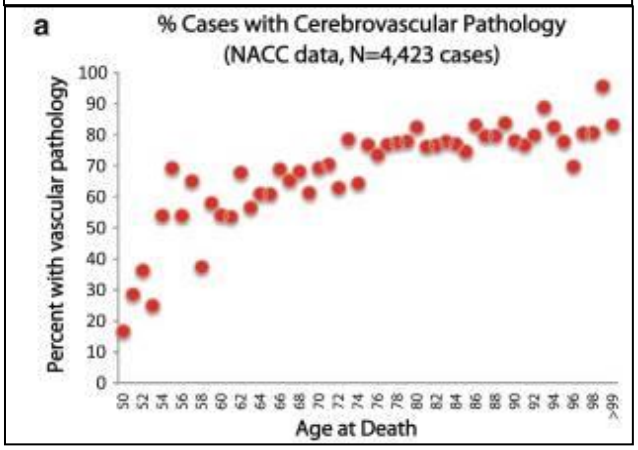
CURRENT AND FUTURE MANAGEMENT OF PATIENTS WITH VCI/DEMENTIA

Gregory A. Jicha, MD, PhD
University of Kentucky
Lexington, KY

Significance: The development of late life dementia is a major issue facing the healthcare system in the US today. Over 5.4 million people in the US alone suffer from dementia, with this number expected to rise dramatically over the next few decades [1]. Current healthcare costs from dementia exceed $200 billion dollars per year and these costs are expected to rise dramatically over the next several decades [1]. While Alzheimer's disease (AD) has captured the headlines and is often considered the major cause of late life dementia, current data suggest that coexistent or independent cerebrovascular disease (CVD) may be the major cause for the development of dementia (Vascular Cognitive Impairment, VCI or Vascular Dementia, VaD)[2]. In the population over the age of 85 years (the fastest growing segment of the population), CVD trumps AD as the major cause for cognitive decline and the development of late life dementia (Figure 1). About 75-90% of patients over the age of 90 years have some degree of CVD pathology [3-6]. The profound impact of CVD on studies pertinent to cognition in the elderly seems to be under-appreciated in dementia research [7-9].

Figure 1. Neuropathology-confirmed CVD increases with advancing age.



AAN Practice Parameter on the Management of Dementia: Originally written in 2001 and reaffirmed in 2003, this Practice parameter is outdated and fails to take into account the growing body of knowledge and therapeutic advances in Dementia as a whole, and this is especially true for VCI/VaD. The Practice Parameter update is currently in progress. The general recommendations for dementia (broadly defined as Alzheimer's disease, vascular or multi-infarct dementia, dementia with associated parkinsonian disorder (diffuse Lewy body disease, dementia with Lewy bodies, Parkinson's disease with dementia), progressive supranuclear palsy, frontotemporal dementia (including Pick's disease), and senile dementia.) described in this practice parameter are as follows:

- Cholinesterase inhibitors benefit patients with AD (Standard), although the average benefit appears small
- Vitamin E likely delays the time to clinical worsening (Guideline)
- Selegiline, other antioxidants, anti-inflammatories, and estrogen require further study
- Antipsychotics are effective for agitation or psychosis in patients with dementia where environmental manipulation fails (Standard)
- Antidepressants are effective in depressed patients with dementia (Guideline)
- Educational programs should be offered to family caregivers to improve caregiver satisfaction and to delay the time to nursing home placement (Guideline)
- Staff of long-term care facilities should also be educated about AD to minimize the unnecessary use of antipsychotic medications (Guideline)
- Behavior modification, scheduled toileting, and prompted voiding reduce urinary incontinence (Standard).
- Functional independence can be increased by graded assistance, skills practice, and positive reinforcement (Guideline).

Specific statements regarding VCI/VaD are as follows:

- Few Class I trials have been performed in populations with pure ischemic vascular or multi-infarct dementia. In a single study of the nootropic oxiracetam, improved functioning on the Blessed Functional scale was reported. Cyclandelate and flunarizine showed pre- to posttreatment benefits on a subset of measures. Two trials of pentoxifylline were negative.
- There are no adequately controlled trials demonstrating pharmacologic efficacy for any agent in ischemic vascular (multi-infarct) dementia.

Given the limitations in data available in 2001, this Practice Parameter is limited in provision of guidance beyond guidance for use of antidepressants in VCI/VaD patients that are depressed, and in the use of education, behavior modification, and occupational therapy approaches. The present review moves beyond this Practice parameter, focusing on more recent developments and discoveries in the field over the last decade and a half.

