Is QT Interval a Marker of Subclinical Atherosclerosis in Nondiabetic Subjects?
The Insulin Resistance Atherosclerosis Study (IRAS)

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Background and Purpose—We studied the relationship of heart rate–corrected QT interval with subclinical atherosclerosis, as determined by ultrasonographic measurement of carotid intima-media thickness (IMT) in nondiabetic subjects in the Insulin Resistance Atherosclerosis Study (IRAS). Prolonged heart rate–corrected QT interval is an unfavorable prognostic factor of cardiovascular morbidity and mortality, and QT interval prolongation may be the result of atherosclerosis.

Methods—B-mode ultrasound imaging of the carotid artery IMT was performed in a large, triethnic, nondiabetic population free of clinical coronary artery disease (n=912). QT interval was measured on resting electrocardiograms with use of a computer program and corrected for heart rate with standard equations.

Results—IMT of the common carotid artery correlated significantly with heart rate–corrected QT interval duration (r=0.15 for QT60 and r=0.14 for QTc), whereas no relationship between IMT of the internal carotid artery and QT interval was found (r=−0.01). The association was somewhat stronger in women than in men. In a multiple regression analysis adjusting for demographic variables, the association of common carotid artery IMT to heart rate–corrected QT interval remained highly significant, but adjustment for cardiovascular risk factors weakened the relationship.

Conclusions—We found a significant relation of heart rate–corrected QT interval to carotid atherosclerosis in nondiabetic subjects that was stronger in women and partly mediated by cardiovascular risk factors, including hypertension. QT interval may therefore serve as a marker for clinically undetected (“subclinical”) atherosclerotic disease. (Stroke. 1999;30:1566-1571.)

Key Words: atherosclerosis ■ carotid arteries ■ electrocardiography

A prolonged QT interval has been identified as a risk factor for cardiovascular mortality in various populations, such as healthy subjects,1,2 subjects referred for Holter monitoring,3 patients with cardiac disease,4,5 and patients with diabetes.6–8 The etiology of acquired forms of prolonged QT interval duration is still poorly defined; involvement of cardiac ion channels—alogous to inherited forms—and cardiac autonomic neuropathy have been suggested.7,9 Because QT interval has also been associated with coronary morbidity,2 myocardial atherosclerotic disease may be another potential etiologic factor contributing to QT interval prolongation. We therefore hypothesized that early, subclinical atherosclerosis, as assessed by carotid ultrasound, might be associated with QT interval duration. Subclinical atherosclerotic disease has been associated with incident coronary heart disease10 and is therefore of particular clinical interest.

The aim of this study was to investigate the association of QT interval to atherosclerosis, as determined by carotid ultrasonography in a triethnic population free of clinical coronary artery disease (n=912). B-mode ultrasound imaging of the carotid artery intima-media thickness (IMT) has been shown to reflect histopathologically verified atherosclerosis11,12 and has therefore been widely used as a noninvasive method for assessing atherosclerosis.13,14 The focus of this report is on nondiabetic subjects to avoid confounding by prevalent type 2 diabetes, which in previous studies has been associated with both increased carotid IMT13 and prolonged QT interval duration.6

Subjects and Methods
The Insulin Resistance Atherosclerosis Study (IRAS) is a multicenter, epidemiological study aiming to explore relationships between insulin resistance, cardiovascular risk factors and cardiovas-
cular disease across different ethnic groups (non-Hispanic whites, blacks, and Hispanics) and varying states of glucose tolerance. A full description of the design and methods of the IRAS has been published.16

A total of 1088 nondiabetic individuals participated in the IRAS. Subjects taking drugs that influence QT interval (antiarrhythmics, β-blockers, and tricyclic and tetracyclic antidepressants; n = 88) were excluded from the present analyses. Furthermore, subjects with clinical coronary artery disease were excluded (n = 27). Coronary artery disease was defined as past myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft confirmed by review of medical records, or a major Q wave or evidence of ischemic heart disease on IRAS examination ECG. Thus, this report includes data on 912 nondiabetic subjects (32% with impaired glucose tolerance), in whom ultrasound images were recorded and analyzed. Because in a previous study17 QT interval was associated with intake of diuretics, we adjusted for this possible confounding variable rather than excluding these subjects (n = 86).

