Vascular cognitive impairment (VCI) has continued to evolve over the past year. Much of the data has been confirmatory with further work on risk factors, silent strokes, leukoaraiosis and lesion volume and location. The importance of the interaction between cerebrovascular disease and other causes of cognitive impairment, most importantly Alzheimer disease (AD) remains a prominent theme. The natural history of VCI remains uncertain and further data on the rate of progression and factors affecting this are presented. It increasingly seems that the rate of progression in well-defined cases is low with no progression over 1 year in 1 study. Interestingly, a novel study from Toronto suggested that steal cases is low with no progression over 1 year in 1 study. New trial data have been scanty but of note 1 long trial of aspirin was negative.

Pathogenesis and Etiology
Silent strokes are the most common form of stroke.¹ In 1998 in the United States it was estimated that there were about 9 million silent infarcts and 2 million silent hemorrhages. Cerebral infarcts are an important cause of dementia; however, there is controversy regarding the role of silent or asymptomatic infarcts, infarct size and location, and vascular risk factors.² Troncoso et al³ report autopsy findings from the Baltimore Longitudinal Aging Study among 122 men and 57 women of whom 92% were white, had 17.5 years of education, and a mean age at death of 86.9 years. The odds of dementia were increased by both asymptomatic and symptomatic infarcts; however, dementia was not increased by risk factors for stroke in the absence of an infarct. Number but not size of hemispherical infarct was important, whereas subcortical infarcts conferred no increased risk of dementia. Macroscopic and microscopic infarcts contributed equally to dementia risk, and hemispherical infarcts, whether silent or clinically manifest, alone or in conjunction with AD pathology accounted for 35% of dementia cases. The findings support a synergism between AD and vascular pathology and the importance of burden and location of infarcts. The study represents a convenience sample of white, well-educated persons and, therefore, is not representative of the community at large. Other study limitations include a lack of a full accounting of microscopic infarcts and analysis of cerebral amyloid angiopathy.

The thalamus has been associated with impairments of memory, executive function, language, and other major functions.³ Stebbins et al⁴ report MRI voxel-based morphometry results among stroke patients with (n=40) and without (n=51) cognitive impairment. The study shows significant gray matter volume reductions in those with stroke with 1 or more cognitive domain impairments, mostly in the thalamus with smaller reductions in the cingulate gyrus and frontal, temporal, parietal, and occipital lobes.³ These findings support a central role for the thalamus in the development of cognitive impairment after ischemic stroke. Other important recent neuroimaging findings in relation to vascular factors which may play a role in brain change associated with cognitive impairment are described in Table 1.⁴⁻¹⁵

In relation to vascular factors which may play a role in cognitive impairment, epidemiological association studies have shown the following: (1) in the Cardiovascular Health Study, having both diabetes and APOE e4 might increase the risk of dementia, particularly for AD and mixed AD¹⁴; (2) in the Three-City Study, an association between high homocysteinaemia and decreased cognition was seen in elderly with low folate levels¹⁵; (3) in the Nurses Health Study, there was evidence of a possible role of higher fasting insulin levels in cognitive decline independent of diabetes mellitus¹⁶; and (4) in a biracial community study taking place on the south side of Chicago, greater body mass index in old age was not predictive of cognitive decline.¹⁷

Progression
Recent studies which summarize factors related to progression in VCI are featured in Table 2.¹⁸⁻²⁰

Noncognitive Deficits
That the predominant cognitive deficits in VCI are subcortical, frontal and executive is increasingly well recognized. Changes in mood are common but are less well recognized. Gait impairment in early disease is poorly recognized. In the nondisabled elderly studied in the LADIS trial,²¹ symptoms of depression correlated with impairment in executive function, and in the speed and motor control domains and memory complaints were related to impairment in the speed and motor control domains. The findings therefore showed a correlation between depression and slowed mental processing which in
The memory impairment is not primarily a cortical amnestic phenomenon but is more probably a subcortical deficit arising because of slowing of working memory and retrieval. The same study also found a correlation between extensive leukoaraiosis (LA) and walking speed and balance.22

### Leukoaraiosis Volumes, Cognition and Functional Imaging

The past year has produced further confirmation of a correlation between cognition and LA, lacunar and silent infarct volumes,23,24 but it is now well established that standard measures of MRI infarct and LA volumes correlate poorly, if at all, with cognitive impairment. This arises partly because of the importance of location and partly because MRI discriminates extremely poorly between different degrees of damage. Methods that more specifically assess function, and in the context of the white matter disease this really means tract integrity, offer the potential for being a much more accurate tool. This has been illustrated by one study in 35 patients with lacunar strokes and LA who underwent MRI using a variety of different measures in addition to standard T2 sequences, and these were compared to neuropsychological performance. Twenty-seven of these patients were re-studied at 1 year. Executive function correlated most strongly with diffusion tensor imaging (DTI) and brain volume but did not correlate with the number of lacunar infarcts or lesion volume. On follow-up, there were detectable changes in the DTI parameters, but no other imaging parameters changed and there was also no measurable cognitive decline over a year. Of the risk factors measured, only systolic blood pressure correlated with this evolution. DTI in conjunction with the premorbid IQ explained 74% of the variance in executive function; the addition of brain and lesion volume explained only 5% more of the variance.25 This type of work provides powerful evidence that the focus of imaging studies

