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Running Head: Atherosclerosis and Alzheimer's Disease

A Case Study Analysis of the Relationship Between Atherosclerosis and
Alzheimer's Disease

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Abstract

Several animal studies have brought the cholinergic hypothesis of Alzheimer's Disease (AD) into question. In addition, recent clinical studies have shown that the number of neuritic plaques and neurofibrillary tangles does not yield a conclusive diagnosis of AD. A reassessment of risk factors involved in AD development has led to findings that atherosclerosis is associated with dementia. The present study is a clinical analysis, through the use of case studies, of the relationship between atherosclerosis severity, based on autopsy results, and AD severity, based on scores from cognitive tests and functional assessments, as well as autopsy results. The age of AD onset as it relates to atherosclerosis has also been examined. The age of participants at AD onset occurring with atherosclerosis has been determined both through examination of medical records and interviews with family members. This is an ongoing study. Unfortunately, no results supporting a relationship between atherosclerosis and AD have yet been found; however, future results may indicate a relationship.

A Case Study Analysis of the Relationship Between Atherosclerosis and Alzheimer's Disease

Four million Americans are currently afflicted by Alzheimer's disease (AD), and due to an aging population, this number is expected to increase by 400% in 50 years. In the U.S., 10% of individuals aged 65 will develop AD, and 47% of those aged 85 or more will also develop the disease (de la Torre, 1997; Morrison-Bogorad, Creighton, & Phelps, 1997). In the general population, there is a 15% lifetime risk of developing AD (Post et al., 1997). Alzheimer's disease affects not only the lives of those diagnosed but also the lives of both the family and friends who provide care and support.

The onset of AD is typically marked by a decrease in ability to recall things such as minor appointments although these initial memory lapses are generally not noticed by family, friends, and co-workers. As the disease progresses, daily life and self care become impaired, and personality changes begin to occur. In the final stages of the disease, speech becomes limited to a single word and then nonexistent. Movement ability slowly decays until the patient can no longer hold up their head (Reisberg, 1988).

The basal forebrain is one of the major areas compromised in AD (Candy et al., 1983; Whitehouse, P., Price, D., Struble, R., Clarke, A., Coyle, J., DeLong, M., 1982). This brain region consists of the medial septal area (MSA), which sends projections to the hippocampus, and the nucleus basalis magnocellularis basalis (NMB), which sends projections to the cortex. As stated above, one of the first recognized impairments in AD is memory loss. Decline in memory is presumably associated with damage to the hippocampus. Often the first neuronal structure compromised in AD,

the hippocampus is involved in learning and memory (DeJong, R., 1969; Garcia, J., 1970; Thomas, G., 1971; Westerhof, P., 1972). Braak et al. have documented increasing damage to the hippocampus throughout the progressive stages of AD.

The nucleus basalis magnocellularis sends projections to both the amygdala and the cerebral cortex. As part of the limbic system, the amygdala plays an important role in emotional behavior. Therefore, destruction of this neuronal formation could account for changes of personality noted in AD patients during the later stages of the disease. The cerebral cortex, particularly the premotor and supplemental motor cortices of the frontal cortex, is involved in the planning and execution of movement (Carlson, 1994). Decline in these functions occurs throughout the progression of AD, as well.

The basal forebrain accounts for 80-95% of the acetylcholine (ACh) neurotransmitter in the brain (Dornan et al., 1996). As a result, with the destruction of the basal forebrain comes a depletion of the acetylcholine neurotransmitter. This finding has led to the development of the "cholinergic hypothesis." The hypothesis states that acetylcholine decrease, brought on by AD, leads to the cognitive deficits associated with Alzheimer's disease (W. A. Dornan, personal communication, March 1997).

Many researchers believe that the protein beta amyloid, found in neuritic plaques, is a primary factor contributing to AD neurodegeneration. Neuritic plaques (NP) consist of a central beta amyloid (AB) protein core surrounded by a cluster of dystrophic neurites and activated glial cells. Neurofibrillary tangles (NFT), of which tau protein is a major constituent, are also found consistently in brain regions affected by AD (Cotman and

Pike, 1994). The presence of neuritic plaques and neurofibrillary tangles are considered a neuropathological characteristic of AD. They are quantified at autopsy in order to make a definite diagnosis of AD. However, the criteria used for diagnosis with regards to location and quantity neuritic plaques and neurofibrillary tangles vary (Tierney, 1988).

Results from histological studies of beta amyloid have been consistent with the cholinergic hypothesis of AD discussed above. An *in vivo* study by Harknay, Jong et al. (1995) injected beta amyloid (1-42) into the medial septal area of rats and found that beta amyloid is selectively toxic to cholinergic neurons. GABAergic neurons, also at the injection site, showed only minor effects. GABAergic neurons in the medial septal area did exhibit some neuritic pruning following beta amyloid exposure, a neuronal reaction also observed in AD patients (Robakis, 1994).

Additional *in vivo* experiments involve beta amyloid injections into the nucleus basalis magnocellularis, hippocampus, or ventricles. Histological results of these studies are again consistent with the cholinergic hypothesis showing reduced acetylcholine release and reduced choline acetyltransferase and cholinesterase activity in the neural region exposed to beta amyloid when compared to controls (Abe, Casamenti, Giovannelli, Scali, Pepeu, 1994; Chen, Harding, Barnes, 1996; Dornan, Tinkler, Litwiller, Fan, Hanin, at press; Harknay, Lengyel et al., 1995; Itoh, Nitta et al., 1996; Maurice, Lockhart, Privat, 1995; Nitta, Itoh, Hasegawa, Nabeshima, 1994). Reduced acetylcholine release as well as reduced choline acetyltransferase and cholinesterase activity indicate degeneration of cholinergic terminals resulting from neurotoxic effects induced by beta amyloid. However, one study by Sigurdsson, Hejna, Lee,

and Lorens (1996) did not find that beta amyloid injections produced histological signs of toxicity in cholinergic neurons.

While histological results of beta amyloid testing are fairly consistent, behavioral results in studies of the cholinergic hypothesis do not yield the same consistency. Among the studies cited above that included animal behavioral testing, only three showed significant learning impairment (Itoh et al., 1996; Maurice et al., 1995; Nitta et al., 1994). The study by Dornan et al. (in press) resulted in only a marginal effect on spatial learning following beta amyloid injections, and the Sigurdsson et al. (1996) study did not find any behavioral affects. These studies indicate degeneration of cholinergic neurons following beta amyloid injection without also yielding the cognitive/learning impairments associated with AD. This suggests that the degeneration of cholinergic neurons may not be responsible for the clinical effects of AD and that the cholinergic hypothesis is either insufficient or incorrect.

