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Carotid Artery Plaque Burden, Stiffness, and Mortality Risk in Elderly Men

A Prospective, Population-Based Cohort Study

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Background—Indicators of carotid atherosclerosis may confer additional prognostic value and guide clinicians in cardiovascular risk assessment. Carotid artery morphology (plaque burden) and function (stiffness indexes) as predictors of all-cause and cardiovascular mortality were prospectively evaluated in elderly men.

Methods and Results—Cardiovascular risk profile was measured in 367 independently living men (mean± SD age, 78±4 years). The number of carotid plaques was assessed by B-mode ultrasound, and arterial stiffness was quantified with a wall tracker system. During 48 months of follow-up, 70 deaths (28 cardiovascular) occurred. The total number of carotid plaques was the parameter most closely related to prognosis. In the age-adjusted multivariate Cox model, all-cause mortality was predicted by number of plaques (hazard ratio [HR] per 1-unit increase, 1.35; 95% confidence interval [CI], 1.12 to 1.64). Predictors of cardiovascular mortality in the respective model were number of plaques (HR, 1.18; 95% CI, 1.04 to 1.33) and Young's elastic modulus (HR, 1.68; 95% CI, 1.26 to 2.26). Number of plaques improved the prognostic utility in any prognosis model when added to commonly available cardiovascular risk information. In contrast, stiffness indexes offered no consistent additive value.

Conclusions—In elderly men, carotid artery plaque burden is a strong independent predictor of all-cause and cardiovascular mortality in the years to come. The additional value of carotid artery stiffness measurements as a pathophysiologically related entity appears to be limited in this age group and, if anything, confined to cardiovascular mortality risk. **(*Circulation*. 2004;110:344-348.)**

Key Words: atherosclerosis ■ carotid arteries ■ elasticity ■ mortality ■ risk factors

Noninvasive, ultrasound-based assessment of arterial characteristics has received increased attention over the last years as both a research tool and a surrogate marker of cardiovascular morbidity and mortality risk. In general, studies have focused on a single vascular property, either morphology (ie, vessel wall characteristics and plaque burden) or function (ie, selected measures of elasticity and stiffness). Moreover, most data were collected in young and middle-aged populations or in highly selected patients. Aortic plaque was reported to predict cardiovascular mortality;[1–3] carotid intima-media thickness (IMT) was shown to predict fatal coronary death[4–6] and fatal stroke;[7] aortic pulse-wave velocity predicted mortality in elderly people;[8] and carotid artery stiffness predicted cardiovascular mortality in end-stage renal disease[3,9] and all-cause mortality in patients with impaired glucose tolerance.[10] However, the evidence required for clinical application remains inconclusive for several reasons: The strength of the observed association varied considerably with the population studied and the technique used; outcome was sometimes restricted to cardiovascular death; and in some studies, few events occurred.

Elderly people constitute a major proportion of patient care in everyday clinical practice. Adequate assessment of risk and prognosis in this growing group of patients may be desirable to target preventive and therapeutic measures but is limited because of lacking data. We therefore estimated the ability of both morphological and functional carotid artery properties to predict all-cause and cardiovascular mortality in a well-characterized cohort of elderly men.

Methods

Study Population and Design

The design of this single-center prospective cohort study has been reported in detail elsewhere.[11] Briefly, 1567 independently living

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men >70 years of age in Zoetermeer, a medium-sized town in the Netherlands, were invited, and 403 men responded and gave written informed consent. The study was approved by the Medical Ethics Committee of the Erasmus University Hospital Rotterdam. Analyses of the current report were restricted to 367 men with complete data on carotid artery characteristics. The reason for incomplete data in 36 men was inability to perform valid vessel wall motion measurements because of obesity (n=7), massive plaque (n=12), or technical failure (n=17). At study entry in 1996, a detailed interview, specifically addressing cardiovascular history, and a complete physical examination were performed. Medication taken for >6 months was recorded. Height and weight were measured, and body mass index (kg/m^2) was calculated. A venous blood sample was collected in the morning after an overnight fast. Four years after the initial investigation, vital status of all participants was ascertained from the general practitioner. Cardiovascular death was assumed if 1 of the following reasons of death was given: Myocardial infarction (n=18), rhythm disturbance with underlying severe coronary artery disease (n=2), heart failure (n=4), aortic dissection (n=2), or cerebrovascular event (n=2).

