Local Stiffness of the Carotid and Femoral Artery Is Associated With Incident Cardiovascular Events and All-Cause Mortality The Hoorn Study

Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 17, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.12.041

Local Stiffness of the Carotid and Femoral Artery Is Associated With Incident Cardiovascular Events and All-Cause Mortality

The Hoorn Study

Thomas T. van Sloten, MD,*†‡ Miranda T. Schram, PhD,*† Katja van den Hurk, PhD,§‖ Jacqueline M. Dekker, PhD,§‖ Giel Nijpels, PhD, MD,§ Ronald M. A. Henry, PhD, MD,*† Coen D. A. Stehouwer, PhD, MD*†

Maastricht and Amsterdam, the Netherlands

Objectives This study sought to investigate the association of local and segmental arterial stiffness with incident cardiovascular events and all-cause mortality.

Background The association of different stiffness indices, in particular of carotid, brachial, and femoral stiffness, with cardiovascular disease and mortality is currently unknown.

Methods In a population-based cohort (n = 579, mean age 67 years, 50% women, 23% with type 2 diabetes [by design]), we assessed local stiffness of carotid, femoral, and brachial arteries (by ultrasonography), carotid-femoral pulse wave velocity (cfPWV), aortic augmentation index, and systemic arterial compliance.

Results After a median follow-up of 7.6 years, 130 participants had a cardiovascular event and 96 had died. The hazard ratios (HRs) (95% confidence intervals [CIs]) per 1 SD for cardiovascular events and all-cause mortality, respectively, were HR: 1.22 (95% CI: 0.95 to 1.56) and 1.51 (95% CI: 1.11 to 2.06) for lower carotid distensibility; HR: 1.19 (95% CI: 1.00 to 1.41) and 1.28 (95% CI: 1.07 to 1.53) for higher carotid elastic modulus; HR: 1.08 (95% CI: 0.88 to 1.31) and 1.43 (95% CI: 1.10 to 1.86) for lower carotid compliance; HR: 1.39 (95% CI: 1.06 to 1.83) and 1.27 (95% CI: 0.90 to 1.79) for lower femoral distensibility; HR: 1.25 (95% CI: 0.96 to 1.63) and 1.47 (95% CI: 1.01 to 2.13) for lower femoral compliance; and HR: 1.56 (95% CI: 1.23 to 1.98) and 1.13 (95% CI: 0.83 to 1.54) for higher cfPWV. These results were adjusted for age, sex, mean arterial pressure, and cardiovascular risk factors. Mutual adjustments for each of the other stiffness indices did not materially change these results. Brachial stiffness, augmentation index, and systemic arterial compliance were not associated with cardiovascular events or mortality.

Conclusions Carotid and femoral stiffness indices are independently associated with incident cardiovascular events and all-cause mortality. The strength of these associations with events may differ per stiffness parameter. (J Am Coll Cardiol 2014;63:1739–47) © 2014 by the American College of Cardiology Foundation

From the *Department of Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands; †Cardiovascular Research Institute Maastricht, Maastricht University Medical Centre, Maastricht, the Netherlands; ‡School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Centre, Maastricht, the Netherlands; §EMGO Institute for Health and Care Research, VU University Medical Centre, Amsterdam, the Netherlands; and the ‖Department of Epidemiology and Biostatistics, VU University Medical Centre, Amsterdam, the Netherlands. The Hoorn Study was supported by grants from the Netherlands Organization for Health Research and Development, the Netherlands Heart Foundation, and the Dutch Diabetes Foundation. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received September 16, 2013; revised manuscript received December 3, 2013, accepted December 3, 2013.

Stiffening of the arterial vasculature leads to increased systolic pressure, decreased coronary perfusion, and an increased pulsatile load on the microcirculation. Thereby,

See page 1748

arterial stiffness can cause stroke, coronary heart disease (CHD), and heart failure (1,2). Stiffness can be measured at different arterial segments or sites and by the use of different techniques. These include segmental carotid-femoral pulse wave velocity (cfPWV); local carotid, femoral,

Abbreviations and Acronyms

Aix = aortic augmentation index
CC = compliance coefficient
cfPWV = carotid-femoral pulse wave velocity
CHD = coronary heart disease
CI = confidence interval
CV = cardiovascular
CVD = cardiovascular disease
DC = distensibility coefficient
DM2 = type 2 diabetes
HR = hazard ratio
IGM = impaired glucose metabolism
PP = pulse pressure
SAC = systemic arterial compliance
YEM = Young's elastic modulus

or brachial artery stiffness; and assessment of systemic arterial compliance (SAC) (1). In addition, aortic augmentation index (Aix) is used as a surrogate for wave reflections (1).

Measurement of arterial stiffness at different sites is important, as stiffness is not uniform along the arterial tree. For example, there are substantial differences in properties between elastic and muscular arteries. Stiffening of elastic and muscular arteries may cause cardiovascular disease (CVD) via different mechanisms (1,2), and, therefore, may be differentially associated with cardiovascular (CV) events and mortality. However, the association of stiffening of different parts of the arterial tree with incident CV events or mortality has not yet been investigated.

Previous studies (3,4) have shown an independent association of cfPWV with incident CVD. cfPWV, however, reflects the properties of a mixed elastic and muscular part of the arterial tree; thus, cfPWV does not discriminate between these segments (1). In contrast, local distensibility measurements of the carotid (a predominantly elastic artery) and the femoral and brachial arteries (predominantly muscular arteries) enable the study of stiffening of elastic and muscular sites (1,2). To date, no study has evaluated the association of local stiffness of the femoral and brachial artery with CV events or mortality, and prospective studies on local carotid stiffness are scarce. Some of these studies reported an association between carotid stiffness and incident CVD (5–7) and/or mortality (7), whereas others did not (8–12). However, most studies (but not all [5]) were relatively small (6,7,11,12) and/or had a relatively short follow-up (<5 years) (7–11). In addition, previous studies (5–8,11,12) used brachial derived pulse pressure (PP) to calculate distensibility coefficients. The use of brachial instead of local PP may underestimate the predictive value of carotid stiffness due to PP amplification (i.e., the increase in PP along the arterial tree) (1,2). The magnitude of amplification, however, diminishes with age (1,2). Consequently, it has been suggested that, in elderly populations (9–12), local stiffness indices calculated with brachial or local PP may yield similar results. This, however, has not yet been investigated.

