Atherosclerosis in Abdominal Aortic Aneurysms: A Causal Event or a Process Running in Parallel? The Tromsø Study

Stein Harald Johnsen, Signe Helene Forsdahl, Kulbir Singh, Bjarne Koster Jacobsen

Objective—The pathogenesis of abdominal aortic aneurysm (AAA) formation is poorly understood. We investigated the relationship between carotid, femoral, and coronary atherosclerosis and abdominal aortic diameter, and whether atherosclerosis was a risk marker for AAA.

Methods and Results—Ultrasound of the right carotid artery, the common femoral artery, and the abdominal aorta was performed in 6446 men and women from a general population. The burden of atherosclerosis was assessed as carotid total plaque area, common femoral lumen diameter, and self-reported coronary heart disease. An AAA was defined as maximal infrarenal aortic diameter >30 mm. No dose-response relationship was found between carotid atherosclerosis and abdominal aortic diameter >27 mm. However, significantly more atherosclerosis and coronary heart disease was found in aortic diameter >27 mm and in AAAs. The age- and sex-adjusted odds ratio (OR) (95% CI) for AAA in the top total plaque area quintile was 2.3 (1.5 to 3.4), as compared with subjects without plaques. The adjusted OR (95% CI) was 1.7 (1.1 to 2.6). No independent association was found between femoral lumen diameter and AAA.

Conclusion—The lack of a consistent dose-response relationship between atherosclerosis and abdominal aortic diameter suggests that atherosclerosis may not be a causal event in AAA but develops in parallel with or secondary to aneurismatic dilatation. (Arterioscler Thromb Vasc Biol. 2010;30:1263-1268.)

Key Words: aneurysms ■ atherosclerosis ■ carotid arteries ■ coronary heart disease ■ risk factors ■ ultrasonic diagnosis

The pathogenesis of abdominal aortic aneurysm (AAA) is poorly understood. AAA is thought to develop through a complex interaction among various risk factors, including aging, gender, cigarette smoking, inflammation, and hemodynamic factors. Familial aggregation, male preponderance, and ethnic variations indicate that genetic factors are involved.1 A relationship between arterial anomalies such as arteriomegaly and the occurrence of aneurysms both within the abdominal aorta and in other arteries has long been recognized. It has been suggested that there exists a generalized arterial dilating diathesis in people developing AAA,2–5 which might be attributable to imbalances in proteolytic matrix proteases and their natural tissue inhibitors, leading to degradation of the connective tissue in the arterial wall.6 Pathologically, aneurismatic formation is characterized by the destruction of elastin and collagen in the media and adventitia,7 loss of medial smooth muscle cells with thinning of the vessel wall, and transmural infiltration of lymphocytes and macrophages.8 This makes the aortic wall more susceptible to the influence of blood pressure and mechanical wall stress.

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Previous studies have attributed the development of AAA to atherosclerosis.9 Atherosclerosis and AAA share risk factors, such as smoking, hypertension, and hypercholesterolemia.10,11 The presence of atherosclerosis in the aneurismatic wall, as well as in other circulatory beds, is a common finding in AAA patients. However, many patients with advanced atherosclerosis do not develop AAA, whereas some patients having no evidence of atherosclerosis do.12,13 Recent case-control studies did not find any evidence for more carotid, coronary, or peripheral atherosclerosis in AAA patients.14,15 Likewise, it is unclear why aneurysms are extremely rare in the carotid or external iliac arteries, despite a high frequency of atherosclerosis in these locations.

In the Tromsø Study, 6525 men and women from the general population were scanned with duplex ultrasound of the carotid artery and the abdominal aorta. In the present study, we investigated how carotid plaque area, common femoral artery lumen diameter, and prevalent coronary heart disease (CHD), all markers of peripheral atherosclerosis, were associated with abdominal aortic diameter and AAA.

