Microvascular and Macrovascular Disease and Risk for Major Peripheral Arterial Disease in Patients With Type 2 Diabetes

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OBJECTIVE

Peripheral arterial disease (PAD) is a common manifestation of atherosclerosis in type 2 diabetes, but the relationship between other vascular diseases and PAD has been poorly investigated. We examined the impact of previous microvascular and macrovascular disease on the risk of major PAD in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

We analyzed 10,624 patients with type 2 diabetes free from baseline major PAD in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) clinical trial. The primary composite outcome was major PAD defined as PAD-induced death, peripheral revascularization, lower-limb amputation, or chronic ulceration. The secondary end points were the PAD components considered separately.

RESULTS

Major PAD occurred in 620 (5.8%) participants during 5 years of follow-up. Baseline microvascular and macrovascular disease were both associated with subsequent risk of major PAD after adjustment for age, sex, region of origin, and randomized treatments. However, only microvascular disease remained significantly associated with PAD after further adjustment for established risk factors. The highest risk was observed in participants with a history of macroalbuminuria (hazard ratio 1.91 [95% CI 1.38–2.64], $P < 0.0001$) and retinal photocoagulation therapy (1.60 [1.11–2.32], $P = 0.01$). Baseline microvascular disease was also associated with a higher risk of chronic lower-limb ulceration (2.07 [1.56–2.75], $P < 0.0001$) and amputation (1.59 [1.15–2.22], $P = 0.006$), whereas baseline macrovascular disease was associated with a higher rate of angioplasty procedures (1.75 [1.13–2.73], $P = 0.01$).

CONCLUSIONS

Microvascular disease, particularly macroalbuminuria and retinal photocoagulation therapy, strongly predicts major PAD in patients with type 2 diabetes, but macrovascular disease does not.

Type 2 diabetes is associated with an increased risk of premature death (1). Cardiovascular disease is the leading cause of morbidity and mortality in patients with type 2 diabetes, who have two to three times the risk of developing myocardial infarction and stroke compared with people without diabetes (2). Peripheral arterial

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disease (PAD) is a common and severe clinical manifestation of atherosclerosis (3,4) and is especially frequent in patients with type 2 diabetes, with an approximately threefold increased risk compared with a population without diabetes (5). In the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) clinical trial, the incidence of PAD was comparable to the incidence of major coronary events and stroke (6). PAD is associated with poor outcomes, leading to a high rate of amputation and death (7), and has been associated with an increased risk of cardiovascular morbidity and mortality (8,9). PAD mainly affects the infrapopliteal arteries and may induce more damage in small than in large vessels in patients with type 2 diabetes (7,10). The impact of prevalent macrovascular or microvascular disease on the risk of developing PAD has not yet been reliably compared in a contemporary cohort of patients with type 2 diabetes. The aim of the current study was to determine the impact of microvascular and macrovascular disease at baseline on the development of major PAD during follow-up in the ADVANCE study.

RESEARCH DESIGN AND METHODS

Participants

ADVANCE was a large, multicenter, international randomized trial in patients with type 2 diabetes (11). Its objectives were to test the effects of intensive glucose control by using a gliclazide modified release–based regimen and blood pressure treatment by using a fixed-dose combination of perindopril and indapamide on the incidence of major microvascular and macrovascular events. The design and clinical characteristics of participants in ADVANCE have been published previously (6,11,12). Briefly, 11,140 patients with type 2 diabetes and at least one additional risk factor for cardiovascular disease were randomly assigned in a 2 × 2 factorial design to *1*) a gliclazide modified release–based intensive glucose-control regimen, targeting an HbA_{1c} ≤6.5%, or to standard glucose control, with targets and regimens based on local guidelines, and *2*) a fixed-dose combination of perindopril 4 mg and indapamide 1.25 mg or matching placebo. The protocol of the ADVANCE study was approved by the institutional ethics committee of each participating center, and all participants provided written informed consent. All participants in ADVANCE were included in the current study except 516 for whom a history of PAD was established at baseline. PAD was defined at baseline as a lower-limb amputation of at least one digit, chronic ulceration of a lower limb (≥6 weeks) believed to be due to arterial insufficiency, or a peripheral revascularization procedure (surgery, angioplasty, or emergency thrombolysis).

