

# Stroke

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## **Vascular Contributions to Cognitive Impairment and Dementia : A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association**

Philip B. Gorelick, Angelo Scuteri, Sandra E. Black, Charles DeCarli, Steven M. Greenberg, Costantino Iadecola, Lenore J. Launer, Stephane Laurent, Oscar L. Lopez, David Nyenhuis, Ronald C. Petersen, Julie A. Schneider, Christophe Tzourio, Donna K. Arnett, David A. Bennett, Helena C. Chui, Randall T. Higashida, Ruth Lindquist, Peter M. Nilsson, Gustavo C. Roman, Frank W. Sellke and Sudha Seshadri

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## Vascular Contributions to Cognitive Impairment and Dementia

### A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

*The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.*

*The Alzheimer's Association participated in the development of this statement to advance knowledge and understanding of the causes of dementia and the factors that contribute to its progression.*

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Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and  
Council on Cardiovascular Surgery and Anesthesia

**Background and Purpose**—This scientific statement provides an overview of the evidence on vascular contributions to cognitive impairment and dementia. Vascular contributions to cognitive impairment and dementia of later life are common. Definitions of vascular cognitive impairment (VCI), neuropathology, basic science and pathophysiological aspects, role of neuroimaging and vascular and other associated risk factors, and potential opportunities for prevention and treatment are reviewed. This statement serves as an overall guide for practitioners to gain a better understanding of VCI and dementia, prevention, and treatment.

**Methods**—Writing group members were nominated by the writing group co-chairs on the basis of their previous work in relevant topic areas and were approved by the American Heart Association Stroke Council Scientific Statement Oversight Committee, the Council on Epidemiology and Prevention, and the Manuscript Oversight Committee. The writing group used systematic literature reviews (primarily covering publications from 1990 to May 1, 2010), previously

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\*Writing Group Section Leader.

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published guidelines, personal files, and expert opinion to summarize existing evidence, indicate gaps in current knowledge, and, when appropriate, formulate recommendations using standard American Heart Association criteria. All members of the writing group had the opportunity to comment on the recommendations and approved the final version of this document. After peer review by the American Heart Association, as well as review by the Stroke Council leadership, Council on Epidemiology and Prevention Council, and Scientific Statements Oversight Committee, the statement was approved by the American Heart Association Science Advisory and Coordinating Committee.

**Results**—The construct of VCI has been introduced to capture the entire spectrum of cognitive disorders associated with all forms of cerebral vascular brain injury—not solely stroke—ranging from mild cognitive impairment through fully developed dementia. Dysfunction of the neurovascular unit and mechanisms regulating cerebral blood flow are likely to be important components of the pathophysiological processes underlying VCI. Cerebral amyloid angiopathy is emerging as an important marker of risk for Alzheimer disease, microinfarction, microhemorrhage and macrohemorrhage of the brain, and VCI. The neuropathology of cognitive impairment in later life is often a mixture of Alzheimer disease and microvascular brain damage, which may overlap and synergize to heighten the risk of cognitive impairment. In this regard, magnetic resonance imaging and other neuroimaging techniques play an important role in the definition and detection of VCI and provide evidence that subcortical forms of VCI with white matter hyperintensities and small deep infarcts are common. In many cases, risk markers for VCI are the same as traditional risk factors for stroke. These risks may include but are not limited to atrial fibrillation, hypertension, diabetes mellitus, and hypercholesterolemia. Furthermore, these same vascular risk factors may be risk markers for Alzheimer disease. Carotid intimal-medial thickness and arterial stiffness are emerging as markers of arterial aging and may serve as risk markers for VCI. Currently, no specific treatments for VCI have been approved by the US Food and Drug Administration. However, detection and control of the traditional risk factors for stroke and cardiovascular disease may be effective in the prevention of VCI, even in older people.

**Conclusions**—Vascular contributions to cognitive impairment and dementia are important. Understanding of VCI has evolved substantially in recent years, based on preclinical, neuropathologic, neuroimaging, physiological, and epidemiological studies. Transdisciplinary, translational, and transactional approaches are recommended to further our understanding of this entity and to better characterize its neuropsychological profile. There is a need for prospective, quantitative, clinical-pathological-neuroimaging studies to improve knowledge of the pathological basis of neuroimaging change and the complex interplay between vascular and Alzheimer disease pathologies in the evolution of clinical VCI and Alzheimer disease. Long-term vascular risk marker interventional studies beginning as early as midlife may be required to prevent or postpone the onset of VCI and Alzheimer disease. Studies of intensive reduction of vascular risk factors in high-risk groups are another important avenue of research. (*Stroke*. 2011;42:00-00.)

**Key Words:** AHA Scientific Statements ■ vascular dementia ■ Alzheimer disease ■ risk factors  
■ prevention ■ treatment

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## 1. Introduction

As people live longer, the burden of cognitive impairment in society becomes increasingly important. Although Alzheimer disease is the most commonly diagnosed cause of cognitive dysfunction among the aged, cognitive impairment caused by vascular disease, including subclinical brain injury, silent brain infarction (SBI), and clinically overt stroke are important as independent causes and contributors to cognitive dysfunction. There are challenges in interpreting the literature because of nosology, criteria, and measurement issues, but the construct of vascular contributions to cognitive impairment and dementia is sufficiently important to merit a detailed review.

Our purpose in this scientific statement is to provide an overview of the evidence on vascular contributions to cognitive impairment and dementia. This statement also serves as an overall guide for practitioners to gain a better understanding of vascular cognitive impairment (VCI) and dementia, prevention, and treatment. Writing group members were nominated by the writing group coauthors on the basis of their previous work in relevant topic areas and were approved by the American Heart Association (AHA) Stroke Council Scientific Statement Oversight Committee, the Council on Epidemiology and Prevention, and the Manuscript Oversight Committee. The writing group used systematic literature reviews (primarily covering publications from 1990 to May 1, 2010), previously published guidelines, personal files, and expert opinion to summarize existing evidence, indicate gaps in current knowledge, and, when appropriate, formulate recommendations using standard AHA criteria (Table 1). All members of the writing group had the opportunity to comment on the recommendations and approved the final version of this document. The document also underwent extensive internal peer review by the AHA, as well as review by the Stroke Council leadership, Council on Epidemiology and Prevention Council, and Scientific Statements Oversight Committee, before receiving consideration and approval from the AHA Science Advisory and Coordinating Committee.



Table 1. Applying Classification of Recommendations and Level of Evidence

		SIZE OF TREATMENT EFFECT			
		CLASS I <i>Benefit &gt;&gt;&gt; Risk</i> Procedure/Treatment <b>SHOULD</b> be performed/administered	CLASS IIa <i>Benefit &gt;&gt; Risk</i> Additional studies with <i>focused objectives needed</i> <b>IT IS REASONABLE</b> to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> Additional studies with <i>broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment <b>MAY BE CONSIDERED</b>	CLASS III <i>No Benefit or CLASS III Harm</i>
				Procedure/ Test	Treatment
				COR III: No benefit	No Proven Benefit
				COR III: Harm	Excess Cost w/o Benefit or Harmful
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>
	LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>
	LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>
	Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit is not recommended is not indicated
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		should not be performed/administered/other is not useful/beneficial/effective	associated with excess morbidity/mortality should not be performed/administered/other

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

\*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

In addition, for the clinical trials section, the writing group searched for the key words *vascular cognitive functioning*, *impairment*, and *dementia* in the Cochrane Reviews of Clinical Trials, Cumulative Index to Nursing and Allied Health Literature, AMED Virtual Library, PubMed, and Medline. Subject headings were combined with treatment, including specific therapies. Past guidelines and previous consensus conference proceedings were reviewed, and a search for evidence for nonpharmacological cognitive-enhancing remedies was conducted on the National Institutes of Health National Center for Complementary and Alternative Medicine Web site and the American College of Physi-

cians PIER (Physician's Information and Education Resource) and Elsevier MD Consult databases.

Some of the literature review was based on the expert panel's knowledge of the field and therefore may be subject to bias. Formal search strategies, however, were used as indicated for evaluation of clinical trial information.

The overall prevalence of dementia in affluent countries is 5% to 10% in people ≥65 years of age. The prevalence of Alzheimer disease doubles every 4.3 years, whereas the prevalence of vascular dementia (VaD) doubles every 5.3 years.<sup>1</sup> VCI is also strongly age related.<sup>2</sup> A recent report from Alzheimer's Disease International indicates that in low- to

middle-income countries, the prevalence of dementia is lower in less affluent countries but is still very strongly related to age.<sup>3</sup> Incidence rates are also quite variable and are age related. Age-adjusted rates for Alzheimer disease and VaD are 19.2 and 14.6, respectively, per 1000 person-years.<sup>4</sup>

A significant factor in interpreting the prevalence and incidence figures from Alzheimer disease and VaD pertains to the issue of diagnostic thresholds. Most older studies use the construct of VaD or multi-infarct dementia (MID) in estimating figures. More recently, the construct of VCI has been introduced to capture the entire spectrum of cognitive disorders ranging from mild cognitive impairment to fully developed dementia.<sup>5</sup> As the threshold is expanded, the frequency rates increase accordingly. Growing awareness of the resultant societal burden underlines the need to identify, prevent, and treat overt and covert cerebral vascular brain injury as early as possible.<sup>6</sup> The term *VCI* was proposed to embrace the spectrum of severity from prodrome (vascular cognitive impairment, no dementia [VCIND]) to full-blown manifestations of cognitive impairment, VaD, and the pathological spectrum from “pure” Alzheimer disease through degrees of vascular comorbidity, so-called mixed disease, to “pure” VaD.<sup>7</sup> Importantly, consensus-based recommendations for standardized imaging, cognitive, and pathological protocols have been developed.<sup>5,8</sup>

In addition to the threshold issue, multiple sets of criteria exist for the constructs of VCI and VaD.<sup>9</sup> For example, the more liberal criteria for VaD proposed by Hachinski et al result in large numbers, whereas the more conservative criteria such as those of the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) yield more modest rates.<sup>10,11</sup> An additional factor affecting the estimates of frequency pertains to the role of neuroimaging. Many recent proposals for criteria incorporate neuroimaging as a factor, and this can have a significant influence on frequency figures. A further complicating issue involves the role of combinations of various underlying pathophysiologies. Some studies contend that mixed pathologies, including the degenerative components caused by Alzheimer disease and vascular factors, are the most common explanation for cognitive impairment in aging.<sup>12,13</sup>

Newly proposed criteria for the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* ([www.dsm5.org](http://www.dsm5.org)) may use another term closely aligned with dementia, such as *major neurocognitive disorder*. The prodementia symptomatic stage similar to mild cognitive impairment may be termed *mild neurocognitive disorder*. Memory loss is still a prominent feature of the syndromes in the Alzheimer disease spectrum but is not required for the mild and major diagnoses, because impairment in any cognitive domain, including executive function, is sufficient. Use by clinicians and overall impact, however, remain to be seen.

Meanwhile, population magnetic resonance imaging (MRI) studies have revealed the high prevalence of covert small-vessel disease in the elderly population (23% for silent lacunes<sup>14</sup> and 95% for incidental hyperintensities<sup>15</sup>) associated with increased risk for stroke and dementia. Population-autopsy series verified the high frequency and pathogenetic importance of combined

Alzheimer disease and vascular disease in the expression of dementia as mentioned previously.<sup>16,17</sup>

From the pathological perspective, there is dispute about the role of various types of vascular lesions that contribute to cognitive impairment, including those of the formerly used term *MID*, large cortical infarcts, lacunar infarcts, subcortical white matter disease, strategically placed subcortical infarcts, or a combination of these. Furthermore, vascular lesions can lower the threshold for the clinical manifestation of Alzheimer disease.<sup>16,18</sup> Finally, there is pathological and clinical evidence for cholinergic compromise in both Alzheimer disease and VCI, and cholinesterase inhibitors have been tested for both disorders in clinical trials.

The overall situation is complex yet vitally important if we are to understand, diagnose, and ultimately prevent and treat cognitive impairment caused by vascular disease. The present statement covers the current state of the field with respect to the definitions of Alzheimer disease and VCI, the basic pathophysiological underlying nature of VCI, challenges in defining vascular effects neuropathologically, and the role of neuroimaging in defining clinical presentation and course. In addition, midlife and late-life risk factors are discussed and clinical trials reviewed. Finally, recommendations for the prevention and treatment of VCI are made and directions for the future described.

In this statement, we favor the use of the term *VCI* as defined below to represent the spectrum of cognitive impairment associated with frank stroke, vascular brain injury, or subclinical disease ranging from the least severe to the most severe clinical manifestations. The latter end of the cognitive severity spectrum of VCI has been referred to traditionally as *VaD*. The reader must keep in mind, however, that the definition of cognitive impairment associated with stroke or vascular brain disease has changed over time, and within individual sections of this statement, terms such as *VaD*, *MID*, *poststroke dementia*, or others may be used in accordance with the original source citations used to discuss key points in relation to the disorder.

## 2. Defining Alzheimer Disease and VCI

### 2.1. Evolution of the Terminology

There has been significant evolution of the terminology to characterize the cognitive syndrome associated with risk factors for cerebrovascular disease and its manifestations, especially the description of dementia. Approximately 30 years ago, the term *MID*<sup>11</sup> was used to identify patients who developed dementia after multiple strokes, although it was also used for patients with a single vascular insult. More recently, the term *VaD* has been used, regardless of the pathogenesis of the vascular lesion— ischemic or hemorrhagic or single or multiple infarct(s).<sup>10,19,20</sup>

Cerebrovascular disease can also cause mild cognitive deficits that can affect multiple cognitive functions, and some authors have proposed the term *vascular mild cognitive impairment (VaMCI)*.<sup>21,22</sup> This is the “vascular” equivalent of mild cognitive impairment (MCI) commonly used to identify subjects in the transition from normalcy to Alzheimer disease.<sup>23</sup> By extension, VCI encompasses all the cognitive disorders associated with cerebrovascular disease, from frank demen-



tia to mild cognitive deficits. Simply put, VCI is a syndrome with evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least 1 cognitive domain. The most severe form of VCI is VaD.

## 2.2. Clinical Criteria for the Diagnosis of VaD

The diagnostic criteria for VaD have been particularly important not only as diagnostic tools in clinical practice but also to establish prevalence and incidence in population studies, determine risk factors, and recruit homogenous cohorts for drug trials. The *Diagnostic and Statistical Manual of Mental Disorders*<sup>24</sup> and the International Classification of Diseases<sup>25</sup> provide criteria used for administrative purposes and tracking disease. In some cases there is low accuracy when these criteria are adopted as diagnostic criteria. The NINDS–AIREN<sup>10</sup> and State of California Alzheimer’s Disease Diagnostic and Treatment Centers<sup>19</sup> criteria for VaD are used in research as diagnostic instruments that operationalize specific signs and symptoms of the VaD syndrome. More recently, clinical criteria have been proposed to capture subcortical VaD syndromes.<sup>20</sup>

To date, all diagnostic criteria to characterize cognitive syndromes associated with vascular disease *should* be based on 2 factors: demonstration of the presence of a cognitive disorder (dementia or VaMCI) by neuropsychological testing *and* history of clinical stroke or presence of vascular disease by neuroimaging that suggests a link between the cognitive disorder and vascular disease. There is substantial variability in the approach to these 2 core issues, however. We provide a practical approach to the classification of dementia and VaMCI (Table 2) and propose that the term *VCI* be used for all forms of cognitive disorder associated with cerebrovascular disease, regardless of the pathogenesis (eg, cardioembolic, atherosclerotic, ischemic, hemorrhagic, or genetic).

All of the major criteria for VaD have a different definition of dementia, and this results in challenges in reliability studies.<sup>26</sup> Dementia criteria based on memory deficits are derived from concepts proposed for Alzheimer disease, but these may not be suitable for the dementia syndrome associated with cerebrovascular disease, in which memory-related structures (eg, mesial temporal lobe, thalamus) could be intact, resulting in relatively preserved memory functions.<sup>27,28</sup> Thus, a memory deficit should not be required for the diagnosis of VCI or VaD.<sup>29</sup>

The second critical clinical feature of VaD is determining the relationship of cerebrovascular disease to the cognitive symptoms. To appropriately diagnose VaD, it is critical to identify the presence of cortical or subcortical infarcts or other stroke lesions with neuroimaging, and these should be associated with clinical symptomatology. It may also be important to consider the source of the cardiac or vascular pathology that underlies the cerebrovascular disease associated with VCI to provide more specific clinicopathologic relationships. Although some authors propose that the symptoms should appear within 3 months after a stroke,<sup>30</sup> this is arbitrary, and symptoms may develop after this time frame. In addition, there are patients who have not had a clinical stroke, and severe cerebrovascular disease is evident only in neuroradiological studies.<sup>31,32</sup> Finally, the presence of white matter lesions (WMLs) or leukoaraiosis (rarefaction of the white matter thought to be secondary to small-vessel occlusive disease) is critical for the diagnosis of cerebral autosomal

dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL),<sup>33</sup> a genetic form of VaD in relatively young people. However, WMLs also occur in older subjects and patients with Alzheimer disease in epidemiological studies.<sup>34</sup> Therefore, although the presence of WMLs has less diagnostic value in the elderly, WMLs could be the only neuroimaging finding in younger people with cognitive deficits secondary to cerebrovascular disease. For example, WMLs with or without infarcts are associated with cognitive deficits and neuropsychiatric disorders in patients with autoimmune disorders (eg, systemic lupus erythematosus, Sjögren disease).<sup>35,36</sup>

## 2.3. Heterogeneity of the VaD Syndrome

VaD can coexist with multiple cerebral and systemic disorders that can affect cognition in the elderly, especially Alzheimer disease. *Therefore, it is often difficult to determine whether the cognitive deterioration is solely a consequence of vascular factors or underlying Alzheimer disease.*<sup>37</sup> Several studies have found that in patients with Alzheimer disease and cerebrovascular disease, less Alzheimer disease pathology is needed to express the dementia syndrome.<sup>16,18</sup> This synergistic effect between Alzheimer disease and cerebrovascular disease pathology may explain why patients with mesial temporal lobe atrophy, presumably attributable to Alzheimer disease, have an increased risk of dementia after stroke compared with those without atrophy, because hippocampal atrophy may also be caused by vascular disease.<sup>38,39</sup> This is the most difficult aspect of the clinical characterization of VaD, because the Alzheimer disease clinical syndrome can begin after a stroke, or patients with Alzheimer disease symptomatology can have strokes during the course of the disease. The present statement proposes to use the term *probable* to characterize the most “pure” forms of VaD and the term *possible* when the certainty of the diagnosis is diminished or the vascular syndrome is associated with another disease process that can cause cognitive deficits. Future studies using specific ligands for amyloid may help clarify the dynamic relationship between Alzheimer disease and VaD.