Methods

Subjects

The Tromsø study is a population-based prospective study with repeated health surveys of inhabitants in the municipality of Tromsø, Norway. As a part of the fourth survey in 1994 to 1995, all subjects...
aged 55 to 74 years and a random 5% to 10% sample in other age groups over 24 years were invited to undergo ultrasound scanning of the carotid artery and the abdominal aorta. In all, 6892 subjects (79% of the eligible population) attended ultrasound screening for AAA, as detailed elsewhere. Of these people, ultrasonography of the right carotid artery was performed in 6727 subjects. The Regional Committee for Research Ethics approved the study, and informed consent for research was obtained from 6645 of the participants who underwent ultrasound scanning. Representative measurements of carotid plaque area and anterior-posterior and transversal aortic abdominal diameter were obtained in 6462 people. However, we excluded 16 subjects who had a prosthetic graft in the abdominal aorta. Thus, the present study comprised 6446 people (3164 men and 3282 women) aged 25 to 84 years.

Ultrasoundography of the Abdominal Aorta and Carotid Artery

The ultrasound examination was carried out with an Acuson 128 XP B-mode Doppler (Acuson Corporation, Mountain View, Calif), equipped with a 3.5-MHz sector probe for the abdominal aorta and a 7.5-MHz linear probe for the carotids. All participants were examined by specially trained personnel (a study nurse, an assistant nurse, a radiographer, and a radiologist). The radiologist supervised. The external and internal (lumen) diameter of the right common femoral artery was measured, as were aortic diameters at the level of the renal arteries and 1 cm distal to this level, and the bifurcation and the maximal infrarenal aortic diameter in both transversal and anterior-posterior planes. The inter- and intraobserver variability of the ultrasound examination has been reported previously. The difference between 2 measurements (both inter- and intraobserver agreement) of the maximal aortic diameter was ≤4 mm in 95% of the pairs. In the present analyses, the maximal infrarenal aortic diameter was defined as the mean of the maximal transversal and anterior-posterior diameters. An AAA was considered present if the maximal infrarenal aortic diameter was ≥30 mm.

The carotid ultrasonography was done by 3 different sonographers (a physician, a technician, and a neurologist with 10 years of experience in ultrasound of the carotid artery). The neurologist supervised. The right carotid artery was scanned longitudinally from the level of the clavicle, through the carotid bulb (bifurcation segment) and the internal carotid artery as far downstream as possible. The lumen of the common carotid artery (CCA) was measured. A plaque was defined as a localized protrusion of the vessel wall into the lumen of at least 50% compared with the adjacent intima-media thickness. In each subject, a maximum of 6 plaques were registered in the near and far walls of CCA, bifurcation, and internal carotid artery. Digitalized longitudinal plaque images were transferred to and standardized in Adobe Photoshop, to calculate the plaque area. In subjects with more than 1 plaque, the areas of all plaques were summarized to give the total plaque area (TPA). The interobserver mean arithmetic difference of plaque area was −1.0 mm² (7.2% of mean plaque area). The intraobserver mean arithmetic difference for sonographer 1 was 0.2 mm². The corresponding values for sonographer 2 were 0.01 mm². All sonographers completed a 2-month prestudy training protocol. When conducting the ultrasound examinations, the sonographers had no information about the readings from other parts of the survey.

Cardiovascular Risk Factors

Information about smoking habits, angina pectoris, myocardial infarction, and use of antihypertensive and lipid-lowering drugs was collected from self-administered questionnaires. The participants were asked the following questions: “Do you have or have you ever had angina pectoris (heart cramp)?” and “Do you have or have you ever had a heart attack (myocardial infarction)?” If the answer to either question was yes, the participant was classified as having CHD. Only 23 and 20 people, respectively, had missing values to these questions. Standardized measurements of height and weight were carried out. Specially trained personnel recorded blood pressure with an automatic device (Dinamap Vital Signs Monitor; Dinamap, Tampa, Fla). Nonfasting serum total cholesterol and triglycerides were analyzed by enzymatic colorimetric methods with commercial kits (CHOD-PAP for cholesterol and GPO-PAP for triglycerides; Boehringer-Mannheim, Mannheim, Germany). Serum high-density lipoprotein-cholesterol was measured after the precipitation of lower density lipoproteins with heparin and manganese chloride. Blood analyses were carried out in the Department of Clinical Chemistry at University Hospital of North Norway.

