# Atherosclerotic Risk Factors, Vascular Cognitive Impairment, and Alzheimer Disease

**Article** *in* Mount Sinai Journal of Medicine A Journal of Translational and Personalized Medicine · November 2012

Impact Factor: 1.62 · DOI: 10.1002/msj.21347 · Source: PubMed



**2 authors:**

Jason Kovacic
Mount Sinai Hospital
**140** PUBLICATIONS **1,539** CITATIONS
SEE PROFILE

Valentin Fuster
Mount Sinai Hospital
**711** PUBLICATIONS **47,036** CITATIONS
SEE PROFILE

# Atherosclerotic Risk Factors, Vascular Cognitive Impairment, and Alzheimer Disease

Jason C. Kovacic, MD, PhD[1,2] and Valentin Fuster, MD, PhD[1,2,3]

[1]The Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY
[2]Marie-Josée and Henry R. Kravis Cardiovascular Health Center, Mount Sinai School of Medicine, New York, NY
[3]National Center for Cardiovascular Research (CNIC), Madrid, Spain

## OUTLINE



## ABSTRACT

The involvement of vascular factors in Alzheimer dementia was first appreciated over 100 years ago. Recently, significant advances in our understanding of these brain-vascular relationships have taken place. Vascular cognitive impairment is now recognized as a distinct group of interrelated vascular-based neurological insults that can accumulate and lead to dementia. Importantly, the pathology of vascular cognitive impairment extends far beyond brain destruction wrought by major stroke. Other subtle changes may also arise that contribute to vascular cognitive impairment and dementia, including subclinical stroke, white-matter changes such as hyperintensities and lipohyalinosis, small lacunar infarcts, cerebral hypoperfusion, and compromise of the blood-brain barrier. In this review we critically examine the emerging body of evidence that relates atherosclerotic risk factors, brain functioning, and Alzheimer disease. ***Mt Sinai J Med 79:664–673, 2012.*** *© 2012 Mount Sinai School of Medicine*

**Key Words:** altered brain parenchyma, Alzheimer dementia, atherosclerotic risk factors, vascular cognitive impairment.

**Address Correspondence to:**

**Valentin Fuster**
Mount Sinai School of Medicine
New York, NY
Email: valentin.fuster@mountsinai.org

Atherosclerosis is an omnipresent pathology that involves virtually the entire human organism. One of the most poignant examples of this systemic nature of atherosclerosis is the link between coronary artery disease (CAD), degenerative brain disease (DBD), and dementia (see for review Kovacic *et al*[1]). The scope of the problem is significant. In the United States in 2007, CAD was the cause of ~1 in every 6 deaths, while >1 million patients underwent cardiac catheterization and >600,000 underwent percutaneous coronary intervention (PCI) for the placement of coronary artery stents.[2]

*Atherosclerosis is an omnipresent pathology that involves virtually the entire human organism.*

Mirroring these data, the current lifetime risk of developing Alzheimer dementia for a 65-year-old is ~10.5% and it is predicted that the number of sufferers will continue to rise.[3–5] It is important to note that Alzheimer dementia is one of a number of degenerative brain diseases that involve primary

Published online in Wiley Online Library (wileyonlinelibrary.com).
DOI:10.1002/msj.21347

degenerative changes to cortical brain tissue (such as amyloid plaques and neurofibrillary tangles) and that typically occur with older age. Thus, the rapid aging of the population is a major additional factor in the extent of this problem. By the year 2030, with the aging of the "baby boomers," nearly 1 in 5 US residents is expected to be aged >65 years.[6]

*The current lifetime risk of developing Alzheimer dementia for a 65-year-old is ~10.5% and it is predicted that the number of sufferers will continue to rise.*

At the biologic level, fundamental changes that occur in the cardiovascular system as a result of aging and atherosclerosis incite a cascade of pathological changes that culminate in vascular cognitive impairment (VCI). Epidemiologic data have now shown a strong link between traditional atherosclerotic risk factors and an increased likelihood of VCI and DBD. This evidence includes associations between the risk of developing DBD/VCI and sedentary lifestyle,[7] diabetes (DM),[8] dyslipidemia/hypercholesterolemia,[9,10] smoking,[11] and hypertension[10,12] and/or obesity[13] during midlife. In this review we dissect this mounting body of evidence that indicates a causative relationship between atherosclerotic risk factors, VCI, and Alzheimer disease (AD).

## VASCULAR COGNITIVE IMPAIRMENT

Vascular cognitive impairment is an increasingly used term that encapsulates many of the key aspects that link CVD to brain health (Figure 1).[14] Though traditionally a term such as VCI may have been taken as a synonym for stroke or multi-infarct dementia, today it is understood that this is an overly simplistic outlook. In particular, the term VCI was proposed to appropriately highlight the important role that vascular disease plays in a broad range of cognitive disorders including the hereditary vascular dementias, multi-infarct dementia, poststroke dementia, subcortical ischemic vascular disease and dementia, mild cognitive impairment, and the degenerative dementias (including AD and dementia with Lewy bodies).[14,15] Indeed, VCI that arises purely due to a single vascular insult is likely to be a rare entity. For example, a common de novo stroke is rarely seen in the absence of concomitant cardiovascular risk factors, and almost universally these cardiovascular disease (CVD) risk factors are linked to many of the factors known to reduce cardiovascular brain health (Figure 1). Therefore, a major conceptual difference when thinking in terms of VCI (versus the traditional outlook of relating atherosclerosis to stroke) is that VCI is a disease complex, rather than a single entity. In many respects, VCI can be considered as a family of distinct but interrelated vascular-based neurological insults that can accumulate and lead to dementia. Another key aspect of VCI is that a broad spectrum of neurological deficits may be encountered that include motor defects, silent infarcts, cognitive impairment without dementia, and dementia-like illnesses.

