Incidence, Manifestations, and Predictors of Brain Infarcts Defined by Serial Cranial Magnetic Resonance Imaging in the Elderly

The Cardiovascular Health Study

W.T. Longstreth, Jr, MD, MPH; Corinne Dulberg, PhD, MPH; Teri A. Manolio, MD, PhD; Michael R. Lewis, MD; Norman J. Beauchamp, Jr, MD, MHS; Daniel O’Leary, MD; Jeff Carr, MD; Curt D. Furberg, MD, PhD

Background and Purpose—MRI-defined infarcts are common in the elderly. We sought to explore incidence, manifestations, and predictors of such infarcts.

Methods—The Cardiovascular Health Study (CHS) is a population-based, longitudinal study of 5888 people aged ≥65 years. Participants have had extensive baseline and follow-up evaluations; 1433 participants underwent 2 MRI scans separated by 5 years and had no infarcts on initial MRI.

Results—On follow-up MRI, 254 participants (17.7%) had 1 or more infarcts. Most were single (75.6%), subcortical (79.9%), and small (3 to 20 mm in 87.0%). Only 11.4% of those with infarcts experienced a documented transient ischemic attack or stroke between the scans. Although participants were similar at initial MRI, those with MRI-defined infarcts on follow-up experienced greater decline than those without infarcts on the Modified Mini-Mental State Examination and Digit-Symbol Substitution test (both \( P < 0.01 \)). Severity of white matter changes on initial MRI was the strongest predictor of incident infarcts. When it was excluded from stepwise multivariable models, predictors were serum creatinine, age, and ankle-arm index.

Conclusions—Incident MRI-defined infarcts commonly affect the elderly. Most are small, subcortical, and not associated with acute symptoms recognized as a transient ischemic attack or stroke. Nonetheless, they cannot be considered silent because of their association with subtle cognitive deficits. These covert infarcts are associated with white matter changes, which may share a common pathophysiology. Whether control of vascular risk factors, such as blood pressure, would reduce the risk of developing these infarcts and associated cognitive decline deserves further investigation.

Key Words: brain infarction ■ creatinine ■ incidence ■ leukoariosis ■ magnetic resonance imaging

Most incident brain infarcts in the elderly fail to cause symptoms or signs that are clinically recognized as stroke.\(^1\) \(^6\) Such infarcts identified with MRI should not be considered silent or benign. They have been associated with cognitive impairments in cross-sectional studies\(^3\) \(^5\) and with future stroke in longitudinal studies.\(^2\) \(^7\)

Wanting to avoid descriptors such as “silent” or “benign,” we use “covert” to describe infarcts discovered in people without a history of transient ischemic attack or stroke. Although overt infarcts cause acute symptoms or signs that are clinically recognized as transient ischemic attack or acute stroke, covert infarcts do not. Rather, they may be associated with subtle neurological deficits. For the elderly, overt infarcts may be less common manifestations of cerebrovascular disease than covert infarcts. Although risk factors for overt infarcts have been evaluated extensively, risk factors for covert infarcts have not. Prevention of covert brain infarcts would reduce the incidence of a condition that commonly affects elderly people, eroding brain function and increasing the risk for more dramatic loss of brain function that occurs with acute stroke.

The Cardiovascular Health Study (CHS) is a population-based, longitudinal study of coronary and cerebrovascular
disease in 5888 participants aged ≥65 years. As part of their comprehensive evaluation, 3660 participants underwent an initial cranial MRI, of whom 2116 underwent a follow-up MRI 5 years later. Of these, a subset of 1433 participants had no infarcts on their initial MRI. With this pair of MRI scans in 1433 participants, we sought to explore the incidence, manifestations, and predictors of MRI-defined infarcts.

Subjects and Methods

Members of the original CHS cohort were recruited from a random sample of the Health Care Financing Administration Medicare eligibility lists in 4 US communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh (Allegheny County), Pennsylvania. Participants had to be aged ≥65 years, able to give informed consent, and able to respond to questions without the aid of a surrogate respondent. More details about the study design and characteristics of the 5888 participants are published elsewhere.6,9

Evaluations

Eligible and consenting participants underwent an extensive baseline evaluation including questionnaires, physical examination, and laboratory testing.4,8 A Doppler stethoscope and a standard mercury manometer were used to measure the posterior tibial and brachial systolic blood pressures, from which the ankle-arm index was calculated.13 Subjects’ cognitive functions were evaluated with the use of a Modified Mini-Mental State Examination14 and the Digit-Symbol Substitution Test.12 Questionnaires were used to assess activities of daily living, instrumental activities of daily living, and depression. Parts of the baseline evaluation have been repeated annually. Variables considered in these analyses as potential risk factors were those from the examination closest in time to the brain imaging. Participants were screened for a history of transient ischemic attack or stroke before the initial MRI13 but were not excluded if they had such events.