The relationship between the severity of AD dementia and the quantity of neuritic plaques and neurofibrillary tangles in the brain is now being questioned as well. A study by Snowdon et al. in 1997, known as the "Nun Study" (the participants were all from The School of Sisters of the Notre Dame congregation), found that among women who met the neuropathological criteria for AD in terms of the number of neuritic plaques and neurofibrillary tangles in the brain at autopsy, 31% did not have prevalent dementia in life based on cognitive testing (Snowdon et al., 1997). A review by de la Torre states that the density of plaque and tangle formation in nondemented individuals increases as a function of age, and neuritic plaques and neurofibrillary tangles may be found in 100% of nondemented persons over 80 years old (de la Torre, 1997). The report

goes on to suggest that neuritic plaques and neurofibrillary tangles are products of a neurodegenerative process associated with both AD and also with normal aging to a lesser extent.

Based on the studies discussed above, a fresh look at the possible risk factors involved in AD development seems warranted. History of cardiovascular disease, stroke, or head trauma have all been implicated as risk factors (de la Torre, 1997). Also, a genetic/familial link has been found with late-onset AD. Mutations at 3 genes have been identified as AD risk factors: 1) beta-amyloid precursor protein (APP), 2) presenilin-2 (PS2) gene, and 3) presenilin-1 (PS1) gene (Lendon, Ashall, and Goate, 1997; Prince, Cullen, and Mann, 1994). The PS1 gene mutation is an exception to the familial late-onset generalization; the mean age of onset associated with PS1 is 46.8 years (Lopera et al., 1997). In addition, the apolipoprotein E4 allele (apoE 4) has been linked to AD (Evans et al., 1997; Gordon, Grauer, Genis, Sehayek, and Michaelson, 1995; Kosunen et al., 1995; Poirier et al., 1993).

Apolipoprotein E is a plasma protein that binds to the low-density lipoprotein (LDL) receptor. Lipoproteins are plasma proteins involved in transport of cholesterol and other lipids to and from cells. Low-density lipoproteins are rich in cholesterol and are therefore involved in the growth, repair, and maintenance of myelin and neuronal membranes following injury (Marieb, 1992; Mahley, 1988). By binding with low-density lipoprotein receptors, apoE acts to clear low-density lipoproteins from their binding sites. This redistributes the lipoproteins into the blood stream (Mahaley, 1988). ApoE mRNA plays an important role during central nervous system (CNS) sprouting and synaptogenesis. Messenger RNA is reduced in the hippocampus of AD patients, and in apoE deficient

mice hippocampal synapse density is reduced (Poirier, Davignon, et al., 1993). These mice also have diminished ability to regenerate synaptic connections following lesions to the hippocampus.

There are three apoE alleles (E2, E3, and E4) resulting in six apoE genotypes (E2/E2, E2/E3, E3/E3, E3/E4, and E4/E4). Of the apoE alleles, E2 has the lowest affinity for the low-density lipoprotein receptor, whereas E4 clears this receptor the most efficiently (Mahley, 1988). However, efficient clearing of cholesterol by apoE 4 could result in poor neuronal reinnervation following injury. Cells rely on cholesterol to build up membranes, and apoE 4 clears away needed cholesterol from the receptor too quickly for membrane rebuilding to occur satisfactorily. Thus, while apoE 4 may clear cholesterol most efficiently, it is also the least efficient in aiding reinnervation following trauma to the brain.

At the same time, because apoE 4 releases the high cholesterol lipoprotein from receptors and back in to the bloodstream at a higher rate, it causes an increase in plasma cholesterol. Increased cholesterol levels have been implicated in the development of atherosclerosis. Atherosclerosis is a thickening of the arterial walls causing them to protrude into the vessel lumen and possibly occlude the vessel entirely (Marieb, 1992).

The "response-to-injury" hypothesis is the most commonly accepted explanation for atherosclerosis development. This hypothesis states that an initial event occurs which causes damage to the *tunica intima*., the endothelial layer lining blood vessels. An initial event can be brought on by blood borne chemicals, viruses, or physical factors such as a blow to the head or hypertension. Injured endothelial cells of the *tunica intima* release chemotactic agents, and growth factors begin to transport greater

amounts of cholesterol picked up from the blood in an effort to repair cell damage. (This involves apoE, and apoE has been shown to upregulate in response to injury (Hall, Oostveen, Dunn, and Carter, 1995).) Monocytes cling to the sites of altered endothelial cells and then migrate beneath the surface of the tunica *intima* where they become macrophages. These macrophages are joined by smooth muscle cells which begin moving toward the *intima* layer from the *tunica media*. Both smooth muscle cells and macrophages begin accumulating cholesterol and take on the appearance of foam cells - the "fatty streak stage." It is at this stage that the excess plasma cholesterol resulting from apoE 4 is most detrimental (Marieb, 1992).

Muscle cells at the *intima* also deposit collagen and elastin fibers. These fibers thicken and harden the *tunica intima* producing lesions - atherosclerotic plaques. When fatty mounds of muscle and fibrous tissue begin to protrude into the lumen of the blood vessel, the individual has full-blown atherosclerosis. Eventually, arterial walls become frayed and ulcerated. These conditions encourage platelet adhesion and thrombus formation. Increased vessel rigidity leads to hypertension, increased risk of myocardial infarction, stroke, and aneurysm (Marieb, 1992).

Damage to blood vessels when apoE 4 is present might also lead to an increase in beta amyloid deposition along arterial walls. A study done by Hall et al. (1995) induced ischemic trauma for 10 minutes in the forebrains of gerbils. Beta amyloid protein and apoE activities were then followed in the hippocampus over a period of 7 days. After two days, a significant increase in both beta amyloid and apoE was recorded in the hippocampus (Hall et al., 1995). Results of other studies have shown that apoE 4 binds to beta amyloid leading to co-deposition of both apoE 4 and

beta amyloid at the cell (Strittmatter et al., 1993; Wizniewski, Golabek, Matsuhara, Ghiso, Frangione, 1993). It has been hypothesized that the upregulation of apoE in response to ischemic trauma together with the binding of apoE 4 and beta amyloid may provide favorable conditions for the formation of neuritic amyloid deposits . In additional studies, apoE 4 is associated with reduced cerebral glucose metabolism. This can lead to improper splitting of beta amyloid and, therefore, an increase in neuritic plaque formation (Mier-Ruge, Bertoni-Freddari, Iwangoff, 1994).

