ELSEVIER

Alzheimer's & Dementia 7 (2011) 436–444

Alzheimer's & Dementia

Intracranial atherosclerosis as a contributing factor to Alzheimer's disease dementia

Alex E. Roher[a,*], Suzanne L. Tyas[b,c], Chera L. Maarouf[a], Ian D. Daugs[a], Tyler A. Kokjohn[a,d], Mark R. Emmerling[a], Zsolt Garami[e], Marek Belohlavek[f], Marwan N. Sabbagh[g], Lucia I. Sue[h], Thomas G. Beach[h]

[a]*The Longtine Center for Neurodegenerative Biochemistry, Banner Sun Health Research Institute, Sun City, AZ, USA*
[b]*Department of Health Studies and Gerontology, University of Waterloo, Waterloo, Ontario, Canada*
[c]*Department of Psychology, University of Waterloo, Waterloo, Ontario, Canada*
[d]*Department of Microbiology, Midwestern University, Glendale, AZ, USA*
[e]*Transcranial Doppler Center, Methodist DeBakey Heart and Vascular Center, The Methodist Hospital, Houston, TX, USA*
[f]*Translational Ultrasound Research Laboratory, Division of Cardiovascular Diseases, Mayo Clinic, Scottsdale, AZ, USA*
[g]*Cleo Roberts Center for Clinical Research, Banner Sun Health Research Institute, Sun City, AZ, USA*
[h]*Harold Civin Laboratory of Neuropathology, Banner Sun Health Research Institute, Sun City, AZ, USA*

Abstract

Background: A substantial body of evidence collected from epidemiologic, correlative, and experimental studies strongly associates atherosclerotic vascular disease (AVD) with Alzheimer's disease (AD). Depending on the precise interrelationship between AVD and AD, systematic application of interventions used to maintain vascular health and function as a component of standard AD therapy offers the prospect of mitigating the presently inexorable course of dementia. To assess this hypothesis, it is vital to rigorously establish the measures of AVD that are most strongly associated with an AD diagnosis.

Methods: A precise neuropathological diagnosis was established for all subjects, using a battery of genetic, clinical, and histological methods. The severity of atherosclerosis in the circle of Willis was quantified by direct digitized measurement of arterial occlusion in postmortem specimens and was compared between AD and nondemented control groups by calculating a corresponding index of occlusion.

Results: Atherosclerotic occlusion of the circle of Willis arteries was more extensive in the AD group than in the nondemented control group. Statistically significant differences were also observed between control and AD groups with regard to Braak stage, total plaque score, total neurofibrillary tangle score, total white matter rarefaction score, brain weight, Mini-Mental State Examination scores, and apolipoprotein E allelic frequencies.

Conclusions: Our results, combined with a consideration of the multifaceted effects of impaired cerebral circulation, suggest an immediate need for prospective clinical trials to assess the efficacy of AD prevention using antiatherosclerotic agents.

© 2011 The Alzheimer's Association. All rights reserved.

Keywords: Alzheimer's disease; Vascular dementia; Intracranial atherosclerosis; Circle of Willis; Brain hypoperfusion

1. Introduction

Genetic investigations suggest that the amyloid-beta (Aβ) peptide has a central role in Alzheimer's disease (AD). However, genetically determined familial AD is rare, whereas sporadic AD is the most common form of this dementia. Approximately 25 years after the Aβ molecule had been identified as a potential therapeutic target, the exact cause(s) of AD dementia remains undefined. For the foreseeable future, the standard pharmacologic treatments are virtually palliative, offering only steadily diminishing functional maintenance without any hope of cure.

*Corresponding author. Tel.: 623-876-5465; Fax: 623-876-5698.
E-mail address: alex.roher@bannerhealth.com

1552-5260/$ - see front matter © 2011 The Alzheimer's Association. All rights reserved.
doi:10.1016/j.jalz.2010.08.228

AD may result from the combined and chronic, cascading effects of multiple systemic diseases, such as cardiovascular, immune/inflammatory, endocrine, and ultimately a dysfunctional energy metabolism of the brain, affecting the elderly population. In the recent past, a broad body of evidence derived from epidemiologic, correlative, and experimental studies has strongly linked atherosclerotic vascular disease (AVD) with AD [1]. Postmortem studies have recently shown that individuals with AD have significantly more atherosclerotic narrowing of the intracranial arteries [1–5].

Despite the epidemiological and neuropathological evidence, the question of whether intracranial AVD has a significant causal role in AD pathogenesis still remains unanswered, although there are data consistent with causation. Because atherosclerosis generally begins much earlier in life as compared with AD, the temporal relationship suggests that AVD may cause or accelerate AD, rather than the reverse. Results from several longitudinal life-history studies have shown that elevated AVD risk factors in midlife are associated with increased AD risk in old age [6–9]. Individuals with higher cholesterol levels at midlife have a higher risk of developing AD, and patients with clinically or neuropathologically diagnosed AD have higher cholesterol levels compared with nondemented control (NDC) individuals [8,10–12]. There is also considerable evidence from experimental studies suggestive of a causative effect for increased blood cholesterol. The production of Aβ precursor protein (APP) and the Aβ peptide, the main biochemical AD marker, in cell culture and animal models is regulated by cholesterol and decreased by cholesterol-lowering drugs such as statins, and some molecular mechanisms have been proposed for these interactions [13]. However, the independent association of AD with multiple AVD risk factors suggests that cholesterol is not the sole culprit in dementia.

It seems improbable that hypercholesterolemia, hypertension, diabetes, hyperhomocysteinemia, tobacco smoking, and other AVD risk factors would produce pathology through completely separate molecular mechanisms. A common mechanism may be hypoperfusion. The circulatory system is preeminent in the development of the brain and the maintenance of its vital functions. Thus, any pathology that impedes circulation, including the normal age-related decline in cardiovascular function and its increasing inability to adapt and repair, is deleterious. Consequently, the importance of recognizing the interrelationship between cardiovascular disease and brain perfusion in AD cannot be overstated.

