

**Absence of peripheral pulses and risk of major vascular outcomes in patients with type
2 diabetes**

Running title: Absent peripheral pulses and vascular outcomes

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Word count: abstract (249 words), main text (2422 words), 3 tables, 1 figure, Online-Only
supplemental materials (1 figure and 7 tables).

1 **ABSTRACT**

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

6 **Methods:** Data were derived from 11120 patients with type 2 diabetes in the Action in
7 Diabetes and Vascular Disease: PreterAx and DiamicroN Modified-Release Controlled
8 Evaluation (ADVANCE) study. Absent peripheral pulses at baseline were defined as absence
9 of at least one dorsalis pedis or posterior tibial pulse.

10 **Results:** Absent, compared to present, peripheral pulses (n=2218) were associated with
11 increased 5-year risks for major macrovascular events (HR 1.47, 95%CI 1.28-1.69,
12 p<0.0001), myocardial infarction (1.45 [1.13-1.87], p=0.003), stroke (1.57 [1.23-2.00],
13 p=0.0003), cardiovascular death (1.61 [1.33-1.95], p<0.0001), heart failure (1.49 [1.21-1.84],
14 p=0.0002), all-cause mortality (1.48 [1.29-1.71], p<0.0001), major microvascular events (1.17
15 [1.00-1.36], p=0.04), nephropathy (1.24 [1.00-1.54], p=0.04), end stage renal disease or renal
16 death (2.04 [1.12-3.70], p=0.02), and peripheral neuropathy (1.13 [1.05-1.21], p=0.0008) after
17 multiple adjustment. Participants with absent dorsalis pedis or posterior tibial pulses displayed
18 comparable HRs. Risks increased proportionally with the number of absent peripheral pulses,
19 with the highest risks observed in patients with 3 or 4 absent pulses. Every additional absent
20 pulse increases risk of all outcomes.

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

1 The prevalence of diabetes mellitus continues to increase worldwide with high risk for
2 premature death (1-3). Cardiovascular disease is the leading cause of morbidity and mortality
3 in people with type 2 diabetes (4; 5). Diabetes confers about 1.5 to 3-fold excess risk for a
4 wide range of atherosclerotic diseases such as stroke, myocardial infarction, and peripheral
5 arterial disease (PAD) (4; 6; 7). It is also a leading cause of lower-extremity amputation,
6 severe eye complications, and end stage renal disease (ESRD) (8-10), and confers a
7 substantial clinical and economic load (11-13). Thus, there is a pressing need for early
8 detection of high risk in patients with type 2 diabetes, in order to improve their treatment and
9 prognosis.

10 There is growing evidence that ankle-brachial index (ABI), the ratio of the ankle and brachial
11 systolic blood pressure, is a marker for cardiovascular events and death (14; 15). However,
12 the simpler clinical assessment of the absence of palpable peripheral pulses has not been
13 tested as a predictor of major vascular outcomes. Hence, in the current study, we aimed to
14 investigate whether the absence of a dorsalis pedis or posterior tibial pulse is associated with
15 major macrovascular and microvascular events, mortality and cognitive decline in patients
16 with type 2 diabetes in the Action in Diabetes and Vascular Disease: PreterAx and DiamicroN
17 Modified-Release Controlled Evaluation (ADVANCE) clinical trial.

18 **RESEARCH DESIGN AND METHODS**

19 **Participants**

20 Details on the design and characteristics of participants in ADVANCE have been published
21 previously (16-18). Briefly, 11140 patients with type 2 diabetes at high vascular risk were
22 randomly assigned to a gliclazide (modified release)-based intensive glucose-control
23 regimen, targeted to achieve an HbA1c \leq 6.5%, or to standard glucose control according to
24 local guidelines. Patients were also randomly assigned to a fixed-dose combination of
25 perindopril (4 mg) and indapamide (1.25 mg) or matching placebo. The Institutional Ethics

Committee of each participating centre had approved the study protocol, and all participants had provided written informed consent.

Definition of absent peripheral pulse

Local ADVANCE investigators had been advised to perform a general physical examination of each participants including palpation of right and left dorsalis pedis and posterior tibial pulses, in patients in supine position. Pulse examinations were performed for all participants, except in 20 subjects who were excluded from current analyses. Absence of peripheral pulses at baseline was defined as absence at palpation of at least one left or right dorsalis pedis or posterior tibial pulse.

