Absence of Peripheral Pulses and Risk of Major Vascular Outcomes in Patients With Type 2 Diabetes

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PATHOPHYSIOLOGY/COMPLICATIONS

OBJECTIVE

The burden of vascular diseases remains substantial in patients with type 2 diabetes, requiring identification of further risk markers. We tested the absence of dorsalis pedis and posterior tibial pulses as predictors of major macrovascular and microvascular events, death, and cognitive decline in this population.

RESEARCH DESIGN AND METHODS

Data were derived from 11,120 patients with type 2 diabetes in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) study. Absent peripheral pulses at baseline were defined as absence of at least one dorsalis pedis or posterior tibial pulse.

RESULTS

Absent compared with present peripheral pulses (n = 2,218) were associated with increased 5-year risks for major macrovascular events (hazard ratio 1.47 [95% CI 1.28–1.69], $P < 0.0001$), myocardial infarction (1.45 [1.13–1.87], $P = 0.003$), stroke (1.57 [1.23–2.00], $P = 0.0003$), cardiovascular death (1.61 [1.33–1.95], $P < 0.0001$), heart failure (1.49 [1.21–1.84], $P = 0.0002$), all-cause mortality (1.48 [1.29–1.71], $P < 0.0001$), major microvascular events (1.17 [1.00–1.36], $P = 0.04$), nephropathy (1.24 [1.00–1.54], $P = 0.04$), end-stage renal disease or renal death (2.04 [1.12–3.70], $P = 0.02$), and peripheral neuropathy (1.13 [1.05–1.21], $P = 0.0008$) after multiple adjustment. Participants with absent dorsalis pedis or posterior tibial pulses had comparable hazard ratios. Risks increased proportionally with the number of absent peripheral pulses, with the highest risks observed in patients with three or four absent pulses. Every additional absent pulse increases the risk of all outcomes.

CONCLUSIONS

Absent dorsalis pedis and/or posterior tibial pulses are independent predictors of major vascular outcomes in patients with type 2 diabetes. These simple clinical indicators should be used to improve risk stratification and treatment of these patients.

The prevalence of diabetes continues to increase worldwide, with a high risk for premature death (1–3). Cardiovascular disease is the leading cause of morbidity and mortality in people with type 2 diabetes (4,5). Diabetes confers about 1.5- to threefold excess risk for a wide range of atherosclerotic diseases, such as stroke, myocardial infarction, and peripheral arterial disease (PAD) (4,6,7). It is also a leading cause of lower-extremity amputation, severe eye complications, and end-stage

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renal disease (ESRD) (8–10) and confers a substantial clinical and economic load (11–13). Thus, a pressing need exists for early detection of high-risk factors in patients with type 2 diabetes to improve treatment and prognosis.

Growing evidence indicates that ankle-brachial index (ABI), the ratio of the ankle and brachial systolic blood pressures, is a marker for cardiovascular events and death (14,15). However, the simpler clinical assessment of the absence of palpable peripheral pulses has not been tested as a predictor of major vascular outcomes. Hence, we investigated whether the absence of a dorsalis pedis or posterior tibial pulse is associated with major macrovascular and microvascular events, mortality, and cognitive decline in patients with type 2 diabetes in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) clinical trial.

RESEARCH DESIGN AND METHODS

Participants

Details on the study design and the characteristics of participants in ADVANCE have been published previously (16–18). Briefly, 11,140 patients with type 2 diabetes at high risk for vascular complications were randomly assigned to a gliclazide (modified release)-based intensive glucose-control regimen targeted to achieve an HbA_{1c} ≤6.5% or to standard glucose control according to local guidelines. Patients were also randomly assigned to a fixed-dose combination of perindopril (4 mg) and indapamide (1.25 mg) or matching placebo. The institutional ethics committee of each participating center approved the study protocol, and all participants provided written informed consent.

Definition of Absent Peripheral Pulse

Local ADVANCE investigators were advised to perform a general physical examination of each participant, including palpation of the right- and left-side dorsalis pedis and posterior tibial pulses while the participant lay supine. Pulse examinations were performed for all participants, except 20 who were excluded from the current analysis. Absence of peripheral pulses at baseline was defined as absence at palpation of at least one left- or right-side dorsalis pedis or posterior tibial pulse.