We now shift our focus from VaD to less severe forms of VCI.

## 2.4. Mild VCI

The term *amnestic MCI* has been used to identify people at risk for Alzheimer disease. Although initially the term *MCI* applied solely to amnestic forms of the syndrome,<sup>23</sup> further studies found that these subjects had deficits in multiple cognitive domains.<sup>40,41</sup> Therefore, the current nomenclature for MCI is much broader and includes amnestic MCI, amnestic MCI plus other cognitive deficit, nonamnestic single domain, and nonamnestic multiple domains.<sup>42</sup> Because epidemiological studies detected executive deficits in subjects with subcortical vascular pathology,<sup>43</sup> it was recommended that VaMCI should be characterized by deficits in executive functions as memory could be normal.<sup>21</sup> However, clinical studies have shown that subjects with VaMCI can present with a broader cognitive impairment, which can also include memory deficits.<sup>22</sup> These definitions are primarily applied in research studies but may provide an initial useful platform for classifying patients in practice.

**Table 2. Vascular Cognitive Impairment**

- 
1. The term *VCI* characterizes all forms of cognitive deficits from VaD to MCI of vascular origin.
  2. These criteria cannot be used for subjects who have an active diagnosis of drug or alcohol abuse/dependence. Subjects must be free of any type of substance for at least 3 months.
  3. These criteria cannot be used for subjects with delirium.
- Dementia**
1. The diagnosis of dementia should be based on a decline in cognitive function from a prior baseline and a deficit in performance in  $\geq 2$  cognitive domains that are of sufficient severity to affect the subject's activities of daily living.
  2. The diagnosis of dementia must be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: executive/attention, memory, language, and visuospatial functions.
  3. The deficits in activities of daily living are independent of the motor/sensory sequelae of the vascular event.
- Probable VaD**
1. There is cognitive impairment and imaging evidence of cerebrovascular disease and
    - a. There is a clear temporal relationship between a vascular event (eg, clinical stroke) and onset of cognitive deficits, or
    - b. There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology (eg, as in CADASIL).
  2. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder.
- Possible VaD**
- There is cognitive impairment and imaging evidence of cerebrovascular disease but
1. There is no clear relationship (temporal, severity, or cognitive pattern) between the vascular disease (eg, silent infarcts, subcortical small-vessel disease) and the cognitive impairment.
  2. There is insufficient information for the diagnosis of VaD (eg, clinical symptoms suggest the presence of vascular disease, but no CT/MRI studies are available).
  3. Severity of aphasia precludes proper cognitive assessment. However, patients with documented evidence of normal cognitive function (eg, annual cognitive evaluations) before the clinical event that caused aphasia *could* be classified as having probable VaD.
  4. There is evidence of other neurodegenerative diseases or conditions in addition to cerebrovascular disease that may affect cognition, such as
    - a. A history of other neurodegenerative disorders (eg, Parkinson disease, progressive supranuclear palsy, dementia with Lewy bodies);
    - b. The presence of Alzheimer disease biology is confirmed by biomarkers (eg, PET, CSF, amyloid ligands) or genetic studies (eg, *PS1* mutation); or
    - c. A history of active cancer or psychiatric or metabolic disorders that may affect cognitive function.
- VaMCI**
1. VaMCI includes the 4 subtypes proposed for the classification of MCI: amnesic, amnesic plus other domains, nonamnesic single domain, and nonamnesic multiple domain.
  2. The classification of VaMCI must be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: executive/attention, memory, language, and visuospatial functions. The classification should be based on an assumption of decline in cognitive function from a prior baseline and impairment in at least 1 cognitive domain.
  3. Instrumental activities of daily living could be normal or mildly impaired, independent of the presence of motor/sensory symptoms.
- Probable VaMCI**
1. There is cognitive impairment and imaging evidence of cerebrovascular disease and
    - a. There is a clear temporal relationship between a vascular event (eg, clinical stroke) and onset of cognitive deficits, or
    - b. There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology (eg, as in CADASIL).
  2. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder.
- Possible VaMCI**
- There is cognitive impairment and imaging evidence of cerebrovascular disease but
1. There is no clear relationship (temporal, severity, or cognitive pattern) between the vascular disease (eg, silent infarcts, subcortical small-vessel disease) and onset of cognitive deficits.
  2. There is insufficient information for the diagnosis of VaMCI (eg, clinical symptoms suggest the presence of vascular disease, but no CT/MRI studies are available).
  3. Severity of aphasia precludes proper cognitive assessment. However, patients with documented evidence of normal cognitive function (eg, annual cognitive evaluations) before the clinical event that caused aphasia *could* be classified as having probable VaMCI.
  4. There is evidence of other neurodegenerative diseases or conditions in addition to cerebrovascular disease that may affect cognition, such as
    - a. A history of other neurodegenerative disorders (eg, Parkinson disease, progressive supranuclear palsy, dementia with Lewy bodies);
    - b. The presence of Alzheimer disease biology is confirmed by biomarkers (eg, PET, CSF, amyloid ligands) or genetic studies (eg, *PS1* mutation); or
    - c. A history of active cancer or psychiatric or metabolic disorders that may affect cognitive function.
- Unstable VaMCI**
- Subjects with the diagnosis of probable or possible VaMCI whose symptoms revert to normal should be classified as having "unstable VaMCI."
- 

VCI indicates vascular cognitive impairment; VaD, vascular dementia; MCI, mild cognitive impairment; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CT/MRI, computed tomography/magnetic resonance imaging; PET, positron emission tomography; CSF, cerebrospinal fluid; and VaMCI, vascular mild cognitive impairment.



## 2.5. Reversibility of VaMCI

Several studies have shown that patients with MCI can return to normal cognition. These people have multiple disease processes that may improve with or without specific treatments, such as depression, heart failure, or autoimmune disorders.<sup>44–46</sup>

Cerebrovascular disease with or without clinical strokes can be associated with depression.<sup>47,48</sup> This raises an important issue for VaMCI, because these behaviors (depression or depressive symptoms) can severely influence patients' activities of daily living and cognitive performance, although some symptoms can revert with treatment (eg, depression), and consequently cognition can improve. This means that there may be a "reversibility" component in VaMCI.<sup>47,48</sup> An added component of VaMCI is poststroke recovery. Patients who are seen soon after stroke may show cognitive impairment. In some of these patients, cognition may improve as part of the stroke recovery process.

## 2.6. Neuropsychological Assessments of VCI

The 2006 NINDS–Canadian Stroke Council VCI harmonization standards suggested different neuropsychological protocols for use in patients with suspected VCI.<sup>5</sup> Detailed discussion of these protocols is beyond the scope of this statement, and the reader is referred to the source reference by Hachinski et al<sup>5</sup> for suggestions for cognitive batteries that may be applied in practice.

The neuropsychological assessment of patients with suspected VCI requires a comprehensive cognitive battery. Executive function has long been considered a salient feature of the disorder and should be included in the neuropsychological battery.<sup>21</sup> Operational definitions of cognitive impairment (eg, performance 1 or 1.5 standard deviations below that of an appropriate comparison group) are preferred over qualitative descriptions of cognitive symptoms.

Attempts to use neuropsychological assessment to differentiate Alzheimer disease from VCI have met with mixed success. Executive dysfunction has not been shown to specifically point to cerebrovascular disease, whereas a pattern of memory deficits may be associated more with Alzheimer disease and its associated pathology than with cerebrovascular disease.<sup>49,50</sup> This research area is complicated by the difficulty of clinically differentiating Alzheimer disease or VCI from mixed (Alzheimer disease plus cerebrovascular disease) disease, which may be more common than either "pure" Alzheimer disease or "pure" VCI.<sup>9</sup> In addition, the heterogeneity of cerebrovascular disease (eg, strokes that differ in location, size, and number) works against a single, unifying neurocognitive pattern of deficits in VCI.

## 2.7. Summary

Traditionally, terms such as *MID* or *VaD* have been used in the classification of cognitive impairment associated with stroke. With newer research classification systems, the term *VCI* is now preferred. VCI represents a syndrome taking into account the spectrum of cognitive severity, which often includes executive dysfunction and the various types of brain vascular disease that could underlie cognitive symptoms,

including subclinical vascular brain injury. The most severe form of VCI is VaD, and new subtypes with milder cognitive symptoms (eg, VaMCI) are being defined. The use of the VCI classification system may prove to be useful for clinicians in practice as they consider pathogenesis and ultimately prevention and treatment of the patient with cognitive impairment. A key to defining the spectrum of VCI is neuropsychological testing, bedside or office clinical examination, and neuroimaging (Table 2).

## 3. Neuropathological Aspects

For decades it has been recognized that cerebrovascular disease is associated with dementia,<sup>11,51</sup> yet defining the pathology underlying VCI has remained elusive.<sup>2,5,52</sup> There are many complexities. For instance, infarcts vary in size, number, and location; occur commonly in older people with and without dementia<sup>13,39,53–56</sup>; often are not associated with clinical stroke<sup>2,39,51,53</sup>; and typically are accompanied by Alzheimer disease and other pathologies.<sup>12,13,16,17,54–57</sup> Many of these obstacles can be navigated by studying people with and without dementia from community-based cohort studies, with clinical data proximate to death, and quantitative measurements of vascular and Alzheimer disease pathologies. Such studies<sup>12,13,16,17,39,53–57</sup> are accumulating and provide new insights into the pathological substrates of VCI and dementia and the importance of vascular pathology or brain injury.

### 3.1. Cerebral Infarctions Are Very Common in Older People

The most important cerebrovascular pathology that contributes to cognitive impairment is cerebral infarcts. Cerebral infarcts are discrete regions of tissue loss observed by the naked eye (macroscopic) or under the microscope (microscopic). Clinical-pathological studies typically focus on chronic (old) infarcts because cognitive evaluations are often performed months before death; the trajectory of cognitive impairment from a recent infarct may be difficult to ascertain; and recent infarcts may be related to perimortem factors. Chronic macroscopic infarcts are very common, occurring in approximately one third to one half of older people,<sup>13,54–56</sup> a frequency far greater than the frequency of clinical stroke. In some community-based studies, microscopic infarcts are more common than macroscopic infarcts.<sup>13,56</sup> In 1 study,<sup>55</sup> the inclusion of other measures of vascular pathology such as microscopic infarcts, small-vessel disease, and white matter changes increased the frequency of cerebrovascular disease in older people to >75%.

### 3.2. Cerebral Infarctions and VCI

In clinical-pathological studies, larger volumes<sup>39,51</sup> and an increased number<sup>11,13,39,55,56</sup> of macroscopic infarcts are associated with an increased likelihood of dementia. However, determining the volume or number necessary for VCI or dementia has proved difficult, and unlike with Alzheimer disease and other neurodegenerative diseases, there are no currently accepted neuropathological criteria to confirm a clinical diagnosis of VCI. Indeed, although Tomlinson et al described 100 mL of tissue loss as sufficient for dementia, those with lesser volumes of loss also had dementia.<sup>51</sup> Studies have

generally shown an inconsistent relation between volume and number of infarcts and cognitive impairment.<sup>13,58</sup> Some of these inconsistencies may relate to infarct location. Regions such as the thalamus, angular gyrus, and basal ganglia may be more likely than other regions to result in cognitive impairment.<sup>2,58,59</sup> However, regional factors have not been clearly defined, and diverse cortical<sup>13,39,56</sup> and subcortical<sup>13,16,58,59</sup> regional infarcts have been related to dementia.

Further challenging these relationships, some studies suggest that multiple microscopic infarcts are related to dementia, even after accounting for macroscopic infarcts.<sup>13,56</sup> Multiple microscopic infarcts may denote a more generalized phenomenon such as diffuse hypoxia, inflammation, oxidative stress, or disruption in the blood-brain barrier (BBB). Other factors governing whether infarcts are related to impairment may include variance in cognitive reserve<sup>60</sup> and coexisting pathologies.

### 3.3. Relation of Infarcts to Alzheimer Disease Pathology and Dementia

Infarcts frequently coexist with Alzheimer disease pathology in the brains of older people.<sup>12,13,16,17,54–57</sup> In addition, most people with dementia<sup>12</sup> and almost half of those with clinically probable Alzheimer disease<sup>61</sup> have mixed pathology, most commonly Alzheimer disease and infarcts. Although there are no pathological criteria to confirm mixed dementia, studies show that infarcts in a brain with Alzheimer disease pathology are not innocuous. One study showed that only people with Alzheimer disease pathology with subcortical infarcts had dementia, raising the possibility of an interaction (a multiplicative effect) between the 2 pathologies.<sup>16</sup> Although the specific importance of subcortical infarcts and interaction has not been confirmed, subsequent studies have established that infarcts are additive with Alzheimer disease pathology in lowering cognitive function<sup>17,57</sup> and increasing the odds of dementia<sup>17,18,62,63</sup> or clinical Alzheimer disease.<sup>61</sup> Moreover, disturbances of episodic memory, considered the hallmark of Alzheimer disease, are associated with infarcts even after accounting for Alzheimer disease pathology.<sup>17,59</sup>

There are multiple implications. First, because they are often clinically unrecognized, the public health importance of infarcts and their role in dementia is likely underestimated. Second, risk factors for infarcts may be erroneously linked to the episodic memory and classic phenotype of clinical Alzheimer disease. Third, prevention and therapies that decrease cerebral infarcts are likely to lower the prevalence of clinically diagnosed dementia.

### 3.4. Relation of Infarcts to Alzheimer Disease Pathology and MCI

Few studies have examined the pathological basis of MCI.<sup>53,61,64–69</sup> Alzheimer disease has been found to be the most common pathology,<sup>61,65,66,69</sup> but mixed pathologies are also common.<sup>61,65–69</sup> In 1 study the frequency of pure infarct and mixed Alzheimer disease and infarct pathology was comparable to the frequency of pure Alzheimer disease pathology in both amnesic and nonamnesic MCI.<sup>61</sup> Thus, assuming the underlying neuropathological substrate of amnesic MCI is

pure Alzheimer disease pathology rather than vascular or mixed pathology, the role of vascular pathology may be underestimated.

### 3.5. Other Vascular Pathologies

There are other common vascular pathologies in the brains of older people, including white matter degeneration<sup>70,71</sup> and primary vessel disease (ie, arteriolosclerosis/lipohyalinosis, atherosclerosis, and cerebral amyloid angiopathy [CAA]).<sup>70,72,73</sup> Cerebral microbleeds, visualized by new imaging techniques, also appear to be a common vascular abnormality.<sup>74–77</sup> White matter degeneration and microbleeds most likely reflect direct tissue damage,<sup>71,78–80</sup> whereas primary vessel disease may be associated with focal (eg, infarct) or diffuse tissue damage (eg, white matter degeneration) or may result in nonmorphologic functional changes. Although neuroimaging studies<sup>70,76,77,81</sup> suggest a role for white matter degeneration and microbleeds in cognitive impairment, it is currently unclear whether these additional pathologies represent separate pathological substrates for VCI. In some studies, neuropathological measurements of WMLs have not been clearly associated with cognitive function unless as part of a combined vascular score that also includes infarcts.<sup>52</sup> Quantitative studies of multiple vascular pathologies in older people with and without dementia with clinical evaluation proximate to death are needed to determine the separate roles of these vascular pathologies in VCI and other dementias.

### 3.6. Neuroimaging and Pathology: Future Directions

Neuroimaging studies provide an excellent tool for identifying many types of vascular pathologies in older people through accurate determination of brain anatomy by high-resolution T1 but also tissue changes that can be quantified by fluid-attenuated inversion recovery, diffusion tensor, magnetization transfer, and even neurochemical changes with hydrogen spectroscopy. However, postmortem evaluations continue to complement neuroimaging studies in several important ways. First, neuroimaging detects macroscopic infarcts,  $\approx 3$  mm or more in size, but microscopic infarcts and small-vessel disease (eg, arteriolosclerosis) are currently not within the resolution of most scans. Second, some vascular pathologies may represent either vascular or degenerative processes. For instance, neuroimaging studies have shown that white matter degeneration, as measured by both fluid-attenuated inversion recovery and diffusion tensor imaging, and microbleeds are associated with both VCI and clinical Alzheimer disease,<sup>70,72,76,77,81</sup> and pathological studies demonstrate white matter degeneration and microbleeds are related to lipohyalinosis.<sup>58,70,79,80</sup> In addition, though, white matter degeneration is related to Alzheimer disease pathology<sup>78</sup> and microbleeds to CAA. Hippocampal volume visualized on antemortem neuroimaging may also be related to either Alzheimer disease or vascular pathology,<sup>82</sup> and pathological studies show that the hippocampus can atrophy as part of both degenerative or vascular processes.<sup>83</sup> Thus, white matter degeneration and microbleeds on MRI often considered specific for vascular disease may signify degenerative

pathology, although recent pathological studies show no relationship between WMLs as measured by MRI and Alzheimer disease neuropathology,<sup>82</sup> whereas hippocampal volume loss, often considered a specific biomarker for early Alzheimer disease,<sup>84</sup> may reflect vascular pathology. These data emphasize the need for prospective quantitative clinical-pathological-neuroimaging studies to fully understand the pathological bases of neuroimaging change. Furthermore, they highlight the complex interplay between vascular and Alzheimer disease pathologies in the evolution of VCI, dementia, and clinical Alzheimer disease.

