Vitamin D Deficiency Is Associated With Subclinical Carotid Atherosclerosis
The Northern Manhattan Study

Angela L. Carrelli, MD; Marcella D. Walker, MD; Hyesoo Lowe, MD; Don J. McMahon, MS; Tatjana Rundek, MD, PhD; Ralph L. Sacco, MD, MS; Shonni J. Silverberg, MD

Background and Purpose—The purpose of this study was to assess the association of vitamin D deficiency and indices of mineral metabolism with subclinical carotid markers that predict cardiovascular events.

Methods—Two hundred three community-dwelling adults (Northern Manhattan Study; age, 68 ± 11; age range, 50 to 93 years) had serum measurements (calcium, phosphorus, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, parathyroid hormone) and carotid ultrasound (plaque presence, number, maximal carotid plaque thickness, intima-media thickness).

Results—Adjusting for cardiovascular risk factors, plaque number was associated with phosphorus levels (β=0.39 per 1-mg/dL increase; \(P=0.02\)) and calcium–phosphorus product (\(\beta=0.36\) per 10-U increase; \(P=0.03\)). In those with plaque (N=116 [57%]), the association of plaque number with phosphorus and calcium–phosphorus product persisted. In addition, 25-hydroxyvitamin D was inversely associated with both intima-media thickness (\(\beta=−0.01\) per 10-ng/mL increase; \(P=0.05\)) and maximal carotid plaque thickness (\(\beta=−0.10\) per 10-ng/mL increase; \(P=0.03\)). In a model containing traditional cardiac risk factors and indices of mineral metabolism, 25-hydroxyvitamin D accounted for 13% of the variance in both intima-media thickness and maximal carotid plaque thickness. Calcium, parathyroid hormone, and 1,25-dihydroxyvitamin D levels were not associated with carotid measures.

Conclusions—After adjusting for cardiovascular risk factors and renal function, serum phosphorus and calcium–phosphorus product were associated with a greater burden of subclinical carotid atherosclerosis. Low 25-hydroxyvitamin D levels were associated with increased intima-media thickness and maximal carotid plaque thickness in those with plaque, and 25-hydroxyvitamin D contributed in a robust manner to the variance in both. These results confirm and extend data on the association of low vitamin D levels with subclinical carotid atherosclerosis. The precise nature of this association and the optimum levels of vitamin D for vascular health remain to be elucidated. (Stroke. 2011;42:2240-2245.)

Key Words: atherosclerosis ■ carotid intimal medial thickness ■ carotid ultrasound ■ endocrinology ■ vitamin D

Carotid plaque thickness and intima-media thickness (IMT) are powerful predictors of future vascular events. Although the development of atherosclerosis is well known to be associated with traditional cardiovascular risk factors, new interest has focused on the role of indices of mineral metabolism in the pathogenesis of cardiovascular (CV) risk because of their potential contributions to vascular calcification. Serum calcium, even within the normal range, has been identified as an independent, prospective risk factor for myocardial infarction and has been associated with increased CV mortality. Increased calcium–phosphorus product raises the risk of CV disease in patients with and without kidney disease and parathyroid hormone (PTH) levels are prospectively associated with CV mortality.