Study End Points

Two primary end points were prespecified as a composite of major macrovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and a composite of major microvascular events (new or worsening nephropathy or retinopathy). The secondary outcomes comprised all-cause mortality, heart failure (death, hospitalization, or worsening New York Heart Association class), ESRD (requirement for renal replacement therapy) or death induced by renal disease, new or worsening peripheral neuropathy (disturbance of 10-g monofilament sensation or absence of ankle or knee reflex), decline in cognitive function (reduction in the Mini-Mental State Examination score by at least 3 points compared with the baseline score), dementia (satisfying the criteria in the DSM-IV), and all-cause hospitalization for ≥24 h. The primary outcomes, their separate components, and all-cause mortality were adjudicated by an independent end point adjudication committee. The other secondary outcomes were reported systematically during the scheduled study visits, every 2 years, from case report forms and 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 the 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.

Statistical Analyses

Quantitative variables were expressed as mean (SD) or median (interquartile range) for variables with skewed distribution. Categorical variables were presented as the number of patients with the corresponding percentage. χ^2, ANOVA, or Wilcoxon tests were used to compare baseline characteristics of participants with the absence of at least one peripheral pulse (left or right side) with those with the presence of all peripheral pulses. Cumulative incidence curves were used to plot survival (outcome-free) rates during follow-up according to the peripheral pulse status at baseline. Incidence curves were compared using the log-rank test. We fitted Cox proportional hazards survival regression models to estimate hazard ratios (HRs) with associated 95% CIs for the effects (absence vs. presence) of peripheral pulses on the various outcomes. Analyses were adjusted for sex, age, region of origin, and study allocation (model 1) and for model 1 plus baseline duration of diabetes, BMI, waist circumference, systolic and diastolic blood pressure with and without antihypertensive treatment, HbA_{1c}, estimated glomerular filtration rate (eGFR), squared eGFR (except for microvascular events), urinary albumin-creatinine ratio (ACR) (normoalbuminuria $<$30 μg/mg, microalbuminuria $>$30 to ≤300 μg/mg, macroalbuminuria $>$300 μg/mg), total and HDL cholesterol, history of ever smoking, and use of lipid-lowering and antiplatelet drugs (model 2). We also analyzed the effects of absence of each of the two separate types of pulse individually, and the dose-response relationship between the number of absent pulses, grouped as none, one to two, and three to four, in a similar way but using only model 2. Furthermore, we evaluated the HR of outcomes for each additional absent pulse.

Six sensitivity analyses were conducted. First, analyses were performed in the glucose control (intensive and standard) and antihypertensive treatment (perindopril-indapamide and placebo) randomized treatment groups separately. Second, we excluded from analyses participants with a baseline history of macrovascular disease (defined as the presence of at least myocardial infarction, stroke, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, hospital admission for unstable angina, or transient ischemic attack). Third, patients with major PAD at baseline (defined as lower-extremity amputation of at least one toe, chronic foot ulceration secondary to vascular disease, or history of a peripheral revascularization procedure by angioplasty or surgery) were excluded from analyses. Fourth, patients with peripheral diabetic neuropathy at baseline were excluded from analyses. Fifth, we evaluated the risk of outcomes in patients with both absent peripheral pulses and chronic ulceration at baseline compared with those without these conditions. Finally, Harrell C-statistics were used to compare discrimination, assessed in the survival analyses, between two prognostic models in patients free at baseline of myocardial infarction, stroke, and macroalbuminuria (19) as follows: *1*) traditional risk factors (age, sex, systolic blood pressure, antihypertensive treatment, HbA_{1c}, eGFR, urinary ACR, total and HDL cholesterol, history of ever smoking, and study allocation) alone and *2*) traditional risk factors plus absent peripheral pulses. $P < 0.05$ was considered significant. Statistical analyses were performed using SAS 9.3 (SAS Institute, www.sas.com) and Stata 13 (StataCorp, www.stata.com) software.

