Treatment of Vascular Dementia: The Route of Prevention

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Abstract
Vascular dementia (VaD), rather than being considered as a univocal nosological entity, should be regarded as a heterogeneous clinical entity which differs in clinical-pathological phenotype as well as in pathophysiological mechanisms, but shares cerebrovascular disease (CVD), resulting from vascular or circulatory pathology, as the cause of dementia. The aim of this review is to discuss VaD treatment focusing particularly on more prevalent ischemic forms. Due to the fact that there are presently no treatments capable of obtaining considerable results once VaD is clinically established, specific emphasis will be given to the therapeutic strategies aimed at the prevention of CVD risk factors. The therapeutic strategies aimed at slowing the progression of the disease will also be discussed.

Introduction
Traditionally, vascular dementia (VaD) has been conceptualized on the basis of two imprecise and misleading concepts: (1) the notion of VaD as a result of stroke with the consequent multi-infarct model and (2) the definition of dementia, which only partially fits the numerous clinical phenotypes of VaD.

The use of brain imaging techniques has revealed that VaD is a more complex entity than suggested by the multi-infarct model, because the intellectual decline can also result from other pathophysiological mechanisms which underlie specific neuropathological subgroups. VaD may arise from multiple infarcts (multi-infarct dementia, MID), from a single stroke in a location critical to mental function (strategic infarct dementia), as well as from small-vessel disease. Also in this latter group is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, a genetically transmitted small-vessel disorder with mutation in the Notch3 gene (table 1). Accordingly VaD, rather than being considered as a univocal nosological entity, should be regarded as a heterogeneous clinical entity which differs in clinical-pathological phenotype as well as in pathophysiological mechanisms, but shares cerebrovascular disease (CVD), resulting from vascular or circulatory pathology, as the only, or primary, cause of dementia.

The inadequacy of the multi-infarct model in explaining the complexity of VaD has been further highlighted by the recognition of mixed dementia, where VaD coexists with other causes of dementia, particularly Alzheimer’s disease (AD). VaD and AD show a synergic interaction in terms of clinical expression of cognitive impairment [1], especially in older people, as well as sharing...
common pathogenetic mechanisms [2, 3] and risk factors [4]. This observation suggests that the reduction of CVD risk factors could be effective in preventing VaD and AD.

Another source of uncertainty is the terminology. By definition, dementia is a syndrome of acquired intellectual deficit resulting in significant impairment of daily functions. This description is fundamentally based on the clinical features of AD, the most common cause of dementia. The diagnostic criteria for VaD are largely borrowed from those for AD and thus require the presence of prominent memory impairment and progressive, irreversible decline, despite the fact that VaD may present a different clinical profile, including mild memory deficit, relatively slow progression, and subcortical pattern. The concept of VaD is thus shifting towards that of vascular cognitive impairment (VCI), a much broader description encompassing all forms of cognitive loss due to CVD [5]. In this paper, due to a lack of fully defined diagnostic criteria for VCI not derived from those for VaD, we will continue to use the term VaD, rather than VCI, being aware that the former can be viewed as a subgroup of a larger syndrome (i.e. VCI).

The aim of this review is to discuss VaD treatment, focusing particularly on ischemic vascular disease leading to dementia, as the latter is more prevalent [6]. Since at present there are no treatments capable of obtaining considerable results once VaD is clinically established, special emphasis will be given to the therapeutic strategies aimed at the prevention of CVD risk factors and at slowing the progression of the clinical course.

### Primary Prevention

The modest efficacy of the pharmacological treatments of cognitive symptoms once VaD is clinically established emphasizes the crucial role of the prevention of CVD risk factors in order to avoid the possible appearance of the clinical symptomatology. The formulation of any effective preventive strategy depends on the knowledge of the pathophysiological mechanisms. Since CVD may be the result of various pathological disorders, strategies for prevention will vary accordingly.

The principal risk factors for CVD, other than age, race and sex, are hypertension, diabetes mellitus, hypercholesterolemia, hyperhomocysteinemia and smoking. Although there is no unanimous consent, excessive use of alcohol, obesity, and limited physical activity can also concur in raising the risk of developing CVD [7]. Other risk factors for CVD are cardioembolic pathologies such as atrial fibrillation or mitral valve prolapse.

