Review

European Neurology

Eur Neurol 2008;60:217–223
DOI: 10.1159/000151696

Received: December 28, 2007
Accepted: March 12, 2008
Published online: August 29, 2008

Treatment of Vascular Dementia: The Route of Prevention

G. Sorrentino[a, b] R. Migliaccio[b, c] V. Bonavita[b, d]

[a]University of Naples 'Parthenope', [b]Istituto di diagnosi e cura 'Hermitage Capodimonte', [c]Second University of Naples, and [d]University of Naples 'Federico II', Naples, Italy

Key Words
Vascular dementia · Prevention · Hypertension · Hypercholesterolemia · Diabetes · Hyperhomocysteinemia · Alzheimer's disease · Mixed dementia

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

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0014–3022/08/0605–0217$24.50/0

Accessible online at:
www.karger.com/ene

Prof. Giuseppe Sorrentino
Via Acton 38
IT–80133 Naples (Italy)
Tel. +39 081 748 3001, Fax +39 081 741 0499
E-Mail giuseppe.sorrentino@uniparthenope.it

Table 1. Synopsis of VaD: nosography, pathophysiology and pathology

Clinical syndromes	Mechanisms	Types of brain injury	Main causes
Multi-infarct dementia	Large-vessel thrombotic/embolic occlusion	Multiple large cortical/subcortical complete infarcts	Atherothrombosis or cardiogenic embolism
Strategic infarct dementia	Large- or small-vessel occlusion	Single strategic cortical/subcortical infarct or strategic lacunar infarct	Atherothrombosis or cardiogenic embolism
Subcortical ischemic dementia			
Lacunar dementia	Small-vessel occlusion	Multiple subcortical lacunar infarcts	Hypertensive/arteriosclerotic angiopathy
Binswanger's disease[1]	Hypoperfusion with partial small vessel occlusion	Periventricular leukoencephalopathy	Hypertensive/arteriosclerotic angiopathy
CADASIL	Partial/complete small-vessel occlusion	Multiple subcortical lacunar infarcts, periventricular leukoencephalopathy	Mutation of *Notch3* gene
Ischemic-hypoxic dementia (hypoperfusive)	Anoxic-ischemic episode	Focal or diffuse white matter lesions	Cardiac arrest/surgery, severe atherothrombotic stenosis/occlusion
Hemorrhagic dementia	Multiple hemorrhagic episodes	Deep cerebral hematomas	Hypertension

CADASIL = Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.
[1] Or subcortical arteriosclerotic leukoencephalopathy.

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]

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 chlorthalidone 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 substudy), 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. 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].

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 Kojro 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 B_6 and B_{12}, 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 B_{12} or folate and cognitive impairment in people over 60. Hence, there is little evidence to justify treating cognitive impairment with vitamin B_{12} 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 underlie 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.

Acknowledgements

This work was supported by grants from MIUR (PRIN); Regione Campania (legge regionale 5/02), Italy; Progetto Strategico Alzheimer (Ministero della Salute-Regione Lazio), Italy, and Provincia di Salerno (Assessorato allo Sport, Salute e Qualità della Vita), Italy.