RESULTS

Characteristics of Participants at Baseline

Among 11,120 participants, left- and right-side dorsalis pedis and posterior tibial pulses were absent at baseline in 1,135 (10%), 1,128 (10%), 1,543 (14%), and 1,485 (13%), respectively (Supplementary Fig. 1*A*). The absence of at least one peripheral pulse at baseline was established in 2,218 (20%) participants. Compared with those with the presence of all peripheral pulses, participants with the absence of at least one peripheral pulse at baseline were older, more frequently men, and from established market economies (Table 1). They had a longer duration of diabetes; higher BMI, waist circumference, and systolic blood pressure; and lower diastolic blood pressure, HbA_{1c}, eGFR, and serum total and HDL cholesterol than those with presence of all peripheral pulses. They also were more likely to use antihypertensive, lipid-lowering, and antiplatelet drugs; to have a history of macrovascular disease, PAD, and peripheral neuropathy; and to have ever smoked (Table 1).

Table 1—Clinical characteristics of participants according to the absence of at least one peripheral pulse (left or right side) at baseline

		Absent peripheral pulse at baseline		
	Overall (*n* = 11,120)	No (*n* = 8,902)	Yes (*n* = 2,218)	*P* value
Male sex	6,394 (57.5)	5,027 (56.5)	1,367 (61.6)	<0.0001
Region of origin				
Asia	4,131 (37.1)	3,797 (42.7)	334 (15.1)	<0.0001
Established market economies	4,862 (43.7)	3,348 (37.5)	1,514 (68.0)	
Eastern Europe	2,140 (19.2)	1,764 (19.8)	376 (16.9)	
Age (years)	65.8 (6.4)	65.3 (6.2)	67.7 (6.7)	<0.0001
Duration of diabetes (years)	7.9 (6.4)	7.8 (6.2)	8.4 (6.8)	<0.0001
BMI (kg/m^2)	28.3 (5.2)	28.1 (5.1)	29.5 (5.5)	<0.0001
Waist circumference (cm)	99 (13)	98 (13)	102 (13)	<0.0001
Systolic blood pressure (mmHg)	145 (22)	145 (22)	147 (21)	<0.0001
Diastolic blood pressure (mmHg)	81 (11)	81 (11)	80 (11)	<0.0001
Use of hypertensive treatment	7,647 (68.8)	6,057 (68.0)	1,590 (71.7)	0.0009
HbA_{1c} (%)	7.5 (1.6)	7.5 (1.6)	7.4 (1.4)	0.006
HbA_{1c} (mmol/mol)	59 (17)	59 (17)	58 (15)	
eGFR (mL/min/1.73m^2)	74 (18)	75 (17)	71 (18)	<0.0001
Urinary ACR (μg/mg)	15 (7, 40)	15 (7, 39)	15 (7, 42)	0.16
Normoalbuminuria (<30 μg/mg)	7,365 (66.2)	5,938 (66.7)	1,427 (64.3)	0.03
Microalbuminuria (≥30 to ≤300 μg/mg)	2,851 (25.6)	2,277 (25.6)	574 (25.9)	
Macroalbuminuria (>300 μg/mg)	403 (3.6)	304 (3.4)	99 (4.5)	
History of microvascular disease	1,152 (10.4)	899 (10.1)	253 (11.4)	0.07
History of peripheral neuropathy	3,180 (28.6)	2,009 (22.6)	1,171 (52.8)	<0.0001
Serum total cholesterol (mmol/L)	5.2 (1.2)	5.2 (1.2)	5.0 (1.1)	<0.0001
Serum HDL cholesterol (mmol/L)	1.3 (0.4)	1.3 (0.4)	1.2 (0.3)	<0.0001
Serum triglycerides (mmol/L)	1.6 (1.2, 2.3)	1.6 (1.2, 2.3)	1.6 (1.2, 2.3)	0.40
Use of lipid-lowering drugs	3,926 (35.3)	2,938 (33.0)	988 (44.5)	<0.0001
Use of antiplatelet drugs	5,191 (46.7)	4,032 (45.3)	1,159 (52.3)	<0.0001
History of current smoking	1,681 (15.1)	1,326 (14.9)	355 (16.0)	0.19
History of ever smoking	4,663 (41.9)	3,423 (38.5)	1,240 (55.9)	<0.0001
History of macrovascular disease	3,452 (31.0)	2,649 (29.8)	803 (36.2)	<0.0001
History of major PAD	506 (4.6)	302 (3.4)	204 (9.2)	<0.0001

