Common Carotid Intima-Media Thickness and Lower Extremity Arterial Atherosclerosis
The Rotterdam Study
Michiel L. Bots, Albert Hofman, Diederick E. Grobbee

Abstract
High-resolution B-mode ultrasonography of the carotid arteries is used to investigate the signs of early atherosclerotic vessel wall disease. To assess whether carotid artery findings reflect atherosclerosis elsewhere, we studied the association between common carotid intima-media thickness and lower extremity arterial atherosclerosis among the first 1000 participants of the Rotterdam Study. The Rotterdam Study is a single-center population-based prospective follow-up study of 7983 subjects, ≥55 years old. Baseline measurements include ultrasound imaging of intima-media thickness of the distal common carotid artery and determination of the ankle-to-arm systolic blood pressure index. Lower extremity arterial disease was defined as an ankle-arm index <0.90 in at least one leg. An increase of 0.1 mm in common carotid artery intima-media thickness was associated with an age- and sex-adjusted reduction of the ankle-arm index of 0.026 (95% confidence interval [CI]: 0.018 to 0.034). The age- and sex-adjusted odds ratio of lower extremity arterial disease for subjects with an intima-media thickness ≥0.89 mm (upper quintile) to that of subjects with an intima-media thickness <0.89 mm was 3.4 (95% CI: 2.2 to 5.2). Analysis among subjects free from symptomatic cardiovascular disease yielded a reduction in ankle-arm index per 0.1 mm increase in intima-media thickness of 0.018 (95% CI: 0.008 to 0.028) and an odds ratio for lower extremity arterial disease of 3.0 (95% CI: 1.7 to 5.1). Adjustments for differences in serum lipids, hypertension, and current smoking status only slightly attenuated the results. This study provides evidence that increased common carotid intima-media thickness reflects generalized atherosclerosis, as indicated by its association with atherosclerosis of the arteries of the lower extremities. (Arterioscler Thromb. 1994;14:1885-1891.)

Key Words • carotid atherosclerosis • lower extremity • elderly • ultrasonography

To further understand the early phase of atherosclerosis, its natural history, and factors that contribute to its development, more information must be directly obtained on the arterial system in nonhospitalized subjects. Recently, it has been shown that with high-resolution B-mode ultrasonography vessel wall characteristics of the carotid arteries can be noninvasively assessed in an effective and accurate way in populations at large.12 This technique facilitates the evaluation of the lumen diameter, the intima-media thickness, and the presence and extent of plaques of the carotid artery and has now been applied in a number of studies.3–7 The applicability of the findings of these studies with respect to the atherosclerotic process is conditional on the extent to which noninvasively assessed common carotid intima-media thickness reflects atherosclerotic vessel wall disease in other arteries that are at high risk of atherosclerosis, such as the coronary arteries, the abdominal aorta, and arteries of the lower extremities.8 In other words, can increased common carotid intima-media thickness be regarded as an indicator of generalized atherosclerosis?

In this study we report on the association of noninvasively assessed common carotid intima-media thickness and atherosclerosis of the lower extremities among the first 1000 participants of the Rotterdam Study.

Methods

Population
The Rotterdam Study is a single-center prospective follow-up study of a cohort of 7983 subjects, ≥55 years old, living in the suburb of Omoomd, Rotterdam, the Netherlands. The study was 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 Study have been described elsewhere.9 In brief, the objective of the Rotterdam Study is to clarify determinants of chronic disabling diseases in an aging population. Incidence and risk factors of cardiovascular diseases, locomotor diseases, neurogeriatric diseases, and ophthalmologic diseases are being studied. The study comprises an extensive home interview followed by two visits at the Rotterdam Study research center for clinical examinations. Overall response of those invited to participate was 78%.

