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REVIEW

Vascular Cognitive Impairment: Disease Mechanisms and Therapeutic Implications

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Abstract The prevalence of vascular cognitive impairment (VCI) is likely to increase as the population ages and cardiovascular disease survival improves. We provide an overview of the definition and disease mechanisms of VCI and present a systematic literature review of the current evidence for the pharmacologic and nonpharmacologic therapies used to treat the VCI symptoms of cognitive dysfunction or to modify VCI through primary and secondary prevention. The Cochrane Database of Systematic Reviews was searched from 2005 to October 2010 using the keywords "vascular dementia" or "vascular cognitive impairment and therapy." MEDLINE was searched for English-language articles published within the last 10 years using the combined Medical Subject Headings (MeSH) "therapeutics and dementia," "vascular" or "vascular cognitive impairment." Although cholinesterase inhibitors and memantine produce small cognitive improvements in patients with VCI, these drugs do not improve global clinical outcomes and have adverse effects and costs. Selective serotonin reuptake inhibitors and dihydropyridine calcium channel blockers may improve short-term cognitive function in patients with VCI. Antihypertensive therapy with an ACE inhibitor-based regimen and statins may prevent the major subtype of VCI known as poststroke cognitive decline. Clinical and effectiveness studies with long-term follow-up are needed to determine the benefits and risks of pharmacologic and nonpharmacologic therapies to prevent and treat VCI. Given its growing health, social, and economic burden, the prevention and treatment of VCI are critical priorities for clinical care and research.

Keywords Vascular cognitive impairment · Vascular dementia · Mechanisms · Therapeutics

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Introduction

Vascular dementia (VaD) is the second leading cause of dementia after Alzheimer's disease (AD) [1, 2]. Coinciding with population aging and improved survival from cardiovascular diseases, including stroke, VaD is more frequent and will likely affect an increasing number of patients in the coming decades [3, 4]. Recently, the terms "vascular cognitive impairment" (VCI) was introduced to comprise the heterogeneous group of cognitive disorders that share a presumed vascular cause and to include both dementia and cognitive impairment without dementia [5–8]. VCI increases the morbidity, disability, and healthcare costs of the growing elderly population, and decreases their quality of life and survival [9–13]. Given the substantial health and economic burden of VCI, its prevention and treatment are critical research and clinical priorities.

This report focuses on VCI as a distinct clinical entity. Compared to AD, VCI, and particularly VaD, is associated with 50% lower median survival (6–7 years *vs* 3–4 years), greater healthcare costs, and higher rates of comorbidity, institutionalization, and caregiver use [9–11, 14–16]. However, VCI and AD mechanisms and pathology frequently coexist to cause mixed dementia [17, 18]. For example, stroke is a potent cause of VaD and worsens the cognitive effects of AD [10–24]. Most dementia cases in older adults have evidence of AD pathology (e.g., neuritic plaques and neurofibrillary tangles) and VCI pathology (e.g., cerebral or lacunar infarctions) [25, 26]. AD and VCI have the same vascular risk factors and vascular pathology may play a major role in the clinical expression of AD or VCI [27]. Despite this frequent overlap, VCI and AD are traditionally treated as unique clinical conditions and are studied separately [28]. Given this current approach to clinical practice and research, we discuss disease mechanisms of VCI and present the results of a systematic literature review of therapies used to treat the VCI symptoms of cognitive dysfunction or to modify VCI through primary and secondary prevention.

Defining Vascular Cognitive Impairment

The construct and diagnosis of VCI have evolved. Previous diagnostic criteria for VaD required the presence of memory loss and a severity of cognitive impairment sufficient to adversely affect independent functioning consistent with dementia [29–32]. However, these diagnostic criteria may not capture the executive dysfunction or less severe cognitive decline commonly observed in VCI [33, 34]. Recently, the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network published harmonization standards for VCI to address these potential limitations and to provide a first step toward developing diagnostic criteria for VCI [35]. Whether mixed dementia is included in VCI or AD remains controversial. Although the exact associations between CVD features (e.g., type, location, severity, volume) and cognitive impairment are not known, the general types of cerebrovascular injuries that occur or co-occur in VCI are large-vessel or small-vessel ischemia, hypoperfusion, hemorrhage, and vasculopathy [36]. For this report, we used the latest definition of VCI [37] for the overview of disease mechanisms, and we also used earlier VCI definitions [29–32] that were relevant during the study period (2000–2010) for the systematic literature review.

