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Research: Complications

Arterial stiffness as a risk factor for cardiovascular events and all-cause mortality in people with Type 2 diabetes

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Abstract

Aim To quantify the risk of different non-invasive arterial stiffness measurements with macrovascular disease and all-cause mortality in high-risk people with Type 2 diabetes.

Methods We conducted a prospective cohort study of 1910 people with Type 2 diabetes included in the Second Manifestations of ARTerial disease (SMART) study. Arterial stiffness was assessed by brachial artery pulse pressure, normal range (≥0.9) ankle–brachial index and carotid artery distension. Cox regression was used to evaluate the effects of arterial stiffness on risk of cardiovascular events (composite of myocardial infarction, stroke and vascular mortality) and all-cause mortality.

Results A total of 380 new cardiovascular events and 436 deaths occurred during a median (interquartile range) follow-up of 7.5 (4.1–11.0) years. A 10-mmHg higher brachial pulse pressure was related to higher hazard of cardiovascular events (hazard ratio 1.09, 95% CI 1.02 to 1.16) and all-cause mortality (hazard ratio 1.10, 95% CI 1.03 to 1.16). A 0.1-point lower ankle–brachial index within the normal range was related to a higher hazard of cardiovascular events (hazard ratio 1.13, 95% CI 1.01 to 1.27) and all-cause mortality (hazard ratio 1.17, 95% CI 1.04 to 1.31). A one-unit ($10^{-3}\times kPa^{-1}$) lower carotid artery distensibility coefficient was related to a higher hazard of vascular mortality (hazard ratio 1.04, 95% CI 1.00 to 1.09) and all-cause mortality (hazard ratio 1.04, 95% CI 1.00 to 1.07).

Conclusion Increased arterial stiffness, as measured by either increased pulse pressure, normal-range ankle–brachial index or carotid artery distensibility coefficient, is related to increased hazard of cardiovascular events and all-cause mortality in people with Type 2 diabetes.

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Introduction

Despite significant advances in both understanding and treatment of Type 2 diabetes, people with Type 2 diabetes are still at a markedly increased risk of (cardiovascular) mortality and morbidity [1]. Part of this increased risk is thought to be explained by increased arterial stiffness [2], which is more prevalent in people with Type 2 diabetes than those without diabetes (39% vs 12%)[3] and is possibly caused by advanced glycation endproduct formation with collagen cross-linking, nitric oxide dysregulation and vascular calcification [4–6]. Although arterial stiffness may be a direct consequence of Type 2 diabetes it is more than an epiphenomenon of diabetes and it is most likely directly causal in the development of cardiovascular disease. A possible mechanism by which arterial stiffness may be directly causal is exposure to increased mechanical forces on the vessel wall. There are two kinds of mechanical forces, namely, shear stress and circumferential stress. In blood vessels, shear stress is the frictional force on the intimal layer attributable to blood flow, and circumferential stress is the repeated pressure and stretch as a consequence of each pulse wave [7]. While shear stress mainly affects endothelial cells, circumferential stress is implicated in the development of atherosclerosis and plaque rupture [8]. Circumferential stress has two components, namely, frequency (heart rate) and

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What's new?

- Increased arterial stiffness has been related to microvascular complications in people with Type 2 diabetes; however, there are few published studies on the relationship between arterial stiffness and macrovascular disease specifically in people with Type 2 diabetes.
- The vasculature in people with Type 2 diabetes is characterized by increased arterial stiffness and might partly explain the observed elevated cardiovascular risk in this population.
- Increased arterial stiffness, as measured by brachial pulse pressure, normal range ankle–brachial index and carotid artery distensibility coefficient, is related to increased risk of cardiovascular events and all-cause mortality.

amplitude (pulse pressure). Increased arterial stiffness leads to an increase in systolic blood pressure and decrease in diastolic blood pressure, and thereby an increase in pulse pressure which, in turn, results in increased circumferential stress [9]. Presumably, smaller arteries and bifurcations might be more prone to damage by shear stress and circumferential stress and therefore the consequences of arterial stiffness may differ for arterial beds.

