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Carotid Plaques Increase the Risk of Stroke and Subtypes of Cerebral Infarction in Asymptomatic Elderly
The Rotterdam Study

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Background—Few studies have quantified the relation between carotid plaques and stroke in asymptomatic patients, and limited data exist on the importance of location of plaques or the association with subtypes of cerebral infarction. We investigated the relationship between carotid plaques, measured at different locations, and risk of stroke and subtypes of cerebral infarction in a population-based study.

Methods and Results—The study was based on the Rotterdam Study and included 4217 neurologically asymptomatic subjects aged 55 years or older. Presence of carotid plaques at 6 locations in the carotid arteries was assessed at baseline. Severity was categorized according to the number of affected sites. After a mean follow-up of 5.2 years, 160 strokes had occurred. Data were analyzed using Cox proportional hazards regression. Plaques increased the risk of stroke and cerebral infarction ≈1.5-fold, irrespective of plaque location. Severe carotid plaques increased the risk of nonlacunar infarction in anterior (RR 3.2 [95% CI, 1.1 to 9.7]) but not in posterior circulation (RR 0.6 [95% CI, 0.1 to 4.9]). A >10-fold increased risk of lacunar infarction was found in subjects with severe plaques (RR 10.8 [95% CI, 1.7 to 69.7]). No clear difference in risk estimates was seen between ipsilateral and contralateral infarction.

Conclusions—Carotid plaques increase the risk of stroke and cerebral infarction, irrespective of their location. Plaques increase the risk of infarctions in the anterior but not in the posterior circulation. It is likely that carotid plaques in neurologically asymptomatic subjects are both markers of generalized atherosclerosis and sources of thromboemboli. **(*Circulation*. 2002;105:2872-2877.)**

Key Words: epidemiology ■ risk factors ■ stroke ■ carotid arteries ■ plaque

Carotid plaques frequently have been found in patients who suffered from a stroke.[1–3] Few studies have quantified the association between carotid plaques and risk of subsequent stroke in asymptomatic subjects.[4,5] Also, limited information is available on the relationship with subtypes of cerebral infarction[4,5] as well as on the impact of location of the carotid plaque in relation to the risk of stroke.[5,6] One could hypothesize that because of a more turbulent blood flow, bifurcation and internal carotid artery plaques carry a higher risk than do plaques in the common carotid artery.[5,7] It also is still controversial whether carotid plaques merely reflect generalized atherosclerosis or are directly causally related to subsequent stroke by release of thromboemboli.[5,8,9] We investigated the association between asymptomatic plaques, measured at 6 locations in the carotid arteries, and the risk of stroke and subtypes of cerebral infarction in a population-based cohort of elderly persons.

Methods

Population

The present study is part of the Rotterdam Study, a population-based cohort study on chronic and disabling diseases in the elderly. All inhabitants of Ommoord, a suburb of Rotterdam, aged 55 years or older were invited. People living in homes for the elderly were included. The participation rate of those invited for the study was 78%, and in total 7983 subjects participated.[10] The Medical Ethics Committee of Erasmus University Rotterdam approved the study. Written informed consent to retrieve information from treating physicians was obtained from all participants. Baseline measurements were obtained from 1990 to 1993 and consisted of an interview at home and 2 visits to the research center for physical examination. From the 7129 subjects who visited the research center, 419 had experienced a previous stroke or transient ischemic attack (TIA). Participants with a previous stroke or TIA were excluded from the present study.

Assessment of Carotid Plaques

At baseline, 5494 participants who were free from previous stroke or TIA underwent B-mode ultrasonography of both carotid arteries with a 7.5-MHz linear array transducer (ATL Ultra-Mark IV) to assess

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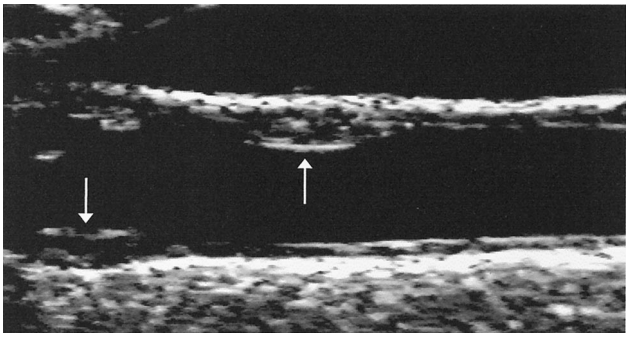