Study endpoints

Two primary endpoints were pre-specified 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, as compared with the baseline score), dementia (satisfying the criteria in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition), and all-cause hospitalization for 24 hours or more. 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 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.

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. Chi-squared, ANOVA, or Wilcoxon tests were used to compare baseline characteristics of participants with the absence of at least one peripheral pulse (left or right) to 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 (HR), with associated 95% confidence intervals (CI), for the effects (absence versus presence) of peripheral pulses on the various outcomes. Analyses were adjusted for sex, age, region of origin, and study allocations (model 1), and for model 1 plus baseline duration of diabetes, body mass index, waist circumference, systolic and diastolic blood pressure with and without antihypertensive treatment, HbA1c, estimated glomerular filtration rate (eGFR), squared eGFR (except for microvascular events), urinary albumin-creatinine ratio (ACR: normoalbuminuria [<30]; microalbuminuria [$>30 - \leq 300$] and macroalbuminuria [>300 $\mu\text{g}/\text{mg}$]), total-, and HDL-cholesterol, history of ever smoking, and use of lipids lowering and antiplatelet drugs (model 2). We also analysed 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, 1-2 and 3-4, in a similar way but using only model 2. Furthermore, we evaluated the HR of outcomes for each single 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 considered 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 ischaemic attack). Third, patients with major PAD at baseline (defined as lower-extremity amputation of at least one toe, leg or chronic foot ulceration secondary to vascular disease, or history of peripheral revascularisation 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 to those without these conditions. Finally, the Harrell's c-statistics were used to compare receiver operating characteristic (ROC) curves assessed in the survival analyses among 2 models: (1) traditional risk factors (age, sex, systolic blood pressure, antihypertensive treatment, HbA1C, eGFR, urinary ACR, total-, and HDL-cholesterol, history of ever smoking, and study allocations), and (2) similar risk factors plus absent peripheral pulses in patients free at baseline of myocardial infarction, stroke and macroalbuminuria (19). A p value less than 0.05 was considered as significant. Statistical analyses were performed using SAS software, version 9.3 (SAS Institute, www.sas.com), and Stata software version 13 (StataCorp, www.stata.com).

RESULTS

Characteristics of participants at baseline

Among 11120 participants, left and right dorsalis pedis and posterior tibial pulses were absent at baseline in 1135 (10%), 1128 (10%), 1543 (14%), and 1485 (13%) participants, respectively (Online-Only Supplemental Figure 1-A). The absence of at least one peripheral

pulse at baseline was established in 2218 (20%) participants. Participants with the absence of at least one peripheral pulse at baseline, compared to those with presence of all peripheral pulses, were older, more frequently men and from established market economies (Table 1). They had a longer duration of diabetes, higher body mass index, waist circumference, and systolic blood pressure, and lower diastolic blood pressure, HbA1c, eGFR, and serum total and HDL-cholesterol than those with presence of all peripheral pulses. They were also more likely to use antihypertensive, lipids lowering, and antiplatelet drugs, and to have a history of macrovascular disease, PAD, and to have ever smoked (Table 1).

Absent peripheral pulses and risks of adverse outcomes during follow-up

During a median of 5 years follow-up, major macrovascular events, major microvascular events, cardiovascular death, heart failure, and all-cause mortality occurred in 1145 (10%), 1130 (10%), 541 (5%), 451 (41%), and 1027 (9%) participants, respectively. As compared to 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 hospitalisation (Table 2). All these associations except cognitive decline remained significant in multi-adjusted Cox models.

Participants with absent dorsalis pedis or absent posterior tibial pulses displayed similar risks for major macrovascular events and its components, heart failure, all-cause mortality, peripheral neuropathy, and all cause hospitalisation (Online-Only Supplemental Table 1). An absent dorsalis pedis pulse was also associated with high risks for major microvascular events, nephropathy, and cognitive decline, while an absent posterior tibial pulse was further associated with increased risks for ESRD or renal death, and dementia.