In his review article, de la Torre lists four primary changes seen in the capillary microanatomy of AD patients: 1) thickening of the vessel wall and the basement membrane, 2) intraluminal distortions produced by kinking or compression of the abluminal region, 3) endothelial cell compression with mitochondrial loss, and 4) amyloid deposition in vessel walls. Atherosclerosis pathology can lead to all four of these changes. Additionally, beta amyloid deposited along vessel walls interferes with the exchange of nutrients and wastes between capillaries and cells, and distorted lumens result in a disturbed blood flow pattern, also making exchange across the capillaries difficult. As mentioned above, reduction of oxygen and nutrients reaching the cells can lead to necrosis (cell death) as well as the build up of beta amyloid in cells resulting from a shortage of ATP necessary to properly split the beta-amyloid precursor protein (Mier-Ruge, Bertoni-Freddari, Iwangoff, 1994).

In a clinical study done by Hoffman et al. (1997), the frequency of AD and of vascular dementia was found to increase with the degree of atherosclerosis (mild, moderate, severe). In the conclusion of this study, it is stated that dementia, and in particular dementia of the AD and the vascular type, is associated with atherosclerosis. It is also concluded

that there is an interaction found in AD etiology between apoE and atherosclerosis (Hoffman et al., 1997). Another clinical study, this one by Kosunen et al. (1995), concluded that the apoE 4 allele is associated with coronary atherosclerosis in elderly AD patients. This study also states a lack of associative findings between the extent of coronary or cerebral atherosclerosis and counts of neuritic plaques. The study by Kosunen reinforces the Nun Study, which found that neuritic plaques sufficient for AD diagnosis did not necessarily coincide with AD dementia. Such findings lead to questions about the role of neuritic plaques in AD dementia just as animal tests investigating the role of acetylcholine in AD dementia have brought the cholinergic hypothesis into question.

New avenues must be explored for risk factors in AD. Atherosclerosis is found in association with several forms of dementia and a study of the relationship between severity of atherosclerosis and severity of AD dementia, regardless of the number of neuritic plaques found is warranted. This study assesses the severity of AD dementia in relation to severity of atherosclerosis in AD patients as well as the age of AD dementia onset when AD is found in association with atherosclerosis with the expectations that as severity of atherosclerosis increases, so does AD severity and that AD onset will be earlier when associated with atherosclerosis.

Methods

Participants

Alzheimer's disease can only be definitively diagnosed by postmortem examination of the brain; therefore, autopsy examination of participants at death is an integral part of this investigation, and brains

are procured from all participants who remain in the study. Consent for this procedure is given by legal next-of-kin upon entry into the study, and results from the brain autopsy are provided to the family free of charge. The present study is part of an ongoing research project beginning in 1996, and twenty-five participants are currently enrolled in this study. Eight are now deceased, and autopsy information is available for seven of these. Participants may withdraw from the study any time they wish.

This study is being conducted primarily in central Illinois, and, therefore, the majority of the participants live in that area. Overviews of the IWU brain donor program are given primarily at area hospitals, schools, nursing homes, etc. As a result, contact regarding participation is generally initiated by the family members of those diagnosed with possible or probable Alzheimer's dementia who have attended these talks. This also means that participants are diagnosed outside of the study by primary care physicians or neurologists. Many of the participants referred to this program are nursing home residents although some do still live at home.

Apparatus and Procedure

Several assessments of daily living (ADL's) scales as well as cognitive tests are given to all participants upon entry into the study. In addition, care givers are be asked to provide demographic information about participants, medical histories are gathered, and participants are assessed by a neuropsychologist for possible depressive disorders (which may skew cognitive data if present). Testing is split into two sessions, separated by a few days, and tests are administered where the participant resides, at the home or in a nursing home. The ADL's and cognitive tests

are re administered every six months. Cognitive testing may be dropped if the participant has progressed to severe dementia and is no longer able to complete these tests, but ADL's are still assessed.

During the first session, ADL's will be filled out by either the primary investigator (PI) or research assistants with the help of a care giver, professional or family. The participant is not required to be present at this time, particularly if discussion about progressing dementia and declining skill becomes upsetting. In all, seven ADL's are given, the Barthel ADL Index, the Brief Cognitive Rating Scale (BCRS), the Blessed Dementia Scale, the Clinical Dementia Rating (CDR Staging), the Functional Assessment Staging (FAST), the Global Deterioration Scale (GDS), and the Modified Rankin Scale (Blessed, G., Tomlinson, B., Roth, M., 1968; Chino, N., Melvin, J., 1996; Haycox, J., 1984; Reisberg, B., 1988; Reisberg, B., Ferris, S., de Leon, M., Crook, T., 1982; Reisburg, B., Schneck, M., Ferris, S., Schwartz, G., de Leon, M., 1983; Mahoney, R., Barthel, D., 1965). Also, the Hachinski Ischemic Score is determined by the PI in consultation with the primary physician or with medical history (Hachinski, V., Ilkff, L., Zilkha, E., 1957). The Hachinski is used to determine whether or not the patient has had any transient ischemic attacks in the past.

After the ADL's have been filled out, the Mini-Mental State Examination (MMSE) is administered (Folstein, M. Folstein, S., McHugh, P., 1975). Cognitive tests are administered by either the PI or by research assistants trained by neuropsychologists at Bromenn Regional Medical Center. Participants are told that they will be asked questions to test their memory. They are instructed that some of these questions are harder than others and that they are not expected to answer them all

correctly. Participants are then be asked if they agree to answer these questions. If they respond "yes," they are further instructed that the test may be halted at any time upon their request. MMSE testing lasts approximately ten minutes. If a participant becomes frustrated with a question, the researcher moves on to the next question, and if the participant is unable to complete the test, the reason is noted on the test sheet and the maximum incorrect score is given for questions not answered. Out of a total of thirty points, a score equal to or greater than twenty-four indicates very mild dementia, a score equal to or greater than twenty indicates mild dementia, a score of between ten and nineteen indicates moderate dementia, and a score between zero and nine indicates severe dementia.

