

Supplementary Material for

Longitudinal Plasma Kallikrein Levels and their Association with the Risk of Cardiovascular Disease Outcomes in Type 1 Diabetes in DCCT/EDIC

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Table S1. Comparison of DCCT baseline characteristics of the 693 participants with plasma kallikrein values versus the full DCCT cohort (n=1441 participants).

Variables	Plasma Kallikrein subgroup (n=693)	Entire DCCT cohort (n=1441)
Group (% experimental)	343 (49%)	711 (49%)
Cohort(% primary)	341 (49%)	726 (50%)
Current smoker (%)	115 (17%)	267 (19%)
Age (year)	26.9±6.9 (22,27,32)	26.8±7.1 (22, 27,32)
Sex (% men)	372 (54%)	761 (53%)
BMI (kg/m ²)	23.3±2.7 (21.2,23.4,25.0)	23.4±2.8 (21.3,23.3,25.2)
Duration of T1D at entry (month)	65.8±48.2 (26,48,102)	67.6±49.9 (26,49,108)
HbA1c(%)	9.0±1.6 (7.8,8.8,9.9)	9.1±1.6 (7.8, 8.8,10.1)
HbA1c (mmol/mol)	75±17 (62,73,85)	76±17 (62,73,87)
SBP (mmHg)	114.8±11.2 (108,115,122)	114.1±11.6 (106,114,122)
HDL (mg/dL)	50.4±12.2 (42,48,57)	50.6±12.3 (42,49,57)
CHL (mg/dL)	173.5±32.7 (151,171,193)	176.4±33.2 (153,174,197)
TRG (mg/dL)	79.6±46.3 (55,69,93)	81.3±47.5 (55,70,94)
Any CVD	77 (11%)	184 (13%)
MACE	35 (5%)	88 (6%)

Table S2. Summary of plasma kallikrein values at the six time points (pass) during the DCCT/EDIC study.

Pass	Plasma Kallikrein				CVD Events	
	Median	Q1	Q3	Missing*	Any CVD**	MACE**
1	65.7	52.7	82.4	4	3	1
2	61.8	49.8	75.7	27	6	3
3	63.3	52.3	77.9	72	13	5
4	90.0	69.4	117.0	146	23	7
5	91.5	73.1	110.7	89	10	5
6	92.9	72.6	113.8	1	22	14

Q1=first quartile; Q3=third quartile

*Out of the 693 participants. **Number of events between pass 1 2, 2 and 3, and so on, and number of events after pass 6. For example, there were 3 any CVD events and 1 MACE event between pass 1 and 2, and there were 22 any CVD events and 14 MACE events after pass 6.

Table S3. The associations between the DCCT baseline plasma kallikrein values and the risk of any CVD and MACE over the combined DCCT/EDIC follow-up.

Outcome	Model*	HR**	95% CI	Z	p-value
Any CVD	1	1.1721	(1.0075,1.3635)	2.0566	0.0397
	2	1.1498	(0.9851,1.3420)	1.7697	0.0768
	3	1.1393	(0.9721,1.3352)	1.6106	0.1073
MACE	1	1.1335	(0.9004, 1.4268)	1.0668	0.2861
	2	1.0691	(0.8354, 1.3680)	0.5308	0.5955
	3	1.1279	(0.8909, 1.4281)	1.0000	0.3173

*Model 1: Plasma kallikrein; Model 2: Plasma kallikrein, age, mean HbA1c; Model 3: Plasma kallikrein, age, mean HbA1c, duration of diabetes, mean HDL, mean total cholesterol, mean BMI, (log) mean Triglycerides, mean SBP, gender, Smoking, menopause, use of statin and lipid-lowering medication.

Hazard ratios (and confidence intervals) are reported per 20 nM higher levels of plasma kallikrein values. HR=hazard ratio, CI=confidence interval. P-values ≤ 0.05 are presented in **bold