Primary and Secondary End Points

The primary composite outcome for this analysis was major PAD, defined as at baseline, or death as a result of PAD. Each PAD outcome was considered separately as a secondary end point. PAD outcomes were collected systematically for all participants during the scheduled study visits every 2 years from case report forms and from reports of serious adverse events, without adjudication. Information about the occurrence of study outcomes and of all serious adverse events was reported at the time of occurrence between visits. When study outcomes or serious adverse events occurred, the responsible investigator of each center ensured that the event was reported immediately by completing a serious adverse events form. The data and safety monitoring committee regularly reviewed all such events for each center.

Selection of Candidate Risk Factors for Major PAD

The initial set of candidate risk factors for the development of major PAD collected in ADVANCE at baseline were all demographic, anthropometric, and clinical parameters; risk factors for cardiovascular diseases; renal function biomarkers; cognitive function; and educational accomplishment. Candidate risk factors were ascertained at baseline for all participants, except for missing data on left-side (n = 2) and right-side (n = 4) dorsalis pedis pulse, left-side (n = 6) and right-side (n = 8) posterior tibial pulse, light touch sensation below the left (n = 3) and right (n = 2) knee, left-side (n = 10) and right-side (n = 9) Achilles reflex, and left-side (n = 4) and right-side (n = 7) patellar reflex.

Definition of Clinical Parameters

Region of origin was categorized as three groups: Asia (Philippines, China, Malaysia, and India), established market economies (Australia, Canada, France, Germany, Ireland, Italy, the Netherlands, New Zealand, and U.K.), and Eastern Europe (Czech Republic, Estonia, Hungary, Lithuania, Poland, Russia, and Slovakia). Asia was considered the reference group on the basis of a previous report of low prevalence of PAD in Asians (13). Estimated glomerular filtration rate (eGFR) was computed using the Chronic Kidney Disease Epidemiology Collaboration equation. Cognitive function was estimated by the Mini-Mental State Examination (MMSE) score and considered as normal (MMSE score ≥28) or reduced (MMSE score <28). Educational accomplishment was defined as age at completion of the highest level of formal education and categorized as basic (≥16 years) or low (≤15 years). History of microvascular disease was defined as the presence at baseline of at least macroalbuminuria (urinary albumin-to-creatinine ratio [ACR] >300 μg/mg), retinal photocoagulation therapy, proliferative retinopathy, macular edema, or blindness. History of macrovascular disease was defined as the presence at baseline of at least myocardial infarction, stroke, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, hospital admission for unstable angina, or transient ischemic attack.

Statistical Analyses

Quantitative variables were expressed as mean (SD) or median (interquartile range) for those with skewed distributions. Categorical parameters were expressed as numbers and percentages. Characteristics of participants according to the incidence of major PAD were compared at baseline in each individual region of origin by using χ^2, ANOVA, or Wilcoxon test. Cox proportional hazards regression models were used to screen risk factors from the selected variables and to estimate hazard ratios (HRs) and 95% CIs for the incidence of major PAD. Serum triglycerides and urinary ACR were log-transformed for analyses. First, we fitted Cox models, adjusted for the randomly assigned glucose control and blood pressure treatments, to test the association of each variable with the incidence of major PAD. Second, a multivariable Cox model was fitted to include variables with at least a nominal

association ($P < 0.2$) with the incidence of major PAD observed in the first step. Variables with significant association with major PAD in the final Cox model ($P < 0.05$) were considered independent risk factors.

Kaplan-Meier curves were used to plot the cumulative incidence of major PAD over time according to history of microvascular or macrovascular disease at baseline. Survival curves were compared by using the log-rank test. Microvascular or macrovascular disease was tested as a predictor for major PAD in Cox models adjusted for the observed independent risk factors and the study randomized treatments. As sensitivity analyses, backward elimination was applied to identify the optimal set of potential prognostic factors, which started with fitting a model with all the candidate variables plus baseline history of microvascular and macrovascular disease. We eliminated variables with $P > 0.05$ and successively refitted reduced models, applying the same rule until P values of all remaining variables were <0.05. The association of history of microvascular and macrovascular disease with the risk for major PAD was also evaluated in subsets of participants with normal (eGFR $\geq$60 mL/min/1.73 m^2) or impaired (eGFR $<$ 60 mL/min/1.73 m^2) renal function at baseline. Sensitivity analyses considered ranges of blood pressure and pulse pressure, which was defined as the difference between systolic and diastolic blood pressure. Statistical analyses were performed using SAS 9.3 software (SAS Institute, www.sas.com).

