Plaque in superficial femoral arteries indicates generalized atherosclerosis and vulnerability to coronary death: An autopsy study

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Objectives: Risk factors for atherosclerosis have limited ability to identify persons at high risk of coronary heart disease. Assessment of subclinical atherosclerosis in peripheral arteries might improve this limitation. We studied the relationship between atherosclerotic plaques in peripheral arteries, coronary plaques, and coronary death.

Methods: Predefined segments from the left anterior descending coronary artery, the right coronary artery, bilateral carotid, and superficial femoral arteries (SFA) were obtained from 100 autopsies (20-82 years, 30 females, 27 coronary deaths). Based on microscopic examination of 4756 sections, the extension of atherosclerosis (plaque burden) and the largest plaque area in each segment were quantified.

Results: Plaque burden in all arteries increased with age and was larger in coronary death ($P < .05$). SFA plaques occurred later than coronary and carotid plaques. When SFA plaque had developed, coronary plaque was also present. SFA plaque (odds ratio, 95% confidence interval: 7.07 [2.40-20.81]), but not carotid plaque, was significantly associated with coronary death, also after age and gender adjustment (21.25 [5.02-89.97]). The area under the receiver operating characteristic curves for the identification of coronary death individuals was 0.72 (95% confidence interval: 0.62-0.83) for coronary plaque, and 0.80 (0.72-0.89) for SFA plaque (age and gender adjusted).

Conclusions: Atherosclerosis develops slower in SFA compared with coronary and carotid arteries. In persons with plaque in the SFA, plaque is always present in the coronary arteries. In younger persons, the presence of SFA plaque indicates a generalized susceptibility to atherosclerosis and vulnerability to coronary death. (J Vasc Surg 2008;47:296-302.)

Atherosclerosis is the most common cause of coronary artery disease, carotid artery disease, and peripheral arterial disease.[1,2] Primary prevention is important because the first manifestation of atherosclerotic vascular disease is often a potentially fatal event, such as stroke or acute myocardial infarction. Cardiovascular risk factors alone can not reliably identify high-risk persons because most events occur in the very large group of people considered at low or intermediate risk based on risk factor scores. Direct assessment by imaging of atherosclerosis, representing the overall result of individual risk exposure and susceptibility, is probably more helpful.[3] The coronary arteries are not easy targets for noninvasive imaging, and therefore, peripheral arteries are often used instead. B mode ultrasound is a widely available technique which permits measurement of intima-media thickness (IMT) and assessment of plaques, if present.[4] Carotid artery IMT measured by ultrasound has been widely used as a surrogate marker for atherosclerotic burden and risk.[5] Although related to outcome, adding carotid IMT to risks scores for coronary heart disease and stroke does not result in a substantial increase in predictive value when used as a screening tool.[6] The ankle-brachial index (ABI) is a highly specific indirect measure of obstructive peripheral, ie, lower-extremity, atherosclerosis. The ABI has been reported to provide incremental risk-assessment information over and above that of traditional risk factors,[7,8] although use in general screening may be of limited value due to a low sensitivity.[9,10] Instead, direct ultrasound imaging of the superficial femoral arteries (SFA) may provide additional prognostic information.[11,12] In order to identify features characterizing high-risk individuals who might benefit from intensified prophylactic therapy, we performed an autopsy study with comparison of plaque formation in the coronary, carotid, and superficial femoral arteries. Plaque formation was related to age, gender, and coronary death. We specifically investigated the relation between carotid or SFA plaque presence and (1) coronary plaque presence and (2) coronary death.

MATERIAL AND METHODS

Autopsy population. Artery segments were obtained prospectively from six predefined atherosclerosis-susceptible locations: the proximal parts of the left anterior descending (LAD) and the right coronary artery (RCA), the right and left carotid arteries, and the right and left SFA (Fig 1). The segments originated from individuals who underwent a forensic autopsy at the Institute of Forensic Medicine, University of Aarhus, Denmark following the coroner's inquest in the jurisdiction of Northern Jutland (from February 1996 to March 1999). The study was approved by the Regional Research Ethics Committee and The Danish Data
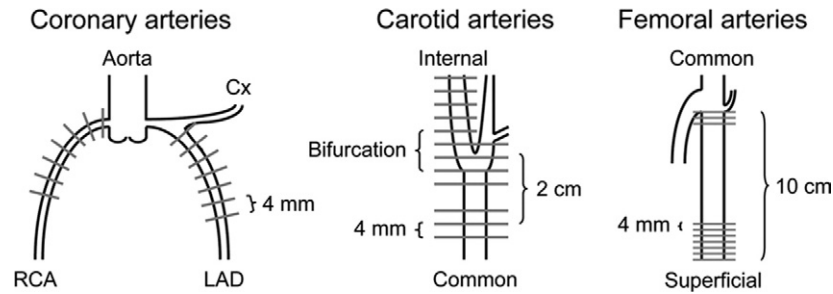
Fig 1. Localization of the predefined artery segments and 4 mm cross-sections in the coronary arteries (left anterior descending [LAD] and the right coronary artery [RCA]: six sections each), the carotid arteries (10 sections in both right and left) and superficial femoral arteries (eight sections in both right and left).