Recent epidemiological studies also demonstrate that 25-hydroxyvitamin D deficiency is a novel CV risk factor, predicting both CV events and mortality. Vitamin D deficiency is, however, accompanied by changes in PTH, calcium, phosphorus, and 1,25-dihydroxyvitamin D levels (1,25(OH)2D). The mechanisms by which vitamin D deficiency affects CV health remain unclear, in part because prior studies have not taken into account the roles of other markers of mineral homeostasis. To better understand the mechanism by which vitamin D might contribute to increased CV risk, we investigated the association of low vitamin D levels with carotid subclinical markers of atherosclerosis and whether this relationship is independent of other indices of mineral homeostasis and traditional CV risk factors.
Study Population
The Northern Manhattan Study (NOMAS) cohort is a multiethnic urban population of 3298 individuals assembled to investigate the incidence of vascular events, risk factors, and vascular outcomes in 3 race–ethnic groups.14 Calcitropic hormones were not originally obtained as part of NOMAS. We therefore initiated this cross-sectional study of 203 consecutive subjects from the NOMAS cohort who were scheduled for their routine follow-up evaluation with high-resolution carotid ultrasound imaging. At the time of their study visit, we obtained serum for calcium, albumin, phosphorus, PTH, 25-hydroxyvitamin D (25OHD), and 1,25(OH)2D. Clinical information collected on all NOMAS subjects includes demographics, body mass index, diabetes mellitus (self-report, fasting blood glucose level ≥7.0 mmol/L, or use of oral hypoglycemic agents or insulin), hypertension (self-report, use of antihypertensive medications, or systolic blood pressure ≥140 mm Hg or diastolic ≥90 mm Hg [blood pressure measured at all study visits]), heart disease (self-report, use of cardiac medications, history of coronary artery disease, myocardial infarction, congestive heart failure), current tobacco use (within 1 year), and alcohol consumption (mild to moderate: >0.5 drinks/day).

Laboratory Measurements
Carotid plaque and IMT were assessed by high-resolution B-mode ultrasound (GE LogIQ 700, 9- to 13-MHz linear-array transducer) performed by a single certified research sonographer using standard scanning and reading protocols (Figure).15,16 Carotid arteries were scanned in 3 segments: (1) near wall and far wall of the segment extending from 10 to 20 mm proximal to the tip of the flow divider into the common carotid artery; (2) near wall and far wall of the carotid bifurcation beginning at the tip of the flow divider and extending 10 mm proximal to the flow divider tip; and (3) near wall and far wall of the proximal 10 mm of the internal carotid artery. Carotid plaques (defined as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value) were measured separately using the same electronic tracer and maximal carotid plaque thickness (MCPT) was measured at the highest plaque by Image Pro software (Microsoft, Inc, Redmond, WA). The carotid artery wall IMT was measured offline from the media–adventitia interface to the intima–lumen interface using an electronic edge-detection tracer in each of these carotid segments and outside the portion of plaque if plaques were present in a given segment. We report the composite mean of IMT measured at 12 carotid sites: the near and far walls of the common carotid artery, bifurcation, and internal carotid artery bilaterally. IMT >0.9 mm was considered abnormal (threshold above which risk of myocardial infarction or stroke increased in the Cardiovascular Health Study).1

All subjects in NOMAS have fasting measures of total cholesterol, low-density lipoprotein and high-density lipoprotein, and creatinine clearance (calculated by Modification of Diet in Renal Disease equation). For this study, serum total calcium, phosphorus, and albumin were measured by standard autoanalyzer techniques (Technicon Instruments, Tarrytown, NY). Serum total calcium levels were corrected for albumin (formula: corrected calcium=total calcium+0.8[4-albumin]). Vitamin D levels (25OHD <20 ng/mL: deficient; 20 to 30 ng/mL: insufficient; 1,25(OH)2D normal range, 25.1 to 66.1 pg/mL) were measured by double antibody radioimmunoassay (Diasorin, Stillwater, MN) and intact PTH by immunoradiometric assay (Scantibodies, Santee, CA; normal range, 14 to 66 pg/mL).

Statistical Analysis
Results are reported as mean±SD for continuous variables or as absolute values or percentages for categorical data. A 2-tailed t test was used to compare continuous variables. Categorical variables were compared by χ2 or Fisher exact test as appropriate. Multiple linear regression analyses of plaque number, MCPT, and IMT by traditional cardiac risk factors (age, sex, current smoking, body mass index, hypertension, diabetes, pre-existing heart disease, creatinine clearance, low-density lipoprotein, high-density lipoprotein, and alcohol) were modeled in the entire group and the subgroup with plaque and of only IMT in those without plaque. Each of the mineral metabolism measures was then entered into these multiple regression models to assess its contribution over and above that of the traditional cardiac risk factors. Because these results indicated that calcium–phosphorus product, phosphorus, and 25OHD interact, we then tested models with the combination of the mineral metabolism measures as well as traditional CV risk factors (listed previously) to determine their relative contributions to the variance in IMT and MCPT. All analyses used SAS Version 9.2 software (SAS Institute, Cary, NC). The study was approved by the Columbia University Medical Center and University of Miami School of Medicine’s Institutional Review Boards and all subjects gave written informed consent.

