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Clinical research

Carotid stiffness and the risk of new vascular events in patients with manifest cardiovascular disease. The SMART study

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Aims To study whether arterial stiffness is related to risk of new vascular events in patients with manifest arterial disease and to examine whether this relation varies between patients who differ with respect to baseline vascular risk, arterial stiffness, or systolic blood pressure (SBP).
Methods and results The study was performed in the first consecutive 2183 patients with manifest arterial disease enrolled in the SMART study (Second Manifestations of ARTerial disease), a cohort study among patients with manifest arterial disease or cardiovascular risk factors. Common carotid distension (i.e. the change in carotid diameter in systole relative to diastole) was measured at baseline by ultrasonography. With the distension, several stiffness parameters were determined. In the entire cohort, none of the carotid artery stiffness parameters was related to the occurrence of vascular events. However, decreased stiffness was related to decreased vascular risk in subjects with low baseline SBP. The relation of carotid stiffness with vascular events did not differ between tertiles of baseline risk and carotid stiffness.
Conclusion Carotid artery stiffness is no independent risk factor for vascular events in patients with manifest arterial disease. However, in patients with low SBP, decreased carotid stiffness may indicate a decreased risk of vascular events.

Introduction

Increased arterial stiffness has been shown to be associated not only with age but also with several other vascular risk factors, especially hypertension and diabetes mellitus.[1] Consequently, it is regarded a summary measure for vascular damage caused by other risk factors. Furthermore, arterial stiffness seems to be a vascular risk factor itself, as it was shown to be independently related to the risk of stroke, myocardial infarction, and cardiovascular death (*Table 1*).[2–11] However, the number of prospective studies on the association of arterial stiffness and vascular disease is limited and mainly confined to individuals with risk factors for vascular disease or to patients with end stage renal disease (ESRD). Whether an association is also present in patients with manifest arterial disease is largely unknown.

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Table 1 Summary of prospective studies examining the relationship between arterial stiffness and vascular events

First author	Arterial stiffness measurement	Clinical events associated with arterial stiffness	FU (years)	Patient details			Unit of stiffness measurement	Adjusted RR (95% CI)	Adjustments[a]
				Type of patient and (*n*)	Age at entry (years)	Male (%)			
Blacher[2]	CCA distensibility	All cause mortality	2.1	ESRD (79)	58	60	Upper vs. three lower quartiles	6.4 (1.8–23.3)	Significant predictors: D, F
Blacher[3]	Aortic PWV	Cardiovascular mortality	6.0	ESRD (241)	51	61	Upper vs. lower tertile	5.9 (2.3–15.5)	Significant predictors: A, D, K
Laurent[4]	Aortic PWV	Cardiovascular mortality	9.3	Hypertension (1980)	50	66	Per 5 m/s increase	1.51 (1.08–2.11)	A, E, I
Boutouyrie[5]	Aortic PWV	Fatal and non-fatal CV event	5.7	Hypertension (1045)	51	64	Upper vs. lower tertile	1.49 (0.82–2.71)	A, B, C, D, F, H, J, L
				Hypertension (697)[b]				3.31 (1.56–7.05)[b]	A, B, C, D, F, H, J, L
Meaume[6]	Aortic PWV	Cardiovascular death	2.5	>70 years (141)	87	30	Per m/s increase	1.19 (1.03–1.37)	C, D, I, J, M, N, O, P, Q
Barenbrock[7]	CCA distensibility	Fatal and non-fatal CV event	7.9	Renal transplant (68)	40	57	Per 10^{-3}/kPa increase	0.79 (not given)[c]	A, B, C, D, F, H, K, L, Q, S, T
	CCA distension						Per μm increase	0.89 (not given)[c]	A, B, C, D, F, H, K, L, Q, S, T
van Dijk[8]	CCA distensibility	All cause mortality	6.6	IGT (140)	66	44	Per 10^{-3}/kPa increase	0.9 (0.5–1.7)	A, B
Stefanadis[9]	Aortic distensibility	Recurrent acute coronary event	3	CAD[d] (54)	55	89	Per $cm^2/dyn.10^{-6}$ increase	0.37 (0.21–0.65)	Significant predictors: none
Laurent[10]	Aortic PWV	Fatal stroke	7.9	Hypertension (1715)	51	59	Per m/s increase	1.39 (1.08–1.72)	Significant predictors: A, H
Shoji[11]	Aortic PWV	Cardiovascular death	5.3	ESRD (265)	55	41	Per m/s increase	1.15 (0.98–1.36)	A, B, C, D, E, F, G, H, P, S, T, U, V