The IRAS examination required 2 visits. Patients were asked before each visit to fast for 12 hours, to abstain from heavy exercise and alcohol for 24 hours, and to refrain from smoking the morning of the examination. A 75-g oral glucose tolerance test was performed according to a standard protocol, and glucose tolerance status was based on the World Health Organization criteria.18

High-resolution B-mode carotid ultrasonography was performed with Toshiba SSA-270A imaging units (Toshiba America Medical Systems) to provide an index of atherosclerosis.11,12,19,20 The scanning and reading protocols were identical to those used in the Cardiovascular Health Study.12 A bilateral assessment of the wall thickness was made in the internal carotid artery (ICA) and common carotid artery (CCA). For the ICA, the sonographer sought the site of maximal thickness at different interrogation angles (proximal, lateral, and anterior). For the CCA, bilateral images were obtained 1 cm proximal to the dilatation of the carotid bulb at a single (lateral) angle. All studies were recorded on super-VHS tape and sent weekly to a central reading center for measurement of the IMT. For each of the 8 available images, the maximal IMT was taken over a 1-cm segment of the arterial wall distant from the skin surface (“far wall”). The maximum IMT of the CCA was defined as the mean of the maximum IMT for the far wall on both the left and right sides (1 view on each side). The maximum IMT of the ICA was defined similarly: the 3 views from each side were averaged, and the mean of the right and left averages was used in the analysis. The number of measurements available for averaging thus ranged from 1 to 2 for the CCA and 1 to 6 for the ICA. A subset of 43 participants from the IRAS population were rescanned for an assessment of intrasonogra-

Figure 1. Mean±SE values of CCA IMT (in millimeters) adjusted for age, gender, ethnicity, and clinic, and stratified by quartiles of QTc (1, <417.8 ms; 2, 417.8 to 433.8 ms; 3, 434.0 to 451.8 ms; and 4, >451.8 ms). *P<0.05, **P<0.01, and ***P<0.0001.

φer variability; Pearson’s correlation coefficient between scans was 0.86 and 0.75 for the CCA IMT and ICA IMT, respectively. Likewise, 64 scans were reread to assess intrareader variability; the correlation coefficient between scans was 0.95 and 0.94 for the CCA IMT and ICA IMT, respectively.

Standard, resting 12-lead electrocardiography (ECG) was performed with the portable MAC/PC ECG (Marquette Electronics) within a maximum of 45 minutes after the oral glucose load during the glucose tolerance test. Computerized tracings were classified by the IRAS central ECG facility at the EPICARE Center, Wake Forest University School of Medicine, Winston Salem, NC, with use of NOVACODE ECG software.21 The program calculates the QT interval from the beginning of QRS to the end of T as a global measurement from 8 simultaneously recorded and sampled independent components of the standard 12-lead ECG. The beginning of the QT interval was defined as the first deflection of the QRS complex. The end of the T wave was defined as the point of maximal change in the slope as the T wave merges with the baseline. QT interval was corrected for heart rate by calculating QTc, and as a more accurate estimate of heart-rate corrected QT interval at high and low heart rates, also QTc. QTc was calculated with Bazett’s equation QTc=QT interval (ms)/√(60/heart rate) and QTc (QT interval corrected for a heart rate of 60/min) with the equation QT+410–656/(1+heart rate/100).