### 3.7. Summary

The interplay between macroscopic and microscopic infarcts and other vascular and degenerative pathologies in the development of clinical Alzheimer disease and VCI is complex. Vascular and degenerative pathologies are 2 common disorders in later life and often coexist, and each separately adds to the likelihood of cognitive impairment and dementia. In addition, vascular and degenerative pathologies may result in overlapping clinical and imaging phenotypes. Longitudinal clinical-pathological-neuroimaging studies hold promise to help us better understand the pathophysiology and phenotypes of these common disorders of cognition in later life, which may lead to improved prevention and treatment strategies.

## 4. Basic Science Aspects: Importance of the Neurovascular Unit and Cerebral Blood Flow

Neurons, glia, and perivascular and vascular cells, collectively termed the *neurovascular unit*, are structurally, functionally, and developmentally interrelated and work in concert to maintain the homeostasis of the cerebral microenvironment.<sup>85</sup> Alterations in neurovascular function are involved in the pathogenesis of VCI.

### 4.1. The Neurovascular Unit and Brain Homeostasis

The brain depends on a continuous blood supply, and interruption of cerebral blood flow (CBF) leads to brain dysfunction and death.<sup>86</sup> Consequently, sophisticated cerebrovascular control mechanisms ensure that the brain's blood supply is well matched to its energy requirements.<sup>87</sup> Thus, neural activity induces a powerful increase in CBF (functional hyperemia) that is thought to deliver energy substrates and remove toxic byproducts of brain activity.<sup>88</sup>

Cerebrovascular autoregulation keeps CBF relatively constant within a range of blood pressures, protecting the brain from unwanted swings in perfusion pressure.<sup>89</sup> Specialized receptors on endothelial cells transduce mechanical (shear stress) and chemical stimuli and release potent signaling molecules such as nitric oxide, endothelin, and prostanoids.<sup>90</sup> These endothelial mediators subserve functions as varied as local flow distribution,<sup>91</sup> immune surveillance (in concert with perivascular cells),<sup>92</sup> and hemostatic balance.<sup>93</sup>

The tight junctions between cerebral endothelial cells, coupled with highly specialized membrane transporters, regulate the trafficking of molecules between blood and brain, which is at the basis of the BBB.<sup>94</sup> Conversely, transporters on the abluminal side of the vessels remove metabolic

byproducts from the brain, including amyloid beta ( $A\beta$ ).<sup>95</sup> Endothelial cells exert trophic actions that are critical in brain development, neuroplasticity, and repair when endothelial growth factors orchestrate the migration and differentiation of neuroblasts.<sup>96–99</sup>

### 4.2. The Neurovascular Unit: A Target of Vascular and Neurodegenerative Dementias

The neurovascular unit is profoundly disrupted in VCI and Alzheimer disease.<sup>95,100–103</sup> The present section will focus on the microvascular changes associated with cerebrovascular disease and neurodegeneration. The alterations that occur in the structure and function of large cerebral arteries are discussed elsewhere in this statement. VCI and Alzheimer disease are associated with marked alterations in cerebral microvascular structure.<sup>104,105</sup> Microvessels have thickened basement membranes, become tortuous, and are reduced in number.<sup>71,105–107</sup> Arterioles exhibit signs of “onion skin”-type changes and undergo hyaline degeneration (lipohyalinosis), a cause of microhemorrhages.<sup>105</sup> In the vulnerable periventricular white matter, reactive astrocytosis and microglial activation are associated with expression of hypoxia-inducible genes, suggesting local hypoxia.<sup>71,108</sup>

As examined in the next section, in Alzheimer disease and CAA, accumulation of  $A\beta$  in the media of cortical arterioles weakens the vessel wall and increases the chance of lobar hemorrhages.<sup>109</sup> In animal models, the major risk factors for VCI and Alzheimer disease—hypertension, aging, and diabetes<sup>110</sup>—impair endothelium-dependent responses in the cerebral microcirculation and blunt functional hyperemia.<sup>101,111,112</sup>  $A\beta$  is a potent vasoconstrictor<sup>113,114</sup> and suppresses endothelium-dependent responses, functional hyperemia, and cerebrovascular autoregulation.<sup>115–117</sup> Cerebral smooth muscle cells of patients with Alzheimer disease have increased constrictor tone,<sup>118</sup> which may contribute to the CBF reduction observed in this condition.<sup>100</sup>

### 4.3. Mechanisms of Neurovascular Dysfunction: Role of Oxidative Stress and Inflammation

Vascular oxidative stress and inflammation are key pathogenic factors in neurovascular dysfunction.<sup>101,119–121</sup> Experimental studies suggest that radicals produced by the enzyme nicotinamide adenine dinucleotide phosphate oxidase are responsible for the cerebrovascular alterations induced by VCI risk factors and  $A\beta$ .<sup>112,122–124</sup> Although free radicals can induce inflammation by activating redox-sensitive proinflammatory transcription factors, the endothelial dysfunction induced by oxidative stress can release vascular endothelial growth factor and prostanoids, which promote vascular leakage, protein extravasation, and cytokine production.<sup>125</sup> Inflammation, in turn, enhances oxidative stress by upregulating the expression of reactive oxygen species-producing enzymes and downregulating antioxidant defenses.<sup>126</sup>

White matter BBB alterations are early findings in VCI.<sup>127</sup> In models of autoimmune white matter injury, extravasation of plasma protein triggers vascular inflammation and axonal demyelination,<sup>127</sup> which in turn disrupts saltatory conduction,<sup>128</sup> slowing the transmission of nerve impulses. In addition,



tion, loss of energy-saving saltatory conduction increases metabolic demands and enhances local energy deficit and hypoxia.<sup>128</sup> A similar process may contribute to the WMLs observed in Alzheimer disease and VCI, which play a prominent role in the expression of dementia.<sup>110</sup>

In addition, the low-density lipoprotein receptor-related protein-1, a critical  $A\beta$  brain clearance receptor, is downregulated in cerebral blood vessels of patients with Alzheimer disease, leading to accumulation of amyloid around blood vessels and worsening of vascular dysfunction.<sup>129</sup> Plasma  $A\beta$ , which is elevated in some patients with VCI and Alzheimer disease, induces cerebrovascular insufficiency and could play a role in the white matter alterations observed in both conditions.<sup>130,131</sup> Vascular oxidative stress and inflammation impede the proliferation, migration, and differentiation of oligodendrocyte progenitor cells and compromise repair of the damaged white matter.<sup>108,132,133</sup> Furthermore, loss of growth factors, such as the brain-derived neurotrophic factor,<sup>96</sup> may contribute to the brain atrophy associated with Alzheimer disease and VCI.<sup>134,135</sup>

#### 4.4. Animal Models of VCI

Although there are relatively few animal models of cognitive impairment and white matter damage, models recapitulating features of CAA, CADASIL, cerebral hypoperfusion, and hypertensive vasculopathy have been developed, mainly in rodents.<sup>5</sup> However, it has proved difficult to reproducibly induce white matter damage and behavioral dysfunction by lowering CBF in a spatial-temporal pattern consistent with the human disease. Furthermore, little has been learned about the effects of BBB alterations and microvascular inflammation on the structure and function of white matter. Rodent models, although well suited to genetic manipulations and large-scale studies, can be problematic because of their small amount of white matter and limited behavioral repertoire. Models in higher-order species would be desirable because of the more complex behaviors and extensive white matter pathology that can be explored. Studies using these models to investigate the effects of CBF, microvascular inflammation, and BBB alterations on white matter and behavior should be a priority for the field.

#### 4.5. Summary

1. There is increasing evidence that alterations in neurovascular function play a key role not only in the pathobiology of VCI but also in Alzheimer disease.
2. The neurovascular unit is a major target of the deleterious effects of vascular risk factors promoting VCI and Alzheimer disease and of  $A\beta$ .
3. Neurovascular dysfunction increases the brain's susceptibility to injury by (a) altering regulation of the cerebral blood supply, (b) disrupting BBB function, and (c) reducing the trophic support and repair potential of the injured brain.
4. Vascular oxidative stress and inflammation underlie many of these deleterious effects and are potential therapeutic targets.
5. Therapies that enhance regenerative and reparative phenomena may also be beneficial, but our understand-

ing is still limited and requires further inquiry. Use of viable animal models to explore the factors linking CBF, microvascular inflammation, and BBB dysfunction to white matter damage and behavioral deficits can provide mechanistic and therapeutic insights, and the development of these models should be eagerly pursued. In the absence of mechanism-based therapies to treat vascular and neurodegenerative dementia, approaches aimed at maintaining cerebrovascular health by controlling vascular risk factors are anticipated to be extremely valuable.

## 5. Cerebral Amyloid Angiopathy and Hereditary Small-Vessel Syndromes

### 5.1. Cerebral Amyloid Angiopathy and Vascular Effects of $A\beta$

Deposition of  $A\beta$  peptide in the walls of penetrating arterioles and capillaries of the leptomeninges and cortex is the hallmark of sporadic CAA, a common pathology in the elderly. CAA appears in  $\approx 10\%$  to  $30\%$  of unselected brain autopsies and  $80\%$  to  $100\%$  when in the presence of accompanying Alzheimer disease.<sup>136</sup> Advanced CAA can trigger a series of destructive changes in the vessel wall, including loss of smooth muscle cells, development of microaneurysms, and concentric splitting and fibrinoid necrosis of the vessel wall and perivascular leakage of red blood cells.<sup>137–139</sup>

Although CAA is most commonly recognized as a cause of spontaneous intracerebral hemorrhage, there is growing evidence that it is an important contributor to age-related cognitive impairment as well. Population-based clinical-pathological studies have identified associations between advanced CAA and worse cognitive performance, and these associations remain independent after controlling for severity of Alzheimer disease pathology.<sup>55,140,141</sup> The precise pathogenic mechanisms responsible for this association have not been established. Possible explanations include radiographic lesions seen in advanced CAA, such as microbleeds,<sup>142</sup> microinfarcts,<sup>143–146</sup> WMLs on computed tomography or MRI,<sup>147,148</sup> and altered fractional anisotropy or mean diffusivity on diffusion tensor MRI.<sup>149</sup> CAA can also trigger vascular or perivascular inflammation,<sup>150,151</sup> manifesting as vasogenic edema of subcortical white matter and more rapidly progressive cognitive decline.<sup>152</sup>

In the absence of direct neuropathological assessment, CAA is most commonly diagnosed by the detection of hemorrhages confined to cortical or cortico-subcortical (“lobar”) brain regions. The presence of multiple strictly lobar hemorrhages in the absence of other definite causes such as head trauma, brain tumor, or supratherapeutic anticoagulation has been defined by the Boston criteria as “probable CAA” and validated against neuropathologically or genetically diagnosed CAA.<sup>153,154</sup> T2\*-weighted gradient-echo MRI sequences provide substantially increased sensitivity for detection of cerebral microbleeds and are key to the diagnosis of probable CAA. Other potential diagnostic approaches have been explored, including detection of reduced  $A\beta$  in cerebrospinal fluid<sup>155</sup> or increased retention of the amyloid ligand Pittsburgh Compound B on positron emission tomography imaging.<sup>156,157</sup> Pittsburgh Compound B retention is not specific for CAA as opposed to

Alzheimer disease, because the compound binds to both vascular and parenchymal amyloid<sup>158</sup>; however, the 2 pathologies may be distinguishable in part by the relative occipital predominance of labeling in CAA.<sup>156,157</sup>

No treatments have been identified to successfully prevent or slow cognitive impairment caused by noninflammatory CAA. A recent study found an association between coincident hypertension and larger volumes of WMLs in patients with CAA,<sup>159</sup> raising the intriguing (but unproven) possibility that blood pressure control may be beneficial. For the subset of patients with CAA-related inflammation, treatment with a course of high-dose corticosteroids or cyclophosphamide has been reported to cause clinical and radiological improvement.<sup>152</sup>

Beyond the effects of A $\beta$  deposits in CAA, soluble A $\beta$  itself may also trigger altered vascular reactivity and brain injury. As discussed in the previous section, evidence for this possibility comes from animal models in which exogenously applied or genetically overexpressed A $\beta$  production diminished vasodilation to pharmacological or physiological stimuli, even in the absence of vascular A $\beta$  deposits.<sup>115,160,161</sup> Because A $\beta$  concentration may be manipulated via direct<sup>160</sup> or indirect<sup>162</sup> metabolic pathways, these experiments raise the intriguing possibility that A $\beta$ -induced vascular dysfunction might prove treatable. This possibility, however, has not been tested in human studies.

## 5.2. Hereditary Small-Vessel Syndromes

The most commonly encountered hereditary cause of VCI is CADASIL. This disorder can present clinically as migraines with aura, mood disturbances, recurrent strokes, or cognitive impairment<sup>163</sup> and radiographically by the appearance of extensive WMLs, lacunar infarcts, microbleeds, and brain atrophy.<sup>164</sup> Nearly all cases of CADASIL are caused by missense mutations of the *Notch3* gene that either create or eliminate cysteine residues.<sup>165</sup> Identification of such mutations, which can also occur de novo in sporadic cases of CADASIL,<sup>166,167</sup> has become the primary method of diagnosis. Most CADASIL patients also appear to demonstrate characteristic ultrastructural changes in skin and muscle vessels, in particular the deposition of granular osmiophilic material in the arteriolar media.<sup>168–170</sup> Although no treatments have been identified to modify the course of CADASIL, it is notable that cardiovascular risk factors such as hypertension, elevated hemoglobin A1c, and smoking may be associated with a worse clinical and radiographic phenotype.<sup>171,172</sup>

Other hereditary small-vessel syndromes of the brain are rare and have generally not been reported as causes of sporadic disease via de novo mutation. These syndromes include familial CAA caused by mutations or duplications of the *APP*  $\beta$ -amyloid precursor protein gene,<sup>173–175</sup> autosomal dominant retinal vasculopathy with cerebral leukodystrophy caused by frameshift deletions in the exonuclease *TREX1*,<sup>176</sup> and cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy caused by missense or nonsense mutations of the transforming growth factor- $\beta$ 1 repressor *HTRA1*.<sup>177</sup> Mutations of the *COL4A1* type IV collagen subunit gene have also been reported in association with congenital porencephaly, leukoencephalopathy, or intracerebral hemorrhage.<sup>178,179</sup> Of note, a single nucleotide poly-

morphism in the *COL4A1* gene was associated with pulse wave velocity, an index of arterial stiffness, in a population.<sup>180</sup>

## 5.3. Summary

CAA appears to be a relatively common and important contributor to age-related small-vessel dysfunction and VCI. Diagnostic approaches to CAA (and to CADASIL, the most common form of hereditary small-vessel disease) have improved, but no disease-modifying therapies have been identified. Coexisting vascular risk factors such as hypertension, diabetes, and smoking may worsen the effects of CAA and CADASIL and are therefore plausible targets for treatment.

## 5.4. Recommendations

1. It is reasonable to use MRI with T2\*-weighted gradient-echo sequences in patients with progressive cognitive impairment for detection of the multiple strictly lobar hemorrhagic lesions characteristic of probable CAA (*Class IIa; Level of Evidence B*).
2. It is reasonable to perform genetic testing for cysteine-altering mutations in *Notch3* in patients with progressive cognitive impairment, characteristic imaging findings, and a family history suggestive of autosomal dominant inheritance (*Class IIa; Level of Evidence A*).
3. *Notch3* testing may also be considered in sporadic patients with suggestive clinical and imaging findings, particularly in the absence of strong cardiovascular risk factors (*Class IIb; Level of Evidence B*).
4. If genetic testing is either unavailable or demonstrates *Notch3* mutations of unclear significance, ultrastructural examination of skin or muscle biopsy specimen for granular osmiophilic deposits may be considered as an alternative or complementary procedure (*Class IIb; Level of Evidence B*).
5. In suspected CAA or CADASIL, treatment of cardiovascular risk factors is reasonable (*Class IIa; Level of Evidence C*).
6. Patients with subacute cognitive decline and evidence of CAA-related inflammation should be treated with a course of immunosuppressive therapy such as corticosteroids or cyclophosphamide (*Class I; Level of Evidence B*).

## 6. Pathophysiology of Arterial Structure and Function

Vascular aging is well exemplified by the strong relationship between age and changes in large-artery structure and function.<sup>181</sup> Several arterial parameters have been selected for clinical investigation, based on the feasibility and repeatability of their measurement and their predictive value of cardiovascular events.<sup>182</sup> They include carotid wall thickening and aortic stiffening, which also likely reflect *atherosclerosis* and *arteriosclerosis*, respectively. Recently a large number of studies have reported strong relationships between indices of vascular aging and either cognitive impairment or silent cerebral small-vessel disease. That these relationships were independent of age and classic cardiovascular risk factors suggests common pathophysiological mechanisms linking large-artery damage to cerebral small-vessel disease.