Drugs we may want to avoid in VCI/VaD: While many discoveries have been made in the area of approaches that may prove beneficial in the treatment of VCI/VaD, there have also been studies that potentially indicate uniquely conferred risks of certain therapeutic approaches in VCI/VaD that deserve mentioning.

In the late 1990's data emerged suggesting that vitamin E therapy may be beneficial in slowing cognitive decline in patients with dementia[10]. This led to widespread use of high dose vitamin E (2,000 I.U. daily) in all persons with dementia of almost any type. In 2004, data from a large meta-analysis emerged that demonstrated potential negative consequences of this treatment option[11, 12]. Specifically increased risk of heart attack, stroke and death that appeared to be largely confined to the studies included that focused on patients with high cardiovascular, cerebrovascular and cancer risks. These data are interpreted by some as related to vitamin E influences on coagulation pathways that could potentially accelerate VCI/VaD. Recommendations to limit vitamin E dose to less than 400 I.U. daily emerged, although have again been challenged by another more recent study in AD that demonstrated benefit of high dose vitamin E supplementation[13]. At present there is no data supporting a potential benefit of vitamin E in VCI/VaD, and some plausible data that such supplementation may actually do more harm than good in VCI/VaD.

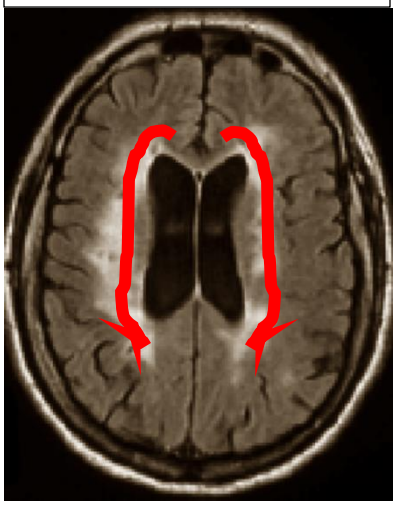
While the AAN Practice Parameter, comments on "Antipsychotics are effective for agitation or psychosis in patients with dementia where environmental manipulation fails", safety concerns stemming from multiple large scale clinical trials of antipsychotic use in dementia led to the issuance of a FDA "black-box" warning that antipsychotics increased risk for cardiovascular and cerebrovascular adverse events as well as pneumonia and death from the aforementioned causes[14-16]. These data raise significant concerns about the use of even atypical antipsychotics in VCI/VaD.

4 Major Categories of Potential Therapeutic Strategies for VCI/VaD: Current treatment options for VCI/VaD can be classified broadly in 4 major categories: 1) Symptomatic therapy, 2) Therapies targeting specific CVD risk factors (i.e. hypertension, diabetes, high cholesterol…) that could be considered disease modifying strategies for the primary or secondary prevention of VCI/VaD, 3) Multicomponent CVD risk factor modulation (more complex interventions involving combinations of the above), and 4) Neurorestorative therapies. The first three categories of therapy are being actively investigated and we have accumulated much data guiding these approaches. The fourth category of neurorestorative therapy remains in its infancy awaiting effective translation from the laboratory and small scale clinical studies into larger scale proof of concept and regulatory pathway engaged human clinical trials. The following sections highlight our current state of knowledge for each of these potential strategies for the treatment of VCI/VaD

Symptomatic Therapies: Two classes of medications have been approved for symptomatic amelioration in AD, including the cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and a partial glutamate antagonist (memantine)[17-20]. There is convincing scientific evidence suggesting that such strategies may be beneficial in VCI/VaD, however definitive clinical trial data are lacking and as of yet no approved medications for the treatment of vascular dementia have traversed the regulatory pathway.

Cholinergic deficits have been identified in the brains of persons with VCI/VaD suggesting potential benefit of acetylcholinesterase inhibitors in VCI/VaD similar to that seen in AD[21-23]. Cortical cholinergic activity is driven by projections from the cholinergic neurons in the Nucleus Basalis of Meynert. These projections traverse the subcortical white matter in the periventricular and deep white matter regions that are specifically injured by small vessel arteriolar sclerosis in VCI/VaD (Figure 2). Several clinical trials of cholinesterase inhibitors have been pursued in VCI/VaD with mixed results[21, 24-29]. It remains unclear if participant selection and outcome measures were optimal in many of these studies. Definitive evaluation of the use of cholinesterase inhibitors in VCI/VaD awaits further exploration in appropriately designed clinical trials.

