Vascular Contributions to Cognitive Impairment and Dementia

A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association

Statement Authors

Philip B. Gorelick MD, MPH,FAHA, Co-Chair; Angelo Scuteri** MD, PhD, Co-Chair; Sandra E. Black† MD, FRCPC; Charles DeCarli† MD; Steven M. Greenberg† MD, PhD, FAHA; Costantino Iadecola† MD, FAHA; Lenore J. Launer† MD; Stephane Laurent† MD; Oscar L. Lopez† MD; David Nyenhuis† PhD, ABPP-Cn; Ronald C. Petersen† MD, PhD; Julie A. Schneider† MD, MS; Christophe Tzourio† MD, PhD; Donna K. Arnett, PhD, MSPH, FAHA; David A. Bennett, MD; Helena C. Chui, MD; Randall T. Higashida, MD, FAHA; Ruth Lindquist, PhD, RN, ACNS-BC, FAAN; Peter M. Nilsson, MD, PhD; Gustavo C. Roman, MD, Frank W. Sellke, MD, FAHA; Sudha Seshadri, MD; on behalf of the American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention and Council on Cardiovascular Surgery and Anesthesia**

** = Co-Chair;
† = Writing Group Section Leader

Slide Set Developed by:

Deborah Bergman ANP, RN

David Nyenhuis PhD, ABPP-Cn

Fernando Testa MD

Introduction

- Burden of Cognitive Impairment becomes increasingly important as people live longer
- While Alzheimer's disease (AD) is the most commonly diagnosed dementia cause, cognitive impairment due to cerebrovascular are also important, independent contributors to cognitive dysfunction

Dementia Prevalence and Incidence

- Overall dementia prevalence in affluent countries is 5 – 10% in individuals age 65 and older
- AD prevalence doubles every 4.3 years
- Vascular dementia (VaD) prevalence doubles every 5.3 years
- Age-adjusted dementia incidence rates (per 1000 person years) AD: 19.2; VaD: 14.6

The Effect of Diagnostic Thresholds on Vascular-related Prevalence and Incidence Rates

- Most older studies use VaD (or Multi-infarct Dementia, MID) when estimating prevalence and incidence
- The construct of Vascular Cognitive Impairment (VCI) refers to the entire spectrum of vascular-related cognitive impairment, from mild to severe
- VCI prevalence and incidence rates are therefore are higher than VaD or MID rates

Vascular Cognitive Impairment (VCI) Includes:

- Prodrome conditions, such as Vascular Cognitive Impairment, No Dementia (VCIND) or Vascular Mild Cognitive Impairment (Vascular MCI)
- “Pure” Vascular Dementia (VaD)
- “Mixed Disease”: concomitant vascular and other pathology, such as pathology associated with AD

The Effect of Different Criteria on the Prevalence and Incidence of VCI and VaD

- Criteria set up by Hachinski et al. for MID yield a relatively large number of cases
- NINDS-AIREN criteria are relatively conservative and yield more modest rates
- Criteria that include neuroimaging data may significantly influence frequency figures
- Inclusion of “mixed disease” will yield higher numbers, as mixed pathologies may be the most common explanation of cognitive impairment in aging
- DSM V may introduce new terms (e.g., Major Neurocognitive Disorder) which may also impact prevalence and incidence rates

The Role of Vascular Lesion Type on the Extent of Cognitive Impairment

- Do large cortical infarcts, lacunar infarcts, subcortical white matter disease, strategically placed subcortical infarcts and a combination of these lesion types have differing cognitive footprints?
- Vascular lesions may lower the threshold for the clinical manifestation of AD
- Evidence of cholinergic compromise in both AD and VCI

This slide set Will Cover the Current State of the Field

- Definitions of AD and VCI
- The basic pathophysiologic underpinnings of VCI
- Challenges in defining vascular effects neuropathologically
- The role of neuroimaging in defining VCI clinical presentation and course
- Mid and late life VCI risk factors
- VCI clinical trials
- Recommendations for VCI prevention and treatment
- Directions for the future in VCI research and treatment

Defining AD and VCI

- A significant evolution in terminology of cognitive deficits associated with cerebrovascular disease (CVD)
- MID: used to identify patients who developed dementia after multiple strokes
- VaD: severe cognitive and functional impairment regardless of CVD etiology
- VCI: encompasses all cognitive disorders associated with CVD, from mild deficits to frank dementia

VCI Definition

"A syndrome where there is evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain."

Clinical Criteria for VCI

- VCI is an overarching condition that includes both VaD and Vascular Mild Cognitive Impairment (vaMCI)
- VCI Criteria is based on two factors: a demonstration of the presence of a cognitive disorder by neuropsychological testing, and a history of clinical stroke or presence of cerebrovascular disease (CVD) by neuroimaging that suggests a link between the cognitive disorder and the vascular disease
- VCI is to be used with all etiologies of CVD, including cardioembolic, atherosclerotic, ischemic, hemorrhagic or genetically-related CVD

The VaD Subgroup of VCI

- The definition of dementia is key in diagnosing VaD; all major VaD criteria sets to date have different dementia definitions
- Many dementia definitions include a requirement of memory deficits; however, this may not be suitable for VaD, where memory-related structures may be intact
- Therefore, memory deficits should not be required for VaD

The Relationship of CVD to VaD

- Neuroimaging of cortical infarcts, subcortical infarcts and other stroke lesions is critical when associating stroke with VaD
- Understanding the source of cardiac or vascular pathology that underlies CVD may provide more specific clinical pathologic relationships
- While cognitive deficits may appear soon after clinical stroke, the deficits may appear more than 3 months after the stroke; therefore, a required time frame after stroke may be arbitrary

The Relationship of CVD to VaD

- White matter lesions (WML), aka leukoaraiosis, are critical in diagnosing CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), a genetic form of VaD in relatively young individual
- WMLs are common in the elderly and may have less diagnostic value in elderly individuals. A high threshold of WMLs may be necessary for extensive cognitive impairment0

VaD Heterogeneity

- VaD may co-exist with multiple cerebral and systemic disorders that can affect cognition in the elderly, especially AD
- It is often difficult to determine whether cognitive deterioration is solely a consequence of vascular factors or to underlying AD
- Determining the presence and effect of AD on dementia associated with CVD is the most difficult aspect of VaD diagnosis

