Microvascular and macrovascular disease and risk for major peripheral arterial disease in patients with type 2 diabetes

Running title: Peripheral arterial disease in type 2 diabetes

Kamel Mohammedi, MD, PHD[1], Mark Woodward, PHD[1,2,3], Yoichiro Hirakawa, MD, PHD[1], Sophia Zoungas, MD, PHD[1,4], *more to be added* ...Michel Marre, MD, PHD[5,6,7], John Chalmers, MD, PHD[1]; on behalf of the ADVANCE Collaborative Group

[1]The George Institute for Global Health, University of Sydney, Australia
[2]The George Institute for Global Health, University of Oxford, UK
[3]Department of Epidemiology, Johns Hopkins University, Baltimore, MD, USA
[4]Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Clayton, Victoria, Australia
[5]INSERM, UMRS 1138, Centre de Recherche des Cordeliers, Paris, France
[6]Assistance Publique Hôpitaux de Paris, Bichat Hospital, DHU FIRE, Department of Diabetology, Endocrinology and Nutrition, Paris, France
[7]Univ Paris Diderot, Sorbonne Paris Cité, UFR de Médecine, Paris, France

Bryan Williams affiliation – Institute of Cardiovascular Sciences University College London (UCL) and NIHR UCL Hospitals Biomedical Research Centre, London, UK.

Author for correspondence:
Professor John Chalmers
The George Institute for Global Health, PO Box M201, Missenden Road, Camperdown, NSW 2050, Sydney, Australia
Phone: +61 (0)2 9993 4587
Fax +61 (0)2 9993 4588
Email: chalmers@georgeinstitute.org.au

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ABSTRACT

OBJECTIVE: Peripheral arterial disease (PAD) is a common manifestation of atherosclerosis in type 2 diabetes, but the relationship between vascular disease and PAD has been poorly investigated. We sought to examine the impact of previous microvascular and macrovascular disease on the risk of PAD in these patients.

RESEARCH DESIGN AND METHODS: We analysed 10624 patients with type 2 diabetes, free from baseline PAD, in the Action in Diabetes and Vascular Disease: PreterAx and DiamicroN Modified-Release Controlled Evaluation (ADVANCE) clinical trial. The primary composite outcome was major PAD, defined as PAD-induced death, requirement for peripheral revascularisation, lower-limb amputation or chronic lower-limb ulceration. The secondary endpoints 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 history of macroalbuminuria (HR 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 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), while baseline macrovascular disease was associated with a higher rate of angioplasty procedures (1.75 [1.13-2.73], p=0.01).

CONCLUSIONS: Microvascular disease, particulary macroalbuminuria and retinal photocoagulation therapy, was strongy predictive for major PAD in patients with type 2 diabetes, but macrovscular disease was not.

INTRODUCTION

Type 2 diabetes mellitus 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 2- to 3-times the risk of developing myocardial infarction and stroke compared to people without diabetes (2). Peripheral arterial disease (PAD) is a common and severe clinical manifestation of atherosclerosis (3; 4). It is especially frequent in patients with type 2 diabetes, with a ~ 3-fold increased risk compared to a non-diabetic population (5). In the Action in Diabetes and Vascular Disease: PreterAx and DiamicroN Modified-Release Controlled Evaluation (ADVANCE) study, the incidence rate 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 also 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 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 multicentre international randomized trial conducted in patients with type 2 diabetes (11). The objectives of ADVANCE were to test the effects of intensive glucose control using a gliclazide-MR based regimen and blood pressure treatment using a fixed-dose combination of perindopril and indapamide on the incidence of major microvascular and macrovacular 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 mellitus, and at least one additional risk factor for cardiovascular disease, were randomly assigned in a 2 X 2 factorial design to: (i) gliclazide (modified release)–based intensive glucose-control regimen, targeting an HbA1c of ≤ 6.5%, or to standard glucose control, with targets and regimens based on local guidelines, and (ii) 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 centre and all participants provided written informed consent. All participants in ADVANCE were included in the present study, except 516 patients for whom a history of PAD was established at baseline.

