

Supplementary Material for

Associations of Microvascular Complications with the Risk of CVD in Type 1 Diabetes: the DCCT/EDIC Study

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Supplementary Table S1. Associations (hazard ratios with 95% confidence intervals and p-values) between microvascular complications and the risk of CVD (panel A) and MACE (panel B) in multivariable Cox PH models with all three complications included, first unadjusted, then minimally adjusted and fully adjusted for other risk factors.

Risk Factor	Unadjusted		Minimally Adjusted*		Fully Adjusted^	
	Hazard Ratio	P-Value	Hazard Ratio	P-Value	Hazard Ratio	P-Value
A. CVD						
PDR and/or CSME	1.47 (1.10, 1.95)	0.0087	1.24 (0.93, 1.66)	0.1397	1.07 (0.79, 1.45)	0.6474
Sustained AER≥30mg/24 hr and/or eGFR<60 ml/min/1.73m	1.94 (1.47, 2.56)	<0.0001	1.84 (1.39, 2.45)	<0.0001	1.52 (1.13, 2.05)	0.0058
Cardiac Autonomic Neuropathy	1.54 (1.16, 2.04)	0.0030	1.17 (0.88, 1.56)	0.2862	1.04 (0.77, 1.40)	0.7823
B. MACE						
PDR and/or CSME	1.77 (1.19, 2.65)	0.0049	1.36 (0.90, 2.06)	0.1393	1.22 (0.80, 1.87)	0.3530
Sustained AER≥30mg/24 hr and/or eGFR<60 ml/min/1.73m	1.95 (1.32, 2.88)	0.0008	1.72 (1.15, 2.59)	0.0087	1.38 (0.90, 2.11)	0.1399
Cardiac Autonomic Neuropathy	1.69 (1.14, 2.53)	0.0089	1.27 (0.84, 1.90)	0.2528	1.07 (0.71, 1.62)	0.7495

*Adjusted for baseline age and mean updated HbA1c.

^ACVD model adjusted for baseline age, mean updated HbA1c, mean updated systolic BP, current triglycerides, mean updated pulse, baseline duration, use of ACE inhibitors, and mean updated LDL.

MACE model adjusted for baseline age, mean updated HbA1c, mean updated pulse, current triglycerides, mean updated systolic BP, baseline duration, use of ACE inhibitors, and current LDL
Associations with p-values less than 0.05 appear in **bold**.

Supplementary Table S2. Associations (hazard ratios with 95% confidence intervals and p-values) between microvascular complications and the risk of CVD first in Cox PH models adjusted for age and mean updated HbA1c (Minimally Adjusted column), and then after further adjustment for risk factors included one at a time (Further Adjustments columns).