Mild Vascular Cognitive Impairment

- Current MCI criteria include “amnestic MCI” and MCI associated with other cognitive impairment (amnestic MCI + other cognitive deficit; non-amnestic, single domain MCI; and non-amnestic, multiple domain MCI)
- vaMCI was first thought to require deficits in executive function; however, clinical studies have shown that vaMCI subjects may present with a broader array of cognitive impairment

Reversibility of vaMCI

- Persons with MCI have been shown to return to normal cognition
- Individuals with vaMCI may revert to normal cognition without specific treatment because of the presence of depression, heart failure or an autoimmune disorder
- In addition, post-stroke recovery may result in cognitive improvement, thus moving an individual from vaMCI to normal cognitive function

Neuropsychological Assessment of VCI

- 2006 NINDS-Canadian Stroke Council VCI Harmonization guidelines include suggested neuropsychological protocols for persons with suspected VCI
- VCI cognitive assessment requires a comprehensive cognitive battery that includes an assessment of executive function, as well as memory, language function and spatial function
- Operational definitions of cognitive impairment (e.g., performance 1 or 1.5 standard deviations below the control mean) are preferred over qualitative descriptions of cognitive symptoms

Neuropsychological Differentiation of AD and VCI

- Differentiation of AD and VCI by neuropsychological assessment alone has met with mixed success
- Executive dysfunction may not specifically point to CVD
- This line of research is complicated by difficulty in clinically differentiating AD or VCI from mixed (AD + CVD)
- The heterogeneity of CVD works against a single, unifying neurocognitive pattern of VCI deficits

VCI Diagnostic Criteria

- What follows is a series of slides that outline criteria for probable and possible VaD and probable and possible vaMCI

VCI Diagnostic Criteria: Introduction

1. The term VCI characterizes all forms of cognitive deficits from VaD to MCI of vascular etiology.
2. These criteria cannot be used in subjects who have an active diagnosis of drug or alcohol abuse/dependence. Subjects must be free of any type of substance for at least 3 months.
3. These criteria cannot be used in subjects with delirium.

VCI Diagnostic Criteria: Dementia

1. The diagnosis of dementia should be based on a decline in cognitive function from a prior baseline and a deficit in performance in two or more cognitive domains that are of sufficient severity to affect the subjects' activities of daily living
2. The diagnosis of dementia must be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: executive/attention, memory, language, and visuospatial functions.
3. The deficits in activities of daily living are independent of the motor/sensory sequelae of the vascular event.

VCI Diagnostic Criteria: Probable VaD

There is cognitive impairment and imaging evidence of CVD, and:

a) There is clear temporal relationship between a vascular event (e.g., Clinical Stroke) and the onset of cognitive deficits; or

b) There is a clear relationship in the severity and pattern of cognitive impairment, and the presence of diffuse, subcortical CVD pathology (e.g., as in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CADASIL)

2) There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a non-vascular neurodegenerative disorder.

VCI Diagnostic Criteria: Possible VaD

There is cognitive impairment and imaging evidence of CVD, **but**:

1) There is no clear relationship (temporal, severity, or cognitive pattern) between the vascular disease (e.g., silent infarcts, subcortical small vessel disease) and the cognitive impairment; or
2) There is insufficient information for the diagnosis of VaD (e.g., clinical symptoms suggest the presence of vascular disease, but there are no CT/MRI studies available); or
3) Aphasia severity precludes proper cognitive assessment. However, patients with documented evidence of normal cognitive function (e.g. annual cognitive evaluations) before the clinical event that caused aphasia *could* be classified as Probable VaD; or
4) There is evidence of other neurodegenerative diseases or conditions in addition to CVD that may affect cognition, such as: a. a history of other neurodegenerative disorders (e.g., Parkinson's disease, progressive supranuclear palsy, Dementia with Lewy bodies, etc.); b. the presence of AD biology is confirmed by biomarkers (e.g., PET, CSF, amyloid ligands) or genetic studies (e.g., PS1 mutation); or c. there is a history of active cancer, or psychiatric or metabolic disorders that may affect cognitive function.

VCI Diagnostic Criteria: Vascular Mild Cognitive Impairment (vaMCI)

1. vaMCI includes the four subtypes proposed for the classification of MCI: Amnestic, Amnestic + other domains, Non-amnestic single domain, and Non-amnestic multiple domain.
2. The classification of vaMCI must be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: Executive/attention, memory, language, and visuospatial functions. The classification should be based on an assumption of decline in cognitive function from a prior baseline and impairment in at least one cognitive domain.
3. Instrumental activities of daily living could be normal or mildly impaired, independent of the presence of motor/sensory symptoms

VCI Diagnostic Criteria: Probable vaMCI

There is cognitive impairment and imaging evidence of CVD, and:

a. There is clear temporal relationship between a vascular event (e.g., Clinical Stroke) and the onset of cognitive deficits; or

b. There is a clear relationship in the severity and pattern of cognitive impairment, and the presence of diffuse, subcortical CVD pathology (e.g., as in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CADASIL)

2. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder.

VCI Diagnostic Criteria: Possible vaMCI

There is cognitive impairment and imaging evidence of CVD, but:

1. There is no clear relationship (temporal, severity or cognitive pattern) between the vascular disease (e.g., silent infarcts, subcortical small vessel disease) and the onset of cognitive deficits; or
2. There is insufficient information for the diagnosis of vaMCI (e.g., clinical symptoms suggest the presence of vascular disease, but there are no CT/MRI studies available); or
3. Aphasia severity precludes proper cognitive assessment. However, patients with documented evidence of normal cognitive function (e.g. annual cognitive evaluations) before the clinical event that caused aphasia *could* be classified as Probable vaMCI; or
4. There is evidence of other neurodegenerative diseases or conditions in addition to CVD that may affect cognition, such as: a. a history of other neurodegenerative disorders (e.g., Parkinson's disease, progressive supranuclear palsy, Dementia with Lewy bodies, etc.); b. the presence of AD biology is confirmed by biomarkers (e.g., PET, CSF, amyloid ligands) or genetic studies (e.g., PS1 mutation); or c. there is a history of active cancer, or psychiatric or metabolic disorders that may affect cognitive function.