The vasculature in people with Type 2 diabetes is characterized by increased arterial stiffness which is related to microvascular complications [10–13]. There is little in the current literature on the relationship between arterial stiffness and macrovascular disease in people with Type 2 diabetes. A few studies have reported on the higher risk of arterial stiffness, measured by pulse pressure or pulse wave velocity, with regard to cardiovascular events and all-cause mortality in people with Type 2 diabetes [14–17].

The aim of the present study was to quantify the effects of different non-invasive arterial stiffness measurements at different arterial locations on hazard of macrovascular disease and all-cause mortality in high risk people with Type 2 diabetes.

Methods

Study population

The Second Manifestations of ARTerial disease (SMART) study includes an ongoing prospective cohort of patients attending the University Medical Centre Utrecht, The Netherlands. People aged 18–79 years with clinically manifest vascular disease or with important risk factors for atherosclerotic disease (e.g. diabetes, hyperlipidaemia or hypertension), who were newly referred to the University Medical Centre Utrecht, are asked to participate. After inclusion, information is obtained on history of vascular disease (coronary artery disease, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm), other medical history, medication use and cardiovascular risk factors (e.g. smoking, alcohol consumption, physical activity, hypertension, hyperlipidaemia) with the use of questionnaires. The study has been approved by the Medical Ethics Committee of the University Medical Centre Utrecht and informed consent is obtained from all participants. A rationale and detailed description of the SMART study has been previously published [18].

The present study included data from a sample of participants enrolled in SMART with Type 2 diabetes at baseline (n=1910) in whom arterial stiffness was assessed by brachial pulse pressure (n=1910), by normal range (≥0.9) ankle–brachial index (ABI; n=1460) and by measurement of carotid artery distensibility coefficient (n=611).

Arterial stiffness

Arterial stiffness was assessed using three different measures: brachial pulse pressure, ABI within the normal range (≥0.9) and carotid artery distensibility coefficient using ultrasonography.

Pulse pressure was defined as the difference between brachial systolic and diastolic blood pressure. Blood pressure measurements were performed bilaterally at the brachial arteries using an automatic blood pressure monitor (Microlife Watch BP office). After the first measurement, the arm with the highest systolic blood pressure was identified. The average systolic and average diastolic blood pressure was then taken from a further two measurements from the arm with the highest blood pressure [18]. Pulse pressure has been shown to be positively correlated to aortic pulse wave velocity, which is considered to be the reference standard measurement for arterial stiffness [19].

The ABI is the ratio between systolic blood pressure in the ankle and systolic blood pressure in the brachial artery. ABI measurements were performed by experienced technicians at the Vascular Laboratory of the University Medical Centre Utrecht, using a VasoGuard (Imex Medical Systems Inc., Golden, Colorado, USA) 8-MHz Doppler probe for the posterior tibial artery and dorsal pedal artery. The highest systolic blood pressure of these two arteries was then used to compute the ABI by dividing it by the systolic blood pressure at the brachial artery. The average ABI was then taken from the left and right leg. The ABI is a less well established measure of arterial stiffness, but in an asymptomatic population it is inversely associated with the aortic augmentation index, a commonly used marker of arterial stiffness [20]; therefore, participants without peripheral artery disease (ABI ≥0.9) were used for the present analysis. This resulted in 1460 participants available for inclusion in the analysis.

Carotid artery distension is a direct measure of the change in diameter of the carotid artery during systole. The displacement of the artery walls was measured with a Wall Track System (Scanner 200; Pie Medical, Maastricht, The

Netherlands) equipped with a 7.5-MHz linear array transducer and vessel wall moving detector system. A more detailed description of the carotid artery distension and luminal diameter measurements has already been published [21]. To summarize, five measurements were performed separately of the right and left common carotid artery, 2 cm proximal to the origin of the carotid bulb. Each assessment lasted 4 s and consisted of several cardiac cycles. Per measurement, the average distension of the carotid artery during cardiac cycles was taken and the results of the five separate measurements were averaged. Finally, the average of the left and right carotid artery measurement was taken as the distension measurement for a participant.

