Supplemental Materials

30-Year Cardiovascular Disease in Type 1 Diabetes: Risk and Risk Factors by Long-Term Patterns of Glycemic Control

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A)

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Figure S1. Flow chart for the Determination of the Analytic Samples for (A) Total CVD and (B) Major Adverse Cardiovascular Event (MACE)

Table S1. Bayesian Information Criteria and Percent of EDC Participants in Each Class for Various Numbers of Latent Classes in Joint Latent Class Mixed Models for Total Cardiovascular Disease (CVD) and Major Adverse Cardiovascular Event (MACE)

Outcome	Number of Latent Classes	BIC	% in each latent class
Total CVD	1	12613	100%
	2	12582	76%, 24%
	3	12581	23%, 3%, 74%
	4	12581	3%, 6%, 50%, 41%
MACE	1	12600	100%
	2	12558	86%, 14%
	3	12573	38%, 8%, 54%
	4	12593	8%, 40%, 1%, 51%

Table S2. Baseline Characteristics by HbA1c Trajectory for 30-Year Total CVD

	Low HbA1c (n=410)	High HbA1c (n=126)	p-value
Age, years	27.2 (7.6)	26.5 (8.0)	0.4120
T1D Duration, years	18.9 (7.3)	18.4 (8.0)	0.4684
Sex, % women	52.9% (217)	39.0% (49)	0.0058
HbA1c, %	8.4 (1.3)	9.6 (1.7)	<0.0001
HbA1c (mmol/mol)	68.3 (14.4)	81.8 (18.5)	<0.0001
BMI, kg/m ²	23.5 (3.2)	23.7 (3.4)	0.6426
Insulin Dose, insulin units/kg body weight	0.78 (0.24)	0.84 (0.27)	0.0218
≥3 Insulin Injections/day or Insulin Pump, % (n)	8.6% (34)	4.0% (5)	0.0906
Hypoglycemia requiring assistance, % (n)	41.2% (162)	41.8% (51)	0.9092
eGDR, mg/kg/min	8.3 (1.7)	6.9 (1.8)	<0.0001
Non-HDLc, mg/dL	129.4 (38.2)	149.0 (41.9)	<0.0001
HDLc, mg/dl	55.0 (12.3)	52.1 (12.0)	0.0205
Triglycerides, mg/dL*	77 (57.5, 110)	93 (70, 158)	<0.0001
Lipid-lowering medications, % (n)	0.5% (2)	0.8% (1)	0.5568
Systolic BP, mmHg	111.3 (13.8)	124.0 (80.9)	0.0054
Diastolic BP, mmHg	71.7 (10.7)	73.7 (10.6)	0.0654
BP-lowering medications, % (n)	7.6% (30)	10.5% (13)	0.3086
Aspirin, % (n)	0.5% (2)	0% (0)	0.99
White Blood Cell Count, x10⁹/L	6.3 (1.8)	7.1 (2.1)	0.0009
Albumin Excretion Rate, µg/min*	11.9 (6.5, 69.3)	23.6 (9.0, 256.9)	0.0008
eGFR, mL/min/1.73²	103.3 (28.6)	110.5 (30.6)	0.0162
Ever smoker, % (n)	33.9% (139)	42.9% (54)	0.0670
Current smoker, % (n)	18.5% (76)	33.3% (42)	0.0005
Family History of MI, % (n)	17.1% (66/386)	16.4% (20)	0.8564

Values are mean (SD) unless indicated. *Median (p25, p75). Bolded values indicate significance at p<0.05

Table S3. Multivariable Baseline Risk Factor Models for 30-Year Total Cardiovascular Disease (CVD) Incidence by HbA1c Trajectory