Summary

- VCI is a syndrome that includes a broad range of cognitive impairment severity
- Executive dysfunction is often, but not always included in the VCI cognitive impairment pattern
- The most severe form of VCI is VaD
- vaMCI includes individuals with cognitive impairment who do not meet dementia criteria
- Keys to defining VCI are neuropsychological testing, bedside or office clinical examination and neuroimaging

Neuropathologic Aspects

- Defining the pathology underlying VCI has remained elusive
- Infarcts vary in size, number and location, and occur commonly in the elderly, with and without dementia
- Infarcts are typically accompanied by AD and other pathologies
- Progress has been made by studying persons in community samples close to the time of death, then again using quantitative measurements of vascular and AD pathology at autopsy

Cerebral Infarctions are Common in Older Persons

- Cerebral infarctions are the most important cerebrovascular pathology that contributes to cognitive impairment
- Cerebral infarcts are discreet regions of tissue loss, observed both macro- and microscopically
- Chronic macroscopic infarcts occur in 1/3 to ½ of older persons, far more frequently than clinical stroke
- In some community-based studies, microscopic infarcts are more common than macroscopic infarcts

Cerebral Infarctions and VCI

- In clinical-pathologic studies, larger infarct volume and increased number of macroscopic infarcts are associated with an increased likelihood of dementia
- There is yet no reliable cut-point for infarct volume and dementia
- Infarct location is important: thalamus, angular gyrus and basal ganglia may be more likely than other regions to result in cognitive impairment
- Still, regional factors have not been clearly defined and many other regions have been related to dementia
- Microscopic infarcts have been related to dementia, even after accounting for macroscopic infarcts
- Cognitive reserve and other co-existing pathologies may be additional factors when relating cerebral infarctions to cognitive impairment and dementia

Infarctions, AlzD Pathology and Dementia or MCI

- Most persons with dementia and almost half of those with clinically probable AlzD have mixed (AlzD + CVD) pathology
- Infarcts appear additive with AlzD pathology in lowering cognitive function, increasing the odds of dementia, and increasing the odds of clinical AlzD
- The public health importance of infarcts and their role in dementia is likely underestimated
- Prevention and therapies that decrease cerebral infarcts are likely to lower the prevalence of dementia
- AlzD has been found to be the most common pathology associated with MCI, though mixed pathologies are also common

White Matter Degeneration and Cerebral Microbleeds

- White matter degeneration and cerebral microbleeds are common in the brains of older persons, and may reflect direct tissue damage
- A role for cognitive impairment associated with white matter degeneration is suggested by neuroimaging studies, but it is currently unclear whether white matter lesions represent separate pathologic substrates of VCI
- Some studies have not shown clear associations between neuropathologic measurements of white matter lesions and cognitive function, unless they were part of a combined vascular score that also included infarcts

Neuroimaging and Pathology: Future Directions

- Post-mortem evaluations complement neuroimaging studies in several ways:
- While neuroimaging detects macroscopic lesions, microscopic infarcts is currently not within the resolution of most scans
- Some vascular pathologies may represent either vascular or degenerative processes (e.g., hippocampal volume visualized on antemortem neuroimaging may be related to either AlzD or vascular pathology)
- More prospective, quantitative clinical-pathologic-neuroimaging studies are needed to fully understand the pathologic bases of neuroimaging change and the complex interplay between vascular and AlzD pathologies in the evolution of VCI, dementia and clinical AlzD

Basic Science Aspects Neurovascular Unit and Cerebral Blood Flow

- Neurons, glia, perivascular and vascular cells working in concert to maintain cerebral microenvironment
- Neuronal activity increases CBF (functional hyperemia)
- Autoregulation: maintains CBF constant within a range of BP
- Endothelial cells exert cerebral trophic actions
- Specialized transporters regulate trafficking of molecules between blood and brain and remove metabolic bioproducts (including Ab)

Basic Science Aspects
Neurovascular Unit: A Target for Dementias

- Profoundly disrupted in VCI and AlzD
- Pathogenesis
    - Ab weakens the vessel wall
    - Ab is a potent vasoconstrictor that impairs autoregulation and functional hyperemia
    - BBB alterations occur in VCI
    - Vascular oxidative stress, as seen in association with VCI risk factors and Ab, leads to inflammation
    - Inflammation, in turn, enhances oxidative stress
    - Both may disrupt saltatory conduction increasing metabolic demands

Basic Science Aspects
Neurovascular Unit: Conclusions

- Neurovascular Unit
  - Major target of vascular risk factors
  - Plays a key role in VCI and AlzD
  - Potential therapeutic targets
    - Vascular oxidative stress
    - Vascular inflammation
    - Therapies enhancing regenerative and reparative processes that may restore neurovascular unit function

CAA and Hereditary SV Syndromes
Cerebral Amyloid Angiopathy

- Characterized by Ab deposition in penetrating arterioles and capillaries of leptomeninges and cortex
- Seen in 10-30% of unselected brain autopsies
- Seen in 80-100% of AlzD brain autopsies
- Associated with important vascular changes
  - Loss of vascular smooth muscle cells
  - Microaneurysms
  - Concentric splitting and fibrinoid necrosis

CAA and Hereditary SV Syndromes

Cerebral Amyloid Angiopathy

- Clinical Presentation
  - Spontaneous ICH
  - Age-related cognitive impairment
    - Seen after controlling for severity of AD
- Pathogenesis of Cognitive Impairment
  - Not well established
  - Related to microbleeds, microinfarcts, white matter disruption (as evidence in CT, MRI, tMRI)
  - CAA is associated with vascular and perivascular inflammation leading to subcortical WM vasogenic edema

CAA and Hereditary SV Syndromes
Cerebral Amyloid Angiopathy

- Diagnosis
  - Largely based on T2* MRI sequences
  - “Probable CAA”: Multiple strictly lobar hemorrhages in the absence of alternative causes
  - PET imaging
    - Pittsburg Compound B (PiB) binds Ab
    - Not specific for CAA
    - Compared to AIzD, PiB retention in CAA has an occipital predominance

CAA and Hereditary SV Syndromes Cerebral Amyloid Angiopathy

- Treatment
  - No specific treatment
  - Optimize vascular risk factor control
  - A subset of patients may have CAA-related inflammation which may respond to immunosuppressive treatment with corticosteroid or cyclophosphamide

CAA and Hereditary SV Syndromes Hereditary Small-Vessel Syndromes - CADASIL

- Most common hereditary cause of VCI
- Caused by a missense mutation of the *Notch-3* gene (autosomal dominant transmission)
- Clinical presentation
  - Migraine with aura
  - Mood disturbances
  - Cognitive impairment
  - Recurrent strokes
  - Radiological evidence of extensive white-matter changes