Ischemic brain disease is the generic designation for a group of closely related syndromes resulting from a disparity between the supply (perfusion) and demand imposed by the brain for oxygenated blood. In addition, it involves reduced availability of nutrient substrates and ineffective removal of CO_2 and noxious metabolites. It has been established that hypoperfusion or chronic oligemia could induce cortical atrophy through slow starvation of brain parenchyma [14]. Intracranial atherosclerosis is a major cause of brain hypoperfusion and stroke. Furthermore, infarcts are present in approximately 40% of subjects with AD and their presence has been shown to significantly increase the likelihood of dementia in subjects harboring both infarcts and AD histopathology [15–18].

The reports by ourselves and others [1–5] of increased intracranial AVD in AD indicate that stenosis of the arteries supplying the brain may be at least partially responsible for reduced cerebral perfusion in AD. Possible molecular mechanisms linking AD pathology and hypoperfusion include ischemia-induced alterations in APP expression and APP cleavage [19], both of which increase Aβ production. In addition, brain ischemia induces the production of hypoxia inducible factor that increases the production of β-secretase and increases Aβ levels [20]. An even simpler hypothesis is that decreased cortical perfusion may reduce Aβ clearance from brain to the blood, analogous to the declining clearance of blood urea to urine with decreased renal perfusion, for example, in congestive heart failure.

It is evident that cardiovascular disease and AD are likely to have a synergistic effect on dementia [21]. This statement is made with a strong caveat that although the statistical linkage between AD and intracranial AVD is significant, it is clear that AVD is not a precondition for the development of AD. The existence of cases of AD with very little AVD, and of very old NDC individuals with severe AVD, demonstrates that the association is not invariant.

AVD arises from the complex interactions of genetic and environmental factors [22,23]. However, some of the complications of AVD are largely preventable by lifestyle modification and pharmacological manipulation [24], suggesting that AD may be at least partially preventable by similar methods. Furthermore, even if AD and AVD are only coincidentally related, about one-half of AD cases have significant contributory AVD that impairs cognition through ischemia and/or hypoxia and infarction in an additive manner [15–17]. On this basis alone, the systematic application of AVD prevention as a component of standard AD therapy should reduce functional impairment and decline in AD. If AVD is synergistic or convergent with AD [21], by accelerating disease onset and cognitive decline, then AVD therapy will have a correspondingly greater clinical effect on AD patients.

The clinical utility of a causal link between AD and AVD can only be definitively established by prospective clinical prevention trials using antiatherosclerotic agents. Postmortem evaluation of the circle of Willis (CW) and major cerebral arteries seeks to establish the groundwork for such trials by revealing those AVD measures most strongly associated with the diagnosis of AD. In the present study, we compared the degree of CW atherosclerosis between AD and NDC individuals by rigorously measuring the index of occlusion in postmortem specimens. In addition, the functional repercussions of arterial stenosis on brain hemodynamics and hydrodynamics are discussed in this study.

2. Methods

2.1. Human specimens

CW specimens were collected at Banner Sun Health Research Institute, a private, nonprofit organization located in Sun City, Arizona. Volunteers for the Brain Donation Program received annual neurological and psychological assessments, as well as apolipoprotein E (*APOE*) genotyping [25]. All CW arteries were removed in the immediate postmortem, rinsed with phosphate buffer, fixed in 10% paraformaldehyde for 7 days, and stored at 4°C in phosphate buffer with 0.01% sodium azide until the time of analysis. For this study, we measured the CW arteries from 36 NDC and 61 AD cases.

2.2. Neuropathological diagnosis

For neurodegenerative diseases, the neuropathologic diagnosis was made as outlined in a published algorithm [26]. Cases with dementia were rated for AD changes according to National Institute on Aging/Reagan Institute [27] and the Consortium to Establish a Registry for Alzheimer's Disease criteria [28], and by Braak stage [29]. The diagnosis of AD was made when a National Institute on Aging/Reagan Institute rating of "high" or "intermediate" was given to a subject clinically diagnosed with dementia.

The average values for age, gender, Braak stage, total amyloid plaque score, total neurofibrillary tangle (NFT) score, total white matter rarefaction (WMR) score, brain weight, and the last Mini-Mental State Examination (MMSE) score as well as *APOE* allelic frequency are summarized in Table 1. The assessment of Braak stage, total amyloid plaque score, total NFT score, total WMR score, and MMSE procedure has been described previously [2].

Table 1
Characteristics of NDC and AD subjects

Characteristic	NDC (n = 36)	AD (n = 61)
	%	
Women	50	57
*APOE**†		
2/2	2.8	0.0
2/3	16.7	5.0
3/3	55.6	58.3
3/4	25.0	30.0
4/4	0.0	6.7
Braak stage*		
I	8.3	0.0
II	25.0	4.9
III	50.0	11.5
IV	16.7	14.8
V	0.0	34.4
VI	0.0	34.4
	Mean (SD)	
Age (years)	84.9 (6.1)	85.1 (7.3)
Total plaque score*	5.5 (4.3)	12.6 (1.9)
Total NFT score*	4.1 (2.3)	11.0 (4.3)
Total WMR score*‡	2.3 (3.1)	5.1 (4.0)
Brain weight*, grams	1175 (108.0)	1061 (145.9)
Last MMSE score*§	28 (1.8)	10 (7.6)
CW index of occlusion*	51.6 (7.5)	58.9 (12.5)

Abbreviations: NDC, nondemented control; AD, Alzheimer's disease; *APOE,* apolipoprotein E; NFT, neurofibrillary tangle; WMR, white matter rarefaction; MMSE = mini-mental state examination; CW, circle of Willis.

Total plaque, total NFT, and total WMR scores are based on 0 to 15. Each of the four cerebral lobes plus the hippocampus is scored from 0 to 3, where 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Braak stage ranges from 0 to VI, according to the increasing regional distribution of the NFT in the brain. The MMSE (range: 0–30) assesses cognitive function, with decreasing scores reflecting lower cognitive performance.

*$P < .001$; all other differences between NDC and AD subjects are not significant ($P > .05$).

†Sample size is 96 (n = 36 NDC, n = 60 AD).

‡Sample size is 94 (n = 34 NDC, n = 60 AD).

