Alzheimer's disease with cerebrovascular disease: current status in the Asia–Pacific region

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Abstract. Chen C, Homma A, Mok VCT, Krishnamoorthy E, Alladi S, Meguro K, Abe K, Dominguez J, Marasigan S, Kandiah N, Kim S, Lee DY, De Silva HA, Yang Y-H, Pai M-C, Senanarong V, Dash A (National University of Singapore; National University Health System, Singapore, Singapore; Research Institute for Dementia Care, Tokyo, Japan; Lui Che Woo Institute of Innovative Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China; Neurokrish Consulting Pvt Ltd, Chennai; Nizam's Institute of Medical Sciences, Hyderabad, India; CYRIC, Tohoku University, Sendai; Okayama University, Okayama, Japan; Memory Center, St Luke's Medical Center, Quezon City; University of Santo Tomas Hospital, Manila, Philippines; National Neuroscience Institute and Duke-NUS Singapore, Singapore, Singapore; Seoul National University College of Medicine; Seoul National University Bundang Hospital; Seoul National University, College of Medicine, Seoul, Korea; University of Kelaniya, Ragama, Sri Lanka; Kaohsiung Medical University Hospital, Kaohsiung Municipal Ta-Tung Hospital; Kaohsiung Medical University, Kaohsiung; Medical College and Hospital, National Cheng Kung University, Tainan City, Taiwan; Mahidol University, Bangkok, Thailand; Eisai Co. Ltd, Mumbai, India). Alzheimer's disease with cerebrovascular disease: current status in the Asia–Pacific region. *J Intern Med* 2016; doi: 10.1111/joim.12495.

Background. There is growing awareness of the coexistence of Alzheimer's disease and cerebrovascular disease (AD+CVD), however, due to lack of well-defined criteria and treatment guidelines AD+CVD may be underdiagnosed in Asia.

Methods. Sixteen dementia specialists from nine Asia Pacific countries completed a survey in September 2014 and met in November 2014 to review the epidemiology, diagnosis and treatment of AD+CVD in Asia. A consensus was reached by discussion, with evidence provided by published studies when available.

Results. AD accounts for up to 60% and AD+CVD accounts for 10–20% of all dementia cases in Asia. The reasons for underdiagnosis of AD+CVD include lack of awareness as a result of a lack of diagnostic criteria, misdiagnosis as vascular dementia or AD, lack of diagnostic facilities, resource constraints and cost of investigations. There is variability in the tools used to diagnose AD+CVD in clinical practice. Diagnosis of AD+CVD should be performed in a stepwise manner of clinical evaluation followed by neuroimaging. Dementia patients should be assessed for cognition, behavioural and psychological symptoms, functional staging and instrumental activities of daily living. Neuroimaging should be performed using computed tomography or magnetic resonance imaging. The treatment goals are to stabilize or slow progression as well as to reduce behavioural and psychological symptoms, improve

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quality of life and reduce disease burden. First-line therapy is usually an acetylcholinesterase inhibitor such as donepezil.

Conclusion. AD+CVD is likely to be under-recognised in Asia. Further research is needed to establish the true prevalence of this treatable and potentially preventable disease.

Keywords: Alzheimer's disease, Asia, cerebrovascular disorders, consensus, dementia.

Introduction

Dementia is one of the biggest public health and social care challenges facing the world today [1]. In 2015, the number of individuals with dementia worldwide was estimated to be 46.8 million and projected to increase to 74.7 million and 131.5 million by 2030 and 2050, respectively [1]. These estimates are 12–13% higher than those of 2009, with increased prevalence estimates in East Asia from 3.2% to 6.6% and in South-East Asia from 4.8% to 5.8%. As the elderly population in the developing world increases, a concomitant rise in the prevalence of dementia is expected [2], with 68% of dementia cases projected to be in low- or middle-income countries by 2050 [3].

Although Alzheimer's disease (AD) and vascular dementia (VaD) have been considered the most prevalent forms of dementia [4, 5], recent attention has focused on the coexistence of AD and cerebrovascular disease (AD+CVD) [5, 6]. It is now apparent that dementia is a continuum of disease with pure AD and pure CVD representing the two, relatively less common, extremes with AD+CVD comprising the majority of cases [4, 5, 7].