### Hypertension

The crucial role of hypertension in the development of dementia has been confirmed by both cross-sectional [8]
Prognosis in the Elderly (SCOPE)

Very elderly was addressed by the Study on Cognition and Prognosis in the Elderly (SCOPE) [20]. This study of almost 5,000 patients aged 70–89, who randomly received angiotensin receptor antagonist (candesartan) or placebo, showed only a trend in the risk reduction of dementia. However, the lack of evident benefits could be attributed to the small difference in blood pressure observed between the treated group and the placebo group. Moreover, to evaluate cognitive impairment, the Mini Mental State Examination was used, whose inability to detect cognitive decline in nondemented subjects is well known. The optimum values of systolic and diastolic blood pressure are still open to debate. The Hypertension Optimal Treatment (HOT) study [21] suggests that the best prophylactic results are obtained with systolic and diastolic values lower than 142 and 80 mm Hg, respectively.

Collectively, these studies have reached encouraging results, suggesting differences among the various classes of drugs tested. ACE inhibitors, used with or without diuretics, reduce the risk of cognitive decline [19] and of post-stroke dementia, but dementia in absence of stroke was not reduced. Calcium antagonists have been reported to remarkably reduce the risk of developing both AD and VaD [17, 18]. β-Blockers, with or without diuretics, have not shown any influence on cognitive impairment [16]. None of these studies have been aimed at identifying a possible mechanism of dementia prevention.

**Hypercholesterolemia**

Hypercholesterolemia is a less significant risk factor for stroke than for coronary heart disease. Most of the available data have been deduced from trials designed to verify the effects of high cholesterol on heart disease. A meta-analysis of 45 prospective cohorts counting 450,000 patients failed to show any correlation between cholesterol and stroke in the 13,000 cases of ictus observed during the follow-up [22]. Numerous randomized, placebo-controlled, double-blind trials such as 4S [23], CARE [24], LIPID [25], HPS [26], PROSPER [27], ALLHAT [28], KLIS [29], and GREACE [30] that focused on the efficacy of statins in stroke prevention have been conducted. These trials with a combined total of 70,020 subjects with established or high risk for coronary heart disease have shown a reduction of relative or absolute risk of 21 and 0.9%, respectively. However, it should be noted that the PROSPER trials failed to show any effect of the therapy. Regarding these results, it should be observed that the absolute risk reduction with statins is only modest as compared to 1.73% of the antiplatelet therapy and 1.7% of the antihypertensive therapy [31]. Finally, a recent meta-analysis showed a 21% reduction in the rate of major vascular events, including a 17% reduction in fatal and nonfatal stroke with a 12% proportional reduction in all-cause mortality per mmol/l reduction in low-density lipoprotein cholesterol [32].

and longitudinal studies of appropriate dimension such as Uppsala [9], HAAS [10], Framingham Hearts Study [11], and ARIC [12]. More specifically: a relatively high diastolic blood pressure (≥75 vs. ≤70 mm Hg) at age 50 [13], a persistently elevated systolic blood pressure in midlife [13], or stage two hypertension (≥160 mm Hg systolic and ≥95 mm Hg diastolic) between ages 59 and 71 [14], consistently predicted worse cognitive performance or, most importantly, white matter lesions at ages ranging from 63 [14] to 79 years [13].

Several large, randomized, placebo-controlled trials have been conducted to establish whether the treatment of hypertension can reduce the risk of developing cognitive impairment. The Systolic Hypertension in the Elderly Program (SHEP) [15] showed that treatment with the diuretic chlorothalidone and/or the β-blocker atenolol lowered the risk of stroke, but had no effect on the incidence of dementia. However, differential dropout could have biased the cognitive evaluation. The Systolic Hypertension in Europe (Syst-Eur and Syst-Eur 2) Study [16, 17] demonstrated that treatment of isolated systolic hypertension in subjects over the age of 60 with a calcium channel blocker (nitrendipine) with or without an ACE inhibitor (enalapril) and a diuretic (hydrochlorothiazide) lowered the rate of development of dementia (AD, VaD and mixed) by 55%. These results indicate that treatment of 1,000 patients for 5 years prevents 20 cases of dementia (95% CI, 7–33). The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) [18] found that the treatment of hypertension with an ACE inhibitor (perindopril) was associated with a 34% reduction of dementia in patients with recurrent stroke, but not in absence of stroke. The association of the ACE inhibitors with the diuretic indapamide was more effective in reducing the risk of dementia. Very interestingly, this study has also evidenced that the treatment was effective only in patients without cognitive impairment at baseline. In the substudy of the PROGRESS trial (PROGRESS MRI sub-study), the ability of blood pressure lowering to influence white matter hyperintensity was addressed. The authors showed that in the group who received active treatment, white matter hyperintensity was stopped or delayed [19]. This effect remained after adjustment of several variables such as age, gender or stroke type.