CAA and Hereditary SV Syndromes Hereditary Small-Vessel Syndromes - CADASIL

- Diagnosis
  - *Notch-3* gene sequencing (*de novo* mutations may occur)
  - Deposition of granular osmiophilic material in the arteriolar media in skin and muscle vessels
- Treatment
  - No specific treatment
  - Patients with hypertension, elevated HbA1c, and smoking may have a worse clinical and radiological outcome

CAA and Hereditary SV Syndromes
Hereditary Small-Vessel Syndromes - Other

MUTATION	SYNDROME
APPb - amyloid precursor protein gene	Familial CAA
Exonuclease - *TREX1* gene	Autosomal dominant retinal vasculopathy with cerebral leukodystrophy
TGF-b1 repressor - *HTRA-1* gene	Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy
Type-IV a1 collagen subunit - *COL4A1* gene	Congenital poroencephaly, leukoencephalopathy, and intracerebral hemorrhage

CAA and Hereditary SV Syndromes Recommendations

1. MRI with T2* sequences can be used to assess patients with suspected CAA *(Class IIa; LOE B)*

2. *Notch-3* genetic testing can be used in patients with suspected CADASIL *(Class IIa; LOC A)*

3. *Notch-3* genetic testing can be used in sporadic cases with suspected CADASIL *(Class IIa; LOC A)*

4. Skin on muscle biopsy looking for granular osmiophilic deposits may be considered an alternative or complementary procedure in suspected cases of CADASIL when *notch-3* testing is unavailable or inconclusive *(Class IIb; LOC B)*

5. Treatment of cardiovascular risk factors is reasonable in suspected cases of CAA and CADASIL *(Class IIa; LOE C)*

6. Patients with subacute cognitive decline and suspected CAA should be treated with a course of immunosuppressive therapy *(Class I, LOE B)*

Pathophysiology of Arterial Function Vascular Aging

- Refers to age-related changes in arterial structure and function
- Includes
  - Carotid was thickening
  - Arterial stiffening
  - Vascular remodelling

Pathophysiology of Arterial Function Carotid Intima-Media Thickness (IMT) and VCI

- IMT increases in:
  - Normal Aging
    - Blood pressure pulsality causes fragmentation and depletion of elastin and increases collagen
  - Pathological conditions
    - Medial thickening increases in response to HTN
    - Intima thickening is seen in atherosclerosis
- IMT Is Associated with Cognitive Function
  - The thicker the artery, the lower the cognitive performance

Pathophysiology of Arterial Function Carotid Intima-Media Thickness (IMT) and VCI

- Linking IMT to VCI
  - Carotid IMT and atherosclerosis are associated with similar cardiovascular risk factors
  - Atherosclerosis may cause VCI via
    - Large vessel occlusive disease with chronic hypoperfusion
    - Artery-to-artery embolism
    - Increased parenchymal oxidative stress
    - Blood pressure dysregulation affecting BBB integrity

Pathophysiology of Arterial Function Arterial Stiffness (AS) and VCI

- Age-related vascular process
- Measured by Carotid-Femoral Pulse Wave Velocity (CFPWV)
- CFPWV is inversily related to cognitive impairment with or without dementia
- Pathways that may link AS to brain damage
  - Endothelial dysfunction and oxidative stress
  - Large-/small-artery cross-talk
  - Exposure of small vessels to high-flow throughout systole and diastole with low vascular resistance

Pathophysiology of Arterial Function Small-artery Remodeling and VCI

- Systemic Age-related vascular process
  - Small vessel narrowing
    - Thickening of basal membrane of capillaries
    - Perivascular collagen deposition
  - Arteriolar dysfunction
  - Endothelial leakage
- Accelerated by vascular risk factors
- Associated with arterial stiffening
- Not well studied in VCI

Neuroimaging Factors in VCI Clinical Presentation

- VCI is a syndrome
  - Stroke or subclinical vascular brain injury based on clinical presentation or neuroimaging
  - Impairment of at least 1 cognitive domain

- Classic presentation
  - Stepwise progression in association with stroke
  - Relatively uncommon considering that asymptomatic brain infarction is more common than stroke

Neuroimaging Factors in VCI Cerebrovascular brain injury (CVBI)

- Prevalence of silent cerebral infarction
  - 5.8-17.7% based on MRI findings in the general population
  - Age related process. In the Framingham study
    - 5^{th} and 7^{th} decade 10%
    - 8^{th} decade 17%
    - 9^{th} decade 30%
  - Lesion location
    - Basal ganglia 52%
    - Other subcortical areas 35%
    - Cortical areas 11%

Neuroimaging Factors in VCI
Vascular Brain Injury and Cognition Are Related

- CVBI
  - May be associate with or without memory-related cognitive deficits
  - Progressive leukoaraiosis or silent brain ischemia correlate with persistent cognitive impairment, especially executive function
- Stroke
  - Doubles the risk of dementia
  - Dementia post stroke is associated with 2- to 6-fold increase in long-term mortality
  - The prevalence of dementia post stroke is 30%

Neuroimaging Factors in VCI Post-Stroke Dementia (PSD)

- Radiological Predictors of PSD
  - Silent cerebral infarcts, white matter changes, and global and medial temporal lobe atrophy
  - Location of the stroke
    - Left hemisphere, anterior and posterior cerebral artery distribution, and multiple infarcts
    - "Strategic location" of the infarct
      - Left angular gyrus, inferomesial temporal, mesial frontal, anterior and dorsomedial thalamus, left capsular genu, and caudate nuclei
- 19-61% of PSD patients may have concomitant AlzD

Neuroimaging Factors in VCI - Role of Neuroimaging in VCI

- Role of Brain MRI in VCI is not well defined
  - High sensitivity
    - can detect asymptomatic vascular abnormalities such as leukoaraiosis and microbleeds
  - Limited accuracy
    - WM changes may be not vascular in origin
    - Not all vascular lesions can be detected by MRI
    - Confounded by coincident AIzD or vascular depression
- Recommendation: use of brain MRI or head CT may be reasonable in making the diagnosis of VCI (Class IIb; LOE B)

Impact of Cardiovascular Risk Factors at Different Ages on the Risk of Cognitive Decline

- Included studies addressing the range of cognitive impairment, including VaD diagnosed with internationally recognized criteria.
- Studies generally included tests that conform to the NINDS-CSVCI harmonization standards, reported at the minimum one non-memory cognitive test of a function typically affected in VCI, or a diagnosis of VCI or VaD

Impact of Cardiovascular Risk Factors: Continued

- This statement excluded studies reporting only on tests of global cognition, memory tests, total dementia, or AlzD.
- This is recognized as a somewhat arbitrary choice, as there are many articles and reviews showing vascular risk factors are also importantly associated with AlzD, mixed dementia, and amnestic MCI.
- Neuropathic studies shows a high proportion of older persons have mixed pathology, AlzD lesions being the most prevalent.