In view of the above, we investigated the association of, on the one hand, local stiffness of the carotid, brachial, and femoral artery, segmental stiffness of the aorta, Aix, and SAC with, on the other hand, incident CV events and all-cause mortality during a median follow-up of 7.6 years in a population-based study of elderly individuals (the Hoorn study). We additionally investigated whether the associations for local stiffness were different when calibrated local PP instead of brachial PP was used.

Methods

Study design. For the present study, we used data from the 2000 Hoorn study examination (n = 648). The Hoorn study is a population-based cohort study of glucose metabolism and CVD risk among the inhabitants of the municipality of Hoorn in the Netherlands. Details of the study have been described elsewhere (13,14).

Local stiffness indices of the carotid, femoral, and brachial arteries. Carotid, femoral, and brachial arterial properties were determined according to international guidelines (13). A detailed description of the assessment of local arterial stiffness is provided in the Online Appendix. Local arterial stiffness indices were calculated according to the following formulas (15):

- Distensibility coefficient (DC):

$$DC = (2\Delta D \times D + \Delta D^2)/(PP \times D^2) \quad (10^{-3}/kPa)$$

- Young's elastic modulus (YEM) (carotid artery only):

$$YEM = D/(IMT \times DC) \quad (10^3 \times KPa)$$

- Compliance coefficient (CC):

$$CC = \pi \times (2D \times \Delta D + \Delta D^2)/4PP \quad (mm^2/kPa)$$

Where D is arterial diameter, ΔD is distension, IMT is intima-media thickness, and PP is brachial pulse pressure (calculated as systolic minus diastolic blood pressure). DC represents arterial stiffness, YEM represents the stiffness of the arterial wall material at operating pressure, and CC represents arterial buffering capacity.

cfPWV, Aix, and SAC. cfPWV, that is, the ratio of travelled distance divided by transit time, was estimated using body height (to estimate the travel distance [16]) and continuous measurement of the distension curves of the carotid and femoral arteries (to estimate transit time [14]). The Aix was determined by radial applanation tonometry (Sphygmocor, Atcor Medical, Sydney, Australia) (1,14). SAC was determined according to 2 methods: the exponential decay method based on the Windkessel method, and the ratio of stroke volume to aortic pulse pressure (14). A detailed description of the assessment of cfPWV, Aix, and SAC is provided in the Online Appendix.

Other measurements. CVD risk factors were assessed as described previously (13,14). Physical activity was assessed by questionnaire (17).

Follow-up. Follow-up was complete as of January 1, 2009. Information on morbidity was extracted from individuals' medical records from their general practitioners and from

the local hospital, and was classified according to the International Classification of Disease-9th edition (ICD-9).

We defined incident CV events (nonfatal and fatal combined) as ICD-9 codes: 410 to 414 (CHD), 427 and 428 (heart failure), 431 to 438 (cerebrovascular disease), 440 to 443 (arterial disease), 798 (sudden death), and ICD-9 clinical modification code 36 (coronary arterial procedures).

Data on the participants' vital status were collected from the municipal population register of Hoorn. The cause of death was extracted from the medical records from the general practitioners and the hospital of Hoorn. Information on cause of death could not be obtained for 21 (22%) deceased participants.

Statistical analysis. All analyses were performed with PASW Statistics (Version 21.0, IBM, Chicago, Illinois). Characteristics of the study population at baseline were compared between participants with and without incident CV events and between those who did and did not survive with the use of the Student *t* test or Mann-Whitney *U* test for continuous variables and a chi-square test for discrete variables. Cox proportional hazard models were used to estimate the associations between, on the one hand, arterial stiffness indices and, on the other hand, incident CV events and all-cause mortality. The associations were first adjusted for the stratification variables of the Hoorn study cohort: age, sex, and glucose metabolism (13) (model 1); additionally for mean arterial pressure (MAP) (model 2); and for CVD risk factors: prior CVD, body mass index, triglycerides, total/high-density lipoprotein cholesterol, estimated glomerular filtration rate, (micro)albuminuria, physical activity, and smoking habits (model 3). cfPWV, Aix, and SAC were additionally adjusted for heart rate. Finally, mutual adjustments were made for each of the individual stiffness indices. The associations are given as standardized hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). We used interaction terms to explore whether any association differed according to sex, prior CVD, and/or glucose metabolism status (13,18).

We tested 12 hypotheses (i.e., whether, on the one hand, local carotid, femoral, and brachial stiffness, cfPWV, Aix, and SAC are associated with, on the other hand, CV events and mortality), each at the 0.05 level. All other tests (i.e., interactions and additional analyses) were considered to be hypothesis generating and were also conducted at the 0.05 or, for interaction analyses, 0.10 level.

Results

Study population. For the present analyses, all participants were included in whom data were available on the carotid, femoral, or brachial stiffness indices, cfPWV, Aix, or SAC. Figure 1 shows the number of participants per stiffness measurement. The main reason for missing data on local stiffness indices was poor definition of the arterial wall due to obesity (the body mass index of those with qualitatively sufficient examinations versus those without was 26.4 ± 3.1 kg/m^2 vs. 30.4 ± 5.2 kg/m^2). Missing data on Aix and SAC was due to device availability, which was not related to the clinical status of the participants. Missing data on cfPWV was due to technical reasons (i.e., no qualitatively acceptable distension curve available for both the carotid and femoral artery), as well as due to later addition of the (automatic) calculation of carotid-femoral transit time to the vascular ultrasound protocol than the local stiffness measurements.