References

1 Henon H, Pasquier F, Durieu I, Godefroy O, Lucas C, Lebert F, Leys D: Preexisting dementia in stroke patients. Baseline frequency, associated factors, and outcome. Stroke 1997;28:2429–2436.
2 Victoroff J, Mack WJ, Lyness SA, Chui HC: Multicenter clinicopathological correlation in dementia. Am J Psychiatry 1995;152:1476–1484.
3 Staessen JA, Richart T, Birkenhäger WH: Less atherosclerosis and lower blood pressure for a meaningful life perspective with more brain. Hypertension 2007;49:389–400.
4 De La Torre JC: Alzheimer's disease as a vascular disorder: nosological evidence. Stroke 2002;33:1152–1162.
5 Hachinski VC, Bowler JV: Vascular dementia. Neurology 1993;43:2159–2160.
6 Kalaria RN, Kenny RA, Ballard CG, Perry R, Ince P, Polvikoski T: Towards defining the neuropathological substrates of vascular dementia. J Neurol Sci 2004;226:75–80.
7 Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, Zheng ZJ, Flegal K, O'Donnell C, Kittner S, Lloyd-Jones D, Goff DC Jr, Hong Y, Adams R, Friday G, Furie K, Gorelick P, Kissela B, Marler J, Meigs J, Roger V, Sidney S, Sorlie P, Steinberger J, Wasserthiel-Smoller S, Wilson M, Wolf P, American Heart Association Statistics Committee and Stroke Statistics Subcommittee: Heart disease and stroke statistics – 2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2006;113:85–151.
8 Qiu C, Winblad B, Fratiglioni L: The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol 2005;4:487–499.
9 Kilander L, Nyman H, Boberg M, Hansson L, Lithell H: Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. Hypertension 1998;31:780–786.
10 Launer LJ, Masaki K, Petrovich H, Foley D, Havlik RJ: The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. JAMA 1995;274:1846–1851.
11 Elias MF, D'Agostino RB, Elias PK, Wolf PA: Neuropsycological test performance, cognitive functioning, blood pressure, and age: the Framingham Heart Study. Exp Aging Res 1995;21:369–391.
12 Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, McGovern P, Folsom AR, Atherosclerosis Risk in Community (ARIC) Study Investigators: Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology 2001;56:42–48.
13 Swan GE, DeCarli C, Miller BL, Reed T, Wolf PA, Jack LM, Carmelli D: Association of midlife blood pressure to late-life cognitive decline and brain morphology. Neurology 1998;51:986–993.
14 Tzourio C, Dufoil C, Ducimetriere P, Alperovicht A, for the EVA Study Group: Cognitive decline in individuals with high blood pressure. A longitudinal study in the elderly. Neurology 1999;53:1948–1952.
15 Di Bari M, Pahor M, Franse LV, Shorr RI, Wan JY, Ferrucci L, Somes GW, Applegate WB: Dementia and disability outcomes in large hypertension trials: lessons learned from the Systolic Hypertension in the Elderly Program (SHEP) trial. Am J Epidemiol 2001;153:72–78.
16 Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, Bulpitt CJ, de Leeuw PW, Dollery CT, Fletcher AE, Forette F, Leonetti G, Nachev C, O'Brien ET, Rosenfeld J, Rodicio JL, Tuomilehto J, Zanchetti A: Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet 1997;350:757–764.
17 Thijs L, Staessen JA, Beleva S, Birkenhager WH, Bulpitt CJ, Celis H, Fletcher AE, Kermova R, Leonetti G, Laks T, Mantov S, Nachev C, Sarti C, Tuomilehto J, Fagard RH, on behalf of the Systolic Hypertension in Europe Investigators: How well can blood pressure be controlled? Progress report on the Systolic Hypertension in Europe Follow-Up Study (Syst-Eur 2). Curr Control Trials Cardiovasc Med 2001;2:298–306.
18 Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, Chalmers J, PROGRESS Collaborative Group: Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med 2003;163:1069–1075.
19 Dufouil C, Chalmers J, Coskun O, Besancon V, Bousser MG, Guillon P, MacMahon S, Mazoyer B, Neal B, Woodward M, Tzourio-Mazoyer N, Tzourio C, PROGRESS MRI Substudy Investigators: Effects of blood pressure lowering on cerebral white matter hyperintensities in patients with stroke. The PROGRESS MRI substudy. Stroke 2005;112:1644–1650.
20 Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P, Zanchetti A: The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens 2003;21:875–886.
21 Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998;351:1755–1762.
22 Prospective Studies Collaboration: Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. Lancet 1995;346:1647–1653.
23 Randomised trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–1389.
24 Plehn JF, Davis BR, Sacks FM, Rouleau JL, Pfeffer MA, Bernstein V, Cuddy TE, Moyé LA, Piller LB, Rutherford J, Simpson LM, Braunwald E: Reduction of stroke incidence after myocardial infarction with pravastatin: The Cholesterol and Recurrent Events (CARE) Study. The Care Investigators. Circulation 1999;99:216–223.
25 The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group: Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349–1357.
26 Collins R, Armitage J, Parish S, Sleight P, Peto R, Heart Protection Study Collaborative Group: Effect of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20,536 people with cerebrovascular disease or other high-risk conditions. Lancet 2004;363:757–767.
27 Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG, PROSPER Study Group, PROspective Study of Pravastatin in the Elderly at Risk: Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623–1630.
28 The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHATLLT). JAMA 2002;288:2998–3007.
29 The Kyushu Lipid Intervention Study Group: Pravastatin use and risk of coronary events and cerebral infarction in Japanese men with moderate hypercholesterolemia: the Kyushu Lipid Intervention Study. J Atheroscler Thromb 2000;7:110–121.

