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Dementia (E McDade, Section Editor)

Treatment of Vascular Cognitive Impairment

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Opinion statement

Cerebrovascular disease (CVD) is an important cause of cognitive dysfunction and dementia. The term vascular cognitive impairment (VCI) is used to describe the entire spectrum of cognitive dysfunction—ranging from mild impairment to dementia—attributable to all forms of cerebrovascular disease. Accurate assessment and management of vascular risk factors are a top priority in the treatment of VCI, particularly early in the disease when prevention strategies may prove to be more effective. There are limited treatment options to improve cognition and function in VCI. Several acetylcholinesterase inhibitors and the NMDA receptor antagonist memantine have been studied in large, well-designed trials. These agents are safe and provide modest cognitive benefits in vascular dementia (VaD) but have demonstrated inconsistent efficacy on functional measures. Other therapies, such as aspirin, calcium channel blockers, and vitamin supplementation, have less evidence to support their use in improving cognition in VCI. Although primary prevention trials suggest that treatment of hypertension, adherence to a Mediterranean diet, physical activity, and smoking cessation may reduce the risk of cognitive decline, there is limited evidence regarding these interventions in helping improve cognition in VCI. The pathophysiology and treatment of cerebral autosomal dominant arteriopathy with subcortical infarcts (CADASIL), cerebral amyloid angiopathy (CAA), and subcortical white matter disease (SWMD) deserves special consideration.

Introduction

Cerebrovascular disease (CVD) is the second most common cause of dementia in the USA and Europe after Alzheimer's disease (AD), accounting for approximately 20 % of all cases of dementia [1]. Emerging evidence also suggests that CVD may play a role in the pathogenesis of other neurodegenerative diseases—up to 50 % of persons

with clinically diagnosed AD also have evidence of CVD post-mortem [2, 3]—the role of vascular disease in mediating AD pathology is currently being intensely investigated. CVD, which contributes to significant dementia burden, is better understood than AD in terms of risk factors predisposing towards it. Cognitive decline related to CVD is currently more amenable towards primary prevention; therefore, a clinician needs to be acutely aware of its role in the cognitive changes being evaluated.

The medical terminology to capture cognitive changes related to CVD has evolved over time. These terminologies, which included Binswanger's disease [4], multi-infarct dementia (MID) [5], post-stroke dementia (PSD) [6], and vascular dementia (VaD) [7], were often inconsistently applied and focused primarily on memory impairment, failing to account for the breadth of cognitive dysfunction associated with CVD (mild attention and processing speed deficits to functional impairment of dementia). The term vascular cognitive impairment (VCI) is increasingly prevalent in the literature and captures the entire spectrum of cognitive impairment attributable to all forms of CVD and also acknowledges the impact that vascular disease has on other neurodegenerative diseases [3]. Recognizing the contribution CVD has on cognitive dysfunction before the stages of dementia maximizes the opportunity to intervene medically and slow the progression of cognitive decline [8]. In its mildest form, VCI affects one cognitive domain (often executive functioning), and in a terminology analogous to mild cognitive impairment (MCI), patients are described as having vascular cognitive impairment, no dementia (vCIND) [9]. In its most severe form, multiple cognitive domains are severely affected and patients are described as having VaD [10]. Given the various pathological manifestations of CVD—including large cortical infarcts, white matter changes, strategically placed infarcts, brain hemorrhage, and mixed neurodegenerative and vascular disease—VCI is best thought of as a heterogeneous syndrome rather than a distinct clinical disorder [11].

Several pharmacological agents have been tested in large phase III trials to overcome cognitive decline in VCI, and several candidates are being developed [12]; however, there are still no FDA-approved treatments for VCI. Three related challenges limit current therapeutic success in VCI: (1) CVD is very often found with other neurodegenerative pathologies; (2) unlike many neurodegenerative diseases, staging of VCI is often not linear due to the role of small strategic infarcts and there often is difficulty in attributing degree of functional deficits to amount of vascular pathology noted on MRI or autopsy; and (3) primary prevention of vascular disease is better understood and has a higher clinical impact than tertiary therapies after the development of significant VCI. The purpose of this paper is to review the data regarding available treatments for VCI and to suggest practical strategies for management of patients with VCI.