Participants were excluded when data on glucose metabolism status (n = 10) or follow-up were missing. CV event follow-up was missing for 46 participants either because they had moved out of the town of Hoorn and could not be contacted (n = 7) or because they had not given permission to access their medical files (n = 39). Individuals without follow-up data did not differ from the study population (data not shown). None of the participants were lost to follow-up for all-cause mortality.

Clinical characteristics. Table 1 shows baseline characteristics of the study population according to CV event and mortality status. A total of 130 participants had a CV event (nonfatal and fatal combined) (median follow-up 7.6 years [range 0.2 to 8.9 years]), of whom 40 had a cerebrovascular event, 58 had a CHD event (7 persons had both a cerebrovascular and a CHD event), and 39 had a CV event other than a cerebrovascular or CHD event (e.g., peripheral arterial disease or heart failure). In addition, 96 participants died (median follow-up 7.8 years [range 0.2 to 8.9 years]), of whom 22 (23%) died of a CVD, 31 (32%) of cancer, 22 (23%) of other causes, and 21 (22%) of causes unknown. The incidence rates per year were 3.1% for CV events, 1.4% for CHD events, 1.0% for cerebrovascular events, and 2.1% for all-cause mortality.

Local arterial stiffness indices and incident CV events. Figure 2 shows Kaplan-Meier curves for incident CV events according to tertiles of the carotid (Fig. 2A) and femoral DC (Fig. 2B). Cox regression analyses adjusted for age, sex, and glucose metabolism showed that lower carotid DC, higher YEM, and lower femoral DC and CC were associated with a higher CV event incidence (model 1) (Table 2). The carotid CC and the brachial DC and CC were not associated with incident CV events (model 1) (Table 2). Further adjustments for MAP (model 2) and CVD risk factors (model 3) did not materially change the associations between YEM and femoral DC, on the one hand, and incident CV events, on the other, whereas the association was attenuated for the carotid DC and the femoral CC. In addition, the associations between the carotid, femoral, and brachial DC or CC and incident CV events did not materially change after mutual adjustments for each of the other stiffness indices (for adjustments for cfPWV, see Online Table S1).

Local arterial stiffness indices and all-cause mortality. Figure 2 shows Kaplan-Meier curves for all-cause mortality according to tertiles of the carotid (Fig. 2C) and femoral DC (Fig. 2D). Cox regression analyses adjusted for age, sex, and glucose metabolism showed that lower carotid

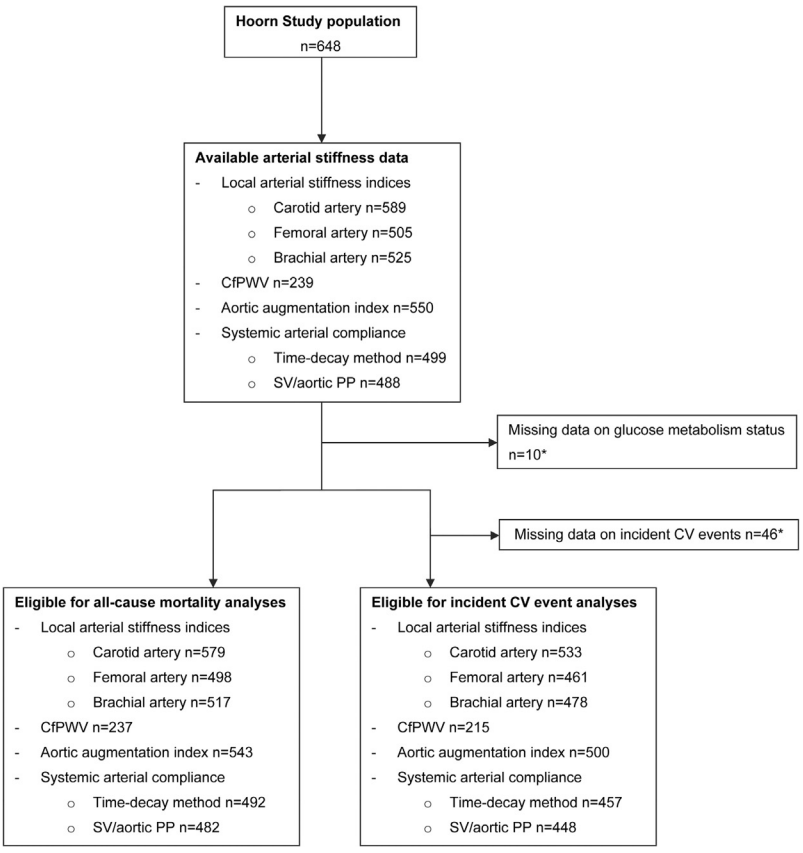

Figure 1 Flow Diagram of the Study

*Number varies per measurement; the maximum number of missing values is indicated. cfPWV = carotid-femoral pulse wave velocity, CV = cardiovascular; PP = pulse pressure; SV = stroke volume.

DC and CC, higher YEM, and lower femoral DC and CC were associated with greater all-cause mortality (model 1) (Table 2). Brachial DC and CC were not associated with all-cause mortality (model 1) (Table 2). Further adjustments for MAP (model 2) and CVD risk factors (model 3) did not materially change the associations between carotid DC, CC, and YEM and all-cause mortality, whereas the association was attenuated for femoral DC and CC. In addition, the associations between the carotid, femoral, and brachial DC or CC and all-cause mortality did not materially change after mutual adjustments for each of the other stiffness indices (for adjustments for cfPWV, see Online Table S1).

cfPWV, incident CV events, and all-cause mortality. Higher cfPWV was associated with a higher CV event incidence (models 1 to 3) (Table 3). In addition, the association between cfPWV and incident CV events did not materially change after adjustments for each of the other stiffness indices (data not shown). cfPWV was not significantly associated with all-cause mortality (models 1 to 3) (Table 3).