The distensibility coefficient, which is a distension measure taking into account pulse pressure and diastolic diameter, is defined as (2× distension/end-diastolic diameter)/pulse pressure and is given in $10^{-3}\times kPa^{-1}$ [22]. The ability of an artery to distend due to pressure (compliance) is the inverse of arterial stiffness; thus, decreased distensibility corresponds to increased arterial stiffness. Distensibility measurements were available for 611 participants as the measurements were performed during a limited time period of the SMART study: between 1996 and August 2003.

Follow-up

During follow-up, information on hospitalization and outpatient clinic visits was obtained through biannual questionnaires. In case of a possible event, including death, all available data (hospital discharge letters and other correspondence and investigations including data from the general practitioner) on that particular event, were collected. The available data on the event were then evaluated independently by three members of the SMART study Endpoint Committee.

The primary outcomes for the present study were a composite of major adverse cardiovascular events [consisting of myocardial infarction, stroke and vascular mortality], and all-cause mortality.

Myocardial infarction was defined as at least two of the following: (1) chest pain for at least 20 min, not disappearing after administration of nitrates; (2) ST-elevation > 1 mm in two following leads on ECG or a left bundle branch block; (3) cardiac enzyme elevation (troponin levels above clinical cut-off value or creatinine kinase at least two times the normal value and a myocardial band fraction >5% of the total creatinine kinase. Sudden cardiac death was also considered as myocardial infarction.

Stroke was defined as a definite stroke when relevant clinical features were present for at least 24 h, causing an increase in impairment of at least one grade on the modified ranking scale, accompanied by a new cerebral infarction on computed tomography (CT) or magnetic resonance imaging (MRI). Stroke was defined as probable stroke when relevant clinical features were present for at least 24 h, causing an increase in impairment of at least one grade on the modified ranking scale, but without a new (haemorrhage) cerebral infarction on CT or MRI.

Vascular mortality was defined as death from myocardial infarction, stroke, congestive heart failure, rupture of abdominal aortic aneurysm and vascular death from other causes.

All-cause mortality was defined as death from any cause.

The period between patient inclusion and first cardiovascular event, death, loss to follow-up or the predefined date of March 2015 was defined as the follow-up duration. In total, 140 participants (7.3%) were lost to follow-up as a result of relocation or discontinuation of the study.

Data analyses

The baseline characteristics are presented in quartiles of brachial pulse pressure in order to visualize potential differences in baseline characteristics in participants with different brachial pulse pressure levels.

The association between arterial stiffness and cardiovascular events and all-cause mortality was evaluated by Cox proportional hazard models. Hazard ratios (HRs) and 95% CIs were calculated for brachial pulse pressure as a continuous variable per 10-mmHg increase, ABI as a continuous variable per 0.1-point decrease, and carotid artery distensibility coefficient as a continuous variable per unit ($10^{-3}\times kPa^{-1}$) decrease. The ABI and distension measurements were analysed per decrease instead of increase as a lower value of these measurements corresponds to higher arterial stiffness [20,22–26]. Three models were used. In model 1, the relationship between arterial stiffness and the endpoint of interest was adjusted for age (in years) and sex. In model 2, additional adjustment was performed for diastolic blood pressure. Model 3 was used to adjust for traditional cardiovascular risk factors: estimated GFR (assessed using the Chronic Kidney Disease Epidemiology Collaboration formula), non-HDL cholesterol and current smoking. The confounder variables in the three models were selected by using directed acyclic graphs based on previous information in the literature. The variables are a set of known traditional cardiovascular risk factors, which are also known to be related to arterial stiffness. Adjustment for diastolic blood pressure was chosen above systolic blood pressure or mean arterial pressure, because diastolic blood pressure seems to be the most important determinant of pulse wave velocity (reference measurement method) and augmentation index. Furthermore, because pulse pressure was used as a determinant in the analyses, adjusting for systolic blood pressure would lead to multicollinearity in the model and reduce the precision of the effect estimates. The proportional hazards assumption was visually checked by use of a hazard function plot and showed no signs of violation. The linearity assumption was visually checked by plotting martingale residuals. The plots showed no violation of the linearity

