Vascular Cognitive Disorder: A Diagnostic and Pharmacological Treatment Updating

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Abstract: Cognitive impairment underpins some of the clinical spectrum of the cerebrovascular disease (CVD), as well as contributes to the patient´s impaired social and behavioral functioning, and the higher mortality. When cognitive function is affected by CVD, we name it as vascular cognitive impairment (VCI). The cognitive impairment may be mild, or may be severe enough to warrant a diagnosis of dementia. Pure vascular dementia is not common. Because of that the concept of mixed dementia has been included in the clinical diagnosis of VCI.

Despite a general emphasis in the international literature on the primary and secondary prevention of CVD to avoid vascular dementia or their combination with Alzheimer's disease, the controversy concerning their diagnostic criteria and optimal treatment is still open. Given its growing burden, the prevention and treatment of CVD and the spectrum of VCI are critical priorities for clinical care and research.

We performed a selective review about the current status of vascular dementia, mild cognitive impairment due to CVD, and mixed dementia, with special emphasis on available evidence of pharmacological strategies for treatment and prevention from controlled clinical trials.

Keywords: Alzheimer's disease, cerebrovascular disease, post-stroke dementia, vascular cognitive impairment, vascular dementia, vascular risk factors.

INTRODUCTION

Although Alzheimer´ s disease (AD) is the most common form of cognitive impairment in the elderly, the burden of cognitive impairment secondary to cerebrovascular disease (CVD) and stroke has become increasingly important. Current estimates of the effect of vascular contributions on cognition in the elderly vary greatly between studies. There are differences in nosology, criteria, and measurement issues. Understanding of the interaction between vascular disease and cognition represents an evolving challenge.

Cognitive impairment secondary to CVD has been defined in many different ways. Current approaches use the term vascular cognitive impairment (VCI) to refer to all forms of cognitive impairment associated with CVD [1]. This modern construct has evolved to describe all forms of mild to severe cognitive impairment, in which the interactions between several vascular etiologies and cognition play an important role [2]. A growing number of experts prefer the term "VCI" rather than "vascular dementia (VaD)" because they understand the concept that vascular and cognitive changes can range from mild to severe, including both VCI without dementia and VaD. This burgeoning area of research intends to focus attention on earlier prevention and treatment.

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In general, the risk factors for VCI are the same as those for heart disease and stroke [3-9]. Conventional risk factors for VCI include aging, cardiovascular disease, CVD, hypertension, diabetes, dyslipidemia, cigarette smoking, and atrial fibrillation [2]. Furthermore, concurrent vascular risk factors and CVD is often seen in older dementia patients even though they may have a slowly progressive degenerative disease most consistent with AD [10]. Of practical significance is that many of these morbidities are modifiable and should be the focus of interventions to minimize the burden of VCI, to ameliorate the course of cognitive decline, to improve quality of life and to decrease mortality in our aging population. The goal of this article is to review the current status of VaD, mild cognitive impairment due to CVD, and mixed dementia, with special emphasis on available evidence of pharmacological strategies for treatment and prevention from controlled clinical trials.

METHODS

Data Sources and Searches

Literature regarding VCI and VCD were searched by the PubMed, Scopus, and Cochrane databases (until February 2014) to identify the eligible studies. An extensive manual search of the literature using the references of the papers was performed. Randomized controlled trials (RCTs) studying the effect of treating hypertension and dyslipidemia, and the effect of aspirin, antidepressants, memantine, and cholinesterase inhibitors on cognitive decline or dementia, in elderly populations were selected.

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Definition and Diagnostic Criteria

The term of VCI replaced VaD [11], which replaced the term multi-infarct dementia [12] as the concept to be used in cognitive impairment due to CVD. Because AD was thought to be the major cause of dementia, all constructs were based on AD paradigm. Separating of AD from VaD has resulted in several published criteria for VaD. Currently eight different clinical diagnostic criteria sets for VaD have been used in clinical and research settings: the Hachinski Ischemic Scale [13]; the Ischemic Scale of Rosen [14]; the DSM-III, DSM-III-R, and DSM-IV criteria; the International Classification of Diseases, 10th Revision (ICD-10); the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) [15]; and the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria (NINDS-AIREN) [16]. The criteria differ in the way they operationalize each of the diagnostic elements. When these criteria were developed, the prodromal phase of VaD was not considered. Most of the old criteria define dementia as the decline in cognitive abilities severely enough to interfere with daily functioning, based primarily on memory deficits (AD type model), and include the presence of vascular events (stroke model). Emphasizing memory loss as the key symptom and strokes as the only etiology of VaD is probably inappropriate, since none of which are necessary for the diagnosis [17].

Over the last 5 years, two separate consensus conference statements have been published [1,18], which evolved towards defining VCI, being the VaD the last phase of the disease. Consequently, VCI is a new and widely accepted paradigm, which include the spectrum of vascular mild cognitive impairment (VaMCI), VaD, and cognitive impairment of mixed etiology [12]. VCI diagnosis should be based on two factors: 1) evidence of lower performance in at least one cognitive domain by neuropsychological testing, and 2) history of clinical stroke or demonstration of abnormalities on neuroimaging that suggests a link between the cognitive disorder and CVD [19].

In summary, the proposed VCI construct takes into account three important concepts. First, VCI includes all the spectrum of cognitive impairment due to CVD, ranging mild cognitive deficits to dementia, being VaD the most severe form [1]. Second, many etiologies apart from multiple infarcts including strategic infarcts, leukoaraiosis, chronic hypoperfusion, and hemorrhages might be responsible of the cognitive profile associated with VCI [5]. Third, there is an increasing recognition of mixed dementia, where VCI co-exists with other pathologies, particularly AD [1,13,18,20].

Definition of Vascular Dementia

In epidemiologic surveys, VaD is identified as the second most common contributor to dementia after AD [20]. Definition of VaD was separated from AD using clinical features and the evidence of risk factors, vascular events, and vascular injuries on neuroimaging. The current consensus statement defines VaD with two designations, clinically probable and clinically possible VaD [1]. The most

Table 1. Subtypes of vascular cognitive impairment.

