Vascular dementia: prevention and treatment

Catherine McVeigh
Peter Passmore

Department of Geriatric Medicine, Faculty of Medicine and Health Sciences, Queen's University of Belfast, Belfast, Northern Ireland, UK

Background: Vascular dementia (VaD) is the most common cause of dementia in the elderly, second only to Alzheimer's disease (AD). Between 1% and 4% of people of 65 years of age suffer from VaD and the prevalence appears to double every 5–10 years after the age of 65.

Summary: Prevention aims to reduce the disease by eliminating its cause or main risk factors, particularly hypertension as well as diabetes mellitus, atherosclerosis, coronary artery disease, smoking, lipid abnormalities, and hyperhomocystinemia. Initial studies of several agents for symptomatic treatment were disappointing. However, there is growing evidence for cholinergic involvement in VaD and recent studies with cholinesterase inhibitors have shown improvement in cognitive, global function, and activities of daily living as compared with placebo and have been well tolerated.

Conclusion: VaD is a common condition and its prevalence is likely to increase. As physicians we need to be diligent with regards to recognition of risk factors and vigorous intervention. Promising results have been seen in several clinical trials of cholinesterase inhibitors and no safety of tolerability issues have been noted.

Keywords: vascular dementia, prevention, treatment

Introduction

Dementia is a syndrome of acquired intellectual deficit resulting in significant impairment of social or occupational functions. Vascular cognitive dementia (VaD) comprises dementias resulting from all types of vascular pathologies. The current classification of VaD includes: cortical vascular dementia; subcortical ischemic dementia; strategic-infarct dementia; hypoperfusion dementia; hemorrhagic dementia; and dementias resulting from specific arteriopathies (O'Brien et al 2003).

The diagnosis requires the presence of cognitive decline (loss of memory and deficits in at least two other domains) resulting in impaired functional abilities. Evidence of cerebrovascular disease (CVD) must be confirmed by neuroimaging for diagnosis of probable VaD and dementia and CVD must be reasonably related in time or temporally. Several specific diagnostic criteria can be used to diagnose VaD including the *Diagnostic Manual of Mental Disorders*, 4th edition (DMS-IV) criteria, the *International Classification of Diseases*, 10th edition criteria, the National Institute of Neurological Disorders and Stroke Association International pour le Recherché at L'Enseignement en Neurosciences (NINDS-AIREN) criteria, the Alzheimer's Disease Diagnostic and Treatment Centre criteria and the Hachinski Ischemic score.

The DSM-IV criteria have good sensitivity, but low specificity, but the NINDS-AIREN criteria are the most specific of all available criteria and are used most commonly in research (see Table 1). As not all patients fulfill the strict criteria for dementia and many may be significantly cognitively impaired without memory loss, the term vascular cognitive impairment (VCI) has been suggested. VCI includes VaD, but also encompasses mixed Alzheimer's disease (AD) and VaD as well as vascular cognitive impairment without dementia and hereditary disorders. It is also becoming clear that there is an overlap between AD and CVD and the concept of

Correspondence: Catherine McVeigh
Department of Geriatric Medicine, Queen's University of Belfast, Whilta Medical Building, 97 Lisburn Road, Belfast BT9 7BL, Northern Ireland, UK
Tel +44 2890 972157
Fax +44 2890 325839
Email catmcveigh@hotmail.com

Table 1 NINDS-AIREN criteria for diagnosis of vascular dementia

Dementia
Cerebrovascular disease: • Focal CNS signs • Evidence of CVD by brain imaging
A relationship between the two manifested by one or more of the following: • Dementia onset within three months after having a stroke • Abrupt deterioration in cognition or fluctuating stepwise course

Abbreviations: CNS, central nervous system; CVD, cardiovascular disease; NINDS-AIREN, National Institute of Neurological Disorders and Stroke Association International pour le Recherché at L'Enseignement en Neurosciences.

mixed dementia has evolved. Patients will have clinical features of both AD and VaD and can share risk factors and pathogenic mechanisms (Meyer et al 1999). Diagnosis is complex due to the current lack of appropriate clinical criteria and terminology (Zekry et al 2002). However, in one recent Canadian cohort study (ACCORD), mixed dementia was found to represent as much as 33% of all dementias with "pure" VaD accounting for only 8.7% of dementia cases (Feldman et al 2003).