Participants who score in the mild to moderate dementia range on the MMSE are scheduled for a second test. This is generally scheduled within a few days or weeks. The Alzheimer's Disease Assessment Scale (ADAS) is the second cognitive test given, and it is the most widely known and commonly accepted cognitive test for assessing AD (Mohs, R., Rosen, W., Davis, K., 1983). On the ADAS, a score of 0-5 is perfect (no dementia), 6-10 is average, 11-23 is mild, 24-35 is moderate, 36-49 is severe, and 50-70 is very severe. Because the ADAS is a longer and more complicated test, if a participant scores in the severe dementia range on the MMSE, the ADAS is not administered. Test instructions given to the participant and scoring procedures for a discontinued test are the same as above. Again, these tests are administered in either the participant's residence or nursing home by the PI or by research assistants. The ADAS takes approximately thirty minutes to complete.

At the time of death, either the nursing home or the family of the participant will contact the funeral home of the family's choice, the McLean County Coroner's Office, and the PI. Arrangements are then made for brain procurement. The funeral home generally transports the body to the McLean County Morgue, and brain procurement takes place no longer than six hours of death with the PI in attendance. Research assistants may also be present.

In addition to brain procurement, an initial assessment also takes place at the McLean County Morgue. The brain is then taken to the Loyola University School of Medicine where autopsy is performed. The brain is cut serially in a coronal fashion using a microtome. Sections one centimeter square are fixed in paraffin to be later stained using Multiple Luxol Fast Blue/H & E and also Bielschowsky silver. These stains are used for diagnostic purposes to reveal amyloid plaques, both diffuse and neuritic, in the cerebral cortex. A cryostat is also used to cut smaller sections of brain (40 microns) which will be frozen and used in future analysis.

Analysis

Blind to the autopsy results, participant data is separated into groups based on medical history as well as cognitive and functional test scores. Data is separated into two groups, probable AD in the absence of atherosclerosis or probable AD with atherosclerosis. Once participant records have been sorted into groups, researcher accuracy is tested by comparing these groups to autopsy reports.

Due to the as of yet small sample size (seven completed autopsy reports), meaningful statistical analysis is not possible. Instead, a case

study for each participant with an autopsy report available has been written. Demographic data, medical history, cognitive test scores, and final autopsy analysis is included. Qualitative analysis based on these seven cases has been conducted.

Results

Case One

This 86 year old white male (12/05/09 - 10/07/96) presented with memory problems that were becoming gradually worse in August of 1991 (at age 81). Based on a physical workup and an MMSE score in the moderate to severe range, a preliminary diagnosis of probable AD was made. Medical history indicates a recovery from cancer several years prior.

Patient had 12 years of education and worked as a general yard master for an oil refinery until his retirement at age 65. For the last 20 years of his life, he lived in a rural, nonfarm, geographic area. In 1996, he moved into a nursing home. The patient was married at the time of his death.

When he was diagnosed, the patient was not oriented to date or month. He could not spell "train" backwards; however, he could spell "box" backwards. Six months following the initial assessment, the patient began to show signs of language impairment. "[The patient] seems to search for words and has trouble finishing a thought." His language ability continued to deteriorate over the next few months. At this point, January 1993, the patient gave up driving.

In December of 1993, this patient was started on Cognex, a drug developed to help combat dementia. Five months later, the family reported noted improvements in the patient's cognition and the dosage was increased. However, a few months later family reported resumed cognitive deterioration. The patient continued on Cognex until April of 1995, including another dosage increase in January of that same year.

Until April of 1995, the patient's ability to care for himself, home hygiene and dressing, remained relatively stable. If his clothes were laid out for him, he could dress himself. By the spring of 1995, however, he could no longer dress himself. His language abilities had also deteriorated to "yes" or "no" responses in reply to questions asked of him. Patient was described as "very confused." Later, that year the patient began "sun-downing," this is when the sleep-wake cycle is disrupted. He would awaken in the evenings.

Between April, 1996 and June, 1996, patient was prescribed Haldol, an antipsychotic, for severe agitation. The patient was admitted to the hospital in June of 1996 with a fractured hip. Evidence of marked arteriosclerosis, a vascular disease, was also noted at this time. The patient died in October of this same year. Before his death, the patient's dementia had progressed to the severe level, with a score of 0/30 on the MMSE. He had lost all verbal abilities and was incontinent.

Brain procurement took place October 7, 1996, and the brain was taken to Loyola that same day. The brain weighed 1039 grams. Gross examination revealed mild focal atherosclerotic plaque in the internal carotid arteries. Mild to moderate atrophy was observed throughout the cerebral cortex. The amygdala was moderately atrophic bilaterally, while

the hippocampus showed moderate atrophy on the left and severe atrophy on the right.

Microscopic examination showed numerous amyloid plaques, both neuritic and diffuse, and neurofibrillary tangles in all cerebral cortical areas as well as the amygdala and hippocampus. Tables of the microscopic neuritic plaque and neurofibrillary tangle findings with respect to location in the brain for all 7 participants are below (Table One and Table Two). Final diagnosis for this patient was severe AD, mild arteriosclerosis, and mild cerebral amyloid angiopathy of the cerebral cortical and leptomeningial (supply to the hippocampus) blood vessels.

Case Two

This 73 year old white male (8/27/24 - 8/23/97) presented with confusion, memory problems, and increasing agitation beginning in about 1992, at age 68. He was brought to a physician in April of 1994 and a preliminary diagnosis of AD or agitated depression was made. During the following month, after a series of tests, depression was ruled out and a diagnosis of probable AD was given.

Patient had 16 years of education and worked as an undertaker for about 35 years. For the last 20 years of his life, he lived in a small city geographic area (50,000-200,000 population). In 1996 he moved into a nursing home. The patient was married at the time of his death.

When he was diagnosed, the patient was slightly unkempt in appearance and was not performing hygiene activities adequately. He was disoriented to time, place, and date, and he was unable to give his date of birth or address. He also could not name his two children. The patient's

speech was clear; however, he did not speak in full sentences, and he spoke only when asked direct questions. He had difficulty initiating his thought and verbalization process. Patient denied any difficulty with memory, activities, or behavior.

A computer topography (CT) was conducted in April 1994. Hemorrhage in the right lateral ventricle was noted and a right intracranial shunt tube was seen. Overall, no abnormality was identified. Haldol was prescribed in June of 1994 for agitation. The prescription was later discontinued in September, 1996, one month before admission into a nursing home.

