Cardiovascular Determinants of Carotid Artery Disease
The Rotterdam Elderly Study

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The objective of the present study was to assess the prevalence of moderate and severe stenosis of the right carotid artery in the elderly and its associations with smoking, blood pressure, serum lipid levels, and hemostatic factors. The Rotterdam Elderly Study is a recently started single-center prospective follow-up study of a cohort of 11,854 elderly people aged 55 years or more. In 1990, 954 participants of the Rotterdam Elderly Study underwent ultrasonic duplex examination of the right internal carotid artery. A reduction of the lumen diameter of 16-49% was found in 29 people (3.0%). Severe stenosis (50% or more) was observed in 13 people (1.4%). With differences in age, sex, and body mass index taken into account, subjects with moderate-to-severe carotid artery disease had, compared with participants without stenosis, lower mean high density lipoprotein cholesterol levels (mean difference, 0.10 mmol/l; 95% confidence interval, 0, 0.20) and higher mean fibrinogen levels (difference, 0.24 g/l; 0.04, 0.45). Among them were more people with hypertension (mean difference, 16%) and more current smokers (mean difference, 13%). Factor VIIc and factor VIIIc activity was higher in subjects with carotid artery disease, without, however, reaching statistical significance (mean difference, 0.06 IU/ml [−0.01, 0.12] and 0.21 IU/ml [−0.05, 0.47], respectively). Our data suggest that hypertension, smoking, and reduced serum high density lipoprotein cholesterol levels, combined with unfavorable increases in hemostatic factors, may be related to carotid artery disease in the elderly.

(Hypertension 1992;19:717–720)

KEY WORDS • carotid artery disease • aged • systolic hypertension • hemostasis

Symptoms of cerebral ischemia have been related to atherosclerotic lesions of the carotid artery.1,2 Furthermore, the presence of severe atherosclerotic carotid artery disease has been associated with an increased risk of cerebral ischemia and infarction.3,4 Data on the prevalence of hemodynamically significant stenosis of the carotid artery and its determinants in a nonhospitalized elderly population are limited. Noninvasive duplex ultrasonography, combined with Doppler spectral analysis, may be used to assess hemodynamically significant stenosis of the carotid artery in an effective and accurate way.5

In this article, we report on the prevalence of hemodynamically significant stenosis of the right carotid artery among the first 1,000 participants in the Rotterdam Elderly Study. In addition, we assessed associations between carotid artery disease and several cardiovascular risk indicators, including hemostatic factors.

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Methods
Population

The Rotterdam Elderly Study is a recently started single-center prospective follow-up study of a cohort of 11,854 elderly people, aged 55 years or more, living in a suburb of Rotterdam, The Netherlands. The study has been approved by the Medical Ethics Committee of Erasmus University, and written informed consent was obtained from all participants. The rationale and design of the Rotterdam Elderly Study have been described elsewhere.6 In short, the objective of the study is to clarify the determinants of occurrence of chronic, disabling cardiovascular, neurogeriatric, locomotor, and ophthalmologic diseases. With respect to cardiovascular disease, the Rotterdam Elderly Study focuses on the contribution of thrombogenic factors to atherosclerotic disease and on the presence and progression of atherosclerosis of the vessel wall. The study comprises an extensive home interview, followed by two visits at the research center for a clinical examination. The participation rate of the cohort at the time of the present analysis was 72%.

Measurements and Definitions

Information on current health status, medical and family histories, drug use, and smoking behavior was obtained using a computerized questionnaire. With respect to smoking behavior, subjects were categorized in groups of current smokers, former smokers, and...
those who had never smoked. During two visits at the research center, several cardiovascular risk indicators were measured. Height and weight were measured according to the guidelines of the World Health Organization. Body mass index (kilograms per square meter) was used as an indicator of obesity. Sitting blood pressure was measured at the right upper arm with a random-zero sphygmomanometer. The average of two measurements, separated by a count of pulse rate, was used in the analysis. Hypertension was defined as a systolic blood pressure of 160 mm Hg or more, or a diastolic blood pressure of 95 mm Hg or more, or use of antihypertensive drugs.