Table 1—Characteristics of participants at baseline according to the incidence of major PAD during follow-up

	Overall (n = 10,624)	Major PAD	
		No (n = 10,004)	Yes (n = 620)
Male sex	6,068 (57.1)	5,677 (56.8)	391 (63.1)
Region of origin*			
Asia	4,040 (38.0)	3,868 (38.7)	172 (27.7)
Established market economies	4,547 (42.8)	4,262 (42.6)	285 (46.0)
Eastern Europe	2,037 (19.2)	1,874 (18.7)	163 (26.3)
Age (years), mean (SD)	65.7 (6.4)	65.7 (6.3)	66.2 (6.6)
Duration of diabetes (years), mean (SD)	7.9 (6.3)	7.9 (6.3)	8.2 (6.8)
BMI (kg/m^2), mean (SD)	28.3 (5.2)	28.3 (5.1)	28.7 (5.4)
Systolic blood pressure (mmHg), mean (SD)	145 (21)	145 (21)	149 (23)
Diastolic blood pressure (mmHg), mean (SD)	81 (11)	81 (11)	81 (11)
Use of antihypertensive treatment	7,281 (68.5)	6,821 (68.2)	460 (74.2)
Absence of dorsalis pedis pulse	1,215 (11.4)	1,101 (11.0)	114 (18.4)
Absence of posterior tibial pulse	1,544 (14.5)	1,411 (14.1)	133 (21.5)
Disturbance of light touch sensation	895 (8.4)	825 (8.2)	70 (11.3)
Absence of Achilles reflex	2,234 (21.0)	2,079 (20.8)	155 (25.0)
Absence of patellar reflex	933 (8.8)	862 (8.6)	71 (11.4)
HbA_{1c} (%), mean (SD)	7.5 (1.5)	7.5 (1.5)	7.7 (1.6)
HbA_{1c} (mmol/mol), mean (SD)	59 (17)	58 (17)	60 (18)
Urinary ACR (μg/mg)	15 (7, 39)	15 (7, 38)	18 (8, 54)
eGFR (mL/min/1.73 m^2), mean (SD)	74 (17)	75 (17)	73 (18)
Serum total cholesterol (mmol/L), mean (SD)	5.2 (1.2)	5.2 (1.2)	5.2 (1.2)
Serum HDL cholesterol (mmol/L), mean (SD)	1.3 (0.3)	1.3 (0.3)	1.2 (0.3)
Serum triglycerides (mmol/L)	1.6 (1.2, 2.3)	1.6 (1.2, 2.3)	1.7 (1.2, 2.3)
Use of lipid-lowering drugs	3,689 (34.7)	3,450 (34.5)	239 (38.5)
Use of antiplatelet drugs	4,896 (46.1)	4,595 (45.9)	301 (48.5)
History of current smoking	1,469 (13.8)	1,360 (13.6)	109 (17.6)
History of ever smoking	4,369 (41.1)	4,074 (40.7)	295 (47.6)
MMSE score $\geq$28	8,304 (78.2)	7,845 (78.4)	459 (74.0)
Educational accomplishment $\leq$15 years	3,806 (35.8)	3,570 (35.7)	236 (38.1)

Data are n (%) or median (Q1, Q2), unless otherwise stated. eGFR computed by the Chronic Kidney Disease Epidemiology Collaboration equation. Educational accomplishment defined as age at completion of the highest level of formal education. *Asia: Philippines, China, Malaysia, and India; established market economies: Australia, Canada, France, Germany, Ireland, Italy, the Netherlands, New Zealand, and U.K.; and Eastern Europe: Czech Republic, Estonia, Hungary, Lithuania, Poland, Russia, and Slovakia.

RESULTS

Baseline Clinical Characteristics and Incidence of Major PAD

Among the ADVANCE study participants, 10,624 were free from major PAD at baseline. Their mean (SD) age was 65.7 (6.4) years; 57% were men, and 38% were from Asia. Their mean duration of diabetes was 7.9 (6.3) years and the mean HbA_{1c} 7.5% (1.5%) (Table 1). Major PAD events occurred in 620 participants during a median (interquartile range) of 5.0 (4.5–5.1) years of follow-up. The cumulative incidence of major PAD was 5.8%, and its incidence rate was 1.24 per 100 person-years. Clinical characteristics of participants at baseline, according to the incidence of major PAD during follow-up, are shown in Table 1. Briefly, the mean age of the participants with major PAD was 66.2 (6.6) years at baseline; 63% were men, and 28% were from Asia. Their mean duration of diabetes was 8.2 (6.8) years and mean HbA_{1c} 7.7% (1.6%). The incidence of major PAD was 4.3%, 6.3%, and 8.0% for participants from Asia, established market economies, and Eastern Europe, respectively. Participants from Asia and established market economies who developed major PAD compared with those who did not were more frequently men and had a higher systolic blood pressure and ACR. In addition, patients with PAD from established market economies compared with those without major PAD were older, had more missed pedal pulses, had a higher HbA_{1c}, and used antihypertensive drugs more frequently. However, patients from Eastern Europe who developed major PAD compared with those who did not were more likely to have a history of current smoking and cognitive decline and less educational accomplishment (Supplementary Table 1).

