Prevalence and Risk Factors of Asymptomatic Extracranial Carotid Artery Atherosclerosis
A Population-Based Study

Johann Willeit and Stefan Kiechl

To evaluate the prevalence and risk factors of asymptomatic carotid artery disease, we analyzed a sample of 909 men and women (aged 40–79 years) drawn from the community-based Bruneck Ischemic Heart Disease and Stroke Prevention Study. For the four decades of age (40–49, 50–59, 60–69, and 70–79 years), respective prevalence rates as assessed by duplex scanning were found to be 8.2%, 39.7%, 66.4%, and 82.5% in men and 3.3%, 22.3%, 48.7%, and 76.7% in women. High-grade stenosis (>80%) classified by Doppler criteria was twice as frequent in men (2.4%) as in women (1.1%). Age and sex were found to be particularly strong and independent predictors of asymptomatic carotid artery disease. Accordingly, separate logistic regression models were developed for both men and women in the elderly (65–79 years) and middle-aged (50–64 years) groups. Systolic blood pressure turned out to be the only attribute with independent significance in all subgroups examined. Cigarette smoking, recorded as pack-years, emerged as the leading risk factor of carotid atherosclerosis in men. Serum fibrinogen levels were found to be highly indicative of carotid artery disease in elderly men and women. For apolipoprotein B predictive significance was observed in the middle-aged populations, whereas apolipoprotein A-I had a protective effect in elderly women. Diabetes mellitus completed the risk factor profile for elderly men. In summary, the relation between cardiovascular risk factors and asymptomatic carotid artery disease showed a dynamic dependence on sex and age. These findings may help to improve the efficacy of risk prediction in the general population and facilitate well-directed preventive measures. (Arteriosclerosis and Thrombosis 1993;13:661–668)

KEY WORDS • carotid atherosclerosis • epidemiology • risk factors • ultrasound

Extracranial carotid artery disease is one of the leading causes of ischemic stroke and is therefore closely related to cardiovascular morbidity and mortality.1–3 Its clinical relevance can be expected to increase in view of the continuously growing number of elderly people with frequent and more advanced atherosclerotic lesions. The high-resolution duplex technique is a noninvasive method that facilitates the assessment and screening of presymptomatic stages of carotid atherosclerosis in apparently healthy subjects.4–9 To date, several population studies have been conducted in middle-aged men and women.10–14 In the elderly, however, so far as we are aware, population-based information on the prevalence and predictors of carotid atherosclerosis (as assessed by duplex scanning) is not yet available. In this report, we present epidemiological data and risk factor profiles of asymptomatic carotid artery disease assessed in a representative population sample of men and women aged 40–79 years.

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Methods

Study Population

The Bruneck Ischemic Heart Disease and Stroke Prevention Study is a prospective, population-based study on the epidemiology, pathophysiology, and prevention of cardiovascular disease. Population recruitment and baseline examination were performed in the community of Bruneck (province of Bozen, northern Italy) from July to November 1990. The study population was selected as a 21% random sample (n=1,000) of all inhabitants aged 40–79 years (N=4,793; prevalence day, May 1, 1990). Men and women were selected equally for inclusion in the study on the basis of an age-stratified, random-sampling strategy (125 subjects for each decade of age). The high participation rate of 93.6% provided a safeguard against potential biasing. Men and women with clinical symptoms or a history of transient ischemic attack or ischemic stroke were excluded (n=14). Further selection criteria for exclusion were missing laboratory data (n=17) and carotid endarterectomy (n=2). Subjects receiving antihypertensive, hypoglycemic, or lipid-lowering drugs were not excluded to maintain a nearly unselected and representative population (n=909).