Subtype	Mechanism	Localization	Characteristics
Poststroke VCI	Single strategic infarct or after multiple strokes (multi-infarct dementia).	Cortical	Abrupt onset. Cortical cognitive impairments: aphasia, apraxia, or agnosia. Correlation between infarction and impairment remains imprecise.
Strategic Infarct VCI	Small but strategically located infarcts. Sites: basal forebrain, medial temporal, thalamic or parieto-occipital infarcts.	Cortical or subcortical	Cognitive impairments: memory impairment, impaired executive function, confusion, and fluctuating levels of consciousness. Behavioral impairments: apathy, lack of spontaneity, and perseveration
Subcortical Ischemic VCI	Small-vessel disease (lacunes and incomplete white matter ischemia). Lesions injure specific prefrontal subcortical circuits.	Subcortical	1) Lacunar state: sudden hemiparesis, dementia, dysarthria, pseudobulbar palsy and affect, crying, small-stepped gait, urinary incontinence, lack of volition and akinetic mutism. 2) Strategic lacunar infarct: abrupt onset of focal neurological symptoms. 3) Binswanger syndrome: slowly progressive decline in cognition, gait apraxia, and early urinary incontinence.
Mixed dementia	Cerebrovascular disease and AD neuropathology	Cortical and/or subcortical	Gradient of features of both AD and VCI.
Silent brain infarcts	Small discrete lesions greater than 3 mm in diameter and/or diffuse periventricular and deep white matter changes.	Cortical and/or subcortical	Association with subtle declines in cognition. Silent infarcts at baseline more than doubled the risk of dementia and stroke.
CADASIL	Small arteries of the brain. Progressive degeneration of vascular smooth muscle cells.	Subcortical	Genetic disorder affecting the Notch3 gene. Recurrent attacks of migraine, ischemic events, microbleeds and progressive subcortical dementia lead to premature death (mean age 65 years).

AD, Alzheimer´s Disease; CADASIL, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy; VCI, vascular cognitive impairment.

important feature is the presence of cognitive decline from a prior baseline and a deficit in performance in ≥ 2 cognitive domains (a memory deficit should not be required for the diagnosis) being severe enough to interfere with activities of daily living [21]. The cognitive domains to detect dementia are specified. Although VaD may result from many forms of CVD, VaD is clearly associated with symptomatic stroke and an abrupt onset of symptoms. It is necessary to establish this temporal and spatial relationship. Some authors propose that the onset of dementia symptoms should appear within 3 months after a recognized stroke [19]. However, this is not universal, and symptoms may develop after this proposed time [1]. When VaD presents in the context of extensive subcortical CVD, the diagnosis of probable VaD is difficult, because their presence is described in healthy elderly and in patients with AD [22, 23].

Definition of Vascular Mild Cognitive Impairment

There is increasing evidence that up to half of patients with cognitive impairment secondary to CVD frequently do not fulfill the proposed criteria of VaD [21,24]. CVD can also cause mild cognitive deficits without functional impact, similar to prodromal AD. This prodromal VaD is named as VaMCI [25,26]. This intermediate state of cognitive impairment is an useful tool for identifying individuals at increased risk of dementia [27]. This stage has been defined using different terms, as VCI not dementia, MCI of vascular type, pre-clinical VCI, vascular pre-dementia MCI and mild VCI [28].

The current consensus statement defines VaMCI as the presence of decline in cognitive function from a prior baseline and impairment in at least one cognitive domain associated with their relationship with CVD to support clinical findings [1]. The most important limitations are the lack of consistent standardized measures and of predictive power for dementia conversion [27]. Several studies have shown that stabilization or even partial reversibility in VaMCI may occur [29,30], caused by depression or expected poststroke recovery or other diseases.

MECHANISMS OF DISEASE

The pathophysiology of VCI continues to be investigated. Understanding of the association between CVD and VCI is necessary to develop prevention strategies and adequate treatment. The possible relationship may be result of a shared mechanism among vascular risk factors, behavioral factors and neuropathology (Fig. **1**).

In general, the risk factors for VCI are the same as those for cardiovascular disease and stroke. Modifiable vascular risk factors (hypertension [3], hyperlipidemia [4], diabetes [5], atrial fibrillation [6]) and behavioral factors (unhealthy diet [31], overweight/obesity [8], physical inactivity [9], and cigarette smoking [7]) are associated with CVD and VCI. In addition, there are some risk factors that cannot be changed (age, gender, family history, and ethnicity). It is known that vascular risk factors and behavioral factors have a synergistic effect on atherosclerotic disease [32], conducting to both CVD and VCI.

Different neuropathological mechanisms such as atherosclerosis, inflammation, oxidative stress, and amyloid deposition have been studied [33,34]. Postmortem neuropathological studies indicate that infarcts vary in size, number, and location; can be silent or clinically eloquent; are the most important determinants of cognitive impairment in the elderly; and typically are mixed degenerative and vascular pathologies. For these reasons, no neuropathological criteria have been established for the definitive diagnosis of VCI.

PATHOPHYSIOLOGICAL SUBTYPES OF VCI

A pathophysiological approach separates different subtypes of VCI, including multi-infarcts, strategic infarcts, subcortical ischaemic vascular disease, and non-infarct ischaemic changes [13]. A summary is presented in Table **1**.

CLINICAL EVALUATION

In the absence of definitive biological or radiological markers of VCI, the diagnosis of VCI remains a clinical approach integrating all available clinical and complementary studies information [13]. A medical history and physical examination are mandatory as a part of evaluating subjects who have cognitive symptoms or risk factors for CVD. Physical examination should include blood pressure, heart rate, body mass index, presence of focal neurological abnormalities, disturbance in gait, bladder symptoms or pseudobulbar palsy [13].

Neuropsychological Assessment

The clinical and neuropathological presentation and progression of VCI is quite heterogeneous, and a variety of cognitive profiles characterizes VCI. Several cognitive domains may be impaired in various severity ranges and combinations related to the contribution of cerebrovascular disease. Single strategically placed infarction can lead to specific cognitive profiles, whereas subcortical small vessel disease is often associated with executive dysfunction as the most prominent symptom [35]. Instruments to assess neuropsychiatric symptoms and functional impairment are also suggested.

The distinctive neuropsychological profile between AD and VCI has been described. AD is often characterized by deficits in episodic memory (particularly delayed recall), whereas subjects with VCI are more impaired than those with AD on tests of executive functions. However, these profiles lose specificity in mixed variants. Furthermore, episodic memory failure in VaMCI is frequent. However, this failure may be secondary to a more general impairment in executive control processes, with intact hippocampus and surrounding cortices [36].