At baseline, 1491 (13%) participants had one or two absent peripheral pulses, and 727 (6 %) had three or four absent pulse (Online-Only Supplemental Figure 1-B). The risk for major outcomes increased proportionally with the number of absent peripheral pulses (Figure 1 and Table 3). Each single absent pulse was associated with increased risks for all outcomes (Online-Only Supplemental Table 2).

Sensitivity analyses

Associations between absent peripheral pulses and outcomes were comparable in each randomized study group considered separately (Online-Only Supplemental 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 to the results observed in the whole study population (Online-Only Supplemental Tables 4 and 5). Among 178 (1.6 %) patients 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 at baseline, compared to those without these conditions, had increased HRs for major macrovascular events, major microvascular events, and all-cause mortality (Online-Only Supplemental Table 6). These HRs were comparable to those observed with absent peripheral pulses alone, but the associations did not reach the significant threshold, probably because of a small number of patients with both conditions. However, significant associations were observed with higher HRs for retinopathy, heart failure, and hospitalisation. Finally, the addition of absent peripheral pulses to the traditional risk factors improved modestly, but significantly, the Harrell's C statistics for the risk of major macrovascular events, heart failure, all-cause mortality, new or worsening peripheral neuropathy, and all-cause hospitalisation (Online-Only Supplemental Table 7).

CONCLUSIONS

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

11 Palpation of peripheral pulses is a routine clinical examination, recommended in patients with
12 type 2 diabetes, especially those with suspected PAD (20). It is a simple, timesaving,
13 noninvasive, and inexpensive procedure, but it has a high interobserver variability, depending
14 on foot anatomic variation, clinician experience, and patient examination conditions (21; 22).
15 The examination of peripheral pulses is also hampered by the presence of medial arterial
16 calcification, which is common in patients with diabetes (23). This condition leads to
17 incompressible arteries with impalpable peripheral pulses, and complicates the ABI
18 assessment and interpretation (24). It has been suggested that vascular cacification may be
19 linked to distal diabetic neuropathy (25). Of note, the associations of absent peripheral pulses
20 with major outcomes we have observed remained significant in patients free of peripheral
21 neuropathy at baseline, suggesting that our findings are most likely to be independent of this
22 condition. Compared to ABI or other non-invasive vascular methods, the pedal pulse
23 examination has a weak performance for the diagnosis of PAD (26-28), especially the dorsalis
24 pedis pulse that may be absent in healthy subjects without PAD (29). The sensitivity and
25 specificity of an abnormal dorsalis pedis pulse for the detection of PAD were estimated at

50% and 73%, respectively. They were 71% and 91%, respectively for an abnormal posterior tibial pulse (26). The sensitivity and specificity of the undetectable pedal pulses varied from 5% to 32% and 98 to 99%, respectively (27; 28). However, previous 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 their accuracy and reproducibility on the diagnosis of PAD (20; 21; 30). It is likely that the scheduled visits in the ADVANCE clinical trial were more conducive to detecting absent pulses compared to 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.

The absence of pedal pulses, particularly the posterior tibial pulse, is a manifestation of PAD (26). We have reported recently that the absence of either dorsalis pedis or posterior tibial pulse were independent risk factors for the incidence of new cases of major PAD during follow-up in ADVANCE participants free of PAD at baseline (31). Interestingly, the associations of absent peripheral pulses at baseline with increased risk of major outcomes observed in the present study remained significant after exclusion of patients with a history of major PAD at baseline. However, our study may have underestimated subclinical PAD, which could 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 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 high incidence of heart failure requiring hospitalization, but not fatal heart failure, in patients with

1 type 2 diabetes (32). An absent peripheral pulse was also associated with major microvascular
2 complications, especially renal events and peripheral neuropathy. Furthermore, each
3 additional absent pulse was significantly associated with all outcomes including retinopathy.
4 Taken together, our findings suggest that an absent peripheral pulse may be a strong marker
5 for systemic atherosclerosis, affecting different vascular beds, in patients with type 2 diabetes.
6 Interestingly, the risk for cognitive decline was high in patients with an absent dorsalis pedis
7 pulse, while the risk of dementia was raised in individuals with absent posterior tibial pulse.
8 Moreover, both of these outcomes increased in patients with 3 or 4 absent peripheral pulses.
9 These observations support previous studies suggesting a role for vascular disease in the
10 neuropathology of cognitive impairment and dementia (33-35). Further investigations are
11 needed to determine whether the absence of peripheral pulse could be used as a marker of
12 cerebrovascular aging.