Clinical History and Examination

To obtain a detailed history of cardiovascular risk factors, all participants were administered a standard-
ized questionnaire; they also underwent a complete neurological and cardiological examination, including an electrocardiogram. The variables used in the current article were defined as follows. "Family history" was classified as positive if at least one of the parents or one sibling had suffered a stroke before the age of 65. The average number of cigarettes smoked per day and the number of years smoked ("pack-years") were noted for each smoker and exsmoker. With a standard mercury sphygmomanometer, the systolic and diastolic blood pressures were taken while the subject was in a sitting position, and the mean was determined from two independent measurements, each of which was made after 10 minutes of rest. The body mass index was calculated as weight (in kilograms) divided by height squared (meters squared). Diabetes mellitus was diagnosed if the subject was being treated with insulin or oral hypoglycemic drugs, if the subject's fasting plasma level of glucose exceeded 140 mg/dL, and/or if the 2-hour value after oral glucose loading exceeded 200 mg/dL. Coronary artery disease was coded as present if the subject had a documented clinical history of myocardial infarction, a codable Q-QS pattern on the electrocardiogram (Q waves with a duration of 0.04 second or more and an amplitude ≥25% of the R wave in the same lead), and/or a documented history of angina pectoris. Leisure-time physical activity was recorded using a three-category scale: 1) subjects who did not exercise at all, 2) regular physical activity of up to 2 hours per week, and 3) regular physical activity of more than 2 hours per week. Alcohol consumption was quantified from each subject's estimate of the average amount of alcoholic beverages ingested daily or weekly. On the basis of the calculated daily alcohol intake (grams per day), the responses were classified into three categories: 1) no alcohol intake or <15 g per day, 2) <100 g alcohol per day, and 3) > 100 g alcohol per day. Finally, two social class categories based on the following criteria were used: occupational status of the person with the highest income in the household and educational level of the subject included in the study.

**Laboratory Methods**

Venous blood samples were taken between 7:30 and 9:30 AM after 12 hours of fasting and abstinence from smoking. If possible, no vein stases were used. In cases of acute infection, a condition well known to interfere with risk factor levels such as fibrinogen, the definitive samples were drawn as long as 6 weeks later. Repeated measurements were also obtained whenever a blood sample clotted or when strict fasting was not observed. All participants except those receiving insulin underwent an oral glucose tolerance test (75 g glucose in 10% solution). Plasma glucose was analyzed colorimetrically using hexokinase and glucose-6-phosphate dehydrogenase.15 Fibrinogen was assayed according to the method of Claus.16 Laboratory protocols included measurement of lipids (cholesterol and triglycerides), lipoprotein subfractions, and lipid compounds (apolipoproteins A-I and B). Commercial enzymatic methods were used for the determination of total cholesterol (CHOD-PAP method, Merck, Darmstadt, FRG) and triglycerides (GPO-PAP method, Merck). High density lipoprotein cholesterol was measured in the supernatant after precipitation of apolipoprotein B-containing lipoproteins with phosphotungstic acid and Mg2+ ions. Low density lipoprotein cholesterol was calculated from the Friedewald formula (Friedewald et al17). Apolipoproteins A-I and B were determined with an immunonephelometric fixed-time method on a Behring nephelometric analyzer with Behring standards and antisera (Behringwerke AG, Marburg, FRG).

**Assessment of Carotid Atherosclerosis**

Sonographic assessment of the extracranial carotid arteries was performed using a duplex ultrasound system (ATL UM8, Advanced Technology Laboratories, Bothel, Wash.) with a 10-MHz imaging probe and 5-MHz Doppler. All subjects were examined in a supine position. The scanning protocol included imaging of the common and internal carotid arteries on both sides in multiple longitudinal and transverse planes. The extent of carotid atherosclerosis was quantified by a plaque scoring system based on a modification of the method of Crouse et al.18 Measurements were performed at the following locations in the left and right carotid arteries: proximal common carotid artery (15–30 mm proximal to the carotid bulb), distal common carotid artery (<15 mm proximal to the carotid bulb), proximal internal carotid artery (carotid bulb and the initial 10 mm of the vessel), and distal internal carotid artery (>10 mm above the flow divider) (Figure 1). The score was calculated by adding the maximum axial thickness of atherosclerotic plaques (in millimeters) on the near and far walls at each imaging site, with plaques defined as echo structures encroaching into the lumen of the vessel. Theoretically, the score from a single subject could be composed of one to 16 different figures.
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depending on how many plaques were identified. Subjects presenting without plaques had a score of zero. The performance of multiple measurements on both the near and far walls carefully considers the occurrence of atherosclerotic disease at variable sites, thus minimizing the risk of false-negative classifications. The advantage of this method is associated with a slight weakness in that near-wall measurements have not yet been validated.5

All measurements were carried out by a single trained physician. The images were recorded on videotape. Rescanning was performed blindly by an independent sonographer in 50 subjects, with the object of estimating the interobserver variability. The correlation coefficient between the first measurements and remeasurements was r=0.84; the mean of the absolute value of differences between both assessments was 0.095 mm. The percentage of maximum diameter reduction in the B-mode images was considered in the latter calculation. For the assessment of stenosis, Doppler criteria (the maximum angle correction permitted was 60%) or, when no hemodynamic disturbances were detectable, the percentage of maximum diameter reduction in the B-mode images was applied.18