Patient's level of ability in activities of daily living continued to decline throughout his stay in the nursing home. Two months before his death, he required feeding from staff, was incontinent, was unable to dress himself or find his way to his room, could not walk without assistance, and his speech was unintelligible. Before his death, this patient's dementia had progressed to the severe level with a score of 0/30 on the MMSE.

Brain procurement took place August 23, 1997, and the brain was taken to Loyola that week. The brain weighed 1187 grams. Gross examination revealed no evidence of atherosclerosis in the intra cranial blood vessels. Mild to moderate atrophy throughout the cerebral cortex was observed. The amygdala was moderately to severely atrophic bilaterally, and the hippocampus was moderately atrophic bilaterally.

Microscopic examination revealed numerous diffuse and neuritic amyloid plaques and neurofibrillary tangles throughout the cerebral cortex, hippocampus, and amygdala. (See Table One and Table Two below.) Additionally, neuronal loss was observed predominantly in the temporal

lobe. Final diagnosis for this patient was severe AD, and mild focal cerebral amyloid angiopathy.

Case Three

This 76 year old white female (1/03/21 - 3/05/97) presented with memory problems that were gradually worsening in June of 1996. The patient had a history of clinical depression, seizures, and she had experienced head injury with loss of consciousness in a train accident 47 years earlier (1943). Depression was ruled out as the cause of dementia, and the patient was admitted to a nursing home.

Patient had 12 years of education, and she worked as a nurses' aid until her retirement in 1989 at age 68. For the last 20 years of her life, she lived in a rural, nonfarm, geographic area. Patient was never married. Her family history indicates a brother with memory problems. Both parents died of heart failure; however, they were well into their 90's at the time of death.

During her stay in the nursing home, the patient was on Haldol and Prozac (and antidepressant). At the time of her death, the patient was incontinent, had to be bathed and fed, could not find her way to her room, and was unable to dress herself. She also had progressed into the severe range of dementia, scoring 0/30 on the MMSE.

Brain procurement took place March 5, 1997, and the brain was taken to Loyola that same day. The brain weighed 1270 grams. Gross examination revealed mild atherosclerotic plaque in the internal carotids and basilar arteries as well as the left vertebral artery. No gross

abnormality was observed in the cerebral cortex. Both the amygdala and hippocampus were also unremarkable at gross examination.

Microscopic analysis revealed numerous amyloid plaques, diffuse and neuritic, throughout all cerebral cortical areas. Neurofibrillary tangles were found primarily in the temporal lobe. The amygdala and hippocampus both had numerous neuritic plaques and neurofibrillary tangles. (See Table One and Table Two below.) Final diagnosis for this patient was moderate to severe AD and mild atherosclerosis involving the internal carotids, basilar, and vertebral arteries.

Case Four

This 85 year old white female (12/01/11 - 4/05/97) began suffering from gradually worsening dementia in July of 1992. She had a history of depression, but this was ruled out as the cause of dementia. The patient also had a history of cancer, arthritis and cataracts.

Patient had over 12 years of education, and she worked as a secretary until she retired in 1968 at 57 years of age. For the last 20 years of her life, she lived in a small city geographic area (50,000-200,000 population). Family history indicates a paternal aunt with suspected AD. Patient's social history shows that she was a smoker for 20-30 years, <1/2 pack per day.

At the time she entered into the study, this patient was unable to feed or dress herself, was occasionally incontinent, and could not find her way to her room. The patient was also showing behavioral changes, but she was not taking any medications.

One week after being admitted into the nursing home, patient became severely dehydrated and had to be hospitalized. The patient

passed away later that week. She had progressed to severe dementia, scoring 0/30 on the MMSE.

Brain procurement took place April 5, 1997, and the brain was taken to Loyola that day. The brain weighed 920 grams. Gross examination showed moderate atherosclerotic plaque of the internal carotids and mild atherosclerotic plaque of the Circle of Willis and the middle cerebral arteries. Moderate to severe generalized atrophy of the cerebral cortex was observed. In the temporal lobe, atrophy on the left was more severe than the right. Mild to moderate atrophy of the amygdala and severe atrophy of the hippocampus bilaterally were also observed.

Microscopic analysis revealed numerous amyloid plaques, diffuse and neuritic, and neurofibrillary tangles in all cerebral cortical areas. Hippocampus examination showed numerous neurofibrillary tangles and neuritic plaques as did the amygdala. (See Table One and Table Two below.) Final diagnosis for this patient was severe AD and mild to moderate atherosclerosis involving the internal carotids and middle cerebral arteries as well as the Circle of Willis.

Case Five

This 84 year old white male (6/30/12 - 2/24/97) presented with memory problems in April of 1986 at the age of 83. The onset of major symptoms was gradual and impairment became gradually worse. Four years later, he was admitted to a nursing home with a diagnosis of probable AD, Parkinson's, angina, and probable transient ischemic attacks.

Patient had 8 years of education, and he was a farmer for most of his life until retirement. For the last 20 years of his life, the patient lived in a rural, farm, geographic area. He was married at the time of his

death. Family history does not indicate any family members with memory problems; however, his eldest brother had Parkinson's disease.

At the time he was admitted into the nursing home, this patient was exhibiting language impairment, behavioral changes, and disorientation to time and place. Over the course of the disease, he became incontinent, unable to feed or clothe himself, and unable to find his way to his room. By June of 1993, he was totally dependent for all care.

After being admitted into a nursing home, the patient began physical therapy which included gait training to improve posture, and balance. Patient was prescribed Carbidopa for his Parkinsonian symptoms in May, 1996. This drug appeared to decrease tremors. Episodes of apnea were observed in October, 1996. By the time of his death, the patient had progressed to severe dementia, scoring 0/30 on the MMSE.

Brain procurement took place February 2, 1997, and the brain was taken to Loyola the following day. The brain weighted 970 grams. Gross examination revealed moderate to severe atherosclerosis, involving the internal carotids, middle and posterior cerebral, and basilar arteries. Anterior cerebral and vertebral arteries had mild atherosclerotic plaque. Mild to moderate atrophy of the cerebral cortex was observed. Both the hippocampus and the amygdala were severely atrophic bilaterally.

