Association of Prior Stroke With Cognitive Function and Cognitive Impairment

A Population-Based Study

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Background: Defining the nature of the contribution of stroke to cognitive impairment remains challenging.

Objective: To describe associations between stroke history, APOE genotype, and subtypes of mild cognitive impairment (MCI).

Methods: We randomly selected residents from Olmsted County, Minnesota, aged 70 to 89 years on October 1, 2004, and invited eligible subjects without documented dementia to participate. Participants (n=2050) were evaluated through an informant interview, a neurological evaluation, and neuropsychological testing. Neuropsychological testing included 9 tests to assess memory, attention, executive function, visuospatial cognition, and language. Subjects were diagnosed by consensus as cognitively normal or as having MCI (either amnestic or nonamnestic) or dementia. A history of stroke was obtained from the subjects and confirmed in their medical records. We computed the odds ratios (ORs) for a clinical diagnosis of MCI or for scoring in the lowest quartile on each cognitive domain.

Results: There were 1640 cognitively normal subjects and 329 subjects with MCI: 241 with amnestic MCI and 88 with nonamnestic MCI. In fully adjusted models with only subjects without dementia, a history of stroke was associated with a higher OR of nonamnestic MCI (OR, 2.85; 95% confidence interval [CI], 1.61-5.04) than amnestic MCI (OR, 1.77; 95% CI, 1.14-2.74). A history of stroke was also associated with impaired function in each cognitive domain except memory. The association was strongest for attention and executive function (OR, 2.48; 95% CI, 1.73-3.53). APOE ε4 genotype was associated only with amnestic MCI and with impaired memory function.

Conclusions: In this population-based sample of persons without dementia, a history of stroke was particularly associated with nonamnestic MCI and impairment in nonmemory cognition. The APOE ε4 genotype was associated with memory impairment and amnestic MCI.


THE RELATIONSHIP BETWEEN stroke and cognitive impairment has been enigmatic. The link between large strokes that lead to immediate and persistent neurological impairment has never been questioned. However, the role of single strokes that may not produce immediate cognitive impairment is less well understood. Several studies have noted that subjects with a history of stroke had a higher risk of cognitive impairment or decline1-3 or dementia4,5 than did persons without such a history. While the profile of cognitive impairment associated with cerebrovascular disease in dementia is not helpful diagnostically,6 the profile of strengths and weaknesses of different cognitive domains in persons who are cognitively normal or who have mild cognitive impairment (MCI) might shed some light on what brain regions are affected by cerebrovascular pathology. It may be easier to recognize the unique contribution of cerebrovascular disease in persons with the least amount of cognitive impairment than in patients with established dementia, because the effect of Alzheimer disease may overwhelm the vascular element.7

We had the opportunity to study the associations of prior stroke and cognition in a large, population-based sample of elderly persons without dementia in Olmsted County, Minnesota. In addition to collecting detailed information about stroke histories, we also collected extensive information on other vascular diseases and risk factors. Our objective for the present study was to examine whether a history of stroke was associated with the diagnosis of MCI or cognitive impairment determined by a battery of neuropsychological tests, independent of cat-
egorical clinical diagnoses. We compared associations of MCI and cognitive function domains with stroke history with associations with APOE (OMIM 107741) genotype as a proxy, albeit an imperfect one, for Alzheimer disease–linked pathogenic mechanisms.

METHODS

STUDY SUBJECTS

Study subjects were participants in a longitudinal study designed to estimate the prevalence and incidence of MCI in Olmsted County. Many of the details of the study design and methodology have been previously published.13,14 The study protocol was approved by the institutional review boards of the Mayo Clinic and the Olmsted Medical Center. From an enumeration of Olmsted County residents aged 70 to 89 years on October 1, 2004 (N=9953), we randomly selected 5227 subjects and invited them to participate in the study. We offered home visits for subjects with mobility problems. We excluded subjects who died before they could be contacted (n=263), who were terminally ill and in hospice care (n=56), who could not be contacted (n=114), and who had previously been diagnosed with dementia (n=402; confirmed by D.S.K.). From an eligible cohort of 4392 subjects invited to participate, 2719 were enrolled in the study (61.8%); 2050 participated in a face-to-face evaluation and 667 participated in a telephone interview. Dementia was diagnosed in 67 of the 2050 persons evaluated face-to-face. This study concerns the 1983 subjects without dementia who completed the face-to-face evaluation.