Statistical Analysis

The performance of kappa statistics, calculated for the categorization used in the risk factor analyses, was excellent, with a coefficient κ=0.90.19 All statistical calculations were performed by applying standard procedures from SPSSX and BMDP software.20,21 Age- and sex-specific differences in the prevalence rates of carotid atherosclerosis were calculated by means of a χ² test (Yates’ correction); differences in the means of the skewed B-mode score were assessed by Kruskal-Wallis and Mann-Whitney U tests. To examine the relations between potential risk factors and carotid atherosclerosis, logistic regression models were developed using a step-forward selection procedure with the hypothesis test based on likelihood-ratio statistics. Each model’s goodness of fit was assessed by the test of Hosmer and Lemeshow.22

For the spectrum of available lipid parameters, preliminary correlation matrices were devised separately for men and women (not presented) to establish a definite (“optimal”) subset of variables appropriate for reliable application of the logistic regression analysis. Apolipoprotein B was selected as the attribute with the highest average correlation coefficient (r=0.57, calculated by Fisher’s z transformation) and consequently the highest representative potential, and apolipoprotein A-I as the attribute with by far the lowest correlation (r=0.27) and possibly highest additional contribution. Both apolipoproteins are not significantly intercorrelated, which is another advantage that they have over their associated cholesterol fractions. Minimizing intercorrelations among independent variables has clear implications on the interpretability of the results. Inclusion of strongly associated parameters in a standard multivariate analysis might be a source of suppression effects caused by the leading variable. Overestimation of insignificant but highly intercorrelated variables might occur as well.

Results

Prevalence

Initial quantification of asymptomatic carotid atherosclerosis was employed separately for the left and the right carotid arteries. The lack of significant hemispheric differences justifies the further use of a single B-mode score for both sides combined. The overall prevalence rates and the 95% confidence intervals for sclerotic lesions were 47.8±4.6% for men and 36.3±4.4% for women (p<0.001, χ² for sex-specific differences). After adjusting for the actual age/sex distribution in Bruneck, community-based prevalence rates of 36.8% and 30.9% were calculated. Involvement

### Table 1. Prevalence of Asymptomatic Carotid Artery Disease in a Population Aged 40–79 Years (n=909)

<table>
<thead>
<tr>
<th>Sex/age (years)</th>
<th>Atherosclerosis present</th>
<th>Score (mean±SEM)</th>
<th>Stenosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>No.</td>
<td>Percent</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>121</td>
<td>4</td>
<td>3.3</td>
</tr>
<tr>
<td>50–59</td>
<td>112</td>
<td>25</td>
<td>22.3</td>
</tr>
<tr>
<td>60–69</td>
<td>113</td>
<td>55</td>
<td>48.7</td>
</tr>
<tr>
<td>70–79</td>
<td>103</td>
<td>79</td>
<td>76.7</td>
</tr>
<tr>
<td>Total</td>
<td>449</td>
<td>163</td>
<td>36.3</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>122</td>
<td>10</td>
<td>8.2</td>
</tr>
<tr>
<td>50–59</td>
<td>116</td>
<td>46</td>
<td>39.7</td>
</tr>
<tr>
<td>60–69</td>
<td>119</td>
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</tr>
<tr>
<td>70–79</td>
<td>103</td>
<td>85</td>
<td>82.5</td>
</tr>
<tr>
<td>Total</td>
<td>460</td>
<td>220</td>
<td>47.8</td>
</tr>
</tbody>
</table>

The score presented is calculated by summing the maximum plaque thickness at eight sites in both common and internal carotid arteries. Values (in millimeters) are mean±SEM. *Stenosis on the basis of atherosclerotic lesions.
of the carotid bifurcation as a site of predilection for severe atherosclerosis was detected in 88.5%; the isolated appearance of plaques in the common carotid arteries accounted for <7%. Detailed age- and sex-stratified results are summarized in Table 1. In both sexes the extent of detectable atherosclerotic disease continuously increased with advancing age (p<0.001); gender-specific differences were significant (p<0.01) in all decades except for the fifth. High-grade stenoses were twice as frequent in men as in women.