Treatment

General considerations

Determining the threshold of cerebral tissue damage required to cause cognitive impairment has proven difficult, and consequently, there are no accepted minimum neuropathological thresholds to confirm a diagnosis of VCI as there is in the Braak staging for Alzheimer's disease (AD) [13]. There is, however, strong evidence from several pathological studies that the likelihood of cognitive dysfunction increases with both lesion volume and number [14–16]. Multiple prospective cohort studies have reported that recurrent stroke is a major independent risk factor for dementia [17, 18]. As a result, the most efficient management of VCI is the prevention of further cerebrovascular injury [19•].

Patients with suspected VCI should be screened for modifiable risk factors including hypertension, impaired fasting glucose, atrial fibrillation, hyperlipidemia, smoking, heavy drinking, kidney disease, obstructive sleep apnea, and smoking as each of these risk factors has been associated with risk of recurrent stroke [20]. Carotid imaging should be considered in patients with prior stroke in stereotypical brain regions. Evidence from a recently completed population-based study has reported an association between vascular risk factor

management (according to standard guidelines) and reduced risk of cognitive decline in subjects with prior ischemic stroke [21••]. Although the benefit of risk factor management in preventing cognitive decline in later life or after the development of cognitive change is less optimistic in other trials, there is very strong evidence that vascular risk factor management can reduce the risk of recurrent stroke and cardiovascular disease [22•]. Consequently, patients with VCI, especially those with prior ischemic stroke, should be advised to adhere to current guidelines for primary and secondary stroke prevention.

As with any patient with cognitive impairment, an important aspect of management of VCI is to screen for any potential contributors to cognitive dysfunction including infections, metabolic or hematologic derangements, medications, sleep disturbances, and neuropsychiatric symptoms. Neuropsychiatric symptoms are very common in VCI and deserve special mention as several studies have reported a prevalence approaching 90 % [23, 24]. High rates of depression, sleep disturbance, apathy, and eating disorders are common in VCI [25, 26]. Neuropsychiatric symptoms in dementia are important because they are associated with increased caregiver burden [27], higher cost of care [28], and nursing home placement [29]. There are very few high-quality studies looking at the treatment of neuropsychiatric symptoms in VCI, and there are no FDA-labeled therapeutics for treatment of neuropsychiatric symptoms of dementia. Clinical experience suggests that patients with VCI can be managed using the same principles used to manage neuropsychiatric symptoms in other dementias such as AD. For review, see Aarsland and Ballard [30].

Pharmacological treatment

Acetylcholinesterase inhibitors overview:

The cholinergic hypothesis of AD posits that deficits in acetylcholine, a neurotransmitter that plays a key role in modulating attention, working memory, and conscious awareness [31], is responsible for cognitive dysfunction seen in AD [32]. Acetylcholinesterase inhibitors (AChEIs) improve cognition in dementia by increasing the availability of acetylcholine in the synaptic cleft. Cholinergic fibers, which travel in the cerebral white mater [33], are susceptible to ischemic damage and there is considerable evidence to suggest the presence of a cholinergic deficit in VaD independent of concurrent AD pathology [34–36]. AChEIs have also been shown to increase cerebral blood flow in patients with AD [37], most likely through direct vasodilatory effects on cerebral endothelium [38]. The concept of cerebrovascular ischemia—driven by the formation of atheromatous plaques and ischemic strokes—underpins the development of most forms of VCI. Reports noting that AChEIs improve cerebral blood flow in AD patients who respond to treatment provide a possible rationale for using these agents in VaD [38].

In phase III trials, AChEIs have produced modest cognitive improvements (1–2 points on Alzheimer's Disease Assessment Scale-cognitive subscale) and have demonstrated good safety profile [22•] (Table 1). No AChEI, however, has been granted FDA approval for use in VaD primarily because of inconsistent efficacy on activities of daily living and global function. Dose–response effects to AChEIs in VaD have not been consistently noted. It is important to note that the VaD trials evaluated functional efficacy with the same measures used in AD trials. In VaD populations, demonstration of functional benefit is harder to achieve given the high prevalence of physical disability due to stroke [22•].

