Vascular Dementia: Cerebrovascular Injury, Clinical Syndromes, Neuroimaging, and Interaction with Alzheimer Pathology

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Abstract

Vascular dementia (VaD) represents a heterogeneous group of cognitive disorders caused by cerebrovascular disease and remains the second most common cause of dementia worldwide after Alzheimer's disease. Rather than a single disease entity, VaD encompasses multiple pathophysiological mechanisms, including large-vessel infarction, small-vessel disease, strategic infarcts, hypoperfusion-related injury, and hemorrhagic lesions. Advances in neuroimaging and neuropathology have refined the understanding of how cerebrovascular injury disrupts distributed neural networks, leading to executive dysfunction, slowed processing speed, and impaired attention that distinguish VaD from primary neurodegenerative dementias. Increasingly, evidence demonstrates that vascular pathology rarely occurs in isolation; instead, mixed dementia, particularly the coexistence of vascular brain injury with Alzheimer-type pathology, is the most common substrate underlying late-life cognitive impairment.

This narrative review provides a comprehensive synthesis of updated literature on vascular dementia, focusing on types of cerebrovascular injury, clinical syndromes, neuroimaging correlates, and interactions with Alzheimer pathology. Emphasis is placed on mechanistic pathways, clinico-radiologic correlations, and implications for diagnosis, prognosis and prevention.

Key words:
Vascular dementia, cerebrovascular injury, clinical syndromes, neuroimaging, Alzheimer pathology

Introduction

Dementia is a leading cause of disability and dependency among older adults, with substantial societal and economic impact. Vascular dementia (VaD) has historically been conceptualized as a consequence of cumulative ischemic brain injury resulting from cerebrovascular disease. However, this traditional view has evolved significantly over the past two decades. Contemporary research highlights the complexity of vascular contributions to cognitive impairment, recognizing VaD as a spectrum disorder with diverse etiologies, clinical presentations, and pathological substrates (O'Brien & Thomas, 2015; Skrobot et al., 2018).

Epidemiological studies suggest that purely "vascular-only" dementia is relatively uncommon, particularly in older populations. Instead, mixed dementia—characterized by the coexistence of vascular brain injury and Alzheimer pathology—accounts for a substantial proportion of cases (Schneider et al., 2007; Toledo et al., 2013). This overlap has important implications for diagnosis, clinical management, and research, as vascular pathology may lower the threshold at which Alzheimer pathology becomes clinically manifest.

Recognition of vascular contributions to cognitive impairment has expanded beyond overt infarction to include small-vessel disease, white matter injury, cerebral microbleeds, blood–brain barrier dysfunction, and chronic hypoperfusion. These processes preferentially affect frontal–subcortical circuits, resulting in characteristic patterns of cognitive impairment that distinguish VaD from Alzheimer's disease (AD), although overlap is common (Roman et al., 1993; Sachdev et al., 2014).

This review synthesizes current knowledge on VaD, with particular focus on cerebrovascular injury types, clinical syndromes, neuroimaging findings, and interaction with Alzheimer pathology.

Conceptual Framework and Definitions

1. Evolution of the Concept of Vascular Dementia

The term "vascular dementia" was initially used to describe dementia resulting from multiple cortical infarcts, often with a stepwise clinical course. Early diagnostic criteria emphasized abrupt onset, focal neurological signs, and temporal association with stroke events (Hachinski et al., 1974). While useful, this framework underestimated the contribution of subclinical vascular injury and small-vessel disease.

Subsequent diagnostic systems broadened the definition to include subcortical ischemic vascular dementia, strategic infarct dementia, and hypoperfusion-related cognitive impairment (Roman et al., 1993). More recently, the concept of vascular cognitive impairment (VCI) has been introduced to encompass the full spectrum of cognitive dysfunction attributable to cerebrovascular disease, ranging from mild cognitive impairment to overt dementia (Sachdev et al., 2014).

2. Vascular Cognitive Impairment Continuum

VCI emphasizes that cognitive impairment due to vascular causes exists along a continuum rather than as a dichotomous state. Mild cognitive deficits may precede dementia by years and offer opportunities for intervention through vascular risk factor modification (Gorelick et al., 2011).

Table 1. Spectrum of Vascular Cognitive Impairment

Stage	Description	Clinical Features
Vascular brain injury without cognitive impairment	Imaging evidence of infarcts or white matter disease	No functional impact
Vascular mild cognitive impairment	Measurable cognitive decline	Preserved activities of daily living
Vascular dementia	Cognitive impairment with functional decline	Loss of independence

This framework underscores the importance of early detection and prevention.

Types of Cerebrovascular Injury in Vascular Dementia

Cerebrovascular injury in VaD arises from multiple mechanisms, often coexisting within the same individual. The type, location, and cumulative burden of vascular lesions determine clinical expression (Pantoni, 2010).

1. Large-Vessel Ischemic Infarction
Large-vessel disease leads to cortical or cortico-subcortical infarcts due to atherosclerosis or cardioembolism. Cognitive impairment results when infarcts involve association cortices or when multiple lesions disrupt distributed networks (Bowler et al., 1997).