§Sample size is 66 (n = 26 NDC, n = 40 AD).

2.3. Measurement of the index of occlusion

Digital photographs of the intact vessels were taken before dissection. The arteries included in this study were right and left vertebral arteries (VA), basilar artery (BA), right and left posterior cerebral arteries (PCA), right and left middle cerebral arteries (MCA), right and left internal carotid arteries (ICA) and right and left anterior cerebral arteries (ACA). All arteries were cut into approximately 5-mm cross-sections and examined under a Leica S8APO (Leica Microsystems, Heerbrugg, Switzerland) dissecting microscope, and the point of minimum cross-sectional lumenal area in each arterial segment was selected for morphometric assessment. A total of 2108 cross-sections were measured. The segments were photographed with an Optronics Magnafire SP camera and software program (Optronics, Goleta, CA). Measurements of the cross-sectional external and lumenal areas were taken from the digital photographs with the calibrated ImagePro Express, v. 4.0 software (Media Cybernetics, Silver Spring, MD). By definition, the arterial wall structure includes the intima, media, and adventitia layers, whereas the arterial external and lumenal areas were obtained by subtracting the area bound by the intima from that calculated for the complete circumference of the outer limit of the adventitia as shown in the Fig. 1A inset. The measurements of these areas, reported in mm^2, were exported to an Excel database spreadsheet (Microsoft, Redmond, WA). Because there is a wide variation in arterial size, an index of occlusion (stenosis) was calculated for each cross-section by subtracting the lumenal area from the external area, dividing the difference by the external area, and multiplying the quotient with 100.

2.4. Medical history assessments

In all, 4 years of private medical records were generally available for each subject, with 2-year histories obtained at the time of program initiation and 2 more years requested at the time of death. We reviewed the medical records of the subjects and recorded the presence or absence of

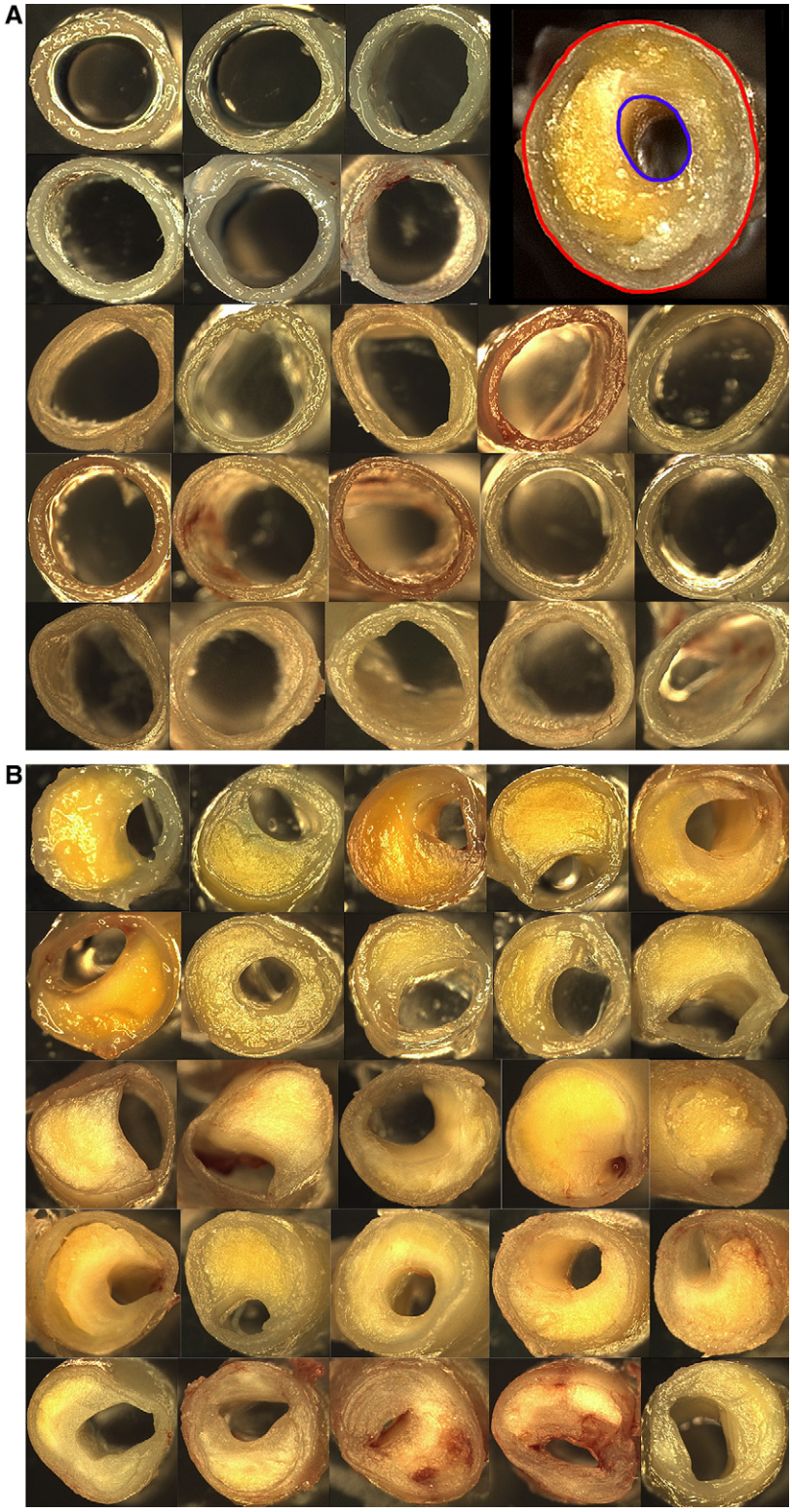


Fig. 1. Representative cross-sections of the circle of Willis arteries. The top panel (A) illustrates a series of arterial sections in which the lumenal area is minimally reduced. The inset indicates the external area (red) and luminal area (blue) that were manually encircled. The area was calculated automatically with ImagePro Express, v 4.0 software and an index of occlusion was derived from these numbers. The bottom panel (B) shows arteries with severe atherosclerosis. In some cases, the arteries are almost completely occluded by the atheroma plaque.

clinically related cardiovascular ailments or interventions, risk factors for AVD, respiratory diseases, and other relevant comorbidities (Table 2).