Prevalence

VaD is historically considered the second most common cause of dementia in the elderly after AD (Jorm 1991). Between 1% and 4% of people over 65 years suffer from VaD (Hebert and Brayne 1995) and the prevalence appears to double every 5–10 years after the age of 65 years (Hofman et al 1991). Post stroke dementia is extremely common and occurs in up to one third of patients with clinically evident ischemic stroke after 65 years (Tatemicihi et al 1994; Pohjasvaara et al 1997). In a recent series (Desmond et al 2000) dementia was reported in 26.3% of patients at three months after stroke. The subtypes were 57.1% with VaD, 38.7% with AD and stroke, and 4.2% with other causes.

Pohjasvaara and colleagues (2002) reported cognitive decline of any kind to be present in 61.7% of stroke patients ranging in age from 55 to 85 years. The prevalence of mixed dementia is much harder to measure as the concept is relatively new and most studies have used pathological evidence, however it is clear that CVD and AD frequently co-exist in the elderly population (Snowdon et al 1997; Heyman et al 1998; MRCCFAS 2001). Autopsy series report that co-existing vascular pathology occurs in 24%–28% of AD cases (Gearing et al 1995) and conversely half of patients with vascular disease who have become demented also have AD pathology (O'Brien 1994).

Clinical features

Due to the variety of pathogenic mechanisms, the clinical manifestations of VaD can be varied and are determined by the size, location, and type of cerebral damage. Classically, the clinical features include an abrupt onset, stepwise deterioration, fluctuating course, and are often accompanied by focal motor and sensory abnormalities including early onset of urinary incontinence and gait disorders. However subcortical VaD can present with a gradual onset and deterioration like AD. Even within VaD, the clinical features can be further subdivided.

Cortical VaD

This is characterized by abrupt onset of unilateral sensorimotor changes along with aphasia, apraxia, or agnosia (cortical cognitive impairments). In particular, most patients have an element of executive dysfunctioning leading to difficulties in areas such as initiation, planning, and organization of activities. There may be day to day fluctuations in severity with long plateaus between events (Erkinjuntti 1999).

Strategic infarct

Single strategic infarcts will produce cognitive and other deficits that entirely depend on the location of the infarct. Particular areas known to produce acute onset VaD include the thalamus, basal forebrain, and caudate (Erkinjuntti 1999; O'Brien et al 2003). Cognitively, memory impairment, impaired executive function, confusion, and fluctuating levels of consciousness may occur. Behavioral changes include apathy, lack of spontaneity and perseveration (Desmond et al 1999).

Subcortical VaD

Cerebrovascular lesions in the subcortical area tend to cause slow but episodic deterioration in executive functioning and abstract thought as well as mood changes including depression, personality changes, and emotional lability. Although memory deficits are less severe, the difficulties with complex tasks lead to decreased performance in activities of daily living (ADLs) (Roman and Royall 1999).

With regard to the course of the disease as a whole, a recent study estimated median survival from dementia onset to death as 3.9 years for those with VaD as compared with 7.1 years for AD and 5.4 years for mixed dementia (Fitzpatrick et al 2005).

Risk factors for VaD

Risk factors for VaD can be divided into two groups: modifiable and non-modifiable. The two most important non-modifiable risk factors are gender and age, followed by genetic predisposition, ethnicity, and a previous history of stroke. Both incidence and prevalence of VaD increase with age and tend to be higher in men (Zhang 1990; Hofman et al 1991; Ruitenburg et al 2001). Dementia affects around 7% of the general population older than 65 years and 30% of people older than 80. As previously mentioned the prevalence doubles every 5–10 years after the age of 65 years (Hofman et al 1991). Genetic defects for several monogenic disorders have been identified in the last decade. These include cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) which is a cause of small vessel disease and stroke leading to cognitive impairment up to 20 years after the onset of symptoms. Other genetic disorders include hereditary cerebral hemorrhage with amyloidosis which leads to cognitive impairment or dementia in the majority of patients with this disorder (Thomas et al 2000).

Ethnicity appears to be of importance when one considers that previous studies suggest that VaD represents over 50% of dementias in Japan (Ueda et al 1992) (however there may have been differences in ascertainment of cases with over-diagnosis of VaD). Conversely, in a recent study of four major regional centers in China, the prevalence of dementia subtypes in China was comparable with that in Western countries (Zhang et al 2005).