Table 1. Pharmacological therapy in VCI, levels of evidence

Medication	Level of evidence	Comments	Recommendations
Donepezil [37–39]	Class IIa, level A, for "pure" VaD	Modest benefit for cognitive scores, less strong evidence for functional improvement. Doses studied: 5 and 10 mg/day. No dose response effects noted	Donepezil can be used to improve cognition in VaD
Galantamine [41, 42]	Class IIa, level A, for mixed dementia; class IIb for "pure" VaD	Modest benefit in cognitive measures in pure VaD. Benefit in both cognition and function in mixed dementia. Doses studied; titration up to 24 mg/day.	Galantamine can be used to improve cognition and functional abilities in mixed dementia (AD+VaD)
Rivastigmine [48, 49]	Class IIa, level A for "pure" VaD	Modest benefit on cognitive measures in pure VaD. Doses studied: 1–4 and 6–12 mg/day	Rivastigmine can be used to improve cognition in VaD
Memantine [50, 51]	Class IIb, level A	Modest cognitive benefits only. Doses studied; titration up to 20 mg/day	Role of Memantine in VaD yet to be clarified

See also reference [22]

Class effects

Contraindications	Bradycardia and heart block. Caution in epilepsy. Active gastric ulcers/gastritis, steroid dependent asthma/chronic obstructive pulmonary disease, pneumonia.
Main drug interactions	CYP2D6 substrate, CYP3A4 substrate. Beta-blockers exacerbate bradycardia. Medications that inhibit the effects of donepezil include antibiotics such as ciprofloxacin, clarithromycin, or erythromycin. Medications with anticholinergic effects such as tricyclic anti-depressants (TCAs), cyclobenzaprine, and bethanechol may interfere with AChEI effects. Non-steroidal anti-inflammatory drugs increase bleeding risk. TCAs and bupropion may have additive effects on lowering the seizure threshold. Exaggerates succinylcholine-type muscle relaxation during anesthesia.
Main side effects	Nausea, vomiting, diarrhea, anorexia, dizziness, muscle cramps, fatigue, and vivid dreams. Bradycardia may cause syncope. Side effects are usually dose dependent.
Cost effectiveness	All AChEIs were more cost-effective than basic supportive care.
Special points	Recommend taking with breakfast to reduce insomnia, nightmares, and nausea. Long-acting formulations may be better tolerated.

Donepezil

Donepezil is a safe, easy-to-use, centrally acting AChEI approved for treatment of all stages of Alzheimer's dementia [37]. It is available as an oral, once-daily formulation. It requires no dosing adjustment in renal or hepatic disease and has few adverse interactions with other drugs.

Special points: Several large randomized controlled trials (RCT) assessing the efficacy of donepezil in VaD have been completed. Each of these trials focused on the efficacy of donepezil in patients with "pure" vascular disease (patients with suspected AD or mixed AD/VaD pathology were excluded). In the first two trials (an identical trial design allowed for combined analysis), which included

patients with mild-to-moderate VaD, donepezil showed efficacy on measures of cognition at both 5 and 10 mg but inconsistent benefit on measures of function and global function [39]. In an open-label extension, cognitive benefits were maintained for an additional 30 weeks [40]. More recently, a large RCT tested only the lower dose of donepezil (5 mg/day) and incorporated a cognitive assessment to better assess executive function in patients with mild-to-moderate VaD. In this trial, a small but significant benefit was seen on cognition but not on function [41]. A subgroup analysis revealed that subjects without evidence of baseline hippocampal atrophy responded more robustly to treatment than those with atrophy.

Donepezil (Aricept)

Standard dose	Oral 10 mg daily but benefit can be seen up to 23 mg daily (off label in VaD)
Contraindications	See class effects.
Main side effects	See class effects.
Drug interactions	See class effects.
Special points	FDA approved for mild, moderate, and severe Alzheimer's dementia. There is data that shows doses of 5 to 10 mg can improve cognition in "pure" VaD [39, 40].
Oral	Start 5 mg daily×30 days followed by 10 mg×90 days. Consider an increase to 15 mg daily for 30–90 days followed by 20 mg daily or 23 mg daily for moderate-to-severe dementia.
Cost	Generic 10 mg US$110.00 (30 tabs). Aricept disintegrating tablet US$400.00 (30 tabs). Aricept 23 mg US$400.00 (30 tabs).

Galantamine

Galantamine is a reversible AChEI that has also been shown to modulate nicotinic receptor activity—a function that may potentiate receptor response to acetylcholine [42]. It is available in both an immediate dose and extended release formulation. Like the other AChEIs, galantamine is generally well tolerated and safe in VCI populations.