Impact of Cardiovascular Risk Factors: Continued

- Most risk factors are drawn from studies providing Class I evidence: the RF is reported as a major finding in a community-based study, that is preferably prospective, or a part of an intervention, with a sample size of >500.
- For specific factors, such as coronary artery bypass grafting and cardiac output, we reviewed studies based on Class II evidence according to carefully analyzed clinical data.

Impact of Cardiovascular Risk Factors: Continued

- Issues specific to studying RFs for cognitive impairment :
  - Questionnaire data rely on the recall of subjects, who by definition of the research may be cognitively impaired
  - Reverse causation must be considered as it is possible the RF level is a response to, rather than a ‘cause’ of the outcome
  - The activity of biomarkers in the brain generally cannot be directly measured
  - The cognitive tests for VCI are, to a degree, non-specific for vascular disease, and the different criteria for VaD identify different sets of individuals
  - The brains of older persons have multiple morbidities that can lead to the same phenotype

Non-modifiable Risk Factors

- Demographic factors
- Genetic Factors

Summary: Demographic and Genetic Factors

- Like most neuro-cognitive disorders of late life, VCI is likely to be more common as age increases
- There is no apparent association of APO E ε4 and VCI
- More genetic candidates are expected to emerge as additional studies on endophenotypes of VCI are studied
- These traits include specific cognitive domains such as speed of processing, vascular lesions (macrovascular) and microvascular lesions

Lifestyle Factors

- Education
- Diet
- Physical activity and physical function
- Alcohol intake
- Obesity
- Smoking
- Social Support/Networks

Summary: Lifestyle Factors

- May be risks for VCI, and for many of them, there is evidence for plausible biologic mechanisms by which they may heighten risk of VCI.
- Gaps in knowledge about the role of such factors in VCI may be bridged by additional well-designed epidemiological studies, harmonization of how lifestyle activity is defined, and clinical trials.

Lifestyle Factors Recommendations

- The following lifestyle interventions in persons at risk for VCI ***are*** reasonable:
  1. Smoking cessation (Class IIa, Level of Evidence A)

Lifestyle Factors Recommendations

- The following lifestyle interventions in persons at risk for VCI ***may be*** reasonable
  1. Moderation of alcohol intake (Class IIb, Level of Evidence B)
  2. Weight Control (Class IIb, Level of Evidence B)
  3. Physical Activity (Class IIb, Level of Evidence B)

The following is not recommended:

The use of antioxidants and B vitamins in persons at risk for VCI are not useful based on current evidence (Class III, Level of Evidence A)

Physiologic Risk Factors

- Depression
- Physiologic Risk Factors
- Blood Pressure
- Hyperglycemia, insulin resistance, metabolic syndrome, and diabetes
- Lipids
- Inflammation

Summary: Physiologic Risk Factors

- Midlife systolic and diastolic blood pressure, history of hypertension, and total cholesterol level predict VCI
- The relation of late-life VCI to measures of BP and cholesterol level in later life suggest higher levels of exposure to these risk factors may be beneficial
- Diabetes and hyperglycemia are associated with vascular cognitive impairment.
- CRP, a marker of inflammation, is associated with VaD.

Physiologic Risk Factors: Recommendations

- Treatment of the following physiologic factor in persons at risk for VCI is recommended:
  - Hypertension (Class I, Level of Evidence A)
- Treatment of the following physiologic factors in persons at risk for VCI may be reasonable:
  - Hyperglycemia (Class IIb, Level of Evidence C)
  - Hypercholesterolemia (Class IIb, Level of Evidence A)
  - It is uncertain if treatment of inflammation will reduce the risk of VCI in persons at risk of VCI. (Class IIb, Level of Evidence C)

Concomitant Vascular Disease

- Preventable chronic vascular conditions have been linked to dementia
  - Coronary Artery Disease (CAD)
  - Chronic Kidney Disease
  - Stroke
  - Atrial Fibrillation
  - Peripheral Artery Disease
  - Low Cardiac Output
- Some of them may cause VCI directly, by brain damage (stroke), or indirectly

Concomitant Vascular Disease

- Coronary Artery Disease (CAD)
  - Independent risk factor for VaD
  - CABG is associated with poorer cognitive function and higher late-life dementia
- Chronic Kidney Disease (CKD)
  - Patients with CKD have increased prevalence of cognitive impairment
  - The association between CKD and cognitive impairment may be confounded by shared vascular risk factors for stroke

Concomitant Vascular Disease

- Stroke
  - Dementia is common after stroke
    - 10% of new strokes may develop new-onset dementia
    - 30% of patients with recurrent stroke
  - Variables that may affect these observations
    - Location, clinical severity, volume of brain tissue affected, early post-stroke complications (eg seizures, hypotension, hypoxia, and delirium)
    - Stronger predictor of post-stroke dementia: previous stroke
    - Other: pre-stroke cognitive impairment, diabetes, low level of education, AFib

Concomitant Vascular Disease

- Atrial Fibrillation
  - AF increases the risk of stroke
  - AF has been proposed as an independent risk factor for VaD, though a few studies have not observed a direct association
- Peripheral Artery Disease and Low Cardiac Output
  - Both have been associated with VaD
  - Low cardiac output may affect cerebral perfusion leading to progression of WML and cognitive decline

Clinical Trials in VCI: Background

Recent pivotal trials to test drugs approved for AlzD in patients with VaD have failed to achieve regulatory approval because:

- only modest benefit on standard cognitive measures which under-sampled executive function has been shown
- inconsistent benefits have been demonstrated to global and daily function (difficult to evaluate when physical deficits with stroke co-exist)
- high specificity but low sensitivity of VaD criteria made recruitment difficult
- inclusion of memory loss in VaD criteria made it challenging to exclude concomitant AlzD
- concern that frontline clinicians could not distinguish AlzD from VaD made regulators reluctant to grant a separate indication