Aix, SAC, and incident CV events and all-cause mortality. Aix and SAC, either determined via the time-decay method or by the stroke volume to aortic PP ratio, were not associated with CV events or all-cause mortality (models 1 to 3) (Table 3).

Additional analyses. Analyses were repeated with distension waveform-calibrated local PP (19) in a subsample of the study population (data on carotid and femoral PP were not available in 68 and 8 participants, respectively). The results of these analyses (Online Table S2) were qualitatively similar to the results that used brachial PP.

We additionally adjusted all analyses for systolic pressure (SP) and PP instead of MAP and for IMT. After these adjustments, results did not materially change (Online Table S3). In addition, further adjustments for the use of antihypertensive and/or lipid-lowering medication did not materially change the results (data not shown).

Analyses with specific cerebrovascular and CHD events did not show statistically significant associations (Online Table S4). When we analyzed the association between arterial stiffness indices and CV events, defined as ICD-9 codes 390 to 459 and 798, results did not materially change (data not shown).

Table 1 Clinical Characteristics of the Study Population at Baseline According to Incident CV Event and Mortality Status*

	Participants Without Incident CV Event (n = 403 [75.6%])	Participants With Incident CV Event (n = 130 [24.4%])	p Value for Difference With vs. Without CV Event	Survivors (n = 483 [83.4%])	Deceased (n = 96 [16.6%])	p Value for Difference Survivors vs. Deceased
General characteristics						
Women	54.8	35.4	<0.001	53.4	36.5	0.003
Age, yrs	69.0 ± 6.4	71.9 ± 6.2	<0.001	68.9 ± 6.0	73.3 ± 6.9	<0.001
Smoking habits						
Current smoker	11.7	22.3	<0.001	13.7	20.8	0.01
Former smoker	44.3	51.5	0.004	44.2	51.0	0.03
Nonsmoker	44.0	26.2	Ref	42.1	28.1	Ref
Physical activity, MET h/week	82 (47–127)	69 (41–125)	0.29	82 (50–130)	69 (30–121)	0.20
Prior cardiovascular disease	47.0	63.8	0.001	49.1	60.9	0.08
Glucose metabolism status						
Type 2 diabetes mellitus	22.1	25.8	0.12	19.7	39.6	<0.001
Impaired glucose metabolism	27.5	34.8	0.07	29.0	29.2	0.08
Normal glucose metabolism	50.4	39.4	Ref	51.3	31.3	Ref
Body mass index, kg/m^2	27.0 ± 3.6	27.0 ± 3.4	0.99	27.0 ± 3.6	27.2 ± 3.5	0.57
Systolic blood pressure, mm Hg	140 ± 20	148 ± 21	<0.001	141 ± 20	147 ± 21	0.008
Diastolic blood pressure, mm Hg	82 ± 11	83 ± 12	0.51	83 ± 11	83 ± 12	0.93
Hypertension	62.9	80.6	<0.001	65.1	77.9	0.02
HbA_{1c}, mmol/mol	42 ± 8	44 ± 8	0.005	41 ± 7	46 ± 9	<0.001
HbA_{1c}, %	5.9 ± 0.7	6.2 ± 0.8	0.005	5.9 ± 0.7	6.3 ± 0.9	<0.001
Total cholesterol, mmol/l	5.7 ± 1.0	5.7 ± 1.1	0.57	5.8 ± 1.4	5.6 ± 1.0	0.17
LDL cholesterol, mmol/l	3.6 ± 0.9	3.7 ± 0.9	0.69	3.7 ± 0.9	3.6 ± 0.9	0.51
HDL cholesterol, mmol/l	1.5 ± 0.4	1.3 ± 0.4	<0.001	1.5 ± 0.4	1.3 ± 0.4	0.50
Triglycerides, mmol/l	1.2 (0.9–1.7)	1.4 (1.1–1.8)	0.09	1.3 (1.0–1.7)	1.5 (1.1–1.9)	0.12
Estimated glomerular filtration rate, ml/min/1.73 m^2	62.5 ± 10.3	60.4 ± 11.6	0.06	63 ± 10.0	59 ± 12.5	0.008
Microalbuminuria (albumin/creatinine ratio >2 mg/mmol)	11.4	21.7	0.004	11.6	26.0	0.37
Lipid-lowering medication	14.4	20.0	0.16	15.6	16.7	0.79
Anti-hypertensive medication	31.3	46.9	0.001	34.9	46.9	0.005
Arterial stiffness indices						
Carotid artery						
Distensibility coefficient, 10^{-3}/kPa	11.2 ± 4.2	9.7 ± 4.0	0.001	11.3 ± 4.1	8.6 ± 3.8	<0.001
Young's elastic modulus, 10^3 × kPa	0.98 ± 0.46	1.20 ± 0.84	0.001	0.96 ± 0.46	1.36 ± 0.89	<0.001
Compliance coefficient, mm^2/kPa	0.53 ± 0.21	0.52 ± 0.23	0.72	0.54 ± 0.22	0.45 ± 0.17	<0.001
Femoral artery						
Distensibility coefficient, 10^{-3}/kPa	5.4 ± 2.4	4.4 ± 1.8	<0.001	5.3 ± 2.4	4.1 ± 2.0	<0.001
Compliance coefficient, mm^2/kPa	0.43 ± 0.22	0.37 ± 0.17	0.008	0.43 ± 0.21	0.32 ± 0.17	<0.001
Brachial artery						
Distensibility coefficient, 10^{-3}/kPa	7.9 ± 4.3	7.9 ± 4.2	0.90	7.9 ± 4.2	7.4 ± 4.1	0.26
Compliance coefficient, mm^2/kPa	0.13 ± 0.07	0.14 ± 0.08	0.02	0.13 ± 0.07	0.13 ± 0.07	0.65
Carotid-femoral PWV, m/s	10.0 ± 3.5	12.4 ± 5.9	<0.001	9.7 ± 3.5	12.4 ± 6.0	0.03
Aortic augmentation index, % point	32 ± 9	33 ± 9	0.39	32 ± 9	33 ± 9	0.25
Systemic arterial compliance, ml/mm Hg						
Time-decay method	0.74 ± 0.31	0.71 ± 0.33	0.52	0.74 ± 0.31	0.66 ± 0.33	0.05
SV/aortic PP	1.07 ± 0.35	1.02 ± 0.36	0.22	1.07 ± 0.34	0.97 ± 0.36	0.03

