

# **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

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## **ABSTRACT**

**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 sought to examine the impact of previous microvascular and macrovascular disease on the risk of major PAD in these patients.

**RESEARCH DESIGN AND METHODS:** We analysed 10624 patients with type 2 diabetes, free from baseline major 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, peripheral revascularisation, lower-limb amputation or chronic 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, particularly macroalbuminuria and retinal photocoagulation therapy, was strongly predictive for major PAD in patients with type 2 diabetes, but macrovascular 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 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 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  $\leq 6.5\%$ , 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. PAD was defined at baseline as a lower-limb amputation of at least one digit, chronic ulceration of a lower limb (6 weeks or more) thought to be due to arterial insufficiency, or peripheral revascularisation procedure (surgery, angioplasty or emergency thrombolysis).

### **Primary and secondary endpoints**

The primary composite outcome for this analysis was major PAD, defined as at baseline, or death due to PAD. 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. 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 centre 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 centre.

### **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  $\geq 28$ ) or reduced (MMSE  $< 28$ ). Educational accomplishment was defined as age at completion of the highest level of formal education, and categorized as basic ( $\geq 16$  years) or low ( $\leq 15$  years). History of microvascular disease was defined as the presence at baseline of at least macroalbuminuria (urinary Albumin to Creatinine Ratio (ACR)  $> 300 \mu\text{g}/\text{mg}$ ), 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. Characteristics of participants according to the incidence of major PAD were compared at baseline in each individual region of origin using chi-squared, ANOVA, or Wilcoxon tests. 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  $< 0.05$ . The association of history of microvascular and macrovascular disease with the risk for major PAD was also evaluated in subsets of participants with normal ( $\text{eGFR} \geq 60$

ml/min/1.73 m<sup>2</sup>) or impaired renal function (eGFR < 60 ml/min/1.73 m<sup>2</sup>) at baseline. Sensitivity analyses were also performed considering ranges of blood pressure and pulse pressure, defined as the difference between systolic and diastolic blood pressure. Statistical analyses were performed using SAS software, version 9.3 (SAS Institute, [www.sas.com](http://www.sas.com)).

## RESULTS

### Baseline clinical characteristics and incidence of major PAD

Among the ADVANCE study participants, 10624 were free for major 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<sup>th</sup> – 75<sup>th</sup> 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 at baseline, 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) %. The incidence of major PAD was 4.3%, 6.3%, and 8.0% in participants from Asia, established market economies, and Eastern Europe, respectively. Participants from Asia and established market economies who developed major PAD, compared to those who did not, were more frequently men, and had higher systolic blood pressure and ACR. In addition, patients from established market economies with major PAD, compared to those without major PAD, were older, had more missed pedal pulses, a higher Hb1Ac, and a more frequent use of antihypertensive drugs. However, patients from Eastern Europe who developed major PAD, compared to those who did not, were more likely to have a history of current smoking and cognitive decline, and less educational accomplishment (Supplemental Table S1).

### **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 who were randomized to active blood pressure treatment compared to placebo (HR 1.08 95% CI 0.92 – 1.26,  $p=0.36$ ), and in those randomized to both intensive glucose control and active blood pressure treatment compared to standard glucose control and placebo group (HR 1.03 95% CI 0.83 – 1.29,  $p=0.77$ ).

### **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 reflex, 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 S2). 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 or from Established market economies. The incidence of major PAD was not significantly different between Asians and people from Established market economies. 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. Higher systolic blood pressure, and lower diastolic blood pressure, both with use of antihypertensive drugs were also independent risk factors for major PAD (Table 2). Furthermore, major PAD was associated with



increasing systolic blood pressure and decreasing diastolic blood pressure, as well as with increasing pulse pressure (Supplemental Table S3).

### **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 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 S4). 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 S5). Impaired renal function was established at baseline in 2298 (21.6%) participants. Its prevalence was similar in patients with and without major PAD (21.6% versus 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 (Supplemental Table S6).