Data are *n* (%), mean (SD), or median (quarter 1, quarter 3). Comparison of qualitative and quantitative parameters were performed using χ^2 and ANOVA tests, respectively. Wilcoxon test was used for variables with skewed distribution (urinary ACR and triglycerides). $P < 0.05$ was significant. Asia includes the Philippines, China, Malaysia, and India; established market economies include Australia, Canada, France, Germany, Ireland, Italy, the Netherlands, New Zealand, and the U.K.; and Eastern Europe includes the Czech Republic, Estonia, Hungary, Lithuania, Poland, Russia, and Slovakia. eGFR was computed by the Chronic Kidney Disease Epidemiology Collaboration equation. History of microvascular disease was defined as macroalbuminuria, retinal photocoagulation therapy, proliferative retinopathy, macular edema, or blindness. History of peripheral neuropathy was defined as disturbance of 10-g monofilament sensation and absence of ankle or knee reflex. History of macrovascular disease was defined as myocardial infarction, stroke, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, hospital admission for unstable angina, or transient ischemic attack. History of major PAD was defined as lower-limb amputation of at least one digit, chronic ulceration of a lower limb (≥6 weeks) believed to be due to arterial insufficiency, or requirement for a peripheral revascularization procedure (surgery, angioplasty, or emergency thrombolysis). History of current smoking was defined as smoking cigarettes and a pipe.

Absent Peripheral Pulses and Risks of Adverse Outcomes During Follow-up

During a median follow-up of 5 years, major macrovascular events, major microvascular events, cardiovascular death, heart failure, and all-cause mortality occurred in 1,145 (10%), 1,130 (10%), 541 (5%), 451 (4%), and 1,027 (9%) participants, respectively. Compared with the presence of all peripheral pulses, the absence of at least one peripheral pulse was significantly associated with a higher incidence of major macrovascular events, nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, heart failure, all-cause mortality, major microvascular events, new or worsening nephropathy, ESRD or renal death, new or worsening peripheral neuropathy, cognitive decline, and all-cause hospitalization (Table 2). All these associations except cognitive decline remained significant in multivariable-adjusted Cox models.

Participants with absent dorsalis pedis or posterior tibial pulses had similar

Table 2—HRs for outcomes according to absence of at least one peripheral pulse (left or right side) at baseline

	Absent peripheral pulse at baseline		Absent peripheral pulse vs. not					
			Model 1			Model 2		
	No (n = 8,902)	Yes (n = 2,218)	HR	95% CI	P value	HR	95% CI	P value
Primary end points								
Major macrovascular events	810 (9.1)	335 (15.1)	1.64	1.43–1.87	<0.0001	1.47	1.28–1.69	<0.0001
Nonfatal myocardial infarction	201 (2.3)	108 (4.9)	1.65	1.29–2.10	<0.0001	1.45	1.13–1.87	0.003
Nonfatal stroke	321 (3.6)	101 (4.6)	1.63	1.29–2.07	<0.0001	1.57	1.23–2.00	0.0003
Cardiovascular death	358 (4.0)	183 (8.3)	1.90	1.57–2.29	<0.0001	1.61	1.33–1.95	<0.0001
Major microvascular events	889 (10.0)	241 (10.9)	1.31	1.12–1.52	0.0005	1.17	1.00–1.36	0.04
New or worsening nephropathy	389 (4.4)	132 (6.0)	1.50	1.21–1.84	0.0002	1.24	1.00–1.54	0.04
New or worsening retinopathy	556 (6.3)	125 (5.6)	0.98	0.80–1.19	0.82	1.12	0.91–1.38	0.28
Secondary end points								
All-cause mortality	693 (7.8)	334 (15.1)	1.69	1.48–1.95	<0.0001	1.48	1.29–1.71	<0.0001
Heart failure	295 (3.3)	156 (7.0)	1.83	1.49–2.25	<0.0001	1.49	1.21–1.84	0.0002
ESRD or renal death	35 (0.4)	24 (1.1)	2.99	1.70–5.26	0.0001	2.04	1.12–3.70	0.02
New or worsening peripheral neuropathy	3,516 (39.5)	1,138 (51.3)	1.14	1.06–1.22	0.0002	1.13	1.05–1.21	0.0008
Dementia	76 (0.9)	33 (1.5)	1.47	0.96–2.27	0.08	1.45	0.93–2.25	0.10
Cognitive decline	1,398 (15.7)	407 (18.4)	1.15	1.03–1.30	0.02	1.11	0.99–1.25	0.08
All hospitalizations	3,648 (41.0)	1,223 (55.1)	1.27	1.18–1.35	<0.0001	1.18	1.10–1.26	<0.0001