Protection Agency. The indications for the autopsy included sudden unexpected death in younger individuals, drug-related deaths, and deaths under unclear or suspicious circumstances, eg, potentially crime- or medical malpractice-related deaths. The mode of death was unnatural in 51 cases (seven suicides, 42 accidents, two homicides) and natural in 49 cases (including two cancer deaths). All individuals were Caucasian and Danish citizens, except two individuals from other Scandinavian countries. Only individuals aged 20 or older (age range 20-82 years) with a post mortem interval ≤4 days were included. The collection of all segments was supervised by the same pathologist (IBK) and 9.5% of all autopsies in the time-period were included (limited by the post mortem interval restriction and presence of the pathologist). Risk factor data were unavailable in most cases.

In each case, the autopsy was followed by microscopic examination of the myocardium (the anterior and the posterior left ventricle, the interventricular septum, and the right ventricle), as well as the internal organs. Post mortem blood alcohol and toxicology screening was only omitted if the cause of death was obvious after the autopsy and microscopic examination. Based on the autopsy findings, microscopy, and toxicology analyses, the individuals were grouped into those dying from coronary atherosclerosis (coronary death; n = 27, mean age 47.2 ± 12.0 years, 18 men) and those dying from other causes (non-coronary death; n = 73, mean age 47.1 ± 14.9 years, 52 men). The age and gender distribution did not differ ($P > .05$). Coronary death was defined as natural death without extracardiac causes in which there was a thrombus superimposed on an atherosclerotic plaque or at least one epicardial coronary artery with ≥75% cross-sectional luminal narrowing by an atherosclerotic plaque.[13,14]

Tissue processing. The coronary arteries, but not the carotid arteries and SFA, were cut open longitudinally as the standard procedure for the forensic examination. All artery segments were fixed in 4% phosphate buffered formalin for 24 hours and decalcified (unless <45 years of age) in 10% formic acid for 24 hours. Cross-sectioning was performed at 4 mm intervals, and the sections were embedded in paraffin, yielding ~48 paraffin blocks from each subject (4756 paraffin blocks in total; 44 sections were

unavailable). All tissue sections were cut at 4 μm thicknesses and mounted on Superfrost + glass slides.

Microscopic examination and image analysis. All sections were stained with hematoxylin and eosin (n = 4756) and analyzed microscopically in random order blinded to subject data. The presence of plaque in each section was recorded using the histological classification of atherosclerotic lesions endorsed by the American Heart Association where lesions ≥type IV represent plaques.[15] For each artery segment, the plaque burden was determined (plaque burden = number of sections with ≥type IV lesion/total number of sections), and the largest plaque was identified and measured (intima or plaque area) after staining with Masson's elastic trichrome. Using the largest plaque as an indicator of disease is well established from intravascular ultrasound studies (IVUS)[16] and other autopsy studies.[17,18] The term largest plaque area is used for largest intimal area although not all artery segments contained lesions ≥type IV. Histological evaluation was performed using a light microscope (Olympus BX51) equipped with polarization filters and an integrated eyepiece graticule. For digital image analysis, we used a personal computer with AnalySIS Docu 3.2 software connected with a Colorview II digital camera mounted on an Olympus SZH10 light microscope. Histological examples are shown in Fig 2.