Statistical Analyses

The maximal infrarenal aortic diameter and the presence of an AAA were the dependent variables in the regression models. Carotid TPA was the main explanatory variable. Femoral artery lumen diameter, an indirect measure of peripheral atherosclerosis, and prevalent CHD were also considered as explanatory variables. Known risk factors for atherosclerosis and AAA were introduced as covariates. First, we assessed the age- and sex-adjusted mean levels of carotid TPA, femoral vessel diameter, CHD, and cardiovascular risk factors according to strata of maximal abdominal aortic diameter and the prevalence of AAA (see Table 2). Then, the age- and sex-adjusted maximal infrarenal aortic diameter and prevalence of AAA according to 6 groups of plaque area (no plaque and quintiles of TPA for subjects with carotid plaque) and 6 groups of common femoral lumen diameter were assessed (see Table 3). Linear trends across strata were tested by logistic regression for categorical variables and by linear regression for continuous variables. An assessment of the independent relationship between TPA and the OR for an AAA was obtained by multiple logistic regressions, in which AAA was the dependent variable and TPA was the main independent variable. Subjects without any plaque constituted the reference category in the analyses. Other cardiovascular risk factors were included as continuous or binary variables in the model to adjust for confounding (see Table 4). Finally, we adjusted for CCA lumen, a potential marker of constitutional arterial dilating propensity. Two-sided probability values less than 0.05 were considered statistically significant. The SAS software, version 9, was used for all statistical analyses.

Results

Baseline characteristics of participants attending the ultrasound survey are shown in Table 1. Men had larger diameters of the carotid artery and abdominal aorta than women. Men also had a higher frequency of 1 or more carotid plaques (52.9% versus 45.5%) and larger TPA (24.5 versus 18.3 mm²). The correlation coefficients between carotid TPA and maximal abdominal diameter was 0.17 (P<0.0001), with no sex differences. Common femoral lumen diameter was positively correlated to maximal abdominal diameter (r=0.18, P<0.0001), with the strongest correlation in men. The common femoral lumen diameter was inversely correlated to carotid TPA (r=−0.15, P<0.0001). An AAA was present in 189 men (6.0%) and 41 women (1.3%). Mean maximal abdominal aortic diameter (range) of aneurysm was 38.7 mm (30 to 84.5 mm) in men and 36.7 (30 to 75 mm) in women. The diameters were distributed as follows: 30 to 39 mm (74%), 40 to 49 mm (15%), and ≥50 mm (11%).

There was, however, no consistent dose-response relationship between carotid TPA and abdominal aortic diameter up to 27 mm (Table 2). Above this diameter, TPA rose sharply, reaching 18.6 mm² in the AAA group, a 50% increase compared with aortic diameter <27 mm. CCA lumen diameter and common femoral external diameter both increased linearly with increasing diameter of abdominal aorta, being widest in the AAA group. In contrast, femoral lumen diam-
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Men (n=3164)</th>
<th>Women (n=3282)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59.5 (10.0)</td>
<td>60.7 (10.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80.1 (11.9)</td>
<td>67.6 (11.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175.2 (6.8)</td>
<td>161.5 (6.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.1 (3.3)</td>
<td>25.9 (4.4)</td>
<td>0.2</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>145.0 (20.4)</td>
<td>145.1 (24.3)</td>
<td>0.8</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>85.0 (12.2)</td>
<td>81.7 (13.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>34.3</td>
<td>31.1</td>
<td>0.008</td>
</tr>
<tr>
<td>Ex-smoker, %</td>
<td>47.9</td>
<td>25.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coronary heart disease, %</td>
<td>15.3</td>
<td>9.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.56 (1.21)</td>
<td>6.94 (1.35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Use of lipid-lowering drugs, %</td>
<td>2.2</td>
<td>1.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Use of antihypertensive medication, %</td>
<td>13.2</td>
<td>13.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Common femoral external diameter, mm</td>
<td>14.9</td>
<td>13.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Common femoral lumen diameter, mm</td>
<td>7.9</td>
<td>6.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Maximal abdominal aortic diameter, mm</td>
<td>22.9 (5.3)</td>
<td>19.6 (3.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Common carotid lumen diameter, mm</td>
<td>6.8 (0.9)</td>
<td>6.2 (0.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Carotid plaque present, %</td>
<td>52.9</td>
<td>45.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total carotid plaque area, mm²*</td>
<td>24.5 (23.3)</td>
<td>18.3 (15.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Presence of AAA, %</td>
<td>6.0</td>
<td>1.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Maximal abdominal aortic diameter, mm†</td>
<td>38.7 (10.3)</td>
<td>36.7 (9.2)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Values are unadjusted means (SD) or percentages.
*In persons with plaque.
†In persons with AAA.