Cardiovascular risk factors, used for adjustment in multivariate analyses, were assessed as follows. Cigarette smoking was categorized into “none,” “past,” or “current” smoking with use of a standard questionnaire. Resting systolic blood pressure (SBP) and fifth-phase diastolic blood pressure (DBP) were measured 3 times, and the second and third measurements were averaged. Hypertension was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg or current use of antihypertensive medication. Alcohol intake was assessed by questionnaire and computed as a categorical variable according to the average daily alcohol intake. Alcohol intake has previously been related to QT interval prolongation.9 Plasma fasting glucose, insulin, plasma lipids (HDL, and LDL cholesterol and triglycerides), and plasminogen activator inhibitor (PAI)-1 were measured with standard techniques, as described previously.22 Insulin sensitivity was assessed by a frequently sampled intravenous glucose tolerance test (FSIGT23) with minimal model analysis.24 Two modifications of the original protocol were used. An injection of regular insulin, rather than tolbutamid, and the reduced sampling protocol (which required 12 rather than 30 plasma samples and shows results similar to the full protocol25) was used because of the large number of subjects. Insulin sensitivity, expressed as the insulin sensitivity index (S), was calculated by mathematical modeling methods (MINMOD, version 3.0, 1994).
TABLE 1. Demographic Characteristics, QT Interval, and Carotid Artery IMT Measurements Stratified by Gender

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male</th>
<th>Female</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>401</td>
<td>511</td>
<td></td>
</tr>
<tr>
<td>Impaired glucose tolerance, %</td>
<td>28</td>
<td>35</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertensive, %</td>
<td>27</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Ethnicity (NHW/B/H), %</td>
<td>42/27/31</td>
<td>38/28/34</td>
<td>NS</td>
</tr>
</tbody>
</table>

| Age, y                    | 54.4±0.4 | 54.6±0.4 | NS   |
| QT, ms                    | 419.5±1.6 | 426.3±1.4 | 0.0016 |
| QTC, ms                   | 428.1±1.3 | 449.3±1.2 | 0.0001 |
| QT60, ms                  | 426.5±1.2 | 443.2±1.1 | 0.0001 |
| ICA IMT, mm               | 0.891±0.02 | 0.796±0.01 | 0.0001 |
| CCA IMT, mm               | 0.816±0.01 | 0.773±0.008 | 0.0015 |

Data are mean±SE; P values are for the Student t test or χ2 test, as appropriate. NHW indicates non-Hispanic whites; B, blacks; H, Hispanics; QT, QT interval in milliseconds; QTC, QT/√(60/heart rate) (Bazett’s formula); and QT60, QT=[410−656/(1+heart rate/100)].

Statistical Analysis

Statistical analyses were performed using the SAS statistical software system (SAS, Cary, NC). Table 1 shows descriptive data stratified by gender. Age, ethnicity, percent hypertensive, and percent with impaired glucose tolerance status were compared with the Student t test (age) or χ2 tests. The remaining variables were compared after adjustment for age, ethnicity, and clinic. Next, we examined the relationship between CCA IMT and QT interval. To do this, we calculated quartiles of QT60 and estimated the mean CCA IMT (adjusted for age, gender, ethnicity, and clinic) for each quartile with use of ANCOVA (Figure). We then calculated a series of Spearman rank correlations between QT interval and metabolic and descriptive variables (Table 2). Partial Spearman rank correlations (adjusted for age, gender, ethnicity, and clinic; Table 3) were also calculated between QT60 and carotid IMT (both CCA and ICA). Before fitting multivariate models, we tested for possible interactions of carotid wall thickness and gender, glucose tolerance status (impaired versus normal glucose tolerance), and ethnicity, respectively, on QT interval. We included in separate models interaction terms for gender×CCA IMT, gender×ICA IMT, etc. All of these interactions were nonsignificant (P>0.10).

Finally, to determine the effect that demographic variables and cardiovascular risk factors had on the relationship between QT interval and carotid IMT, we fit multiple linear regression models. In these models, we considered QT60 (Table 4) and QTc (in separate models) as the dependent variables. The metabolic variables that demonstrated significant univariate associations with QT interval (from Table 2) were included in these models. We fit 2 models for each dependent variable: a “demographic model” that included age, gender, ethnicity, clinic, glucose tolerance status, use of diuretics, and CCA IMT, and a “cardiovascular risk model” that included—in addition to the variables in the “demographic model”—body mass index, hypertension, triglycerides, and PAI-1. Finally, these regression models were stratified by gender. In analyses, a value of P<0.05 (2-sided) was considered statistically significant.