Mechanisms of Disease

Shared mechanisms between cerebrovascular disease (CVD) and dementia may contribute to VCI. CVD and dementia share risk factors and neuropathology [28]. Vascular risk factors (hypertension, hyperlipidemia, diabetes) and behavioral factors (obesity, physical inactivity) are associated with both CVD and, particularly when present in mid-life dementia (Fig. 1) [37, 38]. Similarly, observational studies in middle-aged or older adults have found associations between VCI and hypertension [39, 40], hyperlipidemia [41], diabetes [27, 42], obesity [43], and physical inactivity [44], even when present later in life. Several pathogenic mechanisms including AD, amyloid deposition, aging, atherosclerosis, and hypertension may converge to cause CVD and dementia through pathways of inflammation and oxidative stress in blood vessels [45–48]. Vascular risk factors may lead to cerebrovascular dysfunction through pathways mediated by beta-amyloid and the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, a major source of vascular oxidative stress [46]. Cerebrovascular dysfunction and blood brain barrier alterations may compromise the cerebral microenvironment and increase the vulnerability of regions critical for cognition (e.g., subcortical white matter, neocortex, hippocampus) to ischemic-hypoxic brain damage leading to neuronal dysfunction and cognitive deficits [46]. Also, insulin resistance, abdominal obesity, dysfunction of the cerebral small-vessel endothelium (i.e., the blood brain barrier) and chronic kidney disease may contribute to or accelerate VCI [48–51]. Whether due to shared or additive toxic vascular effects [52], CVD and dementia coexist frequently, particularly with increasing age [17, 18, 26].

Hematologic and inflammatory factors may have etiological roles in VCI. Although atrial fibrillation is known to

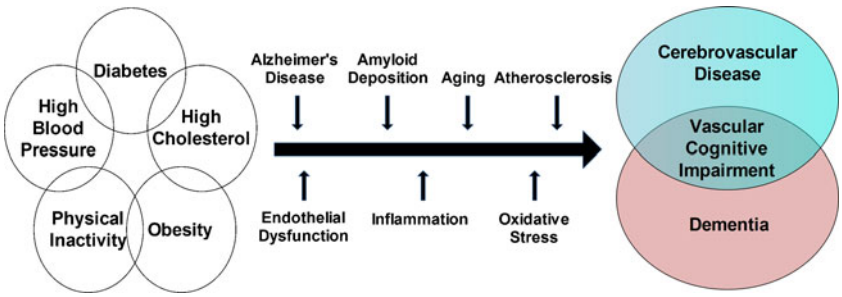

Fig. 1 Potential mechanisms between vascular risk factors, cerebrovascular disease, and dementia may lead to vascular cognitive impairment. Adapted from Middleton and Yaffe [48] in 2009

cause macroembolic complications, such as stroke, cardioembolic disorders may cause microembolic complications that lead to CVD and cognitive impairment [53] or accelerate cognitive and functional decline in VCI [54]. Also, recent data may implicate clot formation and microinfarctions as mechanisms of VCI through hemostatic pathways. High levels of fibrinogen, factor VIII, or plasminogen activation inhibitor 1 have been associated with an increased risk of VCI [55, 56]. Moreover, observational studies suggest potential roles of inflammation in VCI. In a Japanese case-control study, elevated high-sensitivity C-reactive protein and antibodies for *Chlamydia pneumoniae* were more prevalent in VaD than AD [57]. A cross-sectional study found that high interleukin-6 plasma levels were associated with functional impairment in older adults with VaD, but not late-onset AD, independently of demographics and clinical factors, including previous stroke and cognitive function [58].

Genetic factors may influence the development or course of VCI. The apolipoprotein E epsilon 3 polymorphism [59] and the epsilon 4 polymorphism [60], particularly in persons with hypertension or diabetes [61], may be associated with increased VCI risk, but the data are not conclusive [62, 63]. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, a genetic form of subcortical ischemic VaD, is associated with Notch3 mutations whose location may differ by geography or demography [64–66]. The identification of quantifiable phenotypes that can be reliably and effectively determined in large samples of subjects is the most critical challenge for genetic studies of VCI [67].

Evidence Acquisition

We first searched the Cochrane Database of Systematic Reviews for full systematic reviews from 2005 to October 2010 using the keywords vascular dementia or vascular cognitive impairment and therapy (i.e., the search terms used were: "cognitive," "dementia," "impairment," "therapy," and/or "vascular"). The title and abstracts of the 50 systematic reviews identified by this search were assessed for relevance to this report. Any review of therapy for vascular dementia, vascular cognitive impairment, or any type of dementia (n=25) was retained. Then we searched MEDLINE for English language articles with human subjects published from December 15, 2000 to December 15, 2010. One author (D.A. L.) reviewed the title and abstracts of all 361 articles identified using the search terms "therapeutics" (MeSH Term) and "dementia, vascular" (MeSH Term) or "vascular cognitive impairment." The searching and selection of articles for review is shown in Fig. 2. Randomized, double-blind, placebo-controlled trials (RCTs) with results reported as intention-to-treat analyses were considered to be the highest quality data and are the focus of this report. Large prospective cohort studies, meta-analyses, and systematic literature reviews were also included to supplement the RCT results.