Neuroimaging

Neuroimaging studies are necessary to correlate clinical profile and vascular injuries. Because at present vascular injuries can be identified *in vivo* only indirectly by

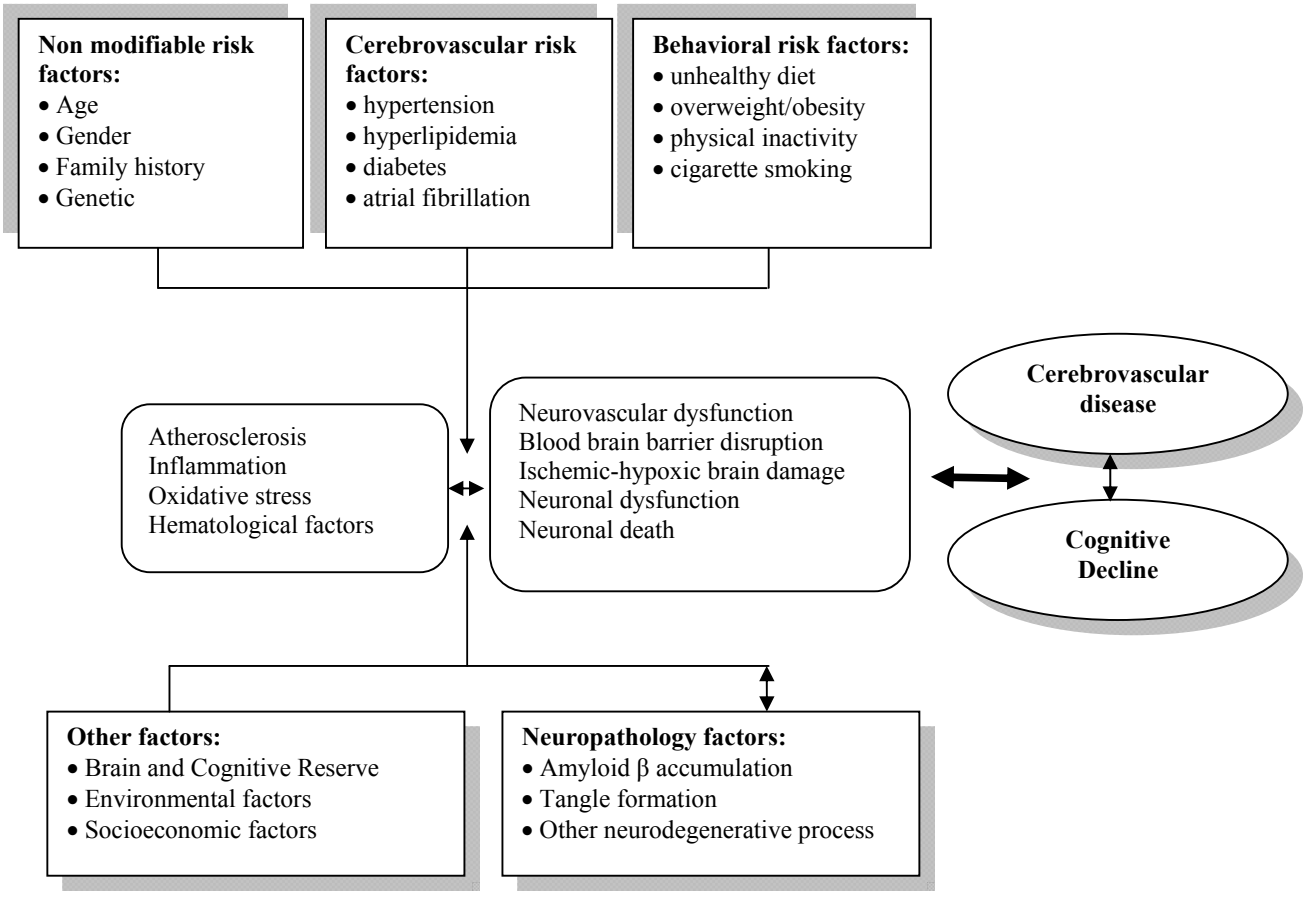


Fig. (1). Risk factors and pathophysiological process leading to cerebrovascular disease and cognitive impairment.

computerized tomography (CT) and mostly by magnetic resonance imaging (MRI), vascular injuries has become a neuroimaging concept [37]. However, neuroimaging does not disclose all forms of vascular injuries and does not confirm neurodegenerative versus vascular etiology. Despite its limitations, clinical criteria require presence of CVD that is thought to be etiologically related to the cognitive impairment [13]. The presence of 1 type of cerebral vascular injuries should therefore be considered a potential predictor of ischemic and hemorrhagic recurrent events with relevant, although unexplored, therapeutic consequences, and a marker of poor prognosis [38].

PHARMACOLOGICAL PREVENTION AND TREATMENT OF VCI

Currently proven pharmacological approaches to prevent or treat VCI are lacking. Numerous drugs have been studied for the treatment of VaD but with inconclusive results. Furthermore, most interventions have not been extensively studied in VCI without dementia.

Advances in CVD management, and the recognition of the overlap between VCI and AD have allowed two approaches for the prevention and treatment of VCI [39]. First, general interventions that may be effective to prevent CVD including antiplatelet agents, statins, antihypertensive therapy, more intensive treatment of diabetes mellitus, and carotid endarterectomy may be applied to patients with VCI. Second, a deficient cholinergic neurotransmission that may be a potential contributor to the cognitive impairment of vascular disease of the brain may justify the use of medications approved by the Food and Drug Administration (FDA) to treat AD.

The field of cognitive impairment with or without dementia research has advanced significantly to where it is sufficient to justify the importance of prevention as the main therapeutic tool. A large number of risk factors and predictive factors for dementia in general and AD in particular have been investigated. Despite conclusive evidence for the role of these risk factors there is considerable uncertainty regarding the efficacy of their treatment for lowering the risk of cognitive impairment or dementia [40]. A relatively limited number of highest-evidence studies are available to convincingly show that the vascular impairment is preventable. Some main trends may explain this so far: first, most studies have focused on preventing dementia rather than on preventing milder, more common forms of cognitive impairment; secondly, CVD and stroke leading to dementia have received less attention than AD; lastly, there is no consensus on how and when to define the primary, secondary or tertiary prevention levels according to clinical o neuropathological criteria.