Carotid Artery Assessment

At study entry, near and far walls of the common carotid artery, bifurcation, and internal carotid artery (right and left side) were scanned for the presence (yes/no) of atherosclerotic lesions with a 7.5-MHz linear-array transducer (ATL Ultramark IV) as described previously.[12,13] The minimum number of plaques present was 0, and the maximum was 12 plaques per subject. Plaque was qualitatively defined as focal widening relative to adjacent segments with protrusion into the lumen, regardless of the presence of hypoechoic or hyperechoic areas.[13] The sizes of the lesions were not quantified. Reproducibility of this plaque assessment method has been reported.[14] In addition, interfaces of the near and far walls of the distal common carotid artery were scanned for the measurement of IMT. Actual IMT measurements were performed offline as described previously.[15]

The vessel wall motion of the right common carotid artery was measured at the same visit with a Duplex scanner connected to a wall tracker system (Pie Medical), as described previously.[16,17] Measurements were carried out with the subject supine and the head tilted slightly to the contralateral side at a region 1.5 cm proximal to the origin of the carotid bulb in an area without overt plaque. Successive values of the end-diastolic diameter (Dd), absolute stroke change in diameter during systole (ΔD), and the relative stroke change in diameter (ΔD/Dd) were computed from the recording over 5 cardiac cycles and stored digitally. Reproducibility was assessed in 15 subjects who underwent a second examination within 1 month. The coefficients of variation for Dd and ΔD were 8.5% and 1.2%, respectively. Blood pressure was read automatically 4 times on the right upper arm during the session (Dinamap, Critikon), and the mean value was used in analyses. Pulse pressure (PP) was calculated as difference between systolic (SBP) and diastolic (DBP) blood pressures.

Definition of Stiffness Parameters

Stiffness was evaluated with the adjusted ΔD as the primary measure.[18] The ΔD (strain) served as a predictor of mortality, and mean arterial pressure (stress) and Dd were entered as covariates in regression models. Traditional indexes of arterial stiffness (stress-to-strain ratio) were also used in this report for comparison with the adjusted ΔD. β Stiffness index was given as follows: β index=Ln(SBP/DBP)/(ΔD/Dd), where SBP indicating systolic blood pressure and DBP indicating diastolic blood pressure. Cross-sectional compliance coefficient (CC) was given as follows: CC=($\pi\times$Dd$\times\Delta$D)/(2$\times$PP) (mm^2/kPa^{-1}). Distensibility coefficient (DC) was DC=(2$\times\Delta$D/Dd)/PP (10^{-3}kPa^{-1}). Peterson's modulus (E_P) was as follows: E_P=(PP$\times$Dd)/ΔD. Finally, Young's elastic modulus (YEM) was written as YEM=(PP$\times$Dd^2)/($\Delta\times$2$\times$IMT) (kPa).

CC and DC are indexes of elasticity and therefore inversely related to stiffness. CC is a measure of the capacity of the vessel to buffer pulsatile blood flow; DC describes intrinsic vessel wall stiffness. E_P is closely related to the inverse of the distensibility coefficient. In addition to the other stiffness indexes, YEM provides direct information about the elastic properties of the wall material independent of the vessel geometry.[18,19]