Primary and secondary endpoints

The primary composite outcome for this analysis, was major PAD, defined as death due to PAD, requirement for a peripheral revascularisation procedure (surgery, angioplasty or emergency thrombolysis), a lower-limb amputation of at least one digit, or chronic (6 weeks or more) ulceration of a lower limb thought to be due to arterial insufficiency. Each PAD outcome was considered separately as a secondary endpoint. 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.

Selection of candidate risk factors for major PAD

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

Definition of clinical parameters

Region of origin was categorized as 3 groups: Asia (Philippines, China, Malaysia, and India), established market economies (Australia, Canada, France, Germany, Ireland, Italy, Netherlands, New Zealand, and United Kingdom) and Eastern Europe (the Czech Republic, Estonia, Hungary, Lithuania, Poland, Russia, and Slovakia). Asia was considered as a reference group based on 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 (CKD-EPI) equation. Cognitive function was estimated by the Mini-Mental State Examination (MMSE) score and considered as normal (MMSE score ≥ 28) or reduced (MMSE < 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 oedema, 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 ischaemic 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 percents. Cox proportional hazards regression models were used to screen risk factors from the selected variables and to estimate hazard ratios and their 95% confidence intervals 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 including variables for whom at least a nominal association ($p<0.2$) with the incidence of major PAD was observed in the first step. Then, variables with significant association with major PAD in a 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 the history of microvascular or macrovascular disease at baseline. Survival curves were compared 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 a p value > 0.05, and successively re-fitted reduced models, applying the same rule, until p values of all remaining variables were <0.05. Statistical analyses were performed using SAS software, version 9.3 (SAS Institute, www.sas.com).

RESULTS

Baseline clinical characteristics and incidence of major PAD

Among the ADVANCE study participants, 10624 were free from PAD at baseline. Their mean (SD) age was 65.7 (6.4) years, 57% were men, and 38% were from Asia. Their mean (SD) duration of diabetes was 7.9 (6.3) years, and the mean (SD) HbA1c was 7.5 (1.5) % (Table 1). Major PAD events occurred in 620 participants during a median of 5.0 (25^{th} – 75^{th} percentile, 4.5 – 5.1) years of follow-up. The cumulative incidence of major PAD was 5.8%, and its incidence rate 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 (SD) age of the participants who developed major PAD was 66.2 (6.6) years, 63% were

men, and 28% from Asia. Their mean (SD) duration of diabetes was 8.2 (6.8) years, and the mean (SD) HbA1c was 7.7 (1.6) %.

Baseline risk factors for major PAD

Age, sex, region of origin, duration of diabetes, body mass index, 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 reflexes, HbA1c, urinary ACR, eGFR, serum LDL-cholesterol, serum triglycerides, use of antiplatelet or lipids 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 randomised treatments (Supplemental Table S1). 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 to those from Asia. Higher systolic blood pressure, and lower diastolic blood pressure, both with use of antihypertensive drugs, higher HbA1c, 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.

History of microvascular and macrovascular disease and the risk of major PAD

At baseline 1065 (10.0 %) participants had a history of microvascular disease, and 3228 (30.4 %) had a a history of macrovascular disease. The mean (SD) age of the participants who had a history of microvascular or macrovascular disease at baseline was 65.8 (6.5) and 65.6 (6.6) years, 58% and 65% were men, their mean (SD) duration of diabetes was 10.2 (7.3) and 7.9 (6.4) years, and their mean (SD) HbA1c was 7.9 (1.7) % and 7.5 (1.5) %, respectively (Supplemental Table S2). The cumulative incidence of major PAD was higher in participants with a history of microvascular or macrovascular disease compared to individuals 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 the study randomized treatments (Table 3, model 2). The highest risk was observed in participants with the history of macroalbuminuria or retinal photocoagulation therapy (Table 3 and Figure 1). Similar results were observed when we performed analyses in each randomized group (intensive glucose control, standard glucose control, perindopril-indapamide and placebo) considered separately (Supplemental Table S3).

Sensitivity analyses

Backward selection showed similar predictors as the foregoing results. Thus, sex, region of origin, systolic and diastolic blood pressure with use of antihypertensive treatment, absence of distal and posterior tibial pulses, HbA1C, current smoking, history of macroalbuminuria and retinal photocoagulation therapy remained significantly associated with the incidence of major PAD (Supplemental Table S4).