B-mode image of the carotid artery with plaques in the common carotid artery (right arrow) and bifurcation (left arrow).

presence of plaques in the common carotid artery, bifurcation, and internal carotid artery.[11] Missing ultrasound data were mainly attributable to restricted availability of ultrasonographers. We defined plaques as focal widenings of the vessel wall of >50% relative to adjacent segments, with protrusion into the lumen, composed of calcified or noncalcified components (Figure). The protrusion was evaluated by eyeballing judgment, without measuring the thickness of the lesions or of the adjacent structure. Plaques were assessed in 5276 randomly selected neurologically asymptomatic participants. The assessment was performed offline in 1471 participants and online in the remainder. Ultrasonographers who did the plaque assessment were blinded to clinical information. The total plaque score reflected the total number of sites with plaques and ranged from 0 to 6 (left- and right-sided common carotid artery, bifurcation, and internal carotid artery). A total of 4217 participants had information on plaques at 6 locations. Participants with a missing plaque score at 1 or more locations on average had a 1.9 mm Hg (95% CI, 0.5 to 3.3) lower diastolic blood pressure, a 2.0 mm Hg (95% CI, 1.3 to 2.8) lower systolic blood pressure, and a 0.5 kg/m^2 (95% CI, 0.2 to 0.7) higher body mass index compared with those with information on plaques at 6 locations. The groups did not differ with regard to other risk factors. A reproducibility study of the online plaque assessment showed κ of 0.66 for the left carotid artery, 0.68 for the right carotid artery, and 0.67 for either side, indicating moderate agreement. Corresponding figures for the offline reproducibility were 0.59, 0.65, and 0.60, respectively.[11] In a subgroup of 954 participants from the Rotterdam Study, assessment of stenosis in the right internal carotid artery was performed online with help of 5-MHz pulsed Doppler.[12] Interpretation of velocity profiles was done according to standard criteria.[13] The prevalence of clinically relevant stenosis was low (stenosis >50%, 1.4%; stenosis >80%, 0.3%).

Assessment of Stroke and Subtypes

During the baseline interview, a previous stroke was assessed by asking, "Did you ever suffer from a stroke, diagnosed by a physician?" Medical records of patients who answered yes were checked to verify the diagnosis.[14] A history of TIA also was assessed during the baseline interview. All TIAs were reviewed by a neurologist.[15] Once subjects enter the Rotterdam Study, they are continuously monitored for major events through automated linkage of the study database with the files from general practitioners. Information on vital status is obtained at regular intervals from the municipal authorities in Rotterdam. When an event or death has been reported, additional information is obtained by interviewing the general practitioner and scrutinizing information from hospital discharge records in case of admittance or referral. A neurologist (P.J.K.) reviewed information on all possible strokes. A stroke was classified as definite if the diagnosis was based on typical clinical symptoms and neuroimaging excluded other diagnoses. A stroke was considered probable if typical clinical symptoms were present but neuroimaging was not performed. For fatal strokes, other causes of death, especially cardiac, should have been excluded. A stroke was classified as possible if clinical symptoms were less typical and neuroimaging was not performed or if a cardiac cause of death could not be excluded in case of a fatal stroke. We only used definite and probable strokes in the analyses. Subclassification in hemorrhagic or ischemic stroke was based on neuroimaging, which was available for 67.5% of all cases. Cerebral infarctions were lacunar if consciousness and higher cerebral function were maintained in the setting of one of the typical lacunar syndromes. CT scan or MRI usually showed a small (<1.5 cm) infarction in the territories supplied by the perforating branches of major cerebral arteries. We additionally classified infarctions as located in anterior or posterior circulation. For the present study, follow-up for stroke was complete for all participants until January 1, 1998.