Brain Imaging

Cranial MRI scanning protocol included sagittal T1-weighted localizer images and axial T1, spin density, and T2-weighted images. All axial images had 5-mm thickness and no interslice gaps.4,14 Without knowledge of any clinical information, neuroradiologists at the reading center identified infarcts and estimated the white matter, ventricular, and sulcal grades using a 10-point system, as detailed previously.4,14 A brain infarct was defined as an area of abnormal signal intensity in a vascular distribution that lacked mass effect. Infarcts had to be hyperintense to gray matter on both spin density and T2-weighted images. To be considered infarcts in the white matter, brain stem, lesions also had to be hypointense on T1-weighted images, from which the ankle-arm index was calculated.6 Subjects’ cognitive functions were evaluated with the use of a Modified Mini-Mental State Examination4 and the Digit-Symbol Substitution Test.11 Questionnaires were used to assess activities of daily living, instrumental activities of daily living, and depression. Parts of the baseline evaluation have been repeated annually. Variables considered in these analyses as potential risk factors were those from the examination closest in time to the brain imaging. Participants were screened for a history of transient ischemic attack or stroke before the initial MRI4,13 but were not excluded if they had such events.

Results

Incidence of MRI-Defined Infarcts

On the follow-up MRI, 254 (17.7%) of the 1433 participants had 1 or more MRI-defined infarcts identified (Table 2). Of these incident infarcts, 192 (75.6%) were single, 203 (79.9%) collecting data on the change in white matter grade between the 2 scans.

Analyses

Participants whose follow-up MRI showed 1 or more infarcts were classified as having incident MRI-defined brain infarct. Cognitive and motor tests performed close in time to the initial scan and to the follow-up scan were compared with the use of ANCOVA on the second measure, controlling for the first measure and for the time between scans. Finally, potential risk factors were sought for incident infarcts. We examined those factors evaluated in previous CHS reports seeking (1) cross-sectional associations with MRI-defined brain infarcts4 and (2) longitudinal associations with incident stroke.15 Factors were evaluated with Fisher exact, χ², and t tests, as appropriate. Factors with significant associations (P<0.05) were eligible for multivariable models with the use of forward stepwise logistic regression in which the outcome variable was incident brain infarct, the P value to enter was set at 0.05, and the P value to remove was set at 0.10. We also controlled for the time between the scans, as a continuous variable, in all models. Results were similar when all factors, regardless of whether they were significantly associated with MRI-defined incident infarcts, were available for the multivariable models. SPSS for Windows, version 10.0.7, was used for these analyses,15 which were based on the updated CHS database incorporating minor corrections through January 2001.

Incidence of MRI-Defined Infarcts

On the follow-up MRI, 254 (17.7%) of the 1433 participants had 1 or more MRI-defined infarcts identified (Table 2). Of these incident infarcts, 192 (75.6%) were single, 203 (79.9%)
were solely subcortical, and 221 (87.0%) were <20 mm in size. Altogether, 209 (82.3%) had 1 or more incident lacunar infarcts. Only 36 participants (14.2%) had solely cortical infarcts.

Although between the scans, 39 participants were adjudicated as meeting criteria for stroke, follow-up MRI showed evidence for any infarct or bleed in only 23 of the 39 (59.0%). For the 18 participants who were adjudicated as meeting criteria for a transient ischemic attack, follow-up MRI showed evidence for any infarct or bleed in 7 of the 18 (38.9%). Two participants were adjudicated as meeting criteria for a transient ischemic attack and stroke. Only 29 (11.4%) of the 254 participants whose follow-up MRI showed evidence for any infarct or bleed in only 23 of the 39 (59.0%). For the 18 participants who were adjudicated as meeting criteria for a transient ischemic attack, follow-up MRI showed evidence for any infarct or bleed in 7 of the 18 (38.9%).

## Manifestations

Associations with performance measures are shown in Table 3. Although scores on the Modified Mini-Mental State Examination and the Digit-Symbol Substitution test were similar at the initial scan, at the follow-up scan, deterioration of cognitive performance was significantly greater in those with an incident MRI-defined infarct compared with those without. Changes in depression scores, number of finger taps in 15 seconds, and time to walk 4.6 m (15 ft) were not significantly different between the 2 groups at the initial or follow-up scan. Results for measures of cognitive performance remained significant after the 55 participants who were adjudicated as having a transient ischemic attack or stroke between the scans were excluded from the analyses.