Statistics. The Intercooled Stata 9.2 software package was used for statistical analysis. The Mann-Whitney U and χ^2 tests were used when comparing variables stratified by either gender or cause of death. Correlations were calculated using Spearman's rank correlation test. The relation between age and plaque growth (measured by the mean intima area of the largest plaques) was illustrated by scatter plots with fitted lines based on fractional polynomial regression analysis. Logistic regression analysis was used in prediction models for coronary plaque and coronary death based on peripheral plaque presence. Likelihood ratio tests were used to determine if inclusion of age and gender data added statistical significant information to the models. Goodness-of-fit of the multivariate logistic regression models was assessed using the Hosmer-Lemeshow test. The ability to correctly classify individuals was measured by the area under the receiver operating characteristic (ROC)
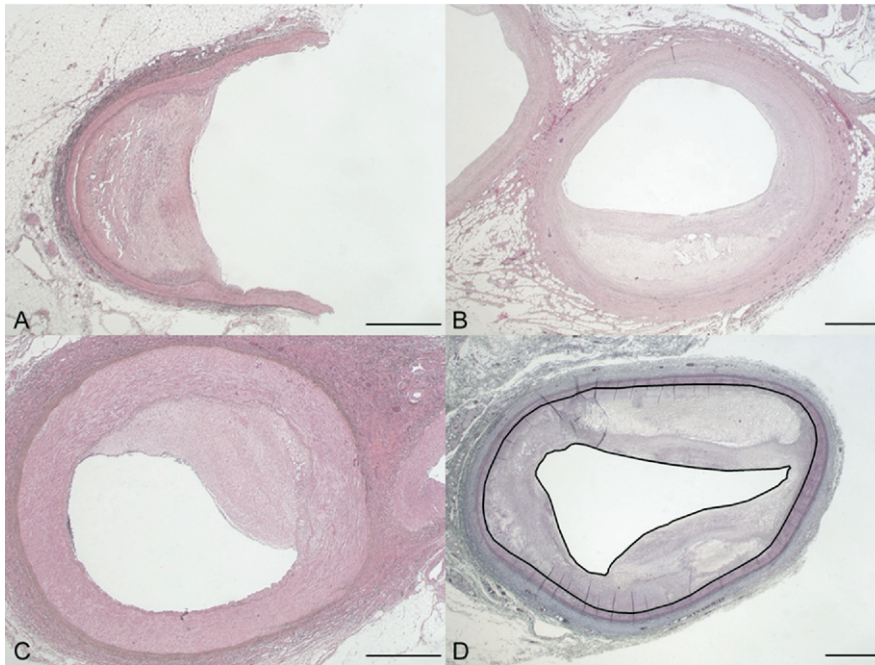
Fig 2. Examples of atherosclerotic plaques (American Heart Association [AHA] lesions ≥type IV[14]) identified on hematoxylin and eosin stained sections from (**A**) the coronary arteries, (**B**) the carotid arteries, and (**C**) the superficial femoral arteries. **D,** Measurement of intima area on a section from a carotid artery stained with Masson's elastic trichrome. The inner and outer circles are the luminal border and the internal elastic lamina, respectively. The intima area (= plaque area) is calculated by subtracting the inner (luminal) area from the outer area. Black bar length = 1 mm.

curve. Values ranging from 0.7 to 0.8 represent reasonable discrimination, and values exceeding 0.8 represent good discrimination.[19] The area under the ROC curves (AUC) for different models was compared using a nonparametric algorithm based on the χ^2 distribution.[20] $P < .05$ was considered statistically significant.

RESULTS

Plaque formation. The burden of atherosclerosis increased with age in all arteries, but the variation was considerable. Plaques were first seen in the coronary arteries in the LAD of a 22-year-old man. Most plaques in the carotid arteries developed in the carotid bifurcation where they were observed from 28 years of age. SFA plaques were not seen before the middle of the fourth decade (a 34-year-old male) and could be absent as late as the eighth decade (a 75-year-old man who had coronary and carotid plaques). Thus, based on our observations, the SFA was least susceptible to atherosclerosis although statistical comparisons were not made due to limited number of individuals in the youngest and oldest age decades. Half of the individuals had plaque in at least one SFA, and of these, all but one also had plaques in both the coronary and carotid arteries (a 34-year-old man had SFA and coronary plaques but no carotid plaque). The relationship between age and plaque growth was visualized by scatter-plots using the largest plaque area (mean of two arteries per individual) in each vascular territory (Fig 3). Intima areas were not adjusted for