Results
Group Characteristics
Group demographic characteristics (37% male; age, 68±11 years), CV risk factors, lipid levels, and calcitropic data are presented in Table 1. Mean IMT was elevated (1.02±0.1 mm; normal, <0.9 mm). Typical of the larger NOMAS cohort, over half of all subjects (N=116 [57%]) had carotid plaque.

Mean levels of serum-corrected calcium, phosphorus, and PTH were normal. Mean 25OHD levels were low with nearly half of all subjects (48%) having levels in the “deficient” range (<20 ng/mL). Only 17% had levels above the threshold for vitamin D sufficiency (≥30 ng/mL).17 25OHD levels did not differ according to creatinine clearance (data not shown). There were no differences in serum-corrected calcium, serum phosphorus, the calcium–phosphorus product, PTH, 25OHD, or 1,25(OH)2D levels between those with and those without carotid plaque.

Traditional CV Risk Factors Predict Subclinical Carotid Measures
Not unexpectedly, those with plaque were older, had lower creatinine clearance, and had a higher prevalence of diabetes, hypertension, and pre-existing heart disease than those without plaque (Table 1). Subjects with carotid plaque also had higher IMT. As expected, multiple regression analysis of carotid...
Table 1. Group Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (N=203)</th>
<th>With Plaque (N=116)</th>
<th>Without Plaque (N=87)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68±11</td>
<td>72±10</td>
<td>63±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, %</td>
<td>37</td>
<td>41</td>
<td>31</td>
<td>NS</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>White</td>
<td>14</td>
<td>16</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>12</td>
<td>12</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>74</td>
<td>72</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.5±5.0</td>
<td>28.5±5.3</td>
<td>28.4±4.7</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>61</td>
<td>69</td>
<td>52</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>19</td>
<td>25</td>
<td>10</td>
<td>0.008</td>
</tr>
<tr>
<td>Current tobacco, %</td>
<td>13</td>
<td>14</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-existing heart disease, %</td>
<td>19</td>
<td>28</td>
<td>8</td>
<td>0.001</td>
</tr>
<tr>
<td>Alcohol use, &gt;0.5 drinks/d, %</td>
<td>32</td>
<td>33</td>
<td>31</td>
<td>NS</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>113±33</td>
<td>112±34</td>
<td>114±31</td>
<td>NS</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>54±16</td>
<td>54±15</td>
<td>56±17</td>
<td>NS</td>
</tr>
<tr>
<td>CrCl, mL/min</td>
<td>80±23</td>
<td>76±23</td>
<td>86±21</td>
<td>0.004</td>
</tr>
<tr>
<td>Corrected calcium, mg/dL</td>
<td>9.1±0.4</td>
<td>9.1±0.4</td>
<td>9.0±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Serum phosphorus, mg/dL</td>
<td>3.7±0.7</td>
<td>3.7±0.7</td>
<td>3.6±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium×PO₄, mg²/dl²</td>
<td>36±7</td>
<td>37±7</td>
<td>36±6</td>
<td>NS</td>
</tr>
<tr>
<td>Intact PTH, pg/mL</td>
<td>40±22</td>
<td>41±25</td>
<td>38±18</td>
<td>NS</td>
</tr>
<tr>
<td>25-hydroxyvitamin D, ng/mL</td>
<td>22±10</td>
<td>23±10</td>
<td>21±10</td>
<td>NS</td>
</tr>
<tr>
<td>1,25-dihydroxyvitamin D, pg/mL</td>
<td>35±16</td>
<td>34±15</td>
<td>36±17</td>
<td>NS</td>
</tr>
<tr>
<td>Plaque no.</td>
<td>1.5±1.9</td>
<td>2.7±1.7</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>MCPT, mm</td>
<td>1.3±1.3</td>
<td>2.4±0.6</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>IMT, mm</td>
<td>1.02±0.1</td>
<td>1.06±0.1</td>
<td>0.97±0.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD.