*Vascular cognitive impairment can be considered as a family of distinct but interrelated vascular-based neurological insults that can accumulate and lead to dementia.*

Setting aside VCI momentarily, it is interesting to note that in some individuals a degree of cognitive decline may be a normal aspect of aging.[16] This phenomenon has been labeled with numerous titles, including mild cognitive impairment, benign senile forgetfulness, and age-associated memory impairment.[17] It is debated whether this normal decline in cortical function is one end of a continuum that includes AD, but it has long been thought that normal cognitive decline with aging does not begin until an age of 60–70 years.[18] Provocatively, Singh-Manoux *et al*[16] recently demonstrated in a large cohort of >10,000 persons that a measurable decline in generalized cortical function may be present by 45–49 years of age. Across the 5 domains of memory, reasoning, vocabulary, and phonemic and semantic fluency, all cognitive scores except vocabulary declined in persons aged >45 years at baseline, with evidence of faster decline in older people. Although the normal loss of brain function with age is not the focus of this article, we mention this process, as it is the background to any added brain pathology such as AD that may occur in elderly persons. Furthermore, this study raises the possibility that not all elderly persons with cortical dysfunction have dementia. Though it is unknown if CAD and atherosclerotic risk factors are related to any normal decline in brain function with age, this will be an important area of research going forward.

Interestingly, a clinically relevant aspect of our increased appreciation of VCI is that many

DOI:10.1002/MSJ

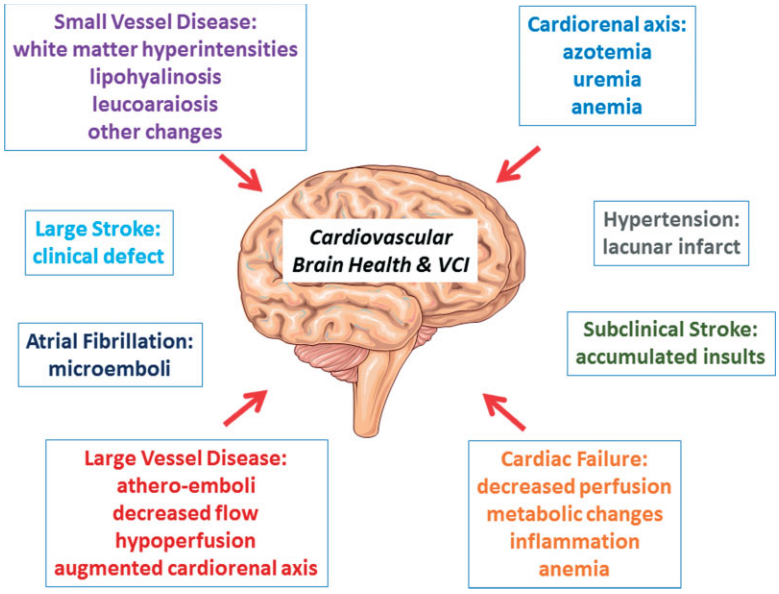


Fig 1. Cardiovascular factors involved in brain health and VCI. **Abbreviation:** VCI, vascular cognitive impairment.

of the traditional neuropsychological differences described between conditions such as AD and multi-infarct dementia may have been overstated. Although subtle phenotypic differences undoubtedly exist, as described in this review the reality is that many patients have a pathologically mixed dementia process.[19] Therefore, defining clinical neuropsychological syndromes that are associated with differing dementia-related illnesses is an increasingly challenging task, especially as a "pure" presentation of an isolated dementia-causing disease is perhaps less common than once believed.[19]

Collectively, the neurological effects of the CVD risk factors and VCI, superimposed upon the normal decline in cognitive function with aging, is a biologically complex system with effects that transcend a simple association with increased atherosclerotic burden. However, though an expanded set of contributory interactions are shown in Figure 1, the traditional CVD risk factors appear to converge on several critical elements that are discussed in detail below, including large-vessel disease, small-vessel disease, and stroke.

## LARGE-VESSEL DISEASE AND STROKE

The role of stroke in dementia has been recognized for several decades and was first considered under the banner of multi-infarct dementia. However, Vermeer *et al*[20] provided a major advance in our appreciation of the important role of subclinical stroke in VCI and dementia. In a landmark study published as recently as 2003, these investigators identified that the presence of silent brain infarcts more than doubled the risk of dementia in patients aged 60–90 years who were free of dementia and clinical stroke at baseline. Furthermore, the presence of silent brain infarcts on baseline magnetic resonance imaging (MRI) was associated with impaired performance on neuropsychological testing and a more rapid decline in cognitive function.[20] This study highlights the fact that small, subclinical strokes are involved in the progression toward dementia, and that clinically detectable motor or cognitive defects are not required for stroke to be a component of VCI.