Large territorial infarcts may produce acute cognitive decline, whereas multiple smaller infarcts accumulate over time, leading to progressive deterioration.

2. Small-Vessel Disease
Small-vessel disease (SVD) is the most common pathological substrate of VaD. It affects penetrating arterioles and capillaries, leading to lacunar infarcts, white matter hyperintensities, microinfarcts, and microbleeds (Pantoni, 2010). Risk factors include hypertension, diabetes, aging, and genetic susceptibility. SVD preferentially damages frontal–subcortical circuits, producing executive dysfunction and psychomotor slowing (Prins & Scheltens, 2015).

3. Strategic Infarcts
Strategic infarct dementia results from single lesions in cognitively critical regions such as the thalamus, hippocampus, angular gyrus, basal forebrain, or caudate nucleus. Despite limited lesion volume, disruption of key hubs can cause disproportionate cognitive deficits (Ghika-Schmid & Bogousslavsky, 2000).

4. Chronic Hypoperfusion and Border-Zone Injury
Chronic cerebral hypoperfusion, often due to cardiac failure or severe carotid disease, contributes to diffuse white matter injury and cortical dysfunction. Border-zone infarcts between major arterial territories are particularly vulnerable (De la Torre, 2012).

5. Hemorrhagic and Microvascular Injury
Cerebral microbleeds and hemorrhages, frequently associated with cerebral amyloid angiopathy or hypertensive arteriopathy, contribute to cognitive decline through direct tissue injury and network disruption (Greenberg et al., 2009).

Table 2. Major Types of Cerebrovascular Injury in VaD

Injury Type	Typical Lesions	Cognitive Impact
Large-vessel infarction	Cortical infarcts	Aphasia, visuospatial deficits
Small-vessel disease	Lacunes, WMH	Executive dysfunction
Strategic infarcts	Thalamus, hippocampus	Memory, attention deficits
Hypoperfusion	Border-zone lesions	Global slowing
Hemorrhagic injury	Microbleeds	Executive and attentional deficits

Clinical Syndromes of Vascular Dementia (Overview)

Vascular dementia presents with heterogeneous clinical syndromes reflecting underlying vascular pathology. Unlike Alzheimer's disease, early memory impairment is often less prominent, while executive dysfunction, slowed processing speed, and attentional deficits are characteristic (O'Brien & Thomas, 2015).

The major clinical syndromes include:

- Multi-infarct dementia
- Strategic infarct dementia
- Subcortical ischemic vascular dementia (small-vessel disease)

These syndromes frequently overlap, particularly in older adults with mixed pathology.

Clinical Syndromes of Vascular Dementia

Vascular dementia (VaD) is best understood as a set of clinical syndromes arising from different patterns of cerebrovascular injury. Contemporary frameworks increasingly use the umbrella term vascular cognitive impairment and dementia (VCID) to emphasize that cognitive impairment due to vascular disease spans from mild impairment to major neurocognitive disorder and often coexists with neurodegenerative pathology (Sachdev et al., 2025). In geriatric practice, differentiating clinical syndromes is valuable for prognosis and for aligning neuroimaging findings with plausible mechanisms of cognitive decline (Ng & colleagues, 2025; Mok et al., 2024).

Across syndromes, VaD typically features disproportionate impairment in processing speed, attention, executive function, and gait/psychomotor features, reflecting disruption of frontal–subcortical networks and white matter connectivity; memory impairment may be present but is often less prominent early than in typical Alzheimer presentations (Mok et al., 2024; Duering et al., 2023). Syndrome boundaries are imperfect because mixed lesion patterns are common, particularly in late life (Ng & colleagues, 2025).

Table 3. Core Clinical Syndrome Patterns in VaD (Practical, Clinic-Oriented)

Syndrome	Typical Course	Core Cognitive Profile	Common Associated Features
Multi-infarct (cortical) dementia	Stepwise or fluctuating, often post-stroke	Variable; may include language/visuospatial deficits	Focal neurological signs; stroke history
Strategic infarct dementia	Abrupt or subacute after a single lesion	Domain-specific deficits (memory/attention/ executive)	Focal deficits depending on lesion site
Subcortical ischemic VaD (small vessel disease)	Insidious, slowly progressive	Processing speed/executive dysfunction > memory	Gait disorder, falls, mood changes, urinary symptoms

(Updated syndrome framing and clinicoradiologic emphasis: Ng & colleagues, 2025; Mok et al., 2024; Duering et al., 2023)

1 Multi-Infarct Dementia (Cortical and Cortico-Subcortical Infarction)

Clinical features and trajectory

Multi-infarct dementia traditionally describes cognitive impairment attributable to multiple ischemic infarcts, often in a stepwise manner following clinically overt strokes. Modern practice recognizes that the “stepwise” pattern is not mandatory; multi-infarct presentations can be progressive, particularly when recurrent silent infarcts occur or when coexisting small vessel disease adds a chronic burden of white matter injury (Ng & colleagues, 2025).