FU, follow-up, RR, relative risk; 95% CI: 95% confidence interval; CCA, common carotid artery; CV, Cardiovascular; IGT, impaired glucose tolerance; CAD, coronary artery disease.

[a]A, age; B, gender; C, systolic blood pressure; D, diastolic blood pressure; E, diabetes mellitus; F, hypercholesterolaemia; G, body mass index; H, smoking; I, history of cardiovascular disease; J, antihypertensive treatment; K, haemoglobin; L, heart rate; M, creatinine clearance; N, autonomy in movement; O, glucose; P, C-reactive protein; Q, nitrate administration; R, end diastolic diameter; S, serum creatinine; T, haemodialysis duration; U, haematocrit; V, serum total protein.

[b]Patients with low vascular risk (first and second tertiles Framingham risk score).

[c]$P < 0.05$.

[d]Patients with hypertension not included.

Furthermore, reported risks associated with increased arterial stiffness differ considerably (*Table 1*). This may be explained by differences in baseline vascular risk, arterial stiffness, or blood pressure. It may be that in individuals at high baseline risk, further increase in risk is not reflected by increasing arterial stiffness, as has been suggested for pulse wave velocity (PWV).[5] Besides, it is possible that arterial stiffness cannot increase beyond a certain limit of maximal stiffness and thus will not be associated with vascular risk in individuals with high baseline arterial stiffness. Finally, blood pressure is an important determinant of arterial stiffness and as change in stiffness may be limited at high blood pressures, baseline blood pressure levels may influence the magnitude and direction of the association.

In this study, we prospectively examined whether carotid artery stiffness is related to the occurrence of cardiovascular events and cardiovascular death in a large cohort of patients with manifest arterial disease, which are referred as part of routine care. Furthermore, we evaluated whether baseline vascular risk, arterial stiffness, and blood pressure modified the relation of arterial stiffness to vascular disease.

Methods

Study population

We used data from patients enrolled in the SMART study (Second Manifestations of ARTerial disease). The SMART study is an ongoing prospective single-centre cohort study in patients with manifest arterial disease or cardiovascular risk factors. Starting from September 1996, consecutive patients aged 18–80, referred to the University Medical Center Utrecht (UMCU) with manifest arterial disease or a cardiovascular risk factor underwent a vascular screening including a questionnaire, blood chemistry, and ultrasonography. Written informed consent was obtained from all participants. The study was approved by the Medical Ethics Committee of the UMCU. The rationale and design of the SMART study have been described in detail elsewhere.[12]

For the current study, the data of the 2476 participants with manifest cardiovascular disease [cerebral, coronary or peripheral artery disease, renal artery stenosis, or aneurysm of the abdominal aorta (AAA)] who were included in SMART before March 1, 2003, were considered. Of 193 participants, stiffness measurements were missing due to equipment failure or logistical problems. Measurements of 94 participants were excluded from the analysis because the intra-individual variance between stiffness measurements was considered out of range. Of six patients, no follow-up information was available. Finally, the data of 2183 participants were used in the analysis.