2.5. Statistical analysis

The association of cognitive status group with subject characteristics, comorbidities, and index of occlusion was analyzed using Fisher's exact chi-square tests and unpaired, two-tailed *t*-tests with Satterthwaite's unequal variance assumption. Multiple logistic regression models were used to examine stenosis as a predictor of AD, and were adjusted for the covariates age, gender, and *APOE* ε4 allele status. Standard lacks of fit and regression diagnostics (residual and collinearity tests) were assessed. Analyses were conducted with SAS software, version 9.1 (SAS Institute Inc., Cary, NC).

3. Results

No significant differences existed between the NDC and AD groups with respect to age or gender (Table 1). However, statistically significant differences were found between these groups for the average CW index of occlusion as well as *APOE* genotype, Braak stage, total plaque score, total NFT score, total WMR score, brain weight, and MMSE score. Because we consider AD as a multifactorial disease that is closely related to the natural decay of multiple systems associated with aging, we reviewed the prevalence of several relevant cardiovascular, respiratory, and other comorbidities in the NDC and AD groups (Table 2). Of the extensive list of comorbidities, only renal disease, cancer, osteoporosis, and dysfunctions of rhythm and conduction differed significantly between the two groups, with these comorbidities more common in NDC subjects. For reasons that are not well understood, previous studies have demonstrated that AD individuals seem to be protected against oncological diseases [30]. The data discussed earlier in the text emphasize the large number of maladies and their complex interactions related to vital functions that alter the blood and oxygen supply to the brain or disrupt its metabolism. Ultimately, the effect of these diseases on the prevention, pathogenesis, or course of AD would reflect their age of onset, intensity of the pathology, combination of morbidities, and their timely and adequate pharmacological or surgical management.

Table 2
Comorbidities of NDC and AD subjects

Comorbidity (%)	NDC (n = 36)	AD (n = 61)
Coronary artery disease	36	36
Angina	11	3
Stent, angioplasty or CABG	14	11
Carotid artery disease	11	3
Valvular diseases	11	7
Myocardial infarction	8	15
Congestive heart failure	33	16
Left ventricular hypertrophy	14	8
Dysfunctions of rhythm and conduction*	61	23
Peripheral vascular disease	8	7
Hyperlipidemia	31	18
Hypertension	64	48
Transient ischemic attack	17	13
Syncope	8	8
Stroke, hemorrhage or embolism	19	28
Diabetes mellitus	19	16
Peripheral neuropathy	17	5
Renal disease*	31	8
COPD	33	18
Emphysema	8	2
Asthma	8	5
Pulmonary embolism	6	2
Severe head trauma	3	7
Cancer*	56	30
Osteoporosis*	28	10
Hypothyroidism	25	30

Abbreviations: NDC, nondemented control; AD, Alzheimer's disease; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease.

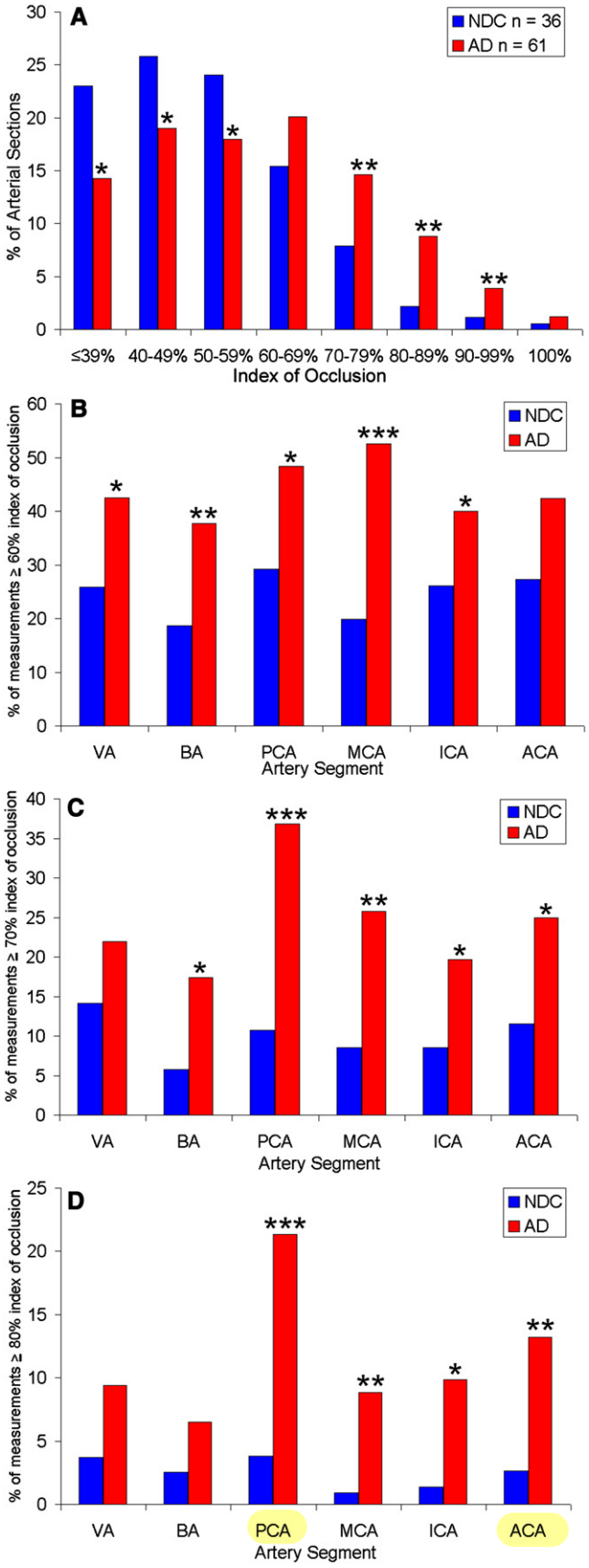
*Difference between NDC and AD subjects significant at $P < .05$.