PARTICIPANT EVALUATION

Participants underwent a nurse evaluation and risk factor assessment that included the Clinical Dementia Rating scale,15 a neurological examination performed by a study physician, including a mental status examination and a structured neurological examination; and neuropsychological testing, including 9 cognitive tests to assess cognitive function in memory, executive function, language, and visuospatial skills, as previously described.10 The data for each participant were reviewed by an expert panel of physicians, neuropsychologists, and the nurse who evaluated the participant, and a diagnosis of normal cognition, MCI, or dementia was reached by consensus.

COGNITIVE DOMAINS

The neuropsychological test battery consisted of subtests from the Wechsler Adult Intelligence Scale–Revised12 and the Wechsler Memory Scale–Revised.15 Four domains of cognitive function were evaluated: (1) executive function (Trail-Making Test A and B15 and the Digit Symbol Substitution test from the Wechsler Adult Intelligence Scale–Revised); (2) language (Boston Naming Test16 and Category Fluency16); (3) memory (Logical Memory–II [delayed recall] and Visual Reproduction–II [delayed recall] from the Wechsler Memory Scale–Revised and the Auditory Verbal Learning Test17,20); and (4) visuospatial ability (Picture Completion and Block Design from the Wechsler Adult Intelligence Scale–Revised).

For the purposes of the consensus clinical diagnoses, the raw scores from the neuropsychological test battery were converted to Mayo’s Older American Normative Studies values that were age-adjusted to norms derived from the same population and transformed to a standardized score with a mean of 10 and a standard deviation (SD) of 3.17,20 Domain scores were calculated for the 4 cognitive domains, as previously described.15 A z score was generated for each domain and subject. The average of the Mayo’s Older American Normative Studies scaled scores in each domain represented the domain score. The values for impairment were determined by inspecting the frequency distributions of the summed scaled scores in each domain. This approach relied on previous normative work and extensive knowledge of the cognitive abilities of the population from which the current participants have been drawn.13-20 Patients with MCI typically score between 1.0 and 1.5 SDs below the mean.13-20 Although the psychometric scores were important in the diagnostic process, the final decision about impairment was based on the clinical interpretation and judgment of the neuropsychologist, in the context of the entire set of data for an individual, taking into account age, level of education, and occupation.

For the purpose of evaluating the individual cognitive domains, the raw scores from the neuropsychological battery were normed to the entire group of subjects who underwent the battery. A z score was generated for each domain.

CLINICAL DIAGNOSES

Based on the face-to-face evaluation, we categorized participants as cognitively normal (controls), as having MCI (cases), or as having dementia.13-20 A diagnosis of normal cognition was assigned according to published criteria.13-20,23 A diagnosis of MCI was made according to the following published criteria: cognitive concern by a physician, patient, or nurse; impairment in 1 or more of the 4 cognitive domains; essentially normal functional activities; and not having dementia.23 Participants with MCI were classified as having amnestic MCI (aMCI) if their memory domain was impaired or nonamnestic MCI (naMCI) if there was no memory impairment. A diagnosis of dementia was made according to Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria.24 Diagnoses of MCI or dementia, as well as diagnoses of MCI subtypes, were entirely based on the above information and not on the presence of stroke or any other vascular risk factor. It was only in a second phase of diagnostic determinations that etiology of the MCI or dementia was considered. Etiological diagnoses is not the subject of this article.

HISTORY OF STROKE

A history of stroke was obtained from the subject through a physician interview. Stroke was defined by standard criteria, namely that the person had had a focal neurological deficit consistent with ischemia in a cerebral vascular territory, the symptoms of which lasted longer than 24 hours. Subjects who gave a history of stroke were also asked whether there were any changes in their thinking that had accompanied it. All strokes were verified in the medical history using the medical records linkage system.25 The medical records of nonparticipants were also screened for a history of stroke to examine nonparticipation bias. As part of the neurological examination performed by the study physician, examination findings relevant to cerebrovascular disease were assessed, including reflex asymmetries, unilateral weakness, hemiparesis, hemianopia, and unilateral Babinski signs. The clinician rated these findings as to whether or not they were indicative of focal neurological signs consistent with cerebrovascular disease.

STATISTICAL ANALYSIS

The characteristics of study subjects are presented using descriptive statistics. Comparisons between MCI cases and controls were made using x² tests for categorical variables and the
RESULTS

There were 1640 cognitively normal subjects and 329 subjects with MCI: 241 with aMCI and 88 with naMCI. There were 183 subjects (9.3%) with a history of stroke. Among the 1651 subjects who refused participation, medical record review showed that they were slightly older and slightly more likely to have a history of stroke (11.7%, \( P = .02 \)) than participants. Table 1 describes the demographic and vascular disease characteristics of the subjects. The evaluating neurologists rated 36 of the subjects with MCI (10.9%) and 67 of the cognitively normal subjects (4.1%) as having focal neurological signs that were consistent with cerebrovascular disease based on their neurological examination. A higher proportion of subjects with MCI with a history of stroke (17 of 56 [30%]) reported changes in thinking following their stroke than did cognitively normal subjects with a history of stroke (14 of 127 [11%]).