The fact that CAD and large-vessel disease frequently occur together has been well described in the literature.[21] As an important cause of stroke, large-vessel disease is often taken to imply stenotic carotid artery atherosclerosis. Although carotid artery stenosis is an important contributor to VCI and a common cause of multi-infarct dementia,[19] even carotid artery atherosclerotic disease may augment VCI by several mechanisms. Traditionally, a carotid artery stenosis is thought to lead to cerebral events by causing cerebral ischemia and acting as a nidus for atherothrombotic emboli. This may lead to transient cognitive dysfunction due to reduced cortical perfusion, or permanent brain damage from embolic stroke. However, carotid artery disease may have additional detrimental effects, such as impaired baroreflex sensitivity and dysfunctional cerebral neurovascular coupling (see below).[22]

DOI:10.1002/MSJ

The vertebral arteries are also likely to be an underappreciated cause of stroke and VCI. The New England Posterior Circulation Registry included 407 patients and identified that occlusive disease of the proximal segment of the vertebral artery(s) was likely to be the primary mechanism of posterior circulation ischemia in up to 9% of these patients.[23] In addition, the aorta is another site for large-vessel atherothrombotic emboli. Amarenco *et al*[24] showed using transesophageal echocardiography that after adjustment for CVD risk factors, the presence of atherosclerotic plaques ≥4 mm in thickness in the aortic arch was associated with an odds ratio for ischemic stroke of 9.1 (95% confidence interval [CI]: 3.3-25.2, $P < 0.001$).

Although not strictly under the purview of VCI, it must also be appreciated that the distant effects of atherothrombotic disease may affect cognition. Most notably renal impairment, which is known to be related to impaired cognitive function,[25,26] may arise due to large-vessel atherosclerotic disease. Direct atherosclerotic causes of renal impairment include renal artery stenosis and atherothrombotic microemboli.[27,28] Also, DM and hypertension can cause direct renal injury even in the absence of renal artery stenosis, adding to renal and cognitive impairment.

## HYPERTENSION, LACUNAR INFARCTION, AND STROKE

Hypertension is a major risk factor for stroke. Of particular relevance to VCI, recent data have demonstrated that 24-hour ambulatory (not office-based) systolic blood pressure recordings may be the most powerful marker of the future risk of cognitive decline and DBD.[29] As a type of stroke, lacunar infarction is closely related to hypertension[30,31] and results from occlusion of one of the penetrating arteries that supply the deep brain structures. Lacunar infarction is a common clinical entity and is detectable by MRI in up to ~25% of persons aged >65 years,[30] and smaller microlacunar infarcts may arise with even greater frequency.[32] Importantly, lacunar infarction is likely to be underdiagnosed, as >85% of these events may be clinically silent.[30] The pathology of lacunar infarction is multifactorial and overlaps significantly with that of small-vessel disease (see below). Microatheroma, small-vessel stenosis, and microembolism are all implicated in the neuropathology of this condition.

In addition to lacunar infarction, hypertension (and also hypotension) may increase the burden of VCI by other mechanisms. To ensure proper cerebral functioning, a number of key elements of the central nervous system, including cortical neurons, astrocytes, glial cells, and vessels, are critically dependent on physiologic blood pressure regulation: so-called

*In addition to lacunar infarction, hypertension (and also hypotension) may increase the burden of vascular cognitive impairment by other mechanisms.*

neurovascular coupling. To maintain correct neurovascular coupling, complex biofeedback pathways interact to properly match regional cortical activity and metabolic demands with vascular perfusion.[33,34] Perturbations in neurovascular coupling lead to decreased cerebral perfusion, oxygenation, and vascular reserve capacity, and are associated with small-vessel disease, stroke, and DBD.[33] Indeed, rather than hypertension, the breakdown in neurovascular coupling may be more directly related to dynamic systemic fluctuations in blood pressure that are uncorrected for by cerebral autoregulation and that result in hypoperfusion (see recent reviews[33–36]). The molecular basis of disturbed neurovascular coupling remains to be completely defined, but it appears to involve alterations in both vascular (nitric oxide, nitric oxide synthase, and prostaglandins) and neuronal (glutamate, calcium handling, and prostaglandins) signaling pathways.[34] Therefore, as well as stroke and atherosclerosis, blood-pressure dysregulation is associated with disturbed brain perfusion and other effects that collectively augment VCI and DBD.

*As well as stroke and atherosclerosis, blood pressure dysregulation is associated with disturbed brain perfusion and other effects that collectively augment vascular cognitive impairment and degenerative brain disease.*

As an extension of stroke and VCI, it must be remembered that CAD and hypertension are leading causes of heart failure and atrial fibrillation—a major source of arterial thromboemboli that may result in stroke. Those seeking further information regarding stroke are referred to any of the excellent recent review articles covering the specifics of this disease.[37–39]

DOI:10.1002/MSJ

## SMALL-VESSEL DISEASE

Small-vessel disease is another potential contributor to DBD (see below) and arguably is the most poorly understood aspect of VCI. Major cellular features of small-vessel disease include endothelial morphologic changes, a reduction in endothelial mitochondrial content, reduced capillary density with fibrotic capillary basement membranes,[40,41] perivascular fibrosis, vascular smooth muscle cell replacement by fibrohyaline material,[42] and small-vessel atrophy.[43] These vascular changes cause a secondary dysregulation of cerebral blood flow and cortical perfusion, disruption of the blood-brain barrier, and increased susceptibility to neurological insults.[44] In addition, amyloid $\beta$ protein deposition in the cerebral vessels, termed amyloid angiopathy, is a frequent contributor to advanced small-vessel disease. Potentially, amyloid $\beta$ protein may be produced locally by cortical neurons, with levels further increased due to an additional failure of amyloid clearance.[45,46] This pathology is compounded by the fact that cerebral amyloid is also a major cause of cerebral hemorrhage[47] and that ~30% of clinically defined Alzheimer patients have lobar microhemorrhages on $T_2$-star MRI images.[48] Thus, a feed-forward pathological process may be initiated, whereby amyloid $\beta$ deposition leads to progression of small-vessel disease, worsening cortical vascular function and blood-brain barrier integrity, thereby facilitating the deposition of even more amyloid.