Evidence Synthesis

This report focuses on pharmacologic and nonpharmacologic therapies used to treat the VCI symptoms of cognitive dysfunction or to modify VCI through primary and secondary prevention. As of June 2010, no drugs were approved by the Food and Drug Administration specifically to treat VaD. Regulatory agency approval of drugs to treat dementia, including VaD, requires efficacy on cognition and clinical global or activities of daily living (ADL) measures [68]. However, medications approved for other indications (e.g., AD) may be efficacious in VCI. Currently, the cognitive dysfunction of VCI is treated with 3 drug classes: 1) cholinesterase inhibitors, 2) N-methyl-D-aspartate (NMDA) antagonists, and 3) anti-depressants. Primary and secondary prevention of VCI is approached generally with stroke prevention and vascular risk factor modification.

Cholinesterase Inhibitors

Acetylcholinesterase inhibitors inhibit the breakdown of acetylcholine and have been shown to improve cognitive function in adults with mild to moderate AD. Cholinergic deficits or reduced acetylcholine-mediated neurotransmission may play a role in VCI [69].

Donepezil

Some RCTs of donepezil in patients with probable or possible VaD have shown modest treatment benefits in cognition but inconsistent benefits in global functioning (Table 1) [70–72]. Interestingly, hippocampal size may modify the effect of donepezil on cognition [72]. A Cochrane review of donepezil for VCI based on two large-scale RCTs [70, 71] concluded that the drug is well-tolerated and has some efficacy in improving cognitive function, clinical global impression, and ADLs in patients with mild to moderate VCI after 6 months of treatment [73]. However, safety remains a concern because 1 donepezil trial found a markedly higher risk of death with treatment compared with placebo (1.7% *vs* 0%; odds ratio, 4.6; 95% confidence interval [CI], 1.3-16.1) [72, 74].

Because trials may include VaD patients with heterogeneous CVD pathology (e.g., differing prevalence rates of white matter disease or cortical lesions) [74], it has been questioned whether there are subtypes of VaD defined by a unique pathology that may be targets for greater treatment efficacy [68]. Specifically, cholinergic deficits may vary by

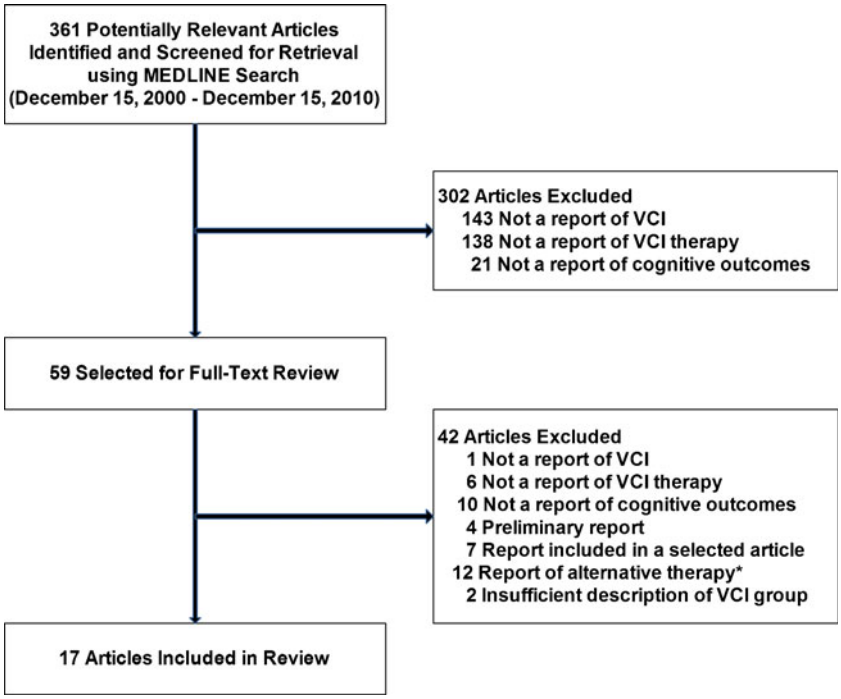

Fig. 2 The search and selection of articles for review. VCI = vascular cognitive impairment. *Alternative therapy includes acupuncture, Tai Chi, and light therapy

VaD subtype. However, a recent trial of donepezil in 168 patients (mean age, 55 years) with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and cognitive impairment found no significant difference in the primary cognitive endpoint after 18 weeks of treatment. Donepezil treatment had modest improvements on several measures of executive function but the clinical relevance of these findings is not clear [75].