	Minimally Adjusted	Further Adjustments*											
		Mean Updated SBP		Current TRG		Mean Updated Pulse		Baseline Duration		ACE Inhibitor Use		Mean Updated LDL	
Risk Factor	Hazard Ratio	Hazard Ratio	PC										
PDR and/or CSME	1.47 (1.11, 1.94)	1.31 (0.99, 1.75)	33.5	1.40 (1.06, 1.86)	14.5	1.39 (1.05, 1.84)	16.9	1.31 (0.98, 1.75)	33.8	1.48 (1.11, 1.96)	-1.5	1.42 (1.08, 1.88)	9.7
PDR	1.44 (1.06, 1.95)	1.28 (0.94, 1.74)	36.4	1.40 (1.03, 1.90)	9.6	1.32 (0.97, 1.80)	26.3	1.26 (0.92, 1.73)	40.0	1.45 (1.07, 1.97)	-1.6	1.42 (1.05, 1.93)	3.9
CSME	1.33 (0.99, 1.77)	1.20 (0.89, 1.60)	NA	1.27 (0.95, 1.70)	NA	1.28 (0.96, 1.71)	NA	1.22 (0.91, 1.63)	NA	1.33 (0.99, 1.78)	NA	1.26 (0.94, 1.68)	NA
3-Step Progression	0.89 (0.66, 1.19)	0.78 (0.58, 1.05)	NA	0.85 (0.63, 1.15)	NA	0.83 (0.62, 1.12)	NA	0.90 (0.67, 1.21)	NA	0.89 (0.66, 1.19)	NA	0.88 (0.65, 1.18)	NA
Sustained AER≥30mg/24hr and/or eGFR<60 ml/min/1.73m ²	1.99 (1.51, 2.61)	1.71 (1.28, 2.28)	28.1	1.83 (1.39, 2.42)	15.6	1.85 (1.41, 2.44)	13.6	1.87 (1.42, 2.47)	11.5	2.03 (1.54, 2.68)	-4.1	1.96 (1.49, 2.58)	2.5
AER≥300 mg/24hr	1.67 (1.16, 2.41)	1.27 (0.86, 1.87)	60.3	1.45 (1.00, 2.11)	32.7	1.58 (1.10, 2.28)	13.6	1.59 (1.10, 2.30)	11.8	1.70 (1.17, 2.47)	-4.0	1.62 (1.13, 2.35)	7.0
Sustained AER≥30 mg/24hr	1.91 (1.45, 2.52)	1.63 (1.22, 2.18)	30.7	1.76 (1.33, 2.32)	17.0	1.79 (1.35, 2.36)	13.5	1.78 (1.35, 2.35)	14.1	1.95 (1.47, 2.58)	-4.5	1.88 (1.43, 2.48)	2.8
eGFR<60 ml/min/1.73m ²	2.12 (1.43, 3.15)	1.73 (1.15, 2.60)	35.4	1.86 (1.25, 2.77)	23.2	1.95 (1.31, 2.91)	15.1	2.11 (1.42, 3.13)	1.4	2.12 (1.43, 3.16)	-0.1	2.10 (1.41, 3.11)	2.4
CAN	1.36 (1.03, 1.80)	1.26 (0.95, 1.67)	29.1	1.33 (1.00, 1.76)	8.5	1.23 (0.92, 1.63)	36.8	1.27 (0.96, 1.68)	25.6	1.36 (1.03, 1.80)	-0.2	1.37 (1.04, 1.81)	-2.9
Presence of retinal and kidney Disease ⁺	1.55 (1.30, 1.85)	1.41 (1.17, 1.69)	26.7	1.48 (1.23, 1.76)	14.0	1.48 (1.24, 1.77)	12.5	1.47 (1.22, 1.76)	15.7	1.58 (1.32, 1.89)	-4.2	1.53 (1.28, 1.82)	5.0

*The adjusting covariates were those previously identified as risk factors for any CVD (2) with the exception of current smoking status that was no longer significant in updated analyses with the current data.

PDR=proliferative diabetic retinopathy; CSME=clinically significant macular edema; CAN=cardiac autonomic neuropathy.

Associations with p-values less than 0.05 are reported in **bold**.

+ Presence of retinal and kidney disease is a quantitative variable defined as 0=no prior complications, 1= prior (PDR and/or CSME) or (severe albuminuria ($AER \geq 300 \text{ mg/24hr}$) and/or sustained $eGFR < 60 \text{ ml/min/1.73m}^2$) but not both; and 2= prior (PDR and/or CSME) and (severe albuminuria ($AER \geq 300 \text{ mg/24hr}$) and/or sustained $eGFR < 60 \text{ ml/min/1.73m}^2$).

PC=percent change in (log) hazard ratio relative to the minimally adjusted model. CSME and 3-Step Progression are not associated with CVD in the minimally adjusted models and their PC values are set to NA.

Supplementary Table S3. Associations (hazard ratios with 95% confidence intervals and p-values) between microvascular complications and the risk of MACE first in Cox PH models adjusted for age and mean updated HbA1c (Minimally Adjusted column), and then after further adjustment for risk factors included one at a time (Further Adjustment columns).