*A feed-forward pathological process may be initiated, whereby amyloid β deposition leads to progression of small-vessel disease, worsening cortical vascular function and blood-brain barrier integrity, thereby facilitating the deposition of even more amyloid.*

Clinical imaging studies have suggested a close relationship between small-vessel disease and cognitive impairment.[49] Cerebral small-vessel disease can be visualized on MRI as lacunar infarcts and/or white-matter lesions in the form of hyperintensities or leucoaraiosis,[50,51] whereas generalized brain atrophy is a characteristic MRI finding of AD[52] that is also associated with CVD risk factors and small-vessel disease.[52,53] Prins *et al*[49] evaluated the relationship between MRI measures of cerebral small-vessel disease and the rate of decline in specific cognitive domains. These investigators studied 832 participants aged 60–90 years who were dementia-free at baseline and underwent neuropsychological testing and MRI assessment of white-matter lesions, cerebral infarcts, and generalized brain atrophy. These measures were then repeated several times over an average follow-up period of 5.2 years. Prins *et al*[49] identified that increasing severity of periventricular white-matter lesions, generalized brain atrophy, and the presence of brain infarcts on MRI were associated with a more rapid decline in cognitive function that was prominent for impairment in information-processing speed and executive function. These associations between MRI measures of cerebral small-vessel disease and cognitive decline did not change after adjustment for CVD risk factors or depressed mood. Godin *et al*[31] further expanded our understanding of the relationship between white-matter lesion progression and hypertension. In a 4-year study involving 1319 elderly individuals, baseline blood pressure was a significant predictor of increased white-matter lesion progression after controlling for potential confounders. In addition, effective treatment with antihypertensive medication reduced the rate of white-matter lesion progression.[31]

Other investigators have explored the optimal MRI parameters and modalities for imaging small-vessel disease and predicting cognitive decline, and it would appear that diffusion tensor MRI imaging has enhanced sensitivity for white-matter pathology and that these changes correlate with decreasing executive cortical function.[54] Advances in diffusion tensor MRI imaging have now provided the ability to resolve exquisite white-matter detail and to undertake fiber-tract mapping (Figures 2 and 3).

## DIABETES

Diabetes mellitus is another major risk factor for CVD, VCI, and AD.[55] As well as increasing the atherosclerotic burden and in a similar fashion to the effects of hypertension, several DM-specific factors may compound its detrimental effects on the central nervous system and add to the burden of small-vessel disease. Animal models of AD have demonstrated that diet-induced insulin resistance promotes cerebral amyloid $\beta$ protein generation, which corresponds with the cortical burden of amyloid plaque and impaired performance in a spatial water maze task.[56] Furthermore, insulin resistance appears associated with a functional decrease in insulin receptor–mediated signal transduction in the brain, which is linked to increased cortical amyloid $\beta$

DOI:10.1002/MSJ

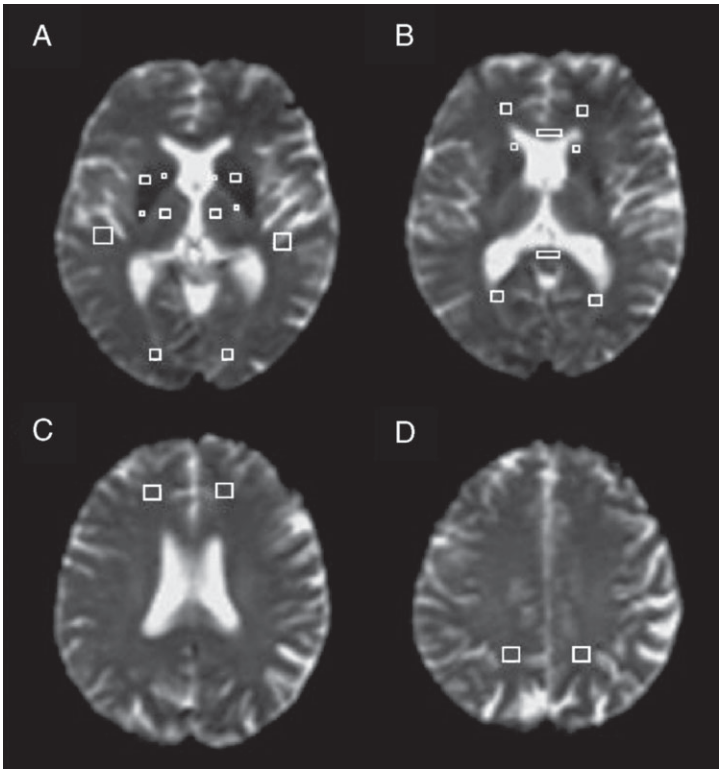


Fig 2. DT-MRI images of a patient with dementia with Lewy bodies. White squares represent regions of interest suspicious of small-vessel disease. (A) Internal capsule, putamen, thalamus, temporal and occipital lobes. (B) Genu and splenium of the corpus callosum, anterior and posterior pericallosal areas, caudate nucleus. (C) Frontal lobes. (D) Parietal lobes. **Abbreviation:** DT-MRI, diffusion tensor magnetic resonance imaging. Reproduced with permission from Bozzali and Cherubini.[76]

production.[56] As additional effects, in vitro and in vivo models have suggested that neurons undergo apoptosis under DM-like conditions, which is marked by caspase-3 activation and is dependent on the concentration of glucose.[57] Interestingly, reduced blood glucose levels due to insulin-induced hypoglycemia may also contribute to neurodegeneration in animal models,[58] although the significance of this effect is yet to be validated in humans.[59]