Galantamine

Galantamine is an acetylcholinesterase inhibitor that also modulates nicotinic receptors [76, 77]. One trial found benefits of galantamine treatment (24 mg/day for 6 months) for cognitive function and global functioning in the VaD subgroup (n=188) that was of similar magnitude, but not statistically significant, to those observed in the overall group (VaD or AD with CVD) and the AD subgroup [78]. A second trial found small benefits of galantamine treatment for cognition, including executive function, but not for independent performance of ADLs or global functioning in a sample of patients with VaD [79]. A Cochrane review of galantamine for VCI concluded that the evidence was inconsistent for its efficacy, but consistently showed a higher risk of adverse gastrointestinal events (nausea and vomiting) [80].

Rivastigmine

Rivastigmine, a dual inhibitor of acetylcholinesterase and butyrylcholinesterase, may have significant, sustained efficacy on cognition and daily function in VCI [81]. The Vascular Dementia Trial studying Exelon (VantagE) found modest benefits of rivastigmine treatment on 3 measures of cognitive performance, but not on global performance, ADLs, or neuropsychiatric symptoms. In addition, the rivastigmine group had higher rates of nausea and vomiting than the placebo group [82]. Pre-specified exploratory subgroup analyses indicated that older patients (≥75 years) had greater efficacy on cognitive outcomes and safety, but younger patients showed no efficacy and possible harm (elevated blood pressure, stroke, and death) [82]. A Cochrane review of rivastigmine for VCI was unable to perform a meta-analysis given the absence of suitable unconfounded RCTs, and the conclusion of the review was no evidence of benefit [83].

NMDA Antagonists

Memantine

Cerebral ischemia may lead to excessive release of glutamate that activates postsynaptic NMDA receptors [84]. Memantine, a noncompetitive NMDA receptor antagonist, may have neuroprotective properties and improve cognition [85]. Two RCTs of memantine, MMM300 and MMM500, have shown modest treatment benefits on cognition, but not global functioning for patients with mild to moderate VaD (Table 1) [86, 87]. A Cochrane review that pooled data from the 2 RCTs indicated a small beneficial effect of memantine (20 mg/day) on cognition (1.9-point improvement on Alzheimer's Disease Assess-

Table 1 Randomized controlled trials of medication treatment for vascular dementia included in this review

Source, Reference, Year	No. of Patients, Age	Medication	Trial Length in Weeks	Primary Outcomes
Wilkinson, et al. [71], 2003	n=616 Mean age, 75 years	Donepezil	24	2.2-Point improvement on the ADAS-cog among treated patients (10 mg dose) *vs* a 0.1-point improvement for those receiving placebo (2.1-point treatment difference; $p<0.001$); 1.8-point improvement on the ADAS-cog among treated patients (5 mg dose) *vs* placebo (1.7-point treatment difference; $p<0.01$). Patients treated with 5 mg (39%) and those treated with 10 mg (32%) showed improvement on the CIBIC-plus *vs* 25% of those receiving placebo ($p=0.004$ for 5 mg comparison, and $p=0.047$ for 10 mg)
Black, et al. [70], 2003	n=603 Mean age, 74 years	Donepezil	24	2.0-Point improvement on the ADAS-cog among treated patients (10 mg dose) *vs* a 0.3-point decrease for those receiving placebo (2.3-point treatment difference; $P<0.001$); 1.6-point improvement on the ADAS-cog among treated patients (5 mg dose) *vs* placebo (1.9-point treatment difference; $p<0.01$). Patients treated with 5 mg (38%) and those treated with 10 mg (31%) showed improvement on the CIBIC-plus *vs* 32% of those receiving placebo ($p<0.05$ for 5 mg comparison, but not significant for 10 mg comparison)
Roman, et al. [72], 2010	n=974, Mean age, 73 years	Donepezil	24	1.0-Point improvement on the V-ADAS-cog among treated patients (5 mg dose) *vs* a 0.1-point decrease for those receiving placebo (1.2-point treatment difference; $P<0.01$); no significant difference in the CIBIC-plus score
Auchus, et al. [79], 2007	n=788 Mean age, 72 years	Galantamine	26	1.8-Point improvement on the ADAS-cog among treated patients *vs* a 0.3-point improvement for those receiving placebo (1.5-point treatment difference; $p<0.001$); no significant difference in the ADCS-ADL score
Ballard, et al. [82], 2008	n=710 Mean age, 73 years	Rivastigmine	24	0.7-Point improvement on the V-ADAS-cog among treated patients *vs* a 0.6-point decrease for those receiving placebo (1.3-point treatment difference; $p=0.028$); no significant difference in the ADCS-CGIC score
Orgogozo, et al. [86], 2002	n=321 Mean age, 76 years	Memantine	28	0.4-Point improvement on the ADAS-cog among treated patients *vs* a 1.6-point decline for those receiving placebo (2.0-point treatment difference; $p=0.002$); no significant difference in the CIBIC-plus score
Wilcock, et al. [87], 2002	n=579 Mean age, 77 years	Memantine	28	0.5-Point decline on the ADAS-cog among treated patients *vs* a 2.3-point decline for those receiving placebo (1.8-point treatment difference; $p<0.001$); no significant difference in the CGIC score.