### 6.1. Carotid Intima-Media Thickness and VCI

Although a number of disease states can lead to vessel wall thickening,<sup>143</sup> cyclic vessel distention in normal aging (ie, beat-to-beat change in vessel diameter in response to the pulsatility of blood pressure) is thought to cause fragmentation and depletion of elastin and increased collagen deposition, resulting in a nearly 3-fold increase in intima-media thickness (IMT) between the ages of 20 and 90 years.<sup>145</sup> The lumen-intima and media-adventitia separation can be determined to within  $\approx 0.1$  mm on longitudinal B-mode ultrasound images of the extracranial carotid arteries where these interfaces are readily apparent.<sup>183,184</sup>

The relationship between carotid IMT and cognitive function has been analyzed cross-sectionally<sup>185,186</sup> and longitudinally<sup>187–189</sup> in few studies. The studies were heterogeneous for the study population (small groups, sex composition, healthy subjects or affected by Alzheimer-type dementia), the definition of carotid IMT (mean of left and right common carotid artery, IMT at bifurcation, sum of IMT at multiple carotid sites), and the neuropsychological test adopted to evaluate cognition (single or repeated measures of the Mini Mental State Examination [MMSE], a neuropsychological battery with specific tests for different cognitive domains). Despite this heterogeneity, a significant inverse relationship between carotid IMT and cognitive function was observed in all studies. Specifically, the thicker the artery, the lower the cognitive performance. This relationship was significant after controlling for age and education; some studies further adjusted for the presence of depressive symptoms<sup>187,189</sup> and/or cardiovascular risk factor level.<sup>189</sup>

The precise causal association of carotid IMT with VCI is uncertain. Carotid IMT can reflect either a media thickening in response to the increase in blood pressure in hypertensive patients, an intima thickening in response to atherosclerotic risk factors, or most often a combination of both. Nearly all types of vascular disease that may increase IMT may also affect cognitive function through a variety of mechanisms, directly or indirectly. Carotid atherosclerosis and IMT have been associated with cardiovascular risk factors, including metabolic, inflammatory, and dietary factors, that have also been associated with cognitive decline.<sup>189–192</sup> In addition, several studies have described associations between cranio-cervical artery atherosclerosis and cognitive impairment. For instance, in participants  $>90$  years of age, intracranial atherosclerosis emerged as an important predictor of dementia in subjects with low Alzheimer disease pathology scores.<sup>193</sup> In an autopsy series, the presence of large-vessel cerebrovascular disease, or atherosclerosis, was strongly associated with an increased frequency of neuritic plaque.<sup>194</sup>

The mechanisms by which atherosclerotic cerebrovascular pathology might be associated with VCI include thrombotic occlusion of large vessels with subsequent chronic cerebral hypoperfusion; cerebral embolism originating from ruptured or thrombotic carotid plaques and targeting distal vessels; increased parenchymal oxidative stress; blood pressure dysregulation affecting BBB integrity; and a common genetic vulnerability to atherosclerosis of large and small vessels.<sup>189,195–198</sup> In all likelihood, common cardiovascular factors influence both IMT and VCI independently, but the

consequences of vascular disease may also directly affect cognitive function.

### 6.2. Arterial Stiffness and VCI

The well-known, age-related arterial stiffening process (*arteriosclerosis*) is associated with quantitatively less elastin and more collagen but is also associated with qualitative changes in the arterial wall.<sup>143,199,200</sup> The most simple, noninvasive, robust, and reproducible method with which to determine aortic stiffness is the measurement of carotid-femoral pulse wave velocity, using the foot-to-foot velocity method from various waveforms (pressure, Doppler, distention).<sup>182</sup> The analysis of aortic pressure waveform allows the calculation of central systolic blood pressure and pulse pressure, which are influenced by aortic stiffness and the geometry and vasomotor tone of small arteries. Central systolic blood pressure and pulse pressure can be estimated noninvasively either from the radial artery waveform, using a transfer function, or from the common carotid waveform. Both aortic pulse wave velocity and central systolic blood pressure and pulse pressure predict cardiovascular events independent of classic cardiovascular risk factors.<sup>182</sup>

Carotid-femoral pulse wave velocity, the “gold standard” for evaluating arterial stiffness,<sup>182</sup> was higher in any group of cognitively impaired subjects with or without dementia.<sup>201</sup> An inverse relationship between pulse wave velocity and cognitive performance was reported cross-sectionally.<sup>186,202,203</sup> Carotid-femoral pulse wave velocity was also associated prospectively with cognitive decline before dementia in studies using a cognitive screening test<sup>204,205</sup> and more specifically tests of verbal learning and delayed recall and nonverbal memory.<sup>205</sup> These relationships remained significant after controlling for age, sex, education, and blood pressure levels. Other studies reported a significant positive relationship between arterial stiffness and volume or localization of WMLs, a known factor predisposing to dementia,<sup>206</sup> on neuroimaging.<sup>207,208</sup>

Several pathways may link aortic stiffness to microvascular brain damage. They include endothelial dysfunction and oxidative stress,<sup>209</sup> a mutually reinforcing remodeling of large and small vessels (ie, large-/small-artery cross talk),<sup>210</sup> and exposure of small vessels to the high-pressure fluctuations of the cerebral circulation,<sup>211</sup> which is perfused at high-volume flow throughout systole and diastole, with very low vascular resistance. Additionally, stiffer large arteries are associated with increased left ventricular mass. Of note, left ventricular remodeling and hypertrophy have been associated with higher frequency and severity of subclinical brain damage.<sup>212</sup> Recently, higher left ventricular mass in older people has been independently associated with a 2-fold higher likelihood of having dementia, independent of blood pressure levels.<sup>213</sup>

### 6.3. Small-Artery Remodeling and VCI

Direct investigation of small resistance arteries harvested from human subcutaneous and omental fat tissue has been possible using wire or pressure myography.<sup>214–216</sup> To the best of our knowledge, no study has investigated the relationship between small-artery remodeling and cognitive decline or WMLs. Noninvasive methods for measuring small-artery remodeling have focused on retinal vessels, using either a



funduscopic methodology or scanning laser flowmetry.<sup>217,218</sup> Retinal arterial narrowing correlates with increased arterial stiffness<sup>219</sup> and cerebral small-vessel disease.<sup>218,220,221</sup>

There is increasing recognition that small-vessel disease is a systemic process.<sup>222</sup> Small-vessel disease increases with age and is accelerated by vascular risk factors, most notably, hypertension and diabetes.<sup>223</sup> Putative mechanisms for this are increasing thickening of the basement membrane of capillaries and perivascular deposition of collagen leading to occlusion of end arterioles.<sup>224</sup> This manifests as systemic arteriolar dysfunction. In addition, brain damage may arise from small-vessel endothelial leakage.<sup>225</sup>

#### 6.4. Summary

The mechanistic pathways linking microvascular brain damage to carotid IMT, aortic stiffness, and small-artery remodeling are complementary. Aortic stiffness predicts cardiovascular events independent of carotid IMT.<sup>226</sup> A large-/small-artery cross-talk has already been described in hypertensive patients.<sup>210</sup> These data suggest that the noninvasive investigation of large and small arteries could demonstrate additional and independent predictive values for VCI and dementia. In addition, such a noninvasive investigation could help in determining the relative weight of each arterial parameter in contribution to all types of dementia (from VaD to Alzheimer disease) in the general population.<sup>227</sup> Finally, whether early vascular aging<sup>228,229</sup> is an important contributor to VCI and dementia and whether the latter can be prevented or delayed by targeted therapy remain to be demonstrated.

### 7. Neuroimaging Factors That May Influence the Clinical Presentation and Course of VCI

VCI is defined as a syndrome in which there is evidence of stroke or subclinical vascular brain injury based on clinical or neuroradiological features and that is linked to impairment in at least 1 cognitive domain. Although stroke is common in the elderly,<sup>230</sup> asymptomatic brain infarction is even more common,<sup>231</sup> and the full spectrum of cerebrovascular disease-associated brain injury (CVBI) measured on brain MRI includes WMLs, brain atrophy, and other findings.<sup>232</sup> This section discusses evidence from imaging studies that examine the influence of CVBI on cognition and cognitive decline.<sup>10</sup>

#### 7.1. Clinical Presentation and Importance of Neuroimaging Studies

As previously discussed, VCI may have a variety of clinical presentations that may depend on the setting in which patients are evaluated. For example, in community-based studies, evidence of CVBI and cognitive impairment is often found *without* a history of a stroke-like event. Furthermore, the relative contributions to VCI of microbleeds seen on MRI or microinfarcts discovered at autopsy remain uncertain, although both occur with increased frequency among people diagnosed with dementia during life.<sup>77,233</sup> Therefore, although the finding of CVBI on MRI is the most sensitive, the relationship between location and volume of infarcts and cognitive impairment is complex and the subject of ongoing investigation.

Two issues related to the accuracy of MRI for detection of CVBI are important for a diagnosis of VCI. First is the sensitivity and specificity for detection of CVBI. Not all lesions attributed to CVBI on MRI are in fact caused by vascular injury,<sup>234</sup> and not all vascular lesions (eg, microinfarcts) can be detected by MRI. The second is the ability to relate these findings to specific domains of cognitive impairment in older people who often have coincident Alzheimer disease pathology. A number of studies have assessed the specificity of MRI findings through neuropathological correlations with postmortem measures of CVBI, particularly pathological correlates of WMLs.<sup>71,108</sup> In a study that examined the pathological correlates of *in vivo* MRI evidence of CVBI,<sup>82</sup> WMLs were highly correlated with pathological features of ischemic white matter injury but not Alzheimer disease pathology. Gray matter volumes, however, were associated with both vascular and Alzheimer disease processes, and hippocampal volumes were associated with both hippocampal sclerosis and Alzheimer disease. It is evident that firm conclusions about imaging of CVBI relate to lack of accurate measures of concurrent Alzheimer disease pathology. Recent amyloid imaging techniques have proved an association with Alzheimer disease pathology<sup>235</sup> and may prove useful for evaluating the independent and combined effects of vascular and Alzheimer disease brain injury on cognitive changes during normal aging in the future. Fortunately, studies using both modalities are currently under way.

Although the specific independent effects of CVBI may remain somewhat uncertain at this time,<sup>236</sup> general conclusions can be drawn from clinical and imaging studies of subject groups with a high likelihood of having CVBI or conversely a low likelihood of concomitant Alzheimer disease. The following sections review key findings of studies of CVBI that may have an impact on the clinical presentation and course of VCI.

#### 7.2. Prevalence of CVBI and Associated Cognitive Findings

Estimates of the prevalence of silent cerebral infarction on MRI in community-based samples vary between 5.8% and 17.7%, with an average of 11%, depending on age, ethnicity, presence of comorbidities, and imaging techniques.<sup>237</sup> In the Framingham study, for example, the prevalence of silent cerebral infarction between the fifth and seventh decades of life is  $\approx 10\%$  but increases rapidly in the eighth decade to 17% and in the ninth decade to nearly 30%. Most have a single lesion, and the infarcts are most often located in the basal ganglia (52%), followed by other subcortical (35%) and cortical (11%) areas.<sup>237</sup> Risk factors for silent cerebral infarction are generally the same as those for clinical stroke.<sup>237,238</sup>

WMLs are even more common and are generally present in most people  $>30$  years of age,<sup>231</sup> increasing steadily in extent with advancing age. WMLs also share risk factors with stroke,<sup>239</sup> although advancing age remains a strong effect. Importantly, age-specific definitions of extensive WMLs can be created<sup>240</sup> and prove useful in defining risk for VCI in a community cohort.<sup>240</sup>

Numerous studies have examined the cross-sectional relationship between MRI evidence of CVBI and cognitive

ability. A recent review<sup>232</sup> of large epidemiological studies summarizes cognitive and behavioral effects of both silent cerebral infarction and WMLs on cognition. Interestingly, although most studies suggest that these measures of CVBI are usually associated with non-memory-related cognitive deficits,<sup>241</sup> a number of studies also show similar associations with memory impairment.<sup>240,242,243</sup> These data are consistent with recent pathological findings of an association between infarctions found at autopsy and episodic memory performance.<sup>12,59</sup> Incident cognitive impairment also occurs in association with CVBI. For example, the presence of SBI more than doubles the risk of dementia and risk of stroke.<sup>240,244,245</sup> Similarly, WMLs have been associated with declining scores in the modified MMSE and the Digit Symbol Substitution Test,<sup>246,247</sup> as well as with incident MCI, dementia, and death.<sup>240</sup> Recent evidence also suggests that progression of WMLs is a better predictor of persistent cognitive impairment than baseline WML burden,<sup>248</sup> although there is a strong association between baseline WML volume and increase in WML volume.<sup>249</sup>

### 7.3. Poststroke Dementia

Among patients who have experienced a first stroke, the prevalence of poststroke dementia (PSD) varies in relation to the interval after stroke, definition of dementia, location and size of the infarct, and other inclusion and exclusion criteria. In a Rochester, MN, community-based study of stroke, the prevalence of dementia was 30% immediately after stroke, and the incidence of new-onset dementia increased from 7% after 1 year to 48% after 25 years.<sup>250</sup> In general, having a stroke increases the risk of dementia 2-fold. Risk of dementia is higher with increased age and fewer years of education, history of diabetes mellitus and atrial fibrillation, and recurrent stroke.<sup>251</sup> Patients with PSD have degrees of functional impairment and high mortality rates. Long-term mortality is 2 to 6 times higher in patients with PSD after adjustment for demographic factors, associated cardiac diseases, stroke severity, and stroke recurrence (for review, see Leys et al<sup>252</sup>).

Among neuroimaging findings, silent cerebral infarcts, white matter changes, and global and medial temporal lobe atrophy are associated with increased risk of PSD.<sup>252</sup> Left hemisphere, anterior and posterior cerebral artery distribution, multiple infarcts, and strategic infarcts have been associated with PSD in at least 2 studies.<sup>40</sup> On the basis of small case studies, locations considered to be “strategic” have traditionally included the left angular gyrus, inferomesial temporal, mesial frontal, anterior and dorsomedial thalamus, left capsular genu, and caudate nuclei. The concept of strategic infarction, however, needs to be reexamined in larger prospective MRI studies, with the extent and location of CVBI defined in relation to cognitive networks.<sup>232</sup>

It is difficult to determine to what extent cognitive impairment may be attributable to stroke versus concomitant Alzheimer disease. Estimates of the proportion of patients with PSD with presumed Alzheimer disease vary widely between 19% and 61%.<sup>40</sup> Approximately 15% to 30% of people with PSD have a history of dementia before stroke,<sup>38,253</sup> and approximately one third have significant medial temporal atrophy.<sup>38</sup> In the Lille study, the incidence of dementia 3 years after stroke was

significantly greater in those patients with versus those without medial temporal atrophy (81% versus 58%).<sup>38</sup> It is plausible that the likelihood of Alzheimer disease is higher among patients with cognitive impairment preceding stroke or with medial temporal atrophy, but this remains conjectural in the absence of neuropathological confirmation.

### 7.4. CVBI and Cognition in Convenience Samples

Cross-sectional studies of CVBI in convenience samples often find increased evidence of both SBI and WMLs in subjects with dementia,<sup>254,255</sup> consistent with recent community-based pathological studies.<sup>12</sup> Unfortunately, a clear pattern of effect of CVBI on cognition in convenience samples is confounded by a general focus on Alzheimer disease and the exclusion of people with coincident VCI.<sup>232</sup> In at least 1 study of people with subcortical vascular brain injury presenting with memory impairment, incident lacunar infarction was associated with subtle declines in executive function performance over time.<sup>256</sup> Conversely, measures of cerebral gray matter and hippocampal volume were both associated with declines in memory performance.<sup>256</sup> Interestingly, the combined effects of CVBI and atrophy persist even among people clinically diagnosed with VaD according to NINDS-AIREN criteria.<sup>257</sup>

### 7.5. Depression on a Cerebrovascular Basis and CVBI

Depression in late life may be associated with vascular disease.<sup>258,259</sup> There may be a higher frequency of brain white matter damage and other subcortical lesions, such as lacunar infarcts. It is believed that the associated brain changes in this condition are linked to atherosclerotic risk factors such as hypertension, diabetes mellitus, and hyperlipidemia. Neuropsychological study may show evidence of executive dysfunction and other findings. Proposed mechanisms for vascular depression in patients with cerebrovascular diseases include but are not limited to autonomic dysfunction, platelet activation, hypothalamic-pituitary axis activation, endothelial dysfunction, inflammatory mechanisms, genetic factors, and hyperhomocysteinemia.<sup>258</sup> Depression with a cerebrovascular basis may respond to treatment with certain selective serotonin-reuptake inhibitors. Depression is further discussed in the section on comorbid neuropsychiatric disease.

### 7.6. Summary

The clinical presentation and course of CVBI are highly variable, with the classic phenotype of stepwise decline in association with stroke<sup>10</sup> being a relatively uncommon presentation for VCI. Structural MRI provides a fairly sensitive and specific marker for CVBI, but the relationship between CVBI and cognitive impairment is confounded by the frequent presence of Alzheimer disease changes of the brain and co-occurrence of depression on a cerebrovascular basis. Recent data from prospective population-based samples (where the likelihood of Alzheimer disease is relatively low) clearly show that progressive SBI and WMLs are correlated with worsening of cognitive impairment, especially executive function. Thus, SBI and WMLs at least offer a readily available surrogate marker for the early detection and prevention of VCI and when found in combination are likely to

indicate significant underlying CVBI. However, the utility of MRI or computed tomography for the diagnosis of VCI is not yet clearly defined.<sup>259a</sup> Ongoing research may further improve MRI detection of microinfarction, and, with the use of amyloid imaging in addition to detection of medial temporal atrophy, may further refine the biological mechanisms whereby imaging evidence of CVBI contributes to VCI.