Ultrasonography of the Carotid Arteries
Ultrasonography of both carotid arteries was performed with a 7.5-MHz linear array transducer with a Duplex scanner (ATL UltraMark IV, Advanced Technology Laboratories). On a longitudinal two-dimensional ultrasound image of the carotid artery, the near and far walls of the carotid artery are displayed as two bright white lines separated by a hypoechoic space.10 The distance from the leading edge of the first bright line of the far wall (lumen-intima interface) to the leading edge of the second bright line (media-adventitia interface) indicates the intima-media thickness.11 Studies have indicated that the posterior (far) wall intima-media thickness as seen with ultrasound truly reflects the anatomic intima-media layer.10,12,13

Received May 20, 1994; revision accepted September 9, 1994.
From the Department of Epidemiology and Biostatistics, Erasmus University Medical School, Rotterdam, the Netherlands.
Correspondence to Prof D.E. Grobbee, Department of Epidemiology and Biostatistics, Erasmus University Medical School, PO Box 1738, 3000 DR Rotterdam, Netherlands.
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According to the Rotterdam Study ultrasound protocol, a careful search was performed for the lumen-intima interface and the media-adventitia interface of the far wall of the distal common carotid artery. When an optimal longitudinal image was obtained, it was frozen on the R wave of the ECG and stored on videotape. This procedure was repeated three times for both sides. The actual measurements of intima-media thickness were performed off-line. From the videotape, the frozen images were digitized and displayed on the screen of a personal computer with additional dedicated software. This procedure has been described in detail previously. In short, the interfaces of the distal common carotid artery are marked over a length of 10 mm with a cursor. The beginning of the dilatation of the distal common carotid artery served as a reference point for the start of the measurement. This method permits the determination of mean values as well as manual values for intima-media thickness. The average of the intima-media thickness of each of the three frozen images is calculated. For each subject a mean intima-media thickness ((left+right)/2) is taken as a measure for current wall thickness of the distal common carotid artery. Findings on the reproducibility of intima-media thickness measurements have been reported elsewhere.

Arteries of the Lower Extremities

The presence of atherosclerosis in the arteries of the lower extremities was evaluated by measuring the systolic blood pressure level of the posterior tibial artery at both left and right sides with an 8-MHz continuous-wave Doppler probe (Huntleigh 500 D, Huntleigh Technology) and a random-zero sphygmomanometer. For each side, a single blood pressure reading was taken with the subject in supine position. The ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm (ankle-arm index) was calculated for each leg. The lowest ankle-arm index in either leg was used in the analysis. In addition, separate analyses were performed in which each subject an estimate of the ankle-arm index was obtained by averaging the ankle-arm index of both legs. In agreement with the approach followed by Fowkes and Schroll and Munck, lower extremity arterial disease was considered present when the ankle-arm index was <0.90 in at least one side.

Cardiovascular Risk Factors

In the Rotterdam Study, information on current health status, medical history, drug use, and smoking behavior was obtained with a computerized questionnaire, which included a Dutch version of the Rose questionnaire for assessment of prevalent coronary heart disease and intermittent claudication. A history of stroke and myocardial infarction was obtained through direct questioning and considered positive when confirmed by a physician. Diabetes mellitus was regarded present when a subject was currently receiving oral antidiabetic drugs or insulin treatment. With respect to smoking behavior, subjects were categorized in groups of current smoker, ever smoker, and those who were never smoked. During two visits at the research center, several cardiovascular risk indicators were measured. Height and weight were measured, and body mass index (kg/m²) was calculated. Systolic blood pressure was measured at the right upper arm using a random-zero sphygmomanometer. The average of two measurements obtained on one occasion, separated by a count of the pulse rate, was used in the present analysis. Hypertension was defined as a systolic blood pressure of ≥160 mm Hg or a diastolic blood pressure ≥90 mm Hg or current use of antihypertensive drugs for the indication hypertension. A venipuncture was performed, when possible without stasis, using a 21-gauge butterfly needle with tube (Surflo winged infusion set). Serum total cholesterol was determined by an automated enzymatic procedure. HDL cholesterol was measured similarly, after precipitation of the non-HDL fraction with phosphotungstate-magnesium.