The cognitive profile depends on lesion distribution. Cortical infarcts affecting language networks can produce aphasia-dominant decline, while parietal or posterior lesions can generate visuospatial deficits and apraxias. When infarcts are dispersed across multiple networks, the result may be global cognitive impairment with prominent executive deficits and impaired attention (Mok et al., 2024).

Recent syntheses emphasize the importance of quantifying lesion burden and network disruption, rather than counting discrete infarcts. Neuroimaging phenotype approaches are increasingly used in research to link patterns of infarction to cognitive outcomes and dementia risk (Chen et al., 2025). Similarly, the field has pushed toward standardized neuropsychological domain mapping to improve diagnostic reliability in VCID (Bentvelzen et al., 2025; Sachdev et al., 2025).

Table 4. Multi-Infarct Dementia: High-Yield Clinical and Imaging Correlates

Feature	Clinical expression	Typical neuroimaging correlate
Post-stroke cognitive decline	Decline after index stroke	Territorial infarct(s), cortical involvement
Recurrent vascular events	Stepwise or episodic deterioration	Multiple infarcts over time, new DWI lesions
Network disruption	Executive/attention impairment	Distributed infarcts, reduced connectivity
Coexisting SVD	Slower progression, gait involvement	WMH, lacunes, microbleeds alongside infarcts

(Phenotype-based and standardized assessment emphasis: Chen et al., 2025; Bentvelzen et al., 2025; Duering et al., 2023; Ng & colleagues, 2025)

2 Strategic Infarct Dementia

Concept

Strategic infarct dementia refers to dementia or major cognitive impairment resulting from a single infarct in a cognitively critical "hub" region or connecting pathway, where lesion location outweighs lesion volume. Updated clinical reviews stress that strategic lesions can be cortical or subcortical and may produce abrupt or rapidly evolving cognitive syndromes (Ng & colleagues, 2025).

Key lesion locations and clinical syndromes

Strategic lesions commonly involve:

- Thalamus (attention, arousal, memory circuitry)
- Basal forebrain (cholinergic projections to cortex)
- Hippocampus/medial temporal structures (memory encoding)
- Angular gyrus/posterior association cortex (language/semantic integration)
- Caudate and frontal-subcortical circuits (executive function and motivation)

Clinically, patients may present with prominent attentional deficits, dysexecutive syndrome, apathy, memory impairment, or language dysfunction depending on lesion site. Because older adults frequently have silent comorbid small-vessel disease or Alzheimer pathology, determining causality requires careful temporal correlation between infarct timing and cognitive decline, supported by imaging (Sachdev et al., 2025; Ng & colleagues, 2025).

Table 5. Strategic Infarct Locations and Typical Cognitive Presentations

Strategic region	Typical cognitive phenotype	Common clinical clues
Thalamus	Attention/executive dysfunction, memory retrieval problems	Somnolence, fluctuating attention
Basal forebrain	Prominent amnestic syndrome, attentional deficits	Abrupt memory decline, apathy
Caudate/frontal-subcortical circuits	Dysexecutive syndrome, slowed processing	Apathy, reduced initiative, gait issues
Angular gyrus/parietal association	Language, calculation, visuospatial deficits	Alexia, acalculia, apraxia
Hippocampal/medial temporal infarct	Memory encoding impairment	Acute anterograde amnesia pattern

(Clinical syndromes contextualized within updated VCID diagnostic logic: Sachdev et al., 2025; Ng & colleagues, 2025)

3 Subcortical Ischemic Vascular Dementia and Small Vessel Disease–Related VCID

Why small vessel disease dominates late-life VCID

Cerebral small vessel disease (cSVD) is now widely recognized as a primary driver of vascular cognitive impairment and a major contributor to dementia burden in aging populations (Duering et al., 2023; Hainsworth et al., 2024). cSVD produces chronic, cumulative injury—often "silent" clinically—manifesting as white matter disconnection, lacunes, microinfarcts, and microbleeds. This injury aligns with a clinical syndrome marked by slowed processing speed, impaired executive function, gait disturbance, mood symptoms, and urinary dysfunction (Mok et al., 2024; Markus, 2023).

Updated standards: STRIVE-2 and imaging harmonization

A major 2022–2025 advance has been the push for improved consistency in describing cSVD imaging features. Research standards have been updated since the original STRIVE recommendations, with emphasis on harmonized acquisition and reporting across studies and clinical trials (Duering et al., 2023). This standardization is critical because cSVD markers are used both for diagnosis and as surrogate outcomes in trials.

Cognitive phenotype in cSVD-related VaD

The neuropsychological pattern is often:

- Processing speed impairment (early and prominent)
- Executive dysfunction (planning, set-shifting, attention)
- Reduced mental flexibility
- Variable memory impairment (often retrieval rather than encoding early)

The syndrome may be subtle initially, making it clinically under-recognized unless structured cognitive testing is used. Recent consensus work has reinforced domain-based assessment in VCID and supports more standardized neuropsychological evaluation to improve diagnostic reliability across settings (Bentvelzen et al., 2025; Sachdev et al., 2025).