## Predictors

Only 9 of the 68 variables from around the time of the initial scan that we evaluated were significantly related to incident MRI-defined brain infarct (Table 4). Components of the ankle-arm index were examined separately. Brachial systolic blood pressure was significantly related to incident infarct, while posterior tibial systolic blood pressure was not. Other variables examined and not found to be significantly different are listed in the footnote to Table 4. Of note, having a transient ischemic attack or stroke before the initial MRI (n=47) was not associated with incident brain infarct, which occurred in 23.4% of the 47 with a previous event and 17.5% of the 1386 without a previous event (P>0.05).

In multivariable model 1, we allowed all of 9 variables, as coded in Table 4, to compete in a stepwise fashion for entry. Only 2 variables entered: creatinine as a continuous variable (odds ratio [OR], 2.09; 95% CI, 1.21 to 3.60) and white matter grade (OR, 1.57; 95% CI, 1.40 to 1.75). Because the same factors that increased the risk of brain infarcts could increase the risk of white matter changes,2,4,14 the MRI variables were withheld from model 2. Three variables entered: creatinine (OR, 1.77; 95% CI, 1.03 to 3.04), age (OR, 1.04; 95% CI, 1.01 to 1.07), and ankle-arm index (OR, 0.36; 95% CI, 0.14 to 0.88). To allow greater ease in interpreting the results, we recoded creatinine, age, and ankle-arm index into quintiles on the basis of participants with incident infarcts. White matter grades 4 through 9 were collapsed into 1 category (4+) because of small numbers. In grade 4, 26 of 62 (41.9%) had incident infarcts; grade 5, 9 of 27 (33.3%); grade 6, 3 of 7 (42.9%); grade 7, 4 of 5 (80.0%); grade 8, 2 of 4 (50.0%); and grade 9, 0 of 0. Using these categorical variables, we repeated model 1, forcing in creatinine and white matter grade, and model 2, forcing in creatinine, age, and ankle-arm index (Table 5).
Cross-sectional studies have shown that overt strokes or transient ischemic attacks are common in the elderly. However, most brain infarcts are either covert or silent. Only 5% of elderly subjects and 10% of younger subjects with overt strokes also have increased white matter lesions. The present study is one of the few that have evaluated the occurrence of incident brain infarcts in elderly subjects without overt strokes.

Incident Infarct on Follow-Up MRI

Incident Infarct on Follow-Up MRI

<table>
<thead>
<tr>
<th>Potential Risk Factors*</th>
<th>n</th>
<th>No</th>
<th>Yes</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at initial MRI, mean, y</td>
<td>1433</td>
<td>73.5</td>
<td>74.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Moderate or vigorous exercise, mean, kcal/wk</td>
<td>1429</td>
<td>1694</td>
<td>1426</td>
<td>0.034</td>
</tr>
<tr>
<td>Instrumental ADL, % any difficulty</td>
<td>1429</td>
<td>16.9</td>
<td>22.4</td>
<td>0.038</td>
</tr>
<tr>
<td>Systolic blood pressure, mean, mm Hg</td>
<td>1433</td>
<td>131.9</td>
<td>135.4</td>
<td>0.009</td>
</tr>
<tr>
<td>Ankle-arm index, mean</td>
<td>1429</td>
<td>1.13</td>
<td>1.10</td>
<td>0.003</td>
</tr>
<tr>
<td>Creatinine, mean, µmol/L‡</td>
<td>1420</td>
<td>89.4</td>
<td>92.9</td>
<td>0.013</td>
</tr>
<tr>
<td>Creatinine, % &gt;110.6 µmol/L‡</td>
<td>1420</td>
<td>11.9</td>
<td>16.7</td>
<td>0.047</td>
</tr>
<tr>
<td>Initial MRI white matter grade, mean</td>
<td>1427</td>
<td>1.67</td>
<td>2.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initial MRI sulcal grade, mean</td>
<td>1427</td>
<td>3.17</td>
<td>3.35</td>
<td>0.025</td>
</tr>
</tbody>
</table>

ADL indicates activities of daily living.