Regardless of these limitations, CVD represents an increasingly recognized target for prevention of cognitive impairment or dementia. Preventing CVD remains the most

promising strategy to avoid VCI and possibly dementia in general. Lifestyle changes are the most obvious preventive approaches; however these changes are not always achieved in the clinical practice. A number of pharmacological agents to reduce known vascular risk factors are suggested as potential options for preventing cognitive impairment and dementia; these are summarized below.

Hypertension - Antihypertensive Therapy

The impact of antihypertensive therapy on cognitive impairment in patients with hypertension was assessed in several studies. Despite the known relationship between hypertension and dementia, clinical trials results have been uncertain regarding their role for reducing the risk of dementia. Ten randomized placebo-controlled trials assessed the effect of antihypertensive therapy to reduce the risk of cognitive decline. All trials were heterogeneous with different designs and outcomes. Cognitive impairment and dementia were included as a secondary outcome [10]. To assess cognitive function, the Mini Mental State Examination (MMSE) was used in most studies (SYST-EUR, SCOPE, PROGRESS, HYVET-COG, TRANSCEND, and ONTARGET) [41-45]. In the SHEP [46] study, cognitive screening was performed by the short-comprehensive assessment and referral evaluation (short-CARE) questionnaire. In the MRC [47] trial, the paired associate learning test (PALT) and the trail making test (TMT) were used.

These clinical trials have had conflicting results. A beneficial effect on the risk of incident dementia was reported in stroke patients (HOPE, PROGRESS) [43,48] and in elderly patients (SYST-EUR) [41] but this was not proved in other trials (MRC, SHEP, HYVET-COG, PROFESS, TRANSCEND, and ONTAGET) [44-47,49]. Their results are summarized in Table **2**. The combined results of these trials are also not conclusive. In a meta-analysis of three randomized clinical trials reporting cognitive decline (PROGRESS, PROFESS, and HYVET-COG) [43,44,49] lowering blood pressure was associated with reduced cognitive decline [50]. Similarly, in a meta-analysis of six randomized clinical trials reporting dementia (HYVET-COG, PROFESS, PROGRESS, SCOPE, SHEP, and SYST-EUR) [41-44,46,49] a trend to less dementia was observed (non-significantly) [50].

The Secondary Prevention of Small Subcortical Strokes (SPS3, n = 3.020) factorial trial has been completed in 2012. The secondary outcome was to know the difference in the rate of cognitive decline among SPS3 participants assigned to receive intensive or standard hypertension treatment, and aspirin alone versus combination of aspirin and clopidogrel, assessed through repeated neuropsychological tests; and major vascular events. No study results have been published (http://www.clinicaltrials.gov/ct2/show/NCT00059306, downloaded 11 May 2014). Three randomized controlled trials are ongoing. PRESsure in established cERebral small VEssel disease (PRESERVE, n = 422) trial is also investigating if intensive or standard, treatment of blood pressure in hypertensive individuals with established cerebral small vessel disease and radiological leukoaraiosis is associated with reduced cognitive decline (http://www.controlled-trials.com/ISRCTN37694103, downloaded 11 May 2014). The ongoing Prevention Of Decline in Cognition After Stroke Trial (PODCAST, n= 600) was designed to determine if intensive hypertension therapy, and/or intensive lipid lowering therapy, after stroke reduces cognitive decline and dementia (http://www.controlled-trials.com/ISRCTN85562386, downloaded 11 May 2014). Finally, the Systolic Blood Pressure Intervention Trial - Memory and Cognition in Decreased Hypertension (SPRINT-MIND) trial is ongoing, but not recruiting participants. This trial will study the effect of lowering systolic blood pressure in cognition and in the brain structure (http://www.clinicaltrials.gov/ct/show/NCT01206062, downloaded 11 May 2014).

Dyslipidemia

There is evidence that high serum cholesterol may contribute to the development of AD and VaD [51]. Initial evidence from observational studies showing that statins could prevent dementia was very promising. However, the evidence from subsequent clinical trials has been negative [52].

Two randomized trials have assessed the role of statins on cognition in patients with vascular disease but no dementia (HPS, PROSPER; Table **3**) [53,54]. Cognitive function was a tertiary outcome in both studies. None showed any benefit in reducing the incidence of AD or dementia [53, 54]. No significant effect of statins on cognition was seen in the last update Cochrane systematic review [52].

Two interesting points must been mentioned. First, the higher risk of intracerebral hemorrhage in statin-treated patients with prior CVD [55]. Finally, the FDA published a warning regarding cognitive impairment from statin use for several years, albeit reversible. Evidence about cognitive impairment associated with statin use in studies are lacking. More studies are needed to provide recommendations [56,57]. The absence of many well designed clinical trials result in low level of evidence. New and better randomized clinical trials are needed to answer these relevant topics.

A large body of evidence from randomized clinical trials using statins consistently reports no benefit in cognition (HPS, PROSPER) [53,54] or dementia prevention (PROSPER) [54]. On the other hand, there are no studies identified assessing roles of statins in treatment of VaD or VCI. Conclusions are based on three small randomized trials of statins in patients with mild to moderate AD (Simons, ADCLT, LEADs) [58-60]. A Cochrane systematic review of three trials (Simons, ADCLT, LEADs) did not show sufficient evidence to recommend statins for the treatment of dementia [52].

A further trial (CLASP; http://www.clinicaltrials.gov/ct2/show/NCT00053599, downloaded 11 May 2014) showed than lowering blood cholesterol with simvastatin in mild to moderate AD was not associated with reduced cognitive decline. The Statin Effects on Beta-Amyloid and Cerebral Perfusion in Adults at Risk for Alzheimer's Disease (SHARP, n= 90) trial is ongoing. The study is recruiting parents with AD from United States. The primary outcome is to assess the changes in beta-amyloid cerebrospinal fluid levels. Cognitive outcome is a secondary outcome (http://clinicaltrials.gov/show/NCT00939822, downloaded 11 May 2014).

Table 2. Antihypertensive therapy.