Ultrasonography of the carotid arteries was performed with a duplex scanner (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, Wash.). Hemodynamically significant stenosis of the carotid artery was assessed with a 7.5-MHz sector transducer in combination with a 5-MHz pulsed Doppler. For reasons of feasibility, only the right carotid artery was measured. Interpretation of velocity profiles was done online according to standard criteria. The right internal carotid artery was categorized as normal (0% reduction of lumen diameter), minimal lesions (1–15% reduction), moderate stenosis (16–49% reduction), or severe stenosis (≥50% reduction). People whose velocity profiles indicated a reduction of the lumen diameter of 16% or more returned to the research center within 2 weeks for a second scanning procedure of both carotid arteries.

A venipuncture was performed, applying minimal stasis, with a 21-gauge butterfly needle. Samples were collected into siliconized Vacutainer tubes containing 3.8% trisodium citrate and were centrifuged for 10 minutes at 1,600g at 4°C. Plasma was separated, subsequently centrifuged for 10 minutes at 10,000g at 4°C, and stored at −80°C before assay. Serum total cholesterol was determined with an automated enzymatic procedure. High density lipoprotein (HDL) level was measured similarly, after precipitation. Plasma fibrinogen level was assessed according to the Clauss method (Diamed AG, Switzerland). Factor VIIc and factor VIIc activity was assayed by means of the Automatic Coagulation Laboratory (ACL) (Instrumentation Laboratory, Waltham, Mass.), using factor VIIc– and factor VIII–deficient plasma (Ortho Diagnostics Systems, West Point, Pa.) and Thromborel P (Behringwerke, FRG) and Thromborel S (Behringwerke, FRG) as reagents, respectively. Plasma obtained from 40 healthy men was pooled and served as a reference for measurements of factor VIIc and factor VIIc activity. Factor VIIc and factor VIIIc levels of the donors were all within a normal range, and no differences between reference pools could be detected.

Data Analysis

The mean levels and proportions of several risk indicators of subjects with minimal lesions and moderate-to-severe stenosis were compared with those of subjects without stenosis. The latter group was considered as a reference group. Multiple linear regression analysis was used for analysis of differences across groups adjusted for several confounding variables. Differences are presented with a 95% confidence interval (CI) and a two-sided p value. For results on factor VIIc activity, subjects currently using anticoagulant drugs were excluded (n=47). Analyses for trends across groups were similarly performed using multiple regression analysis.

Results

Of the first 1,000 participants of the Rotterdam Elderly Study, 769 people were aged 55–75 years and 231 aged 75 years or more. In 27 people, ultrasonography could not be performed because of technical or logistic reasons. In 19 subjects, it was not possible to obtain reliable measurements of the internal carotid artery, mainly because of extreme tortuosity of the artery. Complete duplex data of the right carotid artery were available for 954 subjects. Table 1 presents baseline characteristics.

A moderate stenosis, 16–49% reduction of the lumen diameter, of the right internal carotid artery was found in 29 subjects (11 men) (3.0%; 95% CI, 2.0–4.1). A stenosis of more than 50% was observed in 13 people (nine men) (1.4%). The prevalence of right-sided severe carotid artery stenosis among men and women aged 55–75 years was 2.4% (95% CI, 0.6–4.1) and 0.7% (95% CI, 0.0–1.4), respectively.

Because of the small number of subjects with severe carotid artery disease, subjects with moderate or severe stenosis were considered as one group in the analysis. Table 2 presents mean values for blood pressure, smoking, serum lipid levels, and hemostatic factors for those with no stenosis, minimal lesions, and moderate-to-severe stenosis of the right carotid artery. The observed differences in serum lipid levels and hemostatic factors between subjects with minimal lesions and those without stenosis did not reach statistical significance. Hypertension, however, significantly differed across groups. This finding remained significant after adjustment for differences in age, sex, and body mass index.

Subjects with moderate-to-severe carotid artery stenosis had, compared with subjects without stenosis, significantly lower mean levels of HDL cholesterol (Table 2). Furthermore, current smoking and hypertension were more common among subjects with moderate-to-severe carotid artery disease. These findings were independent of age, sex, and body mass index. Current smoking was strongly associated with elevated levels of fibrinogen (p<0.01), and mean fibrinogen levels across groups were compared for smoking. Elevated plasma fibrinogen was related to atherosclerotic carotid artery disease independently of age, sex, body mass index, and
smoking. Mean levels of factor VIIc and factor VIIIc activity were higher in the stenotic group compared with the reference group, without, however, reaching statistical significance. Across groups with increasing severity of carotid atherosclerosis, significant trends were found for hypertension ($p<0.01$), smoking ($p=0.01$), HDL cholesterol ($p=0.03$), and fibrinogen ($p=0.03$).