Values are %, mean ± SD, or median (interquartile range). *Numbers correspond with the number of participants with available carotid artery ultrasound data.

CV = cardiovascular; HbA_{1c} = glycosylated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MET = metabolic equivalent of task; PP = pulse pressure; PWV = pulse wave velocity; SV = stroke volume.

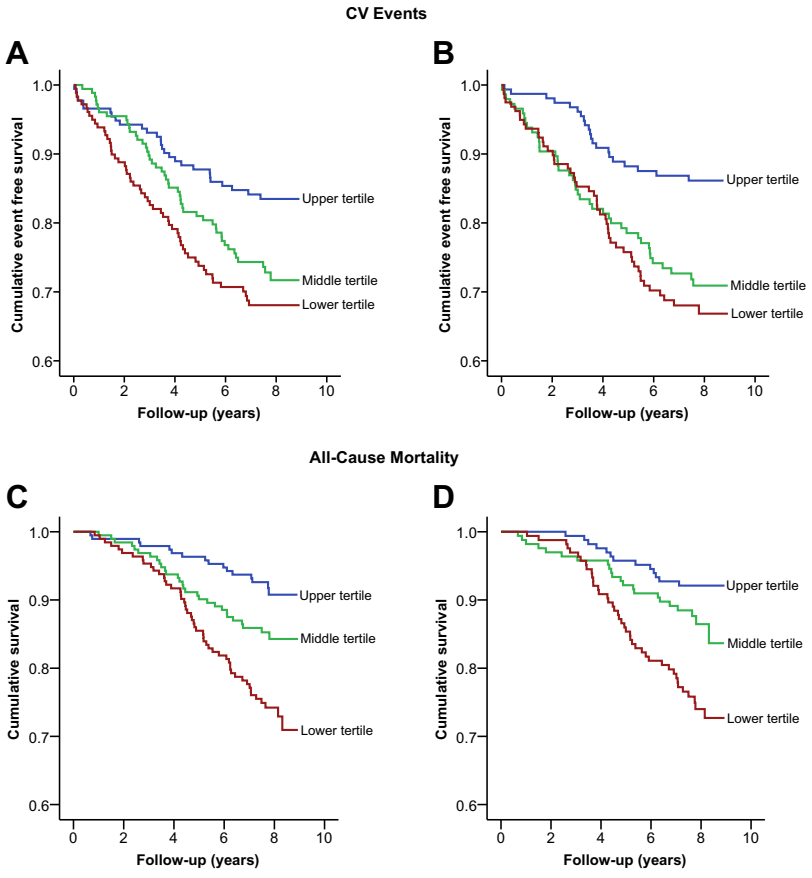

Figure 2 Kaplan-Meier Curves for Incident CV Events and All-Cause Mortality

Kaplan-Meier curves for incident cardiovascular (CV) events and all-cause mortality according to tertiles of distensibility coefficients (DCs) of the carotid **(A and C)** and femoral arteries **(B and D)**.

The elastance wall thickness product of the carotid artery was significantly associated with incident CV events and all-cause mortality (Online Table S5).

Finally, associations of the stiffness indices with incident CV events and all-cause mortality may differ according to sex, presence of prior CVD, or glucose metabolism status (13,18). We found no such interactions (p for interactions >0.10), except for the associations between brachial CC with CV events. A significant association was present between lower brachial CC and incident CVD in persons with prior CVD (HR per 1 SD: 0.78 [95% CI: 0.64 to 0.94]), but not in persons without prior CVD (HR: 0.90 [95% CI: 0.64 to 1.26]) (p for interaction = 0.07), after adjustment for all potential confounders. In addition, significant associations between lower brachial DC and CC and incident CV events were present in persons with impaired glucose metabolism (IGM) (HR: 0.68 [95% CI: 0.50 to 0.93] and 0.69 [95% CI: 0.51 to 0.93], respectively), and in persons with type 2 diabetes (DM2) (HR: 0.68 [95% CI: 0.43 to 1.09] and 0.53 [95% CI: 0.33 to 0.84], respectively), but not in persons with normal glucose tolerance (NGM) (HR: 0.94 [95% CI: 0.67 to 1.32] and 0.93 [95% CI: 0.70 to 1.24], respectively) (p for interactions <0.10), after adjustment for all potential confounders.

Discussion

Main findings. This population-based study is the first to show an association between local stiffness of both the carotid and femoral arteries and incident CV events and all-cause mortality. These associations were independent of age, sex, blood pressure, glucose metabolism, and CVD risk factors. Furthermore, the associations between carotid and femoral stiffness indices and incident CV events and mortality did not materially change after adjustments for each of the other stiffness indices. In addition, cfPWV was associated with a higher CV event incidence, but not with all-cause mortality, whereas Aix, SAC, and brachial stiffness were not associated with either incident CV events or mortality.