Vascular dementia (VaD) was determined by the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia and computed tomography or magnetic resonance imaging evidence in all trials. The Vascular-Alzheimer's Disease Assessment Scale-cognitive subscale (V-ADAS-cog) comprises the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) plus the Maze and Number Cancellation test (NCT) to assess executive function

ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living inventory total score; ADCS-CGIC = Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change; CGIC = Clinical Global Impression of Change; CIBIC-plus = Clinician's Interview-Based Impression of Change plus Caregiver Input

ment Scale-cognitive subscale [ADAS-cog], 95% CI, 0.9-2.8; $p<0.001$), but this was not supported by clinical global measures [88]. Memantine appeared to be well tolerated.

Summary of Cholinesterase Inhibitors and Memantine in Vascular Dementia

Kavirajan and Schneider [74] recently published a meta-analysis of RCTs of cholinesterase inhibitors and memantine in VaD that included the 3 donepezil, 2 galantamine, 1 rivastigmine, and 2 memantine trials listed in Table 1. In patients with mild to moderate VaD, the authors found small benefits in cognition of uncertain clinical significance (Table 2). There was evidence of clinical global improvement for 5 mg daily donepezil only and no behavioral or functional benefits were observed, except for a −1.0-point difference (95% CI, −1.7-−0.2) with 10 mg daily donepezil on the Alzheimer's Disease Functional Assessment and Change Scale. Cholinesterase inhibitors, but not memantine, were associated with greater odds of dropouts and adverse events (Table 2). The validity and mechanisms of the lower risk of stroke for memantine are unknown.

Although cholinesterase inhibitors and memantine produce small cognitive improvements compared to placebo, these drugs have not been shown to improve global clinical outcomes and have adverse effects and costs [89]. In 2010, the British Association for Psychopharmacology recommended against prescribing cholinesterase inhibitors or meman-

tine to patients with VaD, although those with mixed VaD and AD may benefit [90]. RCTs of cholinesterase inhibitors and memantine in VaD have been limited by heterogeneity in the type, location, and severity of CVD, use of predominantly white cohorts, variability in the requisite diagnostic imaging, small sample size precluding analyses of subgroups with greater (or less) benefit, short-treatment duration, and lack of VaD specific outcomes [74]. In addition, all trials were sponsored by the drugs' manufacturers and subsequent cost-effectiveness analyses used a short (i.e., 24–28 week) time horizon [91]. Moreover, effectiveness studies that determine the effect on clinical outcomes (e.g., cognition, function, neuropsychiatric symptoms, and behaviors), the real-world tolerability and the adherence of VCI treatments in unselected, nontrial patients are warranted. These effectiveness data would help inform patients, caregivers, and clinicians' treatment decisions in often medically-complex VCI patients.

Cardiovascular Agents

Antihypertensives

Longitudinal studies have found that high blood pressure (BP), in mid-life [92] or late-life [39], is associated with late-life VaD. Moreover, antihypertensive medication use is associated with a decreased risk of VaD [93], with each year of treatment associated with a 5% reduction in VaD risk [94]. For secondary prevention, one cohort study (n=52) of hypertensive patients with VaD or mixed dementia showed improved or stabilized cognitive scores with control of systolic BP in the upper limits of normal range (135 to 150 mm Hg), even after controlling for age, cerebral blood flow, diastolic and mean arterial BP, and pulse pressure; interestingly, systolic BP levels below 135 mm Hg were associated with steeper cognitive declines [95]. Few large-scale RCTs have assessed whether BP control influences the course of VCI.