Study Name	Study Aim	Current Status of Trial	Intervention	Population Characteristics	Health Status/ Diagnosis	Cognitive Test	Effect on Cognitive Function
MRC [47]	Prevention dementia	Completed	Atenolol or Hydrochlorothiazide plus Amiloride or Placebo	n= 2584 aged 65-74,	Hypertension	PALT, TMT	Non-significant effect on cognitive function
SHEP [46]	Prevention dementia	Completed	chlorthalidone (± Atenolol or Reserpine) or Placebo	n= 4736 ≥ 60 years	Elderly Hypertension	short-CARE	Reduction of dementia 16% (non significant)
SYST-EUR [41]	Prevention dementia	Completed	Nitrendipine (± Enalapril and Hydrochlorothiazide) or Placebo	n= 579 > 60 years	Elderly Hypertension	MMSE	*Reduction of dementia 50% (0 to 76%)*
HOPE [48]	Prevention dementia	Completed	Ramipril or Placebo	n= 9500 ≥ 55 years	Cardiovascular disease	Not defined	*Reduction of cognitive decline related to stroke 41% (6%-63%)*
PROGRESS [43]	Prevention dementia	Completed	Perindopril/Indapamide or Placebo.	n= 6105 mean age: 64	Stroke or TIA	MMSE	*Reduction of dementia (12%) and of cognitive decline (19%).*
SCOPE [42]	Prevention dementia	Completed	Candesartan or Placebo	n= 4964 aged 70-89 years	Elderly Hypertension	MMSE	Reduction of dementia 7% (non significant).
PRoFESS [49]	Prevention dementia	Completed	Telmisartan or Placebo	n= 817	Hypertension	MMSE	There were no significant differences in the rate of cognitive decline/dementia
TRANSCEND [45]	Prevention dementia	Completed	Telmisartan or Placebo	n= 5926 ≥ 55 years	Cardiovascular disease	MMSE	There were no significant differences in the rate of cognitive decline/dementia
ONTARGET [45]	Prevention dementia	Completed	Ramipril or Telmisartan or combination	n= 25620 ≥ 55 years	Cardiovascular disease	MMSE	There were no significant differences in the rate of cognitive decline/dementia
HYVET-COG [44]	Prevention dementia	Completed	Indapamide ± Perindopril or Placebo.	n= 3336 ≥ 80 years	Elderly Hypertension	MMSE	Reduction of dementia 14% (non significant)
SPS3	Prevention dementia	Completed	Intensive or Standard hypertension treatment, and Aspirin or Aspirin plus Clopidogrel	n= 3020 ≥ 30 years	Small Subcortical Ischemic Stroke or Subcortical TIA	Neurocognitive battery	Not published
PRESERVE	Prevention dementia	Ongoing	Intensive or Standard hypertension treatment	n= 422 ≥ 40 years	VCI Hypertension.	MMSE	-
PODCAST	Prevention dementia	Ongoing	Intensive hypertension treatment, and/or Intensive lipid lowering treatment	n= 600 ≥ 70 years	Stroke	ACE	-
SPRINT-MIND	Prevention dementia	Ongoing	Intensive or Standard hypertension treatment	n= 2800 ≥ 50 years	Hypertension, Presence of CVD other than stroke	MoCA, Digit Symbol Coding test, Logical Memory Test	-

MRC, Medical Research Council's; SHEP, Systolic Hypertension in the Elderly Program; SYST-EUR, Systolic Hypertension in Europe; HOPE, Heart Outcomes Prevention Evaluation; PROGRESS, Perindopril Protection against recurrent Stroke Study; SCOPE, Study on Cognition and Prognosis in the Elderly; PRoFESS, Prevention Regimen for Effectively Avoiding Second Strokes; TRANSCEND, Telmisartan Randomized AssessmeNt Study in aCE iNtolerant subjects with cardiovascular Disease; ONTARGET, ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; HYVET-COG, Hypertension in the Very elderly Trial; SPS3, Secondary Prevention of Small Subcortical Strokes; PRESERVE, PRESsure in established cERebral small VEssel disease; PODCAST, Prevention Of Decline in Cognition After Stroke Trial; SPRINT-MIND, Systolic Blood Pressure Intervention Trial: Memory and Cognition in Decreased Hypertension; TIA, transient cerebral ischemic attack; CVD, cardiovascular disease; VCI, vascular cognitive impairment; PALT, paired associate learning test; TMT, trail making test; short-CARE, short-Comprehensive Assessment and Referral Evaluation; MMSE, Mini Mental State Examination; ACE, Addenbrooke's Cognitive Examination; MoCA, Montreal Cognitive Assessment.

Table 3. Dyslipidemia.

Study Name	Study Aim	Current Status of Trial	Intervention	Population Characteristics	Health Status/Diagnosis	Cognitive Test	Effect on Cognitive Function
MRC/HPS [53]	Other	Completed	Simvastatin or Placebo	n= 5806 ≥ 70 years	Elderly/ Cardiovascular disease	TICS	Negative results
PROSPER [54]	Prevention dementia	Completed	Pravastatin or Placebo	n= 5804 aged 70-82	Elderly/ Vascular disease	MMSE	Negative results
Simons [58]	Treatment dementia	Completed	Simvastatin or Placebo	n= 44	AD	ADAS-Cog, MMSE	*Simvastatin may favorably influence the pathology of AD and thereby slow the clinical progression.*
ADCLT [59]	Treatment dementia	Completed	Atorvastatin or Placebo	n= 63 ≥ 51 years	Mild to moderate AD	ADAS-cog, Clinical Global Impression of Change Scale	*Atorvastatin may have a positive effect on the progressive deterioration of cognitive function and behavior in mild to moderate AD.*
CLASP	Treatment dementia	Completed	Simvastatin or Placebo	n= 406 ≥ 50 years	Mild to moderate AD	ADAS-cog, MMSE, NPI	Negative results
LEADe [60]	Treatment dementia	Completed	Atorvastatin or Placebo	n= 640 aged 50-90	Mild to moderate AD	ADAS-cog, ADCS-CGIC	Negative results
SHARP	Prevention dementia	Ongoing	Simvastatin or Placebo	n= 90 aged 45-65	Parent diagnosed with AD	Memory test (not defined)	-

MRC/HPS, Medical Research Council/British Heart Foundation Heart Protection Study; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; ADCLT, Alzheimer's Disease Cholesterol-Lowering Treatment trial; CLASP, Cholesterol Lowering Agent to Slow Progression of Alzheimer's Disease Study; LEADe, Lipitor's Effect on Alzheimer's Dementia; SHARP, Statin Effects on Beta-Amyloid and Cerebral Perfusion in Adults at Risk for Alzheimer's Disease; AD, Alzheimer´s disease; TICS, Telephone Interview for Cognitive Status; ADAS-cog, AD assessment scale cognitive subscale; MMSE, Mini Mental State Examination; NPI, Neuropsychiatric Inventory; ADCS-CGIC, Activities of Daily Living Inventory- Clinical, Global Impression of Change.

