

Supplemental Material for Vehik et al., *Rising Hemoglobin A1c in the Non-Diabetic Range Predicts Progression of Type 1 Diabetes As Well As Oral Glucose Tolerance Tests*

Supplemental Table 1. Characteristics of TEDDY Children included in the analysis by whether or not Stage 3 diabetes diagnosed

	All Children	Stage 3	Not Stage 3
Total N	707	235	472
Genetic sex, N(% Male)	387(55)	128(54.5)	259(54.9)
Family history in first degree relative, N(% Yes)	127(18)	54(23.0)	73(15.5)
HLA-DR N(% DR3/4)	333(47)	128(54.5)	205(43.4)
Years followed from baseline, median (IQR)	5.17(2.7-7.6)	3.64(1.9-5.6)	6.07(3.3-8.3)
Age at baseline HbA1c measure, median (IQR) years	4.25(2.6-6.8)	3.10(2.3-4.3)	5.14(3.3-8.2)
Age at seroconversion, median (IQR) years	3.61(1.9-7.3)	2.26(1.3-3.6)	5.04(2.5-8.5)
Age at T1D diagnosis or last visit for non-progressors, median (IQR) years	11.07(9.0-12.8)	7.74(5.1-9.9)	12.11(10.6-13.5)
HbA1c % at baseline, median (IQR)	5.10(5.0-5.3)	5.10(4.9-5.3)	5.10(5.0-5.3)
HbA1c % at time 10%+ threshold met, median (IQR)	5.30(5.1-5.5)	5.50(5.3-5.9)	5.20(5.1-5.4)
HbA1c % at T1D diagnosis, median (IQR)	-	6.50 (6.0-7.3)	-
Number of HbA1c measures, median (IQR)	16(10-24)	13(8-20)	18(11-26)
Maximum Number of autoantibody (Ab), N(%)			
1 Ab	304(43.0)	22(9.4)	282(59.7)
2 Abs	163(23.1)	62(26.4)	101(21.4)
3 Abs	240(33.9)	151(64.3)	89(18.9)

*Follow-up through 31 December 2019

Supplemental Table 2. Characteristics of TrialNet subjects included in the analysis by whether or not Stage 3 diabetes diagnosed

	All Subjects	Stage 3	Not Stage 3
Total N	1190	193	997
Genetic sex N(% Male)	601 (50.5)	102 (52.8)	499 (50.1)
HLA-DR N(% DR3/4)	252 (21.2)	62 (32.1)	190 (19.1)
Years followed from baseline, median (IQR)	2.15 (1.2-4.0)	1.93 (1.1-3.0)	2.34 (1.2-4.2)
Age at baseline HbA1c measure, median (IQR) years	10.06 (6.6-13.3)	8.64 (6.2-12.2)	10.28 (6.8-13.4)
Age at T1D diagnosis or last visit for non-progressors, median (IQR) years	12.95 (9.2-16.3)	11.16 (7.9-14.5)	13.26 (9.6-16.5)
HbA1c % at baseline, median (IQR)	5.10 (4.9-5.3)	5.20 (5.0-5.4)	5.10 (4.9-5.2)
HbA1c % at time 10%+ threshold met, median (IQR)	5.10 (4.9-5.3)	5.40(5.1-5.8)	5.10(4.9-5.2)
HbA1c % at T1D diagnosis, median (IQR)	-	6.35 (5.6-7.6)	-
Number of HbA1c measures, median (IQR)	4 (2-6)	4 (3-6)	3 (2-6)
Maximum Number of autoantibody (Ab), N(%)			
1 Ab	356 (29.9)	13 (6.7)	343 (34.4)
2 Abs	282 (23.7)	35 (18.1)	247 (24.8)
3 Abs	295 (24.8)	67 (34.7)	228 (22.9)
4 Abs	257 (21.6)	78 (40.4)	179 (17.9)

*Follow-up through 31 December 2012

Supplemental Table 3. Multivariable effect of known type 1 diabetes risk factors associated with predicting a $\geq 10\%$ change in HbA1c in TEDDY and TrialNet youth <21 years with islet autoimmunity