Secondary endpoint analyses

Chronic lower-limb ulceration, lower-limb amputation, angioplasty procedures, and death caused by 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 of these outcomes by the history of microvascular and macrovascular disease at baseline is shown in Table 4. Prior microvascular disease was associated with increased risk of chronic ulceration and lower-extremity amputation, while prior macrovascular disease was associated with a higher rate of angioplasty procedures.

CONCLUSIONS

In the present study we investigated the influence of previous microvascular and macrovascular disease as predictors for the development of major PAD during 5-year follow-up in patients with type 2 diabetes in the ADVANCE trial. The cumulative incidence of major PAD was 5.8%. The history of microvascular disease at baseline was more likely to be an independant 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, while macrovascular disease was linked with increased rate of angioplasty procedures.

As far as we know, this is the first report of the comparison of 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, while the association of PAD with macrovascular disease was weaker and was not independent of traditional risk factors. Analyses of the secondary endpoints suggest that macrovascular disease may better predict the risk for proximal PAD and large vessel disease, and 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. However, eGRF was not associated with the outcome suggesting that PAD is more likely to be linked to diabetic microangiopathy than kidney failure in patients with type 2 diabetes. Urine ACR is now accepted to be an independent cardiovascular risk factor in patients with and without type 2 diabetes (14). Diabetic retinopathy is also thought to be a putative predictor of heart disease, stroke and major macrovascular events including lower-extremity amputation in patients with type 2 diabetes (15-18). The potential pathophysiological links by which microvascular disease might predispose to major PAD have

not yet been fully elucidated. As a common feature in both microvascular disease and PAD, arterial stiffness may be a key mechanism linking these conditions (19-21). Increased aortic stiffness, which is characterized by a reduction in elastin and an increase in collagen in the arterial wall, is a hallmark for arteriosclerosis across the whole arterial tree, with a predilection for distal arteries rather than proximal ones (22; 23). Noteworthy, previous studies had shown increased arterial stiffness in patients with high urinary albumin excretion rate and decreased glomerular filtration rate, as well as diabetic retinopathy (21; 24-28).

Few studies have prospectively investigated predictors for the development of PAD in patients with type 2 diabetes (8; 29; 30). In the UK Prospective Diabetes Study (UKPDS), age, HbA1c, systolic blood pressure, HDL-cholesterol, previous cardiovascular disease, and current smoking were found to be independent risk factors for PAD (29). A trend toward an association of diabetic retinopathy with the risk of PAD was also observed (29). However, time-to-events were 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, HbA1c, and ACR were independent risk factors for PAD (30). These results are comparable to our findings, except for contrasting results for sex, and a different incidence rate of PAD, 3.5 times higher in BARI 2D trial than in ADVANCE. In addition to differences in the inclusion criteria, the definitions of PAD were different in these two studies (11; 31) compared to the severe form of PAD that we studied. The predominant use of the ankle-brachial index (ABI) diminution in BARI 2D could be insufficient to screen all PAD outcomes, because of its U-shaped relationship with major cardiovascular outcomes (32).

The main strength of our work is the use of a large contemporary study of 10624 type 2 diabetic patients, with appropriate data on the history of microvascular and macrovascular disease at baseline as well as new cases of major PAD during follow-up. Moreover, the ADVANCE study enrolled different populations across the world enabling us to test the developement of PAD

according to differences in region of origin. Interstingly, we observed an increased risk for major PAD in Eastern Europeans compared to Asians. However, our study has some limitations, notably in issues related to the post hoc analyses of a randomized controlled trial. This study also lacks data regarding other putative risk factors, such as ABI, or chronic inflammation biomarkers, which have been shown to be, associated with PAD (33-36).

In conclusion, our findings highlight macroalbuminuria and severe diabetic retinopathy as 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. Our results suggest also that diabetic microangiopathy may play an important role in the pathogenesis of PAD in such patients. Further studies are needed to investigate the physiopathological pathways linking diabetic microangiopathy and PAD.

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Footnotes

Clinical trial reg. no. NCT00145925, clinicaltrials.gov.