30 Athyros VG, Papageorgiou AA, Mercouris BR, Athyrou VV, Symeonidis AN, Basayannis EO, Demitriadis DS, Kontopoulos AG: Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention: the Greek Atorvastatin and Coronary-Heart-Disease Evaluation (GREACE) Study. Curr Med Res Opin 2002; 18:220–228.
31 Amarenco P, Lavallée, Touboul PJ: Stroke prevention, blood cholesterol, and statins. Lancet Neurol 2004;3:271–278.
32 Cholesterol Treatment Trialists' (CTT) Collaborators: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005; 366:1267–1278.
33 Rockwood K, Darvesh S: The risk of dementia in relation to statins and other lipid lowering agents. Neurol Res 2003;25:601–604.
34 Rea TD, Breitner JC, Psaty BM, Fitzpatrick AL, Lopez OL, Newman AB, Hazzard WR, Zandi PP, Burke GL, Lyketsos CG, Bernick C, Kuller LH: Statin use and the risk of incident dementia: the Cardiovascular Health Study. Arch Neurol 2005;62:1047–1051.
35 Sorrentino G, Kanfer JN: Relationship between amyloid β peptide, cholesterol and statins. Recent Res Dev Biochem 2004;5: 157–172.
36 Wolozin B, Kellman W, Rousseau P, Celesia GG, Siegel G: Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. Arch Neurol 2000;57:1439–1443.
37 Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA: Statins and the risk of dementia. Lancet 2000;356:1627–1631.
38 Naidu A, Xu Q, Catalano R, Cordell B: Secretion of apolipoprotein E by brain glia requires protein prenylation and is suppressed by statins. Brain Res 2002;958:100–111.
39 Fassbender K, Simons M, Bergmann C, Stroick M, Lutjohann D, Keller P, Runz H, Kuhl S, Bertsch T, von Bergmann K, Hennerici M, Beyreuther K, Hartmann T: Simvastatin strongly reduces levels of Alzheimer's diseases beta-amyloid peptides Abeta 42 and Abeta 40 in vitro and in vivo. Proc Natl Acad Sci USA 2001;98:5856–5861.
40 Kojro E, Gimpl G, Lammich S, Marz W, Fahrenholz F: Low cholesterol stimulates the nonamyloidogenic pathway by its effect on the alpha-seceretase ADAM 10. Proc Natl Acad Sci USA 2001;98:5815–5820.
41 Pasquier F: Diabetes mellitus and dementia. Diabetes Metab 2006;32:403–414.
42 Mooradian AD: Central nervous system complication of diabetes mellitus: a prospective from the blood-brain barrier. Brain Res Brain Res Rev 1997;23:210–218.
43 Wong TY, Klein R, Sharrett AR, Nieto FJ, Boland LL, Couper DJ, Mosley TH, Kleim BE, Hubbard LD, Szklo M: Retinal microvascular abnormalities and cognitive impairment in middle-aged persons. The Atherosclerosis Risk in Communities Study. Stroke 2002;33: 1487–1492.
44 Meneilly GS, Cheung E, Tessier D, Yakura C, Tuokko H: The effect of improved glycaemic control on cognitive functions in the elderly patients with diabetes. J Gerontol 1993;48: 117–121.
45 Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet 2000;355:253–259.
46 McIlroy SP, Dynan KB, Lawson JT, Patterson CC, Passmore AP: Moderately elevated plasma homocysteine, methylenetetrahydrofolate reductase genotype, and risk for stroke, vascular dementia and Alzheimer disease in Northern Ireland. Stroke 2002;33:2351–2356.
47 Quadri P, Fragiacomo C, Pezzati R, Zanda E, Forloni G, Tettamanti M, Lucca U: Homocysteine, folate, and vitamine B_{12} in mild cognitive impairment, Alzheimer disease and vascular dementia. Am J Clin Nutr 2004; 80:114–122.
48 Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, Wilson PW, Wolf PA: Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 2002;346:476–483.
49 Luchsinger JA, Tang MX, Shea S, Miller J, Green R, Mayeux R: Plasma homocysteine levels and risk of Alzheimer's disease. Neurology 2004;62:1972–1976.
50 Snowdon DA, Tully CL, Smith CD, Riley KP, Markersbery WR: Serum folate and the severity of atrophy of the neocortex in Alzheimer disease: findings from the Nun study. Am J Clin Nutr 2000;71:993–998.
51 Ellinson M, Thomas J, Patterson A: A critical evaluation of the relationship between serum vitamin B, folate and total homocysteine with cognitive impairment in the elderly. J Hum Nutr Diet 2004;17:371–383.
52 Malouf M, Grimley EJ, Areosa SA: Folic acid with or without vitamin B_{12} for cognition and dementia. Cochrane Database Syst Rev 2003;4:CD004514.
53 Gorelick PB: Stroke prevention therapy beyond antithrombotics: unifying mechanisms in ischaemic stroke pathogenesis and implications for therapy. Stroke 2002;33: 862–875.
54 Collaborative overview of randomized trials of antiplatelet therapy. 1. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. BMJ 1994;308:81–106.
55 Harbison JW: Ticlopidine versus aspirin for the prevention of recurrent stroke: analysis of patients with minor stroke from Ticlopidine Aspirin Stroke Study. Stroke 1992;23: 1723–1727.
56 A randomized, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996;348:1329–1339.
57 Sturmer T, Glynn RJ, Field TS, Taylor Jo, Hennekens CH: Aspirin use and cognitive function in the elderly. Am J Epidemiol 1996; 143:683–691.
58 Richards M, Meade TW, Peart S, Brennan PJ, Mann AH: Is there any evidence for a protective effect of antithrombotic medication on cognitive function in men at risk of cardiovascular disease? Some preliminary findings. J Neurol Neurosurg Psychiatry 1997;62: 269–272.
59 Meyer JS, Rogers RL, McClintic K, Mortel KF, Lofti J: Randomized clinical trial of daily aspirin therapy in multi-infarct dementia. A pilot study. J Am Geriatr Soc 1989;37:549–555.
60 Voko Z, Bots ML, Hofman A, Koudstaal PJ, Witteman JC, Breteler MM: J-shaped relation between blood pressure and stroke in treated hypertensives. Hypertension 1999; 34:1181–1185.