001</b>	1.0001	0.9999	1.0003	0.0546
Any	2.5955	1.8467	3.6480	<b>&lt;0.0001</b>	2.7054	1.9226	3.8069	<b>&lt;0.0001</b>	1.5364	1.0848	2.1761	<b>0.0155</b>

SUPPLEMENTARY DATA

Macroalbuminuria												
Coma/Seizure	0.9813	0.8624	1.1166	0.7750	0.9831	0.8633	1.1194	0.7971	1.0036	0.8847	1.1385	0.9545
Required Assistance	0.9516	0.8809	1.0280	0.2083	0.9539	0.8831	1.0303	0.2306	0.9861	0.9166	1.0608	0.7080
HbA1C at baseline	1.2588	1.1942	1.3269	<b>&lt;0.0001</b>	1.2779	1.2109	1.3485	<b>&lt;0.0001</b>	1.0561	0.9926	1.1237	0.0843
HbA1c	1.4907	1.4089	1.5772	<b>&lt;0.0001</b>	1.5095	1.4254	1.5985	<b>&lt;0.0001</b>	1.0295	0.9392	1.1284	0.5340
Mean HbA1C	1.8379	1.7134	1.9715	<b>&lt;0.0001</b>	1.8989	1.7681	2.0392	<b>&lt;0.0001</b>	-	-	-	-

SUPPLEMENTARY DATA

**Supplementary Table S6.** Hazard ratios for Ocular Surgery per unit change in each time-dependent covariate with no adjustment, adjusted for age and adjusted for age and mean HbA1c

	Unadjusted				Adjusted for Age				Adjusted for Age and mean HbA1c			
	HR	LL	UL	p-value	HR	LL	UL	p-value	HR	LL	UL	p-value
Treatment group	1.6536	1.3019	2.1004	<0.0001 <0.0001	1.7533	1.3789	2.2293	<0.0001 <0.0001	1.0596	0.8212	1.3672	0.6560
Cohort	1.6083	1.2599	2.0529	<b>0.0001</b>	1.5722	1.2315	2.0071	<b>0.0002</b>	1.7128	1.3407	2.1883	<0.0001 <0.0001
Sex	0.8171	0.6461	1.0333	0.0917	0.7794	0.6161	0.9861	<b>0.0378</b>	0.7738	0.6117	0.9788	<b>0.0325</b>
Age	1.0484	1.0303	1.0669	<0.0001 <0.0001	-	-	-	-	-	-	-	-
Adult vs. adolescent	1.1492	0.8110	1.6283	0.4341	0.4018	0.2452	0.6583	<b>0.0002</b>	0.5804	0.3525	0.9555	<b>0.0324</b>
Weight	0.9991	0.9924	1.0059	0.8090	0.9981	0.9914	1.0049	0.6007	0.9975	0.9907	1.0042	0.4696
BMI	1.0049	0.9825	1.0279	0.6660	1.0043	0.9819	1.0272	0.7057	1.0036	0.9808	1.0269	0.7565
Mean weight	0.9999	0.9917	1.0082	0.9868	0.9971	0.9889	1.0054	0.5045	0.9963	0.9881	1.0046	0.3929
Mean BMI	1.0138	0.9831	1.0455	0.3809	1.0094	0.9787	1.0410	0.5512	1.0062	0.9750	1.0383	0.6984
Weight gain males	0.9890	0.9746	1.0035	0.1377	0.9959	0.9810	1.0110	0.5964	0.9993	0.9849	1.0140	0.9315
Weight gain females	0.9906	0.9771	1.0042	0.1771	0.9929	0.9790	1.0070	0.3245	0.9951	0.9816	1.0088	0.4891
Smoking status	1.6183	1.2057	2.1721	<b>0.0013</b>	1.6511	1.2297	2.2169	<b>0.0008</b>	1.2335	0.9141	1.6645	0.1698
Drinking status	0.8088	0.6358	1.0288	0.0839	0.7781	0.6114	0.9903	<b>0.0414</b>	0.8577	0.6734	1.0925	0.2138
Exercise	0.8249	0.6189	1.0994	0.1891	0.8756	0.6566	1.1677	0.3659	0.8459	0.6343	1.1281	0.2546
Family history of HT	1.2094	0.9521	1.5361	0.1191	1.2307	0.9689	1.5633	0.0889	1.1462	0.9014	1.4576	0.2654
Family history of MI	1.0771	0.8521	1.3617	0.5341	1.0491	0.8298	1.3265	0.6882	1.0680	0.8445	1.3506	0.5824
Family history of T1D	1.3020	0.9565	1.7723	0.0933	1.1817	0.8665	1.6114	0.2914	1.1600	0.8495	1.5840	0.3502
Family history of T2D	1.4193	0.9867	2.0414	0.0590	1.2411	0.8607	1.7896	0.2473	1.2426	0.8631	1.7888	0.2426
Systolic BP (SBP)	1.0161	1.0085	1.0238	<0.0001 <0.0001	1.0125	1.0047	1.0203	<b>0.0015</b>	1.0046	0.9970	1.0123	0.2268
Diastolic BP	0.9879	0.9749	1.0010	0.0719	0.9913	0.9782	1.0045	0.1974	0.9893	0.9766	1.0022	0.1053