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FIGURE LEGEND

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

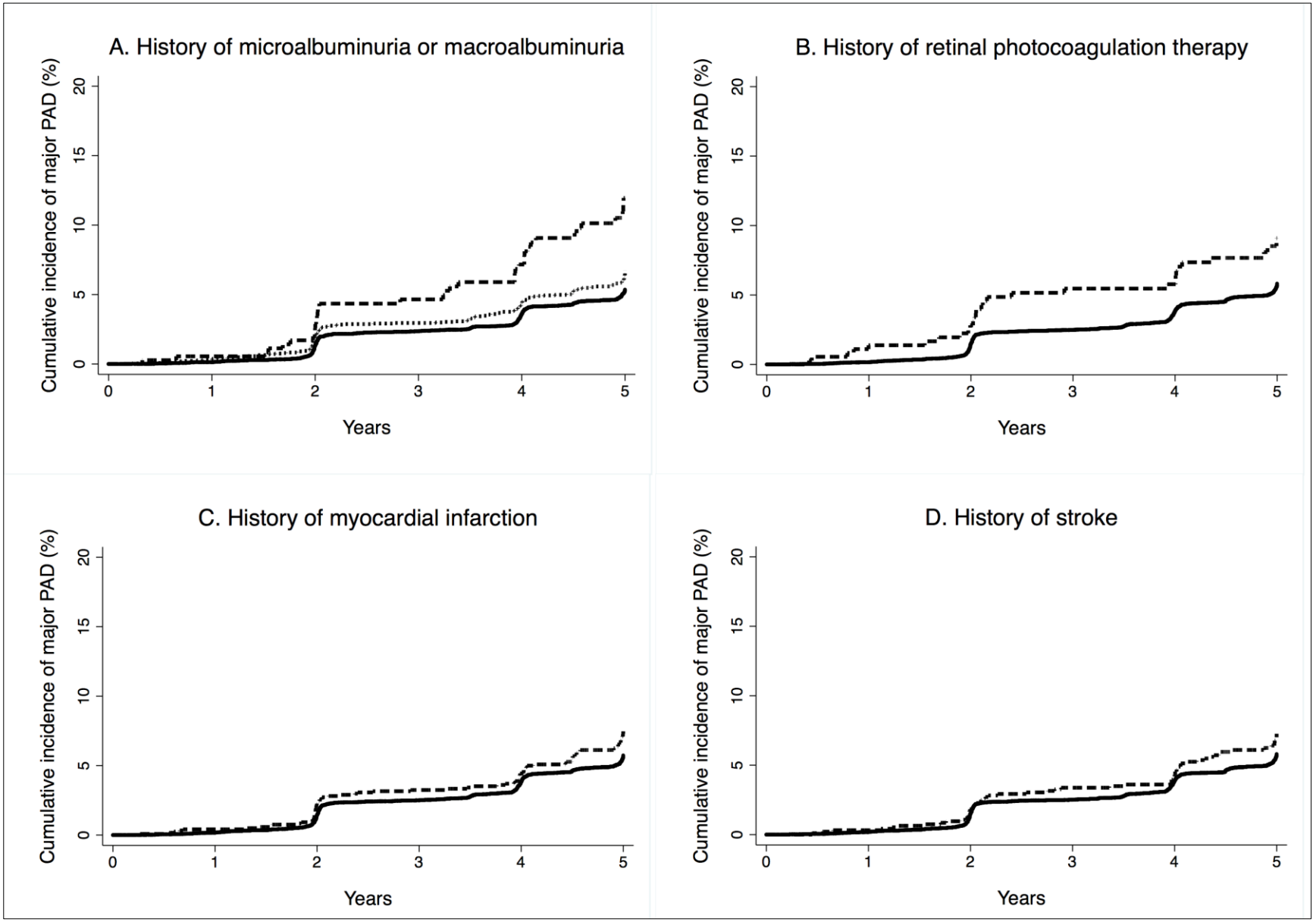
A. History of microalbuminuria or macroalbuminuria
Cumulative incidence of major PAD (%)
0
5
10
15
20
0
1
2
3
4
5
Years
B. History of retinal photocoagulation therapy
Cumulative incidence of major PAD (%)
0
5
10
15
20
0
1
2
3
4
5
Years
C. History of myocardial infarction
Cumulative incidence of major PAD (%)
0
5
10
15
20
0
1
2
3
4
5
Years
D. History of stroke
Cumulative incidence of major PAD (%)
0
5
10
15
20
0
1
2
3
4
5
Years