*As well as increasing the atherosclerotic burden and in a similar fashion to the effects of hypertension, several diabetes-specific factors may compound its detrimental effects on the central nervous system and add to the burden of small-vessel disease.*

Although numerous epidemiologic studies have found an association between DM and clinically diagnosed AD,[55] autopsy studies in community- and population-based cohorts have failed to find a positive association with the characteristic pathologies of AD (plaques and tangles).[60–63] Rather, these postmortem studies have consistently found a strong positive association between DM and ischemic vascular pathologies,[60,61] thus underscoring the importance of VCI in the overall dementia process.

## CARDIAC FAILURE AND DEGENERATIVE BRAIN DISEASE

Chronic cardiac failure is now being increasingly recognized as another cause of cerebral hypoperfusion, VCI, and dementia. First proposed at least as early as 1977 with the now-disused term

DOI:10.1002/MSJ

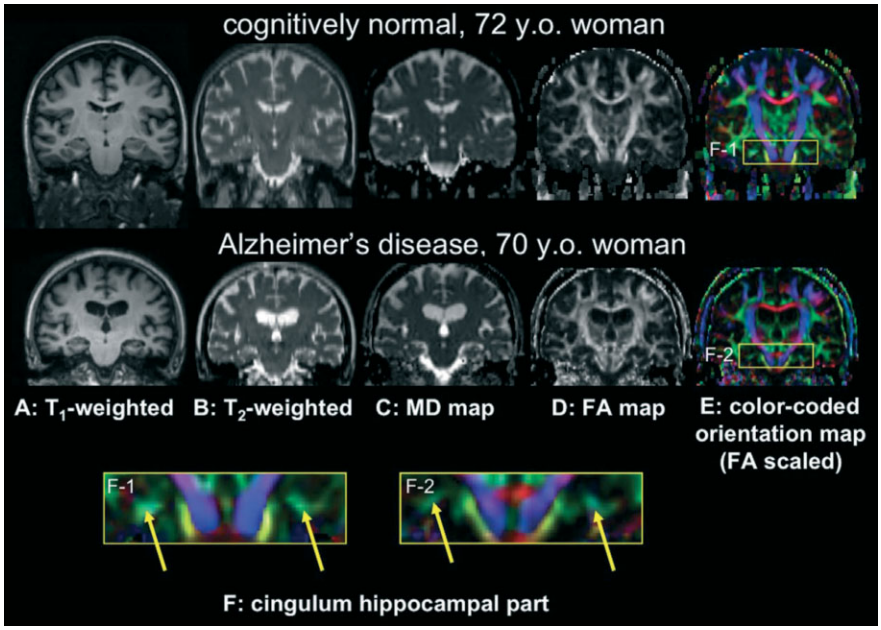


Fig 3. Comparison of conventional and DT-MRI of a cognitively normal 72-year-old woman (upper row) and a 70-year-old woman with AD. (A) Conventional $T_1$-weighted images. (B) Conventional $T_2$-weighted images. (C) DT-MRI–derived mean diffusivity. (D) DT-MRI–derived fractional anisotropy. (E) DT-MRI–derived color-coded orientation maps. The yellow rectangles in (E) are magnified and shown in (F), with (F-1) from the cognitively normal woman and (F-2) from the AD patient. The yellow arrows indicate the cingulum hippocampal regions. **Abbreviations:** AD, Alzheimer disease; DT-MRI, diffusion tensor magnetic resonance imaging; FA, fractional anisotropy; MD, mean diffusivity; y.o., year-old. Reproduced with permission from Oishi *et al.*[77]

"cardiogenic dementia,"[64] as described below abundant evidence has accumulated showing that cardiac failure is associated with VCI and DBD. The effects

> *Chronic cardiac failure is now being increasingly recognized as another cause of cerebral hypoperfusion, vascular cognitive impairment, and dementia.*

of cardiac failure on the brain include structural changes like white-matter hyperintensities and lacunar infarcts,[65] impaired global cognition,[66] impaired executive function,[67] and dementia.[68] Specifically, in a community-based Swedish cohort of 1301 individuals aged ≥75 years and without dementia at baseline, heart failure was associated with a multiadjusted hazard ratio of 1.84 (95% CI: 1.35–2.51) for dementia and 1.80 (95% CI: 1.25–2.61) for AD.[68] Furthermore, there is evidence to indicate that these effects, at least to a certain extent, are truly due to cardiac failure and not to collateral effects of CVD or CVD risk factors that may lead to cardiac failure. Thus, when compared with CVD patients with normal cardiac function, cardiac failure patients have an increased burden of structural brain changes on MRI[65] and perform worse on neuropsychological tests of attention, global cognition, memory, and verbal fluency.[69]

Although theories exist,[70] it is not yet fully understood how cardiac failure and reduced cardiac output lead to VCI and DBD. However, it would appear likely that the combined influences of the direct effects of reduced cardiac output, coupled with the shared environmental and genetic risk factors for both reduced cardiac output and DBD, lead to this phenomenon. Further research in these pathways is critically needed, including on the additional effects of epiphenomena such as the anemia of chronic disease and metabolic disturbances that arise in chronic cardiac failure.