In the Systolic Hypertension in Europe (Syst-Eur) trial, treatment of isolated systolic hypertension with a regimen based on the calcium-channel blocker nitrendipine, with the addition of the ACE inhibitor enalapril or hydrochlorothiazide, if necessary, reduced the incidence of dementia by 50% (3.8 *vs* 7.7 cases per 1000 patient-years; $p=0.05$) for a 2–year span and 55% during extended follow-up [96, 97]. The small number of dementia cases (n=32; only 2 cases of VaD) precluded an analysis of incident VaD. Among patients with CVD, the Perindopril Protection against Recurrent Stroke Study (PROGRESS) trial demonstrated that antihypertensive treatment with perindopril ± indapamide did not reduce the risk of dementia, a secondary endpoint, but did reduce the risk of recurrent stroke, and dementia or cognitive decline associated with recurrent stroke [98, 99]. These findings are consistent with the data from The Heart Outcomes Prevention Evaluation (HOPE) RCT showing that treatment with the angiotensin-converting enzyme inhibitor ramipril decreased stroke incidence and the risk of stroke-related cognitive decline in patients with, or at high-risk for, vascular disease [100]. Conversely, the Hypertension in the Very Elderly Trial (HYVET) found that treatment with indapamine ± perindopril did not reduce the risk of VaD (unadjusted hazard ratio, 0.87; 95% CI, 0.57-1.34), cognitive decline or total dementia in patients ages 80 years or older with hypertension [101]. The treatment targets for BP (150/80 mm Hg) may have been too high for optimal cognitive benefits, a potential explanation applicable to the PROGRESS trial as well. Two recent RCTs reported no benefit of angiotensin II receptor blocker treatment on cognition or dementia in patients with hypertension [102] or ischemic stroke [103].

Meta-analyses have found conflicting evidence that BP lowering in late life prevents cognitive decline or dementia with positive results if the PROGRESS trial is included [101], and negative results if the PROGRESS trial is excluded [104], suggesting greater efficacy in populations with CVD. Previous RCTs were limited by measurement of secondary study outcomes, few VCI cases, premature discontinuation of the study, imprecision regarding effect estimates, differential drop-outs, and contamination (i.e., placebo patients receiving active therapy or premature discontinuation of study treatment) [105]. Another challenge is that age may modify the relationship between BP, CVD, and cognition [105, 106]. Taken together, the PROGRESS and HOPE trials suggest that BP lowering or other possible mechanisms (e.g., renin-angiotensin-aldosterone system blockade) may reduce the risk of a major VCI subtype, poststroke cognitive decline, but not other cognitive outcomes; these findings were consistent with other recent clinical studies [107]. Future research is needed to determine whether long-acting dihydropyridine calcium channel blockers have efficacy in the primary prevention of VCI.

In regard to secondary prevention, a Cochrane review of nimodipine for patients with dementia identified 10 trials that included patients with VaD. When VaD trials were pooled separately, significant efficacy was noted for clinical global impression and cognitive function, but not on scales assessing ADL for the 90 mg/day dose of nimodipine at 12 weeks [108]. Although nimodipine had evidence of short-term benefit and was well tolerated with a low rate of adverse events, the meta-analyses were based only on participants who completed the study and were not intention-to-treat analyses. One small, randomized prospective trial compared rivastigmine to nimodipine for 14 months among older adults (n=100) stratified by VCI subtype. Although rivastigmine improved behavioral symptoms compared to nimodipine, there were no differences in clinical dementia or cognitive scores between treatments [109]. These data suggest that long-acting dihydropyridine

Table 2 Efficacy and adverse events of cholinesterase inhibitors and memantine in vascular dementia: summary of results of a meta-analysis of randomized controlled trials*

Treatment	Cognitive Outcomes	Global Change Outcomes	All-Cause Dropouts	Adverse Events
	Change in ADAS-cog subscale from baseline, WMD† (95% CI)	Change in CIBIC-plus or CGIC‡, Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)§
Donepezil 5 mg *vs* placebo	−1.2 (−1.7–−0.6)	1.5 (1.1–2.1)	1.2 (0.9–1.8)	Anorexia, 2.0 (1.0–3.8) Insomnia, 2.2 (1.0–4.7) Diarrhea, 1.5 (1.0–2.3)
Donepezil 10 mg *vs* placebo	−2.2 (−3.0–−1.4)	1.2 (0.9–1.6)	1.9 (1.4–2.7)	Anorexia, 2.5 (1.3–4.7) Nausea, 2.5 (1.6–3.9) Diarrhea, 1.8 (1.2–2.7)
Galantamine 24 mg *vs* placebo	−1.6 (−2.4–−0.8)	1.1 (0.8–1.4)	1.7 (1.3–2.2)	Anorexia, 4.5 (2.0–10.1) Nausea, 3.6 (2.4–5.4) Diarrhea, 1.6 (1.0–2.4) Vomiting, 3.1 (1.8–5.1) Insomnia, 3.3 (1.6–7.0)
Rivastigmine 12 mg *vs* placebo	−1.1 (−2.2–−0.1)	1.0 (0.8–1.4)	2.0 (1.4–3.0)	Anorexia, 3.1 (1.2–7.9) Nausea, 8.9 (4.9–16.2) Diarrhea, 2.2 (1.2–4.1) Vomiting, 11.9 (5.6–25.0)
Memantine 20 mg *vs* placebo	−1.9 (−2.8–−0.9)	1.3 (0.9–2.2)	1.1 (0.8–1.5)	Stroke, 0.4 (0.2–0.9)