### Table 1. Summary of Other Key Neuroimaging Findings in Relation to Vascular Factors Which May Be Associated with Brain Changes and Cognitive Impairment

<table>
<thead>
<tr>
<th>Factor and Comment</th>
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<tbody>
<tr>
<td>1. <strong>Homocysteine:</strong> In the Framingham Offspring Study, higher plasma homocysteine was associated with smaller brain volume and presence of silent brain infarcts on high-resolution MRI, even in healthy, middle-aged adults.4</td>
</tr>
<tr>
<td>2. <strong>Older Age and Vascular Disease:</strong> In the Washington Heights-Inwood Columbia Aging Project, older age and vascular disease, especially among blacks, was associated with increased brain atrophy and white matter hyperintensity burden on MRI.5</td>
</tr>
<tr>
<td>3. <strong>Mean Apparent Diffusion Coefficient (ADC) and Microstructural Change:</strong> In a single-center prospective longitudinal cohort study of patients at the Massachusetts General Hospital, mean ADC was independently associated with preintracerebral hemorrhage cognitive impairment in cerebral amyloid angiopathy (CAA) suggesting that global MRI diffusion changes may be sensitive to clinically relevant microstructural alterations and serve as markers of CAA-related tissue damage.6</td>
</tr>
<tr>
<td>4. <strong>Body Mass Index (BMI):</strong> Among 50 healthy middle-aged controls at University of California San Francisco, increased BMI in midlife was associated with MRI and proton magnetic resonance spectroscopic imaging neuronal and/or myelin abnormalities predominantly in the frontal lobe suggesting accelerated aging in persons with high levels of adiposity.7</td>
</tr>
<tr>
<td>5. <strong>Cardiorespiratory Fitness (CRF):</strong> In referral-based subjects enrolled in the Kansas Brain and Aging Project, increased CRF was associated with reduced brain atrophy in AD as determined by high-resolution MRI.8</td>
</tr>
<tr>
<td>6. <strong>Steal Phenomenon and White Matter Disease:</strong> In Toronto, functional MR mapping of cerebrovascular response to hypercapnea among healthy volunteers showed a steal phenomenon in the white matter occurring in locations where elderly develop leukoaraiosis suggesting that the steal might have a pathogenic role.9</td>
</tr>
<tr>
<td>7. <strong>Microbleed Location and Leukoaraiosis:</strong> In the Sunnybrook Dementia Study, microbleeds with corresponding parietooccipital leukoaraiosis were observed in patients with AD demonstrating the complexity of AD vasculopathy.10</td>
</tr>
<tr>
<td>8. <strong>Type-2 Diabetes and Brain Atrophy:</strong> In the Secondary Manifestations of Arterial (SMART) disease study, in patients with symptomatic arterial disease, type-2 diabetes mellitus was associated with global brain atrophy.11</td>
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<tr>
<td>9. <strong>Fish Consumption and Subclinical Brain Abnormalities:</strong> In the Cardiovascular Health Study, among older adults modest tuna or other fish consumption but not fried fish was associated with a lower prevalence of subclinical infarcts and white matter abnormalities on MRI suggesting that fish with higher eicosapentaenoic acid and docosahexaenoic acid content may have brain health benefits.12</td>
</tr>
<tr>
<td>10. <strong>Unrecognized Myocardial Infarction (MI):</strong> In the Rotterdam Scan Study, among men unrecognized MI might increase the risk of dementia and more cerebral small vessel disease.13</td>
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</tbody>
</table>

### Table 2. Factors Related to Progression of Vascular Cognitive Impairment

<table>
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<tr>
<th>Factor and Comment</th>
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<tbody>
<tr>
<td>1. <strong>Subcortical Hyperintensities (SHs):</strong> In Lille, France, Bombois et al provide evidence from an observational study that mild cognitive impairment (MCI) patients with a large amount of SHs at baseline have an increased the risk of vascular or mixed dementia, but not other forms of dementia. The findings were independent of medial temporal atrophy, age, gender, vascular risk factors, education, and cognitive functions.18</td>
</tr>
<tr>
<td>2. <strong>Periventricular White Matter Hyperintensity (PVWH) and Subcortical White Matter Hyperintensity (SWMH):</strong> In the Oregon Brain Aging Study, increased total and PVWH burden and progression of burden on MRI were associated with decreased gait performance during follow-up, whereas progression of SWMH volume was associated with memory decline in cognitively intact very elderly.19</td>
</tr>
<tr>
<td>3. <strong>Antidepressants:</strong> In the Cardiovascular Health Study, a multivariate model showed that worsening of white matter was associated with tricyclic antidepressants (odds ratio = 1.77, 95% CI, 1.07, 2.94) but was not significantly increased with serotonergic agents (odds ratio = 1.36, 95% CI 0.87, 2.12).20</td>
</tr>
</tbody>
</table>
needs to move from T2 lesion volumes to DTI based parameters.