13 The present study has several strengths including the use of a large contemporary trial of
14 11120 patients with type 2 diabetes with comprehensive baseline data on clinical parameters,
15 as well as pre-specified endpoints during follow-up. The principal limitations were the post-
16 hoc nature of our analyses, and the use of a clinical trial population, which may not be
17 representative of type 2 diabetes in the general population. However, the main results were
18 consistent in the four groups assigned to the various randomised treatments considered
19 separately, and after excluding patients with macrovascular disease, major PAD, or peripheral
20 neuropathy at baseline suggesting robustness of our findings. Although several adjustments
21 were performed to reduce confounding effects, we cannot exclude the possibility of residual
22 confounding as part of the explanation for our findings. Differences in conditions of clinical
23 examination and experience of investigators could also bias our findings.

24 In conclusion, the absence of peripheral pulses is a strong and independent predictor of risk
25 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 centres, and technical resources.

ACKNOWLEDGEMENTS

KM was supported by grants from the *Société Francophone du Diabète* (SFD) and the *Association Diabète Risque Vasculaire* (ADRV).

Duality of Interest.

Dr. Mohammedi reports personal fees from Novo-Nordisk, outside the submitted work; Dr. Woodward reports personal fees from Amgen, outside the submitted work; Dr. Harrap reports grants from National Health and Medical Research Council of Australia, grants from The George Institute for Global Health, during the conduct of the study; other from Servier, outside the submitted work; Dr. Patel reports grants from Servier, grants from NHMRC, during the conduct of the study; Dr. Marre reports grants and personal fees from Novo Nordisk, grants and personal fees from Sanofi, grants and personal fees from Eli Lilly, personal fees from Servier, grants and personal fees from Merck Sharp and Dohme, personal fees from Abbott, grants and personal fees from Novartis, personal fees from Astra Zeneca, outside the submitted work; and Dr. Chalmers reports grants from National Health and Medical Research Council of Australia, grants and personal fees from Servier, outside the submitted work. No other potential conflict of interest relevant to this article was reported.

Author contributions. K.M., and J.C. designed the study; K.M. wrote the manuscript with assistance from J.C.; L.Q. reviewed the statistical analyses; M.W., S.Z., S.H., A.P., 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

1 the integrity of the data and the accuracy of the data analysis. All authors approved the current
2 version of the manuscript.