The mean TPA was 18.8 mm²; for 40 to 49 mm, it was 18.6 mm²; and for ≥50 mm, it was 19.4 mm² (P for trend=0.9). The corresponding measures for common femoral lumen diameter were 7.4, 7.0, and 7.0 mm, respectively (P for trend=0.25).

Table 3 displays the maximal infrarenal aortic diameter, aneurismal diameter, and AAA prevalence according to carotid plaque burden and common femoral lumen diameter. We found a positive linear relationship between the maximal infrarenal aortic diameter and TPA (P for trend=0.001). The prevalence of AAA increased linearly with increasing TPA. An AAA was present in 7.4% in the highest TPA quintile, compared with 2.7% in the group without carotid plaque. No relationship, however, was seen between aneurismal diameter and TPA. For the common femoral lumen diameter, the strata were reversed, ie, the first group had the widest diameter and the last had the narrowest. The maximal infrarenal aortic diameter increased linearly with the common femoral lumen diameter (P for trend <0.0001). The prevalence of AAA was slightly higher, though not significant, in the narrowest hexile. Again, no correlation was found between aneurismal diameter and femoral lumen diameter. A total of 781 (12.1%) people had CHD. In people with CHD, the mean maximal infrarenal aortic diameter was 22.0 mm, and the prevalence of AAA was 8.1% (data not shown in Table 3). In those without CHD, the corresponding values were 21.1 mm and 2.9% (for both differences, P<0.0001). However, when people with AAA were excluded from analysis, the aortic diameter was identical in the 2 groups (20.6 mm).

Table 4 shows the risk for AAA in quintiles of TPA compared with subjects without carotid plaque. The age- and sex-adjusted OR (95% confidence interval) for AAA in the top plaque quintile was 2.3 (1.5 to 3.4) compared with the no-plaque group. The risk weakened but remained significant after adjusted for other cardiovascular risk factors. When we introduced CCA-lumen diameter into the fully adjusted model, the risk estimates for AAA were no longer significant (not shown). In sex-specific analyses (not shown), the risk was significant in both men and women. The relationship between TPA and AAA was seemingly stronger in women, but a test for interaction was not statistically significant.
Discussion

In the present study, carotid TPA was positively correlated to maximal infrarenal aortic diameter and the prevalence of AAA. There was an increased risk for having AAA with increasing carotid atherosclerosis after adjustment for body size and cardiovascular risk factors, such as smoking, systolic blood pressure, and cholesterol. The relationship between aortic diameter and common femoral atherosclerosis, assessed as femoral lumen diameter, was in fact inversely, and no independent association was found between femoral lumen diameter and AAA. People with CHD had wider aortic diameter and more AAA than those without CHD.