## 7.7. Recommendation

1. **The use of brain imaging with computed tomography or MRI may be reasonable in making a diagnosis of VCI (Class IIb; Level of Evidence B).**

## 8. Impact of Cardiovascular Risk Factors at Different Ages on the Risk of Cognitive Decline

This section includes studies on the range of cognitive impairment, including VaD diagnosed with internationally recognized criteria.<sup>10,19,25</sup> The studies generally included tests that conformed to the NINDS-Canadian Stroke Council VCI harmonization standards, reported at the minimum 1 nonmemory cognitive test of a function typically affected in VCI, or included a diagnosis of VCI or VaD. Because the present statement is focused on VCI, studies reporting only on tests of global cognition, memory tests, total dementia, or Alzheimer disease were excluded. We recognize that this is a somewhat arbitrary choice, because many articles and reviews show that vascular risk factors are also importantly associated with Alzheimer disease, mixed dementia, and amnesic MCI.<sup>110,260,261</sup> Furthermore, several pathophysiological pathways leading to vascular and neurodegenerative processes are similar.<sup>262</sup> Also, neuropathic studies show a high proportion of older people have mixed pathology, with Alzheimer disease lesions and vascular lesions being the most prevalent.<sup>18</sup>

For most risk factors, we drew from studies providing Class I evidence (ie, the risk factor is reported as a major finding in a community-based study that is preferably prospective or part of an intervention, with a sample size >500). For specific factors, such as coronary artery bypass grafting and cardiac output, we reviewed studies based on Class II evidence according to carefully analyzed clinical data.

Several issues specific to studying risk factors for cognitive impairment should be accounted for when interpreting the literature:

1. Questionnaire data rely on the recall of subjects who by definition of the research may be cognitively impaired.<sup>263</sup>
2. Reverse causation must be considered because it is possible that the risk factor level is a response to rather than a “cause” of the outcome.<sup>260</sup> This is a particular concern in studies that measure cognitive function in late life, shortly after or simultaneously with the measure of a risk factor.
3. The activity of biomarkers in the brain generally cannot be measured directly.
4. The cognitive tests for VCI are, to a degree, nonspecific for vascular disease, and different criteria for VaD identify different sets of people.<sup>29</sup>
5. The brains of older people have multiple morbidities that can lead to the same phenotype.<sup>18</sup>

## 8.1. Nonmodifiable Risk Factors

### 8.1.1. Demographic Factors

Prevalence estimates of VaD vary widely. A recent study reporting on the prevalence of VaD in developing countries reported a range of 0.6% to 2.1%.<sup>3,33</sup> In a pooled analysis of major European population-based studies, VaD was prevalent in 1.6% of subjects >65 years of age, but there was a large variation in 5-year age-specific prevalence.<sup>264</sup> In general, however, after age 65 years, there is an exponential increase in prevalence and incidence of VaD as age increases,<sup>265,266</sup> although the trends after 90 years of age have not been well established.<sup>4,267,268</sup> This age-related increase in VaD follows the pattern of stroke,<sup>269</sup> although dementia after stroke may be more frequent in people <80 years old.<sup>270</sup> Some studies report a higher incidence of VaD in men than in women,<sup>4,271</sup> although a pooled analysis of incidence studies found no difference.<sup>272</sup> MCI may not differ by sex,<sup>273</sup> but additional studies are needed to answer this question. The incidence of VaD appears to be higher in blacks than in whites<sup>4</sup> or in Hispanics with a history of stroke,<sup>274</sup> possibly reflecting group differences in cerebrovascular risk profile. Recent studies have shown that similar to Western countries, Alzheimer disease is the leading cause of dementia in Asian populations.<sup>275</sup> Until there is a harmonization of criteria and a better understanding of how the population-level vascular burden and mortality patterns affect frequency estimates, it will not be possible to exclude methodological differences in case definition as a reason for differences in estimates of prevalence and incidence of vascular-related cognitive disorders.

### 8.1.2. Genetic Factors

The apolipoprotein E  $\epsilon$ 4 allele is associated with increased levels of cardiovascular risk factors<sup>276</sup> and is a strong indicator of genetic risk for Alzheimer disease. Despite this, several studies report no association of the polymorphism with VaD.<sup>34,277</sup> Many more genetic candidates are expected to emerge with the publication of results from genome-wide association studies,<sup>278,279</sup> although the immediate clinical relevance of these findings is unclear. An important factor limiting the study of genetic factors of VCI is the lack of a clear determination of the phenotype, because superimposed Alzheimer disease processes cannot be ruled out.

### 8.1.3. Summary: Demographic and Genetic Factors

As with most neurocognitive disorders of late life, VCI is likely to be more common as age increases. There is no apparent association of apolipoprotein E  $\epsilon$ 4 and VCI. However, more genetic candidates are expected to emerge as additional studies on endophenotypes of VCI are conducted. These traits include specific cognitive domains such as speed of processing, vascular lesions such as macrovascular infarcts detected on MRI, and microvascular lesions detected in neuropathological samples.

## 8.2. Lifestyle Factors

### 8.2.1. Education

Low educational level has been reported to be associated with an increased risk for VaD.<sup>280</sup> However, cognitive tests have an education component, which may reflect years or quality of



schooling, socioeconomic status, chronic disease or less healthy lifestyle patterns, acculturation, racial socialization, or cognitive reserve.<sup>281</sup> Thus, there are a number of possible explanations or confounders in relation to education level and VCI.

### 8.2.2. Diet

The association of diet with cognitive function has a long history grounded not only in studies of cardiovascular risk factors but also in studies of brain development and physiology.

Antioxidants, which include vitamins E,<sup>282</sup> C, and beta carotene,<sup>283</sup> consumed either as a part of the diet (fruits and vegetables) or as supplements, have been reported to reduce the risk of cognitive impairment.<sup>284</sup> However, several prospective<sup>285</sup> and interventional<sup>286,287</sup> studies show no benefit of consuming antioxidants to preserve cognitive function or reduce decline.

Fish oil n-3 polyunsaturated fatty acids are of interest because of their antioxidant and antiinflammatory properties and because they are major components of membrane phospholipids in the brain and play a critical role in neuronal function.<sup>288</sup> In studies of cognition, levels of n-3 polyunsaturated fatty acids are estimated by dietary intake or directly as blood markers. A 3-year observational study of cognitive decline in elderly men reported high fish intake to be inversely associated with cognitive impairment.<sup>289</sup> Some,<sup>290–292</sup> but not all,<sup>293</sup> studies of middle-aged and older subjects with 5 to 6 years of follow-up suggest increasing levels of n-3 polyunsaturated fatty acids are associated with better cognitive function and less cognitive decline.

Vitamin D is an emerging risk factor for an increased risk of cardiovascular disease and stroke. Recently, 1 study found an association of lower circulating vitamin D levels with poorer cognitive function,<sup>294</sup> but another found no association.<sup>295</sup> Additional studies are needed to further understand how vitamin D levels may be associated with cognitive function and impairment.

Folic acid and vitamins B<sub>12</sub> and B<sub>6</sub> are key components of the pathways leading to the production and metabolism of homocysteine.<sup>296</sup> Homocysteine is a risk factor for vascular damage.<sup>296</sup> Cross-sectional and longitudinal studies consistently show that increasing levels of plasma homocysteine are associated with poorer performance in global as well as multiple cognitive domains.<sup>297–299</sup> In a randomized trial of women with cardiovascular disease or risk factors for cardiovascular disease,<sup>285,300</sup> there was no benefit to cognitive function from a 6-year intervention that used a supplement with B vitamins to lower plasma homocysteine levels.

There is some evidence that a Mediterranean diet can reduce cognitive decline.<sup>301</sup> However, despite the key role studies of diet have played in shaping our understanding of cardiovascular disease, it has been much more difficult to study the role of diet in shaping late-life trajectories of cognition. Diet-cognition associations are difficult to interpret for the reasons described. To advance this area of research, we need better information on how dietary and peripheral biomarkers of nutritional status reflect brain resources and metabolism, more valid measures of remote diet, studies of dietary patterns, and studies of younger people.

### 8.2.3. Physical Activity and Physical Function

Physical activity may increase brain neurotrophins, such as brain-derived neurotrophic factor, improve cerebrovascular

functioning and brain perfusion, reduce response to stress, and increase brain plasticity through synaptogenesis and neurogenesis.<sup>302</sup> The Chicago Health and Aging Project (CHAP), which was based on a cohort with low physical activity, found no association between cognitive decline and physical activity carried out in the 2 weeks before the study examination.<sup>303</sup> However, long-term regular physical activity, including vigorous activity and walking, was strongly associated with higher levels of cognitive function, less cognitive decline, and less VaD.<sup>303–306</sup> Physical activity or exercise is recommended to maintain aerobic fitness and function and for its potential cognitive benefits.<sup>307</sup> For those able to engage in exercise, the American Heart Association recommends 30 minutes of exercise of moderate intensity on most days. For those with a disability, a supervised therapeutic regimen may be implemented. Physical activity has been identified as having potential protective benefits in brain health and plasticity and in VCI and related conditions.<sup>308–314</sup>

There is a relative paucity of data on the type and frequency of physical activity and what the short- and long-term benefits of physical activity are for preservation of brain health. The Lifestyle Interventions and Independence for Elders Study (LIFE),<sup>314a</sup> a clinical trial testing the effects of a 4-year exercise intervention on physical function, will measure cognitive function as a secondary outcome; it is expected to be completed in 2013.

### 8.2.4. Alcohol Intake

The risks and benefits of alcohol intake have been debated for years, with the only clear risk for cognitive impairment being heavy alcohol use. Comparisons of studies on cognitive dysfunction are made difficult by the disparate definitions of alcohol intake, reference groups (ie, people who never drink, prior drinkers who now abstain, or people who drink infrequently compared with drinkers), and different outcome measures. Despite this, several longitudinal studies, including those with measures of exposure in middle age, have found some benefit in relation to cognition of more use of alcohol compared with infrequent use or no (“never”) use of alcohol.<sup>315–317</sup> However, studies vary in the amount of alcohol associated with a positive effect; the relative significance of global, memory, and executive function; and whether the effect varies by sex.

### 8.2.5. Obesity

Obesity, or body fat, is an emerging risk marker of interest because of its metabolic consequences and recent reports of associations with total dementia.<sup>318</sup> Body mass index has a U-shaped relationship with total dementia and VaD, so that subjects at the lower and upper ends of body mass index distribution had a higher frequency of dementia relative to subjects with a normal body mass index.<sup>319</sup> Body mass index measured in midlife is more strongly associated with VCI, whereas body weight measured later in life has an inverse association with cognitive impairment, where obesity is associated with a lower risk of dementia.<sup>320</sup> The differences in study results may reflect the different weight trajectories in midlife and late life relative to the age when cognition is measured or dementia occurs.<sup>321</sup> In the Framingham Offspring Study, higher waist-hip ratio was associated with lower cognitive function, which was measured 12 years later.

High waist-hip ratio strengthened the association with hypertension and dementia in the highest quartile of waist-hip ratio. It is unclear what confounding factors were taken into account in these analyses.<sup>322</sup> A recent meta-analysis shows that high waist-hip ratio is associated with greater risk of dementia in all studies.<sup>319</sup>

#### 8.2.6. Smoking

Smoking has well-known effects on the cardiovascular system and neurons, which are mediated generally by oxidative stress and inflammation. Several prospective studies show an increased risk for cognitive decline in smokers compared with nonsmokers,<sup>323,324</sup> although risk may be specific for certain cognitive domains,<sup>325</sup> possibly because nicotine may also stimulate cholinergic pathways within the brain.<sup>326</sup>

#### 8.2.7. Social Support/Networks

Social networks and patient and family support have been associated with cognitive functioning in elderly populations in longitudinal and cross-sectional epidemiological studies.<sup>327–330</sup> However, these observations have not been tested in randomized controlled trials, and data can only be extrapolated to patients with VCI.

#### 8.2.8. Summary: Lifestyle Factors

Lifestyle factors may be risk factors for VCI, and for many there is evidence for plausible biological mechanisms by which these factors may heighten risk of VCI. Gaps in knowledge about the role of such factors in VCI may be bridged by additional well-designed epidemiological studies, harmonization of how lifestyle activity is defined, and clinical trials.

#### 8.2.9. Recommendations

1. In people at risk for VCI, smoking cessation is reasonable (*Class IIa; Level of Evidence A*).
2. In people at risk for VCI, the following lifestyle interventions may be reasonable: moderation of alcohol intake (*Class IIb; Level of Evidence B*); weight control (*Class IIb; Level of Evidence B*); and physical activity (*Class IIb; Level of Evidence B*).
3. In people at risk for VCI, the use of antioxidants and B vitamins is not beneficial, based on current evidence (*Class III; Level of Evidence A*).

### 8.3. Depression

Depression may impact cognitive functions and may mimic cognitive decline. It can be considered a comorbidity, prodromal factor, or a consequence of VCI rather than a factor that specifically alters vascular physiology or neuronal health, leading to cognitive impairment.<sup>47</sup> In general, large epidemiological studies of older people use measures of depression symptoms such as the Center for Epidemiological Studies Depression Scale.<sup>331</sup> Some studies suggest symptoms of depression predict cognitive decline.<sup>332–334</sup> However, when investigators in the Three City Study controlled for current depressive symptoms, there was attenuation of a significant association between 4-year cognitive decline and history of major depression. Investigators in the Cardiovascular Health Study (CHS) could not confirm that vascular factors mediated an association of depressive symptoms with incident MCI.<sup>335</sup>

### 8.4. Physiological Risk Factors

Physiological factors are continuous traits that contribute to or are biomarkers of disease processes and can be measured in a clinical examination, with imaging, or in biological specimens.

#### 8.4.1. Blood Pressure

High blood pressure has long been known to cause stroke.<sup>336</sup> Midlife hypertension ranks as an important modifiable risk factor for late-life cognitive decline,<sup>337</sup> mild cognitive impairment,<sup>338,339</sup> and VaD.<sup>340,341</sup> In longitudinal cohort studies, higher systolic blood pressure has been associated with greater late-life cognitive decline, although some studies have reported a J- or U-shaped relation.<sup>342</sup> Findings from these prospective cohort studies for diastolic blood pressure and cognitive decline are less consistent; however, many have reported a similar inverse relation. The data on the role of blood pressure and hypertension in later life are not consistent, leaving open the issue of blood pressure treatment in older people. The controversy about the association between later life hypertension and cognitive decline arises because the longitudinal relationship between cognitive change and blood pressure is sensitive to the effects of age, duration of follow-up and number of blood pressure measurements, hypertensive treatment status, comorbidity with cardiovascular diseases and stroke, and possibly subclinical dementia.<sup>343</sup>

#### 8.4.2. Hyperglycemia, Insulin Resistance, Metabolic Syndrome, and Diabetes

Multiple mechanisms related to diabetes-related glucose and insulin dysregulation can lead to vascular and neuronal damage.<sup>344</sup> Chronic hyperglycemia, increased insulin, the metabolic syndrome, and diabetes are associated with VCI,<sup>337,345–348</sup> as well as VaD or dementia with stroke.<sup>349,350</sup> Of note, hyperglycemia is associated with functional changes in cerebral blood flow that are reversible when good glycemic control is restored.<sup>351</sup> These findings have been reported across multiple populations. Studies suggest that the longer the duration of diabetes, the poorer the cognitive function.<sup>347,348,352</sup> It is remarkable to consider that recurrent episodes of hypoglycemia may cause permanent cognitive impairment in older subjects<sup>353</sup> and that cognitive disturbance, in turn, represents a risk factor for hypoglycemia in older adults.

#### 8.4.3. Lipids

In the Finnish study Cardiovascular Risk Factors Aging and Dementia (CAIDE), midlife measures of total cholesterol significantly predicted cognitive impairment 21 years later, an association that was attenuated after accounting for statin therapy.<sup>354</sup> In a study based on medical records, high midlife cholesterol level increased the risk for VaD that developed over a 30-year period.<sup>355</sup> Findings in late-life cohorts vary, with some finding higher levels of cholesterol associated with a lower risk<sup>356</sup> and others finding a higher risk for VaD.<sup>357</sup> As with blood pressure, inconsistencies may reflect timing of the cholesterol measurements relative to age, older people possibly being less likely to receive lipid-lowering therapy (“generational effect”), and clinical onset of dementia. A trial of pravastatin in older people at risk for cardiovascular disease found no difference between the placebo and treatment arms in multiple cognitive domains.<sup>358</sup>

#### 8.4.4. Inflammation

Inflammation is a key process linking many cardiovascular risk factors to vascular and neuronal damage. Plasma levels of inflammatory proteins, specifically  $\alpha$ 1-antichymotrypsin and C-reactive protein, were found to be increased before the onset of VaD over an 8-year follow-up period<sup>359</sup>; C-reactive protein levels were increased 25 years before the onset of VaD.<sup>360</sup> In the Conselice Study of Brain Aging, with 4 years of follow-up, the combination of high levels of C-reactive protein and interleukin-6 led to a nearly 3-fold increased risk of VaD.<sup>361</sup>

#### 8.4.5. Summary: Physiological Risk Factors

Midlife systolic and diastolic blood pressure, history of hypertension, and total cholesterol level predict VCI. The relation of late-life VCI to measures of blood pressure and cholesterol in later life remains uncertain and requires further study, although higher levels of exposure to these risk factors may prove to be beneficial. Diabetes and hyperglycemia are associated with VCI. C-reactive protein, a marker of inflammation, is associated with VaD.

