Carotid Intima-Media Thickness, Systemic Inflammation, and Incidence of Heart Failure Hospitalizations

Gunnar Engström, Olle Melander, Bo Hedblad

Objectives—This study explored the relationships between carotid intima-media thickness (IMT), plasma levels of C-reactive protein (CRP), and incidence of heart failure hospitalizations.

Methods and Results—Men and women from the general population (n=4691), without history of myocardial infarction or stroke, were examined. Incidence of hospitalizations attributable to heart failure was studied over a mean follow-up of 13 years. A total of 75 subjects were hospitalized with a primary diagnosis of heart failure. Adjusted for risk factors, the hazards ratios (95% CI) were 1.00, 0.98 (0.36 to 2.7), 1.9 (0.80 to 4.6), and 2.7 (1.1 to 6.2), respectively, for the 1st, 2nd, 3rd, and 4th quartiles of IMT (P for trend=0.003). The HR associated with CRP levels ≥3 mg/L (versus <1 mg/L) was 2.0 (95% CI: 1.06 to 3.9) after adjustments for risk factors. There was a significant interaction between IMT and CRP on heart failure incidence (P=0.028). Subjects with CRP ≥3 mg/L and IMT in the 4th quartile had an adjusted HR of 3.7 (1.9 to 7.1) compared to those with CRP <3 mg/L and IMT in quartile 1 to 3.

Conclusion—High IMT and high CRP are both independent risk factors for incidence of heart failure requiring hospitalization. The joint exposure to both risk factors substantially increases the risk. (Arterioscler Thromb Vasc Biol. 2009;29:1691-1695.)

Key Words: heart failure • atherosclerosis • inflammation • epidemiology

Heart failure is a heterogeneous disorder, which can be the result of different disease processes that reduce the cardiac function. Coronary heart disease is one of the most important causes. Traditional risk factors for atherosclerotic diseases (eg, hypertension, diabetes, smoking, and overweight), have also been associated with incidence of heart failure. Recent studies have shown that incidence of heart failure is increased in subjects with raised plasma levels of various markers of systemic inflammation, and it is often suggested that inflammatory processes could be part of the etiology of heart failure.

Development of atherosclerosis is a slow process with a long silent phase before the clinical manifestations disease. Intima-media thickness in the carotid arteries (IMT) is generally considered to be an early indicator of subclinical atherosclerosis. Many studies have shown that IMT is associated with incidence of acute coronary events and stroke even after adjustments for hypertension and other atherosclerotic risk factors. A study from the Multi-Ethnic Study of Atherosclerosis (MESA) reported that IMT correlated with different measures of the regional myocardial function in asymptomatic individuals. It is conceivable that carotid IMT reflects the generalized atherosclerotic disease processes of an individual that ultimately results in heart failure. However, it is largely unknown whether IMT is a risk factor for developing clinical heart failure.

The purpose of the present study was to explore the relationships between IMT and incidence of heart failure. We also sought to explore whether this relationship was modified by systemic low-grade inflammation, as measured by plasma levels of C-reactive protein (CRP).

Study Population
From 1991 to 1996, all men and women born between 1923 and 1950 and living in Malmö, Sweden were recruited into the Malmö Diet and Cancer (MDC) study. A detailed description of the MDC study has been given previously. The cohort consists of 28,449 subjects from the eligible population of about 74,000 individuals. A random 50% of participants who entered the MDC study between October 1991 and February 1994 were invited to take part in a study of the epidemiology of carotid artery diseases. During this period, a total of 6103 subjects (2572 men and 3531 women) were examined by B-mode ultrasound of the right carotid artery, and 5540 participants returned to donate blood samples for measurements of blood lipids and glucose status. For the present study, the sample was restricted to those with complete information on IMT, CRP, N-terminal B-type natriuretic peptide (NT-BNP), blood pressure, diabetes, low-density and high-density lipoprotein cholesterol (LDL, HDL), and waist circumference. Furthermore, 13 subjects with a hospitalization attributable to heart failure before the baseline examination, and 143 subjects with history of myocardial infarction or stroke were excluded. A total of 4691 subjects remained after the exclusions.