arterial size, thus, although the coronary and SFA intima areas look similar, the smaller coronary arteries are much more diseased than the SFA. The carotid and SFA are approximately equal in size and are therefore more readily comparable. In spite of the considerable variation, it was apparent that the intima area increased with age in an artery-dependent fashion with different inception and speed of progression. The pattern of disease progression was also gender-related (men versus women) and differed between coronary and non-coronary deaths. In women dying from non-coronary causes, progression was slow until their mid-forties, ie, near menopause (Fig 3). The fraction of individuals with plaques had a similar pattern. The fraction increased with age and all individuals dying from coronary causes had plaques in the coronary, carotid, and SFA by the fifth decade (Fig 4). Accordingly, plaque burden, ie, the fraction of sections with plaque in each artery segment, was significantly higher in coronary death compared to non-coronary death ($P < .05$ for all arteries). Coronary ($P < .05$), but not carotid and SFA plaque burden, was significantly higher in men than in women. When stratified by cause of death, coronary and SFA plaque burden was higher in men than in women in non-coronary death ($P < .05$), but significant gender differences were not found in coronary death. The differences in intima area (Fig 3) and plaque prevalence (Fig 4) between coronary death and non-coronary death were largest in the SFA. This was particular evident below 50 years of age where the intima
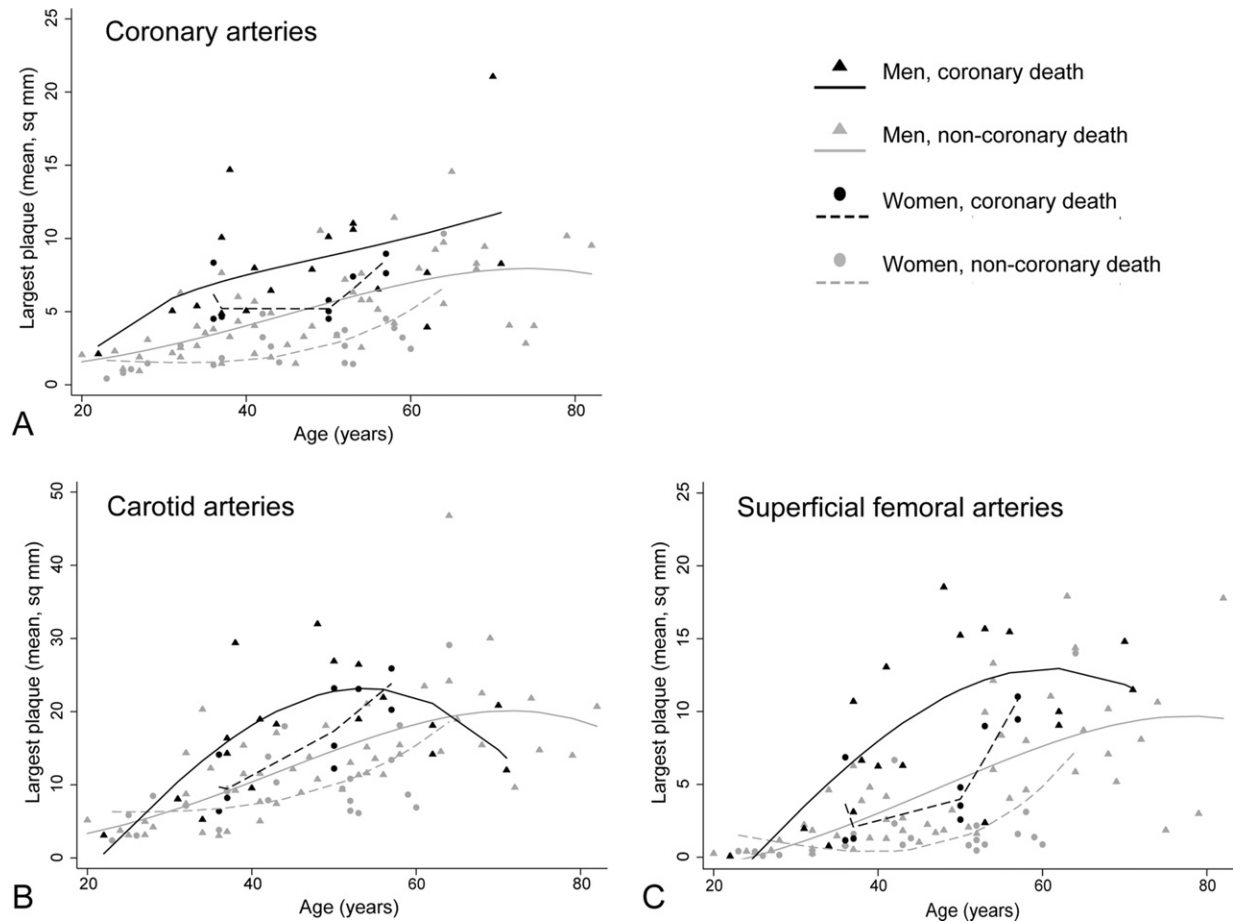
Fig 3. Relationship between age and plaque growth illustrated by scatter-plots using the mean of the two largest intimal areas (two arteries per individual) in coronary (**A**), carotid (**B**), and superficial femoral (**C**) arteries. The circles and triangles represent the individual data points. The lines are fitted from the original data using fractional polynomial regression analysis for better visualization of the general pattern; they should solely be interpreted as approximations.