Data Analysis

The association of vascular characteristics with all-cause and cardiovascular mortality was studied by Cox proportional-hazard regression. After identification of univariate predictors ($P<0.15$), multivariate modeling was used to evaluate the independent relationship between these parameters and the respective outcome. Results in prognostic models are expressed as hazard ratio (HR) with 95% confidence interval (CI). Age was forced into all models. Number of plaques was tested as both a categorical and a continuous variable because χ^2 of the log-likelihood between models justified a continuity assumption. The plaque score consisted of 5 categories: 0=0 plaques (ie, reference), 1=1 to 2 plaques, 2=3 to 4 plaques, 3=5 to 6 plaques, and 4=7 to 12 plaques. To estimate the prognostic capacity of different sets of predictors (models), we constructed receiver-operating characteristic (ROC) curves. Using the Cox model, we compared the linear predictor with the outcome, and the area under the curve was calculated by the nonparametric trapezoidal rule, with its SE and 95% CI.[20] Differences in the discriminative value between models were estimated by differences in the ROC area, taking into account the correlation between models because they were based on the same cases.[21] Statistical analysis was performed with SPSS 11.0.1.

Results

During a follow-up period of 48 months, 70 men had died: 7 in the first year, 16 in the second, 19 in the third, and 28 in the fourth. The mean$\pm$SD time of death was 30$\pm$12 months since study start (range, 3 to 47 months). Twenty-eight deaths (40%) were attributable to cardiovascular causes. General and vascular characteristics of the study population are given in Table 1.

All-Cause Mortality

Age-adjusted predictors of all-cause mortality were as follows: Total number of carotid plaques per patient, history of heart failure, chronic obstructive pulmonary disease, use of nitrates, and never smoking (Table 2). A trend toward stiffer vessels as expressed by YEM and β index in subjects who died during follow-up vanished after adjustment for age (Table 2). The numbers of plaques in the left and right carotid arteries were significantly correlated (r=0.49). In the age-adjusted multivariate Cox model, number of plaques (HR per 1-unit increase, 1.35; 95% CI, 1.12 to 1.64) and heart failure episodes (HR, 2.59; 95% CI, 1.28 to 5.24) remained predictive. Numbers of events with risk estimates for different plaque strata are summarized in Table 3. Compared with the reference group (with no plaques), the risk increased 2.9-fold when 1 to 2 plaques were present and 4.9-fold when >4 plaques were present. Presence of any plaques was associated with a 3.5-fold increased risk but also with a wider CI.

Cardiovascular Mortality

Age-adjusted predictors of cardiovascular mortality were presence of carotid plaques, E_P, YEM, β index, low-density lipoprotein cholesterol, history of myocardial infarction, heart failure, chronic obstructive pulmonary disease, and use of diuretics or angiotensin-converting enzyme inhibitors (Table 2). In the age-adjusted multivariate Cox model, YEM (HR,

TABLE 1. General Characteristics of the Study Cohort

Variable	
Age, y	77.9 (3.6)
Body mass index, kg/m^2	25.5 (3.0)
Systolic blood pressure, mm Hg	142 (21)
Diastolic blood pressure, mm Hg	79 (11)
Mean arterial pressure, mm Hg	100 (14)
PP, mm Hg	63 (14)
Heart rate, bpm	69 (12)
Total cholesterol, mmol/L	5.76 (1.13)
HDL cholesterol, mmol/L	1.35 (0.39)
LDL cholesterol, mmol/L	3.78 (1.01)
Triglycerides, mmol/L	1.40 (0.86)
Glucose, mmol/L	5.60 (1.39)
Never smoking, %	12.5
Former smoking, %	70.0
Current smoking, %	17.4
Hypertension, %	24.0
Myocardial infarction, %	15.6
Heart failure episodes, %	5.4
Cerebrovascular accident, %	8.7
Chronic obstructive lung disease, %	14.4
Diuretics, %	12.0
β-Blockers, %	12.0
Nitrates, %	12.8
ACE inhibitors, %	10.4
Calcium channel blockers, %	10.9
Lipid-lowering drugs, %	1.6
Antidiabetic medication, %	5.7
Antithrombotic therapy, %	25.3
Carotid artery wall morphology	
Plaques (range, 0 to 12), n	3.4 (2.6)
No plaque, %	16.4
1 to 2 plaques, %	26.8
3 to 4 plaques, %	24.7
5 to 6 plaques, %	20.5
7 to 12 plaques, %	11.5
$\geq$1 Plaque on both sides, %	60.6 (0.5)
Any carotid plaque, %	83.6 (0.4)
Common carotid IMT near wall, m/10^3	0.93 (0.21)
Common carotid IMT far wall, m/10^3	0.97 (0.16)
Common carotid IMT walls combined, m/10^3	0.95 (0.19)
Carotid artery stiffness	
Diastolic lumen diameter, m/10^3	8.19 (0.96)
Stroke change in diameter, m/10^3	0.32 (0.12)
Cross-sectional compliance, mm^2/kPa	0.51 (0.22)
Distensibility, kPa$^{-1}\times10^{-3}$	9.68 (4.18)
Peterson's modulus, kPa$\times10^3$	0.25 (0.12)
YEM, kPa$\times10^3$	1.13 (0.67)
β Index	17.1 (7.6)