The opportunity of lowering blood pressure in the very elderly was addressed by the Study on Cognition and Prognosis in the Elderly (SCOPE) [20]. This study of almost 5,000 patients aged 70–89, who randomly received angiotensin receptor antagonist (candesartan) or placebo, showed only a trend in the risk reduction of dementia.
The data on the effect of statins on VaD are scarce and conflicting. There is evidence suggesting that these drugs may protect against dementia [33], but contrasting results were shown by Rea et al. [34]. However, recent observations offer an interesting prospect for use of statins in preventing AD [35]. Two extensive retrospective studies, a cross-sectional analysis and a case-control study, indicated that patients undergoing statin treatment had a statistically significantly lower incidence of AD [36, 37]. What mechanisms of action are involved is still unclear. Likely, this effect is not linked to the drug’s ability to lower cholesterol since it is recognizable only with lovastatin and pravastatin, but not with simvastatin [36]. A possible explanation might be found in ApoE and β-amyloid metabolism. Animal studies have shown that statins are able to suppress ApoE secretion that in turn reduces plaque load and improves cognitive function [38]. Fassbender et al. [39] demonstrated that simvastatin inhibited β-secretase, which is in accordance with the observation by Kojo et al. [40] that statins may favor the nonamyloidogenic pathway through α-secretase stimulation. Considering the high incidence of mixed dementia, where both components (vascular and degenerative) coexist, prospective studies assessing the effects of statins on the risk of dementia are to be encouraged.

Diabetes
Diabetes is another risk factor for stroke and VaD. Diabetic patients have twice the risk of developing cognitive impairment [41]. A possible mechanism is the impaired brain perfusion due to endothelial oxidative damage, and alteration of the blood-brain barrier resulting from excessive glycosylation [42]. Diabetic patients also present high blood viscosity, which is, according to Poiseuille’s law, a blood flow-reducing factor. Although it has never been strictly shown that controlling blood sugar levels can reduce the risk of CVD, the evidence of its beneficial effect on diabetic retinal disease allows to assume a similar beneficial effect on small cerebral arteries. On the other hand, visible changes of retinopathy have been independently associated with poorer cognitive function [43]. Two nonrandomized studies suggested that improved glycemic control improves cognitive function [44].

Concerning the possible effects of coexistence of both hypertension and diabetes risk factors, the ARIC study, which recruited 10,963 patients, showed that those with hypertension (32.4%) as well as diabetes developed a greater deficit in attention span, memory, and executive skills in the 6-year follow-up as compared to patients without hypertension [14]. A further study of 3,577 diabetic patients over 55 with at least one other risk factor for CVD and treated for 4.5 years has shown that the ACE inhibitor ramipril (10 mg/day) is able to reduce the risk of stroke by 33% [45].

Hyperhomocysteinemia
Hyperhomocysteinemia was previously associated with VaD in many case-control or cross-sectional studies [46, 47]. Only two prospective studies have examined the association between homocysteine and dementia. The Framingham Study has shown that homocysteine levels over 14 μmol/l double the risk of AD and dementia [48]. However, the other study did not replicate this finding [49]. Elevated homocysteinemia can be associated with dietary factors limiting intake of folic acid and vitamins B₆ and B₁₂, or with genetic deficiency of methylenetetrahydrofolate reductase. Although in the Nun Study [50] low serum folate was strongly associated with cortical atrophy, the evidence does not support a correlation between serum vitamin B₁₂ or folate and cognitive impairment in people over 60. Hence, there is little evidence to justify treating cognitive impairment with vitamin B₁₂ or folate supplementation [51]. This is consistent with the findings from recent systematic reviews of randomized double-blind trials, which have not found any evidence of potential benefits from supplementation strategy [52].

Treatment to Contrast Progression
Once VaD is clinically established, the therapy is aimed primarily at slowing the progression of disease by means of secondary prevention. Although probably less common than previously thought, the prevalence of post-stroke dementia is nearly 20% [13]. It is important to highlight that post-stroke dementia is not a specific entity as it includes cases with multiple corticosubcortical infarcts, strategic infarcts, subcortical ischemic VaD and AD. Evidence suggests heterogeneity of the underlying pathogenic mechanisms; nevertheless, prevention of stroke recurrence is mandatory in order to reduce the risk of developing dementia. Pharmacological treatments aimed at reducing the number of relapses after the first stroke are well established [53] and include carotid endarterectomy, warfarin for atrial fibrillation, blood pressure lowering, and, above all, antithrombotic drugs.