## CONCLUSION

The links between atherosclerotic risk factors, cognitive dysfunction, and DBD are incontrovertible.

DOI:10.1002/MSJ

As described, vascular changes may account for a significant burden of dementia-related illness that is independent of primary Alzheimer pathology. Indeed, in addition to the traditional atherosclerotic risk factors discussed above, emerging data have shown that newer risk markers, such as genetic variability at the 9p21 locus, are also implicated in stroke,[71] VCI, and AD.[72,73] Nevertheless, despite the progress highlighted in this review, numerous aspects of small-vessel disease and other components of VCI remain incompletely understood. Perhaps the most pressing research that needs to be conducted is to define what treatments can be utilized to reduce or mitigate VCI. The appropriate treatment of CVD risk factors would appear a logical starting point. The question of whether progression to VCI could be slowed or even avoided by improved glucose, blood pressure, and lipid control is an especially important clinical question, about which we have few definitive studies at the current time. Another key research question that requires urgent attention is the molecular basis of the association between VCI and DBD. Not only is this important to our understanding of the dementia process, but it may open the door to novel therapeutic interventions to prevent or treat DBD. Given current projections of an aging population and these major research questions, this field is in critical need of continued scientific funding, with a vision toward improved understanding of the VCI-DBD disease pathobiology and novel therapeutic interventions.

It is now more than 100 years since Dr. Alois Alzheimer published his seminal description of the disease that now bears his name.[74,75] It is interesting to note that even at that time, Dr. Alzheimer noted characteristic "arteriosclerotic change" in the brain of the first described AD patient. What an incredibly astute observation that has turned out to be.

## ACKNOWLEDGEMENTS

No specific funding or grant was used to prepare this manuscript. Jason C. Kovacic is supported by National Institutes of Health Grant 1K08HL111330-01.

Figure 1 was produced by the authors using Servier Medical Art (Servier Laboratories Ltd., Wexham, United Kingdom).

## DISCLOSURES

*Potential conflict of interest:* Nothing to report.

## REFERENCES

1. Kovacic JC, Castellano JM, Fuster V. The links between complex coronary disease, cerebrovascular disease, and degenerative brain disease. *Ann N Y Acad Sci* 2012; 1254: 99–105.
2. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics–2011 update: a report from the American Heart Association. *Circulation* 2011; 123: e18–e209.
3. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005; 366: 2112–2117.
4. The three stages of Alzheimer's disease. *Lancet* 2011; 377: 1465.
5. Ballard C, Gauthier S, Corbett A, et al. Alzheimer's disease. *Lancet* 2011; 377: 1019–1031.
6. Kovacic JC, Moreno P, Hachinski V, et al. Cellular senescence, vascular disease, and aging: part 1 of a 2-part review. *Circulation* 2011; 123: 1650–1660.
7. Larson EB, Wang L, Bowen JD, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Ann Intern Med* 2006; 144: 73–81.
8. Ott A, Stolk RP, Van Harskamp F, et al. Diabetes mellitus and the risk of dementia: the Rotterdam Study. *Neurology* 1999; 53: 1937–1942.
9. Chandra V, Pandav R. Gene-environment interaction in Alzheimer's disease: a potential role for cholesterol. *Neuroepidemiology* 1998; 17: 225–232.
10. Kivipelto M, Helkala EL, Hanninen T, et al. Midlife vascular risk factors and late-life mild cognitive impairment: a population-based study. *Neurology* 2001; 56: 1683–1689.
11. Ott A, Slooter AJ, Hofman A, et al. Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. *Lancet* 1998; 351: 1840–1843.
12. Kennelly SP, Lawlor BA, Kenny RA. Blood pressure and the risk for dementia: a double edged sword. *Ageing Res Rev* 2009; 8: 61–70.
13. Luchsinger JA, Gustafson DR. Adiposity and Alzheimer's disease. *Curr Opin Clin Nutr Metab Care* 2009; 12: 15–21.
14. O'Brien JT, Erkinjuntti T, Reisberg B, et al. Vascular cognitive impairment. *Lancet Neurol* 2003; 2: 89–98.
15. Barber R, Scheltens P, Gholkar A, et al. White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer's disease, vascular dementia, and normal aging. *J Neurol Neurosurg Psychiatry* 1999; 67: 66–72.
16. Singh-Manoux A, Kivimaki M, Glymour MM, et al. Timing of onset of cognitive decline: results from Whitehall II prospective cohort study. *BMJ* 2012; 344: d7622.
17. Whitehouse PJ. Classification of the dementias. *Lancet* 2003; 361: 1227.
18. Hedden T, Gabrieli JD. Insights into the ageing mind: a view from cognitive neuroscience. *Nature Rev Neurosci* 2004; 5: 87–96.
19. Hulette C, Nochlin D, McKeel D, et al. Clinical-neuropathologic findings in multi-infarct dementia: a report of six autopsied cases. *Neurology* 1997; 48: 668–672.