Values are unadjusted means (SD) or proportions. N=367.

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; and ACE, angiotensin-converting enzyme.

TABLE 2. Age-Adjusted General Characteristics of All-Cause and Cardiovascular Mortality During 4 Years of Follow-up Among 367 Subjects

	Hazard Ratio (95% CI)	
	All-Cause Mortality	Cardiovascular Mortality
Body mass index	0.97 (0.89–1.05)	1.03 (0.91–1.17)
Systolic blood pressure	1.00 (0.99–1.01)	1.01 (0.99–1.03)
Diastolic blood pressure	1.00 (0.98–1.02)	1.00 (0.97–1.03)
Mean arterial blood pressure	1.00 (0.98–1.02)	1.01 (0.98–1.03)
PP	1.00 (0.98–1.01)	1.02 (0.99–1.05)
Heart rate	1.01 (0.99–1.02)	1.01 (0.98–1.04)
Total cholesterol	1.00 (0.81–1.25)	1.16 (0.84–1.61)
HDL cholesterol	0.89 (0.47–1.69)	0.58 (0.19–1.77)
LDL cholesterol	1.03 (0.81–1.31)	1.34 (0.95–1.90)
Triglycerides	1.10 (0.85–1.43)	0.93 (0.58–1.48)
Glucose	0.97 (0.81–1.17)	0.96 (0.72–1.29)
Never smoking	0.38 (0.15–0.95)	0.76 (0.23–2.55)
Former smoking	1.64 (0.94–2.86)	2.11 (0.80–5.61)
Current smoking	0.96 (0.51–1.78)	0.36 (0.09–1.51)
Hypertension	0.95 (0.54–1.69)	1.28 (0.56–2.92)
Myocardial infarction	1.72 (0.99–3.01)	2.37 (1.05–5.39)
Decompensated heart failure episode	2.87 (1.42–5.78)	3.42 (1.18–9.89)
Cerebrovascular accident	0.82 (0.33–2.04)	1.22 (0.37–4.03)
Chronic obstructive pulmonary disease	1.82 (1.03–3.22)	2.54 (1.12–5.79)
Diuretics	1.80 (0.99–3.25)	3.30 (1.44–7.55)
β-Blockers	0.59 (0.24–1.46)	0.26 (0.04–1.94)
Nitrates	2.16 (1.22–3.83)	1.72 (0.65–4.53)
ACE inhibitors	1.21 (0.60–2.45)	2.44 (0.99–6.03)
Calcium channel blocker	1.43 (0.71–2.91)	1.42 (0.49–4.11)
Lipid-lowering drugs	0.81 (0.11–5.80)	2.09 (0.28–15.38)
Antidiabetic medication	1.09 (0.40–3.00)	1.95 (0.59–6.47)
Antithrombotic therapy	1.27 (0.76–2.12)	1.38 (0.63–3.05)
Carotid artery wall morphology		
No. of carotid plaques (0 to 12)	1.13 (1.04–1.23)	1.18 (1.05–1.34)
Score for carotid plaques (0 to 4)	1.38 (1.14–1.66)	1.60 (1.17–2.17)
Common carotid IMT near wall	0.69 (0.20–2.41)	1.27 (0.23–7.02)
Common carotid IMT far wall	0.87 (0.18–4.23)	2.59 (0.27–24.92)
Common carotid IMT walls combined	0.84 (0.19–3.31)	2.22 (0.26–18.21)
Carotid artery stiffness parameters		
Diastolic lumen diameter	1.06 (0.83–1.36)	1.14 (0.78–1.66)
Stroke change in diameter	0.37 (0.05–2.81)	0.36 (0.01–9.25)
Cross-sectional compliance	0.97 (0.34–2.76)	0.50 (0.08–3.07)
Distensibility	0.99 (0.93–1.05)	0.95 (0.86–1.06)
Peterson's modulus	2.31 (0.48–11.02)	14.39 (2.47–83.79)
YEM	1.26 (0.95–1.66)	1.59 (1.19–2.14)
β Index	1.01 (0.99–1.04)	1.05 (1.01–1.08)