assumption. As missing data and complete case analysis can lead to bias, single imputation by weighted probability matching, using additive regression, bootstrapping and predictive mean matching was used to reduce missing covariate data. Single imputation was performed using the aregImpute function of the package Hmisc as part of the statistical software R. Missing data were imputed for diastolic blood pressure (n=13, 0.7%), kidney function (n=9, 0.5%), non-HDL cholesterol (n=15, 0.8%) and smoking (n=14, 0.8%).

For evaluation of whether the relationship between arterial stiffness and cardiovascular events or all-cause mortality was different for participants with a history of vascular disease, a multiplicative interaction term was included in the Cox models. Effect modification was considered to be present if the P value of the interaction term was <0.05.

The use of blood pressure-lowering medication can influence arterial stiffness and, in turn, the non-invasive measurements used to assess arterial stiffness; therefore the association between arterial stiffness and cardiovascular events or all-cause mortality may be different in participants already using blood pressure-lowering medication. Additional sensitivity analyses were performed to assess whether the results were influenced by the proportion of participants using blood pressure-lowering medication by excluding these participants.

Analyses were performed using statistical package R 3.2.2 and for all analyses a P value <0.05 was considered statistically significant.

Ethics

The study was approved by the Medical Ethics Committee of the University Medical Centre, Utrecht, and informed consent was obtained from all participants.

Results

Baseline characteristics

The mean ABI in the normal range was 1.2 ± 0.1 (range 0.9–1.8) and the mean carotid artery distensibility coefficient was 13.0 ± 6.2 10^{-3} × kPa^{-1} (range 2.2–47.4). The baseline characteristics are presented in quartiles of brachial pulse pressure (Table 1). Over the quartiles of pulse pressure, age and systolic blood pressure increased, while diastolic blood pressure remained the same. Kidney function decreased across the quartiles, while albuminuria

Table 1 Baseline characteristics according to quartiles of brachial pulse pressure