Our study is in accordance with previous studies that showed an association between cfPWV and CV events (3,4); therefore, cfPWV can be regarded as an internal

Table 2 Associations of Arterial Stiffness Indices of the Carotid, Femoral, and Brachial Arteries With Incident CV Events and All-Cause Mortality

Model	Carotid Artery			Femoral Artery		Brachial Artery	
	DC	YEM	CC	DC	CC	DC	CC
Incident Cardiovascular Events							
1	1.27 (1.02–1.57)	1.22 (1.04–1.42)	1.07 (0.88–1.30)	1.39 (1.07–1.81)	1.29 (0.99–1.67)	0.90 (0.74–1.08)	0.84 (0.71–1.01)
2	1.24 (0.98–1.58)	1.20 (1.02–1.42)	1.04 (0.86–1.28)	1.37 (1.04–1.80)	1.26 (0.97–1.65)	0.87 (0.72–1.06)	0.84 (0.70–1.00)
3	1.22 (0.95–1.56)	1.19 (1.00–1.41)	1.08 (0.88–1.31)	1.39 (1.06–1.83)	1.25 (0.96–1.63)	0.88 (0.72–1.07)	0.85 (0.71–1.02)
All-Cause Mortality							
1	1.62 (1.24–2.13)	1.33 (1.15–1.55)	1.50 (1.16–1.95)	1.35 (0.97–1.88)	1.59 (1.11–2.28)	0.98 (0.77–1.25)	1.06 (0.84–1.33)
2	1.52 (1.13–2.05)	1.27 (1.08–1.50)	1.41 (1.08–1.84)	1.27 (0.90–1.78)	1.52 (1.06–2.19)	0.92 (0.72–1.17)	1.02 (0.82–1.28)
3	1.51 (1.11–2.06)	1.28 (1.07–1.53)	1.43 (1.10–1.86)	1.27 (0.90–1.79)	1.47 (1.01–2.13)	0.90 (0.70–1.15)	0.99 (0.78–1.25)

Values are hazard ratio (95% confidence interval). Hazard ratios are indicated per 1 SD lower distensibility (DC) and compliance coefficient (CC) and per 1 SD higher Young's elastic modulus (YEM). Model 1: adjusted for age, sex, and glucose metabolism status. Model 2: model 1 plus mean arterial pressure. Model 3: model 2 plus prior cardiovascular disease, body mass index, triglycerides, total/HDL cholesterol ratio, estimated glomerular filtration rate, microalbuminuria, physical activity, and smoking habits. The number of participants and events available for analysis with incident CV events/all-cause mortality for carotid DC, CC, and YEM: 533 (130 events)/579 (96 events); for femoral DC and CC: 461 (111 events)/498 (77 events); and for brachial DC and CC: 478 (116 events)/517 (81 events).

Abbreviations as in Table 1.

validation marker of the present study. In addition, the present study extends these findings as it shows that local carotid and femoral stiffness is also independently associated with incident CV events and mortality. Advantages of the present study are the comprehensive assessment of multiple stiffness indices, both local and segmental and at different arterial sites, the use of both brachial and calibrated local PP to compute local stiffness indices, and the long duration of follow-up.

Currently, 2 population-based studies have evaluated the association of local carotid stiffness and incident CVD and/or mortality (5,10), whereas no studies have evaluated the association of local femoral or brachial stiffness and incident CVD or mortality. The ARIC (Atherosclerosis Risk in Communities) study (5) indicated an independent association between carotid stiffness and stroke. The Rotterdam study (10) also observed an association between carotid stiffness and incident CVD and all-cause mortality, although this association was attenuated and became statistically nonsignificant after adjustments for potential confounders. This study, however, did not measure concurrent blood pressures (i.e., during the time of the stiffness measurement), which may have led to an underestimation of the observed associations.

Associations of local stiffness with CV events and all-cause mortality. In the present study, local carotid stiffness indices were more strongly associated with all-cause mortality than with incident CV events. This finding is difficult to interpret, and may have several explanations. First, incident CVD is more likely subject to misclassification than is all-cause mortality. Second, arterial stiffness may be a marker of biological aging (2) and, thus, may affect the mortality risk of an individual for any age-related disease, not just CVD. In the elderly population that we studied, this mechanism may well be operative. Nevertheless, we cannot exclude the play of chance, and this issue needs further study.

Carotid versus femoral artery stiffness. The present study showed that stiffness of the carotid and femoral arteries is associated with incident CV events and mortality independently of each other. This may suggest that stiffening of these arteries increases CVD and mortality risk via distinct pathways. The ARIC study (5) indicated that carotid stiffness is more strongly associated with cerebrovascular disease compared with CHD, possibly because stiffening of this artery (or of other elastic arteries for which this artery might serve as a proxy) leads to a high pressure load on the brain. In contrast, femoral stiffness may be more strongly associated with CHD compared with cerebrovascular disease, because femoral and coronary arteries show similar wall characteristics (i.e., both are muscular vessels [2] and have a high collagen/elastin ratio [20]), and, therefore, stiffening of the femoral artery may serve as a proxy for stiffening of the coronary vasculature. The present study had insufficient power to detect associations with specific CV events, and this issue requires further study.