Results

Table 1 shows descriptive data stratified by gender. Women had longer QT interval duration, whereas carotid artery IMT was thicker in men (Table 1).

Age, body mass index, systolic and diastolic blood pressures, triglyceride, and PAI-1 were positively related to heart rate–corrected QT interval, but LDL and HDL cholesterols and fasting insulin were not (Table 2). SI was inversely related to QTc but not to QT60. QT60 was longer in females (Table 1), Hispanics, and non-Hispanic whites [441.7±1.4 in Hispanics and 436.2±1.3 in non-Hispanic whites versus 428.4±1.6 ms in blacks; P<0.001 Hispanic and non-Hispanic whites versus blacks, respectively], and in subjects taking diuretics [446.9±2.8 (diuretics) versus 434.7±0.9 ms (no diuretics), P=0.0001]. Alcohol intake and smoking were not positively associated with heart rate–corrected QT inter-

TABLE 2. Unadjusted Spearman Correlation Analysis of Heart Rate–Corrected QT Interval With Age and Metabolic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>QT60</th>
<th>QTc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.20**</td>
<td>0.17**</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.09*</td>
<td>0.13**</td>
</tr>
<tr>
<td>SBP</td>
<td>0.19**</td>
<td>0.21**</td>
</tr>
<tr>
<td>DBP</td>
<td>0.14**</td>
<td>0.18**</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>−0.01</td>
<td>0.06</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>0.08*</td>
<td>0.09*</td>
</tr>
<tr>
<td>PAI-1</td>
<td>0.21**</td>
<td>0.23**</td>
</tr>
<tr>
<td>SI</td>
<td>−0.05</td>
<td>−0.11*</td>
</tr>
</tbody>
</table>

Definitions for QT variables as in Table 1. *P<0.01, **P<0.0001.

TABLE 3. Partial Spearman Correlation of Carotid Artery MT and QT Interval (Adjusted for Age, Gender, Ethnicity, and Clinic)

<table>
<thead>
<tr>
<th>Variable</th>
<th>QT</th>
<th>QT60</th>
<th>QTc</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA IMT</td>
<td>0.03</td>
<td>−0.01</td>
<td>−0.01</td>
</tr>
<tr>
<td>CCA IMT</td>
<td>0.13**</td>
<td>0.15**</td>
<td>0.14**</td>
</tr>
</tbody>
</table>

Definitions for QT variables as in Table 1. *P<0.01, **P<0.0001.

TABLE 4. Regression Coefficients (B) and their SEs for Covariates of Heart Rate–Corrected QT Interval (QT60) From a Multiple Linear Regression Analysis After Adjustment for Age, Gender, Ethnicity, and Clinic

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>B</th>
<th>SE (B)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics (yes=1, no=0)</td>
<td>9.1</td>
<td>2.7</td>
<td>0.0008</td>
</tr>
<tr>
<td>CCA IMT (mm)</td>
<td>19.8</td>
<td>4.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>R2 for the model: 24.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Risk Model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (yes=1, no=0)</td>
<td>8.5</td>
<td>2.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>PAI-1, ng/mL</td>
<td>0.14</td>
<td>0.05</td>
<td>0.0034</td>
</tr>
<tr>
<td>CCA IMT, mm</td>
<td>14.8</td>
<td>4.4</td>
<td>0.0008</td>
</tr>
<tr>
<td>R2 for the model: 26.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Independent variables in addition to CCA IMT were as follows: in the Demographic Model, glucose tolerance status and use of diuretics; in the Cardiovascular Risk Model, demographic model and BMI, hypertension, triglycerides, and PAI-1. Only independent variables significantly contributing to the models are shown.
val. The same significant differences reported herein for QT₆₀ as outcome variable were also found for QTc.