There is a history of prior stroke in 76% of patients with vascular dementia and in 57% of those with vascular cognitive impairment as compared with only 5%–7% of people with AD (Rockwood 1997).

The modifiable risk factors for VaD should be those that reduce CVD ie, hypertension, diabetes mellitus (DM), ischemic heart disease (IHD), peripheral vascular disease (PVD), white matter lesions, smoking, and hyperlipidemia (Desmond et al 1993; Meyer et al 1995; Rockwood 1997).

Epidemiological data shows that hypertension is one of the most potent risk factors for VaD and it has been shown that control of hypertension can decrease the risk of VaD (In't Veld et al 2001).

With regards to diabetes and the risk for VaD, Luchsinger and colleagues (2001) have shown that in a population of elderly subjects followed up for an average of 4.6 years, those with diabetes were over three times more likely to experience stroke-associated dementia.

White matter lesions seen on magnetic resonance imaging (MRI) scans of elderly patients with CVD strongly correlated with the development of dementia (Liu et al 1992) implying that neuroimaging may prove a useful tool as a predictor of cognitive decline in post stroke patients.

Cognitive impairment is seen in 26% of patients discharged from hospital after treatment for heart failure, correlating with the degree of left ventricular dysfunction and systolic blood pressure levels below 130 mm Hg (Cacciatore et al 1998).

Coronary artery bypass graft (CABG) surgery is increasingly common, with a particular increase in the older population. In this group, widespread atherosclerotic disease can predispose to vascular sequele leading to neurological dysfunction. This has been the subject of a recent review (Royter et al 2005). The reported incidence of early cognitive disturbance ranges from 33% to 83%. Long term cognitive outcome seems to be more favourable for off-pump CABG, but late post-operative dementia is predicted by early cognitive deterioration. It has also been suggested that aggressive post-operative risk factor control could favorably impact on cognitive outcome (Ross et al 1999).

Dyslipidemia, a well established risk factor for ischemic heart disease, has not yet been convincingly demonstrated as a factor associated with VaD or AD. However, a recent cross sectional and prospective study of 4316 patients in the US showed that elevated levels of non-high-density lipoprotein cholesterol (non-HDL-C), low-density lipoprotein cholesterol (LDL-C) and decreased levels of HDL-C were weak risk factors for VaD (Reitz et al 2004).

The evidence for smoking and dementia is somewhat ambivalent however a recent study showed that current smokers had an increased risk of AD (relative risk [RR]=1.98; confidence index [CI]=1.63–5.42) and VaD (RR=1.98; CI=1.53–3.12) whereas past smokers did not have an increased risk of dementia (Juan et al 2004) (Table 2).

Prevention

Primary prevention

Primary prevention aims to reduce the incidence of VaD by early detection and optimum treatment of known vascular factors for CVD and stroke (O'Brien et al 2003). Targeting high risk groups (elderly patients, patients with hypertension, diabetes, atrial fibrillation, past transient ischemic attack or stroke, hypercholesterolemia, and smokers) affords the best chance of minimizing dementia

Table 2 Common risk factors for vascular dementia

Age
Gender (male)
Ethnicity
Hypertension
Atherosclerosis
Hyperlipidemia
Diabetes mellitus
Smoking
Atrial fibrillation
Hyperhomocystinemia

in the population. As well as simple measures such as recommending lifestyle changes and optimizing control of diabetes, control of hypertension appears to be of paramount importance. Initially evidence for the effects of antihypertensive treatment on dementia was conflicting. Epidemiological data came from the Rotterdam study which was a longitudinal study of 7046 elderly and showed that the relative risk of vascular dementia was reduced by over one third over a mean of 2.2 years follow up in those who were receiving antihypertensives at baseline (In't Veld et al 2001). Two subsequent prospective studies were less positive. The Medical Research Council (MRC) trial of hypertension in older adults with a diuretic/β blocker-based regimen showed no benefit in prevention of dementia (MRC 1985) and the Systolic Hypertension in the Elderly Programme (SHEP) study showed no protective effect against dementia with treatment with diuretics +/–β blockers (SHEP 1991). However further evaluation of this trial has revealed that cognitive and functional evaluations may have been biased toward the null effect by differential dropout, thus obscuring the appraisal of a protective effect of treatment on the cognitive and functional decline (Di Bari et al 2001). More positive evidence came in the form of the Systolic Hypertension in Europe trial which demonstrated a 55% reduction in the incidence of dementia in the active treatment group (receiving a calcium channel blocker) over two years. However only small numbers of new cases of dementia were identified and therefore the results should be interpreted with caution (Pahor et al 1999).