Vascular screening

Vascular screening was conducted on a single day at the UMCU. Blood samples were collected after an overnight fast. Glucose, total cholesterol, triglycerides, and HDL-cholesterol were measured. LDL-cholesterol was calculated by use of Friedewald's formula. Height and weight were measured without shoes and heavy clothing. Blood pressure was measured in supine position at the right brachial artery every 4 min during the arterial stiffness measurement with a semiautomatic oscillometric device (Omega 1400, Invivo Research Laboratories Inc., Broken Arrow, OK, USA). Medical history, use of current medication, and pack-years smoked were derived from a questionnaire described elsewhere.[12] Common carotid intima-media thickness (CIMT) was measured at the left and right common carotid arteries with an ATL Ultramark 9 (Advanced Technology Laboratories, Bethel, WA, USA) equipped with a 10 MHz linear array transducer as previously described elsewhere.[12] The mean CIMT was calculated in each patient. Duplex scanning of the carotid arteries was performed for assessment of presence of an internal carotid artery stenosis.[12,13]

Carotid artery stiffness

Stiffness was assessed by measurement of distension of the left and right common carotid arteries. The distension of an artery is the change in diameter in systole relative to the diastolic diameter during the cardiac cycle. The displacement of the walls of the left and right common carotid artery 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. After a rest of at least 5 min in supine position, patients were examined in supine position with the head turned $\sim 45^{\circ}$ away from the side examined. The left and right carotid arteries were examined separately. Measurements were performed in the distal common carotid artery 2 cm proximal to the origin of the carotid bulb as described elsewhere.[14] In short, at the right carotid artery, five measurements were performed. Each assessment lasted 4 s and comprised several cardiac cycles. First, the distension of the cardiac cycles within a single measurement was averaged. Next, the results of the five assessments were averaged. A similar procedure was used for the left carotid artery. The mean of the left and right carotid artery measurements was taken as distension measurement for one individual. The same procedure was followed for lumen diameter measurements. An intra-observer variability study on distension and end-diastolic lumen diameter measurements showed a coefficient of variation of 6.2 and 2.1%, respectively. Between observers, the coefficient was 7.3 and 3.5%, respectively.[14]

Adjusted carotid distension was the primary stiffness measure,[15,16] using blood pressure simultaneously measured at the brachial artery at 4 min intervals. In addition, traditional indexes of arterial stiffness were used for comparison. β stiffness index was determined as $\ln(SBP/DBP)/(\Delta D/D_d)$ with SBP indicating systolic blood pressure, DBP indicating diastolic blood pressure, ΔD indicating the mean carotid distension, and D_d indicating end-diastolic diameter. Cross-sectional compliance coefficient (CC) in $mm^2\,kPa^{-1}$ was given as $(\pi \times D_d \times \Delta D)/(2 \times PP)$ with PP indicating pulse pressure ($SBP - DBP$). Distensibility coefficient (DC) in $10^{-3}\,kPa^{-1}$ was $(2 \times \Delta D/D_d)/PP$. Peterson's modulus ($E_P$) in kPa 10^2 was defined as $(PP \times D_d)/\Delta D$. Young's elastic modulus (YEM) in kPa was $(PP \times D_d^2)/(\Delta D \times 2 \times IMT)$. Increasing distension, CC, and DC imply decreasing stiffness. Distensibility is the relative change in diameter and compliance is the absolute change in diameter with pressure. Peterson's (elastic) modulus is the pressure change required for (theoretic) 100% increase in diameter, and Young's modulus is the pressure per square millimetre required for (theoretic) 100% extension.[17]

SMART risk score

To obtain information on baseline vascular risk, the previously developed SMART risk score, which has been previously described, was used.[14] The SMART risk score is based on baseline data of

pre-existing disease and risk factors. Patients receive points for gender, age, body mass index, smoking behaviour, hyperlipidaemia, hyperglycaemia, hypertension, medication use, medical history, and prevalent vascular disease at baseline.

Follow-up

Patients were biannually asked to fill in a questionnaire on hospitalizations and outpatient clinic visits in the preceding 6 months. Events of interest for this study were vascular death, ischaemic stroke, coronary ischaemic disease, and the composite of these vascular events. Definitions have been described previously.[12] When a possible event was recorded by the participant, hospital discharge letters and results of relevant laboratory and radiology examinations were collected. With this information, all events were audited by three members of the SMART study Endpoint Committee comprising physicians from different departments.[12]