BMI indicates body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CrCl, creatinine clearance; PTH, parathyroid hormone; MCPT, maximal carotid plaque thickness; IMT, intima-media thickness; NS, not significant; N/A, not applicable; SD, standard deviation.

*P values for differences between those with and without carotid plaque.

indices showed significant associations with traditional CV risk factors: IMT was associated with age (P<0.0001), male sex (P<0.001), and body mass index (P<0.05); plaque number was associated with age (P<0.001), diabetes (P<0.001), low-density lipoprotein (P=0.002), and creatinine clearance (P<0.01); and MCPT was associated with age (P<0.0001) and diabetes (P<0.04).

Associations of Carotid Parameters With Indices of Mineral Metabolism

In the group as a whole (Table 2), plaque number was associated with serum phosphorus levels (β=0.39 per 1-mg/dL increase; P=0.02) and calcium–phosphorus product (β=0.36 per 10-U increase; P=0.03) after adjusting for CV risk factors, including age, sex, smoking, body mass index, creatinine clearance, lipids, hypertension, diabetes, heart disease history, and alcohol use. In the entire group, there were no associations between indices of mineral metabolism and IMT (Table 2) or MCPT. In those with carotid plaque (Table 3), 25OHD concentration was inversely related to carotid IMT (β=−0.01 per 10-ng/mL increase; P=0.05) and MCPT (β=−0.10 per 10-ng/mL increase; P=0.03). Like in the entire group, plaque number remained associated with serum phosphorus levels (β=0.43 per 1-mg/dL increase; P=0.03) and the calcium–phosphorus product (β=0.41 per 10-U increase; P=0.03). There was also a trend toward an association between phosphorus and IMT (β=0.02 per mg/dL increase; P=0.08). In those without carotid plaque, IMT was not associated with indices of mineral metabolism. Serum calcium, PTH, and 1,25(OH)₂D levels were not associated with any carotid measures.

To better understand the relevance of markers of mineral metabolism to subclinical atherosclerosis, we assessed the contribution to the variance in IMT and MCPT uniquely accounted for by demographics (age and sex), traditional CV risk factors (current smoking, body mass index, hypertension, diabetes, pre-existing heart disease, creatinine clearance, low-density lipoprotein, high-density lipoprotein, and alcohol) and by the indices of mineral metabolism in the group with plaque. Although demographics and traditional CV risk factors accounted for the vast majority of the explained variance in these indices (80% of IMT and 86% of MCPT), we found a similar and significant proportion of the explained variance of both (13%) was determined by 25OHD. Contributions to the variance of <5% were attributable to the calcium–phosphorus product (5% of IMT; <1% MCPT) and serum phosphorus (2% of IMT; 1% MCPT). It is important to note, however, that the CV and mineral metabolism contributions to the variance in the carotid indices account for only approximately 31% of the total variance. Thus, other unmeasured factors remain responsible for two thirds of the variance in these indices.

Discussion

This study confirms an association between the calcium–phosphorus product and markers of subclinical carotid atherosclerosis in a free-living, stroke-free multiethnic urban cohort with normal renal function. The data also support an association between vitamin D deficiency and carotid vascular abnormalities that predicts the development of myocardial infarction and stroke. Among those with carotid plaque, we found that lower 25OHD levels are associated with thicker plaque and higher IMT. Finally, 25OHD contributes in a relatively robust manner to the explained variance in both IMT and carotid plaque thickness.