SUPPLEMENTARY DATA

(DBP)												
Pulse	1.0293	1.0189	1.0397	<0.0001 <0.0001	1.0336	1.0232	1.0441	<0.0001 <0.0001	1.0157	1.0049	1.0267	<b>0.0042</b>
Mean SBP	1.0466	1.0323	1.0610	<0.0001 <0.0001	1.0380	1.0233	1.0529	<0.0001 <0.0001	1.0261	1.0117	1.0408	<b>0.0003</b>
Mean DBP	1.0394	1.0164	1.0629	<b>0.0006</b>	1.0358	1.0127	1.0595	<b>0.0022</b>	1.0213	0.9987	1.0444	0.0647
Mean Pulse	1.0737	1.0552	1.0925	<0.0001 <0.0001	1.0826	1.0638	1.1018	<0.0001 <0.0001	1.0448	1.0253	1.0646	<0.0001 <0.0001
Pulse pressure	1.0288	1.0200	1.0377	<0.0001 <0.0001	1.0233	1.0140	1.0327	<0.0001 <0.0001	1.0132	1.0038	1.0227	<b>0.0055</b>
Hypertension	1.9509	1.4977	2.5411	<0.0001 <0.0001	1.7248	1.3167	2.2595	<0.0001 <0.0001	1.4281	1.0931	1.8659	<b>0.0089</b>
History of Hypertension	2.2574	1.6127	3.1599	<0.0001 <0.0001	2.0549	1.4633	2.8858	<0.0001 <0.0001	1.6208	1.1512	2.2820	<b>0.0056</b>
Any ACE	1.6786	1.3154	2.1419	<0.0001 <0.0001	1.5403	1.2046	1.9697	<b>0.0005</b>	1.4008	1.0974	1.7879	<b>0.0067</b>
Any ARB	1.4221	1.0181	1.9864	<b>0.0388</b>	1.2907	0.9226	1.8057	0.1362	1.2629	0.9044	1.7636	0.1705
Any beta blockers	2.4289	1.7502	3.3706	<0.0001	2.1244	1.5244	2.9606	<0.0001	1.5584	1.1182	2.1721	<b>0.0088</b>
Lipid lowering	1.3125	1.0143	1.6983	<b>0.0386</b>	1.0866	0.8320	1.4192	0.5416	1.0300	0.7881	1.3461	0.8282
Calcium channel blockers	2.0506	1.4257	2.9495	<b>0.0001</b>	1.7200	1.1871	2.4920	<b>0.0041</b>	1.5800	1.0937	2.2827	<b>0.0148</b>
Total cholesterol (CHL)	1.0018	0.9986	1.0051	0.2473	1.0019	0.9987	1.0051	0.2295	0.9991	0.9959	1.0023	0.5986
Triglycerides (log)	1.5603	1.2681	1.9197	<0.0001	1.5799	1.2784	1.9523	<0.0001	1.2309	0.9846	1.5387	0.0680
LDL cholesterol	0.9998	0.9959	1.0038	0.9594	1.0004	0.9964	1.0044	0.8296	0.9969	0.9931	1.0008	0.1276
HDL cholesterol	0.9983	0.9915	1.0052	0.6454	0.9968	0.9900	1.0037	0.3765	0.9996	0.9926	1.0066	0.9139
Mean CHL	1.0069	1.0023	1.0115	<b>0.0028</b>	1.0051	1.0005	1.0098	<b>0.0292</b>	0.9970	0.9923	1.0018	0.2274
Mean TRG (log)	1.9646	1.5064	2.5620	<0.0001	2.0265	1.5538	2.6430	<0.0001	1.3805	1.0421	1.8287	<b>0.0245</b>
Mean LDLc	1.0048	0.9996	1.0101	0.0696	1.0031	0.9978	1.0085	0.2458	0.9946	0.9892	1.0000	0.0508
Mean HDLc	0.9973	0.9879	1.0067	0.5798	0.9945	0.9852	1.0038	0.2497	0.9964	0.9868	1.0061	0.4688
Duration (years)	1.0654	1.0378	1.0938	<0.0001	1.0616	1.0341	1.0899	<0.0001	1.0990	1.0680	1.1295	<0.0001
Stimulated C-peptide (< 5yr)	0.4572	0.1151	1.8162	0.2661	0.3489	0.0859	1.4161	0.1407	0.2661	0.0636	1.1123	0.0696
Stimulated C-	0.2104	0.0021	20.307	0.5037	0.1195	0.0011	12.0846	0.3671	0.1695	0.0018	15.875	0.4434