Because atherosclerosis is a common finding in the walls of aneurysms, AAA has been thought to be caused by atherosclerosis. Atherosclerosis and AAA also share several common risk factors. However, it is unclear whether atherosclerosis causes AAA or vice versa.²¹ The pathology of AAA is largely defined from tissues acquired at the end stage of the disease. There is a paucity of data defining the sequential cellular events of human AAA as they develop and progress. In experimental models, atherosclerotic lesions were detected after the development of the aneurysm, suggesting that the formation of AAA precedes the development of atherosclerotic lesions.

Although atherosclerotic lesions are frequently present at the site of AAA formation, they might not be a causal factor. Our findings lend support to this view in several ways. Even if carotid TPA was positively correlated to maximal infrarenal aortic diameter, no dose-response relationship was found between TPA and abdominal aortic diameter <27 mm (Table 2). Beyond this diameter, carotid TPA increased sharply. The common femoral lumen diameter did not decrease by increasing aortic diameter, but when aortic diameter was ≥27 mm, we observed a reduction in common femoral lumen diameter which is most likely attributable to atherosclerosis. Even if CHD, the hallmark disease of atherosclerosis, was nearly 50% more common beyond the 27-mm diameter and the aortic diameter was significantly wider in people with than without CHD, the aortic diameters were identical when the AAAs were excluded from analysis. An AAA was present in 8% of those who reported to have CHD. Previous hospital-based studies have found the prevalence of AAA in CHD patients to range between 10% and 20%.²²–²⁴ CHD has been found to be an independent risk marker for AAA,²⁵ but the difference in aortic diameter between people with and without CHD in our study was solely explained by the presence of an AAA and not by a wider diameter in nonaneurismal aortas. Also noteworthy is the lack of correlation between atherosclerotic burden and aneurismal diameter. The coefficient of correlation between TPA and aneurysm diameter was 0.01 (P=0.8) and between femoral lumen diameter and aneurism diameter, 0.04 (P=0.6). The lack of a consistent linear dose-response relationship between atherosclerosis and aortic diameter but finding of significantly more atherosclerosis above the 27 mm threshold, may indicate that aneurysm formation and atherosclerosis, under influence of some common risk factors develop in parallel but as partly independent processes and through different pathogenetic mechanisms.

Table 4. OR for AAA by Strata of Total Plaque Area

<table>
<thead>
<tr>
<th>Total Carotid Plaque Area, mm²</th>
<th>Age- and sex-adjusted OR (95% CI)*</th>
<th>Multivariate-adjusted OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Plaque (n=3308)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1.5–7.7 (n=633)</td>
<td>0.6 (0.3–1.3)</td>
<td>0.6 (0.3–1.2)</td>
</tr>
<tr>
<td>7.8–12.3 (n=634)</td>
<td>1.4 (0.8–2.3)</td>
<td>1.3 (0.6–2.2)</td>
</tr>
<tr>
<td>12.4–18.9 (n=633)</td>
<td>2.1 (1.4–3.3)</td>
<td>1.9 (1.2–2.9)</td>
</tr>
<tr>
<td>19.0–31.1 (n=635)</td>
<td>2.0 (1.3–3.1)</td>
<td>1.6 (1.0–2.5)</td>
</tr>
<tr>
<td>31.2–246.4 (n=633)</td>
<td>2.3 (1.5–3.4)</td>
<td>1.7 (1.1–2.6)</td>
</tr>
</tbody>
</table>

*Adjusted with logistic regression.
†Adjusted for age, sex, body mass index, smoking, systolic blood pressure, total cholesterol, and use of lipid-lowering and antihypertensive medication.
The higher levels of smoking, systolic blood pressure, and cholesterol, all risk factors for both AAA and atherosclerosis, can explain some of these findings. In addition, constitutional factors linked to the collagen and elastin metabolism of the aortic wall may be crucial for determining progression toward either aneurysmal dilatation or obliterate atherosclerosis.5–26

