SAGE-Hindawi Access to Research
Cardiology Research and Practice
Volume 2011, Article ID 250970, 7 pages
doi:10.4061/2011/250970

Review Article

Cardiovascular Prevention of Cognitive Decline

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Received 8 September 2010; Accepted 23 December 2010

Academic Editor: Christina Chrysohoou

Midlife cardiovascular risk factors, including diabetes, hypertension, dyslipemia, and an unhealthy lifestyle, have been linked to subsequent incidence, delay of onset, and progression rate of Alzheimer disease and vascular dementia. Conversely, optimal treatment of cardiovascular risk factors prevents and slows down age-related cognitive disorders. The impact of antihypertensive therapy on cognitive outcome in patients with hypertension was assessed in large trials which demonstrated a reduction in progression of MRI white matter hyperintensities, in cognitive decline and in incidence of dementia. Large-scale database correlated statin use and reduction in the incidence of dementia, mainly in patients with documented atherosclerosis, but clinical trials failed to reach similar conclusions. Whether a multitargeted intervention would substantially improve protection, quality of life, and reduce medical cost expenditures in patients with lower risk profile has not been ascertained. This would require appropriately designed trials targeting large populations and focusing on cognitive decline as a primary outcome endpoint.

1. Introduction

As a result of the increased life expectancy, the proportion of older people with cognitive impairment increases continuously. Alzheimer disease, which affects about 35 million people worldwide today, is estimated to afflict more than 100 million people by 2050 [1–3]. Amnestic mild cognitive impairment is found in about 20% of people older than 85 years with a conversion rate to Alzheimer disease of 10%–15% per year [4]. As a consequence, management of patients with cognitive disorders is quite common in daily cardiology practice. More recently, several studies have highlighted the deleterious role of cardiovascular risk factors on the incidence and progression of cognitive disorders in elderly people. This endorses the potential protection provided by therapeutic cardiovascular risk control.

2. Vascular Dementia and Alzheimer Disease

Besides Alzheimer disease, which account for about 60%–80% of cases of dementia in the elderly, vascular dementia has been increasingly recognized over the past decades as a late consequence of previous symptomatic [5] or clinically silent [6] stroke in patients with cerebrovascular disease, multifocal atherosclerosis, and cardiovascular risk factors. The spectrum of vascular dementia has subsequently expanded to include patients without stroke past history in whom brain magnetic resonance imaging (MRI) showed subcortical lesions such as white matter hyperintensities (Figure 1), lacunar infarctions and/or microhemorrhages [7]. Similar MRI lesions were also found in patients with cardiovascular risk factors only, especially hypertension [8, 9], and, paradoxically, in patients with Alzheimer disease. In addition, several studies showed that a past history of stroke or cerebral microinfarcts were associated with an increased risk of subsequent Alzheimer disease, its early onset and/or its accelerated clinical progression rate [10–14]. Consistent with these findings, pathological examinations revealed cerebral damages belonging to both forms of dementia in some instances, for example, coexisting senile plaques and neurofibrillary tangles with vascular lesions [15]. Furthermore, pathways common to progression of

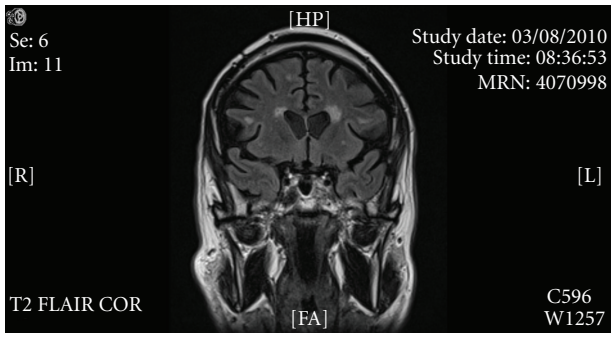

Figure 1: Periventricular and subcortical white matter hyperintensities. MRI, T2-weighted sequence, flair.

both diseases were also reported [16]. Finally, epidemiological studies demonstrated a correlation between late life occurrence of Alzheimer disease and the presence of midlife hypertension or cardiovascular risk factors [17, 18].