Data analysis

Cox proportional hazards analysis was performed to estimate hazard ratios and 95% confidence intervals (CI) for the association of arterial stiffness and the occurrence of cardiovascular events. If a patient had multiple events, the first was used in the analyses. Three models were used. In model I, the unadjusted association of carotid stiffness and cardiovascular events was examined. In model II, age was added. Additional adjustment for the confounders mean arterial pressure (MAP) [$(2 \times \text{DBP} + \text{SBP})/3$], sex, packyears smoked, and use of antihypertensive medication at baseline was performed in model III, because these variables altered the regression coefficient $> 10\%$ after entering the model. The variables diabetes mellitus, body mass index, triglycerides, HDL-cholesterol, LDL-cholesterol, use of lipid-lowering medication, and a carotid artery stenosis of 50–69 or $\geq$70% were not included in the model because these variables did not change the magnitude or the direction of the association. Quadratic terms were entered for continuous variables and remained in the model if statistically significant to adjust optimally and thus reduce residual confounding. The proportional hazards assumption was satisfied based on logminlog plots for tertiles of the stiffness parameters. The linearity assumption was assessed by comparing the estimates of the stiffness parameters in models including the continuous variables as such and models in which the percentile dummies of the continuous variables were included. The linearity assumptions were satisfied.

The primary measure of carotid stiffness was distension divided by the standard deviation of the mean population ($\sim$147 μm), adjusted for MAP.[16] Additionally, analyses were performed for the other indexes of arterial stiffness. First, analyses were conducted for all patients with manifest arterial disease and secondly, for patients with coronary artery disease, cerebrovascular disease, or peripheral arterial disease separately. The number of patients with an AAA was too small for separate analysis. To determine whether the relation between arterial stiffness and vascular disease in all patients was influenced by inclusion of AAA patients, the analysis was additionally performed in patients without an AAA.

To evaluate whether baseline risk (with the SMART score) and SBP were effect modifiers, interaction terms were computed and stratified analyses were performed in tertiles of baseline risk and SBP with a model with all vascular events as outcome in all patients with manifest arterial disease. To examine whether the relation of arterial stiffness with the occurrence of vascular events varies between patients with different levels of arterial stiffness, the relation was studied in tertiles of the stiffness parameters distension and DC.

Finally, for interpretation of the results of the stratified analysis, a linear regression model was constructed to study the distension as a function of SBP. Quadratic terms were entered if statistically significant. To describe the association of SBP and carotid distension independently, adjustments were made for the confounders in model III. The association was graphically displayed, with mean values for the other variables in the SBP model. *P*-values were two-sided and $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of the study population are given in *Table 2*. Mean age was 59.7 and 82% of the patients aged $\geq$50. During a mean follow-up of 2.8 years (range: 0.1–6.5 years), 192 patients experienced a new vascular event, 107 of whom died from a vascular cause. In *Table 3*, the hazard ratios of the relation of different

Table 2 General characteristics of the study population ($n = 2183$)

Men (%)	75
Age (years)	59.7 (10.4)
SBP (mm Hg)	141 (20)
DBP (mm Hg)	79 (10)
MAP (mm Hg)	99 (12)
Triglycerides (mmol/L)	2.0 (1.7)
Total cholesterol (mmol/L)	5.5 (1.1)
HDL-cholesterol (mmol/L)	1.17 (0.34)
Body mass index (kg/m^2)	26.4 (3.7)
Cigarette packyears	22 (20)
Current smoking (%)	35
Ever smoking (%)	81
Diabetes mellitus[a] (%)	15
Carotid artery stenosis >50% (%)	4
Carotid artery stenosis >70% (%)	10
Distension (mm)	0.43 (0.15)
End-diastolic diameter common carotid artery (mm)	8.01 (1.11)
β stiffness index	12.3 (6.2)
DC (kPa$^{-1} \times 10^{-3}$)	14.1 (6.4)
CC (mm^2/kPa)	0.68 (0.29)
Peterson's modulus (kPa $\times 10^2$)	1.78 (0.99)
YEM (kPa $\times 10^3$)	0.78 (0.45)
ACE-inhibitor or AT1-antagonist (%)	20
Alpha-blocking agent (%)	1
Beta-blocking agent (%)	41
Calcium-antagonist (%)	22
Diuretics (%)	12
Lipid-lowering medication (%)	41

ACE-inhibitor, angiotensin converting enzyme inhibitor; AT1-antagonist, angiotensin II-antagonist; DC, distensibility coefficient; CC, compliance coefficient; YEM, Young's elastic modulus. Data are mean (SD) or %.