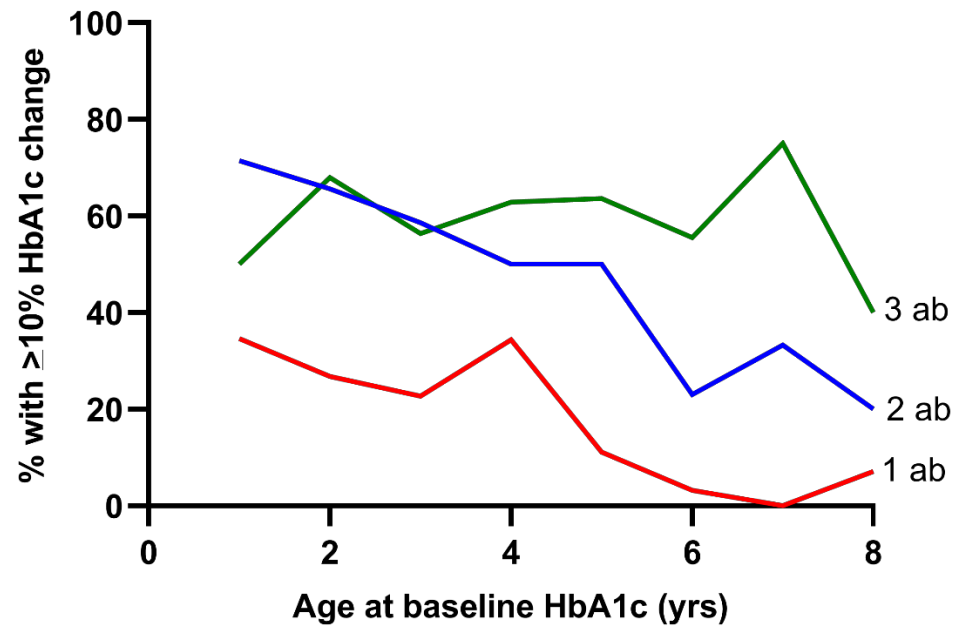
Known type 1 diabetes risk factors	TEDDY			TrialNet**		
	HR	95% CI	p-value	HR	95% CI	p-value
Family history in first degree relative (Yes vs. No)	1.14	0.8-1.5	0.39	na	na	na
Maximum Number of Abs by time of HbA1c change	1.87	1.6-2.2	<0.0001	1.97	1.56-2.49	<0.0001
Maximum rate of change between repeated HbA1c*	1.23	1.2-1.3	<0.0001	1.30	1.24-1.37	<0.0001
HLA (DR3/4 vs Other)	1.08	0.8-1.4	0.55	0.72	0.40-1.30	0.27
Age at Baseline HbA1c visit (Years)	0.92	0.9-0.98	0.014	0.92	0.86-0.97	0.003
HbA1c at Baseline visit (%)	0.06	0.03-0.1	<0.0001	0.14	0.06-0.29	<0.0001
Genetic sex (Female vs Male)	0.72	0.6-0.9	0.009	0.95	0.58-1.54	0.83

*The maximum rate of change in relative HbA1c from baseline is defined as greatest percent HbA1c change between consecutive HbA1c measures up to the time when the overall HbA1c change threshold percent is achieved