Age and Sex

On account of the very low prevalence of sclerotic lesions in the population aged 40-49, which did not allow the reliable application of advanced statistical procedures, the following analyses focus on the age range 50-79 years. In the first orientation analysis, special attention was paid to the factor "sex" and its potential multivariate significance as a predictor of carotid atherosclerosis. On comparing subjects with and without carotid artery disease, male gender was closely (p<0.01) and independently associated with a higher probability (odds ratio, 1.63) of detectable atherosclerosis. The obvious differences in the manifestation and severity of carotid atherosclerosis according to age and sex suggest evident differences in the underlying atherogenic processes and sensitivity of exposure to various risk factors (effect modification25). Therefore, the following analyses were designed to establish risk factor profiles of asymptomatic carotid atherosclerosis as a function of age and sex. Separate logistic regression models were employed in four subpopulations, each covering an equal age range of 15 years. In line with comparable ongoing studies, men and women reaching
or exceeding a cutoff value of 65 years were termed “elderly" 2,24 and those <65 years as “middle-aged.” 10

The number of subjects in each group was found sufficient for reliable application of advanced statistical procedures. This stratification provided the further advantage of a fairly homogeneous expression of carotid atherosclerosis within the subgroups. Age effects were eliminated by applying an age-matched, random-sampling strategy (see below). In an effort to ensure a correct attribution to the “high-risk group,” the 66th percentile of the B-mode score was defined as indicative of advanced atherosclerosis. Men and women in the first tertile of the B-mode score were regarded as control subjects.

Risk Factor Profiles

The descriptive data of case and control subjects are summarized in Table 2. For all candidate cardiovascular risk factors, the mean values in the pathological group were consistently higher than in the control group except for apolipoprotein A-I, physical activity, and social status, for which a reverse relation was obtained.

All analyses were performed in an unselected population sample including subjects with coronary artery disease. Because of the overrepresentation of such patients among those with carotid atherosclerosis, risk factors preferentially related to coronary artery disease might gain unjustified relevance in the latter group as well. 27 To estimate the significance of this potential bias, the equations were repeated without data for coronary patients. The patterns of the assessed risk factors in the corresponding regression models, however, were not essentially different.

Discussion

Duplex ultrasound imaging is the method of choice for the evaluation of carotid atherosclerosis in clinical practice. To date, however, reference values for the appearance and extent of asymptomatic carotid athero-
sclerosis in the general population, particularly in the elderly and in women, are not well documented. In most of the previous studies, epidemiological data were collected in highly selected groups or in population samples of particular sex and age. The design of our study facilitates a depiction of the prevalence data of both sexes for the whole age range of 40–79 years (Table 1).

Only a few studies address the question “to what extent does the prevalence of carotid atherosclerosis differ between the sexes?” Two recent studies failed to find significant sex-specific differences in unselected populations. In the current study, a 2:1 preponderance of men was assessed for the 40–59-year age group. With advancing age, however, the differences, although still detectable, were found to decrease (Table 1), which possibly reflects the loss of the protective premenopausal status. As to the extent of carotid artery disease, we found a 10-year difference between men and women, as a rough estimate. For example, a B-mode score of slightly below 4 mm represents the mean value for both men aged 50–59 years and women aged 60–69 years (Table 1). The age range of 60–64 years in men and of 65–69 years in women was found to be the crucial period for the development of advanced atherosclerotic lesions (stenosis >40%). In the higher age groups, the prevalence of asymptomatic carotid stenosis remains more or less constant, reflecting a steady state between the manifestation of new stenosis and clinical events (stroke).

The variable “age” was no doubt the strongest and most consistent indicator of carotid atherosclerosis. The strong relation of age to carotid atherosclerosis, however, is probably an indirect expression of the continuous exposure to various risk factors rather than the result of an intrinsic process of aging. Age satisfies the criteria of a confounder; intercorrelations with the other cardiovascular risk factors examined are in part very high, a factor that is known to interfere with the reliability and interpretability of the results obtained. For these reasons we decided to eliminate age effects by means of a matching technique. Only after this procedure did a number of variables such as fibrinogen obtain their actual significance.

Cigarette smoking has been identified as one of the strongest predictors of ischemic stroke. As a mechanism through which it enhances the risk of cardiovascular disease, a noncumulative triggering effect (mediated by rheological alterations) has been suggested. In agreement with other reports, pack-years smoked emerged in our study as a strong predictor of atherosclerosis in men and had a great impact in elderly women as well (Table 3). In middle-aged women the addition of smoking did not improve the fit of the logistic regression model employed. Inconsistencies between the sexes may be explained by different smoking habits and possibly by the low smoking prevalence in women and the subsequent lower statistical power.

Previous cross-sectional population studies yielded a close association between carotid atherosclerosis and both hypertension and systolic blood pressure. Regarding diastolic blood pressure, however, a similar relation was not observed. The current study underscores the importance of systolic hypertension in middle-aged men and women and extends these findings to the elderly as well. Diastolic blood pressure emerged as a predictor for carotid atherosclerosis except for men aged 65 or older, although its effect was far less pronounced than that of systolic pressure. These results were not essentially modified when individuals who were receiving antihypertensive medication were excluded from the analysis.