### **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 S7).

### **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 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, while macrovascular disease was linked with increased

rate of angioplasty procedures. No effect of the glucose control and/or blood pressure intervention was observed for the risk of major PAD.

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 major 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. 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. Notably, recent histopathological study showed microangiopathic abnormalities in patients with type 2 diabetes undergoing amputation for ischemic diabetic foot (15). Urine ACR is now accepted to be an independent cardiovascular risk factor in patients with and without type 2 diabetes (16). Diabetic retinopathy is also thought 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. As a common feature in both microvascular disease and PAD, arterial stiffness may be a key mechanism linking these

conditions (21-23). We have observed association of major PAD with increasing systolic blood pressure, decreasing diastolic blood pressure, and particularly with 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 had also shown increased arterial stiffness in patients with 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 (UKPDS), age, HbA1c, 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-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 (14). 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. These discrepancies may be explained by differences in the inclusion criteria in each study. ADVANCE trial enrolled participants with type 2 diabetes at a high risk of vascular events, while 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 completely different between the two studies. In our study, major PAD was likely to be more severe, defined as lower-limb ulceration or amputation, peripheral revascularisation, 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 PAD were identified solely on the basis of ABI (14). We are aware that the definition of PAD in our 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 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 a robust characterization of new cases of major PAD during follow-up. Moreover, the ADVANCE study enrolled different populations across the world enabling us to test the development of PAD according to differences in region of origin. Interestingly, we observed a relatively low incidence of major PAD in Asians, supporting previous studies showing a lower prevalence of PAD in patients with diabetes and cardiovascular disease from South Asia compared to White European descent (13). We also observed an increased risk for major PAD in Eastern Europeans compared to either Asians or people from established market economies, which could be explained at least in part by a high rate of current smoking in the first group. Our 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 our results, but our group has previously shown that the central endpoint adjudication process had no significant impact on the main findings in ADVANCE trial (35). 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 (36-39).

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 major PAD in such patients.

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### Duality of Interest.

Dr. Mohammedi reports receiving personal fees from Novo Nordisk and Proteor, and travel support from Novo Nordisk, Boehringer Ingelheim, and Takeda; Dr. Zoungas, receiving fees for serving on advisory boards from Merck Sharp and Dohme, Bristol-Myers Squibb–AstraZeneca, Sanofi-Aventis, Novo Nordisk, and Amgen, lecture fees from Servier, Merck Sharp and Dohme, and Bristol-Myers Squibb–AstraZeneca, and fees to her institution for research contract work with Bristol-Myers Squibb–AstraZeneca; Dr Williams, receiving honoraria for lectures from Servier, Novartis, Boehringer Ingelheim and Daiichi Sankyo; Dr. Mancina, receiving lecture fees from Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, Novartis, Menarini International, Recordati, Servier, and Takeda; Dr. Neal, receiving honoraria from Abbott, Novartis, Pfizer, Servier, and Roche and grant support from Roche, AbbVie, Janssen, and Dr. Reddy's Laboratories; Dr. Harrap, receiving lecture fees from Servier, Takeda, and Novartis; Dr. Marre, receiving personal fees from Novo Nordisk, Sanofi, Eli Lilly, Servier, Merck; Sharp and Dohme, Abbott, Novartis, and AstraZeneca and grant support from Novo Nordisk, Sanofi, Eli Lilly, Merck Sharp and Dohme, and Novartis; and Dr. Chalmers, receiving research grants and lecture fees from Servier for the ADVANCE trial and ADVANCE-ON post-trial study. No other potential conflict of interest relevant to this article was reported.

**Author contributions.** K.M. wrote the manuscript with assistance from M.W. and J.C.; K.M., M.W. and J.C. designed the study; Y.H. contributed to statistical analyses and reviewed

the manuscript; S.Z., B.W., L.L., A.R., G.M., B.N., S.H., and M.M. contributed to discussion and reviewed the manuscript. J.C. and K.M. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the current version of the manuscript.

**Footnotes**

Clinical trial reg. no. NCT00145925, [clinicaltrials.gov](https://clinicaltrials.gov).