In all trials and the meta-analyses, primary outcomes were determined using intention-to-treat analyses with last observation carried forward sample. The outcomes and numbers of patients in each randomization group were statistically combined using fixed-effects models.

*Kavirajan and Schneider [74].

† Change in Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) from baseline calculated as a weighted mean differences (WMD) with 95% confidence interval (CI)

‡ Change in clinical global improvement measured by Clinical Global Impression of Change (CGIC) for 1 memantine trial (MMM500) or measured by Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus) for all other trials

§ Odds Ratios dervied from Yousef-Peto fixed effects models for dichotomous clinical outcomes, dropouts, and adverse events

ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale

calcium channel blockers may have efficacy in the secondary prevention of VCI, but trials with long-term follow-up are needed.

Aspirin

Aspirin may prevent or reduce VCI through several potential biological mechanisms including reduced platelet aggregation, vasodilatation, decreased circulating β-amyloid production (derived from platelets), and fewer superoxide radicals [110]. However, a Canadian observational study of older adults showed an association between aspirin use and an increased risk of incident VaD [60]. Confounding by indication may bias investigations of the aspirin-VCI association because older adults with existing vascular disease or vascular risk factors (and possible subclinical CVD) are more likely to be prescribed aspirin. In a small, randomized clinical trial (n=70; mean follow-up, 15 months), cognition, cerebral blood flow, and functional status improved in multi-infarct patients (mean age, 67 years) treated with daily aspirin (325 mg); however, differences in recurrent stroke may have explained these findings [111]. To date, no RCTs of aspirin have been reported for the treatment of VCI [112].

Statins

Observational studies have found associations between elevated levels of serum total cholesterol, low-density lipoprotein (LDL) cholesterol, and nonhigh-density lipoprotein, and decreased levels of high-density lipoprotein and risk of VaD [41, 113, 114]. In a prospective longitudinal community-based study spanning a 7-year period (1991–1998), LDL cholesterol levels were associated with an increased risk of dementia with stroke [115]. Compared with the lowest quartile, the highest quartile of

LDL cholesterol was associated with approximately a 3-fold increase in risk of dementia with stroke, after adjusting for vascular risk factors and demographic variables (relative risk, 3.1; 95% confidence interval [CI], 1.5-6.1) [115]. However, observational studies have not shown a decreased risk for VCI associated with statin or lipid-lowering therapy [114].

No RCTs have demonstrated that statins given in late life to individuals at risk of vascular disease prevents dementia [116]. In the Heart Protection Study, simvastatin treatment for 5 years did not prevent cognitive decline or dementia incidence among individuals with a history of coronary heart disease or risk factors for it, or CVD [117, 118]. Similarly, in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), pravastatin treatment did not affect cognitive decline during 3 years of follow-up among older adults at risk for vascular disease [119, 120]. Although statins may reduce the risk of VCI by preventing primary and recurrent stroke [117, 118, 121], whether treatment of elevated LDL cholesterol levels will reduce the risk of VCI independently of stroke needs to be determined.

Vascular Care

Comprehensive vascular care may represent 1 approach to the primary or secondary prevention of VCI. However, in a recent RCT, multi-component vascular care that combined pharmacological and nonpharmacological interventions did not slow functional or cognitive decline in 130 patients with AD and CVD [122]. A larger cluster, randomized trial with a 6-year follow-up in 3700 elderly subjects (70 to 78 years) will assess whether nurse-led intensive vascular care in primary care decreases the incidence of dementia, including VaD, and whether it reduces disability; secondary outcomes are mortality, incidence of vascular events, and cognitive functioning [123]. Given that recurrent stroke accelerates VCI, secondary stroke prevention is an important strategy to prevent cognitive declines in VCI [124].