Accordingly, the diagnosis of vascular dementia, as defined using specifically selected clinical criteria only [23] has turned to a revisited framework in which vascular dementia and Alzheimer disease interplay with each other. Their incidence, the delay after which they appear, and their progression rate are promoted by cardiovascular risk factors [24]. As a result, control of cardiovascular risk factor may delay onset and slow down progression of cognitive disorders in elderly.

3. Diabetes

Cognitive disorders are observed with an increased prevalence among diabetics who suffered previous stroke [25]. In the *Honolulu-Asia Aging Study* (HAAS), a cardiovascular risk factor study initiated in 1965, cognitive function and brain MRI were assessed between 2004 and 2006 in 3734 survivors with regards to the presence of type 2 diabetes (38% of the population). Subjects with diabetes type 2 or impaired glucose tolerance have an increased risk of cerebral lacunes (odds ratio, OR: 1.6), hippocampal atrophy (OR: 1.7), and microinfarcts (OR: 1.9). The prevalence of either vascular dementia or Alzheimer disease with cardiovascular disease was 5.4% in diabetics and 2.9% and 2.5% in nondiabetics, respectively [26].

Although cognitive disorders are common in older diabetics, they develop slowly. They are limited to mild cognitive disorders in most patients for many years before more severe manifestations occur [35].

Several mechanisms have been advocate.

(i) Hyperinsulinemia: after crossing the blood brain barrier, insulin competes in the brain with amyloid β for insulin degradising enzyme, a pathway which is enhanced in patients with the apolipoprotein APOE-ε4 allele [36]. Conversely, rosiglitazone reduces progression of cognitive impairment and Alzheimer disease in diabetics by decreasing insulin blood levels and insulin resistance [37].

(ii) Advanced glycosylation end products (AGEs) resulting from glucose intolerance accumulate in senile plaque and neurofibrillary tangles. This pathway is enhanced by amyloid β binding to membrane AGEs receptors and further neuronal injury [36].

4. Hypertension

Large-scale epidemiological cohort studies initiated 4 decades ago correlated midlife hypertension to late life cognitive impairment. Among 392 aged survivors of the *NHLBI Twin study*, prevalence of dementia and white matter hyperintensities was higher in subjects whose blood pressure was increased at the follow-up visit in 1970, 1980, and 1985 [38]. Similar correlations between midlife hypertension and late life prevalence of dementia and/or extent of white matter hyperintensities were found in several other longitudinal follow-up studies [39–41].

Among 226 participants of *PROGRESS* (Perindopril Protection against Recurrent Stroke Study) in whom brain MRI was performed, the extent of white matter hyperintensities predicted development of dementia during followup: the relative risk increased from 1.6 (0.4–6) in patients with mild to moderate lesions to 7.7 (2.1–28.6) in patients with severe lesions [41]. Progression of white matter hyperintensities over time is increased in patients with either systolic or diastolic elevated blood pressure [40–42]. A similar relationship between midlife systolic or diastolic blood pressure levels and subsequent hippocampal volume reduction was observed in the *Honolulu-Asia Aging Study* [43].

The impact of antihypertensive therapy on cognitive impairment in patients with high blood pressure (HBP) was assessed in several trials. *SCOPE* (Study on Cognition and Prognosis in the Elderly) included 4964 patients with mild hypertension ($160 < \text{SBP} < 179$ mmHg; $90 < \text{DBP} < 99$ mmHg), aged 70 to 89 years and Mini Mental State Examination (MMSE) score ≥ 24. Double-blind treatment consisted of candesartan or placebo. Open label therapy was added to control blood pressure. Blood pressure reduction was significantly higher in patients receiving candesartan (21.7/10.8 mmHg) than in controls (18.5/9.2 mmHg), resulting in a decreased stroke incidence after a 3.7 years followup (-23.6%). There were no significant differences in MMSE scores between intervention and control group [44]. However, when patients were stratified according to baseline MMSE score, the incidence of dementia was higher among those with a low cognitive function ($24 < \text{MMSE} < 28$) when compared with those with a preserved cognitive function ($\text{MMSE} > 28$). Among patients with a low baseline cognitive function, the MMSE score declined less in the candesartan group (mean difference 0.49, $P = .04$). Of note, patients with a low baseline cognitive function were older and had more cardiovascular risk factors [45].