Secondary prevention

In secondary prevention, the target is stroke management and prevention of recurrent stroke. More recently, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial confirmed the benefits of blood pressure lowering in secondary prevention (PROGRESS 2001). Although the primary outcome of PROGRESS was stroke incidence, dementia and cognitive function were secondary outcomes. The active treatment group received the long-acting angiotensin-converting enzyme (ACE) inhibitor perindopril combined with the diuretic indapamide. After four years of follow up in the entire population, the reduction in risk of dementia in the active treatment group was 12% (not significant). However, a significant reduction in dementia of 34% in the active treatment group was observed in patients with recurrent stroke (p=0.03). A similar pattern was seen for cognitive decline with an overall risk reduction of 19% with active treatment in the whole population (p=0.01) but a significant risk reduction of 45% in the group with prior stroke (p=0.001). Combination therapy induced a mean difference of blood pressure of 12/5 mm Hg and was more effective in reducing the risk of dementia than monotherapy, the difference of blood pressure on monotherapy being 5/3 mm Hg.

Among the patients without cognitive impairment at baseline, a 50% reduction in the risk of dementia was seen in those with prior stroke compared with a 16% reduction in those without stroke.

Further evidence was demonstrated in a PROGRESS sub study (MRI study). This looked at whether blood pressure lowering could arrest the progression of white matter hyperintensities (WMH). We know that WMH are associated with cognitive impairment or dementia (Breteler et al 1994; Longstreth et al 1996; Vermeer et al 2003) and are often observed on brain MRI in elderly patients (Bots et al 1993; Breteler et al 1994; Lindgren et al 1994; Longstreth et al 1996; Dufouil et al 2001) and those who have suffered a stroke (Miyao et al 1992; Van Zagten et al 1996; Inzitari 2003). At 36 months the mean total volume of new WMHs was significantly reduced in the active treatment group receiving perindopril +/– indapamide (p=0.012), therefore the results indicated that an active blood-pressure lowering regimen stopped or delayed the progression of WMHs in patients with CVD (Dufouil et al 2005).

The treatment of another risk factor, hypercholesterolemia, has also become topical. It is clear that the use of 3-hydroxy-3 methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (ie, statins) have a well defined role in the secondary prevention of stroke. What is less obvious is their role in preventing cognitive decline. Observational studies have suggested that treatment with statins lower the risk of developing dementia or cognitive decline however most of the available data does not distinguish between AD, VaD and other forms of dementia (Jick et al 2000; Kivipelto et al 2001; Rockwood et al 2002).

The Heart Protection Study which investigated the effects of simvastatin on vascular outcomes including stroke, showed no significant benefit of simvastatin on 5-year cognitive outcomes (HPSCG 2002). However, the study design for this particular outcome could be criticized as there was no measure of baseline cognitive function. The Prospective Study of Pravastatin in the Elderly at Risk study (PROSPER) followed 6000 individuals aged 70 to 82 for 3.2 years. Pravastatin reduced the risk of coronary disease in elderly individuals but had no significant benefit on stroke, cognition, or ADL. It has been hypothesized though, that the studies involving statins have been of insufficient duration to detect cognitive benefits (Shepherd et al 2002).

Other less studied strategies for prevention of VaD focus on prompt stroke diagnosis and treatment and good after care. They should impact on cognitive function at least through event reduction. These include: early intervention (within 3 hours) in selected patients with stroke to achieve reperfusion with thrombolytic agents, antiplatelet agents for patients with past transient ischemic attack (TIA) or non-hemorrhagic stroke, anticoagulants for atrial fibrillation as indicated, carotid endarterectomy for severe carotid stenosis and intensive rehabilitation after stroke (Sachdev et al 1999).

Symptomatic treatment

Initial studies of several agents in VaD including vasodilators, nootropics, antithrombotics, ergot alkaloids, antioxidants, hyperbaric oxygen and thyrotropin-releasing hormone analogue have had mostly negative results (Erkinjuntti 1999; Roman 2000). However the study designs were not ideal as they were based on small numbers, had short treatment periods and there were varying end points of the various trials.