Effects of Glucose Control and Blood Pressure Interventions on the Risk for Major PAD

As published previously in the whole study (6), the intensive glucose intervention did not influence the risk for major PAD in participants free from PAD at baseline (HR 0.96 [95% CI 0.82–1.12],

$P = 0.62$). The risk for PAD was also similar in participants randomly assigned to active blood pressure treatment compared with placebo (1.08 [0.92–1.26], $P = 0.36$) and in those assigned to both intensive glucose control and active blood pressure treatment compared with standard glucose control and placebo (1.03 [0.83–1.29], $P = 0.77$).

Baseline Risk Factors for Major PAD

Age, sex, region of origin, duration of diabetes, BMI, systolic and diastolic blood pressure with and without use of antihypertensive treatment, absence of dorsalis pedis and posterior tibial pulses, disturbance of the light touch sensation, absence of Achilles or patellar reflex, HbA_{1c}, urinary ACR, eGFR, serum LDL cholesterol, serum triglycerides, use of antiplatelet or lipid-lowering drugs, current or ever smoking, and decline of cognitive function were the potential risk factors to have significant ($P < 0.2$) associations with the incidence of major PAD after adjustment for randomized treatments (Supplementary Table 2). The final multivariable Cox model included nine independent risk factors for major PAD (Table 2). The incidence of major PAD was higher in men than in women and in participants from Eastern Europe compared with those from Asia or established market economies. The incidence of major PAD was not significantly different between participants from Asia and established market economies. Higher HbA_{1c} and urinary ACR levels, absence of dorsalis pedis and posterior tibial pulses, and current smoking history at baseline were all independently associated with the risk for major PAD. Higher systolic and lower diastolic blood pressures, both with use of antihypertensive drugs, were also independent risk factors for major PAD (Table 2). Furthermore, major PAD was associated with increasing systolic and decreasing diastolic blood pressure as well as with increasing pulse pressure (Supplementary Table 3).

History of Microvascular and Macrovascular Disease and the Risk of Major PAD

At baseline, 1,065 (10.0%) participants had a history of microvascular disease, and 3,228 (30.4%) had a history of macrovascular disease. The mean (SD) age of the participants with a history of microvascular or macrovascular disease at baseline was 65.8 (6.5) and 65.6 (6.6) years, respectively. Fifty-eight percent and 65% were men, their mean duration of diabetes was 10.2 (7.3) and 7.9 (6.4) years, and their mean HbA_{1c} was 7.9% (1.7%) and 7.5% (1.5%), respectively (Supplementary Table 4). The cumulative incidence of major PAD was higher in participants with a history of microvascular or macrovascular disease compared with those without these conditions ($P < 0.0001$ and $P = 0.007$, respectively). The Cox proportional hazards survival regression analyses confirmed the associations of the history of microvascular and macrovascular disease with the risk for major PAD after adjustment for age, sex, region of origin, and the study randomized treatments (Table 3, model 1). However, only the history of microvascular disease remained significantly associated with the incidence of major PAD after adjustment for established independent risk factors and for study randomized treatments (Table 3, model 2). The highest risk was observed in participants with a history of macroalbuminuria or retinal photocoagulation therapy (Table 3 and Fig. 1). Similar results were observed from analyses in each randomized group (intensive glucose control, standard glucose control, perindopril-indapamide, and placebo) considered separately (Supplementary Table 5). Impaired renal function was established at baseline in 2,298 (21.6%) participants. Its prevalence was similar in patients with and without major PAD (21.6% vs. 22.7%) during follow-up. Association of history of microvascular disease at baseline with the risk for major PAD remained significant in both subgroups but was greater in patients with impaired renal function than in those with normal renal function (Supplementary Table 6).