VaD Therapeutic Targets and Methods

- Management of vascular risk factors and symptomatic pharmacotherapy for VaD has been the primary approach
- Standardized screening and monitoring across trials (e.g., cognitive screening, brain imaging) are essential
- Factors that may exacerbate clinical disease manifestations (e.g., pain, sleep disorders) must be addressed
- Providers must also support caregivers (e.g.,identify community resources, transportation access, education regarding VCI psychological and cognitive symptoms and course)

Summary of VCI Pharmacotherapy Recommendations

Treatment	Recommendation, Class/Level of Evidence	Comments
Donepezil	Level A, Class IIa for "pure" VaD	Study 307, 308 (N=1219): modest benefit for cognitive & global, less robust for function; Study 319 (N=974): only cognitive benefit
Galantamine	Level A, Class IIa for mixed AlzD-CVD; Class IIb for "pure" VaD	Pure and mixed VaD Gal-Int-6 (N=592): benefit in all primary outcomes overall; only cognitive benefit in pure disease; "Pure" VaD (Gal-Int-26 – N=788): modest benefit in cognitive/executive measures
Rivastigmine Memantine	Level C, Class IIb Level A, Class IIb	VCIND study (N=50): modest benefit in some executive functions (N=900): modest cognitive benefit only

Pharmacologic Treatment of VCI: Donepezil

- There is pathological and clinical evidence for cholinergic compromise in VCI, as in AD
- In donepezil trials, cognitive benefit was found, but global and functional efficacy was less consistent
- Donepezil side effect profile is similar to AD donepezil trials; one recent trial with more deaths in the treatment group than the placebo group was shown to have had fewer than expected deaths in the placebo group
- A recent trial with CADASIL patients was neutral; post-hoc analyses showed a beneficial effect in executive function measures

Pharmacologic Treatment of VCI: Galantamine

- Showed benefit in a mixed (AlzD + CVD) sample, but not in an under-powered “pure” VaD group
- A second, larger study showed cognitive benefit, but no daily function benefit; also a trend for global benefit (p = .06)

Pharmacologic Treatment of VCI: Rivastigmine and Memantine

- Rivastigmine has been less well studied, with promising preliminary beneficial effects seen in two small samples
- Memantine, an NMDA antagonist, has shown cognitive, but not global or functional benefit

Pharmacologic Treatment of VCI: Cochrane Review and Meta-analysis Conclusion of VaD Trials

- Cochrane Reviews: donepezil studies have provided the best available evidence for a beneficial effect for VaD; galantamine studies have provided best available evidence for a beneficial effect for mixed dementia (AD + CVD); memantine and rivastigmine benefit is not yet proven
- A meta-analysis comments that the cognitive benefits of cholinergic agents and memantine are of uncertain significance in VaD

Pharmacologic Treatment of VCI: Future Directions

- More clinical trial evidence would be helpful, including pharmacoeconomic evaluations
- Future studies should use updated case selection and outcome criteria, including more sensitive executive function measures
- Use of advanced neuroimaging biomarkers that better define atrophy and vascular brain injury is recommended
- Amyloid labeling and/or cerebrospinal fluid markers might be considered to detect concomitant Alzheimer pathology

Pharmacologic Treatment of VCI: Recommendations

1. Donepezil can be useful for cognitive enhancement in patients with VaD (Class IIa, Level of Evidence: A)
2. Administration of galantamine can be beneficial for patients with mixed AlzD/VaD (Class IIa, Level of Evidence: A
3. The benefits of rivastigmine and memantine are not well established (Class IIb, Level of Evidence: A)

Non-pharmacologic Treatments

- Few non-pharmacologic therapies have been tests and found to be beneficial in the VCI population
- Cochrane review: cognitive rehabilitation/ cognitive stimulation so far have not proven effective, though there are few randomized controlled trials and many methodological limitations in this area
- Cochrane review: acupuncture in human VaD was inconclusive; more studies are needed
- No formal recommendations are offered for non-pharmacologic treatments, as evidence is limited

Prospects for Prevention of VCI and AD by Risk Factor Control

- Even a modest delay in the appearance or worsening of cognitive deterioration could translate into a relatively large reduction of the incidence of disease
- Midlife vascular and metabolic risk factors should be regarded as potential major targets for dementia prevention
- Safeguarding normal cognitive development during childhood and adolescence (e.g., through proper nutrition) may also be an important preventative factor of later cognitive decline and impairment

Main Longitudinal Studies on the Relationship between Antihypertensive Drug Use and Risk of Dementia
(1st of 2 slides)

First author and year of publication	Study	Sample size	Type of sample	Follow-up in years	Effect of antihypertensive drug overall	Effect by type of antihypertensive drug
Guo et al., 1999	Kungsholmen project	1301	Community-based; no dementia	3	Dementia: RR = 0.7 (0.6 to 1.0)	Treatment effect mainly due to diuretics
in't Veld et al, 2001	Rotterdam study	6416	Community-based; no dementia	2.2	Dementia overall: RR = 0.76 (0.52–1.12) ; VaD: RR = 0.33 (0.11–0.99) ; AD: RR = 0.87 (0.56–1.37)	No differences among antihypertensive drugs
Morris et al, 2001	EPESE	634	Random sample	4	AD: RR = 0.66 (0.68 to 2.61)	No differences among antihypertensive drugs
Lindsay et al, 2002	Canadian Study of Health and Aging	4088	national sample	5	AD: RR = 0.91 (0.64 to 1.30)	
Qiu et al, 2003	Kungsholmen project	1270	Community-based; no dementia	5	Dementia: RR = 0.8 (0.6 to 1.0); AD: RR = 0.7 (0.5 to 0.9)	
Yasar et al, 2005	Baltimore Longitudinal Study of Aging	1092	Community-based; no dementia	19	–	AD: RR = 0·30 (0·07 to 1·25) for dihydropyridine type of CCB; RR = 0.82 (0.37 to 1.83) for non-dihydropyridine type of CCB;

Main Longitudinal Studies on the Relationship between Antihypertensive Drug Use and Risk of Dementia
(2nd of 2 slides)