Special points: Galantamine has been investigated in the treatment of both "pure" VaD and mixed VaD/AD populations. In the "pure" VaD trial, galantamine improved cognition and performance on a measure of executive function after 24 weeks of treatment [43]. Subgroup analyses reported that greater improvement was seen in subjects with baseline mini-mental status examination (MMSE) scores less than 18, being diagnosed with VaD for longer than 6 months, and in subjects with various types of vascular disease (only subjects with single strategic infarcts did not show cognitive improvement). In the other large trial, patients with either (1) AD plus evidence of CVD on neuroimaging or (2) probable vascular dementia were enrolled in a 24-week trial [44]. Analyzed together, treatment with galantamine resulted in significant improvement in cognition and significantly less decline in function. Although not powered to detect treatment differences between the two subgroups, the efficacy on functional measures appeared to be driven by the patients with the mixed AD/VaD group [45]. In the open-label extension, cognitive and functional benefits were maintained during the entire 12-month study period [46].

Galantamine (Razadyne)

Standard dose	16–24 mg daily. Immediate release formulation is divided into twice a day dosing (off label in VaD).
Contraindications	See class effects. Discontinue if QTc interval >500 ms
Drug interaction	See class effects. Medications that prolong the QTc interval.
Main side effects	Prolongation of QTc interval can occur. Monitor potassium and magnesium levels, which can exacerbate arrhythmia.
Special points	FDA approved for mild to moderate AD dementia. There is data that shows that doses of 16–24 mg/day may improve cognition in VaD or mixed AD/VaD [43, 44].
Oral	Eight milligrams daily for 30 days followed by 16 mg daily for 30 days and then 24 mg daily. Consider increasing to 32 mg daily for persistent cognitive symptoms or treatment of neuropsychiatric symptoms.
Cost	Galantamine 8 mg tabs US$520.00 (60 tabs). Razadyne ER 16 mg US$270.00. 24 mg US$835.00 (30 tabs).

Rivastigmine

In addition to inhibiting the enzyme acetylcholinesterase, rivastigmine has been also shown to inhibit the action of butyrylcholinesterase, another centrally acting cholinesterase [47]. Rivastigmine is available as an oral preparation and as a transdermal patch.

Special points: In one large trial looking at the effects of rivastigmine on "pure" VaD, treatment resulted in significant improvements in cognition but not function [48]. In a small trial in China of patients with subcortical vascular dementia, treatment with rivastigmine did not result in significant improvement in any domain but patients in this trial had significantly lower baseline MMSE scores than in the other trials [49]. There is some evidence that rivastigmine may offer benefit in patients with mixed AD/VaD disease [50]. In a post hoc analysis stratification of subjects based on the presence or absence of vascular risk factors, subjects with vascular risk factors showed more cognitive and functional improvement than those without vascular risk factors [50].

Rivastigmine (Exelon)

Standard dose	Transdermal 4.6–13.3 mg/24 h (off label in VaD).
Oral	1.5 mg twice daily to 6 mg twice daily.
Contraindications	See class effects.
Drug interactions	See class effects.
Main side effects	See class effects.
Special points	FDA approved for mild, moderate, and severe Alzheimer's dementia. There is data that shows oral rivastigmine up to 12 mg/day can improve cognition in "pure" VaD [48].
Oral	Start at 1.5 mg twice daily, increase each dose by 1.5 mg every 2–4 weeks max dose 6 mg twice daily. Best taken with food. Re-titrate if treatment is interrupted >3 days. Oral tablets are often poorly tolerated consider switch to patches.

Transdermal patch Start at 4.6 mg/24 h for one month. Can increase to 9.5 mg/24 for 1 month and then 13.3 mg/24 h (moderate-to-severe dementia) thereafter.

Cost Exelon patch 4.6, 9.5, and 13.3 mg approximately US$300.00 (30 patches). Exelon oral solution 2 g/ml (120 ml) US$540.00.

Memantine

Memantine is an NMDA receptor antagonist approved for the use of moderate-to-severe dementia in AD. It is safe and well tolerated in this population and is generally thought to have a lower incidence of side effects compared to the AChEIs [51]. Memantine is available in both an immediate release (requiring twice daily dosing) and an extended release formulation.

Special points: The efficacy of memantine in mild to moderate VaD has been investigated in two large 28-week RCTs [52, 53]. In both trials, treatment with memantine was associated with modest cognitive benefits.