Data Analysis

The present analysis is based on findings in the first 1000 participants of the Rotterdam Study. Carotid ultrasound scans could not be obtained in 12 subjects because of equipment failure. Similarly, Doppler readings from both posterior tibial arteries were not available in 18 subjects. Measurement of intima-media thickness at either the left or the right carotid artery could not be performed from the stored images in 31 subjects because of poor visualization. With respect to the measurement of the ankle-arm index, data on the left or the right side were not available for 16 subjects. In both situations, the estimate of intima-media thickness and of ankle-arm index for each subject was based on the measurement of the side for which a value was available.

The association between common carotid intima-media thickness and ankle-arm index was evaluated by linear regression analysis. Multiple linear regression was used for analyses, adjusted for age, sex, and several cardiovascular risk factors, such as hypertension, smoking, body mass index, serum total cholesterol, and serum HDL cholesterol. To assess the risk of presence of lower extremity arterial disease associated with a common carotid intima-media thickness ≥0.89 mm (upper quintile) compared with intima-media thickness <0.89 mm, logistic regression analysis was used. The associations are presented with a 95% confidence interval (CI). χ² tests according to Hosmer-Lemeshow were used to evaluate the goodness of fit of the logistic models used. For all models, the P values were found to be ≥.26, indicating a good fit. Analyses of trend across groups of increasing levels of common carotid intima-media thickness were performed with linear regression analysis. All analyses were performed using BMDP statistical package.

The distributions of the measurements of common carotid intima-media thickness and ankle-arm index were skewed. Analyses in which the values were logarithmically transformed yielded results similar to those with untransformed data. Because interpretation of results from logarithmically transformed data is rather difficult, the nontransformed results are presented. A positive history of a major cardiovascular event, ie, a positive history of stroke, angina pectoris, myocardial infarction, or intermittent claudication was significantly associated with an increased common carotid intima-media thickness and a reduced ankle-arm index. Since this may bias the association between intima-media thickness and the ankle-arm index toward a positive finding, separate analyses were performed among subjects free from symptomatic cardiovascular disease. The presented findings include subjects with an ankle-arm index of ≥1.5 (n=18). Exclusion of these subjects did not alter the results.

Results

Data on carotid arteries and arteries of the lower extremity were available for 970 (97%) of the subjects. Baseline characteristics of this group are presented in Table 1.

Intima-Media Thickness and Ankle-Arm Index

Linear regression analysis showed a significant inverse association between common carotid intima-media thickness and the ankle-arm index (Fig 1, top). The age- and sex-adjusted results indicated that an increase of 0.1 mm in common carotid intima-media thickness was associated with a mean reduction of the ankle-arm index of 0.026 (95% CI: 0.018 to 0.034). For men, a gradual decrease of the ankle-arm index was observed with increasing levels of common carotid intima-media thickness, whereas for women, the ankle-arm index decreased beyond a common carotid intima-media...
TABLE 1. General Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>592</td>
<td>378</td>
</tr>
<tr>
<td>Age, y</td>
<td>68.7 (7.9)</td>
<td>68.4 (7.6)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.1 (4.2)</td>
<td>25.9 (3.1)</td>
</tr>
<tr>
<td>Smoking, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>Former</td>
<td>30</td>
<td>64</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>134 (22)</td>
<td>134 (19)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>70 (11)</td>
<td>72 (10)</td>
</tr>
<tr>
<td>Hypertension, %*</td>
<td>33</td>
<td>23</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>7.0 (1.2)</td>
<td>6.4 (1.2)</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/L</td>
<td>1.4 (0.3)</td>
<td>1.2 (0.4)</td>
</tr>
<tr>
<td>Prevalent cardiovascular disease, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>8.4</td>
<td>6.8</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5.2</td>
<td>14.9</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.4</td>
<td>5.3</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Diabetes mellitus, %†</td>
<td>3.7</td>
<td>4.5</td>
</tr>
<tr>
<td>Carotid intima-media thickness, mm</td>
<td>0.76 (0.19)</td>
<td>0.81 (0.19)</td>
</tr>
<tr>
<td>Ankle-arm index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left side</td>
<td>1.17 (0.22)</td>
<td>1.19 (0.21)</td>
</tr>
<tr>
<td>Right side</td>
<td>1.17 (0.24)</td>
<td>1.20 (0.23)</td>
</tr>
<tr>
<td>Lower extremity arterial disease, %‡</td>
<td>13.2</td>
<td>10.3</td>
</tr>
</tbody>
</table>

Values are percentages and means with standard deviation in parentheses.