Data are n (%) unless otherwise indicated. HRs computed by Cox proportional hazards survival regression analyses. Model 1: adjusted for sex, age, region of origin, and study treatments; model 2: adjusted for model 1 plus duration of diabetes, BMI, waist circumference, systolic and diastolic blood pressure with and without antihypertensive treatment, HbA_{1c}, eGFR, squared eGFR (except for microvascular events), urinary ACR (normoalbuminuria, microalbuminuria, and macroalbuminuria), total and HDL cholesterol, history of ever smoking, and use of lipid-lowering and antiplatelet drugs. $P < 0.05$ was significant.

associations with major macrovascular events (and their components), heart failure, all-cause mortality, peripheral neuropathy, and all-cause hospitalization (Supplementary Table 1). An absent dorsalis pedis pulse was also associated with an excess risk of major microvascular events, nephropathy, and cognitive decline, whereas an absent posterior tibial pulse was further associated with increased risks for ESRD or renal death and dementia.

At baseline, 1,491 (13%) participants had one or two absent peripheral pulses, and 727 (6%) had three or four absent pulses (Supplementary Fig. 1*B*). The risk of major outcomes increased proportionally with the number of absent peripheral pulses (Fig. 1 and Table 3). Each single absent pulse was associated with increased risks for all outcomes (Supplementary Table 2).

Sensitivity Analyses

Associations between absent peripheral pulses and outcomes were comparable in each randomized study group considered separately (Supplementary Table 3). Furthermore, associations between absent peripheral pulses and outcomes in the three subsets of participants free of *1*) macrovascular disease, *2*) major PAD, or *3*) peripheral neuropathy at baseline were comparable with the results observed in the whole study population (Supplementary Tables 4 and 5). Among 178 (1.6%) participants with a history of chronic ulceration secondary to vascular disease at baseline, 72 (0.7%) had absent peripheral pulses. These few patients with both absent peripheral pulses and chronic ulceration compared with those without these conditions had increased HRs for major macrovascular events, major microvascular events, and all-cause mortality (Supplementary Table 6). These HRs were comparable with those observed with absent peripheral pulses alone, but the associations did not reach the significance threshold due to lack of statistical power. However, significant associations were observed, with higher HRs for retinopathy, heart failure, and hospitalization. Finally, the addition of absent peripheral pulses to the traditional risk factors improved modestly, but significantly, the Harrell C-statistics for the risk of major macrovascular events, heart failure, all-cause mortality, new or worsening peripheral neuropathy, and all-cause hospitalization (Supplementary Table 7).

CONCLUSIONS

This report is the first to our knowledge of the strong and independent associations between absence of peripheral pulses and risk of a range of adverse outcomes in patients with type 2 diabetes. The absence of at least one dorsalis pedis or one posterior tibial pulse compared with the presence of all peripheral pulses was associated with increased 5-year risks for major macrovascular events, myocardial infarction, stroke, cardiovascular death, heart failure, all-cause mortality, major microvascular events, nephropathy, ESRD or renal death, peripheral neuropathy, and all-cause hospitalization. The strongest risks were observed in patients with the greatest number of absent peripheral pulses. The addition of absent peripheral pulses to the traditional risk factors improves the prediction of major macrovascular events, heart failure, all-cause mortality, peripheral neuropathy, and all-cause hospitalization.