Prior work has shown that high calcium–phosphorus product is associated with subclinical markers of atherosclerosis (increased carotid IMT and coronary calcification) as well as increased mortality in adults with chronic kidney disease and is an independent risk factor for angiographically proven coronary disease in those with normal renal function. The finding of our group and others, that CV markers and coronary disease in those with normal renal function.
this relationship may be driven by phosphorus.\textsuperscript{7,20,21} Serum phosphorus has also been linked to carotid IMT in older men and in a cohort of healthy young adults.\textsuperscript{22,23} The association of serum phosphorus and calcium–phosphorus product with plaque number but not plaque thickness or IMT suggests that the pathogenesis of these processes may differ.

Previous data on the relationship between 25OHD and carotid IMT have been inconsistent. An inverse association has been reported in diabetic patients.\textsuperscript{24} Although no relationship was seen in a nondiabetic Amish population, this cohort had very few CV risk factors and lacked data on calcium, phosphorus, and 1,25(OH)\textsubscript{2}D levels, making the conflicting results difficult to interpret.\textsuperscript{25} Reis et al recently reported an inverse relationship between 25OHD and internal, although not common, carotid IMT in a multiethnic population (74% Hispanic and 12% black) in whom vitamin D levels are less replete. The fact that our cohort had more prevalent vitamin D deficiency may have allowed us to confirm a broader association with IMT than that seen by Reis et al. Finally, although IMT in the internal carotid artery and bulb in the report of Reis et al may have included plaque commonly present in these carotid segments, our study provides the first specific data supporting an association between low levels of vitamin D and increased carotid plaque thickness.

The negative association of vitamin D levels with IMT and plaque thickness suggests that vitamin D deficiency may play a role in the development and/or progression of atherosclerosis, which may help to explain the increased

\begin{table}
\centering
\caption{Predictors of Carotid Plaque Number and Intima-Media Thickness: Multiple Regression Analysis in the Entire Cohort}
\begin{tabular}{lcccc}
\hline
Predictors in the Entire Cohort & Plaque No. & & & Plaque Thickness & Intima-Media Thickness \\
Model Partial $R^2$ & $\beta$ & SE & $P$ & Model Partial $R^2$ & $\beta$ & SE & $P$ & \\
\hline
CV risk factors\textsuperscript{*} & 0.293 & N/A & N/A & 0.001 & 0.240 & N/A & N/A & 0.001 \\
Calcium, mg/dL & 0.005 & $-0.255$ & 0.254 & 0.32 & 0.001 & 0.006 & 0.014 & 0.70 \\
Phosphorus, mg/dL & 0.029 & 0.394 & 0.164 & 0.02 & 0.009 & 0.012 & 0.009 & 0.20 \\
Calcium–phosphorus product per 10 units & 0.026 & 0.359 & 0.157 & 0.03 & 0.011 & 0.013 & 0.009 & 0.16 \\
PTH per 10 pg/mL & 0.007 & 0.056 & 0.048 & 0.26 & 0.001 & 0.001 & 0.003 & 0.77 \\
25-hydroxyvitamin D per 10 ng/mL & 0.001 & $-0.039$ & 0.106 & 0.72 & 0.009 & $-0.008$ & 0.006 & 0.19 \\
1,25-dihydroxyvitamin D per 10 pg/mL & 0.001 & 0.024 & 0.068 & 0.73 & 0.001 & $-0.001$ & 0.004 & 0.73 \\
\hline
\end{tabular}
\textsuperscript{*}CV risk factors: age, sex, smoking, body mass index, creatinine clearance, low-density lipoprotein, high-density lipoprotein, alcohol use, and presence of hypertension, diabetes, or heart disease.
\end{table}
risk of CV events and mortality observed in epidemiological studies.10–13,27 Low 25OHD levels are known to influence macrophage and lymphocyte activity in atherosclerotic plaques and to promote chronic inflammation in the artery wall.28 In vitro studies demonstrate that vitamin D receptor activation inhibits production of atherogenic cytokines (interferon-γ, interleukin-1β, and interleukin-6) and upregulates antiatherogenic interleukin-10.30 Vitamin D receptor knockout mice have increased levels of proatherogenic factors including interleukin-6 and tumor necrosis factor-α.29
It is interesting that we observed the association between low 25OHD and IMT only in the subjects who had carotid plaque. This observation raises interesting questions concerning the exact role of vitamin D in the etiology of atherosclerosis. Perhaps low levels of vitamin D exert an effect only in those with other predisposing CV risk factors or exacerbate atherosclerosis only when the process is already underway. This unexpected finding will be important to address in future studies.