Medical History and Risk Factors

At baseline, information on present health status, medication use, and medical history, including previous myocardial infarction, coronary bypass surgery, and coronary angioplasty, was obtained using a computerized questionnaire. All reported myocardial infarctions were verified with medical records. History of intermittent claudication and angina pectoris was assessed by use of the Rose questionnaire.[16] Participants were classified as present, former, or never smokers. Nonfasting blood samples were taken, and serum total cholesterol and high-density lipoprotein (HDL) cholesterol were measured with an automated enzymatic procedure. Sitting blood pressure was measured twice on the right arm with a random-zero sphygmomanometer. We used the average of the 2 measurements in the analyses. Diabetes mellitus was defined as use of oral blood glucose–lowering drugs or insulin or random or postload serum glucose level >11 mmol/L. Atrial fibrillation was assessed by an ECG. A history of cardiovascular disease was coded if participants had a history of myocardial infarction, angina pectoris, intermittent claudication, atrial fibrillation, coronary bypass surgery, or coronary angioplasty.

Data Analysis

The relation between carotid plaques and the risk of stroke was assessed with Cox proportional hazards regression. We tested for linearity of the plaque score by comparing the log likelihood of models including plaque score as categorical and continuous variable by means of a χ^2 test. We assessed the relation between total plaque score and risk of stroke and cerebral infarction. Participants without any plaques were taken as the reference. We also examined the presence of 1 or more plaques at different locations (left- or right-sided common carotid artery, bifurcation, and internal carotid artery) in relation to the risk of stroke and cerebral infarction. To distinguish between generalized atherosclerosis and thromboembolism, we assessed whether the association between left- and right-sided plaque score (0 to 3) and risk of infarction were different for ipsilateral and contralateral infarction. Additionally, we determined the relation between carotid plaques and subtypes of infarction (nonlacunar infarction in the anterior and posterior circulation and lacunar infarction). All analyses were adjusted for age and sex and additionally for cardiovascular risk factors (blood pressure, diabetes mellitus, smoking, and HDL and total cholesterol). We performed additional analyses adjusting for statin use, stratified for aspirin use and excluding subjects with a history of cardiovascular disease. Results are presented as rate ratios with corresponding 95% CIs.

Results

Table 1 shows the baseline characteristics of the study population. During 21 967 person-years of follow-up (mean follow-up, 5.2 years), 160 definite or probable strokes occurred. Subtyping revealed 85 cerebral infarctions and 12 intracerebral hemorrhages. A total of 63 strokes could not be subtyped because neuroimaging was lacking or because of limited information. The infarction was lacunar in 17 cases (24%). A total of 52 infarctions were nonlacunar, 34 of which were located in the anterior and 18 in the posterior circula-

TABLE 1. Baseline Characteristics of the Study Population

	Study Population (n=4217)	Stroke (n=160)
Age, y	68.8 (838)	74.3 (8.9)
Sex, % female	60.1	53.8
Systolic blood pressure, mm Hg	139.4 (22.4)	149.0 (23.8)
Diastolic blood pressure, mm Hg	73.9 (11.7)	75.1 (13.5)
Total cholesterol, mmol/L	6.6 (1.2)	6.5 (1.3)
HDL cholesterol, mmol/L	1.4 (0.4)	1.3 (0.4)
Diabetes, %	9.9	21.3
Previous myocardial infarction, %	11.3	16.9
Smoking, % present smokers	23.2	24.1
Atrial fibrillation, %	2.4	5.6
Cardiovascular disease, %	20.1	28.1
Any carotid plaques, %	60.0	74.4
Common carotid artery plaques, %	15.1	25.0
Bifurcation plaques, %	53.2	70.6
Internal carotid artery plaques, %	34.5	44.4
Left carotid artery plaques, %	49.3	64.4
Right carotid artery plaques, %	48.1	64.4
Total plaque score, range 0–6	1.5 (1.7)	2.3 (2.0)

Values represent mean (SD) or percentages.

tion. We could not determine the exact type in 16 infarctions. The numbers of plaques in the left and right carotid arteries were significantly correlated (Spearman correlation coefficient, 0.63).