Although designed to include cognitive function in the assessment of benefits of antihypertensive therapy in elderly, *HYVET* (Hypertension in the Very elderly Trial) failed to reach definite conclusions about this specific issue. Indeed, the trial was stopped early after 2.2 years because

treatment resulted in a reduction in stroke and total mortality. This double-blind, placebo-controlled trial enrolled 3336 patients aged 80 years or more with hypertension (160 < SBP < 200 mmHg; DBP < 110 mmHg). Patients received inda-pamide (1.5 mg daily) ± perindopril (2–4 mg daily) or placebo. Although blood pressure was lower in the intervention group, the difference in dementia incidence rate was not statistically different between patients receiving therapy and controls (33 versus 38 per 1000 patients-years). However, when the authors combined their data in a meta-analysis with other placebo-controlled trials of antihypertensive treatment, results reached statistical significance [46].

Two other trials, PROGRESS and SYST-EUR, provided convincing data on the protection of cognitive decline in older patients treated with antihypertensive agents.

PROGRESS (Perindopril Protection against recurrent Stroke Study) included 6105 patients (mean age: 64 years) with previous stroke or transient cerebral ischemic attack and assessed incidence of (vascular) dementia and cognitive decline (MMSE score reduction >2) with regards to therapy consisting of either perindopril/indapamide or placebo. After a 3.9-year mean followup, treatment reduced the incidence of dementia by 12%, of cognitive decline by 19% and of a combination of cognitive decline or recurrent stroke by 34% [47]. A substudy compared baseline and followup brain MRIs in 192 patients to assess progression of white matter hyperintensities in patients receiving therapy and in controls. Whereas the extent of baseline white matter hyperintensities was similar in both groups, new hyperintensities appeared in 16% of controls and 9% of patients receiving therapy. Although these changes were not statistically significant, the mean total volume of new white matter hyperintensities was reduced in the treatment group (0.4 versus 2 mm^3, $P = .012$) [48].

Whereas *PROGRESS* by selecting patients with cerebrovascular disease targeted the impact of antihypertensive therapy on vascular dementia mainly, *SYST-EUR* (Systolic Hypertension in Europe) was intended to include a broad population, consisting of patients > 60 years with systolic hypertension (160 < SBP < 219 mmHg; DBP < 95 mmHg). The initial double-blind trial randomized 579 patients with either nitrendipine (10–40 mg daily), completed by enalapril (5–20 mg daily) and hydrochlorothiazide (12.5–25 mg daily) if required to control BP or placebo [49]. After a 2-year followup, the trial was continued on the basis of an open-label active treatment study in which a total of 2902 patients received therapy. After a mean follow up of 3.9 years, blood pressure control, though improved, remained suboptimal in the control group ($156 \pm 12/82.5 \pm 6$ versus $149 \pm 9.7/79 \pm 6$ mmHg at the last follow up visit), in connection with fewer patients receiving antihypertensive drugs (nitrendipine: 48.1% versus 70.2%; enalapril: 26.4% versus 35.4%; hydrochlorothiazide: 11.4% versus 18.4%). This was associated with a decreased incidence of dementia in the intervention group when compared with the control group (dementia all causes: 3.3 versus 7.4 per 1000 patient-year; Alzheimer disease: 1.9 versus 5 per 1000 patient-year; mixed or vascular dementia: 1.1 versus 2.1 per 1000 patient-year) [50].

5. Hyperlipemia

Although increased levels of total and LDL-cholesterol are associated with cardiovascular risk, atherosclerosis, and vascular dementia, similar correlations failed to be demonstrated with the incidence of Alzheimer disease [51]. However, Helzner et al. showed that both parameters are correlated with Alzheimer disease progression, each 10 mG/dL decrease in either being associated with a 0.10-SD decrease in cognitive score per year of followup [52].