	Total (N=1910)	Q1 (n=343)	Q2 (n=406)	Q3 (n=506)	Q4 (n=656)
Pulse pressure range, mmHg	5–177	15–51	52–61	62–72	73–131
Men, n (%)	1329 (70)	327 (70)	325 (75)	292 (70)	378 (64)
Age, years	61 (54–68)	56 (47–62)	59 (54–66)	63 (56–69)	66 (60–71)
BMI (kg/m^2)	29.0 ± 5	29.3 ± 5.3	29.1 ± 4.7	29.2 ± 5.2	28.3 ± 4.7
Smoking current, n (%)	466 (24)	136 (29)	113 (26)	87 (21)	104 (24)
Pack-years	13 (0–31)	12 (0–28)	14 (1–32)	14 (0–33)	14 (0–33)
Alcohol use, n (%)	867 (45)	204 (44)	219 (50)	193 (46)	169 (39)
Systolic blood pressure, mmHg	145 ± 21	126 ± 11	140 ± 12	150 ± 12	169 ± 18
Diastolic blood pressure, mmHg	83 ± 12	82 ± 10	83 ± 11	83 ± 12	84 ± 13
Duration of diabetes, years	4 (1–10)	2 (0–6)	3 (1–9)	4 (1–10)	5 (1–11)
Medication, n (%)					
Glucose-lowering	1262 (66)	290 (62)	286 (66)	285 (68)	286 (66)
Insulin	455 (24)	98 (21)	98 (23)	106 (25)	108 (25)
Lipid-lowering	1218 (64)	255 (54)	274 (63)	265 (63)	263 (61)
Blood pressure-lowering	1168 (62)	237 (51)	262 (60)	274 (65)	295 (68)
Vascular disease, n (%)					
Coronary artery disease	842 (44)	175 (37)	210 (48)	197 (47)	184 (42)
Cerebrovascular disease	364 (19)	67 (14)	64 (15)	74 (18)	128 (30)
Peripheral artery disease	269 (14)	42 (9)	49 (11)	63 (15)	99 (23)
Abdominal aortic aneurysm	92 (5)	18 (4)	28 (6)	20 (5)	16 (4)
Laboratory measurements					
Glucose, mmol/l	8.7 ± 2.9	8.6 ± 3.2	8.6 ± 2.7	8.8 ± 3.0	9.0 ± 2.8
HbA1c, mmol/mol	54 ± 14	55 ± 16	52 ± 12	54 ± 12	55 ± 12
HbA1c, %	7.1 ± 1.3	7.2 ± 1.5	7.0 ± 1.2	7.1 ± 1.2	7.2 ± 1.2
Estimated GFR, ml/min/1.73 m^2	77.1 ± 22.5	82.6 ± 23.0	79.3 ± 20.8	76.3 ± 20.7	71.7 ± 20.6
Micro-albuminuria, n (%)	417 (23)	90 (19)	94 (22)	108 (26)	132 (30)
Total cholesterol, mmol/l	4.8 ± 1.4	4.8 ± 1.4	4.8 ± 1.5	4.8 ± 1.3	5.0 ± 1.4
HDL cholesterol, mmol/l	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.2 ± 0.3
LDL cholesterol, mmol/l	2.7 ± 1.1	2.8 ± 1.1	2.7 ± 1.0	2.7 ± 1.1	2.9 ± 1.1
Non-HDL cholesterol, mmol/l	3.7 ± 1.4	3.7 ± 1.4	3.7 ± 1.4	3.6 ± 1.3	3.8 ± 1.5
Triglycerides, mmol/l	1.7 (1.2–2.5)	1.7 (1.1–2.5)	1.7 (1.1–2.6)	1.6 (1.2–2.4)	1.7 (1.2–2.5)

Continuous variables are shown as mean ± SD, count variables as n(%), and non-normally distributed variables as median (interquartile range).

increased. Medication use was fairly similar across the quartiles with the exception of blood pressure-lowering treatment, which increased per quartile of brachial pulse pressure.

Association between arterial stiffness and cardiovascular events

A total of 380 new cardiovascular events (composite of MI, stroke, vascular mortality) occurred during a median (interquartile range) follow-up of 7.5 (4.1–11.0) years. A 10-mmHg higher brachial pulse pressure was related to a higher risk of stroke (HR 1.17, 95% CI 1.03 to 1.32), vascular mortality (HR 1.14, 95% CI 1.05 to 1.23) and cardiovascular events (HR 1.09, 95% CI 1.02 to 1.16). A 10-mmHg higher brachial pulse pressure was related to a higher hazard of myocardial infarction, but the association was not statistically significant (HR 1.05, 95% CI 0.95 to 1.15; Table 2).

A 0.1-point lower ABI in the normal range was related to a higher hazard of vascular mortality (HR 1.24, 95% CI 1.06 to 1.46) and cardiovascular events (HR 1.13, 95% CI 1.01 to 1.27). A 0.1-point lower ABI was related to a higher hazard of myocardial infarction and stroke, but this was not statistically significant (HR 1.09, 95% CI 0.92 to 1.28, and HR 1.10, 95% CI 0.88 to 1.38, respectively; Table 3).

A 1-unit lower carotid artery distensibility coefficient was related to a higher hazard of stroke (HR 1.07, 95% CI 1.00 to 1.15) and vascular mortality (HR 1.04, 95% CI 1.00 to 1.09); however, the relationship between a 1-unit lower carotid artery distensibility coefficient and myocardial infarction was inconclusive (HR 0.99, 95% CI 0.95 to 1.04; Table 4). Subgroup analyses did not support effect modification by history of vascular disease (Tables 2, 3 and 4).

