

# Treatment of vascular cognitive impairment

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## **Abstract**

Vascular cognitive impairment is spectrum of cognitive change related to vascular pathology from early cognitive decline to dementia. Management of risk factors that may increase damage to the brain vasculature is an important treatment strategy. There is substantial evidence that treating risk factors may improve outcomes and help delay further decline. Thus, pharmacological therapy primarily helps to prevent worsening of vascular dementia by controlling the underlying disease, such as hypertension, hyperlipidemia or diabetes mellitus. To date, there is no approved drug for vascular dementia, and the use of acetylcholinesterase inhibitors should not be routinely prescribed.

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**Keywords:** vascular dementia, vascular cognitive impairment, clinical trial, treatment, prevention

## **Introduction**

Vascular lesions such as infarctions of the cerebral hemispheres, at least in part, can lead to development of dementia. Changes in cognitive function may occur suddenly after a stroke or begin slowly and as gradually worsen, depending on types of stroke. The term “vascular cognitive impairment (VCI)” is increasingly preferred by experts on “vascular dementia”, because the former express the concept that cognitive deficits can range from mild to severe. Stroke and dementia share common risk factors including hypertension, the strongest risk factor, diabetes mellitus, hyperlipidemia, and metabolic syndrome.<sup>1-3</sup> Silent infarctions are also an important risk factor for developing dementia.<sup>4</sup> In addition, vascular brain pathology often coexists with changes related to other types of dementia, including Alzheimer’s disease (AD) and dementia with Lewy bodies.<sup>5</sup> Clinically, although the neuropsychological profiles in vascular dementia vary considerably, it is rare for vascular dementia to present with isolated memory loss without executive function deficits.<sup>6</sup>

Based on the diagnostic approach recommended in the joint scientific statement on vascular contributions to mild cognitive impairment (MCI) and dementia issued by the American Heart Association and American Stroke Association in 2011,<sup>7</sup> the following criteria suggest the greatest likelihood for MCI or dementia to be caused by vascular changes:

1. The diagnosis is confirmed by neurocognitive testing, that provides detailed evaluation of specific cognitive function such as judgment, planning, problem-solving, reasoning and memory
2. There is imaging evidence, usually with magnetic resonance imaging (MRI), showing evidence of either a recent stroke or other vascular changes consistent with the types of impairment documented in neurocognitive testing
3. There is no evidence of other factors that are contributing to cognitive decline.

## **Neuropathogenesis of vascular cognitive impairment**

In addition to small ischemic lesions in the brain that can directly affect cognitive function by damaging areas essential for cognitive function, other more complex interactions between vascular disease and cognitive function exist. The angiotensin II system can lead to increased production of amyloid, involved in the pathogenesis of AD, and this interaction is thought to occur at the endothelium of brain microvasculature, where amyloid peptide is made.<sup>8</sup> Another factor is a gene that regulates vascular differentiation such as MEOX2. This gene, expressed at low level in the brains of AD patients, also regulates angiogenesis, reduces apoptosis, and increases production of a protein involved in the clearance of amyloid.<sup>9</sup> Research on the interaction of vascular factors with amyloid deposition may shed light on the pathogenesis of vascular dementia.

## **Treatment of vascular cognitive impairment**

Vascular dementia can be considered a preventable dementia. Primary prevention is primary care of vascular risk factors or a secondary prevention of factors that could cause recurrence of stroke. In this review, guidelines are summarized only on symptomatic treatment: pharmacologic or non-pharmacologic treatments, based on the criteria published in the recommendations of the American Academy of Neurology Classification of Evidence – Therapeutic Studies (*Tables 1 and 2*).<sup>10</sup>

Table 1 Summarized classification of studies.

Class I	A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
Class II	A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e in Class I or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e in Class I. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
Class III	All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.
Class IV	Studies not meeting Class I, II or III criteria including consensus or expert opinion.

Table 2 Levels of evidence.