DOI:10.1002/MSJ

20. Vermeer SE, Prins ND, Den Heijer T, et al. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med* 2003; 348: 1215–1222.
21. Kovacic JC, Roy PR, Baron DW, et al. Staged carotid artery stenting and coronary artery bypass graft surgery: initial results from a single center. *Catheter Cardiovasc Interv* 2006; 67: 142–148.
22. Mense L, Reimann M, Rudiger H, et al. Autonomic function and cerebral autoregulation in patients undergoing carotid endarterectomy. *Circ J* 2010; 74: 2139–2145.
23. Wityk RJ, Chang HM, Rosengart A, et al. Proximal extracranial vertebral artery disease in the New England Medical Center Posterior Circulation Registry. *Arch Neurol* 1998; 55: 470–478.
24. Amarenco P, Cohen A, Tzourio C, et al. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. *N Engl J Med* 1994; 331: 1474–1479.
25. Madan P, Kalra OP, Agarwal S, et al. Cognitive impairment in chronic kidney disease. *Nephrol Dial Transplant* 2007; 22: 440–444.
26. Kurella M, Chertow GM, Luan J, et al. Cognitive impairment in chronic kidney disease. *J Am Geriatr Soc* 2004; 52: 1863–1869.
27. Venturelli C, Jeannin G, Sottini L, et al. Cholesterol crystal embolism (atheroembolism). *Heart Int* 2006; 2: 155–160.
28. Onuigbo MA, Onuigbo NT. Worsening renal failure in older chronic kidney disease patients with renal artery stenosis concurrently on renin angiotensin aldosterone system blockade: a prospective 50-month Mayo-Health-System clinic analysis. *QJM* 2008; 101: 519–527.
29. White WB, Wolfson L, Wakefield DB, et al. Average daily blood pressure, not office blood pressure, is associated with progression of cerebrovascular disease and cognitive decline in older people. *Circulation* 2011; 124: 2312–2319.
30. Longstreth WT Jr, Bernick C, Manolio TA, et al. Lacunar infarcts defined by magnetic resonance imaging of 3660 elderly people: the Cardiovascular Health Study. *Arch Neurol* 1998; 55: 1217–1225.
31. Godin O, Tzourio C, Maillard P, et al. Antihypertensive treatment and change in blood pressure are associated with the progression of white matter lesion volumes: the Three-City (3C)-Dijon Magnetic Resonance Imaging Study. *Circulation* 2011; 123: 266–273.
32. Sonnen JA, Santa Cruz K, Hemmy LS, et al. Ecology of the aging human brain. *Arch Neurol* 2011; 68: 1049–1056.
33. Novak V, Hajjar I. The relationship between blood pressure and cognitive function. *Nat Rev Cardiol* 2010; 7: 686–698.
34. Petzold GC, Murthy VN. Role of astrocytes in neurovascular coupling. *Neuron* 2011; 71: 782–797.
35. Perlmuter LC, Sarda G, Casavant V, et al. A review of orthostatic blood pressure regulation and its association with mood and cognition. *Clin Auton Res* 2012; 22: 99–107.
36. Nicolakakis N, Hamel E. Neurovascular function in Alzheimer's disease patients and experimental models. *J Cereb Blood Flow Metab 2011*; 31: 1354–1370.
37. Luitse MJ, Biessels GJ, Rutten GE, et al. Diabetes, hyperglycaemia, and acute ischaemic stroke. *Lancet Neurol* 2012; 11: 261–271.
38. Balami JS, Chen RL, Grunwald IQ, et al. Neurological complications of acute ischaemic stroke. *Lancet Neurol* 2011; 10: 357–371.
39. Van Der Worp HB, Van Gijn J. Clinical practice. Acute ischemic stroke. *N Engl J Med* 2007; 357: 572–579.
40. Farkas E, Luiten PG. Cerebral microvascular pathology in aging and Alzheimer's disease. *Prog Neurobiol* 2001; 64: 575–611.
41. Iadecola C, Park L, Capone C. Threats to the mind: aging, amyloid, and hypertension. *Stroke* 2009; 40: S40–S44.
42. Kawai M, Kalaria RN, Cras P, et al. Degeneration of vascular muscle cells in cerebral amyloid angiopathy of Alzheimer disease. *Brain Res* 1993; 623: 142–146.
43. Thompson CS, Hakim AM. Living beyond our physiological means: small vessel disease of the brain is an expression of a systemic failure in arteriolar function: a unifying hypothesis. *Stroke* 2009; 40: e322–e330.
44. Kovacic JC, Moreno P, Nabel EG, et al. Cellular senescence, vascular disease, and aging: part 2 of a 2-part review: clinical vascular disease in the elderly. *Circulation* 2011; 123: 1900–1910.
45. Herzig MC, Winkler DT, Burgermeister P, et al. Abeta is targeted to the vasculature in a mouse model of hereditary cerebral hemorrhage with amyloidosis. *Nat Neurosci* 2004; 7: 954–960.
46. Bell RD, Zlokovic BV. Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. *Acta Neuropathol* 2009; 118: 103–113.
47. Itoh Y, Yamada M, Hayakawa M, et al. Cerebral amyloid angiopathy: a significant cause of cerebellar as well as lobar cerebral hemorrhage in the elderly. *J Neurol Sci* 1993; 116: 135–141.
48. Pettersen JA, Sathiyamoorthy G, Gao FQ, et al. Microbleed topography, leukoaraiosis, and cognition in probable Alzheimer disease from the Sunnybrook dementia study. *Arch Neurol* 2008; 65: 790–795.
49. Prins ND, Van Dijk EJ, Den Heijer T, et al. Cerebral small-vessel disease and decline in information processing speed, executive function and memory. *Brain 2005*; 128: 2034–2041.
50. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. *Stroke* 1997; 28: 652–659.
51. Lammie GA. Pathology of small vessel stroke. *Br Med Bull* 2000; 56: 296–306.
52. Scahill RI, Schott JM, Stevens JM, et al. Mapping the evolution of regional atrophy in Alzheimer's disease: unbiased analysis of fluid-registered serial MRI. *Proc Natl Acad Sci U S A* 2002; 99: 4703–4707.
53. Walters RJ, Fox NC, Schott JM, et al. Transient ischaemic attacks are associated with increased rates of global cerebral atrophy. *J Neurol Neurosurg Psychiatry* 2003; 74: 213–216.
54. Nitkunan A, Barrick TR, Charlton RA, et al. Multimodal MRI in cerebral small vessel disease: its relationship with cognition and sensitivity to change over time. *Stroke* 2008; 39: 1999–2005.
55. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: the Honolulu-Asia Aging Study. *Diabetes* 2002; 51: 1256–1262.
56. Ho L, Qin W, Pompl PN, et al. Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer's disease. *FASEB J* 2004; 18: 902–904.