Table 6. cSVD-Related VCID: Clinical Profile and Common Imaging Markers

Domain	Typical clinical finding	Imaging correlate
Executive function	Dysexecutive syndrome, reduced planning	WMH, lacunes, strategic subcortical lesions
Processing speed	Slowed thinking, psychomotor slowing	Diffuse WMH, microstructural damage
Gait/balance	Gait instability, falls	WMH burden, lacunes
Mood/behaviour	Apathy, depression	Frontal-subcortical disconnection
Vascular vulnerability	Fluctuating cognition with illness	Chronic cSVD + reduced reserve

(Updated imaging/reporting and clinic mechanisms: Duering et al., 2023; Hainsworth et al., 2024; Mok et al., 2024; Markus, 2023)

Total cSVD burden concepts (2024–2025)

Recent studies and reviews increasingly use "total cSVD burden" scores, combining WMH, lacunes, microbleeds, and perivascular spaces to reflect cumulative injury. Systematic evaluation of these scores' reliability and validity is expanding, supporting their use in research and potentially in clinical stratification (Silva et al., 2025). This is aligned with the broader movement toward quantitative and harmonized cSVD characterization (Duering et al., 2023).

Neuroimaging in Vascular Dementia: Introduction to the Diagnostic Role

Neuroimaging is central to modern diagnosis of VaD/VCID because it provides objective evidence of vascular brain injury, helps attribute causality, identifies mixed pathology patterns, and supports prognostication (Sachdev et al., 2025; Ng & colleagues, 2025). In clinical practice, MRI is preferred over CT because it better visualizes white matter hyperintensities, lacunes, microbleeds, and strategic infarcts that define syndromic subtypes (Duering et al., 2023; Mok et al., 2024).

Table 7. Imaging Modalities and the VaD/VCID Questions they Answer

Modality	Strengths	Best for
MRI (FLAIR)	Sensitive to WMH	cSVD burden, disconnection patterns
MRI (DWI)	Detects acute/subacute ischemia	New infarcts, post-stroke cognition
MRI (SWI/T2*)	Sensitive to microbleeds	Hemorrhagic injury, amyloid angiopathy suspicion
CT	Rapid, accessible	Large infarcts/hemorrhage screening

(Updated standards and diagnostic emphasis: Duering et al., 2023; Sachdev et al., 2025; Mok et al., 2024)

1. Neuroimaging findings in VaD/VCID (WMH patterns, lacunes, microbleeds, cortical infarcts, strategic lesions, total cSVD burden) with multiple tables aligned to contemporary standards (Duering et al., 2023; Hainsworth et al., 2024; Silva et al., 2025).

2. Interaction with Alzheimer pathology (mixed dementia, amyloid angiopathy, vascular lowering of AD threshold, biomarker-era diagnostic framing), including how new AD biological criteria intersect with VCID frameworks (Alzheimer's Association workgroup, 2024; Sachdev et al., 2025).

Neuroimaging Findings in Vascular Dementia

Neuroimaging is indispensable for the diagnosis and characterization of vascular dementia and vascular cognitive impairment and dementia (VCID). Contemporary diagnostic frameworks emphasize that cognitive symptoms must be plausibly attributable to vascular brain injury demonstrated on imaging, rather than inferred solely from vascular risk factors or clinical history (Sachdev et al., 2025). Magnetic resonance imaging (MRI) is the modality of choice, as it provides superior sensitivity for small-vessel disease markers, strategic infarcts, and hemorrhagic lesions that are central to VaD pathophysiology (Duering et al., 2023; Mok et al., 2024).

1 White Matter Hyperintensities

White matter hyperintensities (WMH), visible on T2-weighted and FLAIR MRI sequences, are the most common imaging abnormality in VaD. WMH reflect chronic ischemic injury, demyelination, axonal loss, and gliosis secondary to small-vessel disease. Recent longitudinal studies demonstrate that WMH burden and progression are strongly associated with executive dysfunction, slowed processing speed, gait impairment, and incident dementia (Hainsworth et al., 2024; Mok et al., 2024).

Importantly, WMH location matters. Periventricular and deep frontal WMH disrupt long-range association fibers and fronto-subcortical circuits, producing the characteristic dysexecutive phenotype seen in subcortical ischemic VaD. Posterior WMH are more strongly associated with visuospatial dysfunction and may overlap with Alzheimer-related processes (Duering et al., 2023).

2 Lacunar Infarcts and Subcortical Lesions

Lacunar infarcts are small (<15 mm) cavities resulting from occlusion of penetrating arterioles. Although individually small, their cumulative effect can be substantial. Recent imaging-pathology correlation studies show that lacunes frequently coexist with diffuse microstructural white matter damage that is not fully captured by conventional MRI, further amplifying cognitive impact (Duering et al., 2023; Markus, 2023).

Clinically, lacunes are associated with executive dysfunction, attention deficits, and gait abnormalities. Thalamic and basal ganglia lacunes are particularly impactful due to their role in cognitive network integration (Mok et al., 2024).