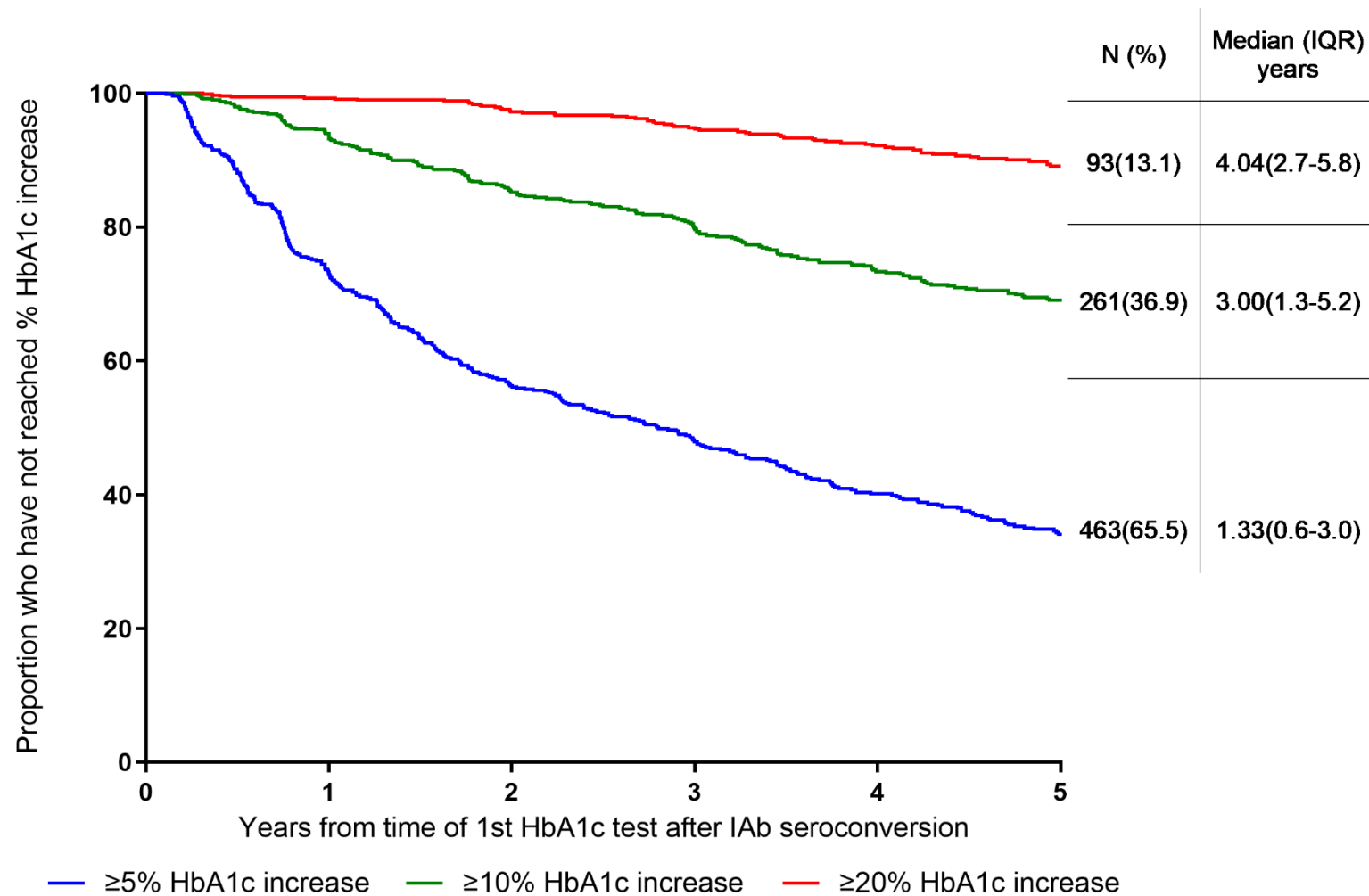
**The TrialNet study population are relatives of patients with type 1 diabetes.

Supplemental Table 4. Known type 1 diabetes risk factors associated with predicting a rise in OGTT ≥ 8 in TEDDY