JACC Vol. 63, No. 17, 2014
May 6, 2014:1739–47

Table 3 Associations of the cfPWV, Aix, and SAC With Incident Cardiovascular Events and All-Cause Mortality

Model	cfPWV	Aix	SAC	
			Time-Decay Method	SV/Aortic PP
		Incident Cardiovascular Events		
1	1.57 (1.29–1.92)	1.08 (0.89–1.31)	1.09 (0.88–1.35)	1.15 (0.90–1.47)
2	1.56 (1.27–1.93)	1.05 (0.86–1.28)	1.03 (0.81–1.30)	1.09 (0.84–1.43)
3	1.56 (1.23–1.98)	0.99 (0.81–1.22)	1.00 (0.79–1.26)	1.13 (0.87–1.47)
		All-Cause Mortality		
1	1.27 (0.99–1.63)	1.05 (0.84–1.32)	1.22 (0.92–1.61)	1.05 (0.70–1.58)
2	1.18 (0.88–1.57)	1.19 (0.92–1.54)	1.06 (0.78–1.43)	1.05 (0.67–1.65)
3	1.13 (0.83–1.54)	0.93 (0.73–1.18)	1.04 (0.76–1.41)	1.01 (0.73–1.41)

Values are hazard ratio (95% confidence interval). Hazard ratios are indicated per 1 SD higher carotid femoral pulse wave velocity (cfPWV) and aortic augmentation index (Aix) and per 1 SD lower systemic arterial compliance (SAC). Model 1: adjusted for age, sex, and glucose metabolism status. Model 2: model 1 plus mean arterial pressure and heart rate. Model 3: model 2 plus prior cardiovascular disease, body mass index, triglycerides, total/HDL cholesterol ratio, estimated glomerular filtration rate, microalbuminuria, physical activity, and smoking habits. Number of participants and events available for analysis with incident cardiovascular events/all-cause mortality for cfPWV: 215 (53 events)/237 (36 events); for Aix: 500 (120 events)/543 (87 events); for SAC (time-decay method): 457 (110 events)/492 (77 events); and for SAC (SV/aortic PP) 448 (106 events)/482 (70 events).

PP = pulse pressure; SV = stroke volume; other abbreviations as in Table 1.

Clinical relevance. Carotid and femoral stiffness are potential separate therapeutic targets for CVD risk lowering therapy. CVD risk factors have different impacts on stiffening of carotid versus femoral arteries (13,18,21). This may be attributed to the marked differences in the architecture of elastic versus muscular arteries, and suggests that stiffness of elastic and muscular arteries may be specifically targeted. Of the currently available drugs, organic nitrates lower stiffness of muscular arteries (22). No therapy is yet available that specifically targets stiffness of elastic arteries. In addition, carotid and femoral stiffness were associated with CV events and mortality even after adjustments for CVD risk factors, IMT, SP, PP, and other stiffness indices (including cfPWV) and, therefore, may carry additional value with regard to CVD prediction.

Aix and SAC. In the present study, Aix and SAC were not associated with incident CV events or mortality. With regard to Aix, this is in contrast to a recent meta-analysis (23) in which Aix independently predicted CVD, and studies (23,24) that showed an association between Aix and CVD in men only (in the present study, no interaction with sex was present). More recent data from the Framingham Heart Study (3) and MESA (Multi-Ethnic Study of Atherosclerosis) (25), however, indicated that Aix was either not associated or weakly associated with CVD, respectively. In addition to the magnitude and timing of wave reflections, Aix is also influenced by hemodynamic phenomena unrelated to wave reflections (2,25), and these phenomena may be different in DM2/IGM as compared with NGM (26). This may result in an underestimation of the association between wave reflections and CVD. Reflection estimates derived from wave separation analysis may more accurately indicate wave reflections than the Aix. In accordance, recent data of MESA (25) showed that these estimates were more strongly associated with CVD than Aix. With regard to SAC, a possible explanation for the lack of an association might be that the assessment of this estimate has a relatively large measurement error (1).

Brachial stiffness. In the total study population, local brachial stiffness was not associated with CV events and mortality. In accordance, a previous study (27) showed that segmental stiffness of the brachial artery (i.e., brachial artery pulse wave velocity) was not associated with CVD mortality. The lack of this association can be explained by the fact that there is no arterial aging of the brachial artery (21). In accordance, in the present study population, the carotid and femoral arteries were stiffer in older patients, whereas brachial stiffness was not associated with age (data not shown). Somewhat surprisingly, however, the results of the interaction analysis showed that, in individuals with, but not in those without prior CVD, lower stiffness of the brachial artery was associated with a greater risk of CV events. In addition, a similar association between lower brachial stiffness and incident CVD was present in individuals with DM2 and IGM, but not in individuals with NGM. A plausible underlying explanation for these observations is lacking, and these findings may represent the play of chance. Further studies are needed to clarify this issue.

The use of brachial derived PP in the calculation of local stiffness indices. The present study supports the hypothesis that, in elderly people (i.e., age >60 years), calculation of local stiffness indices with brachial derived PP is as accurate as the use of local PP. The use of brachial derived versus local PP is an important methodological issue in the assessment of local stiffness because of the phenomenon of PP amplification (1,2). This phenomenon, however, may play a less important role in elderly people, as the magnitude of amplification diminishes with age (1,2). In accordance, the results of the present analyses were qualitatively similar when brachial or calibrated local PP were used.

Study limitations. First, unavoidable survival bias will, in general, have led to an underestimation of the reported associations. Second, the present study had insufficient power to quantify the additive predictive value of local stiffness beyond standard CVD risk factors. Studies are needed to further clarify this issue. Third, data on cfPWV were

available in a subsample of the study population only (cfPWV analysis: n = 237; 53 CV events and 36 deaths). This may explain why we did not observe an association between cfPWV and all-cause mortality. To our knowledge, carotid-femoral transit time as determined by distension curves has not been validated against any other method. Nevertheless, it has been shown that this method is highly reproducible (28), and the present results are in accordance with studies that used applanation tonometry to determine cfPWV (4). Finally, a relatively large number of statistical tests were done. The aim of the present study was to evaluate the prognostic value of multiple stiffness indices, which, as a consequence, involves carrying out multiple tests. The associations with CV events and mortality were, however, consistent across the different stiffness indices studied. It is, therefore, unlikely that these findings are the result of the play of chance.