Microscopic examination revealed numerous amyloid plaques, diffuse and neuritic, throughout the cerebral cortex. Many neurofibrillary tangles were noted as well. The temporal lobe was most affected. It contained many neuritic plaques and neurofibrillary tangles. (See Table One and Table Two below.) Final diagnosis for this patient was severe AD, moderate to severe cerebral amyloid angiopathy, severe arteriosclerosis, moderate to severe atherosclerosis, and micro infarction of the remote

right frontal/orbital surface. No pathological evidence for Parkinson's disease was found. Parkinson-like symptoms were probably due to the severity of AD combined with vascular disease.

Case Six

This 81 year old white female (1/22/16 - 5/10/97) was found lying on the floor by a neighbor on August 19, 1994 and was subsequently hospitalized. She had been experiencing memory problems for the past several years, beginning at approximately age 78. She had a history of transient ischemic attacks as revealed by her medical charts. Also, a 1992 carotid Doppler revealed 70-75% stenosis of the left carotid, and she had a pacemaker.

Patient had 14 years of education, and she worked as a teacher for some years before becoming a housewife. For the last 20 years of her life, she lived in a rural, farm, geographic area. She was admitted into a nursing home in September of 1994. At the time of her death, the patient was widowed.

While she was in the nursing home, the patient experienced increasing tearfulness, and she was placed on Pazil, an antidepressant. She was diagnosed as having a recurrent major depressive disorder. Her cognitive abilities continued to deteriorate, and she experienced episodes of confusion. A diagnosis of probable AD was made. The patient was still able to recognize her daughter and her surroundings. She was also ambulatory and could find her way around the nursing home although episodes of wandering off the premises were noted. She was not oriented to date and time, and she required assistance in most of her activities of

daily living but was not totally dependent. At the time of her death, the patient had progressed to severe dementia, scoring 3/30 on the MMSE.

Brain procurement took place May 13, 1997, and the brain was taken to Loyola the same day. The brain weighed 970 grams. Gross examination revealed mild to moderate atherosclerosis in the internal carotids, basilar, and vertebral arteries. Mild atherosclerotic plaque was noted in the anterior, middle, and posterior cerebral arteries and the Circle of Willis. Mild generalized atrophy was observed throughout the cerebral cortex. The amygdala was mildly atrophic, and the hippocampus was moderately atrophic bilaterally.

Microscopic examination revealed numerous amyloid plaques throughout the cerebral cortex, mostly of the diffuse type. However, the temporal lobe revealed numerous neuritic plaques and neurofibrillary tangles. Neurofibrillary tangles were noted scattered in the frontal and parietal lobes as well. Numerous neuritic plaques and neurofibrillary tangles were observed in both the amygdala and hippocampus. Final diagnosis for the patient was moderate AD, focal cerebral amyloid angiopathy involving leptomeningeal vessels, and mild to moderate atherosclerosis.

Case Seven

This 89 year old white female (10/19/17 - 12/13/96) began presenting gradual onset memory problems in the early spring of 1974 at the age of 66. These memory problems were becoming gradually worse although the patient denied confusion. Her medical history indicates heart disease hypertension, angina, and seizures. Early examinations in 1977

resulted in a diagnosis of probable early dementia. By 1985 the diagnosis had become probable AD.

Patient had 8 years of education, and she was a housewife. For the last 20 years of her life she lived in a small city (50,000-200,000 population) geographic area. In 1985, she was admitted into adult daycare, and by 1986, she was in long-term care. At the time of her death, the patient was widowed. Family history indicates that her mother died of a stroke and her father died after a heart attack.

In 1985, the patient began a prescription of Haldol for agitation. She experienced episodes of confusion and disorientation to her surroundings. At this time, she was also prescribed Inderal and Digoxen for her heart. A CT revealed cortical atrophy, and a later abdominal series in 1986 revealed evidence of arteriosclerotic vascular disease.

In 1986, after being admitted into long-term care, the patient experienced much confusion and disorientation. She could not understand where she was and why she could not go home. Her language abilities continued to deteriorate until she could no longer "make her wants or needs known," 1994. She remained ambulatory until 1995. Even then, she could walk a few steps with assistance. She was however, totally dependent in her activities of daily living. She was unable to feed and dress herself or find her way to her room, and she was also incontinent. By her death, the patient had progressed to severe dementia, scoring a 1/30 on the MMSE.

Brain procurement took place December 13, 1996, and the brain was taken to Loyola the same day. The brain weighed 720 grams. Gross examination revealed moderate atherosclerotic plaque in the internal carotids, middle and posterior cerebral, basilar, and vertebral arteries.

Mild generalized atrophy was observed in all cerebral cortical areas. The amygdala was mildly atrophic bilaterally, and the hippocampus showed moderate to severe atrophy bilaterally.

Microscopic examination revealed numerous amyloid plaques, diffuse and neuritic, and neurofibrillary tangles throughout all cerebral cortical areas. The amygdala showed numerous neurofibrillary tangles, and hippocampal examination revealed numerous neuritic plaques and neurofibrillary tangles. (See Table One and Table Two below.) Final diagnosis for this patient was severe AD, Parkinson's, moderate to severe arteriosclerosis, and moderate atherosclerosis involving the internal carotids, middle and posterior cerebral, basilar, and vertebral arteries.

Table One- Number of Amyloid Plaques (Neuritic Plaques) for Patients One-Seven

Patient: Area	<u>One</u>	<u>Two</u>	<u>Three</u>	<u>Four</u>	<u>Five</u>	<u>Six</u>	<u>Seven</u>
Premotor:	10 (5)	18 (14)	22 (1)	7 (4)	12 (5)	N/A	N/A
Frontal:	>30 (>3)	N/A	>30 (>3)	36 (7)	20 (16)	N/A	20 (16)
Temporal:	15 (6)	>30 (24)	25 (6)	20 (12)	20 (18)	N/A	>30 (>27)
Parietal:	8 (6)	>30 (>9)	10 (3)	28 (6)	20 (4)	N/A	>30 (>6)
Occipital:	14 (11)	10 (8)	8 (1)	12 (10)	18 (16)	N/A	10 (8)
Amygdala	10 (8)	22 (20)	15 (11)	8 (6)	N/A	N/A	12 (10)

Number of amyloid plaques per brain region in bold, number of amyloid plaques which are neuritic in parentheses. (200x Magnification)