Figure 2. Ascending cholinergic projections from the nucleus Basalis of Meynert lie directly in the path of small vessel ischemic damage in VCI/VaD



Memantine was originally developed by the Eli Lilly Company in 1968. It is a non-competitive antagonist of the NMDA receptor. Experiments have shown that it may help protect against glutamate-induced excitotoxicity in laboratory experiments[30]. It was originally tested in Europe for use post-stroke and in TBI, but did not appear efficacious in these conditions. It was later tested in AD, demonstrating significant improvement on cognitive and functional outcomes, leading to its approval by the FDA in 2003 for this indication[20]. It is thought to exert its action through reductions in baseline/background calcium levels in cells, enhancing the signal to noise ratio of calcium influx stimulated by glutamate signaling effectively facilitating NMDA-receptor dependent long term potentiation[30]. Definitive in vivo evidence for either a neuroprotective effect or a definitive mechanism of action remains lacking. Several early studies suggested that memantine may be beneficial in VCI/VaD[31-35], and this popularity has had a resurgence in recent years with several publications suggesting a benefit in VCI/VaD[36-39]. Despite the suggestive evidence to date, memantine has not been approved for use in VCI/VaD by any regulatory authority as definitive trials remain lacking.

Therapies Targeting Specific Risk Factors: While disease modifying therapies for AD and other forms of degenerative dementia, such as dementia with Lewy bodies and frontotemporal dementia, are currently being developed and tested, the success of such programs is unclear and to date there is no effective treatment that will slow or stop such processes [1]. In contrast, effective disease modifying therapies for CVD exist and are in widespread use today. Recent data suggest that the utilization of such therapeutic interventions is beginning to reverse trends in mortality for cardiovascular and CVD death [1, 40, 41]. The impact of such interventions on late life cognitive decline and dementia is slowly being elucidated through systematic study of modulation of specific CVD risk factors for VCI/VaD.

Hypertension, hyperlipidemia, diabetes, hyper-homocysteinemia, smoking, obesity, poor diet, among others are all recognized as major risk factors for cerebrovascular disease, stroke, and VCI/VaD[42]. A large number of studies studying such specific risk factor modification have included cognitive endpoints allowing a glimpse at the therapeutic potential in preventing further cognitive decline for those with VCI/VaD[42]. A summary of recommendations has been put forth by the AHA/ASA in 2011[42].

While the best available data focuses on management of hypertension, clinical trials for the prevention of future cognitive decline have shown mixed results. Negative results are often attributed to subject attrition, heterogeneity in diagnosis, and poor sensitivity of cognitive outcome measures[43-45]. With this being said, several prospective studies and trials have shown positive results with hypertension management, reducing risk of VCI/VaD by as much as 50%[46-48].

Little prospective data exists for effects of lipidemic modulation on the prevention of cognitive decline, although many practitioners favor such use despite the lack of data[49]. Likewise, there is little evidence for prevention of cognitive decline with prospective treatment of diabetes. Indeed, two recent trials of diabetes management failed to demonstrate benefit on cognitive outcomes at 8 and 9 years of followup[50, 51]. The effects of antiplatelet and anticoagulant therapies are likewise inconclusive in regards to the prevention or modulation of VCI/VaD[52]. Arecent study of EC-IC bypass examined this surgical procedure vs. conservative medical management for 41 subjects

with perfusion deficits indicated by oxygen extraction fractions > 1.13, demonstrating no benefit of surgical intervention over medical management for the prevention of cognitive decline at 24 months, despite the finding that cognitive improvement was significantly more likely to occur in followup for those with less impaired OEF. Likewise, there is wide variability in reported cognitive outcomes following carotid endarterectomy or carotid stenting for high grade stenosis[53]. No clear benefit can be established for these interventions which have been clearly shown shown to reduce primary and secondary stroke risks. It is clear that further work is needed to test the potential for specific risk factor modulation to impact the course of VCI/VaD.

Multicomponent CVD risk factor modulation: Given the controversies that have emerged in the field regarding clinical trials of specific risk factor modulation and the realization that VCI/VaD is likely the result of the impact of many discrete risk factors combining additively or even synergistically, the field has moved towards interventions targeting multimodal lifestyle modulation for the prevention of VCI/VaD.