That the vast majority of the explained variance in IMT and MCPT are accounted for by traditional risk factors (demographic and CV) is expected. The robust contribution of 25OHD to both, however, suggests that it may also play an important role in subclinical atherosclerosis. The finding that our models, which included CV risk factors and indices of mineral metabolism, account for only a portion of the variance in carotid measures is consistent with prior reports suggesting that >50% of the variance in these indices is explained by genetic factors, which we did not study.16,20

We do not believe that the findings regarding vitamin D were mediated by reduced renal function. There was no difference in creatinine clearance between patients who were vitamin D-replete (25OHD ≥30 ng/mL) and those who were not and the relationship between vitamin D deficiency and carotid parameters persisted in the multiple regression analysis, which controlled for renal function. The effects of phosphorus and vitamin D deficiency on carotid vascular abnormalities are also not likely to be associated. Although hyperphosphatemia inhibits 1,25(OH)2D production, it does not affect 25OHD. It is vitamin D excess, not deficiency, that would be expected to induce hyperphosphatemia.

This study has several limitations. First, we are limited by the study design. We unfortunately do not have more detailed evaluation of glycemic status in NOMAS and data on plaque area and volume would have been a valuable addition. More importantly, the cross-sectional design does not allow us to extrapolate that observed associations portend an increased risk of stroke. It is also possible that had we looked at a larger cohort, other associations might have emerged. However, we did fully characterize our population, measuring multiple indices of mineral metabolism at the same time as carotid ultrasound was performed. Furthermore, measuring and controlling for potential confounders (ie, PTH and vitamin D, renal status, and CV risk factors) allowed us to avoid many of the pitfalls of prior studies. Second, most of our subjects had lower levels of vitamin D than are currently considered desirable, and the investigation would have benefited from a wider spectrum of vitamin D levels. However, vitamin D insufficiency is common and our cohort is not atypical.31 The most recent National Health and Nutrition Examination Survey (NHANES) analysis (2001 to 2004) found a similarly low percentage (23%) of the population to have a 25OHD ≥30 ng/mL. Other studies investigating the link between cardiovascular risk or mortality and vitamin D status report low or lower mean 25OHD levels.10,11,13 Third, we cannot impute causality in the relationships between the measured parameters of mineral metabolism and carotid findings. However, the persistence of the relationship between carotid vascular abnormalities and vitamin D deficiency after accounting for multiple known CV risk factors suggests that vitamin D does independently contribute to the underlying mechanism. Finally, our findings do not provide insight into the important issue of threshold levels of vitamin D needed to prevent CV abnormalities. Although controversy persists concerning desirable vitamin D levels for bone health despite a plethora of information, there are virtually no data to support specific goals for serum vitamin D for CV health.

Despite these limitations, this report confirms and extends available data on the association of vitamin D levels and other indices of mineral metabolism with subclinical carotid atherosclerosis. We corroborate the increasing body of data supporting an association with serum phosphorus and calcium–phosphorus product in those with normal renal function and conclude that in this cohort of older adults, vitamin D deficiency is common and is associated with the burden of subclinical carotid imaging markers of CV disease. The precise nature of this association and the optimum levels of vitamin D for vascular health remain to be elucidated.

Sources of Funding
Supported by the National Institutes of Health (DK066329, DK074457, NINDS R37 NS 29995).

Disclosures
T.R. reports receiving speaking fees from Bristol-Myers Squibb.

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*Stroke*. 2011;42:2240-2245; originally published online June 30, 2011; doi: 10.1161/STROKEAHA.110.608539

*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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