Conclusions

The present study shows that local stiffness of the carotid and femoral arteries is associated with incident CV events and all-cause mortality independently of CVD risk factors and each of the other stiffness indices. These data suggest that local carotid and femoral stiffness indices may serve as a target for lowering of CVD risk and can have predictive value. Further studies are needed to quantify the predictive value of local stiffness beyond standard CVD risk factors.

Reprint requests and correspondence: Dr. Coen D. A. Stehouwer, Department of Medicine, Maastricht University Medical Centre, Prof. Debyelaan 25, 6229HX Maastricht, the Netherlands. E-mail: cda.stehouwer@mumc.nl.

REFERENCES

1. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006;27:2588–605.
2. Safar ME, O'Rourke MF. Arterial Stiffness in Hypertension. Amsterdam, the Netherlands: Elsevier, 2006.
3. Mitchell GF, Hwang SJ, Vasan RS, et al. Arterial stiffness and cardiovascular events: the Framingham Heart Study. Circulation 2010; 121:505–11.
4. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010;55:1318–27.
5. Yang EY, Chambless L, Sharrett AR, et al. Carotid arterial wall characteristics are associated with incident ischemic stroke but not coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) study. Stroke 2012;43:103–8.
6. Barenbrock M, Kosch M, Joster E, Kisters K, Rahn KH, Hausberg M. Reduced arterial distensibility is a predictor of cardiovascular disease in patients after renal transplantation. J Hypertens 2002;20:79–84.
7. Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM. Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end-stage renal disease. Hypertension 1998;32:570–4.
8. Dijk JM, Algra A, van der Graaf Y, Grobbee DE, Bots ML. Carotid stiffness and the risk of new vascular events in patients with manifest cardiovascular disease. The SMART study. Eur Heart J 2005;26: 1213–20.
9. Leone N, Ducimetiere P, Gariepy J, et al. Distension of the carotid artery and risk of coronary events: the three-city study. Arterioscler Thromb Vasc Biol 2008;28:1392–7.
10. Mattace-Raso FU, van der Cammen TJ, Hofman A, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation 2006;113:657–63.
11. Stork S, van den Beld AW, von Schacky C, et al. Carotid artery plaque burden, stiffness, and mortality risk in elderly men: a prospective, population-based cohort study. Circulation 2004;110:344–8.
12. van Dijk RA, Dekker JM, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD. Brachial artery pulse pressure and common carotid artery diameter: mutually independent associations with mortality in subjects with a recent history of impaired glucose tolerance. Eur J Clin Invest 2001;31:756–63.
13. Henry RM, Kostense PJ, Spijkerman AM, et al. Arterial stiffness increases with deteriorating glucose tolerance status: the Hoorn Study. Circulation 2003;107:2089–95.
14. Schram MT, Henry RM, van Dijk RA, et al. Increased central artery stiffness in impaired glucose metabolism and type 2 diabetes: the Hoorn study. Hypertension 2004;43:176–81.
15. Van Bortel LM, Duprez D, Starmans-Kool MJ, et al. Clinical applications of arterial stiffness, Task Force III: recommendations for user procedures. Am J Hypertens 2002;15:445–52.
16. Weber T, Ammer M, Rammer M, et al. Noninvasive determination of carotid-femoral pulse wave velocity depends critically on assessment of travel distance: a comparison with invasive measurement. J Hypertens 2009;27:1624–30.
17. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol 2003;56:1163–9.
18. Stehouwer CD, Henry RM, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. Diabetologia 2008;51:527–39.
19. Van Bortel LM, Balkestein EJ, van der Heijden-Spek JJ, et al. Noninvasive assessment of local arterial pulse pressure: comparison of applanation tonometry and echo-tracking. J Hypertens 2001;19: 1037–44.
20. Maher E EM, Creane A, Lally C, Kelly DJ. Site specific inelasticity of arterial tissue. J Biomech 2012;8:1393–9.
21. Benetos A, Laurent S, Hoeks AP, Boutouyrie PH, Safar ME. Arterial alterations with aging and high blood pressure. A noninvasive study of carotid and femoral arteries. Arterioscler Thromb 1993;13:90–7.
22. Van Bortel LM, Struijker-Boudier HA, Safar ME. Pulse pressure, arterial stiffness, and drug treatment of hypertension. Hypertension 2001;38:914–21.
23. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. Eur Heart J 2010;31:1865–71.
24. Wang KL, Cheng HM, Sung SH, et al. Wave reflection and arterial stiffness in the prediction of 15-year all-cause and cardiovascular mortalities: a community-based study. Hypertension 2010;55:799–805.
25. Chirinos JA, Kips JG, Jacobs DR Jr., et al. Arterial wave reflections and incident cardiovascular events and heart failure: MESA (Multiethnic Study of Atherosclerosis). J Am Coll Cardiol 2012;60:2170–7.
26. Safar ME, Balkau B, Lange C, et al. Hypertension and vascular dynamics in men and women with metabolic syndrome. J Am Coll Cardiol 2013;61:12–9.
27. Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM. Stiffness of capacitive and conduit arteries: prognostic significance for end-stage renal disease patients. Hypertension 2005;45:592–6.
28. van Dijk RA, van Ittersum FJ, Westerhof N, van Dongen EM, Kamp O, Stehouwer CD. Determinants of brachial artery mean 24 h pulse pressure in individuals with type II diabetes mellitus and untreated mild hypertension. Clin Sci (Lond) 2002;102:177–86.

Key Words: arterial stiffness ■ cardiovascular events ■ all-cause mortality.

APPENDIX

For an expanded Methods section and supplemental tables, please see the online version of this article.