Propentofylline is a glial modulator which has been studied in more detail. Several double blind, placebo-controlled randomized, parallel group trials carried out in Europe and Canada showed significant symptom improvement and long term efficacy in the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and Clinician's Interview Based Impression of Change (CIBIC-plus) up to 48 weeks compared with placebo (Kittner et al 1997; Mielke et al 1998). The calcium antagonist nimodipine which is known to have specific effects on small vessels was studied in a double-blind, placebo controlled study in VaD. Although there was no overall evidence of efficacy in VaD, nimodipine had beneficial effects on attention and psychomotor performances in the subcortical group (Pantoni et al 2000).However, the effects appear to be short term. Memantine, which is a moderate affinity noncompetitive N-methyl-D-aspartate receptor antagonist, is another treatment which shows promise and is well tolerated. It is licensed for use in moderate AD but a number of studies of memantine in VaD have shown improvement in mini-mental state examination (MMSE) as well as functional levels and reduced care dependency compared with placebo. Interestingly, the cognitive treatment effect for memantine was more pronounced in the small vessel group (Gortelmeyer and Erbler 1992; Mobius and Stoffler 2002; Wilcock et al 2002).

There is growing evidence for cholinergic involvement in VaD. Autopsy patients with VaD have shown significantly reduced choline acetyl-transferase activity in several brain regions including the caudate and putamen, hippocampus and temporal lobe cortex (Gottfries et al 1994). This equates to a 40% loss of cholinergic neurons as compared with 70% in AD cases (Court et al 2002). Again, in rodent models such as the stroke-prone spontaneously-hypertensive rats, there is a significantly reduced level of cholinergic markers including acetylcholine in the neocortex, hippocampus, and cerebrospinal fluid that appears to correlate with impaired learning and memory (Gottfries et al 1994; Kimura et al 2000). It is reasonable therefore to hypothesize that in a similar way to AD, enhancing cholinergic transmission may be a rational approach to treatment of VaD. As a result, three of the acetylcholinesterase inhibitors approved for use in AD: donepezil, rivastigmine, and galantamine have also been used in VaD. Rivastigmine is a second generation cholinesterase inhibitor with the capacity to inhibit both acetylcholinesterase and butyrylcholinesterase. In a randomized open label one year study, 208 patients with VaD were treated with rivastigmine. There was slight improvement in executive function (clock drawing tests) and in behavior (Moretti et al 2003), however the results of a randomized double-blind trial with rivastigmine are awaited. The most positive results have been seen with donepezil and galantamine. Donepezil is a piperidine-based agent and is a noncompetitive, reversible antagonist of cholinesterase and is highly selective for acetyl-cholinesterase. Efficacy and safety has been shown in two large randomized placebo-controlled trials (Black et al 2003; Wilkinson et al 2003) and confirmed in a recent Cochrane review (Malouf and Birks 2004). Altogether 1219 patients with VaD, according to the NINDS-AIREN criteria, were recruited for 24 week trials. The patients were randomized to one of three groups: placebo, donepezil 5 mg per day, or

donepezil 10 mg per day. From week 6 through week 24 both active treatment groups showed statistically significant improvement in cognitive, global function, and ADLs as compared with placebo and the drug was well tolerated. Galantamine is a cholinesterase inhibitor that also modulates central nicotinic receptors. In a multicenter, double-blind 6 month randomized control trial, patients diagnosed with probable VaD or AD combined with CVD received galantamine or placebo. Primary end points were cognition and global functioning and secondary end points included assessment of behavioral symptoms according to the Neuropsychiatric Inventory (NPI) and ADL using the Disability Assessment in Dementia (DAD) (Cummings et al 1994). In analysis of both groups as a whole, galantamine demonstrated efficacy on all outcome measures. It showed greater efficacy than placebo on ADAS-cog (2.7 points; $p<0.001$) and CIBIC-plus (74% vs 59% of patients remained stable or improved; $p<0.001$). ADL and behavioral symptoms were also significantly improved compared with placebo (both $p<0.05$) (Erkinjuntti et al 2002). Although the overall population showed improvement, the VaD subgroup changes did not achieve significance. There are two further large randomized controlled trials in VaD with galantamine awaiting publication. Preliminary results have shown that while benefits were seen for galantamine in executive dysfunction and cognition, the global outcomes were unaffected.

Conclusion

Vascular dementia is a common condition and its prevalence is likely to increase. As physicians we need to be diligent with regards to recognition of risk factors and vigorous intervention. Promising results have been seen in several clinical trials of cholinesterase inhibitors and no safety or tolerability issues have been noted.