SUPPLEMENTARY DATA

peptide (> 5)			3							2		
Insulin dose (per kg)	1.3309	0.9804	1.8066	0.0667	1.3517	1.0064	1.8153	<b>0.0451</b>	1.1035	0.7357	1.6549	0.6338
Mean insulin dose	2.3135	1.2398	4.3168	<b>0.0083</b>	3.9979	2.1385	7.4741	<b>&lt;0.0001</b>	2.2370	1.1537	4.3375	<b>0.0171</b>
Estimated GFR	0.9823	0.9770	0.9877	<b>&lt;0.0001</b>	0.9855	0.9795	0.9916	<b>&lt;0.0001</b>	0.9936	0.9881	0.9991	<b>0.0241</b>
Any eGFR < 60	3.4501	2.4162	4.9264	<b>&lt;0.0001</b>	2.8832	2.0003	4.1557	<b>&lt;0.0001</b>	1.8229	1.2629	2.6312	<b>0.0013</b>
AER	1.0002	1.0001	1.0003	<b>&lt;0.0001</b>	1.0002	1.0002	1.0003	<b>&lt;0.0001</b>	1.0001	1.0000	1.0002	<b>&lt;0.0001</b>
Any Macroalbuminuria	3.4011	2.5620	4.5150	<b>&lt;0.0001</b>	3.5899	2.7029	4.7681	<b>&lt;0.0001</b>	1.7934	1.3185	2.4393	<b>0.0001</b>
Coma/Seizure	1.0336	0.9497	1.1250	0.4431	1.0370	0.9505	1.1314	0.4125	1.0321	0.9344	1.1400	0.5332
Required Assistance	0.9948	0.9346	1.0590	0.8720	0.9976	0.9368	1.0623	0.9410	0.9970	0.9364	1.0615	0.9253
HbA1C at baseline	1.2752	1.1946	1.3612	<b>&lt;0.0001</b>	1.3131	1.2284	1.4036	<b>&lt;0.0001</b>	1.1129	1.0329	1.1991	<b>0.0049</b>
HbA1c	1.2684	1.1733	1.3713	<b>&lt;0.0001</b>	1.3103	1.2080	1.4211	<b>&lt;0.0001</b>	0.8153	0.7307	0.9097	<b>0.0002</b>
Mean HbA1C	1.8964	1.7230	2.0873	<b>&lt;0.0001</b>	2.0502	1.8529	2.2686	<b>&lt;0.0001</b>	-	-	-	-

SUPPLEMENTARY DATA

**Supplementary Figure S1.** Kaplan-Meier event-free (survival) curves (lines) and 95% CIs (shaded areas) for PDR (red solid line), CSME (green dashed line) and Ocular Surgery (blue dotted line), with number of subjects at risk for each at baseline and 10, 20, 25 and 30 years of follow-up. The number at risk beyond 25 years declines as a function of staggered entry into the study from 1983 to 1989.

