Cardiovascular Determinants of Carotid Artery Disease
The Rotterdam Elderly Study

Michiel L. Bots, Paul J. Breslau, Ernest Briët, Anthony M. de Bruyn, Huub H.D.M. van Vliet, Frank A. van den Ouweland, Paulus T.V.M. de Jong, Albert Hofman, and Diederick E. Grobbee

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 VIIic 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. Furthermore, the presence of severe atherosclerotic carotid artery disease has been associated with an increased risk of cerebral ischemia and infarction. 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.

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.

From the Department of Epidemiology and Biostatistics (M.L.B., A.M. de B., F.A. van den O., A.H., D.E.G.), Erasmus University Medical School, Rotterdam; Department of Vascular Surgery (P.J.B.), Rode Kruis Hospital, The Hague; Department of Haematology and Thrombosis (E.B.), Academic Hospital Leiden, Leiden; Department of Haematology (H.H.D.M. van V.), Academic Hospital Dijkzigt, Rotterdam; and Department of Ophthalmology (P.T.V.M. de J.), Oogziekenhuis, Rotterdam, The Netherlands.

Address for correspondence: Dr. D.E. Grobbee, Department of Epidemiology and Biostatistics, Erasmus University Medical School, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.

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. 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 10,000g at 4°C, and stored at −80°C before assay. Serum total cholesterol was determined with an automated enzymatic method. Factor VIIc and factor VIIIc activity was assayed by means of the Automatic Coagulation Laboratory (ACL) (Instrumentation Laboratory, Usselstein, The Netherlands), using factor VII- and factor VIII-deficient plasma (Ortho Diagnostic Systems, Beijing, Belgium) with Thromborel S (Behringwerke, FRG) and Thrombostil I (Ortho Diagnostic Systems) as reagents, respectively. Plasma fibrinogen level was assessed according to the Clauss method 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
### TABLE 2. Comparisons of Cardiovascular Characteristics at Baseline of Subjects With Minimal and Moderate-to-Severe Stenosis of the Carotid Artery Relative to Reference Group (0% Stenosis)

<table>
<thead>
<tr>
<th>Cardiovascular determinants</th>
<th></th>
<th>Baseline values</th>
<th>Adjusted values*</th>
<th>Adjusted difference between moderate/severe stenosis and reference group</th>
<th>[95% CI]</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carotid artery stenosis</td>
<td>0%</td>
<td>1–15%</td>
<td>≥16%</td>
<td>0%</td>
<td>1–15%</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td></td>
<td>133.4 (0.7)</td>
<td>139.7 (1.5)</td>
<td>138.2 (3.3)</td>
<td>133.8 (0.71)</td>
<td>138.6 (1.36)</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td></td>
<td>70.3 (0.4)</td>
<td>72.0 (0.8)</td>
<td>67.7 (1.8)</td>
<td>70.3 (0.39)</td>
<td>72.1 (0.74)</td>
</tr>
<tr>
<td>Hypertension (yes)</td>
<td></td>
<td>34%</td>
<td>47%</td>
<td>53%</td>
<td>33% (2)</td>
<td>44% (3)</td>
</tr>
<tr>
<td>Current smoking (yes)</td>
<td></td>
<td>23%</td>
<td>26%</td>
<td>32%</td>
<td>22% (2)</td>
<td>28% (3)</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td></td>
<td>6.74 (0.04)</td>
<td>6.76 (0.08)</td>
<td>6.60 (0.23)</td>
<td>6.74 (0.04)</td>
<td>6.77 (0.08)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td></td>
<td>1.35 (0.01)</td>
<td>1.32 (0.02)</td>
<td>1.21 (0.04)</td>
<td>1.35 (0.01)</td>
<td>1.32 (0.02)</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td></td>
<td>2.72 (0.02)</td>
<td>2.81 (0.05)</td>
<td>3.02 (0.13)</td>
<td>2.73 (0.02)</td>
<td>2.77 (0.05)</td>
</tr>
<tr>
<td>Factor VIIc (IU/ml)†</td>
<td></td>
<td>1.08 (0.01)</td>
<td>1.09 (0.02)</td>
<td>1.11 (0.04)</td>
<td>1.08 (0.01)</td>
<td>1.09 (0.02)</td>
</tr>
<tr>
<td>Factor VIIIc (IU/ml)‡</td>
<td></td>
<td>2.06 (0.03)</td>
<td>2.10 (0.06)</td>
<td>2.28 (0.14)</td>
<td>2.06 (0.03)</td>
<td>2.07 (0.06)</td>
</tr>
</tbody>
</table>

---

Values are percentages or means with SEM in parentheses.

*Values are adjusted for differences in age, sex, body mass index, and, when appropriate, for cholesterol and smoking.

†Those currently using anticoagulant drugs (n=47) have been excluded.

‡Test for trend \( p<0.05 \).

---

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%: 2.4% in men and 0.7% in women. For subjects aged 55–74 years, Josse and coworkers\(^3\) observed a prevalence of right-sided carotid artery stenosis of 5-6%.\(^{12,13,14}\) 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.\(^{12,15,16}\)

In previous studies, the presence of hypertension and current smoking was associated with moderate and severe carotid artery disease.\(^{12,13,15,16}\) 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.\(^{17}\)

Results from several studies have suggested an important role for coagulation and hemostasis in the initiation and progression of cardiovascular disease.\(^{14,16}\) An elevated fibrinogen level is a major cardiovascular risk factor.
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.

References

Cardiovascular determinants of carotid artery disease. The Rotterdam Elderly Study.
M L Bots, P J Breslau, E Briët, A M de Bruyn, H H van Vliet, F A van den Ouweland, P T de Jong, A Hofman and D E Grobbee

doi: 10.1161/01.HYP.19.6.717

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/19/6_Pt_2/717

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/