Sensitivity Analyses

Backward selection showed similar predictors as the foregoing results. Thus,

Table 2—Independent risk factors for major PAD

	Major PAD			
	Absence of the risk factor	Presence of the risk factor	HR (95% CI)	*P* value*
Male sex	229 (5.0)	391 (6.4)	1.30 (1.09–1.54)	0.003
Region of origin†				
Established market economies (vs. Asia)	172 (4.3)	285 (6.3)	1.17 (0.95–1.44)	<0.0001
Eastern Europe (vs. Asia)	172 (4.3)	163 (8.0)	1.95 (1.54–2.46)	
Eastern Europe (vs. established market economies)	285 (6.3)	163 (8.0)	1.67 (1.35–2.06)	
SBP (per 10-mmHg increase) with antihypertensive drugs	—	—	1.13 (1.07–1.19)	<0.0001
SBP (per 10-mmHg increase) without antihypertensive drugs	—	—	1.05 (0.95–1.16)	
DBP (per 10-mmHg increase) with antihypertensive drugs	—	—	0.83 (0.74–0.92)	0.001
DBP (per 10-mmHg increase) without antihypertensive drugs	—	—	0.92 (0.76–1.11)	
Absent dorsalis pedis pulse	505 (5.4)	114 (9.4)	1.47 (1.15–1.88)	0.002
Absent posterior tibial pulse	486 (5.4)	133 (8.6)	1.29 (1.02–1.63)	0.03
HbA_{1c} (per 1% increase)	—	—	1.07 (1.02–1.13)	0.008
Urinary ACR (per 1 log μg/mg increase)	—	—	1.21 (1.06–1.38)	0.005
History of current smoking	511 (5.6)	109 (7.4)	1.37 (1.11–1.70)	0.004

Data are *n* (%) unless otherwise indicated. Multivariable Cox proportional hazards survival regressive analysis adjusted for the study randomization treatments. DBP, diastolic blood pressure; SBP, systolic blood pressure. *$P < 0.05$ was significant. †Asia: Philippines, China, Malaysia, and India; established market economies: Australia, Canada, France, Germany, Ireland, Italy, the Netherlands, New Zealand, and U.K.; and Eastern Europe: Czech Republic, Estonia, Hungary, Lithuania, Poland, Russia, and Slovakia.

Table 3—Relative risk for major PAD according to history of microvascular and macrovascular disease at baseline

	Major PAD		Model 1		Model 2	
	Absence of the predictor	Presence of the predictor	HR (95% CI)	*P* value*	HR (95% CI)	*P* value*
History of microvascular disease (yes vs. no)	527 (5.5)	93 (8.7)	1.73 (1.39–2.16)	<0.0001	1.63 (1.30–2.03)	<0.0001
Microalbuminuria (vs. normoalbuminuria)	407 (5.4)	172 (6.3)	1.21 (1.01–1.45)	0.03	1.10 (0.92–1.32)	0.29
Macroalbuminuria (vs. normoalbuminuria)	407 (5.4)	41 (11.1)	2.23 (1.62–3.08)	<0.0001	1.91 (1.38–2.64)	<0.0001
Retinal photocoagulation therapy (yes vs. no)	586 (5.7)	34 (9.3)	1.80 (1.28–2.55)	0.0008	1.60 (1.11–2.32)	0.01
Proliferative retinopathy (yes vs. no)	596 (5.8)	24 (6.8)	1.37 (0.91–2.06)	0.13	1.23 (0.78–1.92)	0.37
Macular edema (yes vs. no)	607 (5.8)	13 (8.2)	1.47 (0.85–2.54)	0.17	1.39 (0.79–2.47)	0.25
Blindness (yes vs. no)	610 (5.8)	10 (10.1)	1.87 (1.00–3.49)	0.05	1.73 (0.89–3.35)	0.10
History of macrovascular disease (yes vs. no)	403 (5.4)	217 (6.7)	1.20 (1.02–1.42)	0.03	1.13 (0.95–1.35)	0.16
Myocardial infarction (yes vs. no)	535 (5.7)	85 (6.9)	1.16 (0.92–1.46)	0.22	1.10 (0.87–1.41)	0.42
Stroke (yes vs. no)	554 (5.7)	66 (6.9)	1.23 (0.95–1.59)	0.11	1.11 (0.84–1.45)	0.46
Hospitalization for unstable angina (yes vs. no)	542 (5.7)	78 (6.9)	1.14 (0.90–1.45)	0.27	1.10 (0.85–1.41)	0.47
CABG or PTCA (yes vs. no)	558 (5.7)	62 (7.3)	1.18 (0.90–1.54)	0.23	1.10 (0.83–1.46)	0.52
Hospital admission for TIA (yes vs. no)	591 (5.8)	29 (5.8)	1.00 (0.69–1.46)	0.99	0.96 (0.65–1.43)	0.85