Memantine (Namenda, Namenda XR)

Standard dose Immediate release: oral 10 mg twice daily (off label in VaD). Namenda XR: oral 28 mg daily.

Contraindications None.

Drug interactions Carbonic anhydrase can reduce clearance of memantine. Concurrent use of memantine and nicotine can result in altered plasma levels of both.

Main side effects Memantine is generally well tolerated. Dizziness, confusion, headache, and constipation have been reported.

Special points FDA approved for the treatment of moderate-to-severe dementia due to Alzheimer's disease. There is data that shows memantine 10 mg twice daily improves cognition in patients with mild to moderate vascular dementia [52, 53].

Oral For immediate release tablets, start with 5 mg once daily and increase by 5 mg each week until a maintenance dose of 10 mg twice daily is reached.
For extended release capsules, start with 7 mg daily and increase by 7 mg each week until a maintenance dose of 28 mg/day is reached.
A titration pack is available for both the immediate release tablets and extended release capsules.

Cost Namenda 10 mg tablet approximately US$375 per month (60).
Namenda XR 28 mg capsules approximately US$356 per month (30).

Nimodipine and nicardipine

Nimodipine and nicardipine are dihydropyridine calcium channel blockers. In the USA, nimodipine is approved for reduction of neurological sequela associated with acute subarachnoid hemorrhage and nicardipine is approved for treatment of acute hypertension and angina. In animal models, these agents demonstrate potent arterial vasodilatory effects [54]. Because of their putative anti-ischemic properties, there have been several RCTs investigating whether these agents are effective in VaD.

Special points: One meta-analysis examining the efficacy of nimodipine in various forms of dementia (AD, VaD, and mixed) has been published [55]. In this meta-analysis, which included 15 trials (2492 patients), treatment with nimodipine at doses of 90 mg/day for 12 weeks was associated with benefits on global impression and cognition but not on activities of daily living. When the AD and VaD trials were pooled separately, this result persisted at 12 weeks [55]. Data on longer-term outcomes that are clinically more meaningful are lacking. A large trial assessing the benefit of nimodipine in preventing cognitive decline following acute ischemic stroke is ongoing [56]. Nicardipine has been shown to slow the progression of cognitive decline in several trials [57]. In one RCT, nicardipine given at a dose of 20 mg three times a day for a year delayed the rate of cognitive decline in subjects with VaD [58]. In an open-label, six-month trial, a single dose of 40 mg per day was shown to improve cognition in 64 % of subjects who were considered to have cognitive deterioration at baseline [59]. Additional RCTs are needed to establish the efficacy of nicardipine in VaD.

Nimodipine (Nymalize)

Standard dose	Oral 30 mg three times daily (off label in VaD).
Contraindications	Angina/MI, hypotension, congestive heart failure, syncope. Nimodipine should never be given IV as life-threatening events have occurred when given parenterally.
Drug interactions	CYP3A4 substrate.
Main side effects	Dihydropyridine calcium channel blockers reduce blood pressure and can slow heart rate. Peripheral edema is a common adverse side effect and usually occurs 2–3 weeks after initiating therapy. Ileus has rarely been reported.
Special points	FDA approved for improvement of neurological outcome following SDH from ruptured berry aneurysm. Meta-analysis shows that nimodipine at 90 mg/day can slow the rate of cognitive decline in VaD at 12 weeks but long-term outcomes are unknown [55].
	Oral In clinical trials for VCI, nimodipine has been given orally 30 mg three times daily. Nimodipine should be taken 1 h before or 2 h after a meal.
Cost	Nimodipine 30 mg tablet (1) approximately US$18/tablet.

Nicardipine (Cardene)

Standard dose	Oral 20 mg three times daily (off label in VaD).
Contraindications	Angina/MI, hypotension, congestive heart failure, aortic stenosis, hepatic impairment (lower dose required), hypertrophic cardiomyopathy with outflow tract obstruction, renal impairment (lower dose required).
Drug interactions	CYP3A4 substrate, CYP2C19 substrate, CYP2D6 substrate, CYP2C9 substrate. Dantrolene
Main side effects	Dihydropyridine calcium channel blockers reduce blood pressure and can slow heart rate. Peripheral edema is a common adverse side effect and usually occurs 2–3 weeks after initiating therapy.
Special points	FDA approved for treatment of hypertension and chronic stable angina. In clinical trials of subjects with VCI, treatment with nicardipine was associated with slower rate of cognitive decline over 12 months [58].