Large-scale database correlated statin use and reduction in the incidence of dementia. Using the US Veteran Affairs database which collected information on approximately 4.5 million subjects and 110 million prescription annually, Wolozin et al. showed a strong reduction in the incidence of dementia in patients receiving simvastatin (HR = 0.46), a moderate reduction in those receiving atorvastatin (HR = 0.91), whereas no change was observed among patients treated with lovastatin [53]. Similar results were obtained using a nested case-control study on 309 patients with Alzheimer disease at the US Veteran Affairs Medical Center of Birmingham between 1997 and 2002. Patients treated with statins had a 39% lower risk of Alzheimer disease related to nonstatin users. Of note, this association was observed in patients with ischemic heart disease, cerebrovascular disease, or hypertension but not among those without any of these conditions [54]. Conversely, data from the specialized register of the Cochrane dementia and cognitive improvement group, which analyzed the 2 double-blind, randomized, placebo-controlled trials *HPS* and *PROSPER*, failed to reach similar conclusions. Indeed, among the 5804 patients aged 70 to 82 years included in *PROSPER*, there was no difference in cognitive performance nor in incidence of dementia between pravastatin treated and placebo group. Also, no difference in incidence of dementia or in cognitive performance tests decline was noted in *HPS*, in which 5806 patients over 70 years received simvastatin or placebo [55].

Thus, although several epidemiological and clinical trials provided evidence and a rationale basis for a preventive role of statins in Alzheimer disease [56], one should also argue that many others showed that this benefit was limited to patients with cerebrovascular, coronary artery disease, or hypertension.

6. Diet and Physical Activity

A lower level of physical performance in ageing adults is associated with an increased risk of dementia. In a prospective cohort study of 2288 people 65 years and older with a 6-years followup, Wang et al. observed an age-specific incidence rate of dementia, reaching 53.1 per 1000 person-year for participants who scored lower on a performance-based physical function test at baseline compared with 17.4 per 1000 person-years for those who scored higher. These impairments in physical function, which are interconnected with onset of cognitive decline, occur during the early, subclinical, stage of the disease. Conversely, a higher level of physical function is associated with a delayed onset of Alzheimer disease [57].

Table 1: Age-dependent prevalence of dementia (%) in selected populations.

	Population	Criteria	Disease	65–69 yrs	70–74 yrs	75–79 yrs	80–85 yrs	>85 yrs
Hofmanet al. [19]	12 European surveys	clinical		1.4	4.1	5.7	13	21.6
Ritchie and Kildea [20]	9 US and European surveys	clinical		1.5	3.5	6.8	13.6	22.3
Anstey et al. [21]	Australia	MMSE		3.78	5.16	10.6	16.3	22.3
Dong et al. [22]	China	clinical	AD (w/m)	0.5/0.3	1.8/0.9	4.4/2.3	11/3.8	23.4/10.6
Dong et al. [22]	China	clinical	VD (w/m)	2/0.9	2/0.4	1.9/0.6	1.1/1.8	0.4/0

AD: Alzheimer disease. VD: vascular dementia w/m: women/men.

Table 2: Prevalence of dementia (clinical criteria) in people aged > 65 years.

	Country	Prevalence rate (%)
Fitzpatrick et al. [27]	USA	6.3
Graham et al. [28], Hébert et al. [29]	Canada	5.3
Berr et al. [30], Riedel-Heller et al. [31]	15 European countries (EURODEM)	5.9
Lobo et al. [32]	Spain	5.2
Nitriniet al. [33]	6 countries, South America	7.1
Kalaria et al. [34]	India	3.4
Dong et al. [22], Kalaria et al. [34]	China	3.1

Several studies have shown that a healthy lifestyle, including diet and exercise training, may prevent cognitive decline in the elderly. Their results migh however have been biased by confounding factors such as educational and socioeconomic status and the impact of diet and exercise on cardiovascular risk factors. These drawbacks were not supported by recent studies suggesting that diet and exercise prevent and slow down dementia independently of such confounding factors.

The *WHICAP* (Washington Heights-Inwood Columbia Aging Project) cohort study enrolled 1880 Medicare beneficiaries in Northern Manhattan in 1991. Food consumption, a Mediterranean-type diet adherence score and a physical activity score were documented. Neuropsychological tests were repeated every 18 months from inclusion through 2006. Dementia developed in 282 subjects. Patients adhering to the Mediterranean-type diet and participating to physical activities with the highest scores have a lower risk of subsequent Alzheimer disease in a model adjusted for age, sex, ethnicity, education, apolipoprotein E genotype, caloric intake, body mass index, smoking status, leisure activities, and a comorbid index [58].