#### 8.4.6. Recommendations

1. In people at risk for VCI, treatment of hypertension is recommended (Class I; Level of Evidence A).
2. In people at risk for VCI, treatment of hyperglycemia may be reasonable (Class IIb; Level of Evidence C).
3. In people at risk for VCI, treatment of hypercholesterolemia may be reasonable (Class IIb; Level of Evidence B).
4. In people at risk for VCI, it is uncertain whether treatment of inflammation will reduce such risk (Class IIb; Level of Evidence C).

### 9. Concomitant Clinical Vascular Disease

#### 9.1. Coronary Artery Disease

In the CHS and Age, Gene, Environment Susceptibility–Reykjavik Study (AGES-RS), computed tomography–based coronary artery calcium, a measure of severity of coronary atherosclerosis, was associated with a higher risk of cognitive impairment.<sup>362,363</sup> Adjustment for WMLs, SBI, cerebral microbleeds, and brain volumes attenuated the observed association between coronary artery calcium and cognition, implicating other vascular mechanisms.<sup>363</sup>

Coronary artery disease has also been identified as an independent risk factor for VaD.<sup>34</sup> Coronary artery bypass graft has been associated with poorer initial cognitive function and a higher late-life dementia risk. However, at 1- or 6-year follow-up, the cognitive decline in these patients was no different from that observed in controls with an equivalent burden of coronary artery disease who opted for medical treatment or percutaneous coronary intervention.<sup>364,365</sup>

#### 9.2. Stroke

The risk of new-onset dementia after a stroke is approximately twice the rate for age- and sex-matched control subjects<sup>270</sup> and averages  $\approx$ 10% after the first stroke, depending on the location, volume of damaged brain tissue,<sup>30</sup> clinical severity, and presence of early poststroke complications (seizure, delirium, hypoxia, hypotension). A recent review identified older age, lower education, prestroke cognitive impairment, diabetes, and atrial fibrillation as factors that increased the risk, but one of the strongest predictors of

cognitive decline after an initial stroke was the occurrence of a second stroke.<sup>269,270</sup> In people with recurrent stroke, the risk of dementia rose to  $\approx$ 30%, regardless of the number and severity of vascular risk factors they had been exposed to before the stroke.<sup>269</sup>

#### 9.3. Chronic Kidney Disease

Severe chronic kidney disease has been associated with metabolic (uremic) and hypertensive encephalopathy and an increased risk of stroke.<sup>366</sup> Data from multiple studies of different populations suggest that among all people with severe and moderate chronic kidney disease (estimated glomerular filtration rate  $<$ 30 and  $<$ 60 mL/min per 1.73 m<sup>2</sup>, respectively), there is a graded increase in the prevalence of cognitive impairment affecting multiple domains.<sup>367,368</sup> In the CHS, moderate chronic kidney disease was related to risk of incident VaD.<sup>369</sup> The association between chronic kidney disease and cognitive impairment could be confounded by shared vascular risk factors for small-vessel brain disease.

#### 9.4. Atrial Fibrillation

Atrial fibrillation, especially if not treated with adequate anticoagulation, is a risk factor for stroke.<sup>370</sup> In several large community-based samples and in a prospectively studied registry of people undergoing cardiac catheterization, cross-sectionally it was an independent risk factor for lower cognitive performance and a higher risk of VaD.<sup>371–374</sup> However, a few studies did not observe an association of atrial fibrillation with dementia.<sup>375,376</sup> Some of these differences could be related to age or sex (the effect was weaker in women and older people) and the administration and effectiveness of anticoagulation.

#### 9.5. Peripheral Arterial Disease

In the Honolulu-Asia Aging Study (HAAS) and CHS, a low ankle-brachial index, a measure of peripheral arterial disease, was associated with an increased risk of VaD.<sup>377,378</sup> A greater carotid-femoral pulse wave velocity was associated with lower cognitive function in the Maine-Syracuse Study.<sup>379</sup> There are scarce data relating flow-mediated endothelial dilatation (brachial artery reactivity) with cognition.

#### 9.6. Low Cardiac Output

A subclinical decrease in cardiac output has also been shown to be associated with lower cognitive function.<sup>380</sup> Specifically, reduced cardiac output has been associated with executive dysfunction (mainly sequencing and planning difficulties)<sup>381</sup> and regional WMLs adjacent to the subcortical nuclei.<sup>382</sup> Chronic reduced systemic perfusion may affect cerebral perfusion homeostasis.<sup>383,384</sup> Animal and human observations suggest that chronic hypoperfusion induces the development and progression of WMLs.<sup>385–387</sup>

Low cardiac output may represent a key factor in the onset and progression of cognitive impairment, especially in older people with systolic heart failure.<sup>380,383</sup>

#### 9.7. Summary: Concomitant Disease

Prevention of chronic vascular diseases may help reduce the population burden of vascular dementia. Initial and recurrent stroke significantly increase the risk of clinical dementia. Although this is caused in part by loss of brain tissue, it may also reflect a direct



effect of vascular risk factors on both risk of stroke and cognitive function. That is, stroke could be serving as a marker of cumulative exposure to vascular risk factors. In an analogous manner, disease of the coronary or peripheral arterial circulations, atrial fibrillation, and clinically detectable renal and cardiac failure have each been associated with cognitive impairment.

## 10. Clinical Trials in VCI and Symptomatic Treatment

### 10.1. Background

Over the past decade, the role of vascular brain disease as a cause of cognitive impairment has become increasingly evident, alone or combined with Alzheimer disease. Pivotal trials to test drugs approved for Alzheimer disease in patients with VaD,<sup>388</sup> however, have failed to achieve regulatory approval. Reasons include only modest benefit on standard cognitive measures, which undersampled executive functioning, and inconsistent benefits in global and daily function, which are difficult to evaluate when physical deficits with stroke coexist. Furthermore, high specificity but low sensitivity of VaD criteria<sup>10</sup> hampered recruitment, and the emphasis on inclusion of those with memory loss made it challenging to exclude concomitant Alzheimer disease. Finally, concern that frontline clinicians could not distinguish VaD from Alzheimer disease made regulators reluctant to grant a separate indication.<sup>389</sup>

Management of vascular risks and symptomatic pharmacotherapy targeting VaD has been the primary approach.<sup>390</sup> Nonpharmacological approaches have also been tried. Standardized screening and monitoring to document baseline, disease trajectory, and treatment response are essential. These include medical history, social and daily functioning, cognitive screening with more detailed assessment as appropriate, blood tests, and vascular and brain imaging. Also, factors that exacerbate clinical disease manifestations (eg, sleep disorders, pain, stress) must be addressed and specific efforts made to optimize quality of life of patients and caregivers.<sup>391</sup>

Many facets of dementia care do not involve therapies directed at disease modification. It is important for providers to also support caregivers, refer caregivers to educational offerings, and identify community resources, including assistance to support performance of activities of daily living and for living in the community, such as access to transportation and referral for assessment of driving safety. Other areas of care are to provide advice and help in the management of psychological symptoms and neurobehavioral complications, preparation for loss of capacity to make financial and medical and placement decisions, and arranging for provision of palliative care in the case of progressive disease. A full discussion of all of these important facets of care is clearly beyond the scope of the present statement; however, these aspects are important, and resources may be found elsewhere, such as in the recommendations for the comprehensive care of patients with dementia recently published by a Canadian consensus group and other evidence-based strategies for care based on those recommendations.<sup>307,391,392</sup>

### 10.2. Pharmacological Treatment of Cognitive Impairment

There is pathological and clinical evidence for cholinergic compromise in VCI as occurs in Alzheimer disease.<sup>393–395</sup>

**Table 3. Pharmacological Treatments for VCI**

Treatment	Recommendation (Class/Level of Evidence)	Comments
Donepezil <sup>396–400</sup>	Class IIa, Level A, for “pure” VaD	Study 307, 308 (n=1219): modest benefit for cognitive and global, less robust for function; Study 319 (n=974): only cognitive benefit
Galantamine <sup>401–403</sup>	Class IIa, Level A, for mixed Alzheimer disease–cerebrovascular disease; Class IIb for “pure” VaD	Pure and mixed VaD Gal-Int-6 (n=592): benefit in all primary outcomes overall; only cognitive benefit in pure disease; “Pure” VaD (Gal-Int-26; n=788): modest benefit in cognitive/executive measures
Rivastigmine <sup>404,405</sup>	Class IIb, Level C	VCIND study (n=50): modest benefit in some executive functions
Memantine <sup>406,407</sup>	Class IIb, Level A	n=900: Modest cognitive benefits only

VCI indicates vascular cognitive impairment; VaD, vascular dementia; and VCIND, vascular cognitive impairment, no dementia. Study 307, 308, and 319 and “Gal-Int-6” and “Gal-Int-26” are names of the studies.

Double-blind, placebo-controlled, randomized clinical trials lasting 6 months have tested the efficacy of cholinesterase inhibitors in cognitive, global, and daily functioning in VaD. The same assessment tools as used in Alzheimer disease trials were administered.<sup>390</sup> The resultant evidence is summarized in Table 3.

The donepezil trials focused on “pure” VaD (n=1219), in which placebo groups were stable over 6 months, requiring improvement to show efficacy. Cognitive benefit was found, but global and functional efficacy was less consistent in the individual studies.<sup>396,400</sup> A post hoc analysis in a recent large randomized controlled trial of donepezil in VaD (n=974) showed that as assessed by a standardized visual rating scale, patients with hippocampal atrophy who received placebo declined more than those without hippocampal atrophy, who remained cognitively stable. This finding suggests that hippocampal volume may need to be accounted for in future VaD trials.<sup>398</sup> The side-effect profile was similar to that of donepezil for Alzheimer disease trials. In a recent study, however, more deaths occurred in the donepezil treatment group; this was attributed to the less than expected death rate in the placebo group.<sup>398</sup> An 18-week study of donepezil in 168 patients with CADASIL had a neutral result but showed benefit in executive function measures in secondary analysis.<sup>408</sup>

Galantamine was evaluated in patients with pure VaD (n=252) and Alzheimer disease/VaD (n=295).<sup>403</sup> There was statistically significant less decline in cognition, function, and behavior with galantamine, driven by the mixed subgroup, whereas subjects treated with placebo showed decline. The pure VaD subgroup was underpowered statistically to show definite benefit. A subsequent study of “pure” VaD patients (n=788) showed cognitive treatment benefits, including benefit for an executive measure but not for daily functions; however, there was an overall trend for global benefit ( $P=0.06$ ).<sup>401</sup>

Rivastigmine has been less well studied, but beneficial effects on an executive measure were found in a 22-month, open-label controlled (n=16) study<sup>409</sup> and in a double-blind placebo-controlled trial targeting vascular cognitive impairment, no dementia (n=50).<sup>405</sup> Two studies with memantine, an N-methyl D-aspartate antagonist, likewise showed cognitive benefit without global or functional benefit.<sup>406,407</sup>

Cochrane reviews of VaD trials concluded that donepezil studies have provided the best available evidence for a beneficial effect for VaD<sup>397</sup> and galantamine for mixed states,<sup>402</sup> whereas a benefit of memantine<sup>410</sup> and rivastigmine is still not proven.<sup>404</sup> The adverse effect safety profile is generally similar to that of Alzheimer disease studies. One meta-analysis commented that the cognitive benefits of cholinergic agents and memantine were of uncertain clinical significance in VaD, and more data are required before widespread use of these agents is to be considered.<sup>411</sup> Whether there are any differential benefits within or between the drug classes is not clear from the available evidence, because no head-to-head trials have been conducted.

Trials have been conducted with other compounds, including cytidinediphosphocholine,<sup>412,413</sup> nimodipine,<sup>414</sup> piracetam,<sup>415</sup> huperzine A,<sup>416</sup> and vinpocetine,<sup>417</sup> but so far without convincing data, although nimodipine and huperzine, especially for small-vessel disease, seem worthy of further study. A small study of sertraline showed benefits on the Executive Interview (EXIT-25), an executive function test.<sup>418</sup>

### 10.3. Summary and Recommendations: Pharmacological Therapy

#### 10.3.1. Summary

Specific pharmacotherapy trials targeting VaD have shown consistent, modest cognitive improvements with donepezil, galantamine, and memantine, but functional and global benefits have been less consistent, with evidence only from 2 large donepezil trials. In trials of galantamine, less decline in cognitive, functional and global outcomes was shown in trial results driven by participants with mixed VaD/Alzheimer disease. The adverse effect profile is similar to that seen in Alzheimer disease trials. More clinical trial evidence would be helpful, including pharmacoeconomic evaluations. In the future, case selection and outcomes should use the updated clinical criteria, more sensitive executive function measures, and advanced imaging biomarkers that better quantify atrophy and vascular brain injury, including diffusion tensor and perfusion imaging, and possibly amyloid labeling or cerebrospinal fluid markers to detect concomitant Alzheimer pathology.

#### 10.3.2. Recommendations

1. Donepezil can be useful for cognitive enhancement in patients with VaD (*Class IIa; Level of Evidence A*).
2. Administration of galantamine can be beneficial for patients with mixed Alzheimer disease/VaD (*Class IIa; Level of Evidence A*).
3. The benefits of rivastigmine and memantine are not well established in VaD (*Class IIb; Level of Evidence A*).

### 10.4. Nonpharmacological Treatments

Nondrug therapies have been examined for treatment or adjunctive management of VCI. Lifestyle factors such as diet,

physical activity, and social support networks were reviewed in the lifestyle section of this statement. Few nonpharmacological therapies have been tested and found to be beneficial in the VCI population. Two therapies reported in the Cochrane reviews are cognitive rehabilitation and acupuncture.

Cognitive rehabilitation and cognitive stimulation so far have not proven effective.<sup>419,420</sup> However, there are few randomized controlled trials, and there are methodological limitations in existing studies in the area. Acupuncture showed cognitive benefit in a rodent model of VaD,<sup>421</sup> but a Cochrane review of acupuncture in human VaD was inconclusive,<sup>422</sup> which indicates that more studies are needed.

#### 10.4.1. Summary

Only limited evidence exists to support nonpharmacological modalities for management of VCI. No formal recommendations for therapy are offered. More research with rigorous designs to study the effects of nonpharmacological interventions, including cognitive rehabilitation and acupuncture, is needed.

## 11. Prospects for Prevention of VCI and Alzheimer Disease by Risk Factor Control

### 11.1. Public Health Aspects

Because the most common forms of dementia affect the elderly, even a modest delay in the appearance or worsening of cognitive deterioration could translate into a relatively large reduction of the incidence of disease. Such people might die of competing causes before manifesting the symptoms of dementia. It has been estimated, for example, that among the 106 million cases of Alzheimer disease expected worldwide by the year 2050, ≈23 million could be avoided completely if it were possible to delay the onset of disease by 2 years.<sup>423</sup>

In relation to the role of vascular risk factors, during midlife the population-attributable risk of dementia has been reported to be highest for hypertension (up to 30% of cases of late-life dementia). Furthermore, on the basis of observational epidemiological data, diabetes conveys a high risk of dementia. Vascular and metabolic risk factors should therefore be regarded as potential major targets for the prevention of dementia. The timing of such interventions may be important, because the association with dementia appears to be stronger for vascular factors and when measured in midlife rather than in old age, which suggests that midlife may be a critical period.<sup>424</sup> In addition, safeguarding normal cognitive development during childhood and adolescence based on the new understanding of the importance of early-life factors for adult health and disease,<sup>425</sup> as well as for cognitive function, is a prerequisite for prevention of cognitive impairment.<sup>426</sup> The importance of balanced nutrition in early life for normal neurocognitive development, a process that is not finished until late adolescence, has been widely recognized.<sup>427</sup>

### 11.2. Results of Main Studies on Vascular Factor Control and the Prevention of Dementia

#### 11.2.1. Hypertension

##### 11.2.1.1. Observational Studies on Antihypertensive Drugs and Risk of Dementia

An association between midlife hypertension and late-life cognitive decline or dementia has been found in a majority of