*Hypertension defined as a systolic pressure ≥160 mm Hg or a diastolic pressure ≥90 mm Hg or currently using antihypertensive drugs.

†Diabetes defined as currently receiving oral antidiabetic drugs or insulin treatment.

‡Defined as ankle-arm index <0.90 in at least one leg.

thickness of 0.87 mm (Fig 1, middle and bottom, respectively). A nonsignificant difference in the magnitude of the association between men and women was observed in the linear regression analysis: for men, 0.029 (95% CI: 0.017 to 0.041) and for women, 0.023 (95% CI: 0.012 to 0.034). Exclusion of subjects with prevalent cardiovascular disease (n=162), did slightly reduce the magnitude of the age- and sex-adjusted findings (mean reduction of 0.018 [95% CI: 0.008 to 0.028]). Adjustments for differences in serum lipids, hypertension, body mass index, and current smoking attenuated the association between common carotid intima-media thickness and ankle-arm index: analysis among all subjects gave a mean reduction of the ankle-arm index of 0.021 (95% CI: 0.013 to 0.029) with an increase of 0.1 mm in common carotid intima-media thickness, whereas analysis among asymptomatic subjects yielded a mean reduction of 0.013 (95% CI: 0.003 to 0.023). When the average of the ankle-arm index of both legs was used in the analysis instead of the lowest value at either leg, similar associations between common carotid intima-media thickness and ankle-arm index were obtained (Table 2).

Intima-Media Thickness and Lower Extremity Arterial Disease

The results for lower extremity arterial disease, defined as an ankle-arm index <0.90 in at least one side,17,18 are presented in Fig 2. For all subjects, the prevalence of lower extremity arterial disease was strongly increased among subjects with an intima-media
TABLE 2. Age-Adjusted Findings on the Association Between Intima-Media Thickness and Ankle-Arm Index When Defined as the Average of the Ankle-Arm Index of Both Legs

<table>
<thead>
<tr>
<th></th>
<th>All Subjects</th>
<th>Asymptomatic Subjects*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>-0.013 (-0.003, -0.023)</td>
<td>-0.011 (-0.001, -0.023)</td>
</tr>
<tr>
<td>Men</td>
<td>-0.025 (-0.014, -0.036)</td>
<td>-0.022 (-0.009, -0.035)</td>
</tr>
<tr>
<td>Both men and women†</td>
<td>-0.019 (-0.011, -0.027)</td>
<td>-0.016 (-0.016, -0.026)</td>
</tr>
<tr>
<td>Both men and women, adjusted‡</td>
<td>-0.013 (-0.007, -0.021)</td>
<td>-0.010 (-0.001, -0.019)</td>
</tr>
</tbody>
</table>

Results are expressed as a mean change in the ankle-arm index (95% confidence index) with an increase of 0.1 mm in intima-media thickness.

*Subjects without a positive history of stroke, angina pectoris, myocardial infarction, and intermittent claudication.
†Adjusted for age and gender.
‡Adjusted for age, gender, hypertension, current smoking, HDL cholesterol, and body mass index.

thickness ≥0.89 mm (upper quintile). A gradual linear increase of the prevalence of lower extremity arterial disease with increasing levels of common carotid intima-media thickness could not be demonstrated (Fig 2, top). Similar findings were observed for men and women (Fig 2, middle and bottom, respectively). The common carotid intima-media thickness in subjects with lower extremity arterial disease was increased as compared with that of subjects without disease with an age- and sex-adjusted difference of 0.107 mm (95% CI: 0.071 to 0.143).