3 **Footnotes**

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

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REFERENCES

1. NCD Risk Factor Collaboration. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet* 2016;387:1513-1530
2. Seshasai SR, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, Whincup PH, Mukamal KJ, Gillum RF, Holme I, Njolstad I, Fletcher A, Nilsson P, Lewington S, Collins R, Gudnason V, Thompson SG, Sattar N, Selvin E, Hu FB, Danesh J: Diabetes mellitus, fasting glucose, and risk of cause-specific death. *The New England journal of medicine* 2011;364:829-841
3. Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, Gudbjornsdottir S, Wedel H, Clements M, Dahlqvist S, Lind M: Excess Mortality among Persons with Type 2 Diabetes. *The New England journal of medicine* 2015;373:1720-1732
4. Almdal T, Scharling H, Jensen JS, Vestergaard H: The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. *Archives of internal medicine* 2004;164:1422-1426
5. Cordero A, Lopez-Palop R, Carrillo P, Moreno-Arribas J, Bertomeu-Gonzalez V, Frutos A, Garcia-Carrilero M, Gunturiz C, Bertomeu-Martinez V: Comparison of Long-Term Mortality for Cardiac Diseases in Patients With Versus Without Diabetes Mellitus. *Am J Cardiol* 2016;117:1088-1094
6. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J: Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;375:2215-2222
7. Howard DP, Banerjee A, Fairhead JF, Hands L, Silver LE, Rothwell PM: Population-Based Study of Incidence, Risk Factors, Outcome, and Prognosis of Ischemic Peripheral Arterial Events: Implications for Prevention. *Circulation* 2015;132:1805-1815
8. Rasmussen BS, Yderstraede KB, Carstensen B, Skov O, Beck-Nielsen H: Substantial reduction in the number of amputations among patients with diabetes: a cohort study over 16 years. *Diabetologia* 2016;59:121-129
9. Williams R, Airey M, Baxter H, Forrester J, Kennedy-Martin T, Girach A: Epidemiology of diabetic retinopathy and macular oedema: a systematic review. *Eye (Lond)* 2004;18:963-983
10. Collins AJ, Foley RN, Chavers B, Gilbertson D, Herzog C, Ishani A, Johansen K, Kasiske BL, Kutner N, Liu J, St Peter W, Guo H, Hu Y, Kats A, Li S, Li S, Maloney J, Roberts T, Skeans M, Snyder J, Solid C, Thompson B, Weinhandl E, Xiong H, Yusuf A, Zaun D, Arko C, Chen SC, Daniels F, Ebben J, Frazier E, Johnson R, Sheets D, Wang X, Forrest B, Berrini D, Constantini E, Everson S, Eggers P, Agodoa L: US Renal Data System 2013 Annual Data Report. *Am J Kidney Dis* 2014;63:A7
11. Caspersen CJ, Thomas GD, Boseman LA, Beckles GL, Albright AL: Aging, diabetes, and the public health system in the United States. *Am J Public Health* 2012;102:1482-1497
12. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo JP, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KM, Nasseri K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA, 3rd, Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De Leon FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA: Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2095-2128

13. Gregg EW, Li Y, Wang J, Burrows NR, Ali MK, Rolka D, Williams DE, Geiss L: Changes in diabetes-related complications in the United States, 1990-2010. *The New England journal of medicine* 2014;370:1514-1523
14. Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, Folsom AR, Hirsch AT, Dramaix M, deBacker G, Wautrecht JC, Kornitzer M, Newman AB, Cushman M, Sutton-Tyrrell K, Fowkes FG, Lee AJ, Price JF, d'Agostino RB, Murabito JM, Norman PE, Jamrozik K, Curb JD, Masaki KH, Rodriguez BL, Dekker JM, Bouter LM, Heine RJ, Nijpels G, Stehouwer CD, Ferrucci L, McDermott MM, Stoffers HE, Hooi JD, Knottnerus JA, Ogren M, Hedblad B, Witteman JC, Breteler MM, Hunink MG, Hofman A, Criqui MH, Langer RD, Fronek A, Hiatt WR, Hamman R, Resnick HE, Guralnik J, McDermott MM: Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA* 2008;300:197-208