A	Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*
B	Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)
C	Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)
U	Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*\*In exceptional cases, one convincing Class I study may suffice for an “A” recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).*

## **1. Treatment of vascular disease-related conditions in patients with VCI**

Management of risk factors for vascular diseases that may contribute to VCI are the mainstream for treating patients with VCI. (Table 3) Systemic arterial hypertension (SAH) is one of the potential risk factors. Although the use of anti-hypertensive agents can reduce the risk of cognitive decline and dementia, including VCI, the HYVET-COG sub-study, a double-blind controlled trial using indapamide and perindopril in older elderly over 80 years of age, showed a non-significant reduction in dementia in the treated sub-group.<sup>11</sup>

In diabetes mellitus, the ACCORD-MIND trial offered benefits of controlling HbA1C < 6% over 7–7.9% for preventing cognitive decline. However, the study showed that strict control increased mortality and is contraindicated in diabetic patients at high risk.<sup>12,13</sup>

Dyslipidemia is considered a risk factor for cognitive decline. Two randomized trials (HPS2002 using simvastatin and PROSPER2002 using pravastatin), which included patients aged > 70 years, failed to confirm any effect on the incidence of dementia or cognitive decline, although both studies found a significant reduction in LDL levels.<sup>14</sup> The LEADe study, a randomized, double-blind, multi-center trial in patients with mild to moderate AD, revealed no benefit of atorvastatin in the treated group over placebo on cognition and global functioning measured by the ADAS-Cog and the ADCS-CGIC, respectively.<sup>15</sup>

In patients with heart failure, a study showed that the use of ACE inhibitors has been associated with cognitive improvement, independently of basal blood pressure levels.<sup>16</sup>

Several studies have assessed cognitive function after carotid revascularization either by surgical approach, carotid endarterectomy (CEA) or endovascular approach by carotid artery stenting (CAS). Among these studies many have shown no changes in cognition after procedure, some have noted improvements while others have found decline.<sup>17–21</sup>

The use of aspirin in patients with cognitive impairment has been investigated. A randomized trial of aspirin and placebo for five years in subjects aged > 50 years found no significant difference in cognition.<sup>22</sup> The PROFESS study, assessing aspirin plus dipyridamole versus clopidogrel and telmisartan, showed no difference between the two antiaggregants on cognitive function.<sup>23</sup> In AD patients, the administration of aspirin showed no benefits on cognition but increased the risk of hemorrhage.<sup>24,25</sup>

Cigarette smokers are at higher risk of developing cognitive impairment in general. In a study of the 23-year follow-up that compared smokers of > two packs a day to non-smokers, showed the former group to be at greater risk for VCI.<sup>26</sup>

Several studies on alcohol have shown that an intake of low amounts of alcohol has a preventive effect on the development of AD and vascular dementia.<sup>27</sup> However, there is a deleterious effect when consumed at high doses. The consumption of two daily drinks (<30 gram/day) is associated with reduced overall risk, whereas ≥ three drinks is associated with increased risk of ischemic or hemorrhagic stroke.<sup>28</sup>

Overweight and obese individuals are at higher risk for dementia. A positive association between body mass index in adult life and occurrence of AD and vascular dementia in later life was found, with a five-fold higher risk of vascular dementia in obese subjects and twice among overweight subjects, regardless of vascular factors.<sup>29</sup>

Increased consumption of fruit, vegetables, grains and unsaturated fatty acids (olive oil), low intake of meat and saturated fatty acids plus moderate intake of alcohol, have been associated with a lower risk for dementia and reduced conversion of mild cognitive impairment to AD.<sup>30,31</sup> Supplementation with omega-3, vitamin C, vitamin E, beta carotene, vitamin B12, folic acid and vitamin B6 in randomized trials has failed to show any effect on cognitive decline prevention.<sup>32–34</sup>

A meta-analysis of prospective studies involving non-demented subjects, followed up for 1 – 12 years, found that a high level of physical exercise was

associated with a 38% reduction in risk of cognitive decline, whereas light to moderate physical exercise was associated to a 35% reduction in risk of decline.<sup>35</sup> In a randomized clinical trial, physical exercise was associated with lower risk of developing mild cognitive impairment and dementia among adults with subjective memory complaints.<sup>36</sup>