References

Black S, Roman GC, Geldmacher DS, et al; Donepezil 307 Vascular Dementia Study Group. 2003. Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. *Stroke*, 34:2323-30.

Bots ML, van Swieten JC, Breteler MM, et al. 1993. Cerebral white matter lesions and atherosclerosis in the Rotterdam Study. *Lancet*, 341:1232-7.

Breteler MM, van Amerongen NM, van Swieten JC, et al. 1994. Cognitive correlates of ventricular enlargement and cerebral white matter lesions on magnetic resonance imaging. The Rotterdam Study. *Stroke*, 25:1109-15.

Breteler MM, van Swieten JC, Bots MLet al. 1994. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. *Neurology*, 44:1246-52.

Cacciatore F, Abete P, Ferrara N, et al. 1998. Congestive heart failure and cognitive impairment in an older population. Osservatorio Geriatrico Campano Study Group. *J Am Geriatr Soc*, 46:1343-8.

Court JA, Perry EK, Kalaria RN. 2002. Neurotransmitter control of the cerebral vasculature and abnormalities in vascular dementia. In: Erkinjuntti T, Gauthier S (eds). Vascular cognitive impairment. London: Martin Duniz Ltd, p 167-85.

Cummings JL, Mega M, Gray K, et al. 1994., The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. *Neurology*, 44:2308-14.

Desmond DW, Erkinjuntti T, Sano M, et al. 1999. The cognitive syndrome of vascular dementia: implications for clinical trials. *Alzheimer Dis Assoc Disord*, 13(Suppl 3):S21-9.

Desmond DW, Moroney JT, Paik MC, et al. 2000. Frequency and clinical determinants of dementia after ischemic stroke. *Neurology*, 54:1124-31.

Desmond DW, Tatemichi TK, Paik MC, et al. 1993. Risk factors for cerebrovascular disease as correlates of cognitive function in a stroke-free cohort. *Arch Neurol*, 50:162-6.

Di Bari M, Pahor M, Franse LV, et al. 2001. Dementia and disability outcomes in large hypertension trials: lessons learned from the systolic hypertension in the elderly program (SHEP) trial. *Am J Epidemiol*, 153:72-8.

Dufouil C, Chalmers J, Coskun O, et al; PROGRESS MRI Substudy Investigators. 2005. Effects of blood pressure lowering on cerebral white matter hyperintensities in patients with stroke: the PROGRESS (Perindopril Protection Against Recurrent Stroke Study) Magnetic Resonance Imaging Substudy. *Circulation*, 112:1644-50.

Dufouil C, de Kersaint-Gilly A, Besancon V, et al. 2001. Longitudinal study of blood pressure and white matter hyperintensities: the EVA MRI Cohort. *Neurology*, 56:921-6.

Erkinjuntti T. 1999. Cerebrovascular dementia: pathophysiology, diagnosis and treatment. *CNS Drugs*, 12:35-48.

Erkinjuntti T, Kurz A, Gauthier S, et al. 2002. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. *Lancet*, 359:1283-90.

Feldman H, Levy AR, Hsiung GY, et al; ACCORD Study Group. 2003. A Canadian cohort study of cognitive impairment and related dementias (ACCORD): study methods and baseline results. *Neuroepidemiology*, 22:265-74.

Fitzpatrick AL, Kuller LH, Lopez OL, et al. 2005. Survival following dementia onset: Alzheimer's disease and vascular dementia. *J Neurol Sci*, 229-30:43-9.

Gearing M, Mirra SS, Hedreen JC, et al. 1995. The consortium to establish a registry for Alzheimer's disease (CERAD). Part X. Neuropathology confirmation of the clinical diagnosis of Alzheimer's disease. *Neurology*, 45:461-6.

Gortelmeyer R, Erbler H. 1992. Memantine in the treatment of mild to moderate dementia syndrome. A double-blind placebo-controlled study. *Arzneimittel-Forschung*, 42:904-13.

Gottfries CG, Blennow K, Karlsson I, et al. 1994. The neurochemistry of vascular dementia. *Dementia (Basel, Switzerland)*, 5:163-7.

[HPSCG] Heart Protection Study Collaborative Group. 2002. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*, 360:7-22.