First author and year of publication	Study	Sample size	Type of sample	Follow-up in years	Effect of antihypertensive drug overall	Effect by type of antihypertensive drug
Khachaturian et al, 2006	Cache County Study	3297	Community-based; no dementia	3	AD: RR = 0.64 (0.41 to 0.98)	Stronger effect for diuretics and specifically potassium sparing diuretics HR = 0.26 (0.08 to 0.64),
Peila R. et al, 2006	Honolulu Asia Aging Study	1294	Community-based cohort	5	HR per year of antihypertensive use: Dementia: HR = 0.94 (0.89 to 0.99) ; AD: HR = 0.96 (0.93 to 0.99) ; VaD: HR = 0.94 (0.89 to 0.99)	
Haag et al, 2009	Rotterdam study	6249	Community-based; no dementia	13	HR per year of antihypertensive use: Dementia: HR = 0.95 (0.91 to 0.99) ; AD: HR = 0.94 (0.90 to 0.99)	No differences among antihypertensive drugs
Lu et al, 2009	US Veteran Affairs	819,491	Administrative database	4	–	HR for dementia : ARB vs. cardiovascular drugs = 0.76 (0.69 to 0.84) ; ARB vs. lisinopril = 0.81 (0.73 to 0.90) ; lisinopril vs. cardiovascular drugs = 0.94 (0.91 to 0.97)

CCB= calcium channel blockers; EPESE: East Boston Established Populations for Epidemiologic Studies of the Elderly

Summary of Main Longitudinal Studies on the Relationship between Antihypertensive Drug Use and Risk of Dementia

- An association between mid-life HTN and late-life cognitive decline or dementia has been found in the majority of observational studies
- Observational studies point to some benefit of anti-HTN treatment on risk of AD
- The longer the duration of treatment, the stronger the preventive effect
- Treatment seems more effective in the youngest old than in the oldest persons
- Few studies suggest a greater effect of some classes of antihypertensive therapy, but evidence to date is limited and subject to bias

Main Randomized Trials of Antihypertensive Drugs that have Included Cognitive Impairment or Dementia as Outcomes: General Characteristics

Study	Sample size for analysis	Mean age (SD)	type of treatment	SBP/DBP difference (active vs. placebo)	Duration of follow-up in years
SHEP	4736	71.6 (6.7)	Diuretic (chlorthalidone) and/or beta-blocker (atenolol) or reserpine	-11 to 14 / -3 to 4	4.5
Syst-Eur	2418	69.9 (6.2)	Ca-channel blocker (dihydropyridine) with or without beta-blocker (enalapril maleate) and/or diuretic (hydrochlorothiazide)	-8.3/-3.8	2.0
PROGRESS	6105	64 (10)	ACEI (perindopril) with or without diuretic (indapamide)	-9.0/-4.0	4
SCOPE	4937	76.4 (–)	ARB (candesartan cilexetil) and/or Diuretics	-3.2/-1.6	3.7
HYVET	3336	83.5 (3.1)	Diuretic (indapamide) with or without ACEI (perindopril)	-15/-5.9	2.2
PRoFESS	20332	66.1 (8.6)	ARB (telmisartan)	-5.4/–	2.4

Table 6. Main Randomized Trials of Antihypertensive Drugs That Have Included Cognitive Impairment or Dementia as Outcomes:
Results on Dementia

		Incidence and Number of Dementia Cases					
		Active		Placebo			
Study	Diagnosis of Dementia	Cases of Dementia/Number of patients	Incidence (per 1000 patient-years)	Cases of Dementia/Number of Patients	Incidence (per 1000 patient-years)	Main Results on Dementia (95% CI)	Type of Dementia (Alzheimer Disease vs VCI or Poststroke Dementia)
SHEP[440]	Expert-based; DSM-III-R	37/2365	Not indicated	44/2371	Not indicated	16% Reduction in dementia; nonsignificant	Not defined
Syst-Eur[442]	Expert-based; DSM-III-R	11/1238	3.8	21/1180	7.7	50% (0% to 76%) Reduction in dementia; *P*=0.05	23 Cases of Alzheimer disease and 7 cases of mixed dementia
PROGRESS[445]	Expert-based; DSM-IV	193/3051	16	217/3054	19	12% (−8% to 28%) Reduction in dementia; *P*=0.2	34% (3% to 55%) Reduction in dementia with recurrent stroke; *P*=0.03 1% (−24% to 22%) for other dementia; *P*=0.9
SCOPE[443]	ICD-10 criteria; Independent Clinical Event Committee	62/2477	6.8	57/2460	6.3	7% Increased risk in active arm; *P*>0.20	Not defined
HYVET[444]	Expert based; DSM-IV	126/1687	33	137/1649	38	14% (−9% to 23%) Reduction in dementia; *P*=0.2	Similar results for Alzheimer disease (164 patients) and vascular dementia (84 patients)
PRoFESS[441]	Clinical impression of dementia	408/8624		409/8646		No reduction of the risk of dementia; *P*=0.48	Not defined

Summary of Main Randomized Trials of Antihypertensive Drugs that have Included Cognitive Impairment or Dementia as Outcomes

- Six large randomized trials of antihypertensive drugs included an assessment of dementia and cognitive function
- Four of these trials reported no clear-cut effect on the risk of dementia or cognitive function
- One study reported a beneficial effect on dementia risk; another reported an effect on risk of post-stroke dementia
- All six trials share common limitations: short follow-up duration; heterogeneity in screening and dementia diagnosis; inclusion of patients at low risk for dementia (young mean age, high baseline MMSE); small numbers of incident cases and low statistical power; and differential dropout

Meta-analyses of Randomized Trials of Blood Pressure Lowering Treatment on Prevention of Dementia

First author	year of publication	Studies	Sample size (N° events/N° patients)	Type of effect	P for heterogeneity	Main results
Birns J et al	2003	PROGRESS SCOPE SHEP Syst-Eur	642/18,196	fixed	0.18	0.89 (95%CI 0.75-1.04) ; P=0.15
Feigin V et al	2005	PROGRESS SCOPE SHEP Syst-Eur	883/23,505	random	0.06	0.80 (95%CI 0.63-1.02) ; P=0.07
Peters R et al	2008	HYVET PROGRESS SHEP Syst-Eur	786/16,595	random	0.49	0·87 (95% CI 0·76–1·00); P=0·045
McGuiness B et al	2008	SCOPE SHEP Syst-Eur	232/15,295	fixed	0.16	0.89 (95%CI 0.69-1.16) ; P=0.38
McGuiness B et al	2009	HYVET SCOPE SHEP Syst-Eur	495/15,427	fixed	0.30	0.89 (95%CI 0.74-1.07) ; P=0.21

Summary of Meta-analyses of Randomized Trials of Blood Pressure Lowering Treatment on Prevention of Dementia