Disease duration did not correlate with the average index of occlusion, percentage of sections that showed ≥60% occlusion, ≥70% occlusion, or ≥80% occlusion (data not shown, $R^2 = 0.17$, 0.17, 0.17, and 0.19, respectively).

Arteries of the CW were more severely occluded by atherosclerotic lesions in the AD group than in the NDC group. A graphic representative example of the magnitude of CW atherosclerosis in AD subjects is illustrated in Fig. 1. Fig. 2A shows the percentage of all arterial measurements taken along the Y-axis and the index of occlusion, in deciles, along the x-axis. For example, the proportion of cross-sectional measurements with the lowest index of occlusion (≤39%) was 23% in the NDC group as compared with 14% in the AD group. The histogram illustrates the gross differences in the degree of atherosclerosis between the control and affected cohorts. Significant differences exist at all levels of occlusion except at those at 60% to 69%. Subjects with AD who had less than 60% to 69% occlusion are significantly less likely to be found in these categories of lower occlusion, whereas those with more than 60% to 69% occlusion are significantly more likely to be found in these categories of higher occlusion. The 60% to 69% occlusion level appears to be a transition point between these patterns and thus shows no significant differences.

In the AD group, an average of 48% of arterial sections showed ≥60% occlusion, 29% showed ≥70% occlusion, and 14% showed ≥80% occlusion. In contrast, the corresponding percentages for the NDC group for the identical index of occlusion were 27%, 12%, and 4%. Comparisons at all three occlusion extent percentiles (≥60%, ≥70%, ≥80%) between AD and NDC groups revealed statistically significant differences at $P < .0001$. The index of occlusion of individual major intracranial arteries (VA, BA, PCA, MCA, ICA, and ACA) differed significantly between the NDC and AD groups, with greater stenosis in AD subjects (Figs. 2B–D).

Multivariate logistic regression models also support an association between stenosis in the CW arteries and the



likelihood of AD, even after adjusting for the effects of age, gender, and *APOE* ε4 (Table 3). Higher levels of stenosis were more likely in subjects with AD as compared with NDC subjects (for all arteries combined, the odds ratio = 1.06; i.e., 6% change per 1-unit increase in index of occlusion). When considering the entire population under study, the mean index of occlusion ranged from 33% (lowest) to 84% (highest); there would thus be a 51-unit or 306% (three-fold) increase in likelihood of AD from the lowest to the highest levels of stenosis. This number is similar to the odds ratios from carrying one *APOE* ε4 allele and agrees with our previous observations using semi-quantitative atherosclerotic scoring on a much larger sample [1]. This association was also significant for specific CW arteries, such as BA, ICA, MCA, and PCA. On assessment of the percentage of the arterial sections that showed ≥60% occlusion, again there were significant associations observed with both individual arteries and all arteries combined.

The index of occlusion for carriers of an *APOE* ε4 allele was compared to noncarriers for each diagnosis group. There was no statistically significant difference between carriers and noncarriers within the AD or NDC group (data not shown; $P > .05$, unpaired, two-tailed *t*-test). These results are similar to those that were found in other studies [1,5,31].

4. Discussion

Atherosclerosis of the CW and major cerebral arteries is almost universal after 80 years of age. It is more severe in men than in women at the age of 60, with the male predominance decreasing with age and finally disappearing by the age of 80 [32]. When compared with NDC individuals, our multivariate regression models clearly indicate a link between the degree of atherosclerosis of the CW and AD (adjusted odds ratio = 1.06 [95% CI = 1.02–1.11, $P = .006$]). Overall, an index of occlusion >60% is more frequent in AD cases than in NDC, whereas a larger number of arterial segments with a lower index of occlusion (<60%) is more abundant in the NDC group. Significant differences were also found between AD and NDC in many individual arteries, with the frequency and degree of occlusion more severe in AD.

The presence of severe atherosclerotic lesions in major cerebral arteries can obstruct the ostia or invade the lumina of important secondary branches which supply vital brain regions [4,33,34], such as the hippocampal arteries

Fig. 2. (A) The *y*-axis represents of the percentage of all arterial measurements taken. The index of occlusion, separated in deciles, is along the *x*-axis. The index of occlusion was also higher in the individual arteries of subjects with AD as compared with NDC subjects when separating by the percentage of measurements ≥60% (B), 70% (C), and 80% (D) index of occlusion. NDC, nondemented control; AD, Alzheimer's disease; VA, vertebral arteries; BA, basilar artery; PCA, posterior cerebral arteries; MCA, middle cerebral arteries; ICA, intracranial arteries; ACA, anterior cerebral arteries. $*P < .05$, $**P < .01$, $***P < .001$.

Table 3
Association of occlusion with AD

Measure of occlusion	n (NDC/AD)	Adjusted* OR	*P*
Mean index of occlusion			
ACA	36/60	1.03	.065
BA	35/60	1.05	.015
ICA	36/60	1.05	.014
MCA	36/60	1.06	.003
PCA	35/60	1.04	.0099
VA	31/49	1.04	.052
All arteries	36/60	1.06	.006
Percentage of sections			
≥60% occluded			
ACA	36/60	1.01	.101
BA	35/60	1.02	.018
ICA	36/60	1.01	.084
MCA	36/60	1.03	.0003
PCA	35/60	1.01	.027
VA	31/49	1.02	.022
All arteries	36/60	1.03	.002

Abbreviations: NDC, nondemented control; AD, Alzheimer's disease; ACA, anterior cerebral arteries; BA, basilar artery; ICA, internal carotid arteries; MCA, middle cerebral arteries; PCA, posterior cerebral arteries; VA, vertebral arteries.