Aspirin Use

Cardiovascular and cerebrovascular atherosclerosis is associated with cognitive decline of aging. Aspirin may have a role in the primary and secondary prevention of atherosclerosis and VCI. There are some clinical trials investigating the effect of aspirin for cognitive impairment (Table **4**). However, there is no evidence that aspirin is effective in preventing [49,61-63] or treating patients with a diagnosis of VaD [64] or cognitive impairment.

Three randomized controlled trials are currently recruiting participants. The Aspirin in Reducing Events in the Elderly (ASPREE, n= 19000) trial of aspirin versus placebo in healthy subjects is investigating the effect of aspirin on cognition (http://clinicaltrials.gov/show/NCT010 38583, downloaded 11 May 2014). The ongoing Efficacy and Safety of Cilostazol in Patients of Vascular Cognitive Impairment-no Dementia has an aim of recruiting 200 patients with VCI. The primary objective is to evaluate the cilostazol or aspirin effect in cognition (http://clinicaltrials. gov/show/NCT01872858, downloaded 11 May 2014). Finally, the Efficacy Study of Cilostazol and Aspirin on Cerebral Small Vessel Disease (Challenge) is an ongoing study, with 238 patients enrolled to date. Patients with cerebral small vessel disease observed on brain MRI will also be randomized to cilostazol versus aspirin. Cognitive outcome is a secondary outcome (http://clinicaltrials.gov/ show/NCT0 1932203, downloaded 11 May 2014).

Antidepressants

Few antidepressants studies have examined the effect of antidepressants on cognitive outcome (Table **5**). In a post hoc subsample analysis (n=129) of a recent multicenter trial of poststroke depression in patients with stroke treated with escitalopram for 12 months improved scores in global cognitive functioning, specifically in verbal and visual memory functions, compared to placebo. This beneficial effect of escitalopram was independent of its effect on depression [65]. The Maintenance Therapies in Late-Life Depression (MTLD III, n= 130) trial is a randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of donepezil combined with antidepressant pharmacotherapy. It was designed to assess whether donepezil plus antidepressant (escitalopram, venlafaxine or duloxetine) was superior to placebo plus antidepressant in improving cognitive performance and instrumental activities of daily living and reducing recurrences of depression, in elderly patients with depression and MCI [66]. There was not benefit in patients treated with donepezil plus antidepressant compared to those given placebo plus antidepressant. The MCI subjects had higher recurrence rates of depression with donepezil than with placebo (44 *vs* 12%). The normal subjects had no benefit with donepezil and without change in recurrence of major depression [66].

Two combination treatment studies in elderly depressed patients with cognitive impairment are ongoing, Concurrent

Table 4. Aspirin use.

Study Name	Study Aim	Current Status of Trial	Intervention	Population Characteristics	Health Status/Diagnosis	Cognitive Test	Effect on Cognitive Function
Women's health study [61]	Prevention dementia	Completed	Aspirin or placebo	n= 6377 ≥ 65 years	Healthy women	Neurocognitive battery	Non-significant effect on cognitive function
PRoFESS [49]	Prevention dementia	Completed	Aspirin plus Dipyridamole or Clopidogrel, and Telmisartan or Placebo	n= 20332 ≥ 55 years	Stroke	MMSE	Non-significant effect on cognitive function and were not affected by the preventive use of telmisartan.
AAA [62]	Prevention dementia	Completed	Aspirin or placebo	n= 2325 aged 55-75	Healthy	MMSE, Mill Hill vocabulary scale.	Non-significant effect on cognitive function
PERFORM [63]	Prevention dementia	Completed	Terutroban or Aspirin	n= 18886 ≥ 55 years	Stroke or TIA	MMSE, IST, ZCT	Non-significant effect on cognitive function
CAVAD	Treatment dementia	Completed	Aspirin or Cilostazol	n= 200 aged 40-80	Stroke, VaD, Mixed dementia	MMSE, MoCA, CDR	Not published
ASPREE	Prevention dementia	Ongoing	Aspirin or Placebo	n= 19000 ≥ 65 years	Elderly	3MS	-
Efficacy and Safety of Cilostazol in Patients of Vascular Cognitive Impairment-no Dementia	Prevention dementia	Ongoing	Aspirin or Cilostazol	n= 200 aged 50-80	VCI no dementia	MoCA, MMSE, CDR, TMT, similarity test, Stroop test	-
Efficacy Study of Cilostazol and Aspirin on Cerebral Small Vessel Disease (Challenge)	Prevention dementia	Ongoing	Aspirin or Cilostazol	n= 238 aged 50-85	Elderly CVD	MMSE, neurocognitive battery	-

PRoFESS, Prevention Regimen for Effectively Avoiding Second Strokes; AAA, Aspirin for asymptomatic atherosclerosis trial; PERFORM; Prevention of Cerebrovascular and Cardiovascular Events of Ischemic Origin with Terutroban in Patients with a History of Ischemic Stroke or Transient Ischemic Attack Study; CAVAD, Cilostazol Verse Asprin for Vascular Dementia in Poststroke Patients With White Matter Lesions; ASPREE, Aspirin in Reducing Events in the Elderly; TIA, transient cerebral ischemic attack; VCI, vascular cognitive impairment; CVD, cerebrovascular disease; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; CDR, Clinical Dementia Rating; 3MS Modified Mini-Mental State examination; IST, Isaac´s Set Test; ZCT, Zazzo´s Cancellation Test; TMT, trail making test.

escitalopram plus memantine (http://clinicaltrials.gov/show/NCT01876823, downloaded 11 May 2014), and citalopram or venlafaxina plus donepecilo (http://www.clinicaltrials. gov/ct /show/NCT01658228, downloaded 11 May 2014) are being tested.

Cholinesterase Inhibitors

Pathological and clinical evidence indicates that a cholinergic deficit, similar to that seen in AD, may be associated with VaD, leading to the hypothesis that these patients may benefit from treatment with cholinesterase inhibitors. In addition, mixed dementias are common [67]. There are no randomized trials of cholinesterase inhibitors for the prevention of cognitive impairment of vascular origin. But, cholinesterase inhibitors approved for use in AD have also been tested for VaD treatment in double-blind, placebo-controlled, randomized clinical trials lasting 6 months (Table **6**).