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

		Major PAD	
	Overall	No	Yes
N (%)	10624 (100%)	10004 (94.2)	620 (5.8)
Male sex, n (%)	6068 (57.1)	5677 (56.8)	391 (63.1)
Region of origin: Asia, n (%)	4040 (38.0)	3868 (38.7)	172 (27.7)
Region of origin: Established market economies, n (%)	4547 (42.8)	4262 (42.6)	285 (46.0)
Region of origin: Eastern Europe, n (%)	2037 (19.2)	1874 (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)
Body mass index (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 hypertensive treatment, n (%)	7281 (68.5)	6821 (68.2)	460 (74.2)
Absence of dorsalis pedis pulse, n (%)	1215 (11.4)	1101 (11.0)	114 (18.4)
Absence of posterior tibial pulse, n (%)	1544 (14.5)	1411 (14.1)	133 (21.5)
Disturbance of light touch sensation, n (%)	895 (8.4)	825 (8.2)	70 (11.3)

Absence of Achilles reflex, n (%)	2234 (21.0)	2079 (20.8)	155 (25.0)
Absence of patellar reflex, n (%)	933 (8.8)	862 (8.6)	71 (11.4)
HbA1c (%): mean (SD)	7.5 (1.5)	7.5 (1.5)	7.7 (1.6)
HbA1c (mmol/mol): mean (SD)	59 (17)	58 (17)	60 (18)
Urinary albumin to creatinine ratio (µg/mg): median (Q1, Q3)	15 (7, 39)	15 (7, 38)	18 (8, 54)
eGFR (ml/min/1.73m^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): median (Q1, Q3)	1.6 (1.2, 2.3)	1.6 (1.2, 2.3)	1.7 (1.2, 2.3)
Use of lipids lowering drugs, n (%)	3689 (34.7)	3450 (34.5)	239 (38.5)
Use of antiplatelet drugs, n (%)	4896 (46.1)	4595 (45.9)	301 (48.5)
History of current smoking, n (%)	1469 (13.8)	1360 (13.6)	109 (17.6)
History of ever smoking, n (%)	4369 (41.1)	4074 (40.7)	295 (47.6)
Mini-Mental State Examination score ≥ 28, n (%)	8304 (78.2)	7845 (78.4)	459 (74.0)
Educational accomplishment ≤ 15 years, n (%)	3806 (35.8)	3570 (35.7)	236 (38.1)

Asia: Philippines, China, Malaysia, India; Established market economies: Australia, Canada, France, Germany, Ireland, Italy, Netherlands, New Zealand, United Kingdom; Eastern Europe: the Czech Republic, Estonia, Hungary, Lithuania, Poland, Russia, Slovakia. eGFR, estimated Glomerular Filtration Rate computed by the Chronic Kidney Disease Epidemiology Collaboration equation. Educational accomplishment: age at completion of the highest level of formal education. SD, standard deviation

Table 2. Independent* risk factors for major PAD

	Major PAD, n (%)			
	Absence of the risk factor	Presence of the risk factor	Hazard Ratio (95% CI)	p
Sex (men *vs.* women)	229 (5.0)	391 (6.4)	1.30 (1.09 – 1.54)	0.003
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)	
Systolic blood pressure (per 10 mmHg) with antihypertensive drugs	-	-	1.13 (1.07 – 1.19)	<0.0001
Systolic blood pressure (per 10 mmHg) without antihypertensive drugs	-	-	1.05 (0.95 – 1.16)	
Diastolic blood pressure (per 10 mmHg) with antihypertensive drugs	-	-	0.83 (0.74 – 0.92)	0.001
Diastolic blood pressure (per 10 mmHg) without antihypertensive drugs	-	-	0.92 (0.76 – 1.11)	
Dorsalis pedis pulse (absent *vs.* present)	505 (5.4)	114 (9.4)	1.47 (1.15 – 1.88)	0.002
Posterior tibial pulse (absent *vs.* present)	486 (5.4)	133 (8.6)	1.29 (1.02 – 1.63)	0.03
HbA1c (per 1%)	-	-	1.07 (1.02 – 1.13)	0.008
Urinary albumin to creatinine ratio (per 1 log µg/mg)	-	-	1.21 (1.06 – 1.38)	0.005
History of current smoking (yes *vs.* no)	511 (5.6)	109 (7.4)	1.37 (1.11 – 1.70)	0.004