In vitro experiments indicate that fibrinogen triggers various mechanisms that are suspected to play a major role in atherogenesis, such as endothelial injury, fibroblast and smooth muscle proliferation, and migration effects. Besides direct effects, fibrinogen has been suggested to enhance or mediate the injurious effect of other risk factors. The clinical relevance of these experiments, however, has not yet been established. Altogether, the few studies addressing the impact of fibrinogen on carotid atherosclerosis and stroke have reported contradictory results. In the current report, a univariate significance was observed in all subgroups except for young women. When focusing on the logistic regression analysis, fibrinogen persisted as an independently significant factor in the risk prediction for elderly men and women. A causal relation between fibrinogen and prevalent carotid atherosclerosis, however, could not be inferred. The concept that high fibrinogen levels are the response of an acute-phase reactant to continuous atherosclerotic vascular damage cannot be ruled out. With this assumption in mind, elevated serum levels would be an epiphenomenon rather than a cause of carotid atherosclerosis.

The predictive value of blood cholesterol levels for coronary artery disease and myocardial infarction is an uncontested fact in the field of epidemiology. Investigations focusing on the carotid arteries, however, have revealed contradictory results. In the current report underscores the importance of apolipoprotein B as a highly significant indicator of carotid atherosclerosis in middle-aged women and men, the significance being slightly less pronounced in men. In accordance with previous studies on ischemic heart disease, we found the relation between hyperlipidemia and carotid atherosclerosis to decrease with advancing age. Notably in elderly women, apolipoprotein A-I still exerted a moderate protective influence, whereas in men, lipids were no longer associated with carotid atherosclerosis. This observation suggests a preferential involvement of apolipoprotein B—containing lipoproteins in the early phase of atherogenesis rather than in advanced sclerotic disease. Apolipoprotein B estimates the combined atherogenic potential of very low density lipoprotein, intermediate density lipoprotein, and low density lipoprotein particles. This approach takes into account recent data that indicate that, apart from low density lipoprotein, intermediate density lipoprotein and very low density lipoprotein can promote atherosclerosis. To date it is still controversial whether apolipoproteins provide information predictive of atherosclerosis beyond that gained from the data of lipid fractions alone. Previous studies have found diabetes mellitus to be associated with carotid atherosclerosis in univariate analysis. In most of these studies, the significant univariate relation disappeared when other well-established risk factors were also considered. However, there are a few exceptions. The definition of diabetes mel-
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litus is usually based on the patient’s history or on fasting glucose levels, which might entail a considerable number of false-negative attributions. In our study an oral glucose loading test was carried out in each subject, and World Health Organization criteria were applied for definitive classification. In no fewer than 25 subjects was previously unknown diabetes disclosed. Multivariate logistic regression analysis identified diabetes mellitus as an independent indicator of carotid atherosclerosis in elderly men. In the interpretation of these results, it should be considered that diabetes does not occur as an isolated entity but is obviously linked to other risk factors, such as hypertension, elevated fibrinogen level, or disturbed lipid metabolism (metabolic syndrome). With the supposition that diabetes partly exerts its influence via these attributes, a standard multivariate analysis, which presents independent associations, would clearly underestimate the actual significance of diabetes mellitus. Furthermore, it cannot be ruled out that a lack of significant association in middle-aged populations is due to the low prevalence rate of diabetes and the resulting high random variability.

None of the behavioral and social variables tested added significantly to the value of the calculated regression models. Nevertheless, a potential influence cannot be excluded, when considering that the fact that these circumstances might substantially contribute to the development of hypertension, hyperlipidemia, or elevated fibrinogen levels.

In summary, atherogenesis appears to be a highly dynamic process with a changing sensitivity to the exposure to various risk factors that are dependent on sex and age. Therefore, analyses including both sexes or a wide age range measure overall effects. Stratification by age and sex (effect modifier) provides a more accurate description of the relation between risk factors and atherosclerosis. In clinical practice our findings may help to improve the efficacy of risk prediction in the general population, in both middle-aged and elderly men and women.

As to the interpretation of the results, some aspects require consideration. The risk factors collected at the time of baseline examination represent a static view of the continuously changing exposure of the carotid arteries to these attributes. Intraindividual variations and the potential influence of medication interfere with the precision of risk prediction and tend to underestimate the actual significance of given risk factors. According to the study design employed, the risk profiles are related to prevalent rather than incident atherosclerotic disease. Future follow-up studies of this cohort will focus on the progression of carotid artery atherosclerosis.

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