Carotid Plaques and Risk of Stroke and Cerebral Infarction

Testing for linearity showed that continuous analysis of total plaque score was justified. The risk of stroke and cerebral infarction gradually increased with increasing total plaque score (RR per plaque increase, 1.15 [95% CI, 1.05 to 1.26] for stroke and 1.17 [95% CI, 1.03 to 1.33] for cerebral infarction). The results were largely similar when we adjusted for cardiovascular risk factors (RR 1.13 [95% CI, 1.03 to 1.24] and 1.12 [95% CI, 0.99 to 1.29], respectively) or restricted the analyses to persons without previous cardiovascular disease (RR 1.15 [95% CI, 1.03 to 1.29] and 1.22 [95% CI, 1.04 to 1.42], respectively). The risk of stroke in subjects with severe plaques (score 5 to 6) was 2.4-fold increased (RR 2.44 [95% CI, 1.42 to 4.20]), and the risk of cerebral infarction almost tripled (RR 2.70 [95% CI, 1.27 to 5.77]) compared with subjects without plaques (Table 2). When we looked at the risk associated with plaques at the different locations, we saw no indication that plaques at locations with a turbulent blood flow, like the carotid bifurcation and internal carotid artery, carried a higher risk than plaques in the common carotid artery (Table 2). Increase in total plaque score remained statistically significantly related to the risk of stroke and cerebral infarction when we put total plaque score and plaque location in one model (RR 1.48 [95% CI, 1.14 to 1.93] and 1.52 [95% CI, 1.04 to 2.20], respectively). However, it should be noted that there is a large overlap between plaques at the different locations, which limits the interpretation of the results.

Carotid Plaques in Relation to Hemisphere and Subtype of Infarction

Table 3 shows that carotid plaques were not consistently related to higher risks of infarction in the ipsi versus contralateral hemisphere. Most cases occurred in participants with plaques in both carotid arteries. The risk of infarction in the left hemisphere significantly increased 3-fold in participants with plaques only in the left and in both carotid arteries (RR 3.23 [95% CI, 1.04 to 10.06] and 2.98 [95% CI, 1.15 to 7.75], respectively). The risk of infarction in the right hemisphere was increased when plaques were present in both carotid arteries, although not statistically significantly.

Severe plaques (5 to 6 plaques) increased the risk of nonlacunar infarction in the anterior circulation >3-fold (RR 3.24 [95% CI, 1.08 to 9.72]) (Table 4). The risk of anterior circulation infarction was very similar for plaques at the different locations (common carotid artery, bifurcation, or internal carotid artery). However, the risk increases for anterior circulation infarction were not statistically signifi-

TABLE 2. Rate Ratio of Stroke and Cerebral Infarction in Relation to Carotid Plaques, Adjusted for Age and Sex

		Stroke		Cerebral Infarction	
Plaque	Subjects at Risk	No. of Events	Rate Ratio (95% CI)	No. of Events	Rate Ratio (95% CI)
No plaque (reference)	1685	41	1.00 (reference)	24	1.00 (reference)
Total plaque score					
1–2 Plaques	1459	55	1.14 (0.74–41.74)	30	1.22 (0.69–2.17)
3–4 Plaques	795	38	1.27 (0.79–2.04)	18	1.38 (0.72–2.65)
5–6 Plaques	278	26	2.44 (1.42–4.20)	13	2.70 (1.27–5.77)
Any plaque	2532	119	1.31 (0.90–1.91)	61	1.40 (0.84–2.34)
Plaques at different locations*					
≥1 Plaque in left or right CCA	638	40	1.58 (0.97–2.59)	17	1.45 (0.72–2.94)
≥1 Plaque in left or right BIF	2242	113	1.42 (0.97–2.09)	59	1.52 (0.90–2.55)
≥1 Plaque in left or right ICA	1452	71	1.25 (0.82–1.91)	37	1.37 (0.78–2.42)

*Groups with plaques at different locations are not mutually exclusive.
CCA indicates common carotid artery; BIF, bifurcation; and ICA, internal carotid artery.