*C factors listed with P value by t test or Fisher exact as appropriate. Other factors not significantly related (P>0.05) to incident infarct include sex; race; income; education; hypertension by self-report or by history; blood pressure, and medications; baseline angina, myocardial infarction, claudication, coronary heart disease, congestive heart failure, any cardiovascular disease, diabetes by American Diabetes Association criteria, and diabetes by self-report; alcohol consumption; current smoking; pack-years of smoking; medications for hypertension; diuretic use; aspirin use; ADL; diastolic blood pressure; drop in systolic blood pressure, drop in diastolic blood pressure, and dizziness on standing; orthostatic hypotension; ankle-arm index <0.9; posterior tibial blood pressure by Doppler; height; weight; body mass index; white blood count; hemoglobin; hematocrit; fasting insulin; fasting glucose; uric acid; triglycerides; total, HDL, and LDL cholesterol; fibrinogen; factor VII; factor VIII; C-reactive protein; forced expiratory volume in 1 second; common and internal carotid artery wall thickness; maximum internal carotid artery stenosis; atrial fibrillation, left ventricular hypertrophy, and major abnormality on ECG; left atrial dimension, left ventricular mass, left ventricular mass in diastole, left ventricular ejection fraction, and left ventricular wall motion abnormality on echocardiogram; and initial MRI ventricular grade.

†Systolic blood pressure measured with a regular stethoscope. Brachial and posterior tibial systolic blood pressure measured with a Doppler stethoscope to derive the ankle-arm index.

‡Multiply by 0.0113 to convert to mg/dL.

Cortical Infarcts
For the 36 participants whose incident MRI-defined infarcts were solely cortical (Table 2), we contrasted their findings on ECG, echocardiography, and carotid ultrasonography with those of participants whose MRI showed no infarcts (n=1179) or showed infarcts that were not solely cortical (n=218). The only variable significantly different across the 3 groups was ECG evidence of atrial fibrillation. It was present in 13.9% of participants with solely cortical infarcts, 1.5% of those without infarcts, and 1.4% of those with infarcts that were not solely cortical (P<0.001). Of the 26 participants with atrial fibrillation on ECG done around the time of the initial MRI, 8 (30.8%) had an incident MRI-defined infarct on their follow-up scan. Five were solely cortical, and the other 3 were lacunes.

Discussion
Incident MRI-defined infarcts are common in the elderly. Over 5 years, 17.7% of 1433 participants in this study developed incident infarcts on follow-up MRI. Over the same period, only 2.7% of participants experienced a stroke. Most of the MRI-defined infarcts were lacunes and were covert, namely, not associated with acute symptoms recognized as a transient ischemic attack or stroke. In another longitudinal study of 75 patients without a history of transient ischemic attacks or stroke followed over 2 years with serial cranial MRI, 9 (12%) developed new lesions without any accompanying symptoms. These observations agree with Fisher’s seminal neuropathological study of cerebrovascular disease in 1042 brains.

The findings of the present longitudinal study support the findings of cross-sectional studies that these infarcts cannot be considered silent or benign. Those with follow-up MRI demonstrating infarcts had significantly worse cognitive performance at follow-up than those without infarcts despite the 2 groups having similar cognitive performance at the time of the initial MRI. These analyses cannot address whether incident infarcts themselves or other processes associated with infarcts, such as changes in white matter grade over time, cause the cognitive decline. One could argue that the differences in scores were statistically significant but not clinically important. Nonetheless, if one assumes a linear decline in the Mini-Mental State Examination score in the participants without MRI-defined infarcts (−0.9 points over 5 years), they would experience over 13 years the same decline seen in participants with MRI-defined infarcts in only 5 years.

Detailed cognitive testing was not done in this study but will be necessary to better define the importance of these findings. Of the many potential risk factors evaluated, only 9 were significantly related to having an incident MRI-defined infarct on follow-up MRI. The strongest association was for the initial white matter grade. White matter grade and brain infarcts, both overt and covert, share many risk factors, suggesting that they may represent different manifestations of cerebrovascular disease.
vascular disease. If so, the presence of one could increase the risk of the other. This study cannot address the question of whether associations found for incident MRI-defined infarcts are mediated through changes in the white matter grade between the 2 scans because these data are still being collected.

When white matter grade was withheld from multivariable models, age, creatinine, and ankle-arm index were significantly and independently associated with developing an incident infarct. Creatinine has been associated in a cross-sectional study with prevalent MRI-defined infarcts and in 2 longitudinal studies with incident stroke. The risk was higher for those with creatinine of $1.3$ mg/dL. The association with creatinine may simply reflect the deleterious effects of hypertension on a vascular bed other than the brain, although direct effects of renal insufficiency on small vessels have also been proposed. In addition, renal insufficiency is associated with elevated plasma homocysteine levels, which in turn have been associated with covert infarcts and white matter changes. In this study the ankle-arm index was also an independent risk factor for incident brain infarction, as it has been for incident myocardial infarction and ischemic stroke. The association with ankle-arm index may reflect the effects of elevated systolic blood pressure, peripheral arterial disease, or both. Evidence that the peripheral vasculature is affected likely increases the chances that other arterial trees are affected, such as those supplying the brain and heart.