		Further Adjustments*											
	Minimally Adjusted	Mean Updated SBP		Current TRG		Mean Updated Pulse		Baseline T1D Duration		Ace Inhibitor Use		Current LDL	
Risk Factor	Hazard Ratio	Hazard Ratio	PC										
PDR and/or CSME	1.61 (1.09, 2.40)	1.43 (0.96, 2.15)	29.6	1.21 (0.79, 1.85)	8.6	1.53 (1.03, 2.28)	13.1	1.38 (0.92, 2.08)	37.2	1.65 (1.11, 2.45)	-5.3	1.63 (1.10, 2.41)	-2.1
PDR	1.34 (0.88, 2.04)	1.17 (0.76, 1.80)	NA	1.56 (1.05, 2.32)	NA	1.24 (0.81, 1.89)	NA	1.13 (0.73, 1.74)	NA	1.36 (0.89, 2.08)	NA	1.36 (0.90, 2.07)	NA
CSME	1.39 (0.93, 2.07)	1.24 (0.83, 1.87)	NA	1.32 (0.86, 2.01)	NA	1.36 (0.91, 2.02)	NA	1.24 (0.83, 1.85)	NA	1.41 (0.94, 2.10)	NA	1.39 (0.94, 2.07)	NA
3-Step Progression	1.00 (0.65, 1.54)	0.87 (0.56, 1.36)	NA	0.97 (0.63, 1.50)	NA	0.94 (0.61, 1.45)	NA	1.02 (0.66, 1.56)	NA	1.01 (0.65, 1.56)	NA	1.01 (0.65, 1.55)	NA
Sustained AER≥30mg/24hr and/or eGFR<60 ml/min/1.73m ²	1.93 (1.31, 2.85)	1.64 (1.09, 2.47)	31.6	1.78 (1.20, 2.63)	16.7	1.81 (1.22, 2.67)	13.8	1.78 (1.20, 2.63)	16.7	2.01 (1.35, 2.97)	-7.7	1.96 (1.33, 2.89)	-2.6
AER≥300 mg/24hr	2.12 (1.33, 3.38)	1.65 (1.00, 2.73)	42.1	1.88 (1.22, 2.91)	23.4	2.04 (1.28, 3.24)	7.7	2.02 (1.27, 3.21)	9.3	2.21 (1.38, 3.54)	-7.6	2.13 (1.34, 3.41)	-0.9
Sustained AER≥30 mg/24hr	1.93 (1.30, 2.85)	1.63 (1.08, 2.47)	31.7	1.77 (1.19, 2.63)	16.8	1.81 (1.22, 2.68)	13.2	1.75 (1.18, 2.60)	18.7	2.00 (1.35, 2.98)	-8.2	1.95 (1.31, 2.88)	-1.9
eGFR<60 ml/min/1.73m ²	2.06 (1.23, 3.44)	1.66 (0.97, 2.83)	38.1	1.86 (1.16, 2.99)	22.6	1.93 (1.16, 3.23)	12.0	2.04 (1.22, 3.41)	1.8	2.06 (1.23, 3.45)	0.1	2.09 (1.25, 3.50)	-3.3
CAN	1.49 (1.01, 2.20)	1.35 (0.91, 2.01)	28.3	1.82 (1.09, 3.05)	9.0	1.33 (0.89, 1.99)	31.9	1.36 (0.91, 2.02)	26.6	1.50 (1.01, 2.22)	-2.1	1.52 (1.02, 2.25)	-6.2
Presence of retinal and kidney disease ⁺	1.59 (1.24, 2.04)	1.43 (1.10, 1.87)	26.9	1.52 (1.18, 1.95)	12.5	1.52 (1.18, 1.96)	11.6	1.46 (1.13, 1.89)	22.1	1.63 (1.27, 2.10)	-7.3	1.60 (1.25, 2.05)	-1.6

*The adjusting covariates were those previously identified as risk factors for any CVD (2) with the exception of current smoking status that was no longer significant in updated analyses with the current data.

PDR=proliferative diabetic retinopathy; CSME=clinically significant macular edema; CAN=cardiac autonomic neuropathy.

Associations with p-values less than 0.05 are reported in **bold**.

+ Presence of retinal and kidney disease is a quantitative variable defined as 0=no prior complications, 1= prior (PDR and/or CSME) or (severe albuminuria ($AER \geq 300 \text{ mg/24hr}$) and/or sustained $eGFR < 60 \text{ ml/min/1.73m}^2$) but not both; and 2= prior (PDR and/or CSME) and (severe albuminuria ($AER \geq 300 \text{ mg/24hr}$) and/or sustained $eGFR < 60 \text{ ml/min/1.73m}^2$).

PC=percent change in (log) hazard ratio relative to the minimally adjusted model. CSME and 3-Step Progression are not associated with CVD in the minimally adjusted models and their PC values are set to NA.

Supplementary Table S4. Associations (hazard ratios with 95% confidence intervals and p-values) between microvascular complications and the risk of CVD first in Cox PH models adjusted for age and mean updated HbA1c (Minimally Adjusted column), and then with further adjustment for various risk factors.