15. Abbott JD, Lombardero MS, Barsness GW, Pena-Sing I, Buitron LV, Singh P, Woodhead G, Tardif JC, Kelsey SF: Ankle-brachial index and cardiovascular outcomes in the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial. *Am Heart J* 2012;164:585-590 e584
16. ADVANCE Management Committee. Study rationale and design of ADVANCE: action in diabetes and vascular disease--preterax and diamicron MR controlled evaluation. *Diabetologia* 2001;44:1118-1120
17. Patel A, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, Harrap S, Poulter N, Marre M, Cooper M, Glasziou P, Grobbee DE, Hamet P, Heller S, Liu LS, Mancia G, Mogensen CE, Pan CY, Rodgers A, Williams B: Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007;370:829-840
18. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompont S, de Galan BE, Joshi R, Travert F: Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *The New England journal of medicine* 2008;358:2560-2572
19. Pencina MJ, D'Agostino RB: Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. *Stat Med* 2004;23:2109-2123
20. American Diabetes Association. Peripheral arterial disease in people with diabetes. *Diabetes Care* 2003;26:3333-3341
21. Lundin M, Wiksten JP, Perakyla T, Lindfors O, Savolainen H, Skytta J, Lepantalo M: Distal pulse palpation: is it reliable? *World J Surg* 1999;23:252-255
22. Mowlavi A, Whiteman J, Wilhelmi BJ, Neumeister MW, McLafferty R: Dorsalis pedis arterial pulse: palpation using a bony landmark. *Postgrad Med J* 2002;78:746-747
23. Lehto S, Niskanen L, Suhonen M, Ronnema T, Laakso M: Medial artery calcification. A neglected harbinger of cardiovascular complications in non-insulin-dependent diabetes mellitus. *Arterioscler Thromb Vasc Biol* 1996;16:978-983
24. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, Fowkes FG, Hiatt WR, Jonsson B, Lacroix P, Marin B, McDermott MM, Norgren L, Pande RL, Preux PM, Stoffers HE, Treat-Jacobson D: Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. *Circulation* 2012;126:2890-2909
25. Jeffcoate WJ, Rasmussen LM, Hofbauer LC, Game FL: Medial arterial calcification in diabetes and its relationship to neuropathy. *Diabetologia* 2009;52:2478-2488
26. Criqui MH, Fronek A, Klauber MR, Barrett-Connor E, Gabriel S: The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. *Circulation* 1985;71:516-522
27. Hiatt WR, Marshall JA, Baxter J, Sandoval R, Hildebrandt W, Kahn LR, Hamman RF: Diagnostic methods for peripheral arterial disease in the San Luis Valley Diabetes Study. *J Clin Epidemiol* 1990;43:597-606
28. Collins TC, Suarez-Almazor M, Peterson NJ: An absent pulse is not sensitive for the early detection of peripheral arterial disease. *Fam Med* 2006;38:38-42
29. Silverman JJ: The incidence of palpable dorsalis and pedis and posterior tibial pulsations in soldiers; an analysis of over 1,000 infantry soldiers. *Am Heart J* 1946;32:82-87
30. Armstrong DW, Tobin C, Matangi MF: The accuracy of the physical examination for the detection of lower extremity peripheral arterial disease. *Can J Cardiol* 2010;26:e346-350
31. Mohammadi K, Woodward M, Hirakawa Y, Zoungas S, Williams B, Lisheng L, Rodgers A, Mancia G, Neal B, Harrap S, Marre M, Chalmers J: Microvascular and Macrovascular Disease and Risk for Major Peripheral Arterial Disease in Patients With Type 2 Diabetes. *Diabetes Care* 2016;
32. Dormandy JA, Betteridge DJ, Schernthaner G, Pirags V, Norgren L: Impact of peripheral arterial disease in patients with diabetes--results from PROactive (PROactive 11). *Atherosclerosis* 2009;202:272-281