Sleep disturbance is a risk factor for vascular dementia. Randomized studies showed that treatment of obstructive sleep apnea in AD patients has benefits for improving some aspects of cognitive function.<sup>37</sup>

## **2. Pharmacological therapy for VCI (Table 4)**

Although clinical trials have shown some efficacy of donepezil and galantamine in patients with vascular dementia, the US Food and Drug Administration (FDA) has not approved these drugs for vascular dementia.<sup>38–48</sup> One study, in which the definition of vascular dementia is imprecise and unclear, reported excess deaths in the donepezil treatment group.<sup>49</sup> Furthermore, a meta-analysis of randomized clinical trials of cholinesterase inhibitors in vascular dementia showed only small benefits in cognitive function, without significant improvement in activities of daily living or behavioral changes.<sup>50</sup> Therefore, use of these acetylcholinesterase inhibitors cannot be routinely recommended. However, it is possible that there are some benefits of these drugs in patients with vascular dementia related to underlying AD pathology.

Memantine, approved for moderate to severe AD, has shown promise in clinical trials including patients with vascular dementia. However, this drug is not FDA approved for vascular dementia.<sup>51,52</sup>

In patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), donepezil did not improve overall cognitive function or memory, although some benefits in executive function were found.<sup>53</sup>

A randomized, double-blind, placebo-controlled trial showed that patients with subcortical vascular dementia receiving nimodipine had less marked decline on the MMSE and Global Deterioration Scale

(GDS) compared with patients given placebo.<sup>54</sup> A long-term benefit from nimodipine has yet to be confirmed by long-term trials. Two trials have been conducted on the use of nicardipine in vascular dementia, both with methodological limitations that impede the result validation.<sup>55,56</sup>

For pentoxifylline,<sup>57</sup> citicoline,<sup>58</sup> and cerebrolysin,<sup>59</sup> good quality of the trials, and randomized studies with a larger number of patients and longer follow-up periods are needed to confirm previous controversial observations. Thus, these drugs are not recommended for the treatment of VCI.

For ginkgo biloba,<sup>60</sup> hydergine,<sup>61</sup> and piracetam,<sup>62</sup> due to heterogeneous diagnostic criteria, inconsistent results, and the small numbers of patients, it can be concluded that these medications should not be used for the treatment of VCI.

## **Conclusion**

Any condition that damages cerebral blood vessels can cause brain changes linked to VCI. Risk factors for VCI coincide with those that increase risk for stroke, heart disease and other conditions affecting blood vessels. Many of these factors are also linked to increased risk of AD. Thus, controlling risk factors that may contribute to damage to the cerebral blood vessels is a major treatment strategy. To date, there is no FDA approved drug for vascular dementia, and the use of acetylcholinesterase inhibitors should not be routinely prescribed.

Table 3 Treatment of vascular disease-related conditions in patients with VCI.