In Table 3, the prevalence of lower extremity arterial disease, defined according to different arbitrarily chosen cutoff levels of the ankle-arm index, is presented in quintiles of common carotid intima-media thickness. Irrespective of the definition of lower extremity arterial disease, an increase of the presence of lower extremity arterial disease with common carotid intima-media thickness was found, in particular, beyond a common carotid intima-media thickness of 0.89 mm.

The age- and sex-adjusted odds ratio (OR) of lower extremity arterial disease for those with a common carotid intima-media thickness ≥0.89 mm to that of subjects with an intima-media thickness <0.89 mm was 3.4 (95% CI: 2.2 to 5.2). Attenuation of the OR was found when additional adjustments were made for differences in serum lipids, hypertension, body mass index, and smoking: OR 2.8 (95% CI: 1.8 to 4.4).

Analyses among men and women separately revealed ORs of 3.8 (95% CI: 1.9 to 7.8) and 3.2 (95% CI: 1.8 to 5.5), respectively. Analysis among subjects free from symptomatic cardiovascular disease yielded an age- and sex-adjusted OR of 3.0 (95% CI: 1.7 to 5.1). Further adjustment for cardiovascular risk factors did not substantially alter the magnitude and significance of the findings.

**Intima-Media Thickness and Symptomatic Lower Extremity Arterial Disease**

Among subjects with intermittent claudication (n=12), the mean ankle-arm index (SD) was 0.84 (0.32) compared with 1.12 (0.22) in subjects without intermittent claudication. Intima-media thickness in subjects with intermittent claudication was 0.87 (0.16) compared with 0.76 (0.16) in subjects free from symptomatic cardiovascular disease, with an age- and sex-adjusted mean difference of 0.089 mm (95% CI: −0.001 to 0.179).

**Discussion**

Our findings in a population-based sample of elderly subjects indicate that a gradual increase in ultrasonographically assessed common carotid intima-media thickness is associated with a steady reduction of the ankle-arm index, in particular in men and less pronounced in women. Furthermore, men and women with a common carotid intima-media thickness in the upper
These results support the view that elevated levels of cardiovascular risk factors. In several studies, ultrasonography cannot discriminate between the intima layer and the media layer of vessel wall. In several studies, smoking, high blood pressure, and ultrasound imaging cannot discriminate between the intima-media thickness of the common carotid artery has been associated with elevated levels of cardiovascular risk factors. In addition, progression of common carotid intima-media thickness over time has been associated with risk factors for atherosclerosis. These results support the view that noninvasively assessed intima-media thickness of the common carotid artery may be regarded as a measure of atherosclerosis.

Our finding among nonhospitalized elderly subjects that an increased common carotid intima-media thickness is associated with a lower ankle-arm index, as an indicator of the presence of atherosclerotic vessel wall abnormalities of the arteries of the lower extremities, demonstrates that intima-media thickness of the common carotid artery may reflect generalized atherosclerosis. This notion is supported by results from a study among 208 hypercholesterolemic men, 25 to 64 years old, in which a strong association was found between ultrasonographically determined presence of atherosclerotic carotid plaques and atherosclerotic plaques in the femoral artery. Furthermore, this view may be strengthened by findings from a population-based study in which ultrasonographically determined increase in intima-media thickness was associated with an increased risk of myocardial infarction and from other studies that were performed among hospital-based populations or among otherwise selected populations, in which a positive association was observed between noninvasively assessed carotid atherosclerotic vessel wall abnormalities and coronary atherosclerosis. Furthermore, the definition of presence or absence of lower extremity arterial disease among nonhospitalized elderly subjects is based on an arbitrarily chosen cutoff point of the level of the ankle-arm index measured in subjects at rest, and at present no agreement exists on the level of the cutoff point. Our findings with respect to the association with common carotid intima-media thickness indicate no superiority for either definition of ankle-arm index or for the level of the cutoff point used to define lower extremity arterial disease.