- 1 33. Roher AE, Tyas SL, Maarouf CL, Dausgs ID, Kokjohn TA, Emmerling MR, Garami Z, Belohlavek M,
2 Sabbagh MN, Sue LI, Beach TG: Intracranial atherosclerosis as a contributing factor to Alzheimer's disease
3 dementia. *Alzheimers Dement* 2011;7:436-444
- 4 34. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL,
5 Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist
6 R, Nilsson PM, Roman GC, Sellke FW, Seshadri S: Vascular contributions to cognitive impairment and
7 dementia: a statement for healthcare professionals from the american heart association/american stroke
8 association. *Stroke* 2011;42:2672-2713
- 9 35. Li JQ, Tan L, Wang HF, Tan MS, Tan L, Xu W, Zhao QF, Wang J, Jiang T, Yu JT: Risk factors for
10 predicting progression from mild cognitive impairment to Alzheimer's disease: a systematic review and meta-
11 analysis of cohort studies. *J Neurol Neurosurg Psychiatry* 2016;87:476-484

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

	Absent peripheral pulse at baseline			
	Overall (n=11120)	No (n=8902)	Yes (n=2218)	p
Male sex, n (%)	6394 (57.5)	5027 (56.5)	1367 (61.6)	<0.0001
Region of origin: Asia, n (%)	4131 (37.1)	3797 (42.7)	334 (15.1)	
Region of origin: Established market economies, n (%)	4862 (43.7)	3348 (37.5)	1514 (68.0)	<0.0001
Region of origin: Eastern Europe, n (%)	2140 (19.2)	1764 (19.8)	376 (16.9)	
Age (years): mean (SD)	65.8 (6.4)	65.3 (6.2)	67.7 (6.7)	<0.0001
Duration of diabetes (years): mean (SD)	7.9 (6.4)	7.8 (6.2)	8.4 (6.8)	<0.0001
Body mass index (kg/m ²): mean (SD)	28.3 (5.2)	28.1 (5.1)	29.5 (5.5)	<0.0001
Waist circumference (cm): mean (SD)	99 (13)	98 (13)	102 (13)	<0.0001
Systolic blood pressure (mmHg): mean (SD)	145 (22)	145 (22)	147 (21)	<0.0001
Diastolic blood pressure (mmHg): mean (SD)	81 (11)	81 (11)	80 (11)	<0.0001
Use of hypertensive treatment, n (%)	7647 (68.8)	6057 (68.0)	1590 (71.7)	0.0009
HbA1c (%): mean (SD)	7.5 (1.6)	7.5 (1.6)	7.4 (1.4)	0.006
HbA1c (mmol/mol): mean (SD)	59 (17)	59 (17)	58 (15)	
eGFR (ml/min/1.73m ²)	74 (18)	75 (17)	71 (18)	<0.0001
Urinary albumin-creatinine ratio (µg/mg): median (Q1, Q3)	15 (7, 40)	15 (7, 39)	15 (7, 42)	0.16
Normoalbuminuria (< 30 µg/mg): n (%)	7365 (66.2)	5938 (66.7)	1427 (64.3)	
Microalbuminuria (≥30–≤300 µg/mg): n (%)	2851 (25.6)	2277 (25.6)	574 (25.9)	0.03
Macroalbuminuria (>300 µg/mg): n (%)	403 (3.6)	304 (3.4)	99 (4.5)	
History of microvascular disease, n (%)	1152 (10.4)	899 (10.1)	253 (11.4)	0.07
Serum total cholesterol (mmol/l): mean (SD)	5.2 (1.2)	5.2 (1.2)	5.0 (1.1)	<0.0001
Serum HDL cholesterol (mmol/l): mean (SD)	1.3 (0.4)	1.3 (0.4)	1.2 (0.3)	<0.0001
Serum triglycerides (mmol/l): median (Q1, Q3)	1.6 (1.2, 2.3)	1.6 (1.2, 2.3)	1.6 (1.2, 2.3)	0.40
Use of lipids lowering drugs, n (%)	3926 (35.3)	2938 (33.0)	988 (44.5)	<0.0001
Use of antiplatelet drugs, n (%)	5191 (46.7)	4032 (45.3)	1159 (52.3)	<0.0001
History of current smoking, n (%)	1681 (15.1)	1326 (14.9)	355 (16.0)	0.19
History of ever smoking, n (%)	4663 (41.9)	3423 (38.5)	1240 (55.9)	<0.0001

History of macrovascular disease, n (%)	3452 (31.0)	2649 (29.8)	803 (36.2)	<0.0001
History of major peripheral arterial disease, n (%)	506 (4.6)	302 (3.4)	204 (9.2)	<0.0001

Comparison of qualitative and quantitative parameters were performed using Chi-square and ANOVA tests, respectively. Wilcoxon test was used for variables with skewed distribution (urinary albumin-creatinine ratio and triglycerides). $p < 0.05$ 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. eGFR, estimated Glomerular Filtration Rate computed by the Chronic Kidney Disease Epidemiology Collaboration equation. History of microvascular disease: macroalbuminuria, retinal photocoagulation therapy, proliferative retinopathy, macular oedema, or blindness. History of macrovascular disease: myocardial infarction, stroke, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, hospital admission for unstable angina or transient ischaemic attack. History of major peripheral arterial disease: 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 requirement for a peripheral revascularisation procedure (surgery, angioplasty or emergency thrombolysis). History of current smoking: cigarettes and pipe.