*****Using a multivariable Cox proportional hazards survival regressive analysis adjusted for the study randomisation treatments. Asia: Philippines, China, Malaysia, India; Established market economies: Australia, Canada, France, Germany, Ireland, Italy, Netherlands, New Zealand, United Kingdom; Eastern Europe: the Czech Republic, Estonia, Hungary, Lithuania, Poland, Russia, Slovakia. $p<0.05$ was significant.

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

	Major PAD, n (%)		Model 1		Model 2	
	Absence of the predictor	Presence of the predictor	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
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 oedema (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

Cox proportional hazards survival regressive analyses adjusted for age, sex, region of origin, and the study randomisation 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, HbA1C, urinary albumin to creatinine ratio (ACR, except for albuminuria and microvascular disease analyses), and history of current smoking (model 2). Normoalbuminuria: ACR < 30 µg µg/mg; microalbuminuria: ACR >30 – ≤300 µg/mg; macroalbuminuria: ACR >300 µg/mg. CABG: Coronary Artery Bypass Graft. PTCA: Percutaneous Transluminal Coronary Angioplasty. $p<0.05$ was significant.

Table 4. Secondary endpoints according to the history of microvascular and macrovascular disease at baseline

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

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, HbA1c, urinary albumin to creatinine ratio (except for microvascular disease analyses), history of current smoking, and the study randomisation treatments. $p<0.05$ was significant.

Supplemental Table S1. Regression analyses of each candidate risk factor for major PAD

	Hazard Ratio	95% CI	p
Sex (men *vs.* women)	1.27	1.08 – 1.49	0.005
Region of origin: Established market economies *vs.* Asia	1.26	1.04 – 1.53	<0.0001
Region of origin: Eastern Europe *vs.* Asia	1.91	1.54 – 2.37	
Age (per 1 year)	1.01	1.00 – 1.03	0.03
Duration of diabetes (per 1 year)	1.01	1.00 – 1.02	0.08
Body mass index (per 1 kg/m^2)	1.01	1.00 – 1.03	0.16
Systolic blood pressure (per 10 mmHg) with antihypertensive drugs	1.07	1.04 – 1.11	<0.0001
Systolic blood pressure (per 10 mmHg) without antihypertensive drugs	1.06	1.02 – 1.10	
Diastolic blood pressure (per 10 mmHg) with antihypertensive drugs	1.03	0.96 – 1.10	0.004
Diastolic blood pressure (per 10 mmHg) without antihypertensive drugs	0.99	0.92 – 1.07	
Dorsalis pedis pulse (absent *vs.* present)	1.80	1.47 – 2.21	<0.0001
Posterior tibial pulse (absent *vs.* present)	1.59	1.31 – 1.93	<0.0001
Light touch sensation (disturbed *vs.* normal)	1.67	1.34 – 2.08	<0.0001
Achilles reflex (absent *vs.* present)	1.38	1.17 – 1.62	0.0001
Patellar reflex (absent *vs.* present)	1.66	1.34 – 2.06	<0.0001