Variables	Low HbA1c, 76%		High HbA1c, 24%	
	HR (95% CI)	p-value	HR (95% CI)	p-value
<i>Primary Model: Individual Risk Factors</i>				
T1D Duration	1.10 (1.07, 1.13)	<0.0001	1.12 (1.09, 1.16)	<0.0001
HbA1c	0.88 (0.76, 1.01)	0.0731	<i>not retained</i>	-
Non-HDLc	1.009 (1.004, 1.014)	0.0001	<i>not retained</i>	-
Systolic BP	1.01 (1.002, 1.02)	0.0215	<i>not retained</i>	-
BP-lowering medication use	1.68 (1.01, 2.78)	0.0441	3.605 (1.64, 7.92)	0.0014
White Blood Cell Count	1.14 (1.04, 1.25)	0.0061	<i>not retained</i>	-
ln(AER)	1.10 (1.00, 1.22)	0.0569	1.14 (0.99, 1.32)	0.0621
AIC:	1494		615	
<i>Alternative Model 1: Offering Hypertension</i>				
T1D Duration	1.10 (1.08, 1.13)	<0.0001	1.13 (1.10, 1.17)	<0.0001
HbA1c	0.86 (0.75, 0.99)	0.0415	<i>not retained</i>	-
Non-HDLc	1.008 (1.004, 1.013)	0.0004	<i>not retained</i>	-
HDLc	0.985 (0.97, 0.999)	0.0332	<i>not retained</i>	-
Hypertension	1.55 (1.03, 2.35)	0.0326	2.91 (1.60, 5.28)	0.0005
White Blood Cell Count	1.13 (1.03, 1.24)	0.0105	<i>not retained</i>	-
ln(AER)	1.13 (1.02, 1.24)	0.0144	<i>not retained</i>	-
ln(Triglycerides)	<i>not retained</i>	-	1.60 (1.11, 2.30)	0.0114
AIC:	1497		619	
<i>Alternative Model 2: Offering eGDR</i>				
T1D Duration	1.12 (1.09, 1.14)	<0.0001	1.14 (1.10, 1.17)	<0.0001
eGDR	<i>not retained</i>	-	0.87 (0.77, 0.98)	0.0182
Non-HDLc	1.007 (1.002, 1.011)	0.0032	<i>not retained</i>	-
HDLc	0.985 (0.97, 0.999)	0.0307	<i>not retained</i>	-
White Blood Cell Count	1.13 (1.03, 1.23)	0.0100	<i>not retained</i>	-
ln(AER)	1.17 (1.68, 1.28)	0.0007	<i>not retained</i>	-
ln(Triglycerides)	<i>not retained</i>	-	1.44 (0.97, 2.14)	0.0726
AIC:	1500		624	

Table S4. Most Recent Characteristics by Total Cardiovascular Disease (CVD) Incidence Status and Hazard Ratios for CVD (95% Confidence Interval) from Time-Varying Cox Models by HbA1c Trajectory