**Table 4. Main Longitudinal Studies on the Relationship Between Use of Antihypertensive Drugs and Risk of Dementia**

Author, Year of Publication	Study	Sample Size	Type of Sample	Age Criteria, y	Mean Age, y	Follow-Up, y	Diagnosis of Dementia	Effect of Antihypertensive Drug Overall (95% CI)	Effect by Type of Antihypertensive Drug (95% CI)
Guo et al, <sup>435</sup> 1999	Kungsholmen project	1301	Community based; no dementia	≥75	83	3	Dementia, Alzheimer disease: DSM-III-R	Dementia: RR=0.7 (0.6–1.0)	Treatment effect mainly because of diuretics
in't Veld et al, <sup>432</sup> 2001	Rotterdam study	6416	Community based; no dementia	≥55	68	2.2	Dementia: DSM-III-R; Alzheimer disease: NINCDS-ADRDA; VaD: NINDS-AIREN	Dementia overall: RR=0.76 (0.52–1.12); VaD: RR=0.33 (0.11–0.99); Alzheimer disease: RR=0.87 (0.56–1.37)	No differences among antihypertensive drugs
Morris et al, <sup>434</sup> 2001	EPESE	634	Random sample	≥65	72	4	Alzheimer disease: NINCDS-ADRDA	Alzheimer disease: RR=0.66 (0.68–2.61)	No differences among antihypertensive drugs
Lindsay et al, <sup>433</sup> 2002	Canadian Study of Health and Aging	4088	National sample	≥65	73	5	Alzheimer disease: DSM-IV	Alzheimer disease: RR=0.91 (0.64–1.30)	
Qiu et al, <sup>437</sup> 2003	Kungsholmen project	1270	Community based; no dementia	≥75	81	5	Dementia, Alzheimer disease: DSM-III-R	Dementia: RR=0.8 (0.6–1.0); Alzheimer disease: RR=0.7 (0.5–0.9)	
Yasar et al, <sup>430</sup> 2005	Baltimore Longitudinal Study of Aging	1092	Community based; no dementia	≥60	78	19	Dementia: DSM-III-R; Alzheimer disease: NINCDS-ADRDA	...	Alzheimer disease: RR=0.30 (0.07–1.25) for dihydropyridine type of CCB; RR=0.82 (0.37–1.83) for nondihydropyridine type of CCB
Khachaturian et al, <sup>436</sup> 2006	Cache County Study	3297	Community based; no dementia	≥65	74	3	Dementia: DSM-III-R; Alzheimer disease: NINCDS-ADRDA	Alzheimer disease: RR=0.64 (0.41–0.98)	Stronger effect for diuretics and specifically potassium-sparing diuretics, HR=0.26 (0.08–0.64)
Peila et al, <sup>431</sup> 2006	Honolulu-Asia Aging Study	1294	Community-based cohort	≥72	76	5	Dementia: DSM-III R and DSM-IV; Alzheimer disease: NINCDS-ADRDA; VaD: CADDTC	HR per year of antihypertensive use: Dementia: HR=0.94 (0.89–0.99); Alzheimer disease: HR=0.96 (0.93–0.99); VaD: HR=0.94 (0.89–0.99)	
Haag et al, <sup>429</sup> 2009	Rotterdam study	6249	Community based; no dementia	≥55	68	13	Dementia: DSM-III-R; Alzheimer disease: NINCDS-ADRDA; VaD: NINDS-AIREN	HR per year of antihypertensive use: Dementia: HR=0.95 (0.91–0.99); Alzheimer disease: HR=0.94 (0.90–0.99)	No differences among antihypertensive drugs
Li et al, <sup>438</sup> 2009	US Veterans Affairs	819 491	Administrative database	≥65	74	4	No specified criteria	...	HR for dementia: ARB vs cardiovascular drugs HR=0.76 (0.69–0.84); ARB vs lisinopril HR=0.81 (0.73–0.90); lisinopril vs cardiovascular drugs HR=0.94 (0.91–0.97)

CI indicates confidence interval; DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition (revised); RR, relative risk; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; VaD, vascular dementia; NINDS-AIREN, National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences; EPESE, East Boston Established Populations for Epidemiologic Studies of the Elderly; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; CCB, calcium channel blocker; HR, hazard ratio; CADDTC, California Alzheimer's Disease Diagnostic and Treatment Centers; and ARB, angiotensin II receptor blocker.

observational studies, including cohort studies with follow-up spanning several decades. Results of studies on blood pressure measured in late life and dementia are less consistent, with most finding no association with hypertension or an association with low blood pressure and dementia.<sup>343,428</sup>

Several longitudinal studies have assessed the impact of the use of antihypertensive drugs on the risk of dementia

(Table 4). Mean duration of follow-up was ≤5 years for most studies, except 2 studies with a follow-up of 13<sup>429</sup> and 19<sup>430</sup> years and that included participants who were a younger age at inclusion. In HAAS there was a large enough range of duration of follow-up to study the effect of duration of treatment >12 years.<sup>431</sup> In none of these studies was antihypertensive treatment associated with an increased risk of



**Table 5. Main Randomized Trials of Antihypertensive Drugs That Have Included Cognitive Impairment or Dementia as Outcomes: General Characteristics**

Study	Sample Size for Analysis	Mean Age (SD), y	Type of Treatment	SBP/DBP Difference (Active vs Placebo)	Duration of Follow-Up, y
SHEP <sup>440</sup>	4736	71.6 (6.7)	Diuretic (chlorthalidone) and/or $\beta$ -blocker (atenolol) or reserpine	-11 to 14/-3 to 4	4.5
Syst-Eur <sup>442</sup>	2418	69.9 (6.2)	Calcium-channel blocker (dihydropyridine) with or without $\beta$ -blocker (enalapril maleate) and/or diuretic (hydrochlorothiazide)	-8.3/-3.8	2.0
PROGRESS <sup>445</sup>	6105	64 (10)	ACEI (perindopril) with or without diuretics (indapamide)	-9.0/-4.0	4
SCOPE <sup>443</sup>	4937	76.4 (...)	ARB (candesartan cilexetil) and/or diuretics	-3.2/-1.6	3.7
HVET <sup>444</sup>	3336	83.5 (3.1)	Diuretic (indapamide) with or without ACEI (perindopril)	-15/-5.9	2.2
PRoFESS <sup>441,446</sup>	20 332	66.1 (8.6)	ARB (telmisartan)	-5.4/...	2.4

SD indicates standard deviation; SBP/DBP, systolic blood pressure/diastolic blood pressure; SHEP, Systolic Hypertension in the Elderly Program; Syst-Eur, Systolic Hypertension in Europe; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; ACEI, angiotensin-converting enzyme inhibitor; SCOPE, Study on Cognition and Prognosis in the Elderly; ARB, angiotensin II receptor blocker; HVET, Hypertension in the Very Elderly Trial; and PRoFESS, Prevention Regimen for Effectively Avoiding Second Strokes.

dementia. In 3 studies there was no association between hypertension treatment and risk of Alzheimer disease,<sup>432–434</sup> whereas in others there was a decreased risk of Alzheimer disease among those receiving antihypertensive treatment.<sup>429,431,435–437</sup> Interestingly, 2 analyses of the same study showed different results according to the duration of follow-up: no effect on dementia and Alzheimer disease in a first study with only 2.2 years of follow-up<sup>432</sup> and a 5% reduction in risk of dementia per year of treatment (6% for Alzheimer disease) in a study with a much longer follow-up.<sup>429</sup> Longer duration of treatment and lower age were associated with a stronger protective effect.<sup>429</sup> This pattern of increased protection for dementia and Alzheimer disease with an increased duration of antihypertensive treatment was also found in HAAS.<sup>431</sup>

Regarding type of treatment, results were less consistent. Several studies were unable to show any evidence of the effect of a particular class of antihypertensive drugs.<sup>429,430,432,434</sup> In both the Kungsholmen project<sup>435</sup> and the Cache County Study,<sup>436</sup> a stronger effect of diuretics and particularly potassium-sparing diuretics for the latter<sup>436</sup> was found compared with other antihypertensive drugs. These findings, however, were based on a limited follow-up, a relatively small number of dementia cases, and confounding by indication. In a recently published study, 3 treatment groups were compared in a large US Veterans Affairs administrative database composed almost exclusively of men (98%). Patients treated with angiotensin receptor blockers were found to have a lower risk of dementia and Alzheimer disease than those treated with lisinopril, an angiotensin-converting enzyme inhibitor, or with other cardiovascular drugs.<sup>438</sup> By comparing angiotensin receptor blockers with an angiotensin-converting enzyme inhibitor, 2 classes of drug similar in novelty and price, this study is a remarkable attempt to overcome confounding by indication. The use of administrative databases, however, is subject to limitations such as a lack of precision concerning diagnosis of dementia and Alzheimer disease or the impossibility of taking into account potential major confounders such as educational level. Furthermore, the follow-up was relatively short, and ethnic dispar-

ities were not assessed. These findings, therefore, need to be confirmed in similar settings or randomized trials.

To summarize:

1. Observational studies point to some benefit of antihypertensive treatment for risk for Alzheimer disease.
2. The longer the duration of treatment, the stronger the preventive effect.
3. Treatment appears more effective in the youngest old than in the oldest people.
4. A few studies suggest a greater effect of some classes of antihypertensive therapy, but the evidence remains limited and is subject to bias so that no firm conclusion can be drawn about this relationship.

### 11.3. Clinical Trials of Blood Pressure-Lowering Drugs and Risk of Dementia

#### 11.3.1. Individual Trials

Six large randomized trials of antihypertensive drugs included an assessment of dementia and cognitive function.<sup>440–445</sup> Four of these trials reported that treatment had no clear-cut effect on the risk of dementia<sup>440,441,443,444</sup> or cognitive function.<sup>441,443,444</sup> However, 1 study reported a beneficial effect on the risk of dementia,<sup>442</sup> and another reported an effect on the risk of PSD<sup>445</sup> (Tables 5 and 6).

In the Systolic Hypertension in the Elderly Program (SHEP),<sup>440</sup> a similar rate of dementia was found in the group receiving active treatment with a diuretic and/or  $\beta$ -blocker (1.6%) and the group receiving placebo (1.9%). A recent reanalysis of the SHEP data suggests that differential dropout may have biased the treatment effect toward the null.<sup>447</sup>

The Study on Cognition and Prognosis in the Elderly (SCOPE)<sup>443,448</sup> was designed to evaluate the effect of treatment with an angiotensin receptor blocker with or without a diuretic on cognitive function in 4937 nondemented elderly hypertensive subjects. There was no major treatment effect on cognition.<sup>443</sup> This lack of benefit must be interpreted in the context of small blood pressure differences observed between the active treatment group and the control group (3.2/

**Table 6. Main Randomized Trials of Antihypertensive Drugs That Have Included Cognitive Impairment or Dementia as Outcomes: Results on Dementia**

Study	Diagnosis of Dementia	Incidence and Number of Dementia Cases				Main Results on Dementia (95% CI)	Type of Dementia (Alzheimer Disease vs VCI or Poststroke Dementia)
		Active		Placebo			
		Cases of Dementia/Number of patients	Incidence (per 1000 patient-years)	Cases of Dementia/Number of Patients	Incidence (per 1000 patient-years)		
SHEP <sup>440</sup>	Expert-based; DSM-III-R	37/2365	Not indicated	44/2371	Not indicated	16% Reduction in dementia; nonsignificant	Not defined
Syst-Eur <sup>442</sup>	Expert-based; DSM-III-R	11/1238	3.8	21/1180	7.7	50% (0% to 76%) Reduction in dementia; $P=0.05$	23 Cases of Alzheimer disease and 7 cases of mixed dementia
PROGRESS <sup>445</sup>	Expert-based; DSM-IV	193/3051	16	217/3054	19	12% (–8% to 28%) Reduction in dementia; $P=0.2$	34% (3% to 55%) Reduction in dementia with recurrent stroke; $P=0.03$ 1% (–24% to 22%) for other dementia; $P=0.9$
SCOPE <sup>443</sup>	ICD-10 criteria; Independent Clinical Event Committee	62/2477	6.8	57/2460	6.3	7% Increased risk in active arm; $P>0.20$	Not defined
HYVET <sup>444</sup>	Expert based; DSM-IV	126/1687	33	137/1649	38	14% (–9% to 23%) Reduction in dementia; $P=0.2$	Similar results for Alzheimer disease (164 patients) and vascular dementia (84 patients)
PROFESS <sup>441</sup>	Clinical impression of dementia	408/8624	Not indicated	409/8646	Not indicated	No reduction of the risk of dementia; $P=0.48$	Not defined

CI indicates confidence interval; VCI, vascular cognitive impairment; SHEP, Systolic Hypertension in the Elderly Program; DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition (revised); Syst-Eur, Systolic Hypertension in Europe; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; SCOPE, Study on Cognition and Prognosis in the Elderly; ICD-10, *International Classification of Disease, 10th edition*; HYVET, Hypertension in the Very Elderly Trial; and PROFESS, Prevention Regimen for Effectively Avoiding Second Strokes.

1.6 mm Hg). Although initially planned as a trial of an angiotensin receptor blocker versus placebo, during the trial and for ethical reasons, antihypertensive drugs were administered to patients in the control group. Therefore, between-group blood pressure differences and the study power were reduced. A post hoc reanalysis of the data in patients not receiving add-on therapy after randomization, although showing evidence of a stronger effect on cardiovascular events, mortality, and vascular mortality, did not change the neutral result on cognition and dementia.<sup>448</sup>

The most compelling support for the prevention of dementia by blood pressure lowering was observed in the Systolic Hypertension Europe (Syst-Eur) trial.<sup>442,449</sup> The trial was stopped prematurely after a median follow-up period of 2 years on evidence of significant benefits from treatment with nitrendipine for lowering the risk of stroke. Dementia was diagnosed in 21 patients from the placebo group and 11 patients from the active treatment group, corresponding to a 50% (95% confidence interval 0% to 76%) decrease in the incidence of dementia in subjects receiving active treatment. Most cases of dementia were Alzheimer disease. In an open-label follow-up study of the same patients in the trial, the principal result was confirmed with twice as many cases of dementia.<sup>450</sup> In the extension study, both Alzheimer disease and VaD were reduced by treatment with nitrendipine.

In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), 6105 patients with a history of stroke or transient ischemic attack were randomly assigned to an angiotensin-converting enzyme inhibitor, perindopril, with or without a diuretic compared with placebo. Combination therapy

reduced systolic and diastolic blood pressure by 12 and 5 mm Hg, respectively, and stroke risk by 43%.<sup>451</sup> During the 4-year follow-up, dementia was diagnosed in 410 patients, of whom 108 had dementia preceded by a stroke. Overall, there was a nonsignificant 12% (range –8% to –28%) reduction in the risk of dementia in the active treatment group. Evaluation within 2 dementia subgroups (with or without prior stroke), however, showed a significant reduction in the risk of dementia with active treatment in patients with a prior history of stroke compared with patients without prior stroke (34% versus 1%;  $P=0.03$ ). A similar result was observed for cognitive decline, defined as a drop of  $\geq 3$  points in the MMSE.<sup>445</sup> Furthermore, in a PROGRESS MRI substudy, it was shown that active blood pressure lowering stopped or delayed the progression of white matter hyperintensities.<sup>452</sup>

In the Hypertension in the Very Elderly Cognitive Function (HYVET-COG) study, 3336 patients >80 years of age with systolic blood pressure >160 mm Hg were treated with slow-release indapamide plus or minus perindopril or placebo. The treatment was found to have no effect on the risk of dementia or cognitive decline.<sup>444</sup> The trial was stopped prematurely, however, after a mean of 2.2 years of follow-up because of a significant reduction in stroke and total mortality.

All published trials share common limitations: (1) short follow-up duration<sup>442,444</sup>; (2) heterogeneity in screening and diagnosis of dementia<sup>441</sup>; (3) patients at low risk for dementia (young mean age)<sup>441,445</sup> and with high baseline MMSE; (4) small numbers of incident cases and low statistical power; and (5) differential dropout, which could lead to overestimating or underestimating the treatment effect.

**Table 7. Meta-Analyses of Randomized Trials of Blood Pressure–Lowering Treatment on Prevention of Dementia**

Author	Year of Publication	Studies	Sample Size (No. of Events/No. of Patients)	Type of Effect	P for Heterogeneity	Main Results
Birns et al <sup>454</sup>	2006	PROGRESS SCOPE SHEP Syst-Eur	642/18 196	Fixed	0.18	0.89 (95% CI 0.75–1.04); <i>P</i> =0.15
Feigin et al <sup>453</sup>	2005	PROGRESS SCOPE SHEP Syst-Eur	883/23 505	Random	0.06	0.80 (95% CI 0.63–1.02); <i>P</i> =0.07
Peters et al <sup>444</sup>	2008	HVET PROGRESS SHEP Syst-Eur	786/16 595	Random	0.49	0.87 (95% CI 0.76–1.00); <i>P</i> =0.045
McGuinness et al <sup>456</sup>	2008	SCOPE SHEP Syst-Eur	232/15 295	Fixed	0.16	0.89 (95% CI 0.69–1.16); <i>P</i> =0.38
McGuinness et al <sup>455</sup>	2009	HVET SCOPE SHEP Syst-Eur	495/15 427	Fixed	0.30	0.89 (95% CI 0.74–1.07); <i>P</i> =0.21

PROGRESS indicates Perindopril Protection Against Recurrent Stroke Study; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; Syst-Eur, Systolic Hypertension in Europe; CI, confidence interval; and HVET, Hypertension in the Very Elderly Trial.

### 11.3.2. Meta-Analyses

To date, 5 meta-analyses have been published on the risk of dementia in antihypertensive trials (Table 7). To summarize:

1. These studies had variable methods in relation to model type (fixed or random) and selection of patients.<sup>453,454</sup>
2. None examined all 5 trials combined, even among those most recently published.<sup>444,455</sup>
3. Only 1 trial found that the risk for dementia was significantly decreased, but it was embedded in the report of the HVET results, and its description was scant, especially concerning selection criteria for the studies.
4. Overall, the variance for reduction of risk for dementia ranged from 11% to 20% (Table 7).

### 11.3.3. Ongoing or Planned Trials

The Systolic Blood Pressure Intervention Trial (SPRINT) is designed to test whether lowering blood pressure beyond recommended levels can provide an added benefit. In this trial, 7500 patients >55 years of age with systolic blood pressure  $\geq 130$  mm Hg and at least 1 other vascular risk factor (hypercholesterolemia, smoking) will be randomized to an “aggressive” treatment arm with a target systolic blood pressure of <120 mm Hg and a more “routine” arm with a target systolic blood pressure of <140 mm Hg. Patients will be followed up for a minimum of 4 years. The trial began in the fall of 2010 and includes a substudy of cognition (SPRINT-MIND) funded by the National Institute on Aging and NINDS.