HbA1c (per 1%)	1.08	1.03 – 1.14	0.0008
Urinary albumin to creatinine ratio (per 1 log µg/mg)	1.35	1.20 – 1.53	<0.0001
eGFR (per 1 ml/min/1.73 m^2)	0.98	0.95 – 1.01	0.08
Squared eGFR (per 1 ml/min/1.73 m^2)	1.00	1.00 – 1.00	
Serum total cholesterol (per 1 mmol/l)	1.04	0.97 – 1.11	0.24
Serum LDL cholesterol (per 1 mmol/l)	1.06	0.98 – 1.14	0.16
Serum HDL cholesterol (per 1 mmol/l)	0.93	0.74 – 1.16	0.52
Serum triglycerides (per 1 log mmol/l)	1.26	0.90 – 1.76	0.18
History of current treatment by lipids lowering drugs (yes *vs.* no)	1.12	0.95 – 1.31	0.18
History of current treatment by antiplatelet drugs (yes *vs.* no)	1.10	0.94 – 1.29	0.22
History of current smoking (yes *vs.* no)	1.36	1.11 – 1.68	0.003
History of ever smoking (yes *vs.* no)	1.24	1.06 – 1.45	0.007
Mini-Mental State Examination score (<28 *vs.* ≥ 28)	1.29	1.09 – 1.55	0.005
Education accomplishment (≤15 *vs.* ≥ 16 years)	1.08	0.92 – 1.27	0.35

Cox proportional hazards survival regressive analysis for each variable adjusted for the study randomisation treatments. Asia: Philippines, China, Malaysia, India; Established market economies: Australia, Canada, France, Germany, Ireland, Italy, Netherlands, New Zealand, United Kingdom; Eastern Europe: the Czech Republic, Estonia, Hungary, Lithuania, Poland, Russia, Slovakia. Estimated glomerular filtration rate (eGFR) computed by the Chronic Kidney Disease Epidemiology Collaboration equation. Educational accomplishment: age at completion of the highest level of formal education.

Supplemental Table S2. Characteristics of participants according to the presence of microvascular or macrovascular disease at baseline

	Microvascular disease		Macrovascular disease	
	No	Yes	No	Yes
N (%)	9559 (90.0)	1065 (10.0)	7396 (69.6)	3228 (30.4)
Male sex, n (%)	5455 (57.1)	613 (57.6)	3954 (53.5)	2114 (65.5)
Region of origin: Asia, n (%)	3569 (37.3)	471 (44.2)	2833 (38.3)	1207 (37.4)
Region of origin: Established market economies, n (%)	4132 (43.2)	415 (39.0)	3222 (43.6)	1325 (41.0)
Region of origin: Eastern Europe, n (%)	1858 (19.4)	179 (16.8)	1341 (18.1)	696 (21.6)
Age (years): mean (SD)	65.7 (6.3)	65.8 (6.5)	65.8 (6.3)	65.6 (6.6)
Duration of diabetes (years): mean (SD)	7.6 (6.1)	10.2 (7.3)	7.9 (6.3)	7.9 (6.4)
Body mass index (kg/m^2): mean (SD)	28 (5)	28 (5)	28.3 (5.3)	28.4 (4.9)
Systolic blood pressure (mmHg): mean (SD)	145 (21)	149 (23)	145 (21)	144 (22)
Diastolic blood pressure (mmHg): mean (SD)	81 (11)	81 (11)	81 (11)	81 (11)
Use of hypertensive treatment, n (%)	6516 (68.2)	765 (71.8)	4774 (64.5)	2507 (77.7)
HbA1c (%): mean (SD)	7.5 (1.5)	7.9 (1.7)	7.5 (1.6)	7.5 (1.5)
HbA1c (mmol/mol): mean (SD)	58 (17)	62 (18)	59 (17)	58 (17)
Urinary albumin to creatinine ratio (µg/mg): median (Q1, Q3)	14 (7, 32)	56 (12, 410)	14 (7, 36)	16 (7, 45)

eGFR (ml/min/1.73m^2): mean (SD)	75 (17)	71 (20)	75 (17)	73 (18)
Serum total cholesterol (mmol/l): mean (SD)	5.2 (1.2)	5.2 (1.2)	5.3 (1.2)	5.0 (1.2)
Serum LDL cholesterol (mmol/l): mean (SD)	3.1 (1.0)	3.1 (1.0)	3.2 (1.0)	3.0 (1.1)
Serum HDL cholesterol (mmol/l): mean (SD)	1.2 (0.3)	1.3 (0.3)	1.3 (0.4)	1.2 (0.3)
Serum triglycerides (mmol/l): median (Q1, Q3)	1.6 (1.2, 2.3)	1.6 (1.1, 2.2)	1.6 (1.2, 2.3)	1.7 (1.2, 2.3)
Use of lipids lowering drugs, n (%)	3324 (34.8)	365 (34.3)	2116 (28.6)	1573 (48.7)
Use of antiplatelet drugs, n (%)	4372 (45.7)	524 (49.2)	2493 (33.7)	2403 (74.4)