		Further Adjustments									
	Minimally Adjusted	Mean Updated SBP		Mean Updated SBP, Current TRG		Mean Updated SBP, Current TRG, T1D Duration		Fully Adjusted Without Mean Updated SBP, TRG, T1D Duration		Fully Adjusted^	
Risk Factor	Hazard Ratio	Hazard Ratio	P-Value	Hazard Ratio	P-Value	Hazard Ratio	P-Value	Hazard Ratio	P-Value	Hazard Ratio	P-Value
PDR and/or CSME	1.47 (1.11, 1.94)	1.31 (0.99, 1.75)	0.0614	1.27 (0.95, 1.69)	0.1000	1.15 (0.86, 1.55)	0.3426	1.36 (1.03, 1.80)	0.0331	1.13 (0.84, 1.53)	0.4033
PDR	1.44 (1.06, 1.95)	1.28 (0.94, 1.74)	0.1182	1.27 (0.93, 1.73)	0.1333	1.14 (0.83, 1.57)	0.4162	1.31 (0.96, 1.79)	0.0870	1.09 (0.79, 1.51)	0.5852
CSME	1.33 (0.99, 1.77)	1.20 (0.89, 1.60)	0.2325	1.15 (0.86, 1.55)	0.3383	1.07 (0.80, 1.45)	0.6394	1.22 (0.91, 1.63)	0.1835	1.03 (0.77, 1.40)	0.8244
3-Step Progression	0.89 (0.66, 1.19)	0.78 (0.58, 1.05)	0.1031	0.76 (0.56, 1.03)	0.0752	0.77 (0.57, 1.04)	0.0931	0.84 (0.62, 1.13)	0.2475	0.76 (0.56, 1.03)	0.0816
Sustained AER≥30mg/24hr and/or eGFR<60 ml/min/1.73m ²	1.99 (1.51, 2.61)	1.71 (1.28, 2.28)	0.0002	1.62 (1.21, 2.16)	0.0011	1.54 (1.15, 2.06)	0.0034	1.87 (1.41, 2.47)	<0.0001	1.54 (1.15, 2.07)	0.0038
AER≥300 mg/24hr	1.67 (1.16, 2.41)	1.27 (0.86, 1.87)	0.2333	1.15 (0.78, 1.71)	0.4740	1.12 (0.76, 1.66)	0.5583	1.57 (1.08, 2.28)	0.0185	1.15 (0.78, 1.70)	0.4884
Sustained AER≥30 mg/24hr	1.91 (1.45, 2.52)	1.63 (1.22, 2.18)	0.0010	1.54 (1.15, 2.06)	0.0039	1.45 (1.08, 1.95)	0.0131	1.81 (1.36, 2.40)	<0.0001	1.47 (1.09, 1.97)	0.0119
eGFR<60 ml/min/1.73m ²	2.12 (1.43, 3.15)	1.73 (1.15, 2.60)	0.0089	1.57 (1.04, 2.36)	0.0316	1.56 (1.03, 2.36)	0.0341	1.87 (1.26, 2.79)	0.0020	1.48 (0.97, 2.23)	0.0658
CAN	1.36 (1.03, 1.80)	1.26 (0.95, 1.67)	0.1156	1.23 (0.93, 1.64)	0.1485	1.16 (0.87, 1.54)	0.3178	1.27 (0.95, 1.69)	0.1059	1.11 (0.83, 1.49)	0.4767
Presence of retinal and kidney disease ⁺	1.55 (1.30, 1.85)	1.41 (1.17, 1.69)	0.0003	1.36 (1.13, 1.64)	0.0014	1.29 (1.06, 1.56)	0.0105	1.49 (1.24, 1.78)	<0.0001	1.28 (1.05, 1.56)	0.0127

PDR=proliferative diabetic retinopathy; CSME=clinically significant macular edema; CAN=cardiac autonomic neuropathy

Associations with p-values less than 0.05 are reported in **bold**.

+ Presence of retinal and kidney disease is a quantitative variable defined as 0=no prior complications, 1= prior (PDR and/or CSME) or (severe albuminuria (AER \geq 300 mg/24hr) and/or sustained eGFR<60 ml/min/1.73m 2) but not both; and 2= prior (PDR and/or CSME) and (severe albuminuria (AER \geq 300 mg/24hr) and/or sustained eGFR<60 ml/min/1.73m 2).

[^]Models adjusted for baseline age, mean updated HbA1c, mean updated systolic BP, current triglycerides, mean updated pulse, baseline duration, use of ACE inhibitors, and mean updated LDL. See (2). Associations with p-values less than 0.05 are reported in **bold**.

Supplementary Table S5. Associations (hazard ratios with 95% confidence intervals and p-values) between microvascular complications and the risk of MACE first in Cox PH models first adjusted for age and mean updated HbA1c (Minimally Adjusted column), and then with further adjustment for various risk factors.