1 **Table 2. Hazard ratios for outcomes according to absence of at least one peripheral pulse (left or right) at baseline**

	Absent peripheral pulse at baseline		Absent peripheral pulse vs. not					
	No (n=8902)	Yes (n=2218)	HR	Model 1 95% CI	P	HR	Model 2 95% CI	P
Primary end points								
Major macrovascular events, n (%)	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, n (%)	201 (2.3)	108 (4.9)	1.65	1.29 – 2.10	<0.0001	1.45	1.13 – 1.87	0.003
Nonfatal stroke, n (%)	321 (3.6)	101 (4.6)	1.63	1.29 – 2.07	<0.0001	1.57	1.23 – 2.00	0.0003
Cardiovascular death, n (%)	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, n (%)	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, n (%)	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, n (%)	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, n (%)	693 (7.8)	334 (15.1)	1.69	1.48 – 1.95	<0.0001	1.48	1.29 – 1.71	<0.0001
Heart failure, n (%)	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, n (%)	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, n (%)	3516 (39.5)	1138 (51.3)	1.14	1.06 – 1.22	0.0002	1.13	1.05 – 1.21	0.0008
Dementia, n (%)	76 (0.9)	33 (1.5)	1.47	0.96 – 2.27	0.08	1.45	0.93 – 2.25	0.10
Cognitive decline, n (%)	1398 (15.7)	407 (18.4)	1.15	1.03 – 1.30	0.02	1.11	0.99 – 1.25	0.08
All hospitalisations, n (%)	3648 (41.0)	1223 (55.1)	1.27	1.18 – 1.35	<0.0001	1.18	1.10 – 1.26	<0.0001

2 Hazards ratio (HR) computed by Cox proportional hazards survival regression analyses. Model 1: adjusted for sex, age, region of origin, and
3 study treatments; model 2: adjusted for model 1 plus duration of diabetes, body mass index, waist circumference, systolic and diastolic blood
4 pressure with and without antihypertensive treatment, HbA1c, estimated glomerular filtration rate (eGFR), squared eGFR (except for
5 microvascular events), urinary albumin-creatinine ratio (normoalbuminuria, microalbuminuria and macroalbuminuria), total-, and HDL-
6 cholesterol, history of ever smoking, and use of lipid lowering and antiplatelet drugs. P<0.05 was significant.

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1 **Table 3. Hazard ratios for outcomes during follow-up according to the number of absent peripheral pulses at baseline**

	Number of absent peripheral pulse			One or two vs.	Three or four vs.	P for trend
	Nil (n=8902)	One or two (n=1491)	Three or four (n=727)	neither	neither	
				HR (95% CI)	HR (95% CI)	
Primary end points						
Major macrovascular events, n (%)	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, n (%)	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, n (%)	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, n (%)	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, n (%)	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, n (%)	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, n (%)	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, n (%)	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, n (%)	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, n (%)	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, n (%)	3516 (39.5)	774 (51.9)	364 (50.1)	1.14 (1.05 – 1.23)	1.11 (0.99 – 1.24)	0.004
Dementia, n (%)	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, n (%)	1398 (15.7)	251 (16.8)	156 (21.5)	1.01 (0.88 – 1.16)	1.33 (1.12 – 1.58)	0.008
All hospitalisations, n (%)	3648 (41.0)	779 (52.3)	444 (61.1)	1.11 (1.02 – 1.20)	1.34 (1.21 – 1.48)	<0.0001

2 Hazards ratio (HR) computed by Cox proportional hazards survival regression analyses, adjusted as in model 2: sex, age, region of origin,
3 duration of diabetes, body mass index, waist circumference, systolic and diastolic blood pressure with and without antihypertensive treatment,
4 HbA1c, estimated glomerular filtration rate (eGFR), squared eGFR (except for microvascular events), urinary albumin-creatinine ratio
5 (normoalbuminuria, microalbuminuria and macroalbuminuria), total-, and HDL-cholesterol, history of ever smoking, use of lipid lowering and
6 antiplatelet drugs, and study treatments. P<0.05 was significant.

7

LEGENDS OF FIGURE

Figure 1: Cumulative incidence of outcomes during follow-up according to the number of absent dorsalis pedis or posterior tibial pulse (left or right): no absent pulse (solid line), one or two absent pulses (dotted line), and three or four absent pulses (dashed line).

Panel A: major macrovascular events ($p<0.0001$). Panel B: nonfatal myocardial infarction ($p<0.0001$). Panel C: cardiovascular death ($p<0.0001$). Panel D: nonfatal stroke ($p=0.0002$). Panel E: all-cause mortality ($p<0.0001$). Panel F: heart failure ($p<0.0001$).