Results of proportional-hazards regression analyses are shown as HRs (95% CI) of the independent variables adjusted for age. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

TABLE 3. Hazard Ratio of Mortality Risk in Relation to Carotid Plaques Adjusted for Age

	Subjects at Risk, n	Events, n	HR (95% CI)
Total plaque score			
No plaque (reference)	60	4	1.00 (reference)
1 to 2 plaques	98	16	2.89 (0.96–8.69)
3 to 4 plaques	90	16	2.91 (0.97–8.73)
5 to 6 plaques	75	23	4.89 (1.69–14.15)
7 to 12 plaques	42	11	4.53 (1.44–14.23)
≥1 Plaque on both sides	220	52	2.00 (1.15–3.46)
Any plaque	307	66	3.48 (1.27–9.54)

1.68; 95% CI, 1.26 to 2.26), number of plaques (HR per 1-unit increase, 1.18; 95% CI, 1.04 to 1.33), and use of diuretics (HR, 3.19; 95% CI, 1.39 to 7.32) remained predictive.

Prognostic Utility

The area under the ROC curve for the predictors from the multivariate Cox model was 0.70 (95% CI, 0.63 to 0.77) for all-cause mortality and 0.71 (95% CI, 0.60 to 0.83) for cardiovascular mortality. A similar prognostic capacity could be reached using detailed information on history, medication, and measurement of common risk factors as illustrated in Table 4. The order of added sets of variables follows the usual clinical diagnostic workup, from history-taking to measuring cardiovascular risk factors to assessing carotid arteries. Carotid plaque assessment improved the prognostic utility to a fair extent when added after the usual diagnostic workup (Table 4). In general, adding information on plaque burden to any set of cardiovascular risk markers improved the prognostic utility for both all-cause and cardiovascular mortality risk assessment, whereas the contribution of carotid stiffness was small in models of all-cause mortality but somewhat larger in models of cardiovascular mortality (detailed data not shown).

TABLE 4. Prognostic Capacity of Different Sets of Cardiovascular Risk Markers

	Area Under the ROC Curve (95% CI)	
Added (Set of) Variable(s)	All-Cause Mortality	Cardiovascular Mortality
Age	0.63 (0.56–0.70)*	0.52 (0.42–0.62)
Plus medical history†	0.68 (0.61–0.75)‡	0.65 (0.54–0.77)‡
Plus medication§	0.70 (0.63–0.77)	0.68 (0.58–0.79)
Plus measured risk factors‖	0.71 (0.64–0.78)	0.71 (0.63–0.82)
Plus carotid plaque measurement	0.74 (0.67–0.80)¶	0.75 (0.66–0.85)#
Plus carotid stiffness measurement	0.75 (0.68–0.81)	0.77 (0.67–0.87)

*$P<0.001$ vs a chance value of 0.5.

†Established diagnosis of heart failure, myocardial infarction, hypertension, chronic obstructive pulmonary disease, diabetes mellitus, or never smoking.

‡$P<0.01$ vs area under the ROC curve of previous set.

§On treatment with diuretics, nitrates, ACE inhibitors, β-blocking agents, or statins.

‖Body mass index, SBP, DBP, and lipid profile.

¶$P=0.04$ vs area under the ROC curve of previous set.