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

	Major PAD		
	Overall (n=10624)	No (n=10004)	Yes (n=620)
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 <sup>2</sup> ): 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, 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 <sup>2</sup> ): 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 $\geq$ 28, n (%)	8304 (78.2)	7845 (78.4)	459 (74.0)
Educational accomplishment $\leq$ 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 (%)		Hazard Ratio (95% CI)	p
	Absence of the risk factor	Presence of the risk factor		
Male sex	229 (5.0)	391 (6.4)	1.30 (1.09 – 1.54)	0.003
Established market economies ( <i>vs.</i> Asia)	172 (4.3)	285 (6.3)	1.17 (0.95 – 1.44)	<0.0001
Eastern Europe ( <i>vs.</i> Asia)	172 (4.3)	163 (8.0)	1.95 (1.54 – 2.46)	
Eastern Europe ( <i>vs.</i> Established market economies )	285 (6.3)	163 (8.0)	1.67 (1.35 – 2.06)	
Systolic blood pressure (per 10 mmHg increase) with antihypertensive drugs	-	-	1.13 (1.07 – 1.19)	<0.0001
Systolic blood pressure (per 10 mmHg increase) without antihypertensive drugs	-	-	1.05 (0.95 – 1.16)	
Diastolic blood pressure (per 10 mmHg increase) with antihypertensive drugs	-	-	0.83 (0.74 – 0.92)	0.001
Diastolic blood pressure (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
HbA1c (per 1% increase)	-	-	1.07 (1.02 – 1.13)	0.008
Urinary albumin to creatinine ratio (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

\*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	Presence	Hazard ratio	p	Hazard ratio	p
	of the predictor	of the predictor	(95% CI)		(95% CI)	
History of microvascular disease (yes <i>vs.</i> no)	527 (5.5)	93 (8.7)	1.73 (1.39 - 2.16)	<0.0001	1.63 (1.30 – 2.03)	<0.0001
Microalbuminuria ( <i>vs.</i> normoalbuminuria)	407 (5.4)	172 (6.3)	1.21 (1.01 – 1.45)	0.03	1.10 (0.92 – 1.32)	0.29
Macroalbuminuria ( <i>vs.</i> 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 <i>vs.</i> 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 <i>vs.</i> 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 <i>vs.</i> 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 <i>vs.</i> 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 <i>vs.</i> 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 <i>vs.</i> 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 <i>vs.</i> 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 <i>vs.</i> 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. Characteristics of participants at baseline according to the incidence of major PAD during follow-up by region of origin**

	Asia			Established market economies			Eastern Europe		
	Absence of major PAD (n=3868)	Presence of major PAD (n=172)	p <sup>*</sup>	Absence of major PAD (n=4262)	Presence of major PAD (n=285)	p <sup>†</sup>	Absence of major PAD (n=1874)	Presence of major PAD (n=163)	p <sup>‡</sup>
Male sex, n (%)	2047 (52.9)	110 (64.0)	0.005	2809 (65.9)	209 (73.3)	0.01	821 (43.8)	72 (44.2)	0.93
Age (years): mean (SD)	64.5 (5.7)	64.3 (5.7)	0.77	67.0 (6.4)	68.0 (6.4)	0.01	65.2 (6.9)	65.0 (7.2)	0.65
Duration of diabetes (years): mean (SD)	8.3 (6.3)	8.7 (6.8)	0.43	7.4 (6.2)	8.1 (7.2)	0.06	8.1 (6.4)	7.9 (6.0)	0.71
Body mass index (kg/m <sup>2</sup> ): mean (SD)	25.3 (3.4)	25.3 (3.2)	0.98	30.0 (5.3)	30.0 (5.6)	0.94	30.6 (4.9)	30.2 (5.5)	0.30
SBP (mmHg): mean (SD)	141 (21)	145 (26)	0.03	146 (20)	150 (22)	0.001	150 (22)	150 (21)	0.94
DBP (mmHg): mean (SD)	79 (11)	80 (13)	0.37	81 (10)	80 (11)	0.62	85 (11)	85 (11)	0.98
Use of antihypertensive drugs, n (%)	2455 (63.5)	110 (64.0)	0.90	2731 (64.1)	206 (72.3)	0.005	1635 (87.3)	144 (88.3)	0.69
Absence of dorsalis pedis pulse, n (%)	178 (4.6)	6 (3.5)	0.49	696 (16.3)	79 (27.8)	<0.0001	227 (12.1)	29 (17.8)	0.04
Absence of posterior tibial pulse, n (%)	214 (5.5)	8 (4.7)	0.62	965 (22.7)	102 (35.9)	<0.0001	232 (12.4)	23 (14.1)	0.52
Disturbance of light touch sensation, n (%)	126 (3.3)	3 (1.7)	0.27	225 (5.3)	22 (7.7)	0.08	474 (25.3)	45 (27.6)	0.52
Absence of Achilles reflex, n (%)	548 (14.2)	22 (12.8)	0.61	1358 (31.9)	113 (39.7)	0.007	173 (9.2)	20 (12.3)	0.20