3 Cerebral Microbleeds and Hemorrhagic Injury

Cerebral microbleeds (CMBs), detected on susceptibility-weighted imaging (SWI) or T2*-weighted MRI, reflect hemosiderin deposition from prior microscopic hemorrhage. Their distribution provides important etiologic clues. Deep and infratentorial microbleeds are typically associated with hypertensive arteriopathy, whereas lobar microbleeds suggest cerebral amyloid angiopathy (CAA) (Greenberg et al., 2009; Charidimou et al., 2022).

Recent studies demonstrate that microbleed burden is independently associated with cognitive decline, particularly in executive and attentional domains, and increases the risk of dementia progression in patients with mixed vascular and Alzheimer pathology (Charidimou et al., 2022; Silva et al., 2025).

4 Strategic Infarcts on Neuroimaging

Strategic infarcts may be subtle on imaging but have disproportionate cognitive consequences. Modern MRI allows precise localization of lesions affecting key nodes such as the thalamus, basal forebrain, hippocampus, caudate nucleus, and angular gyrus. Network-based imaging analyses increasingly show that disconnection of white matter tracts linking these hubs contributes as much to cognitive impairment as the focal lesion itself (Duering et al., 2023; Chen et al., 2025).

Table 8. Key Neuroimaging Markers in VaD and Their Cognitive Correlates

Imaging marker	Typical MRI sequence	Cognitive domains affected
White matter hyperintensities	FLAIR	Executive function, processing speed
Lacunes	T1/T2	Executive function, gait
Strategic infarcts	DWI/T1	Domain-specific deficits
Microbleeds	SWI/T2*	Executive function, attention
Cortical infarcts	DWI/FLAIR	Language, visuospatial skills

(Updated imaging-clinic correlations: Duering et al., 2023; Mok et al., 2024; Silva et al., 2025)

5 Total Cerebral Small Vessel Disease Burden

An important conceptual advance in recent years has been the shift from single-marker interpretation to total cSVD burden assessment. Composite scores incorporate WMH, lacunes, microbleeds, and enlarged perivascular spaces to represent cumulative vascular injury (Silva et al., 2025).

Studies from 2022–2025 show that higher total cSVD burden predicts faster cognitive decline, poorer functional outcomes, and greater dementia risk, even after adjusting for age and Alzheimer pathology biomarkers (Hainsworth et al., 2024; Silva et al., 2025). This approach aligns with the network-disruption model of VaD and supports its use in both research and clinical stratification.

Interaction Between Vascular Dementia and Alzheimer Pathology

1 Mixed Dementia as the Predominant Late-Life Phenotype
Accumulating neuropathological and biomarker evidence indicates that pure vascular dementia is relatively uncommon in older adults. Instead, most individuals with late-life dementia exhibit mixed pathology, most frequently vascular brain injury coexisting with Alzheimer-type changes (Schneider et al., 2007; Toledo et al., 2013; Sachdev et al., 2025).

Recent population-based autopsy studies confirm that vascular lesions—particularly small-vessel disease and microinfarcts—lower the threshold at which Alzheimer pathology becomes clinically manifest. Even modest vascular injury can unmask or accelerate cognitive decline in individuals with subclinical amyloid and tau pathology (Alzheimer's Association Workgroup, 2024).

2 Mechanistic Links Between Vascular Injury and Alzheimer Pathology
Several mechanisms have been proposed to explain the synergistic interaction between vascular and Alzheimer pathology:

1. Reduced cognitive reserve: Vascular injury decreases network redundancy, making the brain more vulnerable to neurodegenerative pathology.
2. Impaired clearance of amyloid-β: Small-vessel disease and blood–brain barrier dysfunction reduce perivascular drainage and glymphatic clearance of amyloid (Hainsworth et al., 2024).
3. Chronic hypoperfusion: Sustained cerebral hypoperfusion promotes amyloidogenic processing and tau phosphorylation (De la Torre, 2012; updated mechanistic reviews in 2024).
4. Neuroinflammation: Vascular injury induces inflammatory cascades that may accelerate neurodegeneration (Mok et al., 2024).

3 Neuroimaging Evidence of Mixed Pathology
Modern imaging demonstrates frequent overlap between vascular lesions and Alzheimer biomarkers. WMH and microbleeds are commonly observed in patients with amyloid-positive positron emission tomography (PET) scans, and their presence predicts more rapid cognitive decline than either pathology alone (Charidimou et al., 2022; Alzheimer's Association Workgroup, 2024).

Amyloid PET and cerebrospinal fluid biomarkers have reshaped diagnostic thinking, emphasizing that biological Alzheimer disease and VCID are not mutually exclusive but often coexist within the same individual (Sachdev et al., 2025).

Table 9. Vascular–Alzheimer Interaction: Key Concepts

Aspect	Vascular contribution	Alzheimer contribution
Cognitive threshold	Lowers reserve	Progressive neurodegeneration
Imaging markers	WMH, lacunes, microbleeds	Amyloid/tau PET, hippocampal atrophy
Clinical phenotype	Executive dysfunction, gait	Amnestic syndrome
Outcome	Faster decline when combined	Greater severity

4 Implications for Diagnosis and Classification
The recognition of mixed pathology has major implications for diagnosis. Contemporary frameworks recommend describing both vascular and Alzheimer contributions, rather than forcing a single etiologic label. This approach improves prognostic accuracy and aligns with biomarker-driven definitions of Alzheimer disease introduced in the early 2020s (Alzheimer's Association Workgroup, 2024; Sachdev et al., 2025).