The ethical committee at Lund University approved the MDC study (LU 51/90). All subjects gave informed consent.

Baseline Examinations
A self-administered questionnaire was used to obtain information on smoking habits, diabetes, blood pressure lowering medication, and history of stroke or myocardial infarction. Information on smoking was missing for 102 subjects (2.2%). This group was coded in a separate category (dummy variable) to keep them in the multivariate analysis.
Body weight, waist and hip girth, and blood pressure were measured as previously described. Diabetes mellitus was defined as self-reported diabetes according to the questionnaire, or treatment with antidiabetic medication or a fasting whole blood glucose level ≥6.1 mmol/L. C-reactive protein (CRP) was analyzed in frozen plasma, gathered at the baseline examination, using Tina-quant CRP latex high-sensitivity assays (Roche Diagnostics) on an ADVIA 1650 Chemistry System (Bayer Healthcare). CRP was categorized into 3 groups: <1 mg/L, 1 to 3 mg/L, and ≥3 mg/L.

N-terminal B-type natriuretic peptide (NT-BNP) was measured using the Dimension RxL N-BNP (Dade-Behring, Germany).

Carotid Artery Measurements
Participants underwent B-mode ultrasonography (Acuson 128 CT system) of the right carotid artery. IMT of the common carotid artery (CCA) and the presence of carotid plaque were measured according to a standardized protocol by trained certified sonographers, as previously published. In short, the bifurcation area of the right common carotid artery was scanned within a predefined “window” comprising 3 cm of the right common carotid artery, the bifurcation, and 1 cm of both the internal and external carotid artery for the presence of plaque. IMT was determined in the far wall of the right distal CCA according to the leading edge principle, using a specially designed computer-assisted analyzing system. IMT was then determined off-line as the mean wall thickness over a 10-mm segment proximal to the bifurcation. The maximum wall intima media thickness in this segment was also determined (IMT-max). Each image was analyzed without knowledge of the subject’s identification code, to minimize the possibility of observer bias.

Intraobserver and interobserver variability with regard to IMT was checked regularly. The mean intraobserver difference was 8.7 ± 6.2% (r = 0.85) and the mean interobserver difference 9.0 ± 7.2% (r = 0.77).

Because IMT in part could depend on lumen diameter, the transsectional intima-media area was also estimated from the IMT and the lumen diameter. The formula:

\[
\text{Intima-media area} = \pi \left( \frac{d}{2} + \text{IMT} \right)^2 - \left( \frac{d}{2} \right)^2
\]

was used, in which d is the lumen diameter (mm), and IMT is mean IMT of the CCA (mm).

Follow-Up
All men were followed from the baseline examination until first hospitalization attributable to heart failure, myocardial infarction, death, emigration from Sweden, or December 31, 2006, whichever came first. Subjects with nonfatal myocardial infarction were followed until the day of infarction and censored thereafter. Subjects with a hospital discharge diagnosis of heart failure (codes 428 and 150 according to the International Classification of Diseases, ICD, 9th and 10th revision, respectively) were considered to have heart failure if the diagnosis was listed as the primary diagnosis. Nonfatal myocardial infarction was defined as ICD-codes 410 or I21. The Swedish Hospital Discharge Register was used for case-retrieval. A validation study has shown that a primary diagnosis of heart failure in the Swedish Hospital Discharge Register has a validity of 95%.