**Leukoaraiosis Location**

Many studies have sought to identify those areas in which ischemic damage most closely correlates with cognitive impairment. Data have been strikingly inconsistent but there has been a theme that thalamic and deep gray lesions are most important. This has been supported by the Sunnybrook dementia study. In this population with mixed dementia, disease in these regions affected short-term and working memory. There has been some debate as to whether periventricular (PVLA) or deep white matter leukoaraiosis (DWMLA) is of greatest importance in cognition. The matter is of some importance as they may not share the same etiology. Findings are again inconsistent but there has been a bias toward greater cognitive impairment in association with etiology. Findings are again inconsistent but there has been a bias toward greater cognitive impairment in association with etiology. Findings are again inconsistent but there has been a bias toward greater cognitive impairment in association with etiology. Findings are again inconsistent but there has been a bias toward greater cognitive impairment in association with etiology. Findings are again inconsistent but there has been a bias toward greater cognitive impairment in association with etiology. The matter is of some importance as they may not share the same etiology. Findings are again inconsistent but there has been a bias toward greater cognitive impairment in association with etiology. Findings are again inconsistent but there has been a bias toward greater cognitive impairment in association with etiology. Findings are again inconsistent but there has been a bias toward greater cognitive impairment in association with etiology. Findings are again inconsistent but there has been a bias toward greater cognitive impairment in association with etiology.

They distinguished between PVLA and DWMLA where these were close to the ventricles by categorizing those lesions with their longest axis along the ventricular wall as periventricular. On this basis age correlated with PVLA but not with DWMLA. The expected correlations were seen between total white matter lesions and subcortical and executive domains. Independently, DWMLA correlated with executive and visuospatial deficits but not with naming or memory, whereas PVLA did not predict performance on any neuropsychological variable. In another study based on patients with MCI recruited from the memory clinic (and in which there would therefore be a considerable contribution from Alzheimer pathology), 92% of individuals had some degree of white matter disease. In 81% there was PVLA and 84% had DWMLA. These white matter changes did not correlate with cognition as measured by the Mini-Mental State Examination or the dementia rating scale and did not distinguish between amnestic and nonamnestic MCI, but both PVLA and DWMLA were independently associated with executive dysfunction. The debate continues.

**Clinical Trials and Treatment**

Dichgans et al tested the hypothesis that donepezil could improve cognition in cerebral autosomal arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a genetic form of subcortical ischemic vascular dementia. The mean age of patients was 54.8 years, and 86 were assigned to 10 mg of donepezil and 82 to placebo. At entry, participants had Mini-Mental State Examination scores 10 to 27 (mean at entry of 26.9 or 26.7) or a trail making test B time score at least 1.5 SD below the mean, after adjustment for age and education. Donepezil had no effect on the primary end point, change from baseline in the score of the vascular AD assessment scale cognitive subscale at 18 weeks. However, there was improvement on several measures of executive function (trail making test B time, EXIT25). The clinical trial had relatively small numbers of participants, but has implications for future trial design.

In another clinical trial, 3350 men and women over 50 years of age at moderately increased cardiovascular risk based on low ankle brachial index and enrolled in the AAA (aspirin for asymptomatic atherosclerosis) study were randomized to receive aspirin 100 mg/d or placebo for 5 years. Tests of memory, executive function, nonverbal reasoning, mental flexibility, information processing and a summary cognitive score were administered. Overall, low dose aspirin did not affect cognitive function in these middle aged and elderly persons. Of note, 30% of study subjects did not complete cognitive tests at follow-up.

In a small exploratory study, intranasal insulin improved cognition among early AD and amnestic MCI patients and raised the short form of β-amyloid peptide (AB40).

**Cognition After Long-Term Follow-Up in Coronary Artery Bypass Grafting**

In a study of cognition 6 years after surgical or medical therapy for coronary artery disease, Selnes et al showed that mild late cognitive decline occurred but did not differ in both groups, suggesting that late cognitive decline is not specific to the use of cardiopulmonary bypass.

**Conclusions**

A wide range of new data has become available over the past year. A major development has been the increasing evidence that the customarily used T2 MRI is a relatively poor technique for assessment of the consequences of small-vessel disease and that DTI is both more specific and more sensitive. Development of this has the potential to resolve many of the current problems concerning lesion site and severity and might become a useful surrogate measure in trials as clinical progression in pure VCI is increasingly revealed to be so slow that trials may otherwise be impractical in all but advanced disease. The important but negative trial of aspirin may illustrate this problem.

**Disclosures**

Dr Gorelick reports serving as a consultant to BMS-Sanofi, Takeda, Pfizer, Savient, Daichi Sankyo, Bayer, Statistical Collaboration; and serving on a Speaker’s Bureau for Boehringer.

**References**


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