In geriatric practice, this translates into diagnosing "dementia due to mixed vascular and Alzheimer pathology"when evidence supports both processes, rather than defaulting to a single category.

Clinical and Research Implications

Understanding the interaction between cerebrovascular injury and Alzheimer pathology reframes vascular dementia from a competing diagnosis to a core modifier of late-life cognitive decline. This perspective has shifted prevention strategies toward aggressive vascular risk factor management across the lifespan and highlights the potential for vascular interventions to delay or attenuate dementia onset, even in biologically defined Alzheimer disease (Mok et al., 2024; Sachdev et al., 2025).

Clinical Implications and Prevention Strategies

1 Vascular Risk Factors as Modifiable Drivers of Cognitive Decline
A central implication of contemporary VaD/VCID research is that vascular risk factors are modifiable contributors to dementia risk across the lifespan. Hypertension, diabetes mellitus, dyslipidemia, smoking, obesity, physical inactivity, and atrial fibrillation are consistently associated with cerebrovascular injury and cognitive decline (Livingston et al., 2024; Mok et al., 2024). Control of these factors reduces stroke incidence and is increasingly recognized as a strategy to delay or prevent dementia onset.

Recent population-based analyses reinforce that midlife vascular risk exposure is particularly detrimental, accelerating later-life cognitive decline and increasing vulnerability to mixed dementia (Livingston et al., 2024). Importantly, risk factor modification remains beneficial even in late life, particularly for reducing progression of small vessel disease and preventing recurrent stroke (Markus, 2023).

2 Blood Pressure Control and Cerebral Small Vessel Disease
Hypertension is the most important modifiable risk factor for cerebral small vessel disease. Longitudinal imaging studies from 2022–2024 demonstrate that intensive blood pressure control slows progression of white matter hyperintensities and reduces incident cognitive impairment, particularly executive dysfunction (Hainsworth et al., 2024; Mok et al., 2024).

However, aggressive blood pressure lowering must be individualized in older adults to avoid cerebral hypoperfusion, orthostatic hypotension, and falls. Current geriatric-focused reviews emphasize balancing vascular protection with functional safety, particularly in frail individuals (Sachdev et al., 2025).

3 Stroke Prevention and Secondary Prevention
In patients with established cerebrovascular disease, secondary stroke prevention is a cornerstone of VaD management. Antiplatelet therapy, anticoagulation for atrial fibrillation, lipid-lowering therapy, and lifestyle modification reduce recurrent vascular events and may stabilize cognitive trajectories (Ng & colleagues, 2025).

Recent observational data suggest that effective secondary prevention is associated with slower cognitive decline in post-stroke populations, particularly when recurrent infarction is prevented (Chen et al., 2025). These findings underscore the importance of integrating stroke and dementia care pathways.

4 Implications of Mixed Pathology for Prevention
Recognition of mixed vascular–Alzheimer pathology reframes prevention strategies. Even in individuals with biomarker-defined Alzheimer disease, vascular risk factor control appears to delay clinical expression and slow functional decline (Alzheimer's Association Workgroup, 2024; Livingston et al., 2024). This reinforces the concept that vascular health is a universal target for dementia prevention, regardless of underlying neurodegenerative pathology.

Diagnostic Challenges and Differential Diagnosis

1 Clinical Overlap With Alzheimer's Disease

Differentiating VaD from Alzheimer's disease remains challenging due to overlapping symptoms and frequent coexistence of pathologies. While VaD typically presents with executive dysfunction, slowed processing speed, and attentional deficits, memory impairment is often present, particularly in mixed dementia (Mok et al., 2024; Sachdev et al., 2025).

Abrupt onset, stepwise decline, focal neurological signs, and prominent gait disturbance favor a vascular contribution, whereas insidious onset and early episodic memory impairment suggest Alzheimer pathology. Nonetheless, reliance on clinical features alone is insufficient, highlighting the importance of neuroimaging and biomarkers.

2 Role of Neuroimaging in Attribution

MRI evidence of vascular brain injury is essential for attributing cognitive impairment to vascular causes. However, imaging findings must be interpreted in context. WMH and lacunes are common in aging and may be incidental unless their burden and distribution plausibly explain cognitive deficits (Duering et al., 2023; Ng & colleagues, 2025).

Recent diagnostic frameworks emphasize causal plausibility, requiring that vascular lesions are sufficient in severity and location to account for observed cognitive impairment (Sachdev et al., 2025). This approach reduces overdiagnosis of VaD based solely on imaging abnormalities.

3 Biomarkers and the Evolving Diagnostic Landscape

The integration of Alzheimer biomarkers into dementia diagnostics has transformed classification systems. Amyloid and tau biomarkers identify biological Alzheimer disease even in the presence of significant vascular pathology (Alzheimer's Association Workgroup, 2024).