Data are *n* (%) unless otherwise indicated. Cox proportional hazards survival regressive analyses adjusted for age, sex, region of origin, and the study randomization treatments (model 1) or for model 1 plus systolic and diastolic blood pressure with and without antihypertensive treatment, absence of dorsalis pedis and posterior tibial pulses, HbA_{1c}, urinary ACR (except for albuminuria and microvascular disease analyses), and history of current smoking (model 2). Normoalbuminuria, ACR <30 μg/mg; microalbuminuria, ACR 30–300 μg/mg; macroalbuminuria, ACR >300 μg/mg. CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischemic attack. *$P < 0.05$ was significant.

sex, region of origin, systolic and diastolic blood pressure with use of antihypertensive treatment, absence of distal and posterior tibial pulses, HbA_{1c}, current smoking, history of macroalbuminuria, and retinal photocoagulation therapy remained significantly associated with the incidence of major PAD (Supplementary Table 7).

Secondary End Point Analyses

Chronic lower-limb ulceration, lower-limb amputation, angioplasty procedures, and death as a result of PAD occurred during follow-up in 320 (3.0%), 288 (2.7%), 88 (0.08%), and 17 (0.02%) participants, respectively. The incidence of each outcome by history of microvascular and macrovascular disease at baseline is shown in Table 4. Prior microvascular disease was associated with an increased risk of chronic ulceration and lower-extremity amputation, whereas prior macrovascular disease was associated with a higher rate of angioplasty procedures.

CONCLUSIONS

We investigated the influence of previous microvascular and macrovascular disease as predictors for the development of major PAD during a 5-year follow-up in patients with type 2 diabetes in the ADVANCE clinical trial. The cumulative incidence of major PAD was 5.8%. The history of microvascular disease at baseline was more likely to be an independent predictor for major PAD than the history of macrovascular disease. The highest risk was observed in participants with a history of macroalbuminuria or retinal photocoagulation therapy. Microvascular disease was associated with a higher risk for chronic lower-limb ulceration and amputation, whereas macrovascular disease was linked with an increased rate of angioplasty procedures. No effect of the glucose control and/or blood pressure intervention was observed for the risk of major PAD.

This report is the first in our knowledge to compare the relationship between microvascular and macrovascular disease and major PAD in patients with type 2 diabetes. Patients with microvascular disease are twice as likely as those without this condition to develop major PAD, whereas the association of major PAD with macrovascular disease was weaker and not independent of traditional risk factors. Analyses of the secondary end points suggest that macrovascular disease may better predict the risk for proximal PAD and large vessel disease and that microvascular disease may better predict distal PAD and small vessel disease in patients with type 2 diabetes.

Macroalbuminuria and diabetic retinopathy requiring photocoagulation therapy were the strongest predictors for major PAD. The association of history of microvascular disease with the risk for major PAD was greater in patients with impaired renal function than in those with normal renal function, but eGFR itself was not associated with the outcome. In line with our observations, previous studies have implicated ACR but not eGFR as an independent risk factor for PAD (8,14). Overall, these findings suggest that PAD is more likely to be linked to diabetic microangiopathy than kidney failure in patients with type 2 diabetes. Of note, a recent histopathological study showed microangiopathic abnormalities in patients with type 2 diabetes who underwent amputation for ischemic diabetic foot (15). Urine ACR is now accepted as an independent cardiovascular risk factor in patients with and without type 2 diabetes (16). Diabetic retinopathy is also believed to be a predictor of heart disease, stroke, and major macrovascular events, including lower-extremity amputation, in patients with type 2 diabetes (17–20). The potential pathophysiological links by which microvascular disease might predispose to major PAD have not yet been fully elucidated. Arterial stiffness, a common feature in both microvascular disease and PAD, may be a key mechanism linking these conditions (21–23). We have observed an association of major PAD with increasing systolic blood pressure,