Table Two- Number of Neurofibrillary Tangles for Patients One-Seven

Patient: <u>Area</u>	<u>One</u>	<u>Two</u>	<u>Three</u>	<u>Four</u>	<u>Five</u>	<u>Six</u>	<u>Seven</u>
Premotor:	2	8	0	2	8	N/A	N/A
Frontal:	22	N/A	0	18	23	N/A	46
Temporal:	36	>20	7	26	>40	N/A	32
Parietal:	28	13	1	10	22	N/A	24
Occipital:	8	6	0	12	3	N/A	3
Amygdala	24	>30	3	16	N/A	N/A	8

Number of neurofibrillary tangles per brain region. (200x Magnification)

The largest number of amyloid plaques among members of this group appear in the temporal lobe. The frontal and parietal lobes are not far behind. When taking into account the number of these which are neuritic, the temporal lobe continues to have the highest number (93). The frontal lobe (45) again comes in second, along with the amygdala (55) and the occipital lobe (54), although these are not as close in number to the temporal lobe as they were when considering the number of plaques

overall. The parietal does not have a high number of neuritic plaques (34), comparatively, even though it was among the top brain regions when considering the number of amyloid plaques. The premotor cortex has a low number of both amyloid plaques and neuritic plaques (29).

With the exception of Patient Two, the brain region with the most neurofibrillary tangles is the temporal lobe in all patients. Patient Two has the largest number of neurofibrillary tangles in the amygdala. It should be pointed out that Patient Two presented with increasing agitation as part of AD onset. He was also on a prescription of Haldol for two years.

Average adult brain weight is 1250 grams (V. Hnilika, personal communication, April 1998). Atrophy, reported in the case studies above, decreases brain weight. Table Three shows brain weights at autopsy for each of the seven patients and the amount of difference between this weight and average adult brain weight. In addition, Table Three lists the duration of the disease.

Table Three- Duration of AD for Each Patient in Comparison to Decrease in Brain Weight, Inferred from Deviance in Weight from Average Adult

Patient:	<u>One</u>	<u>Two</u>	<u>Three</u>	<u>Four</u>	<u>Five</u>	<u>Six</u>	<u>Seven</u>
Brain (gm):	1039 gm	1187 gm	1270 gm	920 gm	970 gm	970 gm	720 gm
Difference (gm):	211 gm	63 gm	Not applicable	330 gm	280 gm	280 gm	530 gm
Duration:	5 years	6 years	1 year	5 years	1 year	3 years	23 years

Difference in patient brain weight from average adult in relation to duration of illness.

In addition to being analyzed in relation to brain weight, duration of illness has been analyzed in relation to cognitive test scores and activities of daily living functional scores. All of the seven patients in this study were too severely demented to take the ADAS cognitive test; therefore, only the MMSE was given. On the MMSE, 30 is the maximum correct score. Patients are scored by the number correct out of 30. Activity of daily living assessments are also included in Table Four. On the Barthel, maximum severity is a score of 0 on a scale of 20. For the remainder of the activities of daily living assessments, a maximum score equates to maximum severity (i.e. the higher the score the more severe the impairment).

Table Four- Cognitive Test and Activity of Daily Living Scores in Relation to Duration of Illness for Each Patient

Patient:	<u>One</u>	<u>Two</u>	<u>Three</u>	<u>Four</u>	<u>Five</u>	<u>Six</u>	<u>Seven</u>
Duration:	5 years	6 years	1 year	5 years	1 year	3 years	23 years
MMSE:	0/30	0/30	0/30	0/30	0/30	3/30	1/30
Barthel:	N/A	6/20	N/A	N/A	N/A	N/A	N/A
FAST:	7b/7f	7c/7f	N/A	6a/7f	7f/7f	N/A	N/A
Blessed:	N/A	15/17	17/17	N/A	N/A	N/A	16/17
Rankin:	N/A	4/5	N/A	N/A	N/A	N/A	N/A
GDS:	7/7	7/7	N/A	6/7	4/7	N/A	N/A

As discussed in Methods, this researcher separated patients into two groups - probable AD with atherosclerosis and probable AD without atherosclerosis - while still blind to autopsy results. This assessment

was done without any medical training and based solely on available medical records/histories as well as cognitive and functional test scores. Assessment was 57% accurate. Research assessment in relation to autopsy assessment is shown below in Table Five.

Table Five- Assessment of Research Diagnosis of Patients One-Seven in Relation to Autopsy Diagnosis

Patients:	<u>One</u>	<u>Two</u>	<u>Three</u>	<u>Four</u>	<u>Five</u>	<u>Six</u>	<u>Seven</u>
AD at Autopsy:	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Athero-sclerosis at Autopsy:	No	No	Yes	Yes	Yes	Yes	Yes
Correct/Incorrect:	Incorrect	Correct	Incorrect	Incorrect	Correct	Correct	Correct

Of the incorrect cases above, Patient Three and Patient Four were placed into the AD without atherosclerosis group by this researcher. Autopsy results show that Patient Three did in fact have mild atherosclerosis present while Patient Four had mild to moderate atherosclerosis present.

Tables Six, Seven, and Eight below deal with the character of AD in relation to atherosclerosis. Table Six shows severity of AD in relation to severity of atherosclerosis. Table Seven shows patient age at AD onset with respect to presence or absence of atherosclerosis, and Table Eight shows length of AD duration, between onset and death, with respect to

presence or absence of atherosclerosis. Dementia for all patients at the time of death was severe, based on cognitive testing.

Table Six- Severity of AD in Relation to Severity of Atherosclerosis in Patients One-Seven

Patient:	<u>One</u>	<u>Two</u>	<u>Three</u>	<u>Four</u>	<u>Five</u>	<u>Six</u>	<u>Seven</u>
AD severity:	Severe	Severe	Moderate-Severe	Severe	Severe	Moderate	Severe
Athero-sclerosis severity:	Condition not present	Condition not present	Mild	Mild-Moderate	Moderate-Severe	Mild-Moderate	Moderate

Table Seven- Age at AD Onset with Respect to the Presence or Absence of Atherosclerosis

Patient:	<u>One</u>	<u>Two</u>	<u>Three</u>	<u>Four</u>	<u>Five</u>	<u>Six</u>	<u>Seven</u>
Age at Onset:	81	67	75	80	83	78	66
Athero-sclerosis?:	No	No	Yes	Yes	Yes	Yes	Yes
Severity of Athero-sclerosis:	N/A	N/A	Mild	Mild-Moderate	Moderate-Severe	Mild-Moderate	Moderate

Severity of atherosclerosis, when present, given for reference.