Condition or treatment option	Recommendation	Level of evidence	Reference
Systemic arterial hypertension	Anti-hypertensive drugs can reduce the risk of cognitive decline, including VCI. However, there is insufficient evidence to recommend the use a specific class of drugs.	B	11
Diabetes mellitus	Strict control of plasma glucose (HbA1C < 6%) is not recommended for exclusively preventing cognitive decline.	B	12, 13
Dyslipidemia	Use of statins in elder (> 70 years old), individuals with vascular risk factors, is not recommended exclusively for the prevention or treatment of dementia.	B	14, 15
Heart failure	Treatment of co-morbidities linked to heart failure in elderly patients (anemia, SAH <sup>1</sup> , electrolyte imbalance, hyperglycemia, hypoalbuminemia) can slow down cognitive decline. - The use of ACE <sup>2</sup> inhibitors can be recommended in patients with heart failure, independently of treatment to control blood pressure.	C C	16
Atrial fibrillation (AF)	Ensure adequate anticoagulation control in patients with AF and cognitive decline.	C	63
Carotid revascularization	CEA <sup>3</sup> or CAS <sup>4</sup> in patients with symptomatic carotid stenosis has no benefit on cognitive performance, and should not be recommended for the purpose of preserving or improving cognitive function.	C	17–21
Anti-platelet agents: - acetylsalicylic acid, dipyridamole, clopidogrel, telmisartan	Use of anti-platelet agents is not recommended for primary prevention of cognitive decline and dementia.	B	22–25
Smoking	Smoking cessation should be recommended.	C	26
Alcohol	High amount consumption of alcohol must be avoided.	C	27, 28
Obesity	Controlling weight within normal levels should be encouraged.	C	29
Diet and supplements	Promoting consumption of healthy foods predominantly vegetables, unsaturated fatty acids, grains and fish is recommended.	B	30–34
Physical exercise	Regular physical exercise should be recommended to healthy subjects, patients with CVD <sup>5</sup> , and to patients with cognitive decline.	B	35, 36
Sleep apnea	Treatment of obstructive sleep apnea can yield some cognitive improvement.	C	37

<sup>1</sup>systemic arterial hypertension; <sup>2</sup>angiotensin-converting enzyme; <sup>3</sup>carotid endarterectomy; <sup>4</sup>carotid artery stenting;

<sup>5</sup>cerebrovascular disease

Table 4 Pharmacological therapy for VCI.

Drug	Recommendation	Level of evidence	Reference
Cholinesterase inhibitors: – donepezil, rivastigmine, galantamine	Assessments of VCI subtypes are needed and use should be dedicated and targeted. – Benefits seem dominant in subcortical VCI patients.	B  C	38–50, 53
Glutamate receptor antagonists: – mimantine	Assessments of VCI subtypes are needed and use should be dedicated and targeted. – Benefits seem dominant in subcortical VCI patients.	B  C	51, 52
Calcium channel blockers: – nimodipine, nicardipine	Both nimodipine and nicardipine cannot be recommended for the treatment of VCI.	C	54–56
Pentoxifylline	Not recommended.	U	57
Citicoline	Insufficient data to recommend.	C	58
Cerebrolysin	Not recommended.	C	59
Ginkgo biloba, hydergine, piracetam	These medications should not be used in the treatment of VCI.	B	60–62

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### **บทคัดย่อ**

ความบกพร่องทางพุทธิปัญญาเนื่องจากโรคหลอดเลือดสมองเป็นการเปลี่ยนแปลงทางพุทธิปัญญาที่มีสาเหตุเกี่ยวกับหลอดเลือด โดยครอบคลุมถึงอาการตั้งแต่การลดลงของระดับพุทธิปัญญาระยะเริ่มต้นจนถึงภาวะสมองเสื่อม การจัดการกับปัจจัยเสี่ยงที่อาจก่อความเสียหายกับหลอดเลือดในสมองถือเป็นกลยุทธ์ที่สำคัญในการรักษา มีหลักฐานจำนวนมากที่สนับสนุนการรักษาปัจจัยเสี่ยงดังกล่าวว่าช่วยชะลอการดำเนินโรคและทำให้ผู้ป่วยมีอาการดีขึ้น การรักษาด้วยยานั้น โดยพื้นฐานแล้วเป็นการรักษาเพื่อป้องกันไม่ให้ภาวะสมองเสื่อมแย่ลง ด้วยการควบคุมปัจจัยเสี่ยง เช่น ความดันโลหิตสูง ไขมันในเลือดสูง หรือเบาหวาน ในปัจจุบันยังไม่มียาที่ได้รับการอนุมัติให้ใช้รักษาภาวะสมองเสื่อมจากโรคหลอดเลือดสมอง และจากหลักฐานในปัจจุบัน พบว่าไม่มีความจำเป็นต้องใช้ยากลุ่มยับยั้งอะเซทิลโคลีนเอสเตอเรสในผู้ป่วยทุกราย

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