area began to increase later in the SFA arteries with subsequent later plaque development.

Association between plaque formation in different arteries. Individuals with plaques in the carotid and/or SFA had more severe coronary atherosclerosis assessed by both coronary plaque burden and the size of the largest plaque, compared with those without such noncoronary plaques ($P < .00001$). The difference was most pronounced for plaque in the SFA. Thus, an individual with carotid or superficial femoral plaque would be expected to have more severe coronary artery disease. There was a strong correlation between plaque burden and the size of the largest plaque in each of the six artery segments (Spearmans ρ between 0.74 and 0.83, $P < .0001$). All individuals with SFA plaque had plaque in the coronary arteries, ie, the specificity for coronary plaque was 100%. Conversely, the absence of SFA plaque was not informative; 29 (58%) of the 50 individuals without SFA plaques had coronary plaques (sensitivity 63%). Presence or absence of carotid plaque provided limited information. Most individuals (81) had plaque in at least one carotid artery, coronary plaques were absent in 9 (11%) of those. Nine (47%) of the 19 individuals without carotid plaque had plaque in the coronary arteries (specificity 91%, sensitivity 57%). The ability to correctly identify individuals with coronary plaque was analyzed by ROC curve analysis. The AUCs were 0.82 (0.73-0.89) for SFA plaque and 0.74 (0.64-0.82) for carotid plaque, but they did not differ significantly. Inclusion of age and gender information in the logistic regression models for identification of individuals with coronary plaque increased the AUCs for both models (carotid plaque: (0.83 [0.73-0.93]); SFA plaque: (0.87 [0.80-0.94])). Age and gender did only add statistical significant information to the model based on carotid plaque ($P < .05$, likelihood-ratio test). The goodness-of-fit was satisfactory for the models including age and gender ($P > .37$).