Finally, an increased common carotid intima-media thickness may not reflect atherosclerosis and may not be a precursor of atherosclerosis. It may merely be an adaptive response of the vessel wall to changes in shear stress and tensile stress. Furthermore, atherosclerosis is viewed as a disorder restricted to the intimal layer of the arterial vessel wall, and ultrasound imaging cannot discriminate between the intima layer and the media layer of vessel wall. In several studies, ultrasonographically determined increased intima-media thickness of the common carotid artery has been associated with elevated levels of cardiovascular risk factors. In addition, progression of common carotid intima-media thickness over time has been associated with risk factors for atherosclerosis. These results support the view that noninvasively assessed intima-media thickness of the common carotid artery may be regarded as a measure of atherosclerosis.

The results from the present study suggest that a common carotid intima-media thickness ≥0.89 mm may be a better predictor of the presence of lower extremity arterial disease than values <0.89 mm. One explanation for finding no uniform association for a value <0.89 mm may be that a common carotid intima-media thickness at that level may be associated with minor atherosclerotic vessel wall abnormalities that do not give rise to a sufficient reduction of systolic blood pressure in the arteries of the lower extremities. In the Rotterdam Study, however, additional information on the extent of atherosclerosis in the arteries of the lower extremities, such as presence or absence of plaques, is not available.

In several studies, smoking, high blood pressure, elevated levels of serum total cholesterol, and low levels of HDL cholesterol have been associated with carotid atherosclerosis, indicated as increased intima-media thickening and with lower extremity arterial atherosclerotic disease. These results may suggest that these cardiovascular risk factors may cause atherosclerosis of both the common carotid artery and the arteries of the lower extremity. Consequently, these risk factors should not be considered as confounding variables of
the observed association between carotid intima-media thickness and lower extremity arterial atherosclerosis and should in principle not be controlled for in the analyses. When, on the other hand, the main interest is to assess whether the observed association between carotid intima-media thickness is independent from cardiovascular risk factors, one may want to additionally adjust for these factors. In the present study among elderly subjects, adjustment for differences in smoking, hypertension, body mass index, and elevated levels of serum lipids did not severely attenuate the observed association between common carotid intima-media thickness and ankle-arm index. This indicates that either, besides these factors, other factors yet unknown may play a role in the development of atherosclerosis of both the common carotid arteries and the arteries of the lower extremity or, alternatively, that the effect of these risk factors on atherosclerosis may be different across different arterial sites.

Some notes of caution are necessary. At present, intima-media thickness measurements of the common carotid artery have not yet found their way into clinical practice. Clearly, a lack of evidence of the value of increased common carotid intima-media thickness as a predictor of stroke and lower extremity arterial disease and the very limited available data to show an association between an increased common carotid intima-media thickness and risk of myocardial infarction should be recognized. Furthermore, at present no data are available on the role of changes in common carotid intima-media wall thickness over time and change in atherosclerosis in other arterial vessels. Results from currently ongoing prospective follow-up studies, for which the follow-up time has yet been too limited to adequately assess the value of increased common carotid intima-media thickness prospectively, may provide answers to these questions in the near future and are urgently awaited.

In conclusion, this study provides evidence that increased common carotid intima-media thickness reflects generalized atherosclerosis, as indicated by its association with atherosclerosis of the arteries of the lower extremities.

Acknowledgments

The Rotterdam Study is supported in part by the NESTOR program for geriatric research (Ministry of Health and Ministry of Education), the Netherlands Heart Foundation, the Netherlands Organization for Scientific Research (NWO), the Rotterdam Medical Research Foundation (ROMERES), and the Municipality of Rotterdam. We are grateful to the participants of the Rotterdam Study. We thank all field workers, ultrasound technicians, computer assistants, and laboratory technicians in the Ommoord research center for their enthusiasm and skilful contributions to the data collection.

References


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Arterioscler Thromb Vasc Biol. 1994;14:1885-1891
doi: 10.1161/01.ATV.14.12.1885
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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