[a]Glucose lowering medication, fasting glucose $\geq$7.0 mmol/L or non-fasting glucose $\geq$11.1 mmol/L.

Table 3 Relation of carotid stiffness with vascular events

Vascular event (no. of events)	Model	Hazard ratio (95% CI)					
		Distension/SD[a]	β Index	DC	CC	E_P	YEM
All vascular events (192)	I	0.87 (0.75–1.01)	1.03 (1.02–1.05)	0.94 (0.91–0.97)	0.55 (0.31–0.95)	1.24 (1.13–1.38)	1.49 (1.21–1.83)
	II	0.97 (0.85–1.17)	1.01 (0.98–1.03)	0.98 (0.95–1.01)	1.11 (0.63–1.94)	1.07 (0.93–1.22)	1.16 (0.89–1.50)
	III	0.95 (0.79–1.13)	1.01 (0.99–1.03)	0.97 (0.93–1.01)	0.84 (0.43–1.64)	1.07 (0.91–1.25)	1.15 (0.84–1.57)
Vascular death (107)	I	0.74 (0.59–0.91)	1.04 (1.03–1.06)	0.88 (0.84–0.92)	0.29 (0.13–0.66)	1.37 (1.22–1.53)	1.79 (1.44–2.23
	II	0.94 (0.75–1.18)	1.00 (0.98–1.03)	0.96 (0.91–1.01)	1.16 (0.53–2.55)	1.07 (0.91–1.26)	1.26 (0.94–1.69)
	III	0.86 (0.67–1.11)	1.01 (0.98–1.04)	0.94 (0.88–1.00)	1.00 (0.39–2.57)	1.07 (0.87–1.30)	1.29 (0.90–1.86)
Ischaemic stroke (47)	I	1.14 (0.87–1.51)	1.03 (0.99–1.06)	0.95 (0.90–1.00)	0.57 (0.19–1.70)	1.19 (1.04–1.37)	1.17 (0.67–2.02)
	II	1.20 (0.89–1.61)	1.02 (0.98–1.06)	0.95 (0.89–1.02)	0.77 (0.24–2.46)	1.00 (0.83–1.21)	0.96 (0.52–1.87)
	III	1.20 (0.86–1.63)	1.01 (0.96–1.06)	0.98 (0.91–1.05)	0.92 (0.26–3.24)	1.04 (0.75–1.44)	0.75 (0.35–1.62)
Coronary ischaemic event (117)	I	0.86 (0.71–1.05)	1.03 (1.00–1.05)	0.96 (0.92–0.99)	0.66 (0.33–1.32)	1.22 (0.99–1.51)	1.38 (1.03–1.85)
	II	0.99 (0.81–1.23)	1.00 (0.97–1.03)	1.00 (0.96–1.04)	1.28 (0.63–2.59)	1.16 (0.90–1.49)	1.05 (0.72–1.51)
	III	0.92 (0.73–1.16)	1.01 (0.98–1.04)	0.97 (0.92–1.02)	0.69 (0.29–1.64)	1.07 (0.86–1.32)	1.14 (0.74–1.76)

Distension/SD: hazard ratio per standard deviation (~147 μm) increase in distension (μm). DC, distensibility coefficient; CC, compliance coefficient; YEM, Young's elastic modulus; Model I, unadjusted association of carotid stiffness parameter; Model II, Model I additionally adjusted for age; Model III, Model II additionally adjusted for MAP, sex, age^2, packyears smoked, and use of antihypertensive medication at baseline.