	Low HbA1c				High HbA1c			
	CVD Incidence (n=156)	No CVD (n=254)	HR (95% CI)	p-value	CVD Incidence (n=97)	No CVD (n=29)	HR (95% CI)	p-value
HbA1c, %	7.67 (1.20)	7.98 (1.28)	0.93 (0.82, 1.06)	0.2823	10.03 (1.68)	10.86 (1.23)	0.93 (0.82, 1.06)	0.2528
BMI, kg/m ²	27.6 (5.3)	27.0 (4.7)	1.03 (0.99, 1.07)	0.0746	27.1 (5.7)	25.1 (4.3)	1.03 (0.99, 1.08)	0.1425
Insulin Dose, units/kg body wt	0.61 (0.47, 0.83)	0.60 (0.44, 0.81)	1.05 (0.98, 1.13)	0.1801	0.66 (0.54, 0.87)	0.72 (0.48, 0.95)	1.07 (0.95, 1.21)	0.2876
≥3 Insulin Injections/day or pump	65.4% (102)	75.2% (191)	0.85 (0.60, 1.20)	0.3536	60.8% (59)	55.2% (16)	1.42 (0.93, 2.17)	0.1032
Hypoglycemia requiring assistance, %	61.5% (96)	60.6% (154)	1.15 (0.84, 1.58)	0.3897	48.5% (47)	51.7% (15)	0.92 (0.61, 1.39)	0.6835
Non-HDLc, mg/dl	124.6 (38.5)	121.5 (35.4)	1.01 (1.00, 1.01)	0.0008	152.5 (50.8)	156.1 (49.5)	1.00 (0.99, 1.01)	0.4464
HDLc, mg/dl	57.4 (17.0)	57.4 (15.0)	1.00 (0.99, 1.01)	0.6899	52.0 (13.6)	53.3 (18.4)	1.00 (0.98, 1.01)	0.8205
Triglycerides, mg/dl	87.5 (63, 122)	70 (50, 101)	1.74 (1.30, 2.32)*	0.0002	114 (85, 160)	119 (99, 174)	1.15 (0.78, 1.69)*	0.4879
Lipid-lowering medications, %	46.2% (72)	29.1% (74)	1.20 (1.06, 1.36)	0.004	37.1% (36)	24.1% (7)	1.48 (1.07, 2.05)	0.0166
Systolic BP, mmHg	124.9 (22.0)	115.0 (14.9)	1.04 (1.03, 1.05)	<0.0001	124.7 (19.1)	118.9 (16.3)	1.02 (1.01, 1.03)	0.0029
Diastolic BP, mmHg	67.7 (13.2)	68.5 (9.6)	1.01 (0.99, 1.03)	0.2155	71.5 (12.8)	76.9 (12.6)	0.99 (0.97, 1.01)	0.1832
BP-lowering medications, %	41.7% (65)	21.7% (55)	2.77 (2.00, 3.84)	<0.0001	47.4% (46)	24.1% (7)	2.50 (1.65, 3.79)	<0.0001
Aspirin, %	46.2% (72)	29.9% (76)	1.78 (1.21, 2.62)	0.0036	40.2% (39)	17.2% (5)	1.34 (0.83, 2.17)	0.2349
White Blood Cell Count	6.8 (1.9)	6.3 (2.1)	1.21 (1.13, 1.29)	<0.0001	8.01 (2.1)	7.57 (2.0)	1.11 (1.02, 1.21)	0.0224
AER, µg/min	18.7 (6.8, 102)	6.6 (4.2, 24.6)	1.32 (1.22, 1.42)*	<0.0001	168 (30, 1059)	53 (11, 418)	1.16 (1.07, 1.27)*	0.0006
eGFR, mL/min/1.73 ²	71.0 (29.3)	90.3 (25.7)	0.98 (0.97, 0.98)	<0.0001	73.0 (34.3)	91.5 (33.6)	0.99 (0.98, 0.99)	<0.0001
Current smoker	14.1% (22)	10.6% (27)	1.33 (0.88, 2.02)	0.1805	22.7% (22)	20.7% (6)	1.17 (0.71, 1.92)	0.5372

*Natural log transformed before modeling

Table S5. Multivariable Models for Time-Varying Most Recent Risk Factors and 30-Year Total CVD Incidence by HbA1c Trajectory

Variables	Low HbA1c		High HbA1c	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Diabetes Duration	1.10 (1.08, 1.13)	<0.0001	1.13 (1.09, 1.16)	<0.0001
SBP	1.01 (1.00, 1.02)	0.0206	<i>not retained</i>	-
BP-lowering medication use	1.51 (1.04, 2.19)	0.0313	2.18 (1.42, 3.35)	0.0004
White Blood Cell Count	1.09 (1.01, 1.17)	0.0205	1.19 (1.07, 1.32)	0.0008
eGFR	0.990 (0.984, 0.996)	0.0009	0.993 (0.987, 0.999)	0.0292
Current smoking	1.58 (1.01, 2.48)	0.0452	<i>not retained</i>	-
ln(Triglycerides)	1.35 (0.97, 1.86)	0.0743	<i>not retained</i>	-

Figure S2. HbA1c Trajectories and Corresponding 30-Year Major Adverse Cardiovascular Event Survival Curves from Joint Latent Class Mixed Models

Table S6. Baseline Characteristics by 30-Year Major Adverse Cardiovascular Event (MACE) Incidence Status and HbA1c Trajectory