TABLE 3. Rate Ratio of Ipsi and Contralateral Infarction in Relation to the Side of Carotid Plaque, Adjusted for Age and Sex

Plaque	Subjects at Risk	Infarction in Right Hemisphere		Infarction in Left Hemisphere	
		No. of Events	Rate Ratio (95% CI)	No. of Events	Rate Ratio (95% CI)
Right carotid artery*					
0 Plaques	2190	8	1.00 (reference)	12	1.00 (reference)
1 Plaque	1085	7	1.58 (0.56–4.42)	12	1.83 (0.81–4.12)
2 Plaques	687	9	3.10 (1.16–8.26)	8	1.92 (0.76–4.81)
3 Plaques	255	3	2.80 (0.72–11.00)	2	1.40 (0.30–6.44)
Any plaques	2027	19	2.23 (0.95–5.23)	22	1.81 (0.87–3.75)
Left carotid artery*					
0 Plaques	2137	9	1.00 (reference)	10	1.00 (reference)
1 Plaque	1147	6	1.12 (0.39–3.17)	11	1.93 (0.81–4.89)
2 Plaques	683	7	2.18 (0.79–6.03)	9	2.75 (1.09–6.93)
3 Plaques	250	5	4.05 (1.28–12.83)	4	3.49 (1.04–11.68)
Any plaque	2080	18	1.77 (0.78–4.04)	24	2.33 (1.09–4.98)
No plaques	1685	7	1.00 (reference)	6	1.00 (reference)
Plaques only in left carotid artery	505	1	0.45 (0.05–3.64)	6	3.23 (1.04–10.06)
Plaques only in right carotid artery	452	2	0.98 (0.20–4.76)	4	2.30 (0.64–8.21)
Plaques in both carotid arteries	1575	17	2.20 (0.88–5.51)	18	2.98 (1.15–7.75)

*Number of locations where plaques were observed (range 0–3).

cant. Neither total plaque score nor plaques at different segments of the carotid artery showed a significant relationship with the risk of nonlacunar infarction in the posterior circulation. Increase in total plaque score gradually increased risk of lacunar infarction. Participants with 3 to 4 plaques had >5-fold increased risk, and participants with 5 to 6 plaques had >10-fold increased risk of lacunar infarction (age- and sex-adjusted RR, 10.84 [95% CI, 1.70 to 69.67]). With adjustment for systolic and diastolic blood pressure and diabetes, the relative risk associated with severe plaques decreased to 7.86 (95% CI, 1.20 to 51.72). Additional adjustment was not possible because of paucity of data.

Medication Use

A total of 372 (8%) and 92 (2%) participants, respectively, reported present use of aspirin and statins. The number of statin users was too low to perform stratified analysis. Additional adjustment for statin use did not change the results. We found that carotid plaques increased the risk of cerebral infarction in participants who did not use aspirin (RR 1.24 [95% CI, 1.08 to 1.42] per plaque increase). Plaques did not increase the risk in aspirin users (RR 0.82 [95% CI, 0.57 to 1.16]). Corresponding relative risks in participants without previous cardiovascular disease were 1.27 (95% CI, 1.08 to 1.50) and 0.92 (95% CI, 0.61 to 1.38), respectively.

TABLE 4. Rate Ratio of Subtypes of Cerebral Infarction in Relation to Carotid Plaques, Adjusted for Age and Sex

Plaque	Subjects at Risk	Non-Lacunar Infarction				Lacunar Infarction	
		Anterior Circulation		Posterior Circulation			
		No. of Events	Rate Ratio (95% CI)	No. of Events	Rate Ratio (95% CI)	No of Events	Rate Ratio (95% CI)
No plaque	1685	9	1.00 (reference)	9	1.00 (reference)	2	1.00 (reference)
Total plaque score							
1–2 Plaques	1459	12	0.97 (0.38–2.48)	5	0.64 (0.21–1.97)	6	3.50 (0.70–17.56)
3–4 Plaques	795	5	0.91 (0.30–2.83)	3	0.60 (0.15–2.36)	6	5.54 (1.03–29.77)
5–6 Plaques	278	8	3.24 (1.08–9.72)	1	0.59 (0.07–4.88)	3	10.84 (1.70–69.67)
Any plaque	2532	25	1.16 (0.51–2.63)	9	0.62 (0.23–1.66)	15	4.64 (1.03–20.96)
Plaques at different locations*							
≥1 Plaque in left or right CCA	638	8	1.27 (0.42–3.83)	2	0.51 (0.10–2.58)	4	5.69 (0.93–34.73)
≥1 Plaque in left or right BIF	2242	23	1.27 (0.56–2.91)	9	0.70 (0.26–1.89)	15	5.35 (1.18–24.20)
≥1 Plaque in left or right ICA	1452	17	1.32 (0.54–3.21)	6	0.62 (0.21–1.88)	9	4.62 (0.93–23.00)

*Groups with plaques at different locations are not mutually exclusive.