[a]In all models adjusted for end-diastolic diameter carotid arteries and MAP.

vascular events with the stiffness parameters are given. Unadjusted, increased distension/SD, DC, and CC (indicating decreased carotid stiffness) were associated with a decreased risk of vascular death, coronary ischaemic events and any vascular event, as were decreased β stiffness index, Peterson's modulus, and Young's modulus (*Table 3*, model I). Relations with the occurrence of ischaemic stroke differed for these parameters. After adjustment for age, the associations disappeared (*Table 3*, model II). Additional adjustment for MAP, sex, age^2, packyears smoked, and use of antihypertensive medication at baseline generally did not further attenuate the relations (*Table 3*, model III). Results were similar when performed in the patients with cerebrovascular, peripheral, or coronary artery disease separately and when performed in the patients with an AAA were excluded (data not shown).

Interaction terms for baseline risk (with the SMART score) and SBP were 0.55 and 0.02, respectively. In the tertile with the lowest SBP, increasing carotid stiffness was associated with a lower risk of vascular events according to most of the stiffness parameters (*Table 4*). In tertiles of baseline risk, distension, and DC, arterial stiffness was not associated with the occurrence of vascular events. In *Figure 1* the cross-sectional relation of carotid distension and SBP is shown.

Discussion

The results of our study show that in patients with manifest arterial disease, increasing arterial stiffness, unadjusted, is associated with an increased risk of vascular events and vascular death (*Table 3*, model I). The relation disappears after adjustment for age (*Table 3*, model II). Thus, in the population as a whole, carotid stiffness is no independent risk factor for the occurrence of vascular events. Moreover, we found that in patients with low SBP, patients with less stiff vessels had a lower vascular risk (*Table 4*).

Before discussing these results in more detail, some methodological aspects need to be addressed. First, we used several parameters of carotid stiffness, most of them ratios of distension, blood pressure, and end-diastolic carotid diameter. As a ratio in a statistical model may obscure the impact of the separate variables, we used carotid distension with adjustment for MAP and end-diastolic carotid diameter separately in the linear regression model as primary measure of carotid stiffness. To determine whether our results could be explained by this approach, the associations of other stiffness parameters and vascular events were evaluated as well, which showed similar results. Secondly, blood pressure was measured at the brachial artery, whereas stiffness measurements were performed at the carotid artery. It is known that the brachial SBP may overestimate the carotid SBP because of changes in amplitude and timing of wave reflections along the arterial tree.[18,19] Adjusting for a blood pressure that is higher than the true carotid blood pressure might lead to an underestimation of the relation of arterial stiffness with vascular

Table 4 Relation of carotid stiffness with vascular events in strata of SBP

	Hazard ratio (95% CI)		
	79–131 mmHg	131–147 mmHg	148–212 mmHg
Distension/SD[a] (μm)	0.67 (0.46–0.98)	0.86 (0.61–1.21)	1.20 (0.94–1.54)
β index	1.06 (1.01–1.10)	1.00 (0.95–1.06)	1.00 (0.97–1.03)
DC ($kPa^{-1} \times 10^{-3}$)	0.92 (0.86–0.98)	0.98 (0.91–1.05)	1.02 (0.94–1.10)
CC (mm^2/kPa)	0.41 (0.14–1.23)	1.59 (0.51–4.94)	1.10 (0.30–4.07)
Peterson's modulus (kPa $\times 10^2$)	1.05 (1.09–2.08)	1.00 (0.67–1.48)	1.01 (0.82–1.24)
YEM (kPa $\times 10^3$)	1.80 (0.78–4.16)	1.18 (0.53–2.63)	1.08 (0.74–1.57)

Distension/SD, hazard ratio per standard deviation (~147 μm) increase in distension. DC, distensibility coefficient; CC, compliance coefficient; YEM, Young's elastic modulus. Adjusted for age, age^2, sex, mean arterial pressure, packyears smoked, and use of antihypertensive medication at baseline. Number of events in strata of SBP: 79–131 mmHg, 43; 131–147 mmHg, 49; 148–212 mmHg, 75.

[a]Additionally adjusted for end-diastolic diameter common carotid artery.