Several recent studies with intreventions ranging from 12-24 months have been completed. A recent 12 month Norwegian study of 195 subjects with first stroke or TIA and no cognitive decline at baseline was performed with a multimodal intervention targeting: Hypertension, Lipids, Homocysteine, Smoking, Diabetes, Physical activity, Overweight, Alcohol Excessive use, and Diet. The study failed to show a benefit on the intervention on cognitive test scores or outcomes of incident VCI/VaD[54]. While one could argue that the number of subjects was likely to small to evaluate incident VCI/VaD effects, the study actually showed that 54.5% of the subjects converted to VCI/VaD in the study period. This high incidence is alarming, suggesting other factors may have been at play.

The Austrian Polyintervention Study to Prevent Cognitive Decline after Ischemic Stroke (ASPIS) trial conducted a trial of 202 subjects assigned to placebo or a 24 month multidomain intervention with focus on improvement in lifestyle and vascular risk factors. At 24 months, 8 of 76 (10.5%) subjects in the intervention group and 10 of 83 (12.0%) subjects in the control group showed cognitive decline corresponding to a relative risk reduction of 0.874 (95% confidence interval, 0.364–2.098). No effects were seen on cognitive test outcomes[55, 56].

In contrast, the recently published Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), randomized 1260 subjects with significant CVD risks to a multi-domain intervention vs placebo for 24 months, demonstrating positive effects of the intervention in this large study[57]. Overall, performance on the neuropsychological test battery (NTB) was significantly improved in the intervention vs. control group ($p=0.03$) [57]. This data suggests that the intervention may be effective, but the effect size may be quite small, possibly explaining the previous negative studies in other cohorts with much smaller subject numbers. Despite the positive results, the small effect size calls into question the practicality of such interventions in the prevention of VCI/VaD in the general population.

Neurorestorative therapies: While the debate rages on regarding possible benefits of symptomatic therapies and risk factor management in the treatment and prevention of VCI/VaD, there is much hope that with advancing knowledge in the area of the neuroscience of ischemic injury newer, possibly restorative therapeutic approaches will be developed[58]. To date, few agents have been tested in prospective, randomized, placebo-controlled clinical trial paradigms. Several approaches, however have shown promise and are actively being explored in addition to a wealth of preclinical work in this exciting area of translational discovery[58]. Of the agents that have been tested, several are worthy of mention here as they are actively being pursued in human trials with preliminary data showing promise, despite variable results in many of the smaller studies conducted to date. It should be noted that this section is not inclusive of the extent of compounds being tested in preclinical and clinical interventional paradigms, which may be also discussed as part of the educational program.

Cerebrolysin has neurotrophic factor-like properties, enhancing neuronal survival and sprouting in culture, and protecting against neurodegeneration induced by hypoxia, ischemia, glutamate, and Aβ toxicity which are all players in the development of VCI/VaD[58]. Early human studies in VaD, demonstrate positive effects on subjects with VaD after just 4 weeks of treatment on both quantitative EEG and standard cognitive testing[59]. Cerebrolysin is currently being tested in ongoing human trials of VCI/VaD to further explore these potential benefits (NCT01582854).

Nimodipine has also attracted significant attention as a potential neuroprotective and neurorestorative therapy in VCI/VaD. Nimodipine is an isopropyl calcium channel blocker with potent CNS activity. Its primary action lies in restricting influx of calcium ions into cells, and is thought to be neuroprotective in this regard, preventing

excitotoxic and ischemic damage to the brain. Several human clinical trials have been performed which again have shown mixed results. A Cochrane meta-analysis has been performed to evaluate the potential effectiveness of this approach, demonstrating a significant effect on both cognition and caregiver impression of change in pooled analysis, including 10 studies meeting criteria for inclusion that focused specifically on VCI/VaD[60]. These data suggest further exploration of this effect is warranted.

Citicoline can potentiate neuroplasticity and also serves as a natural precursor of phospholipid synthesisand as a choline source in the metabolic pathways for biosynthesis of acetylcholine. Multiple studies have shown beneficial effects of citicoline administration in VCI/VaD[61]. The VITA and IDEALE studies, among others have demonstrated that citicoline is both effective and safe for the treatment of VCI/VaD[62, 63]. While several other studies have cast doubt on these findings, citicoline is a promising agent with the potential to improve cognition in VCI/VaD[61]. Ongoing studies evaluating the potential for citicoline as an intervention for VCI/VaD remain a focus in the field.

Conclusions: Clinical exploration that hopes to expand our armament of therapeutic agents for the current and future treatment of VCI/VaD is an active process with much hope for the future. Lessons learned over time have enabled the development of enhanced clinical protocols for the evaluation of potential therapeutics, taking into consideration the complexity of this common cause of dementia in the elderly today. Updated practice parameters and guidelines are needed to help navigate treatment options in VCI/VaD.

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