*Models were adjusted for age at death, gender, and presence of an apolipoprotein E ε4 allele. In this multivariate analysis, the maximum possible sample size for the AD group is 60 because of the absence of apolipoprotein E genotyping of one individual.

arising from the PCA [35], which are the most affected arteries in our study (Figs. 2C and D). Likewise, occlusion of the small anterior perforating branches originating from the ACA that supply the cholinergic nucleus basalis of Meynert [36] would have dire consequences for both cognition and cholinergic/nitric oxide-mediated vasodilatation of the cerebral arteries. Metabolic and electrophysiological functions decline and eventually fail in cases with a chronic, progressive regional decrease of blood flow [37]. Moreover, lacunar infarcts result from perforating artery obstruction triggered by cardiac disease, atherosclerosis, and hypertension [38] and play a role in modifying the clinical expression of AD, as shown by the Nun Study [17]. In addition, hypoxic/ischemic conditions can result in a gross disruption of the integrity of the blood–brain barrier and bleeding [39,40]. It has been suggested that microhemorrhages may induce a localized, beneficial cerebrovascular amyloidosis in an attempt to patch up the ruptured capillary and arteriolar walls [41,42]. However, the global, untargeted deposition of amyloid in the walls of capillaries, arterioles and small arteries in the cerebral cortex and leptomeningeal vessels, characteristic of AD may represent the ultimate pathological consequence of brain ischemia and hypoxia.

The normal arterial tree is morphologically and functionally designed as both a conduit and cushion. Failure to cushion systolic pulsation because of stiffening of the arterial wall results in larger amplitude of intracranial blood beating and microvasculature damage [43,44], and consequent shedding of endothelial cells, myocyte damage, blood–brain barrier failure, and vessel rupture [45]. In general, accumulating diffuse microangiopathic disease promotes increased vascular resistance [46–48] escalating hypertension and impaired venous outflow [43,49].

In addition to declining brain perfusion, the loss of arterial elasticity from atherosclerosis, arteriosclerosis, and calcification has ominous hemodynamic and hydrodynamic cerebrospinal fluid (CSF) consequences for the maintenance of brain homeostasis. Magnetic resonance phase imaging has demonstrated that when an arterial pulse wave enters the rigid cranium, the force propagates perpendicular to the skull surface, resulting in an immediate increase in CSF pressure which will be offset by the rigidity of the calvarium, propelling the CSF through the tentorial notch and foramen magnum into the spinal canal. The pulsatile movements result in arterial expansion and concomitant enlargement of brain volume assisted by systolic capillary dilation and venous and subarachnoid space engorgement. Recoil of CSF from the spinal canal into the subarachnoid space of the brain occurs during diastole [50,51]. Dilation of the brain ventricles in AD correlates with the degree of cerebral blood flow impingement created by advanced atherosclerotic and arteriosclerotic lesions. Increased resistance in the CSF and cerebral vessels may also impair venous drainage and further contribute to a decrease in the cerebral blood flow [52]. Furthermore, the microvascular pulsations also impel the drainage of the brain's interstitial fluid (IF) along the perivascular spaces that drain into the deep lymphatics of head and cervical venous circulation [53,54]. Clogging of the perivascular spaces in the cerebral cortex by amyloid deposition results in the stagnation of the IF in the white matter with dilation of the periarterial spaces (état criblé) and overflow into the ventricular space [55]. In this loop of detrimental events, decreased velocity of cerebral blood flow in the arteries of the brain may ultimately be a result of reduced metabolic demands of the brain [56].

In summary, mechanical obstruction and reduction in cerebral arterial inflow because of atherosclerotic lesions damages the microvasculature, eventually leading to severe brain hypoxia, leukoariosis, lacunar infarcts, brain atrophy, ventricular dilation, retention of IF, and accumulation of noxious substrates [57,58]. The cumulative effects of these interdependent hemodynamic and hydrodynamic dysfunctions play a pivotal role in accelerating and augmenting the pathogenesis and evolution of AD [59].

Preventative therapies for both AVD and AD would be most efficacious if implemented before the development of clinically evident AVD. For this reason, systematic, preemptive diagnostic studies involving lipid screenings, hemodynamic imaging, and ultrasound studies should be a routine aspect of patient assessment to enable early recognition of impending AD. It has been recently found that timely treatment of vascular risk factors slows the decline in the progression of AD [60]. For example, several clinical trials suggest that aggressive intervention with statins leads to a reduction of low-density lipoprotein cholesterol and regression of

coronary atherosclerosis as measured by intravascular ultrasound [61,62]. In contrast, evidence exists from retrospective clinical trials that statins, when given late in life, offer no prevention of dementia or benefit of amelioration [63]. However, this disappointing result must be balanced with a caveat that these trials were performed on elderly patients exhibiting clinically evident mild to moderate AD. At this stage, the virtually universal presence of advanced atherosclerotic/calcification damage and permanent brain injury may have precluded any hope for clinically meaningful beneficial effects. Therefore, it is imperative that statin therapies commence before the establishment of advanced AVD and any appearance of brain lesions associated with AD. In addition, statins may have other important contributory factors to the reduction of atherosclerosis through their antithrombotic, vasodilatory antihypertensive, and antimitotic effects [64]. The predictive strength of a family history and preclinical evidence of AVD must also be considered as critical rationalizations for the recommendation of intense pharmacological intervention, lifestyle and dietary modifications, as well as the adoption of disciplined exercise regimens to preempt the development of dementia. Systematic implementation of educational campaigns promoting radical changes in cultural and societal values will be important factors in the adoption of proactive AD-defeating strategies by patients in a broad sense. In addition, such actions may provide potentially huge dividends by preventing both cardiovascular disease and dementia.

Acknowledgments

This work was in part supported by Science Foundation Arizona, the Arizona Department of Health Services (Contract 211002 Arizona Alzheimer Disease Research Consortium), the National Institute on Aging (R01-AG19795 and R01-NS38674), the Arizona Alzheimer's Disease Core Center (P30 AG-19610) and the Prescott Family Initiative of the Michael J. Fox Foundation for Parkinson's Research. The authors thank Dr. Douglas Walker for *APOE* genotyping and to Drs. Walter M. Kalback, Dean C. Luehrs, and R. Lyle Patton for helpful discussions. Dr. Marwan N. Sabbagh received grant/clinical trial support from Baxter, Lilly, Wyeth, Avid, BMS, Medivation, and Elan. Dr. Sabbagh is a consultant for Lilly, Wyeth, Glaxo Smith Kline, and Amerisciences. The rest of the authors involved in this project declare no competing interests.