With regard to antiplatelet drugs, their efficacy in secondary stroke prevention is largely demonstrated. In stroke patients, the risk reduction of cerebral ischemic
events with aspirin is 20–30% [54]. The Ticlopidine-Aspirin Stroke Study [55] showed slightly more efficacy of ticlopidine as compared to aspirin in preventing nonfatal stroke or death (6.3 vs. 10.8%). However, ticlopidine has been shown to cause neutropenia in 2.4% of treated individuals. Finally, clopidogrel, a drug similar to ticlopidine but with a higher antiplatelet effect, has been compared to aspirin in the CAPRIE (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events) study [56]. The results of this trial suggest an overall relative risk reduction for stroke of 7.3% in favor of clopidogrel. Most importantly, the risk of neutropenia was comparable to that of aspirin. However, at the moment, the possibility that prevention of recurrent stroke is able to prevent cognitive decline is still open to debate, but as the reduction of stroke plays a key role in decreasing the risk of dementia (both VaD and mixed dementia), it can be inferred that antiplatelet drugs probably reduce the risk of cognitive decline. Although the efficacy of antithrombotic therapy in stroke prevention is well documented, the role of this approach in preventing cognitive decline is still to be proved. A large prospective study (3,809 subjects over the age of 65) over 3 and 6 years failed to show any statistically significant effect of aspirin in preventing any form of dementia [57]. Two other studies [58, 59] showed that the antithrombotic agents (aspirin, warfarin or a combination of both) may prevent cognitive decline.

A comment on the specific management of hypertension has to be made. The strong association between subcortical ischemic VaD and hypertension suggests that control of hypertension may be particularly important in preventing progression. On the other hand, treatment requires great caution, especially in elderly patients. Chronically hypertensive patients have a shifted autoregulatory range for cerebral blood flow to accommodate higher perfusion pressures. Thus, these patients are easily susceptible to hypotension, even at otherwise normal pressure. This may be important, as periodic hypotension is a suggested mechanism for white matter changes observed in these patients. Voko et al. [60] have shown that there is an increased risk of stroke when diastolic pressure drops below 65 mm Hg.

**Conclusions and Future Directions**

Once VaD is clinically established no really effective treatment is currently available; consequently, a therapeutic approach based on prevention is strongly recommended. Nevertheless, while the association of coronary heart disease and stroke with risk factors such as hypertension, diabetes mellitus, hypercholesterolemia, and hyperhomocysteinemia is well recognized, a definite relationship of these factors with dementia remains to be established. For instance, with regard to hypertension many studies have been able to show an association with dementia [9, 10, 11, 12], but there is a lack of consensus about the ability of antihypertensive therapy to prevent dementia [15, 18]. That cholesterol is an unequivocal risk factor for stroke remains to be demonstrated and still less significant is its association with dementia. However, considering the relationship between VaD and AD, an interesting perspective in this field is gained from the observation of the effects of statins in preventing AD. Similar considerations may be proposed concerning diabetes and hyperhomocysteinemia.

The lack of universal agreement may have two main causes. The methodological features of the studies, such as the neuropsychological tests used and study design (cross-sectional vs. longitudinal, observational vs. experimental, sample size, covariances, statistical methodologies and primary endpoints considered) may contribute to such uncertainty. More importantly, a further source of complexity arises from the heterogeneity of pathophysiological mechanisms that underline the different clinical forms of VaD. Accordingly, VaD should be regarded as a heterogeneous clinical entity that may require a multifaceted preventive approach. Finally and paradoxically, the growing evidence that risk factors for CVD are also risk factors for AD makes these studies more difficult to interpret.

Based on previous observations, two main targets in future clinical trials of VaD prevention should be addressed: (1) assessing the interdependence between risk factors and (2) defining more distinct and homogeneous clinical forms to include VaD, mixed dementia and AD. Further subgroup analyses for VaD should include, at least, subcortical versus cortical forms and small- versus large-vessel disease. However, although several questions remain unanswered, the prevention of CVD risk factors is the most promising approach to VaD.

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