Oral In clinical trials, nimodipine has been given orally 20 mg three times daily [58] and 40 mg once daily [59].

Cost Nimodipine 20 mg tablet approximately US$200 (90 capsules).

Antiplatelet agents

Despite strong evidence of secondary stroke prevention, there is little data regarding the efficacy of antiplatelet agents on cognitive dysfunction in VaD. In a large RCT, treatment with low-dose aspirin for 5 years did not affect cognitive function in non-demented subjects with vascular risk factors [60]. In another trial of patients with prior ischemic stroke, cognitive decline as assessed by MMSE did not differ whether subjects were assigned to aspirin (plus dipyridamole) or clopidogrel [61].

Homocysteine lowering and vitamin B supplementation

Elevated homocysteine is an independent risk factor for CVD [62] and has been associated with both an increased risk of cognitive decline and VaD in several observational studies [63, 64]. Treatment of elevated homocysteine with vitamin B and folic acid can lower serum homocysteine levels by approximately 20 %.

Special points: The cognitive effects of vitamin B and folic acid supplementation have been examined in several studies, including cohorts with dementia. Due to heterogeneity in trial designs and outcome measures, a meta-analysis was unable to pool data [65]. Most studies have not reported benefits on cognition [66–68]; however, one large study reported that folic acid supplementation for 3 years was associated with improved cognitive performance in a (dementia-free) cohort with elevated homocysteine levels [69].

Non-pharmacological treatments

Diet

Accumulating epidemiological data suggests a link between diet and cognitive decline [70]. Adherence to the Mediterranean diet has been reported to be associated with slower cognitive decline in two observational studies of elderly populations [71, 72], and there is some evidence to suggest a neurocognitive benefit of vitamin E from food sources, omega-3 fatty acids, and a high ratio of polyunsaturated to saturated fats [73]. No studies have looked at the effect of diet in cohorts with pre-existing VCI.

Exercise

The physiologic benefits of physical activity include improved cerebral blood flow, increased vascular plasticity, and enhancement of endothelial function [74, 75]. These benefits may offset the loss of vasodilatory function that accompanies normal aging. Physical activity has been shown to improve cognition in older people [76, 77] as well as reduce the risk of incident VaD [78]. In the Leukoaraiosis and Disability study, non-demented subjects with evidence of white matter disease were followed for 3 years. In this cohort, physical activity was associated with significantly reduced risk of cognitive impairment, all-cause dementia, and vascular dementia [79].

Cognitive rehabilitation

Cognitive rehabilitation is a non-pharmacological therapy designed to improve cognitive dysfunction in dementia. Although two meta-analyses have reported that cognitive rehabilitation may offer some efficacy in AD dementia [80, 81], these meta-analyses included very few high-quality studies in addition to other limitations [82]. There have been no high-quality studies investigating the benefits of cognitive rehabilitation in VCI populations.

Primary prevention of CVD and VCI

Blood pressure reduction

Observational studies suggest a strong link between midlife hypertension and dementia [22•]. The association between hypertension in late life and dementia is mixed [83], but recent reports note higher pulse pressure, an index of vascular aging, was associated with change in biomarkers of neurodegeneration prior to the onset of dementia across a broad age range. With advanced age (>80 years), higher pulse pressure was also associated with cerebral amyloidosis in the presence of neurodegeneration and more rapid progression to dementia [84]. There is also evidence to suggest an association between late-life diastolic hypotension (≤70 mmHg) and AD and dementia in general [85]. Several prospective cohort studies have reported an association between treatment of hypertension and a reduction in the incidence of VaD [86, 87].

Special points: No large placebo-controlled trials have directly investigated the effect of blood pressure reduction in cohorts with preexisting VaD; several large trials have assessed the cognitive effects of antihypertensives in subjects with vascular risk factors. Each of these trials demonstrated treatment benefits on cerebrovascular measures; however, most trials failed to demonstrate an association between treatment and a reduction in the incidence of dementia [88–90] or improvement in cognition [89, 90]. Two trials have reported a benefit: In the Systolic Hypertension Europe trial, lowering systolic blood pressure to less than 150 mmHg in subjects with systolic hypertension reduced the incidence of dementia in half over the 2-year study period [91]. In the open-label extension, treatment was associated with a significant reduction in the incidence of VaD [92]. In the PROGRESS trial, subjects with prior TIA or stroke were randomized to antihypertensive treatment or placebo. Over the 4-year trial period, antihypertensive treatment (with an angiotensin-converting inhibitor and diuretic) significantly reduced the risk of stroke, dementia due to recurrent stroke, and cognitive decline [93]. In the MRI substudy of PROGRESS, active treatment was also shown to stop or delay the progression of white matter hyperintensities [94].