ASSOCIATION OF STROKE WITH MCI

A history of stroke was associated with MCI in unadjusted models (odds ratio [OR], 2.44; 95% confidence interval [CI], 1.74-3.43). In models that adjusted for age, sex, and education, a history of stroke was also associated with a higher risk of MCI (Table 2). When examined by MCI subtype, there was a difference between aMCI

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<table>
<thead>
<tr>
<th>Variable</th>
<th>aMCI vs naMCI</th>
<th>All MCI vs Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td></td>
<td></td>
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<tr>
<td>Male sex</td>
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<tr>
<td>Education, median (IQR), y</td>
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<tr>
<td>Education, y</td>
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<td>Cigarette smoking</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td></td>
<td></td>
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<tr>
<td>Focal neurological signs</td>
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<td>Hemiparesis</td>
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</table>

Abbreviations: aMCI, amnestic mild cognitive impairment; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; MCI, mild cognitive impairment; naMCI, nonamnestic mild cognitive impairment.
and naMCI. The association of stroke with naMCI was of greater magnitude than that with aMCI. Separate models in which diabetes (with complications), coronary heart disease, APOE genotype, and hypertension were added to the models did not alter the differential associations between history of stroke and the MCI subtypes either. Secondary analyses that excluded subjects with a history of stroke-related cognitive changes or subjects with focal neurological signs consistent with a prior stroke yielded nearly the same ORs.

In contrast to the pattern of association of stroke with MCI subtypes, APOE genotype, when included in a model with stroke, was associated with aMCI but not naMCI (Table 2). Inclusion of APOE genotype and stroke in the same models, with an interaction term, revealed no significant interaction between APOE genotype and history of stroke for either aMCI (OR, 0.68; 95% CI, 0.26-1.79) or naMCI (OR, 0.58; 95% CI, 0.13-2.48). Thus, a history of stroke was associated with both aMCI and naMCI, while APOE ε4 genotype was associated with aMCI only.

ASSOCIATION OF STROKE WITH COGNITIVE DOMAINS IN ALL SUBJECTS

Separate analyses to investigate associations of stroke with cognitive function (assessed through neuropsychological testing) were conducted with all 1969 subjects without dementia included in the models (Table 3). A history of stroke was significantly associated with lower cognitive function in each cognitive domain except memory. The magnitude of the association was strongest for the executive function domain in unadjusted analyses (OR, 2.83; 95% CI, 2.03-3.95) and after adjusting for age, sex, and education (OR, 2.48; 95% CI, 1.73-3.53) but was also elevated about 2-fold for language and visuospatial domains. Addition of diabetes, coronary heart disease, APOE genotype, and hypertension to the models did not affect the significant associations of stroke with the 3 nonmemory cognitive domains. Secondary analyses that excluded subjects with a history of stroke-related cognitive changes or subjects with focal neurological signs consistent with a prior stroke yielded nearly the same ORs.

APOE ε4 genotype was only associated with poor performance in the memory domain (Table 3). With APOE genotype, stroke history, and an interaction term for APOE and stroke history in the same model, there was no significant interaction with any of the cognitive domains.

ASSOCIATION OF STROKE WITH COGNITIVE DOMAINS IN COGNITIVELY NORMAL SUBJECTS

In a final set of models, we restricted the analyses to subjects who were assigned a diagnosis of being cognitively normal. In this subset of subjects, a history of stroke was associated with lower performance in the language and executive domains (Table 3). There were no interactions with APOE genotype. Addition of diabetes and hypertension did not alter the associations. APOE ε4 genotype only showed a trend for association with poorer memory function.

Using a case-control design in a population-based cohort, we have shown that a history of stroke was associated with a particular pattern of cognitive impairment, based not only on the categorical diagnoses of MCI vs normal cognition, but also on continuous measures of cognitive performance in the entire group of subjects without dementia. A history of stroke was independently associated with cognitive impairment in nonmemory domains after adjustment for potential confounders. The association of a history of stroke with cognition was independent of APOE ε4 genotype, and there was no interaction between the two. The association was not substantially attenuated by other vascular risk factors.