Palpation of peripheral pulses is a routine clinical examination recommended in patients with type 2 diabetes, especially those with suspected PAD (20). The procedure is simple, time-saving, noninvasive, and inexpensive, but it has high interobserver variability, depending on foot anatomic variation, clinician experience, and patient examination conditions (21,22). The examination of peripheral pulses also is hampered by the presence of medial arterial calcification, which is common in patients with diabetes (23). This condition leads to incompressible arteries with

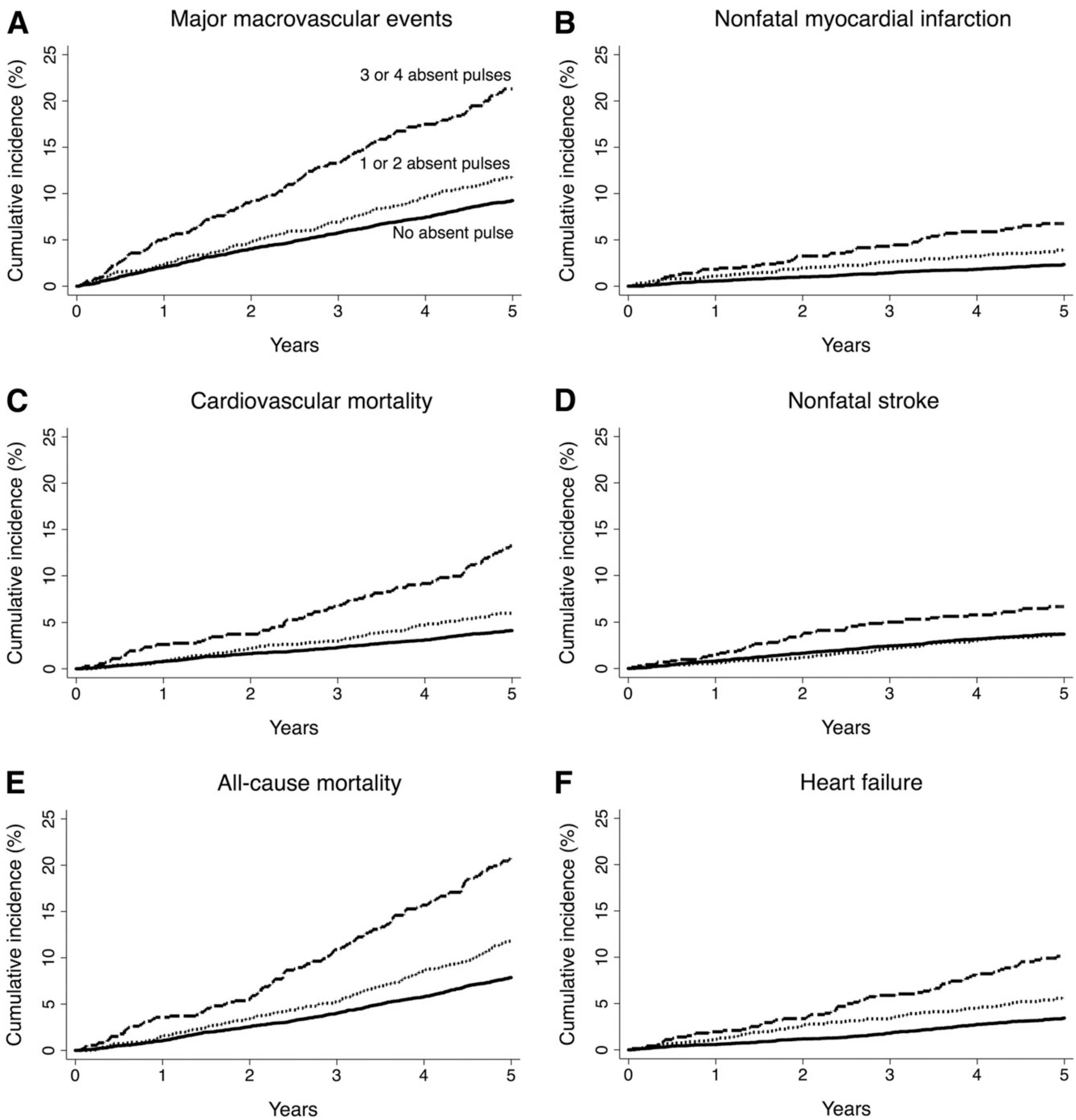

Figure 1—Cumulative incidence of outcomes during follow-up according to the number of absent dorsalis pedis or posterior tibial pulses (left or right side). *A*: Major macrovascular events ($P < 0.0001$). *B*: Nonfatal myocardial infarction ($P < 0.0001$). *C*: Cardiovascular death ($P < 0.0001$). *D*: Nonfatal stroke ($P = 0.0002$). *E*: All-cause mortality ($P < 0.0001$). *F*: Heart failure ($P < 0.0001$).

impalpable peripheral pulses and complicates ABI assessment and interpretation (24). Vascular calcification also may be linked to distal diabetic neuropathy (25). Of note, the associations of absent peripheral pulses with the major outcomes we observed remained significant in patients free of peripheral neuropathy at baseline, suggesting that the findings are most likely to be independent of this condition. Compared with ABI or other noninvasive vascular methods, the pedal pulse examination has a weak performance for the diagnosis of PAD (26–28), especially the dorsalis pedis pulse, which may be absent in healthy subjects without PAD (29). A previous study estimated the sensitivity and specificity of an abnormal dorsalis pedis pulse for the detection of PAD at 50% and 73%, respectively, and at 71% and 91%, respectively, for an abnormal posterior tibial pulse (26). Other studies reported that the sensitivity and specificity of undetectable pedal pulses varied from 