Treatment of hyperlipidemia

High cholesterol in middle age is a risk factor for both cognitive impairment and VaD [95, 96]. There is mixed evidence regarding the role of statin therapy in reducing the risk of dementia, and there have been no controlled trials looking at the effect of statins on cognition in subjects with pre-existing VaD [97]. In AD, adding atorvastatin to donepezil did not improve cognition or function [98]. Two trials have examined the effects of statin therapy on cognition in cohorts of patients with vascular risk factors but who were

dementia free at baseline. In the Heart Protection Study, simvastatin did not reduce the risk of dementia [99], and in the PROSPER study, pravastatin did not improve cognitive performance [100].

Treatment of hyperglycemia and diabetes

Diabetes is a well-established risk factor for both AD and VaD [101]. Diabetes is also associated with poorer performance on cognitive testing [102], and among patients with type II diabetes, indicators of poorer glycemic control correlate with worse cognitive function [103]. There is limited evidence regarding the intensity of glycemic control to prevent or manage cognitive impairment in type II diabetes [104].

Special points: Several studies have indicated that aggressive glycemic regimens may have deleterious effects without providing additional cognitive benefits. In the Memory in Diabetes study, intensive glycemic control (targeting a hemoglobin A1c of less than 6) was associated with a slower decline in total brain volume but did not improve cognitive performance and was also associated with increased mortality [105]. In the ADVANCE trial, intensive diabetes control was associated with a higher rate of dementia than a more conservative approach [106]. The benefits of tight glucose control must be weighed against the risk of inducing episodes of hypoglycemia, as episodes of severe hypoglycemia have been associated with an increased risk of dementia [107].

Smoking cessation

Smoking is a well-known risk factor for vascular disease and stroke. Smokers have also been shown to perform more poorly on cognitive testing and are at increased risk for cognitive decline [108–110]. No randomized trials have looked at the benefit of smoking cessation in patients with pre-existing dementia. In a longitudinal study investigating the efficacy of smoking cessation on cognition in older smokers, subjects who were unable to quit smoking experienced greater cognitive decline, performed more poorly on measures of memory, and experienced gray matter atrophy than subjects who completed an 18-month smoking cessation program [111].

Special populations

Cerebral amyloid angiopathy

Cerebral amyloid angiopathy (CAA) is characterized by the progressive accumulation of amyloid β (Aβ) in the medium-sized arteries, arterioles, and capillaries supplying the cerebral cortex and leptomeninges [112]. CAA is a common cause of microbleeds, chronic ischemia, and spontaneous intracranial hemorrhage (ICH) in the elderly [113]. Although CAA commonly coexists with AD, the amyloid deposition in CAA is primarily of Aβ 40 species (rather than Aβ 42 in AD), suggesting that amyloid deposition in CAA is a distinct pathological process from amyloid deposition in AD [114]. Emerging evidence suggests that CAA is an under-recognized contributor to VCI and increases the risk of cognitive impairment independently of stroke [115].

Special points: Treatment of acute ICH in CAA should follow standard management practices for ICH [116•]. Patients with ICH due to CAA are at increased

risk of reoccurrence with a 2-year reoccurrence rate of approximately 20 % [117]. Although there is limited data from large RCTs regarding prevention of recurrent ICH, both antiplatelet and antithrombotics have been associated with increased risk of reoccurrence in CAA [118, 119] and should be avoided unless there is a compelling indication [116•]. Although hypertension is not felt to contribute to CAA pathology, antihypertensive treatment has been shown to significantly reduce risk of reoccurrence of ICH in CAA [120]. The use of statins after ICH has engendered some controversy following results of one large trial showing an increased risk of ICH with atorvastatin [121]. At this time, there are no clear recommendations regarding the use of statins in probable CAA and the cardiovascular benefits of lipid lowering should be weighed against the possible increased risk of ICH in each individual [116•]. There have been no studies looking at treatments to enhance cognition in CAA, and given the overlap between AD and CAA, treatment with medications approved for AD can be attempted in patients with suspected AD pathology. In a small subset of patients, CAA can trigger a potent inflammatory response leading to extensive vasogenic edema. The presentation of CAA-related inflammation (also called amyloid β-related angiitis) includes rapid cognitive decline, seizures, headache, and diffuse white matter changes on MRI [122]. Recognition of CAA-related inflammation is important because it is potentially reversible with immunotherapy [123].