While studies have shown that a history of stroke was associated with cognitive impairment, our findings may offer the clearest view of the domain specificity of the association. We found that the scores on the Trail-Making Test B and Digit Symbol Substitution test (which we labeled as exemplifying the executive function domain) were most strongly linked to a history of stroke. The 1 prior study of stroke and MCI that we are aware of also found that a history of transient ischemic attack or stroke was associated with naMCI.

The association between nonmemory cognitive impairment and cerebrovascular disease other than prior stroke is a recurrent theme. Clinically diagnosed vascular dementia has been associated with impairment in executive dysfunction. Imaging studies of subjects with white matter hyperintensity have found that nonmemory cognitive dysfunction was more prominent than anterograde amnesia. Analyses of patients with lacunar infarcts and extensive white matter hyperintensity burden have also revealed more pronounced associations between evidence of infarction and nonamnestic cognition.

Table 2. Associations of Stroke and APOE Genotype With All MCI and With Cognitively Normal Subjects as Reference Group

<table>
<thead>
<tr>
<th>Model</th>
<th>All MCI</th>
<th>aMCI</th>
<th>naMCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1a</td>
<td>Stroke</td>
<td>2.10 (1.48-2.98)</td>
<td>1.69 (1.11-2.55)</td>
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<tr>
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<td>APOE ε4</td>
<td>1.52 (1.15-2.01)</td>
<td>1.68 (1.23-2.30)</td>
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<tr>
<td>Model 2b</td>
<td>Stroke</td>
<td>2.04 (1.42-2.95)</td>
<td>1.74 (1.13-2.69)</td>
</tr>
<tr>
<td></td>
<td>APOE ε4</td>
<td>1.52 (1.14-2.01)</td>
<td>1.67 (1.22-2.29)</td>
</tr>
<tr>
<td>Model 3c</td>
<td>Stroke</td>
<td>2.03 (1.40-2.94)</td>
<td>1.77 (1.14-2.74)</td>
</tr>
<tr>
<td></td>
<td>APOE ε4</td>
<td>1.54 (1.16-2.05)</td>
<td>1.71 (1.24-2.34)</td>
</tr>
</tbody>
</table>

Abbreviations: aMCI, amnestic mild cognitive impairment; MCI, mild cognitive impairment; naMCI, nonamnestic mild cognitive impairment.

a Represents associations of stroke and APOE ε4 genotype with MCI in separate models, with each model controlling for age (<80 vs ≥80 years), education (<12 vs ≥12 years), and sex.
b Includes both APOE ε4 genotype and stroke history in the same model, with adjustment for age, sex, and education.
c Includes model 2 variables with additional adjustment for diabetes (with complications), hypertension, and coronary heart disease.
Disruption of subcortical white matter pathways that link the frontal cortex to other regions by ischemic mechanisms is an attractive explanation, as it accounts for both the clinical observations in the present study as well as the evidence from imaging linking white matter hyperintensities and lacunar infarcts to executive deficits.28,32 Both, however, go well beyond the concept of vascular dementia as a disease that is insidious and cumulative. Both could account for the cumulative rather than apoplectic development of dementia due to cerebrovascular disease. One is that prior strokes, in causing brain injury, reduce brain reserve, which allows the impact of subsequent diseases such as Alzheimer disease to be manifested clinically at an earlier time.33 A second explanation posits that overt strokes are associated with progressive cerebral microvascular disease, with the latter leading to ongoing brain injury and eventually dementia. Both could account for the predilection for executive, nonmemory functions and the lack of attenuation of associations between stroke and cognitive impairment by other vascular risk factors is noteworthy. A history of stroke was independently associated with cognitive impairment, even with diabetes (with complications), hypertension, or coronary heart disease in the models. Diabetes with complications34 and certain types of coronary heart disease35 were also independently associated with naMCI when stroke history was in the model. This implies that there are other pathways for cerebrovascular disease besides stroke that are correlated with diabetes or heart disease. Alternatively, the latter diseases might have a direct link with neurodegenerative disease.

APOE ε4 genotype behaved quite differently as a risk factor than stroke history. It was associated both more strongly with aMCI and poor memory domain performance but not with any other cognitive domain. The association of APOE ε4 genotype with subsequent risk of cognitive decline36 and Alzheimer disease is well established.37,38 The differential associations of a history of stroke and nonmemory cognition and APOE ε4 genotype and memory suggest that the pathophysiological processes driven by cerebrovascular disease and APOE genotype are distinct.