Of note, diabetes and cigarette smoking were not associated with incident MRI-defined infarcts, consistent with prior cross-sectional studies in which these factors were associated only with symptomatic infarcts. In addition, the few participants (n=47) with a history of transient ischemic attack or stroke before the initial MRI were not at increased risk of incident MRI-defined infarcts compared with participants without such a history. Possibly the history was in error in that the initial MRI was free of infarcts.

Only 36 (2.5%) of the 1433 participants had incident brain infarcts solely involving the cerebral cortex. We suspected that these participants were more likely to have had an

<table>
<thead>
<tr>
<th>Table 5. Results of Multivariable Models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>White matter grade</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4+</td>
</tr>
<tr>
<td>Creatinine, μmol/L†</td>
</tr>
<tr>
<td>44–75</td>
</tr>
<tr>
<td>76–84</td>
</tr>
<tr>
<td>85–93</td>
</tr>
<tr>
<td>94–111</td>
</tr>
<tr>
<td>112–239</td>
</tr>
<tr>
<td>Age at initial MRI, y</td>
</tr>
<tr>
<td>65–70</td>
</tr>
<tr>
<td>71–72</td>
</tr>
<tr>
<td>73–74</td>
</tr>
<tr>
<td>75–78</td>
</tr>
<tr>
<td>79–91</td>
</tr>
<tr>
<td>Ankle-arm index</td>
</tr>
<tr>
<td>0.33–1.02</td>
</tr>
<tr>
<td>1.03–1.09</td>
</tr>
<tr>
<td>1.10–1.15</td>
</tr>
<tr>
<td>1.16–1.20</td>
</tr>
<tr>
<td>1.21–2.18</td>
</tr>
</tbody>
</table>

* n=1401. Time between scans was included as a continuous variable in all regressions. Models 1 and 2 are based on the variables listed in Table 4; see text for details. In model 1, all the variables competed in a stepwise fashion. In model 2, white matter grade was withheld. For these analyses, variables were recoded to help with interpretation. The reference group is the first quintile except for the ankle-arm index, where it is the fifth quintile.

†Multiply by 0.0113 to convert to mg/dL. Quintiles are based on creatinine measured in mg/dL: 0.5–0.8; 0.9; 1.0; 1.1–1.2; 1.3–2.7.
embolic event. A significant association was found with atrial fibrillation on ECG done close in time to the initial MRI but not carotid ultrasound measures. These findings confirm the importance of atrial fibrillation as a risk factor for incident infarcts in the elderly, but for a relatively uncommon type of infarct.

This study has its limitations. Participants in CHS, and especially those included in these analyses, are likely healthier than the general population of elderly people. Although MRI was performed on a large number of elderly people and interpreted in a standard fashion without any clinical information, we do not know that the findings being interpreted as infarcts on the MRI are in fact brain infarcts and that the white matter changes do not include some infarcts. We have no MRI-pathological correlation and are unlikely to have such information given the low rate of autopsies in CHS. Nonetheless, prior studies have shown good MRI-pathological correlation, and we assume that subcortical lesions on MRI are a consequence of ischemia in the distribution of penetrating arteries. Finally, risk factor status could have changed between the initial MRI and the incident infarct, and participants may have been misclassified on the basis of information from around the time of the initial scan. Only more frequent brain imaging could diminish such misclassification in future studies.

In this study incident covert brain infarcts were common in the elderly and associated with a deterioration of cognitive function. Brain infarcts were associated with both risk factors for and evidence of disease in other vascular beds, specifically the renal and peripheral vasculature. We suspect that measures directed at preventing vascular disease might have the additional salutary effect of preserving cognition with aging, as suggested in a trial of treating systolic hypertension. Future trials aimed at preventing vascular disease should consider assessing serial cranial MRI and cognitive function as outcome measures.

Appendix

Participating Institutions and Principal Staff


Acknowledgments

This research was supported by contracts N01-HC-85079 through N01-HC-85086, N01-HC-35129, and N01-HC-15103 from the National Heart, Lung, and Blood Institute, Bethesda, Md.

References


Incidence, Manifestations, and Predictors of Brain Infarcts Defined by Serial Cranial Magnetic Resonance Imaging in the Elderly: The Cardiovascular Health Study

W.T. Longstreth Jr, Corinne Dulberg, Teri A. Manolio, Michael R. Lewis, Norman J. Beauchamp Jr, Daniel O'Leary, Jeff Carr and Curt D. Furberg

Stroke. 2002;33:2376-2382
doi: 10.1161/01.STR.0000032241.58727.49
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/33/10/2376

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/