Consequently, many patients previously labeled as VaD are now recognized as having mixed dementia.

This paradigm shift encourages dual attribution and supports tailored management strategies addressing both vascular and neurodegenerative processes.

Table 10. Diagnostic Considerations in VaD and Mixed Dementia

Feature	Suggests Vascular Contribution	Suggests Alzheimer Contribution
Cognitive profile	Executive dysfunction, slowed processing	Early episodic memory impairment
Course	Stepwise or fluctuating	Gradual, progressive
Neurological signs	Focal deficits, gait disturbance	Typically absent early
MRI findings	WMH, lacunes, infarcts	Medial temporal atrophy
Biomarkers	Usually negative	Amyloid/tau positive

Disease-Modifying Drugs for Alzheimer's Disease in the Context of Vascular Dementia and VCID

Overview and core principle

Disease-modifying drugs (DMDs) for Alzheimer's disease (AD) currently refer primarily to anti-amyloid monoclonal antibodies (mAbs) that reduce brain amyloid-β and modestly slow clinical decline in early symptomatic AD(typically mild cognitive impairment due to AD or mild AD dementia) with biomarker confirmation of amyloid pathology (Cummings et al., 2023; Rabinovici et al., 2025). These therapies are not designed to treat vascular brain injury, and therefore are not indicated for "pure" vascular dementia (VaD) where cognitive impairment is attributable predominantly to infarcts, small-vessel disease, hemorrhagic lesions, or hypoperfusion (Ng et al., 2025).

In clinical reality, many older adults present with mixed pathology (vascular brain injury plus biological AD). In these cases, DMDs may be considered only if the patient meets AD-therapy eligibility (clinical stage and amyloid biomarker positivity) and does not have vascular imaging features that substantially raise hemorrhagic risk (Rabinovici et al., 2025; Cogswell et al., 2024).

Why DMDs generally do not apply to pure VaD

Anti-amyloid mAbs target amyloid plaques and associated downstream processes; they do not reverse infarction, repair white matter disconnection from small-vessel disease, or address the hemodynamic/inflammatory mechanisms of vascular cognitive impairment (Ng et al., 2025). Accordingly, the evidence base and appropriate-use recommendations restrict treatment to AD-spectrum phenotypes with amyloid confirmation, not dementia caused predominantly by cerebrovascular disease (Cummings et al., 2023; Rabinovici et al., 2025).

The practical "mixed dementia" pathway

For a patient labeled clinically as "vascular dementia," the key question becomes whether there is coexisting AD biology sufficient to justify AD-directed DMDs. The practical pathway is:

1. Establish clinical stage consistent with early AD treatment populations (mild cognitive impairment or mild dementia due to AD) (Cummings et al., 2023; Rabinovici et al., 2025).
2. Confirm amyloid positivity (amyloid PET or CSF biomarkers) (Cummings et al., 2023; Rabinovici et al., 2025).
3. Evaluate MRI for hemorrhagic markers and vascular lesion burden that increase risk and/or indicate that vascular disease is the major driver (Cogswell et al., 2024; Rabinovici et al., 2025).
4. Counsel on realistic benefit (modest slowing), monitoring burden (serial MRI), and the risk profile, especially ARIA (amyloid-related imaging abnormalities) (Cummings et al., 2023; Cogswell et al., 2024).

ARIA and why vascular pathology matters

The dominant safety issue with anti-amyloid mAbs is ARIA, which includes:

- **ARIA-E** (vasogenic edema/effusion)
- **ARIA-H** (microhemorrhages and superficial siderosis)

ARIA risk is influenced by baseline MRI findings consistent with cerebral amyloid angiopathy (CAA) (e.g., multiple lobar microbleeds, cortical superficial siderosis) and by APOE ε4 genotype; importantly, vascular brain disease markers can complicate risk assessment and management (Cummings et al., 2023; Cogswell et al., 2024). Specialized vascular neurology guidance emphasizes the need to integrate cerebrovascular risk factors, antithrombotic use, and hemorrhage-prone imaging features when considering anti-amyloid therapy (Greenberg et al., 2025).

Baseline MRI exclusions and "vascular-heavy" phenotypes

Appropriate-use recommendations commonly exclude patients with MRI patterns suggesting high hemorrhagic risk (notably multiple microbleeds or superficial siderosis) and those with a major vascular contribution to cognitive impairment, because the benefit-risk balance becomes unfavorable when vascular injury is the primary driver or when hemorrhagic complications are more likely (Rabinovici et al., 2025). For example, donanemab appropriate-use guidance explicitly notes exclusion in settings such as >4 microbleeds, cortical superficial siderosis, or major vascular contribution to cognitive impairment (Rabinovici et al., 2025). Lecanemab appropriate-use recommendations similarly stress MRI screening, ARIA monitoring schedules, and careful avoidance of high-risk scenarios (Cummings et al., 2023).