Vitamins and Other Compounds

Some observational studies suggest a protective role of antioxidants in VCI. In the Canadian Study of Health and Aging, the history of anti-oxidant vitamin use (vitamin E and C supplements, and/or multivitamins) was associated with a lower incidence of VCI, but not dementia or AD for 5 years [125]. Cytidine 5′-diphosphocholine (CDP-choline or citicoline), a precursor needed for the synthesis of phosphatidylcholine, may attenuate ischemic injury by accelerating re-synthesis of phospholipids in brain cell membranes, by suppressing the release of free fatty acids, and perhaps by increasing noradrenaline and dopamine levels in the central nervous system [126]. Several small RCTs of chronic cerebrovascular patients ($n \leq 100$) and 1 large ($n=536$) unpublished RCT of VCI patients suggest improved cognition, particularly in the areas of attention and perceptual-motor performance with oral citicoline treatment [126]. However, a recent RCT ($n=30$) showed no improvement in neuropsychological performance in VaD patients treated with citicoline for 12 months [127]. An unpublished study ($n=347$) found that citicoline treatment for 6 months may prevent poststroke cognitive decline [128]. Although the drug seems to be safe and well tolerated, more study of its symptomatic and disease-modifying effects on VCI is needed. Despite some intriguing data, the efficacy of several compounds, including Hydergine [129], Ginkgo biloba [130], Huperzine A [131], and propentofylline [132] for VCI has not been established.

Anti-Depressants

Selective serotonin reuptake inhibitors (SSRIs) may improve cognitive function by effecting neural circuits that process cognitive information [133] and increase hippocampal neurogenesis [134]. In a retrospective case series of 35 nondepressed male veterans with VCI, open-label sertraline use was associated with improved executive function measured by the Executive Interview (EXIT25) perhaps through a dopaminergic mechanism [135]. In a post hoc subsample analysis ($n=129$) of a recent multicenter trial of poststroke depression in patients treated within 3 months of recent hemorrhagic or ischemic stroke, escitalopram for 12 months improved scores in global cognition, and immediate and delayed memory, compared to placebo or problem solving therapy, even after controlling for depressive symptoms [133]. Future research is needed to study the effects of anti-depressants on cognition and neuropychiatric symptoms or behaviors linking mechanisms (e.g., serotonergic, noradrenergic, or dopaminergic) to cognitive or behavioral effects, and identifying subgroups or phenotypes of VCI with greater benefit.

Nonpharmacologic Therapies

Carotid Revascularization

Some data suggest that carotid artery stenosis (CAS) may be associated with cognitive dysfunction even in persons without stroke; however, whether revascularization influences the course of VCI is uncertain. In a recent observational study of 4,006 right-handed individuals aged 65 or older from the Cardiovascular Health Study, left-sided CAS $\geq$ 75% was associated with cognitive impairment at baseline and cognitive decline during a 5-year span [136].

Because the associations persisted after adjustment for right-sided CAS and vascular risk factors, the study authors postulated mechanisms independent of vascular risk factors or cardiovascular disease. A recent systematic review did not find consistent evidence that carotid revascularization affected cognition due to methodological differences and limitations among studies [137].

Lifestyle Modification

Several observational studies suggest that physical activity may reduce the risk of VCI [44, 138]. Recently, a blinded, randomized pilot study of chronic stroke survivors showed that a brief 2-month aerobic exercise intervention improved cognitive performance and sensorimotor learning, including information processing speed [139]. In addition, smoking cessation was associated with improved cognition among normotensive patients with VaD or mixed dementia (n=14) [95]. These preliminary data suggest avenues for future clinical and interventional studies of lifestyle modification for the primary and secondary prevention of VCI.

Cognitive Training and Rehabilitation

Cognitive training and cognitive rehabilitation represent possible nonpharmacological therapies for VCI. However, a Cochrane review found no evidence for the efficacy of cognitive training based on 9 RCTs for VCI, and insufficient evidence to evaluate individualized cognitive rehabilitation [140].

Future Directions

Key gaps remain in our understanding of the risk factors, causal pathways, and pathophysiology of VCI. Potential biological, pathological, environmental, and genetic mechanisms of VCI warrant further investigation. In addition, how vascular risk factors and their treatments affect VCI independent of primary or recurrent stroke needs to be determined. Clinical studies are contributing to our understanding of vascular risk factor treatments in cognition among middle-aged and older adults with or at risk for VCI [141–143]. Despite limited efficacy and frequent adverse effects, drugs for dementia are prescribed off-label to a substantial proportion of VCI patients, with a prescription rate of 35 to 45% for cholinesterase inhibitors [144]. [47] Clinical and effectiveness studies are needed to determine whether there are subgroups of patients with VCI who may tolerate and receive benefit from symptomatic treatments. Research and clinical approaches to VCI will likely need to advance beyond primary and secondary stroke prevention and the use of AD therapies. Moreover, these research and clinical approaches will need to consider the pathological and clinical heterogeneity of VCI. Given its substantial health, social, and economic burden in the growing population of older adults, the prevention and treatment of VCI are critical priorities for clinical care and research.

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