CCA indicates common carotid artery; BIF, bifurcation; and ICA, internal carotid artery.

Discussion

The present study shows a dose-dependent relation between carotid plaques and the risk of stroke and cerebral infarction, irrespective of location of plaques. The risk estimates were highest for lacunar infarctions. Carotid plaques increase the risk of infarction in the anterior but not in the posterior circulation. A few methodological issues need to be addressed. First, apart from slightly lower blood pressure levels and higher body mass index in subjects with compared with subjects without missing plaque values, we found no differences in cardiovascular risk factors. Therefore, we think that restriction to participants with complete plaque score did not lead to a selection bias. The reproducibility of plaques showed moderate agreement, and some misclassification may have occurred. We may also have misclassified some strokes, especially when information was limited. However, because plaque assessment was performed blinded for case status and vice versa, misclassification, if any, was nondifferential, leading to an underestimation of the true associations.[17] For stroke subtypes we restricted ourselves to CT scan–confirmed or MRI-confirmed infarctions to reduce possible misclassification. In clinical practice, cerebral infarctions are often classified according to presumed pathogenesis.[18] Using such a classification in etiologic research would introduce a circular argument. For example, carotid atherosclerosis would by definition be related to large-vessel strokes. Therefore, we deliberately classified cerebral infarctions according to size and location.

The present study was performed in neurologically asymptomatic subjects in whom carotid stenosis was rare. Most studies on carotid plaques and stroke have been performed in patients with carotid stenosis or in patients who suffered from a stroke or TIA.[1–3,19] The Cardiovascular Health Study is the only other population-based cohort study that has investigated carotid plaques in relation to subsequent stroke in asymptomatic subjects.[4] In that study, 4886 participants were monitored for 3.3 years, and 175 strokes occurred. The study focused on characteristics of the most prominent plaque in the bifurcation or internal carotid artery and concluded that hypoechogenic but not hyperechogenic plaques increased the risk of ischemic stroke. In the present study, we add to those findings in that we show a dose-dependent relation between number of sites affected with plaques and risk of stroke but no differences in risk associated with plaques located at different sites in the carotid arteries.

An important question is whether carotid plaques are related to stroke as markers of generalized atherosclerosis or as sources of thromboemboli. Observations in favor of the generalized atherosclerosis hypothesis include: (1) The risk of cerebral infarction does not depend on plaque location. However, the considerable overlap of plaques at different locations limits the potential to decisively assess this. (2) In line with findings in a few other studies,[8,20] we found no differences between risk of infarction in the ipsi and the contralateral hemisphere in relation to the side of the carotid plaque, as we would have expected if plaques were primarily sources of emboli. (3) Plaques were related to lacunar infarction. Because only a few lacunar infarctions are caused by thromboemboli,[21] this suggests that carotid plaques are associated with lipohyalinosis or intracranial atherosclerosis on small-vessel level. There are 2 findings that argue in favor of thromboemboli. First, we observed that carotid plaques increase the risk of anterior but not of posterior circulation infarction. The anterior cerebral circulation mostly is supplied by the carotid arteries, whereas the posterior circulation is not. Emboli from the carotid arteries most likely will go to the anterior circulation. Second, carotid plaques do not increase the risk of stroke in aspirin users. Underlying this may be that aspirin stabilizes plaques, which results in fewer thromboemboli. Because the effects of aspirin are manifold and confounding by indication may play a role, this should not be overinterpreted.

We conclude that carotid plaques are associated with increased risk of stroke, irrespective of their location. It is likely that carotid plaques in neurologically asymptomatic subjects are both markers of generalized atherosclerosis and sources of thromboemboli.

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