References

[1] Beach TG, Wilson JR, Sue LI, Newell A, Poston M, Cisneros R, et al. Circle of Willis atherosclerosis: association with Alzheimer's disease, neuritic plaques and neurofibrillary tangles. Acta Neuropathol 2007; 113:13–21.

[2] Roher AE, Esh C, Kokjohn TA, Kalback W, Luehrs DC, Seward JD, et al. Circle of Willis atherosclerosis is a risk factor for sporadic Alzheimer's disease. Arterioscler Thromb Vasc Biol 2003;23:2055–62.

[3] Kalback W, Esh C, Castano EM, Rahman A, Kokjohn T, Luehrs DC, et al. Atherosclerosis, vascular amyloidosis and brain hypoperfusion in the pathogenesis of sporadic Alzheimer's disease. Neurol Res 2004; 26:525–39.

[4] Roher AE, Esh C, Rahman A, Kokjohn TA, Beach TG. Atherosclerosis of cerebral arteries in Alzheimer disease. Stroke 2004;35:2623–7.

[5] Honig LS, Kukull W, Mayeux R. Atherosclerosis and AD: analysis of data from the US National Alzheimer's Coordinating Center. Neurology 2005;64:494–500.

[6] Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging 2000;21:49–55.

[7] Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology 2001;56:42–8.

[8] Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ 2001; 322:1447–51.

[9] Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kareholt I, Winblad B, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol 2005; 62:1556–60.

[10] Kalmijn S, Launer LJ, Ott A, Witteman JC, Hofman A, Breteler MM. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann Neurol 1997;42:776–82.

[11] Notkola IL, Sulkava R, Pekkanen J, Erkinjuntti T, Ehnholm C, Kivinen P, et al. Serum total cholesterol, apolipoprotein E epsilon 4 allele, and Alzheimer's disease. Neuroepidemiology 1998;17:14–20.

[12] Kuo YM, Emmerling MR, Bisgaier CL, Essenburg AD, Lampert HC, Drumm D, et al. Elevated low-density lipoprotein in Alzheimer's disease correlates with brain abeta 1-42 levels. Biochem Biophys Res Commun 1998;252:711–5.

[13] Wolozin B, Brown J III, Theisler C, Silberman S. The cellular biochemistry of cholesterol and statins: insights into the pathophysiology and therapy of Alzheimer's disease. CNS Drug Rev 2004; 10:127–46.

[14] Caroli A, Testa C, Geroldi C, Nobili F, Guerra UP, Bonetti M, et al. Brain perfusion correlates of medial temporal lobe atrophy and white matter hyperintensities in mild cognitive impairment. J Neurol 2007; 254:1000–8.

[15] Schneider JA, Wilson RS, Bienias JL, Evans DA, Bennett DA. Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology. Neurology 2004;62:1148–55.

[16] Petrovitch H, Ross GW, Steinhorn SC, Abbott RD, Markesbery W, Davis D, et al. AD lesions and infarcts in demented and non-demented Japanese-American men. Ann Neurol 2005;57:98–103.

[17] Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA 1997;277:813–7.

[18] Jellinger KA. Alzheimer disease and cerebrovascular pathology: an update. J Neural Transm 2002;109:813–36.

[19] Bennett SA, Pappas BA, Stevens WD, Davidson CM, Fortin T, Chen J. Cleavage of amyloid precursor protein elicited by chronic cerebral hypoperfusion. Neurobiol Aging 2000;21:207–14.

[20] Zhang X, Zhou K, Wang R, Cui J, Lipton SA, Liao FF, et al. Hypoxia-inducible factor 1alpha (HIF-1alpha)-mediated hypoxia increases BACE1 expression and beta-amyloid generation. J Biol Chem 2007; 282:10873–80.

[21] Casserly I, Topol E. Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. Lancet 2004;363:1139–46.

[22] Ding K, Kullo IJ. Genome-wide association studies for atherosclerotic vascular disease and its risk factors. Circ Cardiovasc Genet 2009; 2:63–72.

[23] Lotta LA. Genome-wide association studies in atherothrombosis. Eur J Intern Med 2010;21:74–8.