Donepezil

The safety and efficacy of donepezil in VaD have been studied in 2 identical trials, 307/309 [68] and 308/309 studies [69]. A Cochrane systematic review of both trials showed that donepezil has a beneficial effect at six months in mild to moderate VCI [70]. Patients with AD or with mixed dementia were excluded [24]. A randomized controlled clinical trial tested the efficacy of donepezil in cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), a genetic model of subcortical VCI [71]. The study had neutral results [2].

Galantamine

In a randomized controlled clinical trial (GAL-INT-6, n= 592), patients diagnosed with probable VaD or with mixed

Table 5. Antidepressants.

Study Name	Study Aim	Current Status of Trial	Intervention	Population Characteristics	Health Status/ Diagnosis	Cognitive Test	Effect on Cognitive Function
Preventing Post-Stroke Depression [65]	Prevention dementia	Completed	Escitalopram or Placebo	n= 129	Stroke	RBANS, TMT, Controlled Oral Word Association, Wechsler Adult Intelligence Scale-III, Similarities, and Stroop tests.	*Improvement in global cognitive functioning, specifically in verbal and visual memory functions.*
MTLD III [66]	Treatment MCI	Completed	Escitalopram Plus Donepezil or Escitalopram plus Placebo	n= 130 ≥ 65 years	Depression MCI	MMSE	The MCI subgroup had higher recurrence rates of depression (44%) with donepezil than placebo (12%). The subgroup with normal cognition showed no benefit with donepezil and no increase in recurrence.
Memantine Plus Escitalopram in Elderly Depressed Patients With MCI	Treatment MCI	Ongoing	Concurrent escitalopram plus memantine	n= 35 aged 50-90	Depression MCI	SRT-IR	
Combination Treatment Study for Memory Impairment and Depression	Treatment MCI	Ongoing	Citalopram or venlafaxina, and donepecilo or placebo	n= 80 aged 55-95	Depression MCI	SRT	

MTLD III, Maintenance Therapies in Late-Life Depression; MCI, mild cognitive impairment; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; TMT, Trail Making Test; MMSE, Mini Mental State Examination; SRT-IR, Selective Reminding Test - total immediate recall; SRT, Selective Reminding Test.

dementia lasting 6 months were tested. Galantamine demonstrated efficacy on all outcome measures [72], especially in a subgroup of patients with mixed dementia [24]. A subsequent study of VaD patients (GAL-INT-26, n= 788) showed only cognitive benefit (on AD assessment scale cognitive subscale, ADAS-cog) but not for daily functions [73]. In addition, galantamine treatment was associated with higher rates of adverse event (nausea and vomiting) and withdrawal [74].

Rivastigmine

Three randomized placebo-controlled trials are completed to date. The participants in one trial (RIVIVE, n= 50) had VCI-not dementia [75], while the other two studies included participants with dementia of different severities [76,77]. The trial in Chinese patients included 40 subjects with criteria for subcortical VaD [76]. This trial did not show benefit on cognition, behavioral disturbance, and daily functions. The Vascular Dementia Trial studying Exelon (VantagE, n= 708) study showed benefit at 24 weeks associated with rivastigmine compared with placebo for the Vascular AD assessment scale cognitive subscale (V-ADAS-cog), ADAS-Cog and MMSE assessments but not for daily functions. In addition, the rivastigmine group had higher rates of nausea and vomiting than the placebo group [77]. The RIVIVE study (n= 50) included only VCI-not dementia subjects but did not show benefits [75]. A Cochrane systematic review of the three trials concluded that only one placebo-controlled, double-blind randomized trial [77] had a large number of participants to detect a clinically significant effect for rivastigmine compared with placebo for important outcomes in VCI [78]. Unfortunately, this trial demonstrated a positive effect of rivastigmine on cognition, but not on other important outcomes. The CENA713B 2310 trial is ongoing and preliminary results have not been published [79].

N-Methyl-D-Aspartate (NMDA) Antagonists

Memantine, a noncompetitive NMDA receptor antagonist, have shown neuroprotective properties and improve cognition. Two randomized clinical trials of memantine, MMM300 and MMM500, have shown modest treatment benefits on cognition, but not global functioning for patients with mild to moderate VaD (Table **6**). In the MMM 300 study [80], 288 patients were included. After 28 weeks, the mean ADAS-cog scores were significantly improved relative to placebo and the response rate for Clinician Interview-Based Impression of Change, plus carer interview (CIBIC-plus) was improved or stable in the memantine group. In the MMM 500 study (n= 548) [81], memantine resulted in improving cognition compared with placebo (ADAS-cog). There were no differences in Clinical Global Impression of Change Dementia Rating (CGIC), MMSE, Gottfries-Brane-Steen scale (GBS), or Nurses' Observation Scale for Geriatric Patients (NOSGER) scores between groups.

APPLICATIONS TO OTHER AREAS OF COGNITIVE DECLINE

Over the past 10 years, a growing body of literature has highlighted the important contribution of vascular risk factors in AD, and others degenerative dementias. Although there are many hypotheses, the role of vascular risk factors

Table 6. Cholinesterase inhibitors and memantine.