Antithrombotics, stroke history, and clinical safety constraints

A major real-world issue is concomitant antithrombotic therapy. Many patients with vascular dementia or VCID are receiving antiplatelets or anticoagulation for secondary stroke prevention or atrial fibrillation. Appropriate-use recommendations advise heightened caution and often avoidance with anticoagulants due to hemorrhage risk and ARIA-H concerns (Cummings et al., 2023; Kane, 2024). Vascular neurology guidance further addresses thrombolysis/anticoagulation considerations and emphasizes structured ARIA monitoring and management pathways (Greenberg et al., 2025).

Table 11. When to consider AD DMDs in a patient with vascular dementia/VCID phenotype

Scenario	DMD use rationale	Practical recommendation
Pure VaD (amyloid negative; vascular injury sufficient to explain dementia)	No AD target	Do not use AD DMDs; focus on vascular prevention and rehabilitation (Ng et al., 2025)
Suspected mixed dementia (vascular + AD), amyloid positive, early clinical stage	Potential benefit for AD component	Consider if MRI risk profile acceptable and monitoring feasible (Cummings et al., 2023; Rabinovici et al., 2025)
VCID with extensive microbleeds/siderosis or strong CAA pattern	High ARIA/ICH risk	Generally avoid; unfavourable benefit-risk (Cogswell et al., 2024; Rabinovici et al., 2025)
VCID requiring anticoagulation (e.g., AF stroke prevention)	Increased hemorrhagic risk	Usually avoid or treat only under strict specialist protocols (Cummings et al., 2023; Kane, 2024; Greenberg et al., 2025)

Table 12. Minimum clinical and imaging prerequisites before initiating anti-amyloid therapy (applied to "vascular dementia" referrals)

Domain	Minimum requirement	Why it matters
Clinical stage	Mild cognitive impairment or mild dementia due to AD	Trial-tested population (Cummings et al., 2023; Rabinovici et al., 2025)
Biomarkers	Amyloid confirmed by PET or CSF	Confirms target engagement relevance (Cummings et al., 2023)
Baseline MRI	Recent MRI with FLAIR + GRE/SWI sequences	ARIA risk stratification (Cogswell et al., 2024; Cummings et al., 2023)
Hemorrhagic markers	Absence of high-risk microbleed/siderosis patterns	Reduce ARIA-H/ICH risk (Rabinovici et al., 2025)
Medication review	Evaluate antithrombotics, especially anticoagulants	Hemorrhage risk and management complexity (Kane, 2024; Greenberg et al., 2025)
Monitoring capacity	Ability to complete scheduled MRIs	ARIA detection and safe continuation (Cummings et al., 2023; Cogswell et al., 2024)

Counseling and expectations

Even when eligible, patients and families should be counseled that anti-amyloid DMDs generally produce modest slowing of decline rather than symptomatic improvement, and that treatment requires frequent visits, infusion capacity, and MRI surveillance—factors that may limit feasibility in frail, multimorbid older adults (Cummings et al., 2023; Jeremic et al., 2025). When vascular disease is prominent, prevention of further vascular injury often delivers clearer benefit (stroke prevention, blood pressure control, rehabilitation) than pursuing an AD-specific DMD with substantial monitoring burden and hemorrhagic risk (Ng et al., 2025).

Practical recommendation statement for your review

In patients with dementia attributed to vascular causes, Alzheimer disease–modifying therapy should be considered only when (1) there is biomarker evidence of AD, (2) the patient is in an early symptomatic stage consistent with clinical trial populations, and (3) MRI does not demonstrate a hemorrhage-prone profile or a major vascular contribution that would shift the benefit-risk balance against treatment (Cummings et al., 2023; Rabinovici et al., 2025; Greenberg et al., 2025).

Synthesis: Reconceptualizing Vascular Dementia

Contemporary evidence supports reconceptualizing vascular dementia not as a discrete disease entity but as a major pathway to cognitive impairment that frequently intersects with neurodegeneration. Cerebrovascular injury disrupts neural networks, lowers cognitive reserve, and accelerates the clinical expression of Alzheimer pathology. This interaction explains the high prevalence of mixed dementia in older populations and underscores the need for integrated diagnostic and management approaches (Sachdev et al., 2025; Livingston et al., 2024).

From a clinical perspective, this synthesis emphasizes prevention, early detection of vascular injury, and aggressive management of vascular risk factors as essential components of dementia care. From a research perspective, it highlights the importance of harmonized imaging standards, domain-based cognitive assessment, and biomarker-informed classification.

Conclusion

Vascular dementia encompasses a heterogeneous group of cognitive disorders arising from diverse cerebrovascular injuries, including large-vessel infarction, small vessel disease, strategic lesions, hypoperfusion, and hemorrhagic injury. Advances in neuroimaging and neuropathology have clarified how these lesions disrupt cognitive networks and interact with Alzheimer pathology to produce late-life dementia. Modern frameworks emphasize vascular cognitive impairment as a continuum, recognize mixed pathology as the dominant phenotype, and prioritize vascular health as a modifiable determinant of cognitive aging. Continued integration of imaging, biomarkers, and clinical assessment will be critical for improving diagnosis, prevention, and patient-centered care.

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