- Five meta-analyses have been published on dementia risk in anti-hypertensive trials
- The studies used various study methods (e.g., model type, selection of patients)
- None examined all available trials combined
- Only one meta-analytic study found that dementia risk was significantly decreased
- Overall, the variance for dementia risk reduction ranged from 11% to 20%

Summary Regarding Blood Pressure Lowering and Cognition

- Observational studies point to some benefit of anti-hypertensive treatment on risk of AD
- Few large blood pressure lowering trials have incorporated cognitive assessment or dementia diagnosis
- Meta-analyses neither prove nor disprove the efficacty of anti-hypertensive treatment on dementia risk

Recommendations Regarding Blood Pressure Lowering and Cognition

1. In patients with stroke, lowering blood pressure is effective for reducing the risk of post-stroke dementia (Class I, Level of Evidence: B)
2. There is reasonable evidence that, in middle-aged and young-elderly, lowering blood pressure can be useful for the prevention of late-life dementia (Class IIa, Level of Evidence: B)
3. The usefulness of lowering blood pressure in individuals age 80+ is not well-established (Class IIb, Level of Evidence: B)

Diabetes

- Persons with diabetes of long duration are at risk for cognitive decline and dementia
- Both hyperglycemia and hyperinsulinanemia are associated with cognitive dysfunction and stroke dementia
- Hyperglycemia treatment has been associated with prevention of both microvascular and to some degree macrovascular events. Stroke prevention has not been shown with careful control of glucose
- No studies have specifically investigated possible protective effects of hyperglycemia control on VCI
- There is no convincing evidence relating type or intensity of diabetic treatment to the prevention or management of cognitive impairment in type 2 diabetes

Diabetes Recommendation

1. The effectiveness of treating diabetes/hyperglycemia for the prevention of dementia is not well established (Class IIb, Level of Evidence C)

Lipids

- Treatment with statin therapy has been documented to protect from stroke
- However, statin therapy do not prevent cognitive decline in the elderly
- There is need for additional studies on the role of hyperlipidemia in cognitive impairment

Lipids Recommendation

1. The usefulness of hyperlipidemia for prevention of dementia is uncertain (Class IIb, Level of Evidence C)

Other Interventions on Vascular Factors: Aspirin

- The few observational studies that have examined the effect of aspirin on cognition have shown inconsistent results
- In both the AAA and PRoFESS trials, aspirin therapy was not found to affect cognitive outcomes

Other Interventions on Vascular Factors: Lifestyle

- A few observational studies have shown a relationship between adherence to a Mediterranean diet and better cognition and lower dementia risk.
- Increased physical activity has been associated with better cognitive function in observational studies and in cognitive improvement in one small intervention study
- Smoking is a risk factor for stroke-associated dementia, but there are no intervention studies relating smoking cessation to better cognitive outcomes
- Folic acid study results are mixed. No cognitive benefits were shown to be associated with folic acid supplementation in a study with older healthy women or in a separate study with patients with mild to moderate cognitive decline and different forms of dementia. However, a third study found improved cognitive function in domains that tend to decline with age in subjects who took 800 mg daily oral folic acid compared to a placebo group

Other Interventions on Vascular Factors: Recommendations

1. A Mediterranean-type dietary pattern has been associated with less cognitive decline in several studies and may be reasonable (Class IIb, Level of Evidence B).
2. Vitamin supplementation is not proven to improve cognitive function, even if homocysteine levels have been positively influenced, and its usefulness is not well established. (Class IIb, Level of Evidence B).
3. Physical activity might be considered for the prevention of cognitive impairment (Class IIb, Level of Evidence B), but the usefulness of other lifestyle or vitamin interventions are uncertain (Class IIb, Level of Evidence B).
4. Effectiveness of antiaggregant therapy for VCI is not well established (Class IIb, Level of Evidence B).

Summary and Course of Action

- In developed countries, we anticipate a rapid increase in the aged population; an estimated 2 billion persons aged 60 or over by 2050
- Dementia affects an estimated 30% of persons over 80 years of age
- Identification of persons at risk for cognitive impairment and dementia hold promise for prevention or postponement of dementia, resulting in increased functional independence of older persons and for public health cost savings
- Cognitive function and its relationship to CV and stroke risks, should be screened for in clinical practice, and these risk factors should be treated

Relationships between Vascular and Neurodegenerative Processes in Cognitive Impairment and Dementia

- It is now accepted that many traditional risk factors for stroke are also risk markers for AD and VCI
- There may be a convergence of pathogenic mechanisms in vascular and neurodegenerative processes which cause cognitive impairment (e.g., an angiogenesis hypothesis for AD)
- Epidemiologic studies also point to linkages between traditional CV risk factors and AD risk

A Possible Shift in Prevention Efforts

- More “upstream targets,” such as shared vascular risk markers, extrinsic (e.g. somatic and mitochondrial mutations) and intrinsic (e.g., telomere shortening) mechanistic pathways which may influence prevention outcomes
- Might consider that AD is actually a group of disorders that could be driven by different pathophysiologic mechanisms, some of which include vascular risk factors such as HTN, diabetes and dyslipidemia
- Consider efforts to better understand “covert” brain injury, such as “silent” strokes and white matter lesions, as they may be associated with neuropsychological deficits and eventual stroke sequelae

Current Recommendations for Clinicians

1. Use screening tools to detect cognitive impairment in their older patients (e.g., www.mocatest.org)
2. Continue to treat vascular risks according to nationally- or regionally-accepted guidelines

Summary – Action Plans for future research in the field

1. Continued development, validation and refinement of practciable cognitive batteries for testing.
2. Continued pursuit of novel neuroimaging methodology to identify biomarkers and risks for CVBI associated with VCI.
3. Establishment of additional longitudinal clinical neuropathological studies with neuroradiological correlation.
4. Development of nationally funded centers of excellence for the study of CVBI and vascular contributions to cognitive impairment and dementia.
5. Midlife and later-life cost0effectiveness research and proper, statistically powered, randomized controlled clinical trials targeting key vascular risk markers and the influence of their control on prevention of VCI and Alz disease.
6. Preclinical and clinical studies to better understand the influence of aging on major arteries and the neurovascular unit.
7. Studies to identify novel risk markers for vascular contributions to cognitive impairment and dementia.
8. Studies to understand the relationship between location, severity, and extent of vascular brain injury dn the resultant cognitive syndromes. These programs should include genetic and other novel factors with the overarching goal to identify new strategies for prevention or treatment of VCI.