Smoking and high blood pressure may cause weakening of the aortic wall because of breakdown of the connective tissue and muscular layer independently of atherosclerosis.27–31 Cigarette smoking has long been recognized as the strongest risk factor for AAA; the strength of association between smoking and AAA in men is 2.5 times greater than the association between smoking and CHD, and 3.5 times greater than the association between smoking and cerebrovascular disease.32 According to previous data, the strength of the association with AAA was independent of the extent of atherosclerosis, suggesting an additional nonatherosclerotic pathway along which cigarette smoking acts.33 One explanation is that smoking constituents may block the active site of α1-antitrypsin, which could promote the destruction of the aortic wall by proteolytic enzymes.27 In addition, other factors, such as copper metabolism and tissue antioxidant levels, may be involved in determining which smokers develop aneurysms independently of atherosclerosis.28,29

Because blood pressure, cholesterol, smoking, and antihypertensive and lipid-lowering treatment are associated with both AAA and carotid TPA, we controlled for these factors. In the multivariate adjusted model, the association between carotid TPA and AAA was attenuated but still significant. However, after further adjustment for CCA-lumen diameter, an independent association between TPA and AAA was found to be no longer present. The CCA is very seldom affected by atherosclerosis (in this study, only 3% had plaque in the CCA). Previous studies have found a correlation between CCA-lumen and abdominal aortic diameter, suggesting it as a potential marker of constitutional arterial dilating propensity.3,5 Our findings suggest that constitutional wide vessels might mediate the effect of atherosclerosis observed in people with AAA.

There are significant limitations to this study. The cross-sectional design makes it impossible to make any causal inferences between atherosclerosis and AAA. Because of misclassification, it is possible that a few AAAs were overlooked in 1994 and included in the group of subjects with no AAA. This may have caused underestimation of the true strength of the relationship between carotid atherosclerosis and AAA. Random errors in ultrasonographic measurements of TPA would also tend to cause underestimation of the association. Atherosclerosis was not assessed in the abdominal aorta but indirectly as carotid plaque burden, reduction in femoral artery diameter, and CHD. Even if the presence of carotid atherosclerosis was considered a good marker of generalized atherosclerosis,34 the study would be more comprehensive with additional measures of peripheral atherosclerosis (femoral artery plaque, ankle-arm index) available.

One major advantage of this study is that it is population-based, not based on hospital patients or other groups of selected subjects. Carotid and abdominal ultrasonography were performed in 75% of the eligible population, where the majority of subjects were aged 55 to 74 years. The attendance rate in those older than 74 years was only 58%, and this is of some concern as this age group has the highest prevalence of AAA and atherosclerosis. However, we find it unlikely that the relationship between carotid atherosclerosis and AAA is very different in subjects who did not attend the examination compared with the rest of the population. The results are thus likely to be representative of the general population. Scanning of the carotid artery and scanning of the aorta were performed on the same day, which gives a true cross-sectional relationship between carotid atherosclerosis and AAA. The reliability of questionnaire information on CHD has been found to be valid; in a similar study in Norway, 84% of the myocardial infarction and 73% of the angina cases according to the questionnaire were verified by medical records.35

We conclude that atherosclerosis was more common in abdominal aortic diameter ≥27 mm and that atherosclerosis was an independent risk marker for AAA. However, our findings may imply that AAA formation is not caused by atherosclerosis. Whether atherosclerosis in AAA patients is a causal event or a process running in parallel is unclear and should be further addressed in prospective studies. Future research on the pathophysiology of aortic aneurysm should go beyond atherosclerosis.

Acknowledgments
We are grateful to Dr. Oddmund Joakimsen, MD, PhD, and Dr. Eva Stensland, MD, PhD, for their contribution to the collection of carotid ultrasound data.

Sources of Funding
This study was supported by grants from the Norwegian Research Council and the Norwegian Council on Cardiovascular Diseases and was conducted in collaboration with the Norwegian Health Screening Services, Oslo, Norway.

Disclosures
None.

References


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Arterioscler Thromb Vasc Biol. 2010;30:1263-1268; originally published online April 1, 2010; doi: 10.1161/ATVBAHA.110.203588
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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