Statistics
IMT, CRP, and NT-BNP were log normalized because of skewed distributions. One-way analysis of variance and logistic regression was used to compare the distribution of risk factors in relation to IMT. The linear trends over the sex-specific quartiles of IMT were used. Cox proportional hazards regression was used to compare incidence of HF in relation to IMT and to calculate hazard ratios (HR). The fit of the proportional hazards model was confirmed by plotting the HF incidence rates over time. The model was adjusted for age, sex, smoking, systolic blood pressure, blood pressure medication, LDL, HDL, diabetes, waist circumference, NT-BNP, and CRP. The covariate adjusted Cox analysis was then repeated in separate analyses of men and women. An interaction term (log IMT* log CRP) was entered into the Cox model to study statistical interaction between IMT and CRP on incidence of heart failure. The joint effect of IMT and CRP on incidence of heart failure was also explored by categorizing the sample into 4 groups; with and without high IMT (ie, 4th quartile versus quartile 1 to 3) and with and without high CRP (ie, ≥3 mg/L versus <3 mg/L). The SPSS software (v11.5) was used for the statistical calculations.

Results
Baseline Characteristics
Median IMT (interquartile range) was 0.77 mm in men (0.68 to 0.88 mm) and 0.73 mm (0.66 to 0.82 mm) in women. The cardiovascular risk factors at the baseline examination are presented in Table 1, in relation to the sex-specific quartiles of IMT. Except for smoking, all major cardiovascular risk factors showed substantial correlations with IMT.

Risk Factors for Heart Failure
Over the mean follow-up of 13.2 years (SD 2.5), a total of 75 subjects (37 men and 38 women) were hospitalized with a primary diagnosis of heart failure. The relationships between different cardiovascular risk factors and incidence of heart failure are presented in Table 2. Age, diabetes, blood pressure treatment, log CRP, and log IMT were significantly associated with incidence of heart failure. The age- and sex-adjusted HR for subjects with CRP ≥3 mg/L (versus <1 mg/L) was 3.5 (CI: 1.9 to 6.3), and the HR was 2.0 (CI: 1.06 to 3.9) after adjustments for risk factors.

Incidence of Heart Failure in Relation to IMT
Incidence of HF by quartile of IMT is presented in Figure 1 and Table 3. The HR, adjusted for age and sex, was 3.9 (95% CI: 1.7 to 9.0) for subjects with IMT in the 4th quartile. After adjustments for risk factors, the HR was 2.7 (CI: 1.1 to 6.2, P for trend = 0.003). This relationship was consistent in men and women (Men 4th quartile: HR = 2.9, CI: 0.81 to 10.4, P for trend = 0.03; Women 4th quartile: HR = 2.3, CI: 0.73 to 7.2, P for trend = 0.06).

Incidence of heart failure showed similar relationships with intima-media area and with IMT-max. The HR for subjects in the 4th quartile (versus 1st quartile) of intima-media area was 4.2 (CI: 1.8 to 9.7) after adjustment for age and sex, and 2.7 (CI: 1.1 to 6.3) after adjustments for risk factors. For IMT-max, the age- and sex-adjusted HR for subjects in the 4th quartile (versus 1st quartile) was 3.3 (CI: 1.6 to 7.0) and 2.1 (CI: 1.00 to 4.6) after adjustment for risk factors.

Incidence of Heart Failure in Relation to IMT and CRP
A statistically significant interaction was observed when the interaction term (log IMT* log CRP, P = 0.028) was entered into the risk factor adjusted Cox model. The sample was therefore categorized into 4 groups according to IMT (4th quartile versus quartile 1 to 3) and CRP (≥3 mg/L versus <3 mg/L; Table 4 and Figure 2). Subjects with high IMT and high CRP had substantially increased risk of heart failure (HR: 3.7, CI: 1.9 to 7.3, adjusted for risk factors). The HRs were significantly lower for subjects who only had one of these risk factors (high IMT only: HR = 1.56, CI: 0.79 to 3.1; high CRP only: HR = 1.56, CI: 0.82 to 3.0; Table 4).

Discussion
Intima-media thickness in the carotid arteries (IMT) is an established marker of subclinical atherosclerosis. Whether IMT...
is associated with development of clinically overt heart failure has been unclear. The present results show that subjects with high IMT had increased incidence of heart failure hospitalizations, even after adjustment for traditional CVD risk factors and after censoring subjects with myocardial infarction. The hazards ratio for heart failure hospitalizations was substantially increased if high IMT occurred in combination with raised CRP levels.