Association between plaque formation in different arteries and coronary death. The association between plaque presence and coronary death was analyzed by logistic regression analysis and ROC curve analysis (Table). All
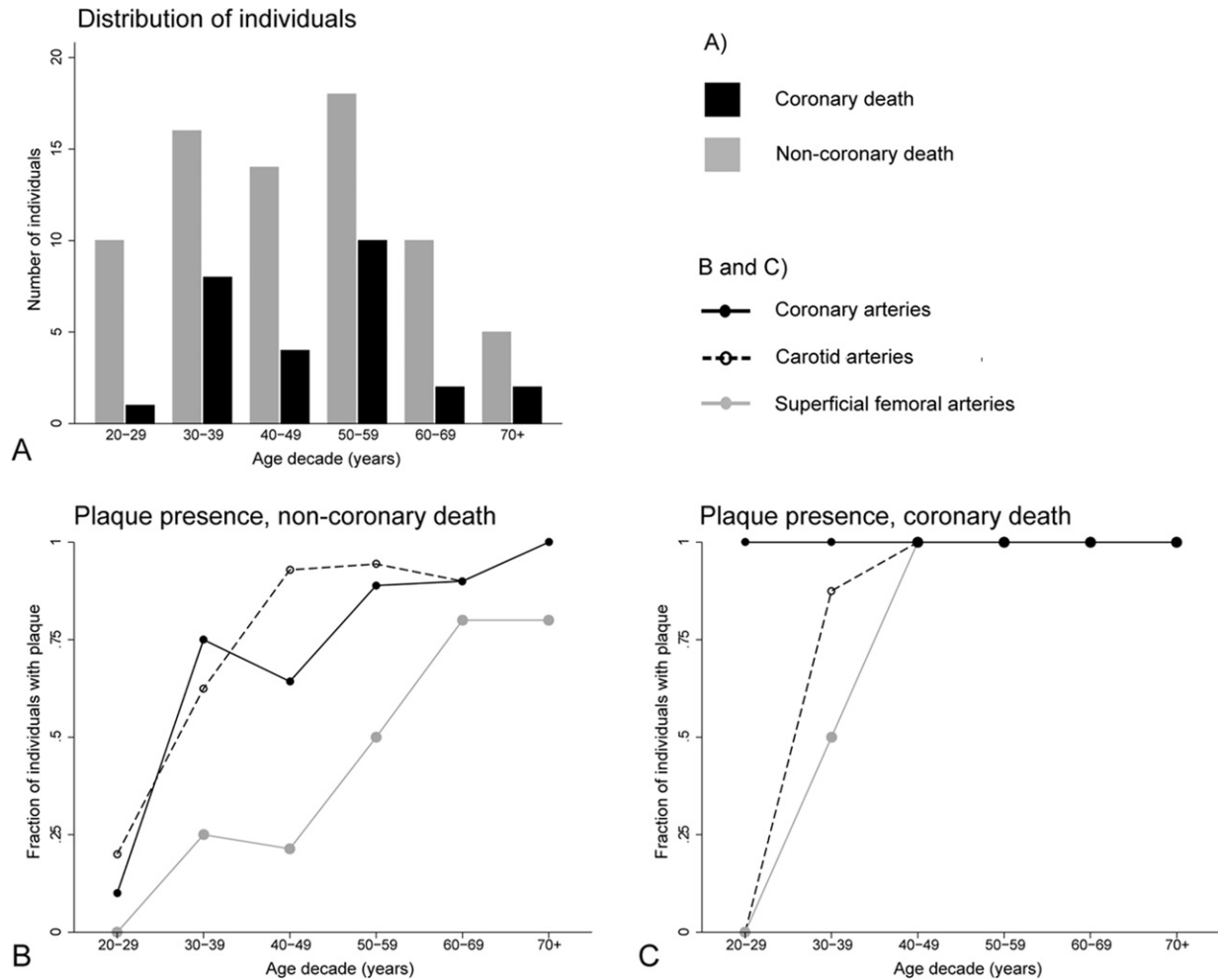
Fig 4. A, Distribution of individuals by cause of death in the different age decades. **B** and **C,** Fraction of individuals with plaque by age decade in (**B**) noncoronary death and (**C**) coronary death (after the age of 40, all coronary death individuals had plaque in all three arterial beds).

multivariate logistic regression models for identification of coronary death individuals had an excellent fit ($P > .76$). Because all who died from coronary causes had coronary plaques, the logistic algorithm did not converge causing the odds ratio for coronary death in the presence of coronary plaque to approach infinity. SFA plaques performed significantly better than carotid plaques and at least as good as coronary plaques (AUC 0.72 versus 0.64, $P = .13$) in identifying those who died from coronary causes. Inclusion of age and gender in multivariate models did only add statistical significant information in the model based on SFA plaque. The AUCs increased for all arteries, but the SFA model still had a significantly larger AUC than the carotid model.

DISCUSSION

In this autopsy study, the principal finding was that the presence of SFA plaque was more informative than carotid plaque and at least as informative as coronary plaque in the

identification of coronary death individuals. In addition, SFA atherosclerosis was specific for concomitant coronary atherosclerosis. The specificity of SFA atherosclerosis was caused by its slower development and later occurrence of plaque compared with coronary and carotid atherosclerosis. The key message is that the presence of atherosclerotic plaque in the SFA, especially in young individuals, is highly suggestive of a generalized susceptibility to atherosclerosis with even more advanced disease elsewhere.

Potential clinical use. In primary prevention, efforts are under way to improve risk stratification by detection of subclinical atherosclerosis.[1] Ultrasound measurements of carotid IMT[5] and computed tomography measurements of coronary artery calcium score,[21] are the prime candidates.[1] Based on the present study, ultrasound detection of SFA atherosclerosis certainly deserves consideration, too. Detection of advanced and flow-limiting atherosclerosis in lower limb arteries, assessed by an ABI < 0.9, has a high positive predictive value for coronary events, but the nega-

Table. Univariate and multivariate (including age and gender) logistic regression analysis for identification of coronary death individuals by plaque presence