		Further Adjustments									
	Minimally Adjusted	Mean Updated SBP		Mean Updated SBP, Current TRG		Mean Updated SBP, Current TRG, T1D Duration		Fully Adjusted Without Mean Updated SBP, TRG, T1D Duration		Fully Adjusted^	
Risk Factor	Hazard Ratio	Hazard Ratio	P-Value	Hazard Ratio	P-Value	Hazard Ratio	P-Value			Hazard Ratio	P-Value
PDR and/or CSME	1.61 (1.09, 2.40)	1.43 (0.96, 2.15)	0.0818	1.41 (0.94, 2.11)	0.0973	1.23 (0.81, 1.87)	0.3271	1.68 (1.13, 2.49)	0.0106	1.29 (0.85, 1.95)	0.2342
PDR	1.34 (0.88, 2.04)	1.17 (0.76, 1.80)	0.4733	1.17 (0.76, 1.81)	0.4667	1.01 (0.65, 1.57)	0.9621	1.34 (0.88, 2.05)	0.1757	1.00 (0.64, 1.56)	0.9877
CSME	1.39 (0.93, 2.07)	1.24 (0.83, 1.87)	0.2919	1.22 (0.81, 1.83)	0.3477	1.10 (0.73, 1.66)	0.6479	1.47 (0.98, 2.18)	0.0599	1.16 (0.77, 1.75)	0.4695
3-Step Progression	1.00 (0.65, 1.54)	0.87 (0.56, 1.36)	0.5375	0.86 (0.55, 1.34)	0.5011	0.88 (0.56, 1.37)	0.5660	0.99 (0.64, 1.52)	0.9466	0.88 (0.56, 1.36)	0.5561
Sustained AER≥30mg/24hr and/or eGFR<60 ml/min/1.73m ²	1.93 (1.31, 2.85)	1.64 (1.09, 2.47)	0.0182	1.54 (1.02, 2.33)	0.0391	1.44 (0.95, 2.18)	0.0841	1.90 (1.28, 2.82)	0.0014	1.43 (0.94, 2.18)	0.0913
AER≥300 mg/24hr	2.12 (1.33, 3.38)	1.65 (1.00, 2.73)	0.0505	1.50 (0.91, 2.49)	0.1138	1.47 (0.88, 2.43)	0.1382	2.19 (1.36, 3.52)	0.0012	1.56 (0.94, 2.59)	0.0878
Sustained AER≥30 mg/24hr	1.93 (1.30, 2.85)	1.63 (1.08, 2.47)	0.0196	1.54 (1.02, 2.33)	0.0419	1.42 (0.94, 2.16)	0.0987	1.89 (1.27, 2.81)	0.0017	1.41 (0.92, 2.14)	0.1134
eGFR<60 ml/min/1.73m ²	2.06 (1.23, 3.44)	1.66 (0.97, 2.83)	0.0645	1.52 (0.89, 2.59)	0.1271	1.51 (0.88, 2.58)	0.1357	2.04 (1.22, 3.41)	0.0066	1.54 (0.90, 2.65)	0.1182
CAN	1.49 (1.01, 2.20)	1.35 (0.91, 2.01)	0.1405	1.32 (0.89, 1.97)	0.1723	1.22 (0.81, 1.82)	0.3417	1.38 (0.92, 2.06)	0.1151	1.14 (0.76, 1.73)	0.5195
Presence of retinal or kidney disease ⁺	1.59 (1.24, 2.04)	1.43 (1.10, 1.87)	0.0078	1.39 (1.06, 1.81)	0.0155	1.28 (0.97, 1.68)	0.0758	1.62 (1.25, 2.08)	0.0002	1.31 (0.99, 1.73)	0.0572

PDR=proliferative diabetic retinopathy; CSME=clinically significant macular edema; CAN=cardiac autonomic neuropathy

Associations with p-values less than 0.05 are reported in **bold**.

+ Presence of retinal and kidney disease is a quantitative variable defined as 0=no prior complications, 1= prior (PDR and/or CSME) or (severe albuminuria ($AER \geq 300$ mg/24hr) and/or sustained eGFR <60 ml/min/ $1.73m^2$) but not both; and 2= prior (PDR and/or CSME) and (severe albuminuria ($AER \geq 300$ mg/24hr) and/or sustained eGFR <60 ml/min/ $1.73m^2$).

[^]Models adjusted for baseline age, mean updated HbA1c, mean updated pulse, current triglycerides, mean updated systolic BP, baseline duration, use of ACE inhibitors, and current LDL. See (2). Associations with p-values less than 0.05 appear in **bold**.