Association between arterial stiffness and all-cause mortality

A total of 436 deaths occurred during a median (interquartile range) follow-up of 7.5 (4.1–11.0) years. A 10-mmHg higher brachial pulse pressure was related to higher risk of all-cause mortality (HR 1.10, 95% CI 1.03 to 1.16; Table 2). A 0.1-point lower ABI and a 1-unit lower carotid artery distensibility coefficient were also related to a higher hazard of all-cause mortality (HR 1.17, 95% CI 1.04 to 1.31 and HR 1.04, 95% CI 1.00 to 1.07, respectively; Tables 2 and 3). Again subgroup analyses did not support effect modification by history of vascular disease (Table 2, 3 and 4).

Table 2 Relationship between brachial pulse pressure (mmHg) and vascular events and all-cause mortality (*N*=1910)

	HR*	95% CI	*P* for interaction History of vascular disease
Myocardial infarction (*n*=195)			
Model 1	1.04	(0.95 to 1.14)	
Model 2	1.07	(0.97 to 1.17)	
Model 3	1.05	(0.95 to 1.15)	0.13
Stroke (*n*=97)			
Model 1	1.19	(1.06 to 1.35)†	
Model 2	1.19	(1.06 to 1.35)†	
Model 3	1.17	(1.03 to 1.32)†	0.57
Vascular mortality (*n*=243)			
Model 1	1.14	(1.05 to 1.23)†	
Model 2	1.16	(1.07 to 1.25)†	
Model 3	1.14	(1.05 to 1.23)†	0.88
Composite of major cardiovascular events (*n*=380)			
Model 1	1.09	(1.02 to 1.16)†	
Model 2	1.11	(1.04 to 1.18)†	
Model 3	1.09	(1.02 to 1.16)†	0.90
All-cause mortality (*n*=436)			
Model 1	1.10	(1.04 to 1.17)†	
Model 2	1.12	(1.05 to 1.18)†	
Model 3	1.10	(1.03 to 1.16)†	0.69

HR, hazard ratio. Model 1: age + sex; model 2: model 1 + diastolic blood pressure + BMI; model 3: model 2 + estimated GFR + non-HDL cholesterol + smoking+ pack-years.
*Per 10-mmHg increase in brachial pulse pressure.
†Statistically significant, $P<0.05$.

Table 3 Relationship between normal range ankle–brachial index (≥0.9) and vascular events and all-cause mortality (*N*=1460)

	HR*	95% CI	*P* for interaction History of vascular disease
Myocardial infarction (*n*=122)			
Model 1	1.14	(0.97 to 1.34)	
Model 2	1.14	(0.97 to 1.34)	
Model 3	1.09	(0.92 to 1.28)	0.17
Stroke (*n*=65)			
Model 1	1.13	(0.91 to 1.41)	
Model 2	1.14	(0.91 to 1.42)	
Model 3	1.10	(0.88 to 1.38)	0.74
Vascular mortality (*n*=129)			
Model 1	1.31	(1.12 to 1.54)†	
Model 2	1.32	(1.12 to 1.54)†	
Model 3	1.24	(1.06 to 1.46)†	0.43
Composite of major cardiovascular events (*n*=237)			
Model 1	1.17	(1.04 to 1.31)†	
Model 2	1.17	(1.04 to 1.31)†	
Model 3	1.13	(1.01 to 1.27)†	0.17
All-cause mortality (*n*=254)			
Model 1	1.23	(1.10 to 1.38)†	
Model 2	1.24	(1.10 to 1.38)†	
Model 3	1.17	(1.04 to 1.31)†	0.14

ABI, ankle–brachial index; HR, hazard ratio.
Model 1: age + sex; Model 2: model 1 + diastolic blood pressure + BMI; model 3: model 2 + estimated GFR + non-HDL cholesterol + smoking + pack-years.
*Per 0.1-point decrease in ABI.
†Statistically significant, $P<0.05$.