Relation of QT Interval to IMT of Carotid Arteries

Spearman Correlation Analysis
In unadjusted analysis CCA IMT was significantly positively related to heart rate–corrected QT interval ($r=0.07$, $P=0.038$ for the association of CCA IMT to QT₆₀), whereas no positive association of ICA IMT and QT interval was found (data not shown). Analyses adjusted for age, gender, ethnicity, and clinic showed a stronger association of CCA IMT with QT interval (Table 3 for correlation analysis and Figure for ANCOVA by quartiles of QT₆₀).

Multiple Linear Regression Analysis

Demographic Model
In a multiple linear regression analysis adjusting for demographic variables, glucose tolerance status (impaired versus normal glucose tolerance), and use of diuretics, the association of CCA IMT to heart rate–corrected QT interval remained highly significant ($P=0.0001$ for the association of CCA IMT to QT₆₀ [Table 4, top] and QTc, respectively).

Cardiovascular Risk Factor Model
After adjustment for cardiovascular risk factors, CCA IMT remained significantly related to QT interval, although the association was weaker than in the demographic model. Analogous models with QTc as dependent variable revealed comparable results ($P=0.0026$ for the association of CCA IMT with QTc). When S₁ was additionally entered in this model, S₁ did not significantly contribute to QT₆₀ and the regression coefficient and $P$ value for the association of CCA IMT and QT₆₀ were comparable to the model as shown in Table 4 (B [SE]: 15.1 [4.5], $P=0.0009$).

Analysis by Gender, Ethnicity, and Glucose Tolerance Status
There was no significant interaction of gender ($P=0.11$ for interaction term), ethnicity ($P=0.9$ for interaction term), or the glucose tolerance status ($P=0.9$ for interaction term) on the association of CCA IMT with heart rate–corrected QT interval after adjusting for age, ethnicity, and clinic (with QT₆₀ as a dependent variable).

The relationship between QT interval and CCA IMT remained significant in both sexes in the demographic model. However, the association was stronger in women and failed to reach statistical significance in men after adjusting for cardiovascular risk factors. Furthermore, the regression coefficient was markedly higher in women than in men in the linear regression models (B [SE]: 27.1 [6.6], $P=0.0001$ in women versus 14.0 [5.8], $P=0.015$ in men for the demographic model, and 20.9 [6.8], $P=0.0022$ in women versus 9.5 [5.8], $P=0.10$ in men for the cardiovascular risk model).

Discussion
In this study, we have shown a positive association of heart rate–corrected QT interval with carotid atherosclerosis in nondiabetic subjects without clinically overt coronary artery disease. This suggests that heart rate–corrected QT interval may serve as a marker of undetected, “subclinical” atherosclerotic disease. This finding may be clinically important; in a previous study, the presence of subclinical atherosclerosis was prospectively associated with coronary artery disease after a mean follow-up of 2.4 years. Accordingly, in a general male population long QTc within the normal range was associated with a higher risk for incident coronary heart disease.³ Due to the epidemiological approach on which the present report is based, it is not possible to state whether an association of carotid IMT with QT interval exists in a single individual; however, the use of surrogate markers of subclinical atherosclerotic disease (such as prolonged QT interval or increased IMT) may provide additional information for identifying a high-risk individual who could potentially benefit from intensive cardiovascular risk factor management. Under clinical conditions the measurement of QT interval may be easier to perform (particularly using a computer-assisted algorithm) than the measurement of carotid IMT.

We suggest that thickening of carotid IMT and prolonged QT interval may be the result of a common etiology, such as atherosclerotic disease or hypertension. Alternatively, though entirely speculative at this time, a common gene might exist which modifies both the atherosclerotic process and the repolarization abnormalities resulting in prolonged QT interval.