### 11.3.4. Summary and Recommendations: Blood Pressure Lowering and Cognition

#### 11.3.4.1. Summary

Observational studies point to some benefit of antihypertensive treatment on the risk for Alzheimer disease, the treatment

being apparently more effective in the youngest old than in the oldest people.

Few large blood pressure–lowering trials have incorporated cognitive assessment and diagnosis of dementia. They share several limitations, and therefore, considerable uncertainty remains about the efficacy of antihypertensive drugs for lowering the risk of dementia in general and Alzheimer disease in particular.

Meta-analyses neither prove nor disprove the efficacy of antihypertensive treatment on the risk of dementia. They are subject to limitations similar to those of therapeutic trials and do not yield any substantial additional information. An individual patient data meta-analysis could be useful because it could allow proper assessment of potentially major effect modifiers such as age, blood pressure level, and cognitive level at baseline. It could also be of help in identifying high-risk groups for further trials.

#### 11.3.4.2. Recommendations

1. **In patients with stroke, lowering blood pressure is effective for reducing the risk of PSD (Class I; Level of Evidence B).**
2. **There is reasonable evidence that in the middle-aged and young-elderly, lowering blood pressure can be useful for the prevention of late-life dementia (Class IIa; Level of Evidence B).**
3. **The usefulness of lowering blood pressure in people >80 years of age for the prevention of dementia is not well established (Class IIb; Level of Evidence B).**

## 11.4. Diabetes

Patients with diabetes of long duration are at increased risk of cognitive decline, dementia, and depression, as well as other phenotypes associated with aging.<sup>438a</sup> Among risk factors for



cognitive dysfunction and dementia, it has been documented that both hyperglycemia and hyperinsulinemia, as part of the metabolic process leading to type 2 diabetes mellitus, are associated with cognitive dysfunction and stroke dementia. This is often accompanied by other disturbances of mental function, such as depression or anxiety, all of these conditions being described as being more prevalent in established type 2 diabetes mellitus.<sup>438a</sup>

The treatment of hyperglycemia is associated with prevention of both microvascular and, to some degree, macrovascular events, based on data from a recent meta-analysis.<sup>457</sup> However, the prevention of stroke has not been shown with careful control of blood glucose, and no studies have specifically investigated possible protective effects by reduction of hyperglycemia in mild VCI or early stages of dementia. Thus, intensified treatment of hyperglycemia is not protective of stroke,<sup>457</sup> a risk factor for cognitive decline. In severe cases of hyperglycemia, the cognitive dysfunction is acutely impaired by hyperosmolar influences and electrolyte disturbances, conditions that are possible to improve by acute insulin therapy.

In the ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation), the combined approach to treat both hyperglycemia and hypertension has been effective to reduce macrovascular end points and mortality. It was concluded that cognitive dysfunction is an independent predictor of clinical outcomes in patients with type 2 diabetes mellitus but does not modify the effects of blood pressure lowering or glucose control on the risk of major cardiovascular events.<sup>458</sup>

On the basis of a systematic review, there is no convincing evidence relating type or intensity of diabetic treatment to the prevention or management of cognitive impairment in type 2 diabetes mellitus.<sup>459</sup> The possible effect of intensive control-induced hypoglycemia on cognitive function represents a relevant and yet-to-be-explored aspect in older people with diabetes.

#### **11.4.1. Summary and Recommendation: Diabetes**

##### *Summary*

Diabetes is an important risk factor for mental symptoms and cognitive impairment, but available data are based mostly on observational studies. The level of evidence for a protective effect of reduction of hyperglycemia is very low. Further intervention studies are needed to elucidate the role of reduction of hyperglycemia in prevention of cognitive impairment and dementia. Also, new antidiabetes drugs have to be tested in relation to prevention of cognitive impairment or dementia. There is a need to support new studies on the role of hyperglycemia and cognitive impairment and whether correction of hyperglycemia with old and new drugs could influence this process.

##### *Recommendation*

- 1. The effectiveness of treating diabetes/hyperglycemia for the prevention of dementia is not well established (Class IIb; Level of Evidence C).**

#### **11.5. Lipids**

Hyperlipidemia or dyslipidemia is a metabolic condition of importance for cognitive function. Treatment with statin

therapy has been documented to protect against stroke, both in primary<sup>460</sup> and secondary studies, based on data from meta-analysis<sup>36</sup> and a single trial, Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL).<sup>461</sup>

In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), after 4 years of treatment, no difference in cognitive function was shown, as evaluated by the MMSE, between patients receiving pravastatin or placebo.<sup>358</sup> Several meta-analyses have concluded that there is no measurable influence of statin therapy on cognitive dysfunction in humans,<sup>462</sup> even if animal experiments in rodents have supported the notion that some protection is offered by statin therapy.<sup>463</sup> One statin intervention study completed in 2007 has not been presented thus far: the Cholesterol Lowering Agent to Slow Progression (CLASP) of Alzheimer's Disease Study.<sup>463a</sup> In the recently published Lipitor's Effect in Alzheimer's Dementia (LEADe) trial, which included 640 randomized patients with mild Alzheimer disease, intensive lipid lowering by the addition of atorvastatin (80 mg) to donepezil did not improve cognitive function over a 72-week period.<sup>464</sup>

#### **11.5.1. Summary and Recommendation: Lipids**

##### *Summary*

Although lipid control by statin therapy is able to prevent stroke, these drugs do not prevent cognitive decline in the elderly. There is scant evidence from observational studies on the effects of statin therapy on cognitive function, and the level of evidence is low. There is a need to support new studies on the role of hyperlipidemia and cognitive impairment and whether correction of hyperlipidemia with drug therapy could influence this process.

##### *Recommendation*

- 1. The usefulness of treatment of hyperlipidemia for prevention of dementia is uncertain (Class IIb; Level of Evidence C).**

#### **11.6. Other Interventions for Vascular Factors**

##### **11.6.1. Antiaggregants**

Some observational studies have suggested a beneficial effect of aspirin on cognition,<sup>465,466</sup> although this was not confirmed in others.<sup>467,468</sup> Few trials on antiplatelet therapy have included a cognitive evaluation.<sup>441,469</sup> In the Aspirin for Asymptomatic Atherosclerosis (AAA) trial, 3350 participants 50 to 75 years of age were randomly assigned to receive long-term use of enteric-coated aspirin 100 mg once daily or placebo. During a 5-year follow-up, no difference in cognitive ability was found between the aspirin and placebo arms.<sup>469</sup> In the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial, 2032 patients with ischemic stroke were randomly assigned in a 2×2 factorial design to receive either 25 mg of aspirin and 200 mg of extended-release dipyridamole twice a day or 75 mg of clopidogrel once a day and either 80 mg of telmisartan or placebo once a day to test primarily for recurrent stroke prevention, with cognitive decline or dementia as a nonprimary end point. After a median follow-up of 2.4 years, no difference was observed between the 2 antiplatelet regimens on any measure of cognition (median MMSE score ≤24) or severe cognitive

decline (decrease in MMSE score  $\geq 3$  points between baseline and penultimate visit) or dementia.<sup>441</sup>

### 11.6.2. Lifestyle

A few observational studies have documented that people who consume a Mediterranean diet have better cognition and less risk of dementia than people consuming other diets.<sup>470</sup> Recently, a better adherence to a Mediterranean-type dietary pattern was associated with less cognitive decline in a community with older subjects.<sup>471</sup> There is no randomized controlled study of similar effects in healthy subjects.

The same beneficial effects of increased physical activity on cognitive function have also been documented in observational studies,<sup>472</sup> but only 1 small intervention trial has followed up subjects for cognitive improvement after increasing physical exercise. Aerobic exercise has been shown to be useful. A study of 6 months' duration in elderly women provides support, using rigorous controlled methodology, for a potent nonpharmacological intervention that improves executive control processes for older women at high risk of cognitive decline.<sup>473</sup> At the same time, it would be informative to understand why some cognitive functions seem to improve with aerobic physical exercise whereas other functions seem to be insensitive to physical exercise.<sup>474</sup> The results of a recently published meta-analysis on the effect of physical activity on cognitive decline, based on 15 observational studies, suggest a significant and consistent protection afforded by all levels of physical activity against the occurrence of cognitive decline.<sup>475</sup>

Smoking is a risk factor for stroke-associated dementia. There are no intervention studies to prove the benefits of smoking cessation on preserving cognitive function.

### 11.6.3. Vitamin Supplements

Studies have been performed to test whether vitamin supplements might improve cognitive function. According to 1 systematic review, there was no beneficial effect of folic acid 750  $\mu\text{g}/\text{d}$  on measures of cognition or mood in healthy older women.<sup>476</sup>

In patients with mild to moderate cognitive decline and different forms of dementia, there was no benefit from folic acid on measures of cognition or mood.<sup>476</sup> However, in another study from The Netherlands, supplementation with 800  $\mu\text{g}$  daily of oral folic acid for 3 years in 818 participants significantly improved domains of cognitive function that tend to decline with age.<sup>477</sup>

With regard to lowering homocysteine by vitamin B supplementation, no benefit was shown in 1 Australian study that included 276 healthy elderly subjects with repeated tests of cognitive function after 1 and 2 years.<sup>478</sup>

### 11.6.4. Summary and Recommendations: Other Interventions

#### Summary

Adherence to a Mediterranean-type dietary pattern has been associated with less cognitive decline in several observational studies.

There is generally a lack of evidence for a positive benefit of antiaggregants and vitamin supplementation on cognitive function. No improvement of cognitive function has been proven when reduction of homocysteine was reached with

supplementation with vitamin B. Therefore, evidence for these interventions is lacking, and they cannot be recommended.

A few observational studies and very few intervention trials have shown that lifestyle modification (eg, diet, physical activity) may improve cognitive function. Even though smoking is a well-known risk factor for vascular pathology, the role of smoking cessation has not been studied in relation to changes in cognitive function.

There is only limited evidence to support the idea that physical therapy could contribute to prevention of cognitive decline. There is a need to support new studies on the role of lifestyle interventions to prevent cognitive impairment and whether smoking cessation could influence this process.

#### Recommendations

1. **A Mediterranean-type dietary pattern has been associated with less cognitive decline in several studies and may be reasonable (Class IIb; Level of Evidence B).**
2. **Vitamin supplementation is not proven to improve cognitive function, even if homocysteine levels have been positively influenced, and its usefulness is not well established (Class IIb; Level of Evidence B).**
3. **Physical activity might be considered for the prevention of cognitive impairment (Class IIb; Level of Evidence B), but the usefulness of other lifestyle or vitamin interventions is uncertain (Class IIb; Level of Evidence B).**
4. **The effectiveness of antiaggregant therapy for VCI is not well established (Class IIb; Level of Evidence B).**

## 12. Summary and Course of Action

In developed countries, a rapid increase in the aged population is anticipated. In 2000, for example, there were 600 million people  $\geq 60$  years of age; it is estimated that by 2050 there will be 1.2 billion people in this age group, and by 2050, 2 billion. The oldest people in our population ( $\geq 80$  years old) are a fast-growing group, and  $\approx 20\%$  experience important difficulties in performance of activities of daily living. Furthermore, cognitive impairment is a relatively common condition of the elderly that significantly affects their ability to live independently. The prevalence of dementia increases with advancing age and is estimated to affect  $\geq 30\%$  of people  $> 80$  years of age,<sup>264,479,480</sup> with the annual cost of care being  $> \$40\,000$  per patient in the United States. Identification of people at risk for cognitive impairment or mild forms of cognitive impairment (eg, MCI, VaMCI) holds promise for prevention or postponement of dementia and its sequelae and for public health cost savings.<sup>23,481,482</sup> The opportunity to prevent or postpone cognitive impairment may be realized by assessment of cardiovascular and stroke risks and appropriate treatment of such risk markers. Cognitive function, an important predictor of morbidity and mortality in the elderly, however, is frequently not screened for in clinical practice as part of global cardiovascular risk and target-organ damage assessments.

As discussed in this statement, understanding of common causes of late-life cognitive impairment and dementia—Alzheimer disease and VCI—has advanced.<sup>483</sup> It is now accepted that many of the traditional risk factors for stroke are also risk

markers for Alzheimer disease and VCI.<sup>16,31,340,484–491</sup> In fact, there is an angiogenesis hypothesis for Alzheimer disease and a possible role for genes in neurovascular unit dysfunction in Alzheimer disease.<sup>107,492</sup> Therefore, it has been proposed that there may be a convergence of pathogenic mechanisms in vascular and neurodegenerative processes that cause impairment of cognition.<sup>101,493</sup> Epidemiological evidence to support the convergence of mechanisms is observed in studies that show traditional cardiovascular risk factors also heighten risk of Alzheimer disease. For example, in a cohort in Finland, the combination of elevated systolic blood pressure, hypercholesterolemia, and obesity increased the risk of Alzheimer disease by  $\approx 6$  times, whereas individually, any of these factors alone increased risk by  $\approx 2$  times.<sup>494</sup>

The epidemiological observations mentioned previously coupled with preclinical study findings have allowed us to consider shifting our prevention focus to more “upstream” targets such as shared vascular risk markers,<sup>484–486</sup> extrinsic (eg, somatic and mitochondrial mutations, advanced glycation end products, proinflammatory cytokines) and intrinsic (eg, telomere shortening, decreased decline in growth factors, apoptosis) mechanistic pathways that may influence prevention outcomes,<sup>495</sup> and other novel approaches.<sup>107</sup> Furthermore, we may now consider the possibility that Alzheimer disease is actually Alzheimer diseases, a group of disorders that could possibly be driven by different pathophysiological mechanisms.<sup>496</sup> Support for this notion is based on evidence of disparate pathophysiological mechanisms by which vascular risk factors such as hypertension, diabetes, and dyslipidemia might cause or potentiate Alzheimer disease. Other data (F.T., P.B.G., unpublished data, 2010).

In addition, as subclinical CVBI, stroke, and vascular risk factors have been a major focus of this statement, a better understanding of the prevention of “silent” strokes and WMLs (ie, “covert” brain injury) is necessary, because these events may be associated with neuropsychological deficits and contribute to VCI and eventual manifest stroke sequelae risk.<sup>498</sup> It is estimated that “silent” strokes outnumber clinically manifest ones by a factor of  $>9:1$ , and the proportion of those with a milder form of VCI is approximately 2-fold greater than those with a severe form of VCI (ie, VaD). This group of patients with covert brain injury might be one that is well suited for proof-of-concept studies of vascular risk factor control strategies.

In summary, this statement has discussed controversies in relation to vascular causes of cognitive impairment and dementia and the evidence for the role of vascular factors, arterial aging, and CVBI in cognitive impairment. A current course of action for furthering our understanding of vascular contributions to cognitive impairment and dementia has been recommended previously.<sup>499</sup> It takes into account transdisciplinary, translational, and transactional opportunities and recommends taking advantage of shared pathophysiological mechanisms of many brain diseases that may influence cognition, cross-disciplinary expertise, new therapeutic targets for planning clinical trials, the underexplored and underexploited borderlands between stroke and Alzheimer disease, the “brain at risk” or in the disease-induction stage, and systematic integration strategies.

To develop an action plan, we need to consider establishment of the following research programs to advance the field:

1. Continued development, validation, and refinement of practicable cognitive batteries for testing people with VCI within and across geographic, cultural, and ethnic regions.<sup>5</sup>
2. Continued pursuit of novel neuroimaging methodology to identify biomarkers and risks for CVBI associated with VCI.<sup>500</sup>
3. Establishment of additional longitudinal clinical-neuropathological studies with neuroradiological correlation.
4. Development of nationally funded centers of excellence for the study of CVBI and vascular contributions to cognitive impairment and dementia with transdisciplinary, translational, and transactional links within and between centers.
5. Midlife and later-life cost-effectiveness research and proper, statistically powered, randomized controlled clinical trials targeting key vascular risk markers and the influence of their control on prevention of VCI and Alzheimer disease.<sup>496</sup>
6. Preclinical and clinical studies to better understand the influence of aging on major arteries and the neurovascular unit.
7. Studies to identify novel risk markers for vascular contributions to cognitive impairment and dementia.
8. Studies to better understand the relationship between location, severity, and extent of vascular brain injury and the resultant cognitive syndromes, while simultaneously accounting for coexisting age-related pathologies and cognitive reserve. These programs should include a search for genetic and other novel factors with an overarching goal to identify new strategies for prevention or treatment of VCI. Preliminary study of interventions among people with vascular risk factors and clinically defined CVBI may be a first step for testing prevention strategies before embarking on full-scale clinical trials.

With such advances in the field in basic science, pharmacology, epidemiology, neuroradiology, and neuropathology, we will then be better positioned to guide clinicians in relation to practice challenges such as the following:

1. Choice of neuropsychological test battery and frequency of neuropsychological testing to detect VCI and related forms of cognitive impairment.
2. Value of and targets for control of various cardiovascular risk factors to prevent cognitive impairment.
3. Application and interpretation of genetic and other novel vascular risk markers for VCI.

Currently, in the absence of such definitive data for guidance, we encourage clinicians to use screening tools to detect cognitive impairment in their older patients (eg, [www.mocatest.org](http://www.mocatest.org)) and to continue to treat vascular risks according to nationally or regionally accepted guidelines. Recently published statements in 2011 from the American Heart Association on the prevention of first and recurrent stroke provide useful targets for risk factor management, although these recommendations have not been specifically tested in patients with VCI.<sup>501,502</sup>



## Disclosures

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\*Modest.

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\*Modest.

†Significant.

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