Hebert R, Brayne C. 1995. Epidemiology of vascular dementia. *Neuroepidemiology*, 14:240-57.

Heyman A, Fillenbaum GG, Welsh-Bohmer KA, et al. 1998. Cerebral infarcts in patients with autopsy-proven Alzheimer's disease: CERAD, part XVIII. Consortium to Establish a Registry for Alzheimer's Disease. *Neurology*, 51:159-62.

Hofman A, Rocca WA, Brayne C, et al. 1991. The prevalence of dementia in Europe: a collaborative study of 1980-1990 findings. Eurodem Prevalence Research Group. *Int J Epidemiol*, 20:736-48.

in't Veld BA, Ruitenberg A, Hofman A, et al. 2001. Antihypertensive drugs and incidence of dementia: the Rotterdam Study. *Neurobiol Aging*, 22:407-12.

Inzitari D. 2003. Leukoaraiosis: an independent risk factor for stroke? *Stroke*, 34:2067-71.

Jick H, Zornberg GL, Jick SS, et al. 2000. Statins and the risk of dementia. *Lancet*, 356:1627-31.

Jorm AF. 1991. Cross-national comparisons of the occurrence of Alzheimer's and vascular dementias. *Eur Arch Psychiatry Clin Neurosci*, 240:218-22.

Juan D, Zhou DH, Li J, et al. 2004. A 2-year follow-up study of cigarette smoking and risk of dementia. *Eur J Neurol*, 11:277-82.

Kimura S, Saito H, Minami M, et al. 2000. Pathogenesis of vascular dementia in stroke-prone spontaneously hypertensive rats. *Toxicology*, 153:167-78.

Kittner B, Rossner M, Rother M. 1997. Clinical trials in dementia with propentofylline. *Ann N Y Acad Sci*, 826:307-16.

Kivipelto M, Helkala EL, Laakso MP, et al. 2001. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ*, 322:1447-51.

Lindgren A, Roijer A, Rudling O, et al. 1994. Cerebral lesions on magnetic resonance imaging, heart disease, and vascular risk factors in subjects without stroke. A population-based study. *Stroke*, 25:929-34.

Liu CK, Miller BL, Cummings JL, et al. 1992. A quantitative MRI study of vascular dementia", *Neurology*, 42:138-43.

Longstreth WT Jr, Manolio TA, Arnold A, et al. 1996. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke*, 27:1274-82.

Luchsinger JA, Tang MX, Stern Y, et al. 2001. Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. *Am J Epidemiol*, 154:635-41.

Malouf R, Birks J. 2004. Donepezil for vascular cognitive impairment, *Cochrane Database Syst Rev*, 1:CD004395.

Meyer JS, Rauch GM, Crawford K, et al. 1999. Risk factors accelerating cerebral degenerative changes, cognitive decline and dementia. *Int J Geriatr Psychiatry*, 14:1050-61.

Mielke R, Moller HJ, Erkinjuntti T, et al. 1998. Propentofylline in the treatment of vascular dementia and Alzheimer-type dementia: overview of phase I and phase II clinical trials. *Alzheimer Dis Assoc Disord*, 12(Suppl 2):S29-35.

Miyao S, Takano A, Teramoto J, et al. 1992. Leukoaraiosis in relation to prognosis for patients with lacunar infarction. *Stroke*, 23:1434-8.

Mobius HJ, Stoffler A. 2002. New approaches to clinical trials in vascular dementia: memantine in small vessel disease. *Cerebrovasc Dis*, 13(Suppl 2):61-6.

Moretti R, Torre P, Antonello RM, et al. 2003. Rivastigmine in subcortical vascular dementia: a randomized, controlled, open 12-month study in 208 patients. *Am J Alzheimers Dis Other Demen*, 18:265-72.

[MRC] Medical Research Council Working Party. 1985. MRC trial of treatment of mild hypertension: principal results. *Br Med J (Clin Res Ed)*, 291:97-104.

[MRCCFAS] Neuropathology Group. Medical Research Council Cognitive Function and Aging Study. 2001. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *Lancet*, 357:169-75.

O'Brien JT, Erkinjuntti T, Reisberg B, et al. 2003. Vascular cognitive impairment. *Lancet Neurol*, 2:89-98.

O'Brien MD. 1994. How does cerebrovascular disease cause dementia? *Dementia*, 5:133-6.