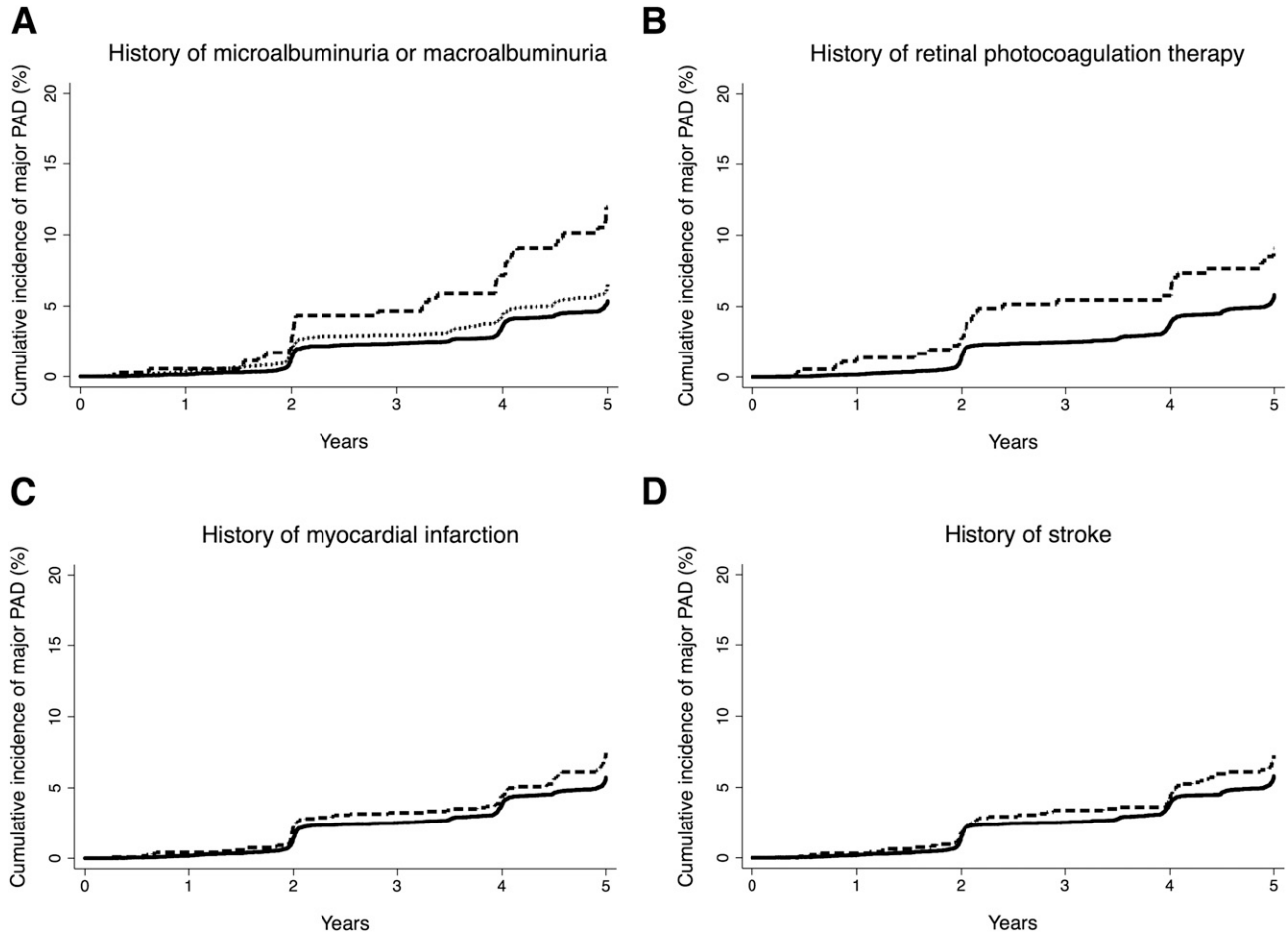

Figure 1—Cumulative incidence of major PAD during follow-up by history of microvascular or macrovascular disease. *A*: Presence of microalbuminuria (dotted line) or macroalbuminuria (dashed line) vs. normoalbuminuria (solid line) ($P < 0.0001$). *B*: Presence (dashed line) vs. absence (solid line) of retinal photocoagulation therapy ($P = 0.001$). *C*: Presence (dashed line) vs. absence (solid line) of myocardial infarction ($P = 0.07$). *D*: Presence (dashed line) vs. absence (solid line) of stroke ($P = 0.05$).

decreasing diastolic blood pressure, and particularly increasing pulse pressure, which is recognized as a surrogate of arterial stiffness (24). Increased arterial wall stiffness is a hallmark for arteriosclerosis across the whole arterial tree, including lower-extremity arteries, in patients with diabetes (25). Previous studies have shown increased arterial stiffness in patients with a high urinary albumin excretion rate and decreased glomerular filtration rate as well as diabetic retinopathy (23,26–30).