### Discussion

Our data indicate that the prevalence of right-sided severe carotid artery stenosis among people aged 55-75 years is 1.4%: 2.4% in men and 0.7% in women. For subjects aged 75 years or more, prevalence was 1.4%. Hypertension is significantly more common in subjects with minimal and moderate-to-severe carotid artery disease. Furthermore, subjects with moderate-to-severe stenosis have a higher mean fibrinogen level and a lower mean HDL cholesterol level compared with subjects without stenosis. Among them were significantly more current smokers. In addition, participants with moderate-to-severe stenosis have higher mean levels of factor VIIc and factor VIIIc activity. Although the differences in hemostatic factors did not reach statistical significance, they may suggest an increased activation of the coagulation system in moderate-to-severe atherosclerotic carotid artery disease. Trend analysis suggested that a gradual increase in severity of carotid atherosclerosis may be associated with an unfavorable change in mean levels of cardiovascular risk factors.

In our present study, only the right carotid artery was evaluated. Because carotid artery disease appears to be randomly distributed across both left and right sides, in a number of subjects in our reference group may have had left-sided carotid artery stenosis. This may reduce the magnitude of observed differences between groups, provided a true association exists between the observed cardiovascular risk factors and stenosis of the carotid artery. Consequently, the observed associations in our study might actually have been stronger if a classification based on two carotid arteries could have been used.

Selective survival and selective nonresponse may have led to underestimation of the prevalence of one-sided carotid artery disease, the extent of which, however, cannot be ascertained. Estimates of prevalence of moderate and severe carotid artery stenosis vary across studies. In a survey among 316 asymptomatic subjects, aged 55-74 years, Josse and coworkers observed a prevalence of 1.6%. Colgan and associates reported a prevalence of 3.2% severe carotid artery stenosis among 348 unscreened asymptomatic subjects. Others found a prevalence of 5-6%. The differences across studies may in part be due to differences in methods of assessing stenosis (duplex versus continuous wave), in definitions of the cutoff point of carotid artery stenosis, in age groups, and in nonresponse. Yet, our estimate is quite similar to those observed by others, when one takes into account that carotid artery disease appears to be randomly distributed across both left and right sides.

In previous studies, the presence of hypertension and current smoking was associated with moderate and severe carotid artery disease. The lack of association with total cholesterol in our study may in part be explained by selective survival. In addition, a decrease in relative importance of this factor with age may also have contributed to this finding.

Results from several studies have suggested an important role for coagulation and hemostasis in the initiation and progression of cardiovascular disease. An elevated fibrinogen level is a major cardiovascular...
risk factor. Increased levels of factor VIIc and factor VIIIc activity have been associated with increased risk of coronary heart disease. In elderly subjects with atherosclerotic disease, raised levels of factor VIIc and factor VIIIc activity were recently observed. Our results support these findings and suggest that these mechanisms are indeed operative in carotid artery disease. Confirmation, however, is needed. The baseline findings of the Rotterdam Elderly Study reflect cross-sectional measurements, so it therefore cannot be ascertained whether the differences between stenotic and nonstenotic groups indicate mechanisms that cause atherosclerotic lesions or are a consequence of atherosclerosis. In view of this, it is important to confirm these associations in prospective follow-up studies.

We conclude that in a considerable proportion of the elderly population, moderate or severe carotid artery stenosis is present. Hypertension, smoking, and low HDL cholesterol levels are significantly associated with atherosclerosis of the carotid artery. Furthermore, elevated fibrinogen levels show an independent relation with carotid artery disease. These findings suggest that an unfavorable cardiovascular risk profile, including changes in hemostatic factors, may be related to carotid artery disease.

Acknowledgments

We are grateful to the participants of the Rotterdam Elderly Study. We thank all field-workers, ultrasound technicians, and laboratory technicians in the Ommoord research center for their enthusiasm and skillful contributions to the data collection.

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_Hypertension_. 1992;19:717-720
doi: 10.1161/01.HYP.19.6.717

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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