	Low HbA1c				High HbA1c			
	MACE Incidence (n=119)	No MACE (n=366)	HR (95% CI)	p-value	MACE Incidence (n=57)	No MACE (n=25)	HR (95% CI)	p-value
Age, years	32.0 (6.8)	25.8 (7.3)	1.11 (1.08, 1.13)	<0.0001	29.8 (7.4)	20.3 (7.2)	1.14 (1.10, 1.91)	<0.0001
T1D Duration, years	24.0 (6.8)	17.5 (6.8)	1.12 (1.09, 1.15)	<0.0001	21.3 (7.9)	12.1 (5.0)	1.14 (1.10, 1.18)	<0.0001
Female Sex	50.4% (60)	50.6% (185)	0.92 (0.64, 1.32)	0.6583	47.4% (27)	36.0% (9)	1.34 (0.79, 2.28)	0.2787
HbA1c, %	8.4 (1.3)	8.6 (1.4)	0.94 (0.82, 1.09)	0.4284	9.8 (1.6)	10.0 (2.3)	0.95 (0.82, 1.10)	0.4778
HbA1c, mmol/mol	67.0 (14.0)	70.1 (15.1)	1.00 (0.98, 1.01)	0.4284	83.1 (17.9)	85.3 (25.2)	1.00 (0.98, 1.01)	0.4779
BMI, kg/m ²	23.9 (3.4)	23.5 (3.2)	1.05 (0.99, 1.11)	0.0884	23.8 (3.4)	22.4 (4.1)	1.07 (0.99, 1.15)	0.0603
Insulin Dose, units/kg	0.75 (0.25)	0.80 (0.23)	0.46 (0.19, 1.08)	0.0747	0.79 (0.27)	0.95 (0.33)	0.15 (0.04, 0.51)	0.0024
≥3 Insulin Injections/day or pump, %	9.5% (11)	7.4% (26)	1.26 (0.68, 2.35)	0.4627	3.6% (2/56)	0% (0)	1.57 (0.38, 6.50)	0.5344
Hypoglycemia requiring assistance, %	46.1% (53)	39.4% (138)	1.21 (0.84, 1.75)	0.3101	45.5% (25/55)	29.2% (7/24)	1.19 (0.69, 2.04)	0.5306
eGDR, mg/kg/min	7.4 (2.0)	8.3 (1.6)	0.72 (0.65, 0.79)	<0.0001	6.4 (2.3)	7.0 (1.8)	0.89 (0.78, 1.01)	0.0695
Non-HDLc, mg/dL	148.6 (40.4)	126.0 (36.0)	1.012 (1.008, 1.015)	<0.0001	162.2 (45.7)	134.7 (42.1)	1.01 (1.008, 1.013)	0.0017
HDLc, mg/dL	52.9 (11.9)	55.2 (12.8)	0.98 (0.97, 0.99)	0.0367	51.4 (10.2)	52.8 (10.4)	0.98 (0.96, 1.01)	0.2391
Triglycerides, mg/dL	95 (68, 133)	75 (56, 102)	2.19 (1.63, 2.93)	<0.0001	113.5 (77, 179)	85.5 (68, 140)	1.49 (0.94, 2.36)	0.0900
Lipid-lowering meds, %	1.7% (2)	0.3% (1)	3.78 (0.93, 15.3)	0.0624	0% (0)	0% (0)	n/a	
Systolic BP, mmHg	120.0 (20.1)	110.1 (12.0)	1.04 (1.03, 1.05)	<0.0001	119.0 (18.1)	108.4 (12.5)	1.03 (1.02, 1.05)	<0.0001
Diastolic BP, mmHg	76.0 (12.7)	71.0 (9.6)	1.05 (1.03, 1.07)	<0.0001	76.1 (12.4)	69.9 (7.6)	1.05 (1.03, 1.07)	<0.0001
BP-lowering meds, %	21.4% (25)	5.4% (19)	4.27 (2.74, 6.66)	<0.0001	17.9% (10/56)	4.2% (1/24)	4.07 (1.98, 8.37)	0.0001
White Blood Cell Count, x10 ⁹ /L	7.3 (2.1)	6.1 (1.6)	1.39 (1.28, 1.51)	<0.0001	7.5 (2.1)	6.4 (2.0)	1.12 (1.01, 1.24)	0.0400
AER, µg/min	60.8 (10.2, 409)	11.5 (6.4, 39.1)	1.32 (1.21, 1.43)	<0.0001	75.1 (12.8, 553)	10.9 (9.0, 45.6)	1.58 (1.36, 1.83)	<0.0001
eGFR, mL/min/1.73 ²	90.7 (34.1)	106.7 (27.3)	0.982 (0.976, 0.987)	<0.0001	100.1 (37.7)	126.7 (29.5)	0.982 (0.976, 0.989)	<0.0001
Ever smoker, %	47.1% (56)	30.9% (113)	2.03 (1.41, 2.91)	0.0001	54.4% (31)	24.0% (6)	2.10 (1.23, 3.59)	0.0070
Current smoker, %	28.6% (34)	17.5% (64)	1.93 (1.30, 2.87)	0.0012	38.6% (22)	20.0% (5)	1.57 (0.91, 2.69)	0.1052
Family History of MI, %	27.1% (31)	14.0% (48)	2.09 (1.38, 3.16)	0.0005	18.2% (10/55)	12.5% (3/24)	1.76 (0.88, 3.51)	0.1122