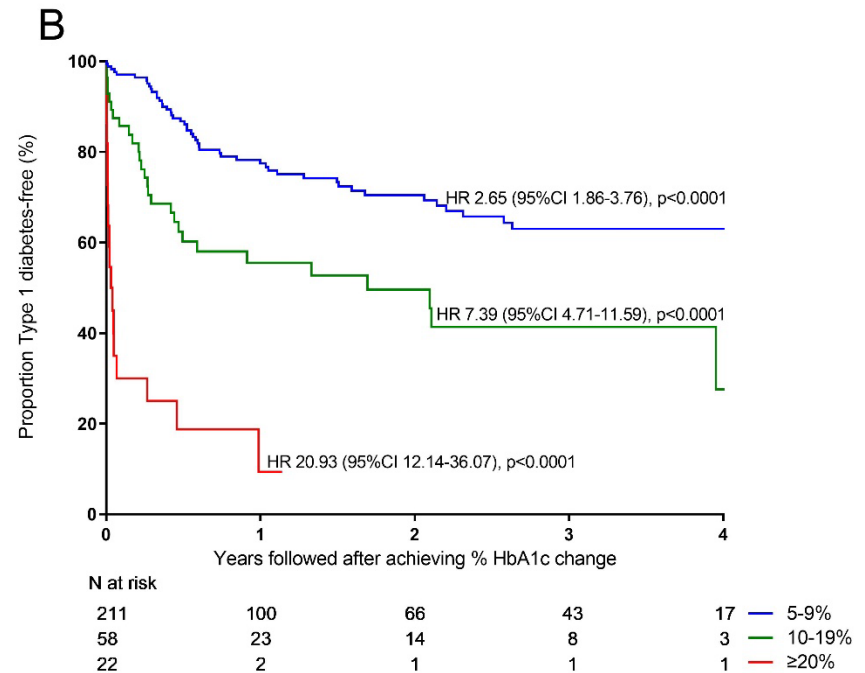
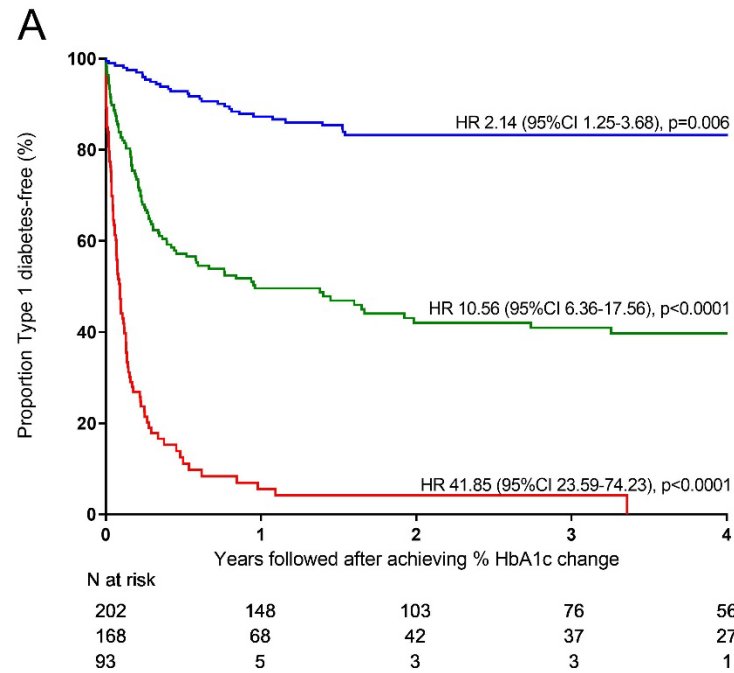
Known T1D Risk Factor	OGTT ≥ 8		
	HR	95% CI	p-value
Family history in first Degree Relative (Yes vs. No)	1.27	0.90-1.81	0.17
Maximum Number of autoantibodies by time of HbA1c change	1.28	1.02-1.59	0.032
HLA (DR3/4 vs Other)	1.02	0.78-1.35	0.87
Age at Baseline OGTT visit (Years)	0.96	0.90-1.03	0.21
OGTT at Baseline visit (%)	1.43	1.35-1.51	<0.0001
Genetic sex (Female vs Male)	0.9	0.69-1.19	0.46



Supplemental Figure 1. Proportion of TEDDY children reaching indicated % HbA1c increase criterion by age at baseline HbA1c test based on number of autoantibodies at time of % HbA1c increase.



Supplemental Figure 2. Proportion of TEDDY children reaching indicated % HbA1c increase criterion by years since baseline HbA1c test.



Supplemental Figure 3. Multivariable Cox proportional hazards models evaluating % HbA1c increase in TEDDY (A) and TrialNet (B) on progression to type 1 diabetes from time at % increase in HbA1c. Reference is <5% HbA1c increase. Models adjusted for age at HbA1c baseline, HbA1c baseline measure, and number of autoantibodies at change.