

**Relationship between diabetic retinopathy stages and risk of major lower-extremity
arterial disease in patients with type 2 diabetes**

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Supplementary material

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Supplemental Table 1. Characteristics of participants according to diabetic retinopathy stages at baseline

	Diabetic retinopathy			
	Absent	Non-proliferative	Proliferative	P
N	762 (58)	475 (36)	83 (6)	
Clinical parameters				
Female	334 (44)	210 (44)	36(43)	0.98
Age (years)	64±11	66±10 ^a	64±9	0.02
Duration of diabetes (years)	11±9	18±10 ^a	18±11 ^a	<0.0001
Body mass index (kg/m ²)	32±6	31±6 ^a	32±6	0.08
Heart rate (beats per minute)	70±14	71±14	74±14	0.06
Systolic blood pressure (mmHg)	130±16	134±19 ^a	138±19 ^a	<0.0001
Diastolic blood pressure (mmHg)	72±11	72±12	76±11 ^{a,b}	0.02
Biological parameters				
HbA1c (%)	7.6±1.5	8.1±1.5 ^a	8.2±1.8 ^a	<0.0001
HbA1c (mmol/mol)	59±17	65±16 ^a	66±20 ^a	
Urinary ACR (mg/mmol)	2 (1, 7)	5 (1, 21) ^a	27 (3, 117) ^{a,b}	<0.0001
eGFR (ml/min/1.73m ²)	77±22	70±26 ^a	65±28 ^{a,b}	<0.0001
Total cholesterol (mg/dl)	184±43	187±48	190±44	0.35
HDL cholesterol (mg/dl)	47±16	46±15	51±16	0.09
LDL cholesterol (mg/dl)	103±34	109±42 ^a	112±40 ^a	0.01
Triglycerides (mg/dl)	142 (101, 208)	134 (93, 200) ^a	121 (101, 185)	0.04
Medical history				
Diabetic macular oedema	0	93 (20)	42 (51)	<0.0001
Diabetic kidney disease	201 (26)	194 (41)	54 (65)	<0.0001

Tabaco smoking				
Never	391 (51)	267 (56)	45 (54)	0.40
Former	282 (37)	165 (35)	31 (37)	
Current	89 (12)	43 (9)	7 (8)	
Number of cigarette packs per year	25 (10,40)	24 (10,40)	25 (10,37)	0.78
Macrovascular disease	244 (32)	174 (37)	33 (40)	0.13
History of treatment use				
Antihypertensive drugs	613 (80)	397 (84)	68 (82)	0.38
Statin	340 (45)	205 (43)	40 (48)	0.67
Fibrate	102 (13)	52 (11)	3 (4)	0.02
Antiplatelet or anticoagulant drugs	289 (38)	200 (42)	37 (45)	0.23
Metformin	407 (53)	212 (45)	28 (34)	0.0002
Insulin therapy	369 (48)	358 (75)	59 (71)	<0.0001

Data presented as numbers (%), mean \pm SD, or median (25th, 75th percentiles) for variables with skewed distribution (urinary albumin-to-creatinine ratio (ACR), triglycerides and number of cigarette packs per year). Comparisons of qualitative and quantitative parameters were performed using Chi-square and ANOVA tests, respectively. Tukey Kramer HSD test was performed following ANOVA to detect significant difference between subjects with absent (a) or non-proliferative retinopathy (b). Kruskal–Wallis test was used for comparisons of variables with skewed distribution. Analyses performed in participants without a baseline history of lower-extremity arterial disease. P<0.05 was considered as significant.

Supplemental Table 2. Primary outcome by diabetic retinopathy stages at baseline using an alternative definition*

		Major LEAD				
		No, n	Yes, n (%)	Incidence rate (95% CI) (per 1000 person-years)	HR (95% CI)	P
Diabetic retinopathy stages at baseline	Absent	731	31 (4.1)	5.5 (3.9 – 7.8)	Reference	
	Simple	343	38 (10.0)	13.5 (9.8 – 18.6)	2.28 (1.37 – 3.82)	0.001
	Severe	152	25 (14.1)	19.7 (13.2 – 29.4)	2.74 (1.49 – 4.99)	0.001

Hazard ratios (HR), with 95% confidence interval (CI), estimated using Cox proportional hazards regression model, for major lower-extremity arterial disease by retinopathy stages*: absent (reference), simple (mild or moderate non proliferative) and severe (severe non-proliferative or proliferative). Analyses adjusted for age, sex, duration of diabetes, BMI, systolic blood pressure, estimated glomerular filtration rate, urinary albumin-to-creatinine ratio, plasma concentrations of HDL and LDL-cholesterol, history of tobacco smoking (never, former, current), history of macrovascular disease, and use of antihypertensive, statin, metformin, and insulin therapies. Analyses performed in participants without a baseline history of lower-extremity arterial disease. P<0.05 was significant.

Supplemental Table 3. Risks for minor and major lower-limb amputations by diabetic retinopathy stages at baseline

		Minor amputation during follow-up				Major amputation during follow-up			
		No, n	Yes, n (%)	HR (95% CI)	P	No, n	Yes, n (%)	HR (95% CI)	P
Diabetic retinopathy stages at baseline	Absent	782	5 (0.6)	Reference		782	6 (0.8)	Reference	
	Non- proliferative	465	13 (2.7)	3.63 (1.25 – 12.09)	0.02	465	19 (3.9)	5.61 (2.09 – 17.85)	0.0004
	Proliferative	76	5 (6.2)	13.57 (3.31 – 56.13)	0.0005	76	4 (5.0)	6.73 (1.28 – 30.19)	0.03
	Non- proliferative or proliferative	541	18 (3.2)	4.48 (1.63 – 14.48)	0.003	541	23 (4.1)	5.72 (2.16 – 18.06)	0.0003

Hazard ratios (HR), with 95% confidence interval (CI), estimated using Cox proportional hazards regression models, for minor and major lower-limb amputations in participants with non-proliferative, proliferative or any retinopathy versus those with no history of retinopathy at baseline (reference). Analyses adjusted for age, sex, duration of diabetes, BMI, systolic blood pressure, estimated glomerular filtration rate, urinary albumin-to-creatinine ratio, HDL and LDL-cholesterol, history of tobacco smoking (never, former, current), history of macrovascular disease,

and use of antihypertensive, statin, metformin and insulin therapies. Analyses performed in participants without a history of lower-limb amputation at baseline. $P < 0.05$ was significant.