*Natural log transformed prior to modeling. Bolded values indicate significance <0.05

Table S7. Multivariable Baseline Risk Factor Models for 30-Year Major Adverse Cardiovascular Event (MACE) Incidence by HbA1c Trajectory

Variables	Low HbA1c		High HbA1c	
	HR (95% CI)	p-value	HR (95% CI)	p-value
T1D Duration	1.08 (1.05, 1.11)	<0.0001	1.09 (1.05, 1.15)	0.0001
Non-HDLc	1.006 (1.002, 1.011)	0.006	<i>not retained</i>	-
Systolic BP	1.02 (1.01, 1.04)	0.0004	<i>not retained</i>	-
BP-lowering medication use	1.70 (1.06, 2.73)	0.03	<i>not retained</i>	-
White Blood Cell Count	1.26 (1.15, 1.38)	<0.0001	<i>not retained</i>	-
ln(AER)	<i>not retained</i>	-	1.45 (1.23, 1.71)	<0.0001
eGDR	<i>not retained</i>	-	0.987 (0.978, 0.996)	0.0007
Ever Smoker	<i>not retained</i>	-	1.98 (1.05, 3.74)	0.03

Table S8. Multivariable Models for Time-Varying Most Recent Risk Factors and 30-Year Major Adverse Cardiovascular Event (MACE) Incidence by HbA1c Trajectory

Variables	Low HbA1c		High HbA1c	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Diabetes Duration	1.11 (1.08, 1.14)	<0.0001	1.15 (1.10, 1.20)	<0.0001
BMI	<i>not retained</i>	-	1.08 (1.02, 1.15)	0.0084
DBP	1.02 (1.00, 1.03)	0.0105	<i>not retained</i>	-
BP-lowering medication use	1.82 (1.21, 2.73)	0.004	<i>not retained</i>	-
White Blood Cell Count	1.16 (1.07, 1.25)	0.0002	<i>not retained</i>	-
eGFR	0.990 (0.984, 0.996)	0.0015	0.988 (0.979, 0.996)	0.0035
Current smoking	<i>not retained</i>	-	3.34 (1.58, 7.06)	0.0017

EDC Subcohort					Allegheny County			
	HbA1c Group	Events	Person Years	Rate per 1,000 Person Years (95% CI)	Events	Person Years	Rate per 1,000 Person Years (95% CI)	Rate Ratio (95% CI)
Total CVD	High	5	196	2551 (822, 5953)	2208	1636861	135 (129, 141)	18.9 (7.9, 45.5)
	Low	10	1151	869 (416, 1598)				6.4 (3.5, 12.0)
MACE	High	5	196	2551 (822, 5953)	1636	1636861	100 (95, 105)	25.5 (10.6, 61.4)
	Low	2	1151	174 (20, 627)				1.7 (0.4, 7.0)

Figure S3. Rate Ratios for Total CVD and MACE in the EDC <45 years old subcohort compared to the background Allegheny Co, PA <45 years old population, 2010-2014. The thick vertical line indicates a ratio of 1 (no difference in risk).