Subcortical white matter disease

Subcortical white matter disease (SWMD), the most common vascular injury associated with VCI, is caused by widespread ischemic changes and small lacunar infarcts in the small arteries that supply subcortical structures [124]. The pathological mechanisms leading to SWMD are unique from the mechanisms causing large vessel disease [12], and the clinical course associated with SWMD is often more insidious [125]. The slow progression of cognitive decline makes early detection of this form of VCI difficult to detect clinically. On neuroimaging, evidence of subcortical white matter disease is most clearly demonstrated by confluent white matter hyperintensities (WMH) on fluid-attenuated inversion recovery sequences (FLAIR), a finding often referred to as leukoaraiosis. Risk factors for WMHs include age, disease [126], and AD [125].

Special points: The role of widespread white matter abnormalities in familial early onset AD that precede the development of dementia opens the possibility that all white matter changes in dementia are not related to vascular disease alone [127•]. The expansion of WMHs has been associated with episodic memory loss, executive dysfunction [128, 129], and incident dementia [130]. WMHs have also been shown to portend a poor prognostic outcome as The Leukoaraiosis and Disability study (LADIS) demonstrated that having WMHs considered "severe" (by an independent rater) more than double the risk of transition from an autonomous to dependent status [131]. Despite its high prevalence in older age populations, little is known about the treatment of either acute or chronic SWMD [12]. There is some evidence that vascular risk factor management can stop or slow the progression of WMHs [132], but it is unclear if treatment improves cognition. In the largest study of subjects with SWMD, treatment with nimodipine failed to improve cognition but was associated with less frequent deterioration in cognition or function [133]. Other studies have included subjects with SWMD but have embedded them in cohorts

with different etiologies of VaD. Several of these studies have reported secondary analyses based on neuroimaging grouping of patients [44] [48], but it is difficult to make conclusions based on these analyses [12].

CADASIL

Cerebral autosomal dominant arteriopathy with subcortical infarcts (CADASIL) is the most commonly encountered hereditary cause of VCI [134]. A missense mutation in the NOTCH3 gene located on chromosome 19 (a genetic test is commercially available) leads to an angiopathy involving small arteries and capillaries. Over time, those harboring the NOTCH3 mutation invariably develop lacunar stroke and widespread ischemic white matter disease. Problems with executive functioning are common, and a stepwise deterioration in cognition is often reported [135]. Approximately 75 % of patients with CADASIL eventually become demented [136].

Special points: Current management principles recommend risk factor management for patients with CADASIL similar to that for ischemic stroke with reduction in blood pressure, antiplatelet therapy, treatment of hyperlipidemia, diabetes management, and lifestyle management [137]. There is a preliminary report to suggest that calcium channel blockers may improve cerebral blood flow in CADASIL (as measured by single photon emission computed tomography) [138], but RCTs are needed to confirm this effect. Currently, there are no known effective cognitive treatments for CADASIL. Although cholinergic deficits have been documented in patients with CADASIL [34], a large RCT investigating the use of donepezil in subjects with CADASIL failed to meet cognitive or functional endpoints [139].

Conclusion

VCI is the term used to describe the contribution of vascular disease to cognitive dysfunction. Despite causing significant disease burden, there very few treatment options to improve symptoms in VCI. Current management strategies emphasize the accurate assessment and treatment of risk factors to prevent further vascular injury. AChEIs and memantine have not been granted regulatory approval for the treatment of VCI but have been well studied in patients with mild-to-moderate VaD. These therapies appear safe and may provide modest cognitive benefits. Other pharmacologic agents have less evidence to support their use in VCI. Therapies which target the underlying pathophysiologic processes leading to cognitive dysfunction in VCI are greatly needed.

Compliance with Ethics Guidelines

Conflict of Interest
Aaron Ritter and Jagan A. Pillai declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by the authors.

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