In previous studies, both carotid IMT and QT interval have been associated with risk factors for atherosclerosis (for IMT, see References 15, 20, and 26; for QT interval, References 1, 2, and 17), prevalent coronary artery disease (for IMT, References 27–29; for QT interval, References 2, 4, and 17), and incident coronary artery disease (for IMT, References 30–32; for QT interval, Reference 2). Accordingly, in the IRAS we found prolonged QT interval duration in a small number of nondiabetic subjects with clinical signs of coronary artery disease (n=27), who were excluded from the present report (data not shown). Given the strong correlation of coronary artery disease and carotid atherosclerosis, as assessed histologically³³ and clinically by B-mode ultrasound,²⁷–²⁹ QT interval may be a marker for not only carotid but also coronary atherosclerosis. Differences in segment-specific carotid artery IMT in relation to coronary disease have been reported.²⁸ In the latter study, a combination of mean IMT thickening of different sites was most strongly related to coronary artery disease; however, the predictive power of CCA IMT alone was also strong.²⁸ In 2 prospective studies CCA IMT has been a prognostic marker for clinical coronary events⁰ and cerebrovascular and cardiovascular events¹¹; however, ICA IMT has not been measured in these studies. In a recent report from the Cardiovascular Health Study,³² CCA IMT, ICA IMT, and a combined measure of both were associated with an increased risk of myocardial infarction and stroke in older adults. Even if it is impossible at this time to determine the relative significance of CCA IMT compared with ICA IMT in predicting organ-specific cardiovascular events, it is reasonable to assume that CCA IMT is a useful general marker of atherosclerotic disease. This concept is also supported by a recent report showing that CCA IMT was increased in subjects with
asymptomatic myocardial ischemia as assessed by exercise ECG and thallium scan.

In the present study, QT interval was related to CCA IMT but not to ICA IMT. Currently, we have no sound explanation for this finding. Results of previous studies suggest that risk factors for increased IMT may be different in the CCA and the ICA. In the IRAS population, increased urinary albumin excretion (microalbuminuria) and fasting glucose levels were positively related to CCA IMT but not ICA IMT, whereas the negative association of insulin sensitivity to IMT was stronger for the ICA than the CCA. Hypertension was somewhat more strongly associated with ICA IMT than CCA IMT in the ARIC cohort.

Hypertension is another potential common etiological factor that has been associated with both thickening of carotid IMT and prolonged QT interval (References 1, 2, and 17 and the present study). The present study suggests that an association between carotid IMT and QT interval may exist beyond the effects of hypertension, especially in women, in whom the association remained significant even after adjusting for hypertension in the multivariate analyses. However, in all these analyses the introduction of hypertension as a covariate considerably weakened the association; hypertension therefore seems to mediate part of the association of QT interval with carotid IMT.

We also found that the association of carotid IMT with QT interval was stronger in women. For reasons as yet unknown, women generally have longer QT interval duration than men (References 1, 4, and 17 and the present study). Sex hormones may play a role in regulating cardiac repolarization (References 17, 11, and 12). In the present population a greater proportion of women presented with impaired glucose tolerance measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. Therefore, in all these analyses the introduction of hypertension as a covariate considerably weakened the association; hypertension therefore seems to mediate part of the association of QT interval with carotid IMT.

In summary, we found a significant relationship between QT interval duration and carotid atherosclerosis in nondiabetic subjects without clinical coronary artery disease. This association was stronger in women and was partly mediated by cardiovascular risk factors, including hypertension. QT interval may therefore serve as a marker for clinically undetected atherosclerotic disease. Further studies are needed to evaluate whether subjects with QT interval prolongation within the normal range represent a high-risk population that may benefit from intensified cardiovascular risk factor management.

Acknowledgments

This work was supported by the National Heart, Lung, and Blood Institute (grants HL47878, HL47889, HL47890, HL47892, HL47902, and HL55208) and the General Clinical Research Centers Program (grants NCRR GCRC, M01 RR431, and M01 RR01346).

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*Stroke*. 1999;30:1566-1571
doi: 10.1161/01.STR.30.8.1566

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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