Table Eight- Duration of AD with Respect to the Presence or Absence of Atherosclerosis

Patient:	<u>One</u>	<u>Two</u>	<u>Three</u>	<u>Four</u>	<u>Five</u>	<u>Six</u>	<u>Seven</u>
Duration of AD:	5 years	6 years	1 year	5 years	1 year	3 years	23 years
Athero-sclerosis?:	No	No	Yes	Yes	Yes	Yes	Yes
Severity of Athero-sclerosis:	N/A	N/A	Mild	Mild-Moderate	Moderate-Severe	Mild-Moderate	Moderate

Severity of atherosclerosis, when present, given for reference.

Out of five severe AD cases, atherosclerosis was found in three. Of these three, atherosclerosis severity ranged from mild-moderate to moderate-severe. Duration of the disease in the moderate-severe case was only one year, much shorter than the other two severe AD cases with associated atherosclerosis. However, of these two remaining cases, the mild-moderate case, Patient 7, had a longer duration than the mild atherosclerosis case. Also, the two cases of AD without atherosclerosis had similar durations to the AD with mild-moderate atherosclerosis case.

One final note, four out of seven patients showed cerebral amyloid angiopathy at autopsy. This is deposition of beta amyloid along blood vessel walls and is consistent with the study by Hall et al. discussed

earlier. Table Nine shows the severity of cerebral amyloid angiopathy, if present, for all seven patients in relation to severity of AD, age at AD onset, and duration of AD.

Table Nine- Cerebral Amyloid Angiopathy in Relation to AD

Patient:	<u>One</u>	<u>Two</u>	<u>Three</u>	<u>Four</u>	<u>Five</u>	<u>Six</u>	<u>Seven</u>
CAA Severity:	Mild	Mild	Not Present	Not Present	Moderate- Severe	Mild	Not Present
AD Severity:	Severe	Severe	Moderate- Severe	Severe	Severe	Moderate	Severe
AD Duration:	5 years	6 years	1 year	5 years	1 year	3 years	23 years
Age at AD Onset:	81	67	75	80	83	78	66

Cerebral Amyloid Angiopathy is abbreviated as (CAA).

Discussion

Alzheimer's research has explored many avenues over the course of the years in search of a cause and ultimately a cure. Two such avenues have been discussed in this paper, the cholinergic hypothesis and the hypothesis relating to the quantity of beta amyloid/neuritic plaques present in the brain. Behavioral studies of the cholinergic hypothesis failed to find learning deficiencies associated with the acetylcholine neurotransmitter in rats. These findings cast doubt on the theory that lowered acetylcholine levels are the underlying cause of AD dementia. With regard to the quantity of neuritic plaques in the brain and their association with AD and AD dementia, criteria for the number of neuritic

plaques present and in what areas of the brain are not definite. Additionally, Snowdon et al.'s "Nun Study" found that a diagnosis of AD could be made at autopsy on the basis of neuritic plaque findings without any corresponding in-life dementia.

The present study showed a wide number range of neuritic plaques in those diagnosed with severe AD (39-75 neuritic plaques), and only as little as 25 neuritic plaques were needed for a diagnosis of moderate-severe AD. Similarly, in those diagnosed with severe AD, the number of neurofibrillary tangles ranged from 84-120, while a moderate-severe AD diagnosis had as little as 11 neurofibrillary tangles. It is, however, interesting to note that the greatest number of neuritic plaques overall were found in the frontal and temporal lobes as well as in the amygdala, areas which are most affected by AD. Also, all patients had the greatest number of neurofibrillary tangles in the temporal lobe except one. Patient Two had the largest number of neurofibrillary tangles present in the amygdala.

Problems with the cholinergic hypothesis and the variable findings in neuritic plaque quantification studies have led to a reexamination of AD risk factors so that perhaps a new hypothesis of AD development and dementia can be constructed. The hypothesis of AD development and dementia examined in this study was that of the relationship between atherosclerosis and AD. In particular, atherosclerosis severity and AD severity, as well as, atherosclerosis as it relates to AD onset were examined.

Researcher assessment and grouping of patients prior to knowledge of autopsy diagnosis was fairly accurate, 57%. That these assessments were made only with available records with out medical training is

encouraging. If a link between AD and atherosclerosis is established, diagnosis of living patients by trained professionals should be very accurate and could eventually aid in AD treatment.

Unfortunately, this study has not established any link between atherosclerosis and AD. Because this was a case study analysis, statistics could not be used. Furthermore, inferences about AD as it relates to atherosclerosis could not be drawn from data gathered on these seven patients.

The range of severity of atherosclerosis corresponding with severe AD is too wide to be meaningful. In addition, atherosclerosis was not present in two out of five severe AD cases. When looking at duration of illness, severe AD with moderate-severe atherosclerosis has the lowest duration, one year. However, mild-moderate atherosclerosis with severe AD has a much shorter duration than moderate atherosclerosis with severe AD, 5 vs. 23 years. Also, the duration of severe AD with mild-moderate atherosclerosis is no different than that of Patients One and Two who had no associated atherosclerosis. Finally, there are no patterns between age of AD onset and presence of atherosclerosis in this data set. Based on these results, no meaningful statements about the relationship between AD and atherosclerosis can be made.

A slight increase in differential brain weights between average adults and AD patients can be seen as AD illness duration increases. Data do not indicate a relationship between duration of illness and cognitive test scores. All patients scored in the severe AD dementia range regardless of AD duration. Also, there does not appear to be a link between cerebral amyloid angiopathy and AD severity at this point in the study.

It should be noted once again that this data set is extremely small. The number of participants in the study continues to grow, and eventually statistical analyses will be available. At that point, a pattern between AD and atherosclerosis may begin to emerge. For the time being, the small data set is a severe limitation to this study.

Continuous testing of participants every six months and performing a brain autopsy on all participants at the time of death are methods not common in the current literature on AD and atherosclerosis. This study has the potential to advance knowledge of AD when it is finally brought to its conclusion. Future researchers may wish to track the time between onset and significant downturn of cognitive abilities in AD patients when atherosclerosis is present. Finally, a more extensive examination of cerebral amyloid angiopathy and its relation to AD severity and atherosclerosis severity could be added in the future.

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