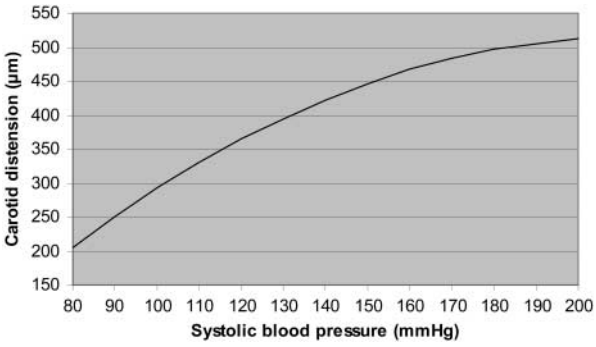

Figure 1. Relation of SBP with carotid distension. Determined with linear regression with distension as a function of SBP, SBP^2, DBP, end-diastolic common carotid diameter, age, age^2, sex, packyears smoked, and use of antihypertensive medication at baseline. Population mean values were used for variables other than SBP.

disease. However, due to decreasing arterial stiffness with increasing age, SPB-amplification is reduced in patients of ≥50 years.[19,20] As all patients with manifest arterial disease probably had relatively stiff arteries and as the majority of the studied population aged ≥50, SBP-amplification is not likely to play an important role. Moreover, we adjusted for MAP and amplification of MAP is less than amplification of SBP.[21] Thirdly, blood pressure was determined at 4 min intervals during the assessment of distension. Possibly, carotid stiffness parameters might have been more precise with simultaneous blood pressure and distension waveforms.[21] Yet, we do not think this would have resulted in materially different findings because blood pressure was measured during the assessment of distension and because assessment of both blood pressure and distension started after a rest of at least 5 min to reduce variability. Furthermore, it was previously shown that timing of blood pressure measurement did not materially influence arterial stiffness values.[22] Finally, results of a study adjusting for both brachial intermittent blood pressure measurement and waveform calibrated PP were similar.[23]

Arterial distension is largely determined by SBP, with the distension increasing as SBP increases.[24] *Figure 1* shows that at high SBP levels, further increase in carotid distension appears to be limited. This may explain our finding that in patients with high SBP no association between carotid stiffness and vascular events is present (*Table 4*). We found no evidence for the hypothesis that the relation of carotid stiffness with vascular events is different according to baseline vascular risk or carotid stiffness.

Up till now, mainly positive relations between arterial stiffness measurements and vascular disease on follow-up were reported, although the magnitude varied considerably (*Table 1*). In our overall patient group, we found no relation between arterial stiffness and vascular events. As published data mainly reported on subjects with risk factors for vascular disease who generally can be considered to have a lower risk than the patients with manifest arterial disease in our study, the different reported relations between arterial stiffness and vascular disease may be explained by an association between arterial stiffness and vascular events in low-risk patients only. However, the observation in studies on patients with ESRD who are known to be at high vascular risk,[25] that arterial stiffness was associated with vascular events,[2,3,11] is not in accordance with this explanation. Moreover, our finding that the association of arterial stiffness and vascular events is not modified by baseline risk does not support this hypothesis either, although opposite findings were observed in a study relating stiffness measured as PWV to vascular events in patients without manifest arterial disease.[5] A second explanation for the differences in reported relative risks may be that different methods of stiffness assessment were used. In most other studies, arterial stiffness was measured as aortic stiffness (*Table 1*), whereas we used carotid distension. Previously, we showed that in patients with manifest arterial disease carotid stiffness is mainly associated with cerebrovascular disease, whereas aortic stiffness may be more closely related to coronary artery disease.[26] As the majority of events in the current study were due to coronary ischaemic disease, this may partly explain the absence of an association with carotid stiffness.

In this study, no relation of arterial stiffness was observed at relatively high levels of SBP. Because in hypertensive patients in the general population, a relation of PWV with vascular events was observed,[4] this may be explained by a different population or by a different technique of assessing arterial stiffness as well. In another study in hypertensive patients, increased arterial stiffness assessed as PWV was associated with vascular events in patients at low vascular risk only;[5] this may imply that effect modification of SBP is only present in patients at high vascular risk.

In conclusion, the findings in this study do not show an association between carotid stiffness and risk of vascular events in patients with manifest arterial disease at large. In patients with low SBP, less stiff arteries may indicate a lower risk of vascular events.

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Appendix

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