Absence of patellar reflex, n (%)	227 (5.9)	12 (7.0)	0.55	491 (11.5)	40 (14.0)	0.20	144 (7.7)	19 (11.7)	0.07
HbA1c (%): mean (SD)	7.7 (1.8)	7.9 (1.7)	0.35	7.3 (1.2)	7.5 (1.4)	0.0002	7.6 (1.7)	7.8 (1.9)	0.18
HbA1c (mmol/mol): mean (SD)	61 (19)	63 (19)		56 (13)	59 (16)		59 (19)	61 (20)	
Urinary ACR ( $\mu\text{g}/\text{mg}$ ): median (Q1, Q3)	18 (9, 48)	23 (10, 79)	0.03	12 (6, 31)	17 (7, 48)	0.003	12 (5, 34)	14 (6, 46)	0.28
eGFR ( $\text{ml}/\text{min}/1.73\text{m}^2$ ): mean (SD)	78 (19)	78 (19)	0.67	73 (16)	72 (17)	0.19	71 (16)	71 (17)	0.88
Total cholesterol (mmol/l): mean (SD)	5.3 (1.2)	5.4 (1.3)	0.27	4.9 (1.0)	4.9 (0.9)	0.41	5.7 (1.3)	5.7 (1.2)	0.67
HDL cholesterol (mmol/l): mean (SD)	1.3 (0.4)	1.3 (0.4)	0.50	1.2 (0.3)	1.2 (0.3)	0.98	1.3 (0.3)	1.3 (0.3)	0.64
Triglycerides (mmol/l): median (Q1, Q3)	1.6 (1.1, 2.3)	1.8 (1.1, 2.3)	0.01	1.6 (1.2, 2.3)	1.7 (1.2, 2.3)	0.70	1.7 (1.3, 2.5)	1.8 (1.3, 2.5)	0.27
Use of lipids lowering drugs, n (%)	731 (18.9)	42 (24.4)	0.07	2135 (50.1)	134 (47.0)	0.31	584 (31.2)	63 (38.7)	0.05
Use of antiplatelet drugs, n (%)	1710 (44.2)	77 (44.8)	0.89	2018 (47.4)	149 (52.3)	0.11	867 (46.3)	75 (46.0)	0.95
History of current smoking, n (%)	520 (13.4)	29 (16.9)	0.20	540 (12.7)	41 (14.4)	0.40	300 (16.0)	39 (23.9)	0.009
History of ever smoking, n (%)	889 (23.0)	50 (29.1)	0.06	2486 (58.3)	176 (61.8)	0.26	699 (37.3)	69 (42.3)	0.20
MMSE score $\geq 28$ , n (%)	851 (22.0)	40 (23.3)	0.70	831 (19.5)	63 (22.1)	0.28	477 (25.5)	58 (35.6)	0.005
Educational $\leq 15$ years, n (%)	1152 (29.8)	41 (23.8)	0.09	2040 (47.9)	149 (52.3)	0.15	378 (20.2)	46 (28.2)	0.02

Characteristics of participants were compared according to the incidence of PAD in Asia (\*), Established market economies (†), and Eastern Europe (‡), using Chi-square (qualitative parameters), ANOVA (quantitative parameters), and Wilcoxon (quantitative parameters with skewed distribution) tests.  $p < 0.05$  was significant.