5 to 32% and 98 to 99%, respectively (27,28). However, other studies have shown that the careful examination of pulses in unhurried clinical settings and the absence of both dorsalis pedis and posterior tibial pulses may improve the accuracy and reproducibility of pulse examination for the diagnosis of PAD (20,21,30). The scheduled visits in

Table 3—HRs for outcomes during follow-up according to the number of absent peripheral pulses at baseline

	Number of absent peripheral pulses			One or two vs. neither	Three or four vs. neither	
	None (n = 8,902)	One or two (n = 1,491)	Three or four (n = 727)	HR (95% CI)	HR (95% CI)	P value for trend
Primary end points						
Major macrovascular events	810 (9.1)	179 (12.0)	156 (21.5)	1.24 (1.05–1.47)	1.92 (1.59–2.30)	<0.0001
Nonfatal myocardial infarction	201 (2.3)	59 (4.0)	49 (6.7)	1.27 (0.94–1.71)	1.81 (1.29–2.53)	0.0005
Nonfatal stroke	321 (3.6)	54 (3.6)	47 (6.5)	1.28 (0.95–1.73)	2.17 (1.56–3.01)	<0.0001
Cardiovascular death	358 (4.0)	91 (6.1)	92 (12.7)	1.34 (1.06–1.70)	2.07 (1.61–2.66)	<0.0001
Major microvascular events	889 (10.0)	147 (9.9)	94 (12.9)	1.08 (0.90–1.29)	1.36 (1.08–1.70)	0.01
New or worsening nephropathy	389 (4.4)	81 (5.4)	51 (7.0)	1.19 (0.92–1.53)	1.36 (0.99–1.85)	0.03
New or worsening retinopathy	556 (6.3)	75 (5.0)	50 (6.9)	0.99 (0.78–1.28)	1.39 (1.03–1.88)	0.09
Secondary end points						
All-cause death	693 (7.8)	180 (12.1)	154 (21.2)	1.31 (1.10–1.55)	1.81 (1.50–2.18)	<0.0001
Heart failure	295 (3.3)	85 (5.7)	71 (9.8)	1.35 (1.05–1.74)	1.73 (1.31–2.28)	<0.0001
ESRD or renal death	35 (0.4)	14 (0.9)	10 (1.4)	1.95 (0.99–3.81)	2.22 (0.99–4.98)	0.02
New or worsening peripheral neuropathy	3,516 (39.5)	774 (51.9)	364 (50.1)	1.14 (1.05–1.23)	1.11 (0.99–1.24)	0.004
Dementia	76 (0.9)	19 (1.3)	14 (1.9)	1.28 (0.76–2.16)	1.78 (0.98–3.27)	0.05
Cognitive decline	1,398 (15.7)	251 (16.8)	156 (21.5)	1.01 (0.88–1.16)	1.33 (1.12–1.58)	0.008
All hospitalizations	3,648 (41.0)	779 (52.3)	444 (61.1)	1.11 (1.02–1.20)	1.34 (1.21–1.48)	<0.0001