Similar results were obtained among 1410 participants included in the Bordeaux cohort study. After a 5-year followup, higher adherence to the Mediterranean-type diet was associated with a slower MMSE cognitive decline [59].

7. Risk Profiles for Dementia

7.1. Multifactorial Prevention. Although numerous studies have linked cardiovascular risk factors profile to subsequent incidence of dementia, most interventions to prevent cognitive decline were performed on a single risk factor control basis. Whether multifactorial prevention will provide substantially improved protection has not been ascertained, especially in patients with a lower risk profile.

Targeting high-risk patients for cardiovascular prevention of vascular dementia and Alzheimer disease requires assessment of aggregation of cardiovascular risk factors and detection of subclinical atherosclerosis in individuals.

In a cohort-study of 1270 dementia-free subjects aged 75 years or more, Qiu et al. scored cardiovascular risk factors at baseline and tracked incident dementia during a 9-year followup. A twofold increased risk for dementia (428 subjects including 328 with Alzheimer disease) was observed in subjects with an atherosclerotic profile (systolic BP > 160 mmHg or diabetes or previous stroke) and cerebral hypoperfusion (diastolic BP < 70 mmHg or pulse pressure <70 mmHg, or heart failure) [60]. Similarly, de la Torre suggested that detection of subclinical atherosclerosis and carotid plaques using carotid artery ultrasound may identify patients at increased risk for subsequent cognitive impairment, thereby allowing reinforced preventive control of cardiovascular risk factors, a strategy which may ultimately reduce the incidence of dementia [61]. Whether translating such an approach to lower risk patients would be clinically relevant remains to be ascertained using appropriately designed trials targeting large populations and focusing on cognitive decline as primary outcome endpoints [62].

7.2. Age-Related Risk. Although prevalence and incidence of Alzheimer disease increase with age, further increase after the age 90 has been questioned, as approximately half of the centenarians (43%) did not experience dementia [63]. In addition, pathological studies also showed that the distribution pattern of neurofibrillary tangles, senile plaque, microvascular impairment, and neuronal loss changes in extreme aging relative to the younger old [64]. As a result, the benefits expected from cardiovascular prevention of cognitive disorders in the oldest-old and centenarians may be more limited than in younger old.

7.3. Risk Control Across Populations. The benefit of cardiovascular risk factors control in preventing cognitive disorders

among elderly may also largely vary across populations living in different geographical areas.

Dementia prevalence rates among people over 65 years ranges from 3% to 11%, depending on diagnosis criteria (clinical, mostly DSM III, or MMSE-guided), age (Table 1), and countries (Tables 1 and 2). However, age-related increases in prevalence are observed independently of the population studied (Table 1), with limited differences in prevalence across populations and geographical areas (Table 2).

The burden of cardiovascular risk factors and its impact on vascular dementia have also been reported to increase with age in patients in western countries [29, 65–67]. Concomitantly, population-based surveys complemented by data from *MONICA* and *INTERSALT* showed a linear association of systolic blood pressure with age in men and women aged 30 to 70 years. This program, which encompassed 230 surveys and over 660 000 participants worldwide showed that age-related increase in blood pressure is observed in all WHO subregions populations [68].

Although this may argue for some rationale for expecting similar results from cardiovascular prevention of cognitive decline among different populations, including in developing countries, trials to support such hypotheses remain to be performed.

8. Conclusion

Optimal treatment of cardiovascular risk factors prevents and decreases progression of vascular dementia and Alzheimer disease. As a 5-year delay in the onset of Alzheimer disease could reduce the prevalence of Alzheimer disease by 50%, epidemiological forecasting estimate about 25% of the 5-fold increases in prevalence of dementia expected to occur until 2050 could effectively be prevented by optimal cardiovascular risk factors control [3, 61].

Thus, facing the worldwide burden of cardiovascular risk factors in a population growing in weight and in age continuously, slowing the incidence and progression of dementia may be a valuable challenge for cardiovascular prevention and cardiology practice. As life expectancy is expected to increase further in the decades to follow, limiting its age-related counterparts such as Alzheimer disease may also be relevant in an individual perspective as well as in a community opportunity to reduce medical cost-expenditures.

Conflicts of Interest

The authors declare that there is no conflicts of interest.

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