	Univariate		*Multivariate (including age and gender)*	
	OR (95% CI)	*AUC (95% CI)*	*OR (95% CI)*	*AUC (95% CI)*
Coronary plaque	~ infinite	0.64 (0.54-0.73)	~ infinite	0.72 (0.62-0.83)
Carotid plaque	3.74 (0.81-17.69)	0.58 (0.47-0.68)	5.32 (0.98-28.75)	0.63 (0.52-0.75)
Superficial femoral plaque	7.07 (2.40-20.81)	0.72 (0.62-0.81)*	21.25 (5.02-89.97)	0.80 (0.72-0.89)*†

OR, Odds ratio; *CI*, confidence interval; *AUC*, area under the receiver operating characteristic curve.
*Larger AUC than that based on the carotid artery, $P < .05$.
†Inclusion of age and gender information adds statistical significant information to the model (likelihood ratio test, $P < .05$).

tive predictive value is low.[9,10] Detection of SFA plaque by ultrasound at an earlier stage of the disease, before a flow-limiting stenosis develops, has the potential to improve the sensitivity, but it may occur at the cost of a lower specificity. We believe that a prospective study of the incremental predictive value of ABI, ultrasound-detected SFA plaque, and circulating biomarkers beyond traditional risk factor assessment is warranted. Some clinical observations suggest that ultrasound screening for plaque presence[12] or aggregate ultrasound-based plaque scores[11] may be more sensitive than the ABI in the detection of high-risk individuals. Under all circumstances, the presence of SFA plaque in a young (<50 years old) individual should always be considered a warning sign.

Delayed plaque formation in the SFA. Autopsy studies comparing SFA atherosclerosis with atherosclerosis in other arterial beds are few, but the available observational data are consistent with our findings, indicating a low to intermediate atherosclerosis susceptibility of the SFA with a male preponderance.[22] Cardiovascular risk factors have different impact in the arterial beds, with smoking and diabetes being particularly important for peripheral arterial disease.[2,23] Local hemodynamic factors are believed to play an important role in the localization and multifocality of atherosclerosis,[24] but the mechanisms responsible for the different impact of risk factors in different arteries are unknown and deserve more attention.

Limitations. It is well-known that autopsy studies are prone to selection bias and extrapolation to the general population may, therefore, not be justified. In our forensic material, the main indication for autopsy in coronary death cases was the lack of known disease in a relatively young individual. Our cases are, therefore, younger and probably more prone to atherosclerosis than the "average" subject dying from coronary atherosclerosis. On the other hand, our cases represent the most serious consequences of atherosclerotic cardiovascular disease (fatal cases) that preventive measures are aiming at. We can not expect equally high AUCs in the general population, but it seems reasonable to conclude that we can extrapolate the relative usefulness of carotid and SFA atherosclerosis. Our material was very large (4756 sections), but the number of individuals in the youngest and oldest age-decades was small, especially after stratification by cause of death (Fig 4, *A*), and our findings should be interpreted in that context. The limited number

of individuals may explain the observed decline in carotid and SFA intima area in men older than 60 years who died of coronary atherosclerosis (Fig 3, *B* and *C*). We only investigated a limited part of the arterial tree, but we specifically targeted those arterial segments known to be especially prone to atherosclerosis and atherosclerosis-related complications, such as the proximal parts of the LAD and RCA,[25] and the carotid bifurcation.[26] The intima area was not adjusted by artery size because of the lack of pressure-fixation. In the absence of pressure-fixation, artery size may be estimated by calculating the area within the internal or external elastic lamina from their perimeters assuming that the artery is circular. However, the longitudinal opening of the coronary arteries caused an underestimation of the perimeters and the calculated areas making these measurements incomparable to those of the carotid and SFA.

CONCLUSION

Atherosclerosis develops slower and advanced disease (plaque) occurs later in SFA compared with coronary and carotid arteries. In persons with plaque in the SFA, plaque is also present in the coronary arteries. In younger persons, the presence of plaque in the SFA indicates a generalized susceptibility to atherosclerosis with more advanced disease in other arteries and vulnerability to coronary death. Detection of SFA atherosclerosis might provide incremental prognostic information beyond traditional risk factor assessment and this hypothesis deserves to be tested in clinical studies.

AUTHOR CONTRIBUTIONS

Conception and design: EF, SD, WP
Analysis and interpretation: SD, EF, WP
Data collection: IK, SD
Writing the article: SD
Critical revision of the article: SD, EF, WP, IK

Final approval of the article: SD, EF, WP, IK
Statistical analysis: SD
Obtained funding: SD
Overall responsibility: SD

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