DOI:10.1002/MSJ

57. Russell JW, Sullivan KA, Windebank AJ, et al. Neurons undergo apoptosis in animal and cell culture models of diabetes. *Neurobiol Dis* 1999; 6: 347–363.
58. Auer RN, Wieloch T, Olsson Y, et al. The distribution of hypoglycemic brain damage. *Acta Neuropathol* 1984; 64: 177–191.
59. Kramer L, Fasching P, Madl C, et al. Previous episodes of hypoglycemic coma are not associated with permanent cognitive brain dysfunction in IDDM patients on intensive insulin treatment. *Diabetes* 1998; 47: 1909–1914.
60. Sonnen JA, Larson EB, Brickell K, et al. Different patterns of cerebral injury in dementia with or without diabetes. *Arch Neurol* 2009; 66: 315–322.
61. Arvanitakis Z, Schneider JA, Wilson RS, et al. Diabetes is related to cerebral infarction but not to AD pathology in older persons. *Neurology* 2006; 67: 1960–1965.
62. Nelson PT, Smith CD, Abner EA, et al. Human cerebral neuropathology of type 2 diabetes mellitus. *Biochim Biophys Acta* 2009; 1792: 454–469.
63. Beeri MS, Silverman JM, Davis KL, et al. Type 2 diabetes is negatively associated with Alzheimer's disease neuropathology. *J Gerontol A Biol Sci Med Sci* 2005; 60: 471–475.
64. Cardiogenic dementia. *Lancet* 1977; 1: 27–28.
65. Vogels RL, Van Der Flier WM, Van Harten B, et al. Brain magnetic resonance imaging abnormalities in patients with heart failure. *Eur J Heart Fail 2007*; 9: 1003–1009.
66. Zuccala G, Cattel C, Manes-Gravina E, et al. Left ventricular dysfunction: a clue to cognitive impairment in older patients with heart failure. *J Neurol Neurosurg Psychiatry* 1997; 63: 509–512.
67. Putzke JD, Williams MA, Rayburn BK, et al. The relationship between cardiac function and neuropsychological status among heart transplant candidates. *J Card Fail* 1998; 4: 295–303.
68. Qiu C, Winblad B, Marengoni A, et al. Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. *Arch Intern Med* 2006; 166: 1003–1008.
69. Trojano L, Antonelli Incalzi R, Acanfora D, et al. Cognitive impairment: a key feature of congestive heart failure in the elderly. *J Neurol* 2003; 250: 1456–1463.
70. Jefferson AL. Cardiac output as a potential risk factor for abnormal brain aging. *J Alzheimers Dis* 2010; 20: 813–821.
71. Wahlstrand B, Orho-Melander M, Delling L, et al. The myocardial infarction associated CDKN2A/CDKN2B locus on chromosome 9p21 is associated with stroke independently of coronary events in patients with hypertension. *J Hypertens* 2009; 27: 769–773.
72. Zuchner S, Gilbert JR, Martin ER, et al. Linkage and association study of late-onset Alzheimer disease families linked to 9p21.3. *Ann Hum Genet* 2008; 72: 725–731.
73. Emanuele E, Lista S, Ghidoni R, et al. Chromosome 9p21.3 genotype is associated with vascular dementia and Alzheimer's disease. *Neurobiol Aging* 2011; 32: 1231–1235.
74. Alzheimer A. Über eine eigenartige Erkrankung der Hirnrinde [article in German]. *Allgemeine Zeitschrift für Psychiatrie und Psychisch–Gerichtliche Medizin* 1907; 64: 146–148.
75. Alzheimer A, Stelzmann RA, Schnitzlein HN, et al. An English translation of Alzheimer's 1907 paper, "Über eine eigenartige Erkrankung der Hirnrinde." *Clin Anat* 1995; 8: 429–431.
76. Bozzali M, Cherubini A. Diffusion tensor MRI to investigate dementias: a brief review. *Magn Reson Imaging* 2007; 25: 969–977.
77. Oishi K, Mielke MM, et al. DTI analyses and clinical applications in Alzheimer's disease. *J Alzheimers Dis* 2011;(26 suppl 3): 287–296.

DOI:10.1002/MSJ