Coronary heart disease is a major risk factor for heart failure, and it is likely that the relationship between IMT and incidence of heart failure largely is explained by a higher burden of generalized atherosclerosis in subjects with high IMT. However, there could also be other links between IMT and heart failure. Hypertension is a major risk factor for heart failure, and hypertension is also the major determinant for IMT. Hypertension causes thickening of the arterial wall, presumably as a physiological adaptation to the high blood pressure, and the major thickening occurs in the media. In contrast to single blood pressure readings, which can vary significantly for the same individual, IMT reflects the exposure of hypertension over a longer time period. This should increase the prognostic value of high IMT, and it could explain why IMT was significantly associated with heart failure even after adjustments for baseline blood pressure and other risk factors for atherosclerosis.

The interaction between IMT and CRP on heart failure hospitalizations reached statistical significance. Recent studies have reported increased incidence of heart failure in subjects with raised levels of various markers of inflammation. The etiologic pathways through which inflammation could increase

Table 1. Baseline Characteristics of the Study Population in Relation to Sex-Specific Quartiles of Carotid Intima-Media Thickness (IMT)

<table>
<thead>
<tr>
<th>Quartiles of IMT</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (men/women)</td>
<td>477/667</td>
<td>459/713</td>
<td>466/712</td>
<td>472/725</td>
<td></td>
</tr>
<tr>
<td>IMT range, mm (men)</td>
<td>0.36–0.67</td>
<td>0.68–0.76</td>
<td>0.77–0.87</td>
<td>0.88–2.06</td>
<td></td>
</tr>
<tr>
<td>IMT range, mm (women)</td>
<td>0.36–0.65</td>
<td>0.66–0.72</td>
<td>0.73–0.81</td>
<td>0.82–1.85</td>
<td></td>
</tr>
<tr>
<td>Intima-media area, mm²*</td>
<td>12.1</td>
<td>14.5</td>
<td>16.8</td>
<td>21.5</td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>54.8 ± 5.7</td>
<td>56.4 ± 5.7</td>
<td>58.4 ± 5.7</td>
<td>60.0 ± 5.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>21.3</td>
<td>21.3</td>
<td>21.0</td>
<td>22.5</td>
<td>0.84</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>134 ± 16</td>
<td>139 ± 18</td>
<td>143 ± 19</td>
<td>148 ± 20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>85.1 ± 8.8</td>
<td>86.3 ± 9.3</td>
<td>87.2 ± 9.6</td>
<td>88.4 ± 9.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood pressure drug, %</td>
<td>11.1</td>
<td>11.9</td>
<td>15.4</td>
<td>20.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>5.2</td>
<td>6.1</td>
<td>7.9</td>
<td>10.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>4.0 ± 1.0</td>
<td>4.1 ± 0.93</td>
<td>4.2 ± 1.0</td>
<td>4.4 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.40 ± 0.37</td>
<td>1.42 ± 0.38</td>
<td>1.40 ± 0.37</td>
<td>1.35 ± 0.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>82.4 ± 12</td>
<td>82.6 ± 12</td>
<td>83.4 ± 13</td>
<td>85.0 ± 13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP, mg/L*</td>
<td>1.19</td>
<td>1.30</td>
<td>1.45</td>
<td>1.55</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*CRP and intima-media area are presented as geometric means due to skewed distributions. Other values are mean ± SD, unless otherwise stated.