Asia: Philippines, China, Malaysia, India; Established market economies: Australia, Canada, France, Germany, Ireland, Italy, Netherlands, New Zealand, United Kingdom; Eastern Europe: the Czech Republic, Estonia, Hungary, Lithuania, Poland, Russia, Slovakia. eGFR, estimated Glomerular Filtration Rate computed by the Chronic Kidney Disease Epidemiology Collaboration equation. SD, standard deviation.

Supplemental Table S3. Relative risk for major PAD according to the history of microvascular and macrovascular disease at baseline in each study randomisation group

	Glucose lowering treatment							Blood pressure treatment						
	Standard				Intensive			Placebo				Perindopril-indapamide		
	Predictor		HR	p	Predictor		HR	p	Predictor		HR	p	Predictor		HR	p
	No	Yes	(95% CI)		No	Yes	(95% CI)		No	Yes	(95% CI)		No	Yes	(95% CI)	
Microvascular disease (yes *vs.* no)	264 (5.5)	52 (9.8)	1.82 (1.35-2.45)	<0.0001	263 (5.5)	41 (7.7)	1.45 (1.04-2.03)	0.03	256 (5.4)	41 (7.6)	1.46 (1.04-2.03)	0.03	271 (5.7)	52 (9.9)	1.81 (1.34-2.44)	0.0001
Macrovascular disease (yes *vs.* no)	209 (5.6)	107 (6.7)	1.05 (0.82-1.35)	0.67	194 (5.3)	110 (6.7)	1.20 (0.93-1.53)	0.15	191 (5.2)	106 (6.6)	1.22 (0.95-1.57)	0.11	212 (5.7)	111 (6.8)	1.05 (0.82-1.34)	0.71

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, HbA1c, urinary albumin to creatinine ratio (except for microvascular disease analyses), history of current smoking, and glucose control (analyses of blood pressure treatment groups) and blood pressure (analyses of glucose lowering treatment groups) study treatments. $p<0.05$ was significant.

Supplemental Table S4. Multiple variable regression analyses of candidate risk factors for major PAD following a backward elimination

	Hazard Ratio	95% CI	p
Sex (men *vs.* women)	1.36	1.14 – 1.61	0.0004
Region of origin: Established market economies *vs.* Asia	1.14	0.92 – 1.39	<0.0001
Region of origin: Eastern Europe *vs.* Asian	1.85	1.48 – 2.31	
Systolic blood pressure (per 10 mmHg) with antihypertensive drugs	1.11	1.06 – 1.17	<0.0001
Diastolic blood pressure (per 10 mmHg) with antihypertensive drugs	0.85	0.77 – 0.93	0.0004
Dorsalis pedis pulse (absent *vs.* present)	1.43	1.11 – 1.82	0.005
Posterior tibial pulse (absent *vs.* present)	1.37	1.08 – 1.72	0.008
HbA1c (per 1%)	1.08	1.02 – 1.13	0.004
History of microalbuminuria (*vs.* normoalbuminuria)	1.11	0.92– 1.33	0.27
History of macroalbuminuria (*vs.* normoalbuminuria)	1.91	1.37– 2.67	0.0001
Retinal photocoagulation therapy (yes *vs.* no)	1.68	1.19 – 2.38	0.003
History of current smoking (yes *vs.* no)	1.33	1.08 – 1.65	0.008

Cox proportional hazards survival regressive analyses in a multivariable model after a backward selection. Analyses adjusted for the study randomisation treatments. Asia: Philippines, China, Malaysia, India; Established market economies: Australia, Canada, France, Germany, Ireland, Italy, Netherlands, New Zealand, United Kingdom; Eastern Europe: the Czech Republic, Estonia, Hungary, Lithuania, Poland, Russia, Slovakia. Normoalbuminuria: Albumin to Creatinine Ratio (ACR) < 30 µg µg/mg; microalbuminuria: ACR >30 – ≤300 µg/mg; macroalbuminuria: ACR >300 µg/mg.