Few studies have prospectively investigated predictors for the development of PAD in patients with type 2 diabetes (8,14,31). In the UK Prospective Diabetes Study, age, HbA_{1c}, systolic blood pressure, HDL cholesterol, previous cardiovascular disease, and current smoking were found to be independent risk factors for PAD (31). A trend toward an association of diabetic retinopathy with the risk of PAD was also observed (31). However, time to event was not considered in these analyses. In the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial, age, female sex, black African origin, smoking, pulse pressure, HbA_{1c}, and ACR were independent risk factors for PAD (14). These results are comparable to the current findings, except for contrasting results for sex and a different incidence rate of PAD, which was 3.5 times higher in BARI 2D than in ADVANCE. These discrepancies may be explained by differences in each study's inclusion criteria. The ADVANCE trial enrolled participants with type 2 diabetes at a high risk for vascular events, whereas the BARI 2D study population was composed entirely of patients with type 2 diabetes and stable coronary artery disease (11,32). Furthermore, the definitions of PAD outcomes were different between the two studies. In ADVANCE, major PAD was more severe, defined as lower-limb ulceration or amputation, peripheral revascularization, or death caused by PAD. In BARI 2D, PAD was defined as new low ankle-brachial index (ABI), lower-extremity revascularization, or lower-extremity amputation, but 290 among 303 incidents of PAD were identified solely on the basis of ABI (14). We are aware that the definition of PAD in the current study may generate heterogeneous outcomes or underestimate asymptomatic PAD, but the predominant use of the diminution of ABI could have been insufficient to capture all PAD outcomes because of its U-shaped relationship with major cardiovascular outcomes, including PAD (33,34).

The main strength of this work is the use of a large contemporary study of 10,624 patients with type 2 diabetes that collected appropriate data on the

Table 4—Secondary end points according to history of microvascular and macrovascular disease at baseline

	Lower-limb ulceration			Lower-limb amputation			Revascularization procedure			PAD-induced death		
Vascular disease	Predictor	HR (95% CI)	*P* value*	Predictor	HR (95% CI)	*P* value*	Predictor	HR (95% CI)	*P* value*	Predictor	HR (95% CI)	*P* value*
Micro (no vs. yes)	261 (2.7) vs. 59 (5.5)	2.07 (1.56–2.75)	<0.0001	246 (2.6) vs. 42 (3.9)	1.59 (1.15–2.22)	0.006	75 (0.8) vs. 13 (1.2)	1.33 (0.74–2.42)	0.34	14 (0.1) vs. 3 (0.3)	1.92 (0.53–6.94)	0.32
Macro (no vs. yes)	217 (2.9) vs. 103 (3.2)	1.00 (0.78–1.29)	0.98	192 (2.6) vs. 96 (3.0)	1.03 (0.79–1.34)	0.81	47 (0.6) vs. 41 (1.3)	1.75 (1.13–2.73)	0.01	10 (0.1) vs. 7 (0.2)	1.26 (0.44–3.63)	0.67

Data are *n* (%) unless otherwise indicated. Cox proportional hazards survival regressive analyses adjusted for age, sex, region of origin, systolic and diastolic blood pressure with and without antihypertensive treatment, absence of dorsalis pedis and posterior tibial pulses, HbA_{1c}, urinary ACR (except for microvascular disease analyses), history of current smoking, and the study randomization treatments. *$P < 0.05$ was significant.

history of microvascular and macrovascular disease at baseline and included a robust characterization of new cases of major PAD during follow-up. Moreover, the ADVANCE study enrolled various populations around the world, enabling us to test the development of PAD according to differences in region of origin. Of note, we observed a relatively low incidence of major PAD in Asians, supporting previous studies that showed a lower prevalence of PAD in patients with diabetes and cardiovascular disease from South Asia compared with those of white European descent (13). We also observed an increased risk for major PAD in Eastern Europeans compared with Asians and people from established market economies, which could be partly explained by a high rate of current smoking in Eastern Europeans.

This study has some limitations, notably in issues related to the post hoc analyses of a randomized controlled trial and the use of a clinical trial population, which may not be representative of all patients with type 2 diabetes. The absence of adjudication of major PAD may have biased the results, but our group has previously shown that the central end point adjudication process had no significant impact on the main findings in ADVANCE (35). This study also lacks data on other putative risk factors, such as ABI and chronic inflammation biomarkers, which have been shown to be associated with PAD (36–39).

In conclusion, we found that macroalbuminuria and severe diabetic retinopathy are strong and independent predictors for major PAD in patients with type 2 diabetes. These results encourage screening and prevention of PAD in patients with type 2 diabetes and microvascular complications and suggest that diabetic microangiopathy plays an important role in the pathogenesis of major PAD in such patients.

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