Table 4 Relationship between carotid artery distensibility coefficient (10^{-3} × kPa^{-1}) and vascular events and all-cause mortality (N=611)

	HR*	95% CI	*P* for interaction History of vascular disease
Myocardial infarction (n=106)			
Model 1	0.99	(0.95 to 1.03)	
Model 2	1.00	(0.96 to 1.05)	
Model 3	0.99	(0.95 to 1.04)	0.68
Stroke (n=51)			
Model 1	1.09	(1.02 to 1.16)†	
Model 2	1.13	(1.01 to 1.16)†	
Model 3	1.07	(1.00 to 1.15)†	0.91
Vascular mortality (n=133)			
Model 1	1.04	(0.99 to 1.09)	
Model 2	1.06	(1.01 to 1.11)†	
Model 3	1.04	(1.00 to 1.09)†	0.76
Composite of major cardiovascular events (n=195)			
Model 1	1.01	(0.98 to 1.04)	
Model 2	1.02	(0.99 to 1.06)	
Model 3	1.01	(0.98 to 1.05)	0.51
All-cause mortality (n=244)			
Model 1	1.04	(1.00 to 1.07)†	
Model 2	1.05	(1.02 to 1.09)†	
Model 3	1.04	(1.00 to 1.07)†	0.99

HR, hazard ratio.
Model 1: age + sex; Model 2: model 1 + diastolic blood pressure + BMI; Model 3: model 2 + estimated GFR + non-HDL cholesterol + smoking + pack-years+ end-diastolic lumen diameter.
*Per 10^{-3} × kPa^{-1} decrease in distensibility coefficient.
†Statistically significant, P<0.05.

Sensitivity analyses excluding participants using blood pressure-lowering medication

The proportion of participants using blood pressure-lowering medication was 77% (n = 1473) and exclusion of these participants resulted in 437 participants (23%) available for additional sensitivity analyses with brachial pulse pressure measurements. In this analysis a 10-mmHg increase was still related to a higher hazard of vascular mortality (HR 1.20, 95% CI 1.06 to 1.37), cardiovascular events (HR 1.12, 95% CI 1.00 to 1.26) and all-cause mortality (HR 1.16, 95% CI 1.06 to 1.28). Although increased brachial pulse pressure did result in a higher hazard of stroke, the association was no longer statistically significant (HR 1.15, 95% CI 0.90 to 1.47; Table S1).

The proportion of participants without blood-pressure-lowering medication and an ABI within the normal range (≥0.9) was 325 (17%) and carotid artery distensibility measurements were only available in 221 participants (11%) without blood pressure-lowering medication. The relationship between a 0.1-unit lower ABI within the normal range and myocardial infarction, stroke, vascular mortality, cardiovascular events or all-cause mortality was inconclusive (Table S1). The relationship between a 1-unit decrease in carotid artery distensibility coefficient and myocardial infarction, stroke, vascular mortality, cardiovascular events or all-cause mortality was also inconclusive (Table S1).

Discussion

Increased arterial stiffness, as measured by brachial pulse pressure, normal range ABI and carotid artery distensibility coefficient, are independently related to higher hazard of cardiovascular events and all-cause mortality in people with Type 2 diabetes with or without clinically manifest vascular disease.