Table 2. Results from Cox Proportional Hazards Regression of Incidence of Heart Failure Hospitalizations

<table>
<thead>
<tr>
<th>Age and Sex</th>
<th>Risk Factors</th>
<th>Age, per 1 year</th>
<th>Male (vs female)</th>
<th>Systolic BP, per 10 mm Hg</th>
<th>Blood Pressure drug (yes vs no)</th>
<th>Smoking (yes vs no)</th>
<th>Waist, per 1 cm</th>
<th>LDL, per 1 mmol/L</th>
<th>HDL, per 1 mmol/L</th>
<th>Diabetes (yes vs no)</th>
<th>Log CRP, per 1 SD</th>
<th>Log IMT, per 1 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1.12 (1.07–1.17)</td>
<td>1.6 (0.99–2.4)</td>
<td>1.2 (1.1–1.4)</td>
<td>3.5 (2.2–5.6)</td>
<td>1.6 (0.97–2.7)</td>
<td>1.04 (1.02–1.06)</td>
<td>0.88 (0.69–1.1)</td>
<td>0.55 (0.27–1.1)</td>
<td>4.0 (2.4–6.7)</td>
<td>1.8 (1.4–2.2)</td>
<td>1.6 (1.3–2.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.08 (1.03–1.13)</td>
<td>1.1 (0.61–1.9)</td>
<td>1.1 (0.95–1.2)</td>
<td>2.4 (1.5–4.0)</td>
<td>1.4 (0.84–2.5)</td>
<td>1.01 (0.99–1.03)</td>
<td>0.85 (0.66–1.1)</td>
<td>1.12 (0.55–2.3)</td>
<td>2.3 (1.3–4.0)</td>
<td>1.5 (1.2–1.9)</td>
<td>1.4 (1.2–1.8)</td>
</tr>
</tbody>
</table>

Presented as hazards ratios (95% CI) adjusted for age and sex (when appropriate) or in a model including all risk factors in the table. SD indicates standard deviation.

Figure 1. Incidence of heart failure hospitalizations in sex-specific quartiles of IMT (Q1 to Q4 [thickest]).
the incidence of heart failure are unclear. CRP could be associated with accelerated atherosclerosis both in the carotids and coronary arteries. Some studies have reported associations between CRP and progression of carotid atherosclerosis, but this relationship could not be replicated in a large population-based study. There are also other possible explanations for the interaction between IMT and CRP on heart failure. Patients with heart failure have increased immune activation. High levels of proinflammatory cytokines may have several adverse effects, including myocardial remodeling, promotion of cardiac arrhythmia, and negative inotrophy. Interleukin 6, which is a major stimulator of CRP synthesis, has been associated with occurrence of atrial fibrillation.

The end points in this study were cases that had been hospitalized with a primary diagnosis of heart failure. It is obvious that this definition only includes the most severe patients, and those who only were treated as out-patients were not included. On the other hand, because the patients had a primary diagnosis of heart failure which was settled during the hospital stay, we can assume that the diagnosis in most cases was valid. A validation study of cases retrieved from the Swedish hospital discharge register showed that the validity of the diagnosis was 95%, irrespective of clinic type, if heart failure was the primary diagnosis. We do not know whether the IMT show the same relationships with less severe heart failure, which is more likely to be treated in a primary care setting. However, in the MESA study, IMT correlated with different measures of the regional myocardial function in asymptomatic individuals. This suggests that IMT could be associated with less severe forms of heart failure, too.

In the present study, the IMT was measured in the right carotid artery, whereas many other studies calculated the mean value from both sides. Even though only one side was scanned in this study, the reproducibility of the IMT measurements and the prediction of myocardial infarction and stroke have been comparable to results from other big cohort studies, which scanned both sides. However, it is still likely that measurements of IMT on both sides could further improve the prognostic value of IMT.