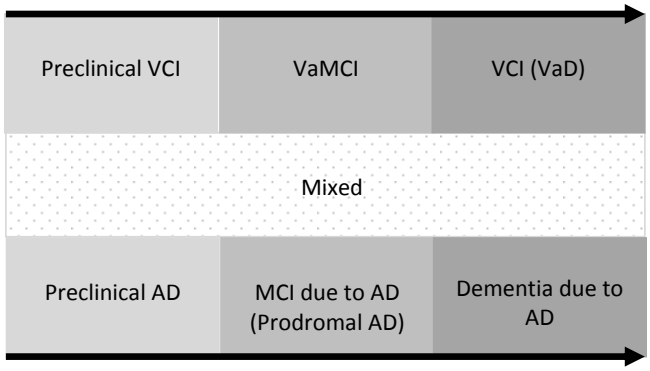
Study Name	Study Aim	Current Status of Trial	Intervention	Population Characteristics	Health Status/ Diagnosis	Cognitive Test	Effect on Cognitive Function
Donepezil							
Study 307/309 [68]	Treatment dementia	Completed	Donepezil or Placebo	n= 603 mean age 73.9 years	VaD	ADAS-cog, CIBIC-plus, MMSE, CDR-SB	*Donepezil groups showed significant improvements on cognition. Only donepezil 5 mg affected significantly the global functioning. Significant adverse effects were seen with 10 mg.*
Study 308/309 [69]	Treatment dementia	Completed	Donepezil or Placebo	n= 616 mean age 75 years	VaD	ADAS-cog, CIBIC-plus, MMSE, CDR-SB	*Significant differences in favor of donepezil 5 and 10 mg/day, compared with placebo, were seen on the ADAS-cog at all end points and on CIBIC-plus.*
The Efficacy, Safety, And Tolerability Of Donepezil HCl (E2020) In Patients With CADASIL Who Have Cognitive Impairment [71]	Treatment dementia	Completed	Donepezil or Placebo	n= 168 aged 25-70	CADASIL, cognitive impairment	V-ADAS-cog	Donepezil had no effect on the primary endpoint (V-ADAS-cog) in CADASIL patients with cognitive impairment. Improvements were noted on measures of executive function, but the clinical relevance of these findings is not clear.
Galantamine							
GAL-INT-26 [73]	Treatment dementia	Completed	Galantamine or Placebo	n= 788 ≥ 40 years	VaD	ADAS-cog, CIBIC-plus	*Benefits on ADAS-cog occurred with galantamine treatment compared with placebo.*
GAL-INT-6 [72]	Treatment dementia	Completed	Galantamine or Placebo	n= 592 aged 40-90	VaD, Mixed dementia	ADAS-cog, CIBIC-plus	*Seventy-five percent of galantamine-treated patients improved or remained stable on CIBIC-plus*.
Rivastigmine							
Rivastigmine in Chinese patients with subcortical vascular dementia [76]	Treatment dementia	Completed	Rivastigmine capsules or Placebo	n= 40 aged 40-90	Subcortical VaD	MMSE, FAB	There was no apparent cognitive benefits associated with use of rivastigmine over the 6 months period.
VantagE [77]	Treatment dementia	Completed	Rivastigmine capsules or Placebo	n=708 aged 50-85	VaD	V-ADAS-cog, MMSE, ADAS-cog	*Rivastigmine demonstrated superiority over placebo on all cognitive measures.*
RIVIVE [75]	Treatment MCI	Completed	Rivastigmine capsules or Placebo	n= 50 aged 55-85	VCI not dementia	Ten Point Clock Drawing Test, Color Trails 1 and 2, ADAS-cog.	There was no statistically significant difference between rivastigmine and placebo groups for cognitive assessments.
MMM 300 study [80]	Treatment dementia	Completed	Memantine or Placebo	n= 288	Mild to moderate VaD	ADAS-cog, CIBIC-plus, MMSE	There was cognitive benefit (ADAS-cog, CIBIC-plus) without global or functional benefit.
MMM 500 study [81]	Treatment dementia	Completed	Memantine or Placebo	n= 548	Mild to moderate VaD	ADAS-cog, CGI-C	Memantine resulted in improving cognition compared with placebo (ADAS-cog).
CENA713B 2310 study	Treatment dementia	Ongoing	Rivastigmine capsules or Placebo	n= 700	VaD	MMSE	-

GAL-INT-26, A Placebo-controlled Trial to Evaluate the Safety and Efficacy of Galantamine in the Treatment of Vascular Dementia; GAL-INT-6, A Study of the Safety and Effectiveness of Galantamine Versus Placebo in the Treatment of Patients With Vascular Dementia or Mixed Dementia; VantagE, Vascular Dementia Trial studying Exelon; RIVIVE, RIVastigmine In Vascular cognitivE Impairment; VaD, Vascular Dementia; CADASIL, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy; VCI, vascular cognitive impairment; ADAS-cog, AD assessment scale cognitive subscale; CIBIC-plus, Clinician Interview-Based Impression of Change, plus carer interview; MMSE, Mini Mental State Examination; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; V-ADAS-cog, Vascular AD assessment scale cognitive subscale; FAB, Frontal Assessment Battery; CGI-C, Clinical Global Impression of Change.

in the pathogenesis and clinical expression of AD are not yet fully known. AD and VCI fall on a continuous spectrum of disease, composed of a gradient of features of both AD and VCI (Fig. **2**). Available evidence suggested that VCD contribute to clinical expression and pathology of AD. Whether mixed dementia is included in VCI or AD remains controversial.

The possibility of superimposed AD must be considered when there is 1- a history of slowly progressive cognitive decline, 2- prominent memory impairment, and 3- atrophy of the medial temporal lobe.

Mixed AD/VCI may likely represent the largest group. Vascular and neurodegenerative biomarkers represent an important key to understanding of underlying pathophysiological process, studies design and prevention of disease.



VCI, vascular cognitive impairment; VaMCI, vascular mild cognitive impairment; VaD, vascular dementia; AD, Alzheimer´s Disease, MCI, mild cognitive impairment.

Fig. (2). Continuous spectrum of Vascular Cognitive Impairment, Alzheimer´s Disease y mixed forms.

CONCLUSION

A recent guideline from the American Heart Association and the American Stroke Association [2] concluded that 1- Donepezil may be useful for improving cognition in patients with VaD; 2. Galantamine may be useful for patients with mixed dementia; 3- The evidence for supporting the benefit of rivastigmine and memantine is inconclusive. On the other hand, a systematic review showed less compliance due to adverse events (gastrointestinal symptoms and insomnia) with the cholinesterase inhibitors, but not with memantine [38].

While no FDA approved treatments exist for all spectrum of VCI, recent and ongoing research shows poor evidence about efficacy of cholinesterase inhibitors, memantine, antidepressants, prevention and treatment of vascular risk factors, and other investigational drugs. With the widespread validation and harmonization of the AHA-ASA diagnostic criteria for VCI [2], the lessons learned from the available studies, and the development of new biomarkers for VCI and AD, could be the initial step for the design of high quality studies.

LIST OF ABBREVIATIONS

AD	=	Alzheimer´s disease
CT	=	Computerized tomography
CVD	=	Cerebrovascular disease
FLAIR	=	Fluid attenuated recovery
MCI	=	Mild cognitive impairment
MRI	=	magnetic resonance imaging
NMDA	=	N-methyl-D-aspartate
VCI	=	Vascular cognitive impairment
VaD	=	Vascular dementia
VaMCI	=	Vascular mild cognitive impairment

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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