Pahor M, Somes GW, Franse LV, et al. 1999. Prevention of dementia: Syst-Eur trial. *Lancet*, 353:235; author reply 236-7.

Pantoni L, Bianchi C, Beneke M, et al. 2000. The Scandinavian Multi-Infarct Dementia Trial: a double-blind, placebo-controlled trial on nimodipine in multi-infarct dementia. *J Neurol Sci*, 175:116-23.

Pohjasvaara T, Erkinjuntti T, Vataja R, et al. 1997. Dementia three months after stroke. Baseline frequency and effect of different definitions of dementia in the Helsinki Stroke Aging Memory Study (SAM) cohort. *Stroke*, 28:785-92.

[PROGRESS] PROGRESS Collaborative Group. 2001. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet*, 358:1033-41.

Reitz C, Tang MX, Luchsinger J, et al. 2004. Relation of plasma lipids to Alzheimer disease and vascular dementia. *Arch Neurol*, 61:705-14.

Rockwood K. 1997. Lessons from mixed dementia. *Int Psychogeriatr*, 9:245-9.

Rockwood K, Kirkland S, Hogan DB, et al. 2002. Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. *Arch Neurol*, 59:223-7.

Roman G. 2000. Perspectives in the treatment of vascular dementia. *Drugs Today*, 36:641-53.

Roman GC, Royall DR. 1999. Executive control function: a rational basis for the diagnosis of vascular dementia. *Alzheimer Dis Assoc Disord*, 13(Suppl 3):S69-80.

Ross GW, Petrovitch H, White LR, et al. 1999. Characterization of risk factors for vascular dementia: the Honolulu-Asia Aging Study. *Neurology*, 53:337-43.

Royter V, M Bornstein N, Russell D. 2005. Coronary artery bypass grafting (CABG) and cognitive decline: a review. *J Neurol Sci*, 229-230:65-67.

Ruitenberg A, Ott A, van Swieten JC, et al. 2001. Incidence of dementia: does gender make a difference? *Neurobiol Aging*, 22:575-80.

Sachdev PS, Brodaty H, Looi JC. 1999. Vascular dementia: diagnosis, management and possible prevention. *Med J Aust*, 170:81-5.

[SHEP] SHEP Cooperative Research Group. 1991. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*, 265:3255-64.

Shepherd J, Blauw GJ, Murphy MB, et al; PROSPER study group. PROspective Study of Pravastatin in the Elderly at Risk. 2002. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*, 360:1623-30.

Snowdon DA, Greiner LH, Mortimer JA, et al. 1997. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *JAMA*, 277:813-17.

Tatemichi TK, Desmond DW, Stern Y, et al. 1994. Cognitive impairment after stroke: frequency, patterns, and relationship to functional abilities. *J Neurol Neurosurg Psychiatry*, 57:202-7.

Thomas NJ, Morris CM, Scaravilli F, et al. 2000. Hereditary vascular dementia linked to notch 3 mutations. CADASIL in British families. *Ann N Y Acad Sci*, 903:293-8.

Ueda K, Kawano H, Hasuo Y, et al. 1992. Prevalence and etiology of dementia in a Japanese community. *Stroke*, 23:798-803.

van Zagten M, Boiten J, Kessels F, et al. 1996. Significant progression of white matter lesions and small deep (lacunar) infarcts in patients with stroke. *Arch Neurol*, 53:650-5.

Vermeer SE, Prins ND, den Heijer T, et al. 2003. Silent brain infarcts and the risk of dementia and cognitive decline. *New Engl J Med*, 348:1215-22.

Wilcock G, Mobius HJ, Stoffler A; MMM 500 Group. 2002. A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). *Int Clin Psychopharmacol*, 17:297-305.

Wilkinson D, Doody R, Helme R, et al; Donepezil 308 Study Group. 2003. Donepezil in vascular dementia: a randomized, placebo-controlled study. *Neurology*, 61:479-86.

Zekry D, Hauw JJ, Gold G. 2002. Mixed dementia: epidemiology, diagnosis, and treatment. *J Am Geriatr Soc*, 50:1431-8.

Zhang M. 1990. Prevalence study on dementia and Alzheimer disease. *Zhonghua yi xue za zhi*, 70:424-8, 30.

Zhang ZX, Zahner GE, Roman GC, et al. 2005. Dementia subtypes in China: prevalence in Beijing, Xian, Shanghai, and Chengdu. *Arch Neurol*, 62:447-53.