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. SBP, Systolic Blood Pressure. DBP, Diastolic Blood Pressure. ACR, Albumin to Creatinine Ratio. eGFR, estimated Glomerular Filtration Rate computed by the Chronic Kidney Disease Epidemiology Collaboration equation. MMSE, Mini-Mental State Examination. Educational: age at completion of the highest level of formal education. SD, standard deviation.

**Supplemental Table S2. Regression analyses of each candidate risk factor for major PAD**

	Hazard Ratio	95% CI	p
Male sex	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 <sup>2</sup> increase)	1.01	1.00 – 1.03	0.16
Systolic blood pressure (per 10 mmHg increase) with antihypertensive drugs	1.07	1.04 – 1.11	<0.0001
Systolic blood pressure (per 10 mmHg increase) without antihypertensive drugs	1.06	1.02 – 1.10	
Diastolic blood pressure (per 10 mmHg increase) with antihypertensive drugs	1.03	0.96 – 1.10	0.004
Diastolic blood pressure (per 10 mmHg increase) without antihypertensive drugs	0.99	0.92 – 1.07	
Absent dorsalis pedis pulse	1.80	1.47 – 2.21	<0.0001
Absent posterior tibial pulse	1.59	1.31 – 1.93	<0.0001
Disturbance of light touch sensation	1.67	1.34 – 2.08	<0.0001
Absence of Achilles reflex	1.38	1.17 – 1.62	0.0001

Absence of patellar reflex	1.66	1.34 – 2.06	<0.0001
HbA1c (per 1% increase)	1.08	1.03 – 1.14	0.0008
Urinary albumin to creatinine ratio (per 1 log µg/mg increase)	1.35	1.20 – 1.53	<0.0001
eGFR (per 1 ml/min/1.73 m <sup>2</sup> increase)	0.98	0.95 – 1.01	0.08
Squared eGFR (per 1 ml/min/1.73 m <sup>2</sup> increase)	1.00	1.00 – 1.00	
Serum total cholesterol (per 1 mmol/l increase)	1.04	0.97 – 1.11	0.24
Serum LDL cholesterol (per 1 mmol/l increase)	1.06	0.98 – 1.14	0.16
Serum HDL cholesterol (per 1 mmol/l increase)	0.93	0.74 – 1.16	0.52
Serum triglycerides (per 1 log mmol/l increase)	1.26	0.90 – 1.76	0.18
History of current treatment by lipids lowering drugs	1.12	0.95 – 1.31	0.18
History of current treatment by antiplatelet drugs	1.10	0.94 – 1.29	0.22
History of current smoking	1.36	1.11 – 1.68	0.003
History of ever smoking	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 S3. Impact of ranges of blood pressure and pulse pressure at baseline on the risk for major PAD**

	Major PAD, n (%)			
	No	Yes	Hazard Ratio (95% CI)	p
Ranges of systolic blood pressure (SBP)				
SBP < 130 mmHg	2403 (95.2)	120 (4.8)	ref.	
130 ≤ SBP < 160 mmHg	5394 (94.3)	327 (5.7)	1.20 (0.95 – 1.52)	0.13
SBP ≥ 160 mmHg	2207 (92.7)	173 (7.3)	1.60 (1.18 – 2.17)	0.002
Ranges of diastolic blood pressure (DBP)				
DBP < 70 mmHg	1528 (94.1)	96 (5.9)	ref.	
70 ≤ DBP < 90 mmHg	6480 (94.3)	395 (5.7)	0.75 (0.59 – 0.96)	0.02
DBP ≥ 90 mmHg	1996 (93.9)	129 (6.1)	0.60 (0.43 – 0.83)	0.002
Pulse pressure (per 10 mmHg increase)	-	-	1.10 (1.05 – 1.16)	<0.0001

Cox proportional hazards survival regressive analyses adjusted for age, sex, region of origin, SBP (analyses of PAD ranges), DBP (analyses of SBP ranges), antihypertensive treatment, absence of dorsalis pedis and posterior tibial pulses, HbA1c, urinary albumin to creatinine ratio, history of current smoking, and the study randomisation treatments.  $p < 0.05$  was significant. Pulse pressure: difference between SBP and DBP.