The strengths of our study were that we derived our observations from a population-based cohort of persons who did not have dementia. The cognitive status of our subjects was evaluated with neuropsychological testing and clinical evaluation by a physician. The history of stroke was verified in the medical records of subjects using the medical records linkage system for Olmsted County residents. The weaknesses of our study were its cross-sectional design and use of prevalent cases of MCI; therefore, the temporality of exposure and disease is not clear. We did not

<table>
<thead>
<tr>
<th>Model</th>
<th>Memory</th>
<th>Language</th>
<th>Executive</th>
<th>Visuospatial</th>
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<tbody>
<tr>
<td></td>
<td>All Subjects Without Dementia</td>
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<td></td>
<td></td>
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<tr>
<td>Model 1a</td>
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<tr>
<td>Stroke</td>
<td>1.23 (0.88-1.74)</td>
<td>1.71 (1.21-2.41)</td>
<td>2.48 (1.73-3.53)</td>
<td>2.15 (1.52-3.06)</td>
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<tr>
<td>APOE ε4</td>
<td>1.51 (1.18-1.95)</td>
<td>1.21 (0.93-1.57)</td>
<td>1.20 (0.92-1.58)</td>
<td>1.28 (0.99-1.67)</td>
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<td>Model 2b</td>
<td></td>
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<tr>
<td>Stroke</td>
<td>1.29 (0.90-1.86)</td>
<td>1.83 (1.27-2.62)</td>
<td>2.42 (1.67-3.51)</td>
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<tr>
<td>APOE ε4</td>
<td>1.51 (1.17-1.95)</td>
<td>1.21 (0.93-1.57)</td>
<td>1.19 (0.91-1.57)</td>
<td>1.28 (0.98-1.67)</td>
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<td>Model 3c</td>
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<tr>
<td>Stroke</td>
<td>1.31 (0.91-1.88)</td>
<td>1.85 (1.29-2.65)</td>
<td>2.37 (1.63-3.44)</td>
<td>2.14 (1.48-3.10)</td>
</tr>
<tr>
<td>APOE ε4</td>
<td>1.52 (1.18-1.96)</td>
<td>1.21 (0.93-1.58)</td>
<td>1.18 (0.90-1.56)</td>
<td>1.29 (0.99-1.68)</td>
</tr>
</tbody>
</table>

| Cognitively Normal Subjects |        |          |           |              |
| Model 1a |         |          |           |              |
| Stroke | 1.20 (0.74-1.94) | 1.63 (1.04-2.54) | 1.94 (1.23-3.05) | 1.54 (0.98-2.42) |
| APOE ε4 | 1.37 (0.98-1.92) | 0.87 (0.62-1.22) | 0.98 (0.69-1.39) | 1.17 (0.85-1.61) |
| Model 2b |         |          |           |              |
| Stroke | 1.33 (0.81-2.18) | 1.83 (1.16-2.89) | 1.98 (1.23-3.18) | 1.56 (0.97-2.50) |
| APOE ε4 | 1.37 (0.98-1.91) | 0.86 (0.62-1.21) | 0.97 (0.68-1.38) | 1.16 (0.84-1.60) |
| Model 3c |         |          |           |              |
| Stroke | 1.34 (0.82-2.20) | 1.83 (1.16-2.90) | 1.94 (1.20-3.11) | 1.57 (0.98-2.53) |
| APOE ε4 | 1.37 (0.98-1.92) | 0.88 (0.62-1.23) | 0.95 (0.67-1.36) | 1.18 (0.85-1.63) |

a Represents associations of stroke and APOE ε4 genotype with cognitive domain in separate models, with each model controlling for age (<80 vs ≥80 years), education (<12 vs ≥12 years), and sex.

b Includes both APOE ε4 genotype and stroke history in the same model, with adjustment for age, sex, and education.

c Includes model 2 variables with additional adjustment for diabetes (with complications), hypertension, and coronary heart disease.
have imaging data on the location of the strokes. More precise definitions of the strokes might have substantially increased the specificity of the estimates of association.

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Author Contributions: Study concept and design: Knopman, Roberts, Ivnik, and Petersen. Acquisition of data: Knopman, Roberts, Geda, Boeve, Tangalos, Ivnik, and Petersen. Analysis and interpretation of data: Knopman, Roberts, Pankratz, Cha, Ivnik, and Petersen. Drafting of the manuscript: Knopman, Roberts, and Cha. Critical revision of the manuscript for important intellectual content: Knopman, Roberts, Geda, Boeve, Pankratz, Tangalos, Ivnik, and Petersen. Statistical analysis: Knopman, Roberts, Pankratz, Cha, and Ivnik. Obtained funding: Knopman, Roberts, and Petersen. Administrative, technical, and material support: Knopman, Boeve, and Petersen. Study supervision: Knopman, Roberts, and Petersen.

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