The results of the present study are generally in line with previous studies that found an association between arterial stiffness and cardiovascular events and mortality in people with Type 2 diabetes, although there are slight differences in the study populations and composite endpoints used. In a population-based study [14], similar results were observed, with increased pulse pressure being related to a higher risk of cardiovascular mortality and all-cause mortality. In people with Type 2 diabetes in primary care [15] increased arterial stiffness, as measured by aortic pulse wave velocity, was related to a higher risk of cardiovascular events. The study population consisted of people with Type 2 diabetes without history of myocardial infarction or stroke, and the association between arterial stiffness and cardiovascular events might be different in patients with a history of vascular disease. Atherosclerosis can be the cause of arterial stiffness through impairment of the elastic properties of the arterial wall, but, as stated before, it may also be a consequence of arterial stiffness and these two mechanisms can lead to a vicious circle. The composite endpoint that was used also differed from the present study as it comprised cardiovascular mortality, hospitalization for myocardial infarction and hospitalization for stroke [15]. In people with Type 2 diabetes with either micro- or macrovascular complications, or at least two other modifiable cardiovascular risk factors, higher aortic pulse wave velocity was related to higher risk of cardiovascular events, but not to all-cause mortality [16]. Additional separate analyses showed an increased risk of cardiac events and cerebrovascular peripheral events with an increase in aortic stiffness. In the present study we did not find an association between increased arterial stiffness and myocardial infarction; however, this discrepancy might be attributed to the difference in the definition of cardiac events which did not include new-onset heart failure and myocardial revascularization procedures. Another difference is that the present study did find that increased arterial stiffness, as measured by brachial pulse pressure and carotid artery distensibility coefficient, is a risk factor for all-cause mortality. This difference is probably attributable to low power for analysis on all-cause mortality as the present study included 1910 people with Type 2 diabetes and a total of 436 deaths occurring during follow-up, in contrast to 565 people with Type 2 diabetes with only 72 deaths occurring during follow-

up [16]. The results of the present study are consistent with the results of another study in a random sample of people with Type 2 diabetes from an outpatient clinic, which also found a relationship between increased aortic stiffness and higher risk of all-cause mortality [17].

These findings indicate that increased arterial stiffness in people with Type 2 diabetes may be an important factor in the development of vascular disease and all-cause mortality. The present study shows that arterial stiffness can be used as a target factor in intervention research in order to confirm the causality of these findings and to assess the magnitude of cardiovascular risk reduction. Also these non-invasive techniques, especially brachial pulse pressure, which can be easily derived from regular blood pressure measurements, can be used in future prognostic research in order to assess their usability in identifying people with Type 2 diabetes at higher risk of cardiovascular events and all-cause mortality.

A consequence of increased arterial stiffness is an increase in systolic blood pressure, which supports a blood pressure-driven mechanism in the pathogenesis of arterial stiffness and vascular events; therefore, strict blood pressure control, might be imperative in this subpopulation of people with Type 2 diabetes with increased arterial stiffness. This is supported by the results of the ACCORD blood pressure trial, in which strict blood pressure control did not reduce the composite outcome of cardiovascular events, but did reduce the rate of strokes in people with Type 2 diabetes [27]. Whether specific classes of drugs, such as calcium channel blockers or β-blockers, are more beneficial in people with Type 2 diabetes and arterial stiffness (as a result of a reduction in circumferential stress), however, remains uncertain [28].

Strengths of this cohort study include the large number of people with Type 2 diabetes at high risk, and the follow-up time making it feasible to perform analyses on separate as well as composite endpoints, which were well adjudicated. Another strength is that arterial stiffness was measured and examined by three different techniques at three different locations in the same participant. Smaller arteries and bifurcations might be more prone to damage by arterial stiffness and therefore the consequences may differ by location of affected arteries. Sensitivity analyses showed that brachial pulse pressure was still related to cardiovascular events and all-cause mortality after exclusion of participants using blood pressure-lowering medication. Unfortunately, exclusion of these participants meant that only a small number were available for analyses on normal range ABI and carotid artery distensibility coefficient, which may therefore have led to inconclusive results. Other study limitations that need to be considered include the fact aortic pulse wave velocity measurements, which is considered the reference standard in measuring arterial stiffness, were not available. It should also be noted that only baseline data were available, and risk factor levels may have changed over the course of follow-up.

In conclusion, increased arterial stiffness, as measured by brachial pulse pressure, normal range ABI and carotid artery distensibility coefficient, is independently related to higher risk of cardiovascular events and all-cause mortality in people with Type 2 diabetes.

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Competing interests

None declared.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Sensitivity analyses; exclusion of patients using blood pressure-lowering medication.