[24] Zaiou M, Benachour H, Marteau JB, Visvikis-Siest S, Siest G. Genomics and the prospects of existing and emerging therapeutics for cardiovascular diseases. Curr Pharm Des 2009;15:3193–206.
[25] Beach TG, Sue LI, Walker DG, Roher AE, Lue L, Vedders L, et al. The Sun Health Research Institute Brain Donation Program: description and experience, 1987-2007. Cell Tissue Bank 2008;9:229–45.
[26] Dickson DW. Required techniques and useful molecular markers in the neuropathologic diagnosis of neurodegenerative diseases. Acta Neuropathol 2005;109:14–24.
[27] Hyman BT, Trojanowski JQ. Consensus recommendations for the postmortem diagnosis of Alzheimer disease from the National Institute on Aging and the Reagan Institute Working Group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. J Neuropathol Exp Neurol 1997;56:1095–7.
[28] Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 1991;41:479–86.
[29] Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991;82:239–59.
[30] Roe CM, Behrens MI, Xiong C, Miller JP, Morris JC. Alzheimer disease and cancer. Neurology 2005;64:895–8.
[31] Luoto TM, Haikonen S, Haapasalo H, Goebeler S, Huhtala H, Erkinjuntti T, et al. Large vessel cerebral atherosclerosis is not in direct association with neuropathological lesions of Alzheimer's disease. Eur Neurol 2009;62:93–8.
[32] Sawabe M, Arai T, Kasahara I, Hamamatsu A, Esaki Y, Nakahara K, et al. Sustained progression and loss of the gender-related difference in atherosclerosis in the very old: a pathological study of 1074 consecutive autopsy cases. Atherosclerosis 2006;186:374–9.
[33] Ostrow PT, Miller LL. Pathology of small artery disease. Adv Neurol 1993;62:93–123.
[34] Caplan LR. Intracranial branch atheromatous disease: a neglected, understudied, and underused concept. Neurology 1989;39:1246–50.
[35] Duvernoy HM. The human hippocampus: functional anatomy, vascularization and serial sections with MRI. 2nd ed. Berlin: Springer; 1998.
[36] Pullicino PM. The course and territories of cerebral small arteries. Adv Neurol 1993;62:11–39.
[37] Hossmann KA. The hypoxic brain. Insights from ischemia research. Adv Exp Med Biol 1999;474:155–69.
[38] Derouesne C, Poirier J. Cerebral lacunae: still under debate. Rev Neurol (Paris) 1999;155:823–31.
[39] Kaur C, Ling EA. Blood brain barrier in hypoxic-ischemic conditions. Curr Neurovasc Res 2008;5:71–81.
[40] Emmrich P, Hahn J, Ogunlade V, Geiger K, Schober R, Mohr FW. Neuropathological findings after cardiac surgery-retrospective study over 6 years. Z Kardiol 2003;92:925–37.
[41] Roher AE, Lowenson JD, Clarke S, Woods AS, Cotter RJ, Gowing E, et al. beta-Amyloid-(1-42) is a major component of cerebrovascular amyloid deposits: implications for the pathology of Alzheimer disease. Proc Natl Acad Sci U S A 1993;90:10836–40.
[42] Cullen KM, Kocsi Z, Stone J. Microvascular pathology in the aging human brain: evidence that senile plaques are sites of microhaemorrhages. Neurobiol Aging 2006;27:1786–96.
[43] Henry-Feugeas MC, Onen F, Claeys ES. Classifying late-onset dementia with MRI: is arteriosclerotic brain degeneration the most common cause of Alzheimer's syndrome? Clin Interv Aging 2008;3:187–99.
[44] Hirata K, Yaginuma T, O'Rourke MF, Kawakami M. Age-related changes in carotid artery flow and pressure pulses: possible implications for cerebral microvascular disease. Stroke 2006;37:2552–6.
[45] O'Rourke MF, Hashimoto J. Arterial stiffness: a modifiable cardiovascular risk factor? J Cardiopulm Rehabil Prev 2008;28:225–37.
[46] Biedert S, Forstl H, Hewer W. The value of transcranial Doppler sonography in the differential diagnosis of Alzheimer disease vs multi-infarct dementia. Mol Chem Neuropathol 1993;19:15–23.
[47] Lee KY, Sohn YH, Baik JS, Kim GW, Kim JS. Arterial pulsatility as an index of cerebral microangiopathy in diabetes. Stroke 2000; 31:1111–5.
[48] Kidwell CS, el-Saden S, Livshits Z, Martin NA, Glenn TC, Saver JL. Transcranial Doppler pulsatility indices as a measure of diffuse small-vessel disease. J Neuroimaging 2001;11:229–35.
[49] Henry-Feugeas MC. MRI of the 'Alzheimer syndrome'. J Neuroradiol 2007;34:220–7.
[50] Greitz D, Wirestam R, Franck A, Nordell B, Thomsen C, Stahlberg F. Pulsatile brain movement and associated hydrodynamics studied by magnetic resonance phase imaging. The Monro-Kellie doctrine revisited. Neuroradiology 1992;34:370–80.
[51] Stivaros SM, Jackson A. Changing concepts of cerebrospinal fluid hydrodynamics: role of phase-contrast magnetic resonance imaging and implications for cerebral microvascular disease. Neurotherapeutics 2007;4:511–22.
[52] Greitz T. Effect of brain distension on cerebral circulation. Lancet 1969;1:863–5.
[53] Weller RO, Subash M, Preston SD, Mazanti I, Carare RO. Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and Alzheimer's disease. Brain Pathol 2008;18:253–66.
[54] Weller RO, Djuanda E, Yow HY, Carare RO. Lymphatic drainage of the brain and the pathophysiology of neurological disease. Acta Neuropathol 2009;117:1–14.
[55] Roher AE, Kuo YM, Esh C, Knebel C, Weiss N, Kalback W, et al. Cortical and leptomeningeal cerebrovascular amyloid and white matter pathology in Alzheimer's disease. Mol Med 2003;9:112–22.
[56] Franceschi M, Alberoni M, Bressi S, Canal N, Comi G, Fazio F, et al. Correlations between cognitive impairment, middle cerebral artery flow velocity and cortical glucose metabolism in the early phase of Alzheimer's disease. Dementia 1995;6:32–8.
[57] Henry-Feugeas MC. Alzheimer's disease in late-life dementia: a minor toxic consequence of devastating cerebrovascular dysfunction. Med Hypotheses 2008;70:866–75.
[58] Weller RO, Massey A, Newman TA, Hutchings M, Kuo YM, Roher AE. Cerebral amyloid angiopathy: amyloid beta accumulates in putative interstitial fluid drainage pathways in Alzheimer's disease. Am J Pathol 1998;153:725–33.
[59] Schreiber SJ, Doepp F, Spruth E, Kopp UA, Valdueza JM. Ultrasonographic measurement of cerebral blood flow, cerebral circulation time and cerebral blood volume in vascular and Alzheimer's dementia. J Neurol 2005;252:1171–7.
[60] Deschaintre Y, Richard F, Leys D, Pasquier F. Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. Neurology 2009;73:674–80.
[61] Sipahi I, Nicholls SJ, Tuzcu EM, Nissen SE. Coronary atherosclerosis can regress with very intensive statin therapy. Cleve Clin J Med 2006; 73:937–44.
[62] Takayama T, Hiro T, Yamagishi M, Daida H, Hirayama A, Saito S, et al. Effect of rosuvastatin on coronary atheroma in stable coronary artery disease: multicenter coronary atherosclerosis study measuring effects of rosuvastatin using intravascular ultrasound in Japanese subjects (COSMOS). Circ J 2009;73:2110–7.
[63] McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. Cochrane Database Syst Rev 2009. CD003160.
[64] Sipahi I, Tuzcu EM. Candidate mechanisms for regression of coronary atherosclerosis with high-dose statins: insight from intravascular ultrasonography trials. Am J Cardiovasc Drugs 2008;8:365–71.