**Supplemental Table S4. Characteristics of participants according to the presence of microvascular or macrovascular disease at baseline**

	Microvascular disease		Macrovascular disease	
	No (n=9559)	Yes (n=1065)	No (n=7396)	Yes (n=3228)
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 <sup>2</sup> ): 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 antihypertensive drugs, 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 <sup>2</sup> ): 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 S5. 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	52	1.82	<0.0001	263	41	1.45	0.03	256	41	1.46	0.03	271	52	1.81	0.0001
	(5.5)	(9.8)	(1.35-2.45)		(5.5)	(7.7)	(1.04-2.03)		(5.4)	(7.6)	(1.04-2.03)		(5.7)	(9.9)	(1.34-2.44)	
Macrovascular disease (yes vs. no)	209	107	1.05	0.67	194	110	1.20	0.15	191	106	1.22	0.11	212	111	1.05	0.71
	(5.6)	(6.7)	(0.82-1.35)		(5.3)	(6.7)	(0.93-1.53)		(5.2)	(6.6)	(0.95-1.57)		(5.7)	(6.8)	(0.82-1.34)	

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 S6. Relative risk for major PAD according to the history of microvascular and macrovascular disease at baseline by renal function status**

	Participants with normal renal function at baseline				Participants with impaired renal function at baseline			
	Predictor				Predictor			
	No	Yes	Hazard ratio (95% CI)	P	No	Yes	Hazard ratio (95% CI)	P
History of microvascular disease (yes vs. no)	424 (5.6)	55 (7.4)	1.42 (1.07 – 1.88)	0.02	103 (5.2)	38 (11.7)	2.44 (1.67 – 3.57)	<0.0001
History of macrovascular disease (yes vs. no)	318 (5.4)	161 (6.6)	1.16 (0.95 - 1.42)	0.14	85 (5.7)	56 (7.0)	1.19 (0.83 - 1.70)	0.34

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 S7. Multiple variable regression analyses of candidate risk factors for major PAD following a backward elimination**

	Hazard Ratio	95% CI	p
Male sex	1.36	1.14 – 1.61	0.0004
Region of origin: Established market economies ( <i>vs.</i> Asia)	1.14	0.92 – 1.39	<0.0001
Region of origin: Eastern Europe ( <i>vs.</i> Asia)	1.85	1.48 – 2.31	
Systolic blood pressure (per 10 mmHg increase) with antihypertensive drugs	1.11	1.06 – 1.17	<0.0001
Diastolic blood pressure (per 10 mmHg increase) with antihypertensive drugs	0.85	0.77 – 0.93	0.0004
Absent dorsalis pedis pulse	1.43	1.11 – 1.82	0.005
Absent posterior tibial pulse	1.37	1.08 – 1.72	0.008
HbA1c (per 1% increase)	1.08	1.02 – 1.13	0.004
History of microalbuminuria ( <i>vs.</i> normoalbuminuria)	1.11	0.92– 1.33	0.27
History of macroalbuminuria ( <i>vs.</i> normoalbuminuria)	1.91	1.37– 2.67	0.0001
Retinal photocoagulation therapy	1.68	1.19 – 2.38	0.003
History of current smoking	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)  $< 30 \mu\text{g} \mu\text{g}/\text{mg}$ ; microalbuminuria: ACR  $>30 - \leq 300 \mu\text{g}/\text{mg}$ ; macroalbuminuria: ACR  $>300 \mu\text{g}/\text{mg}$ .

**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 ( $p=0.05$ ).