Incidence of HF was increased for subjects with IMT in the 3rd and 4th quartiles of IMT. Because the number of events was limited in this study, we cannot draw any conclusions about possible cut-off levels. Whether there is a threshold effect for IMT remains to be evaluated, both for different age-groups and in relation to other risk factors. Ischemic heart disease is an important etiologic factor for heart failure. Subjects with history of cardiovascular disease at baseline were excluded. Subjects with myocardial infarction during the follow-up were censored in the analysis. Thus, the present results could not be explained by more coronary events in subjects with high CRP or IMT. However, many infarctions are subclinical, and it is still possible that silent

<table>
<thead>
<tr>
<th>Quartiles of IMT</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (men/women)</td>
<td>477/667</td>
<td>459/713</td>
<td>466/712</td>
<td>472/725</td>
</tr>
<tr>
<td>Heart failure, n</td>
<td>7</td>
<td>9</td>
<td>21</td>
<td>38</td>
</tr>
<tr>
<td>Per 1000 py</td>
<td>0.45</td>
<td>0.57</td>
<td>1.36</td>
<td>2.51</td>
</tr>
<tr>
<td>HR, age, sex</td>
<td>1.00</td>
<td>1.1 (0.42–3.0)</td>
<td>2.4 (1.0–5.6)</td>
<td>3.9 (1.7–9.0)</td>
</tr>
<tr>
<td>+ Risk factors</td>
<td>1.00</td>
<td>1.1 (0.40–2.9)</td>
<td>2.1 (0.87–5.0)</td>
<td>3.2 (1.4–7.3)</td>
</tr>
<tr>
<td>+ CRP and NT-BNP†</td>
<td>1.00</td>
<td>0.98 (0.36–2.7)</td>
<td>1.9 (0.80–4.6)</td>
<td>2.7 (1.1–6.2)</td>
</tr>
</tbody>
</table>

HR hazards ratio (95% confidence interval) adjusted for age and sex or risk factors.

Adjusted for age, sex, systolic blood pressure, blood pressure medication, smoking, waist circumference, HDL, LDL, diabetes.

†Also adjusted for CRP and NT-BNP (log transformed).

Table 4. Incidence of Heart Failure Hospitalizations in Relation to High IMT (4th Quartile) and CRP (≥3 mg/L)

<table>
<thead>
<tr>
<th>Categories of IMT and CRP</th>
<th>Low IMT CRP &lt;3</th>
<th>Low IMT CRP ≥3</th>
<th>High IMT CRP &lt;3</th>
<th>High IMT CRP ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (men/women)</td>
<td>1122/1635</td>
<td>280/457</td>
<td>344/553</td>
<td>128/172</td>
</tr>
<tr>
<td>Heart failure, n</td>
<td>23</td>
<td>14</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Per 1000 py</td>
<td>0.62</td>
<td>1.44</td>
<td>1.56</td>
<td>5.52</td>
</tr>
<tr>
<td>HR, age, sex</td>
<td>1.00</td>
<td>2.3 (1.2–4.4)</td>
<td>2.0 (1.1–3.7)</td>
<td>6.9 (3.7–12.7)†</td>
</tr>
<tr>
<td>+ Risk factors*</td>
<td>1.00</td>
<td>1.6 (0.79–3.1)</td>
<td>1.6 (0.82–3.0)</td>
<td>3.7 (1.9–7.3)†</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, systolic blood pressure, blood pressure lowering medication, smoking, waist circumference, HDL, LDL, diabetes, NT-BNP (log transformed).

†P<0.05 vs all other groups.
myocardial infarctions could contribute to the increased incidence of heart failure.

The present results show that subjects with high IMT had increased incidence of heart failure hospitalizations, independently of traditional CVD risk factors and development of myocardial infarction. It is our conclusion that subjects with high IMT or high CRP have increased incidence of heart failure hospitalizations, and that the joint exposure to both risk factors substantially increases the risk.

**Sources of Funding**

This study was supported by grants from the Swedish Heart-Lung foundation, the Swedish Research council, and funds from University of Lund and Region Skåne.

**Disclosures**

G.E. is employed as senior epidemiological scientist by AstraZeneca R&D, Lund, Sweden.

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Arterioscler Thromb Vasc Biol. 2009;29:1691-1695; originally published online July 30, 2009;
doi: 10.1161/ATVBAHA.109.193490

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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