#$P=0.07$ vs area under the ROC curve of previous set.

Discussion

The principal finding of this study was that, among a variety of noninvasively assessed morphological and functional carotid artery parameters, only plaque burden consistently predicted both all-cause and cardiovascular mortality. Blood pressure variables, heart rate, IMT, and lumen diameter were not predictive, and among various stiffness indexes, only YEM was associated with cardiovascular but not all-cause mortality. The relation with traditional risk factors seemed very modest.

Potential limitations need to be considered. Predictors of all-cause and cardiovascular mortality were derived with stringent statistical criteria, yet the limited number of events may have restrained statistical power. The effect of a single baseline measurement on future events is subject to regression dilution.[22] Hence, we may have underestimated the true associations with mortality. Calculating stiffness parameters from brachial rather than carotid PP may have introduced a bias[23,24] that is known to depend on risk factors.[25,26] Thus, we may have overestimated PP in individuals with more risk factors and may have correctly estimated or underestimated PP in those with fewer risk factors. Given that risk factor status relates to death risk, this reasoning results in an overestimation of the true association of stiffness to death. In our analyses, this relation was very modest, whereas in a biased situation, one would expect a positive relationship. Thus, a bias as mentioned above, albeit potentially important, is not likely to have invalidated our findings.

The graded relation of number of carotid plaques and mortality has not been described earlier, but we are aware of 3 reports on the presence of aortic calcification and cardiovascular[1–3] and all-cause mortality.[3] In middle-aged patients with end-stage renal disease, using a composite index of aortic, iliofemoral, and carotid calcification, an HR was found per 1-unit increase of all-cause and cardiovascular mortality of 1.9 (95% CI, 1.4 to 2.6) and 2.6 (95% CI, 1.5 to 4.4), respectively.[3] Data from the Framingham cohort using aortic calcification at mean age of 61 years to predict cardiovascular mortality after 20-years of follow-up gave an HR of similar magnitude (HR, 1.6; 95% CI, 1.2 to 2.3, highest versus lowest tertile)[2] that is somewhat lower than the 2- to 4-fold increase in risk observed in the present study. In clinical terms, we interpret the currently available data as showing that plaque presence, measured noninvasively at 1 vascular site, is at least as good a predictor of mortality.

If all parameters that characterize a patient's risk profile from a clinician's point of view were put into a multivariate model (age, medical and smoking histories, medication, measured risk factors), the addition of number of plaques still predicted risk significantly, as opposed to all other variables (Table 4). Established cardiovascular risk factors exhibited a very limited ability to identify those individuals with the greatest risk of dying. Application of available risk stratification models in old and very old subjects is therefore a matter of debate. Age itself is among the most important cardiovascular risk factors, also heavily modifying the strength of others. Plaque burden seemed to offer additional information on prognosis, possibly because it serves as a

summary parameter of lifelong individual risk factor exposure.

In contrast to previous reports,[4–7] blood pressure variables, heart rate, IMT, and arterial lumen diameter did not predict mortality in this study. We attributed this finding to the older age and narrow age range in our study compared with others, which possibly reduced discriminatory power. Whereas plaque burden contributed to the fit of the model to a larger extent, the contribution of stiffness indexes was either absent or, for cardiovascular prediction models, small. Only 1 among many stiffness markers, namely YEM, added to the explanatory power of the respective model. However, arterial stiffness and plaque burden are pathophysiologically related entities and were related to each other in several studies in younger populations.[27,28] The lack of consistent additive prognostic value of stiffness parameters in our cohort does not exclude a causal role and/or a modifying effect of stiffness in the course of atherosclerosis progression. Studies that discern between soft and calcified plaque and its effect on stiffness may help to expand our knowledge in this respect.

In conclusion, we reported in detail the prognostic utility of morphological and functional carotid artery characteristics of elderly men, given full cardiovascular risk profiling. Risk prediction in this age group may require a different approach compared with that in younger populations. In this context, noninvasive vascular imaging will improve our ability to predict cardiovascular and all-cause mortality in this growing group of subjects.

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