Data are n (%) unless otherwise indicated. HRs computed by Cox proportional hazards survival regression analyses, adjusted as in model 2: sex, age, region of origin, duration of diabetes, BMI, waist circumference, systolic and diastolic blood pressure with and without antihypertensive treatment, HbA$_{1c}$, eGFR, squared eGFR (except for microvascular events), urinary ACR (normoalbuminuria, microalbuminuria, and macroalbuminuria), total and HDL cholesterol, history of ever smoking, use of lipid-lowering and antiplatelet drugs, and study treatments. $P < 0.05$ was significant.

the ADVANCE clinical trial likely were more conducive to detecting absent pulses than conditions in busy outpatient clinics or emergency departments. In this context, we have observed clear associations between the absence of the dorsalis pedis and posterior tibial pulses, either separately or in combination, with major outcomes in patients with type 2 diabetes.

Despite these limitations, the absence of pedal pulses remains a manifestation of PAD (26). We reported recently that the absence of either dorsalis pedis or posterior tibial pulse was an independent risk factor for the incidence of new cases of major PAD during follow-up in ADVANCE participants free of PAD at baseline (31). Of note, the associations of absent peripheral pulses at baseline with increased risk of major outcomes observed in the current study remained significant after exclusion of patients with a history of major PAD at baseline. However, the current study may have underestimated subclinical PAD, which might have contributed to the observed associations of absent peripheral pulses with major outcomes. The associations were also independent of the main cardiovascular risk factors and persisted when participants with prevalent macrovascular disease at baseline were excluded. Furthermore, we observed an association of absent peripheral pulses with a high rate of major heart failure–related events, including worsening, hospitalization, and death. This association is consistent with observations in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study, which reported an association of PAD with a high incidence of heart failure requiring hospitalization, but not fatal heart failure, in patients with type 2 diabetes (32). An absent peripheral pulse was also associated with major microvascular complications, especially renal events and peripheral neuropathy. Furthermore, each additional absent pulse was significantly associated with all outcomes, including retinopathy. Taken together, the current findings suggest that in patients with type 2 diabetes, an absent peripheral pulse may be a strong marker for systemic atherosclerosis, affecting different vascular beds.

The risk of cognitive decline was high in patients with an absent dorsalis pedis pulse, whereas the risk of dementia was increased in those with an absent posterior tibial pulse. Moreover, both outcomes increased in patients with three or four absent peripheral pulses. These observations support previous studies that suggested a role for vascular disease in the neuropathology of cognitive impairment and dementia (33–35). Further investigations are needed to determine whether the absence of peripheral pulse could be used as a marker of cerebrovascular aging.

The current study has several strengths, including the use of a large contemporary trial of 11,120 patients with type 2 diabetes with comprehensive baseline data on clinical parameters as well as prespecified end points during follow-up. The principal limitations were the post hoc nature of the analyses and the use of a clinical trial population, which may not be representative of type 2 diabetes in the general population. However, the main results were consistent in the four groups assigned to the various randomized treatments considered separately and after excluding patients with macrovascular disease, major PAD, or peripheral neuropathy at baseline, suggesting robustness of the findings. Although several adjustments were performed to control for the effects of confounding, we cannot exclude the possibility of residual confounding as part of the explanation for the findings. Differences in conditions of the clinical examination and in the experience of investigators also could have affected the findings.

In conclusion, the absence of peripheral pulses is a strong and independent predictor of risk for major outcomes, especially major macrovascular events, cardiovascular and all-cause mortality, heart failure, and renal events, in patients with type 2 diabetes. These findings should encourage the examination of peripheral pulses to improve the early detection and treatment of vascular complications in patients with type 2 diabetes, especially in areas with limited access to specialized medical centers and technical resources.

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