Alzheimer's disease and cerebrovascular disease is usually diagnosed when dementia clinically presenting as AD is accompanied by evidence of CVD on brain imaging. AD+CVD may also be diagnosed when dementia clinically presenting as VaD is accompanied by biomarker evidence of AD such as amyloid on positron emission tomography (PET) imaging [8]. Distinguishing between AD, VaD and AD+CVD is needed because of differences in the clinical course and clinical responses to pharmacotherapy between the conditions. Moreover, the cognitive profile of AD+CVD is different from that of AD, as it varies depending on the size and location of the injury, as for all brain disorders [9, 10]. Amnesia and hippocampal atrophy are characteristics of AD, whilst vascular brain injury is usually represented by infarcts, haemorrhages and white matter hyperintensity. AD and CVD contribute additively, but independently, to the risk of dementia [9] whilst, in older patients with AD, vascular pathology may be as important as amyloid plaques in determining the disease course [11].

Although the actual prevalence of AD+CVD remains unknown, autopsy studies indicate that the condition may be considerably more common than was previously realized. The Medical Research Council Cognitive Function and Ageing Study, a large UK multicentre study of dementia and cognitive decline in the population aged 65 years and older, found that CVD (78%) and AD (70%) were the most common pathologies amongst the first 209 autopsy studies of patients with and without dementia [12]. Cerebrovascular pathology was so common that only 21% had pure AD [13]. Magnetic resonance imaging (MRI) showed that white matter lesions were common (94%) and represented an independent risk factor for dementia [13].

In the Rush Memory and Aging Project, a community-based clinicopathological study of older persons who underwent annual clinical evaluation and agreed to brain donation for autopsy investigation [5], there were three main findings: (i) more than 50% of participants had neuropathology that could contribute to cognitive impairment; (ii) more than 50% of patients with dementia had mixed pathology, most commonly AD and CVD in the form of infarcts; and (iii) patients with multiple pathologies were almost three times more likely to have dementia than those with a single pathology [age-adjusted odds ratio (OR) 2.8, 95% confidence interval (CI) 1.2–6.7]. These results are consistent with the finding of the Nun study that, amongst participants who met the neuropathological criteria for AD, individuals with lacunar infarcts in the basal ganglia, thalamus or deep white matter had poorer cognitive function and a higher prevalence of dementia than those without infarcts (OR 20.7, 95% CI 1.5–288.0), suggesting that CVD may have an additive effect on the clinical symptoms of AD [14].

Moreover, Esiri *et al.* [6] showed that AD and CVD commonly occur together and that CVD increases

dementia severity in patients with AD. Langa *et al.* [15] also demonstrated that dementia is more likely to occur in mixed disease than in AD alone. Jellinger and Attems found that cerebrovascular lesions were significantly more common in patients with AD than in individuals without dementia, suggesting overlap between the two pathologies [16].

The population of Asia is ageing with a concomitant increase in diseases of old age, of which dementia is one of the most prominent [17]. In 2001, China, India, Japan and Indonesia were four of the top seven countries worldwide with the greatest number of persons with dementia [3]. Although there has traditionally been a lower prevalence of AD and a higher prevalence of VaD in Asia, the results of a literature review in 2012 suggest that this is changing as the prevalence of AD increases, with the overall dementia prevalence now matching that of western countries [17].

Meguro *et al.* [18] found a dementia prevalence of 12.4% amongst an elderly population in Japan. The most common cause was AD+CVD, followed by AD, other types of mixed dementia and VaD [19]. An earlier study by the same group had demonstrated a prevalence of dementia of 8.5% in adults aged 65 years and older [20]. According to the Alzheimer's Disease Diagnostic and Treatment Centers criteria, possible AD+CVD was common (31.3%), whereas VaD was less often observed (18.8%) according to the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) criteria [21]. In a recent Asian study, 28.4% of patients with mild AD and 39.7% of those with moderate-to-severe AD had concomitant CVD in the form of white matter hyperintensity [22].

Challenges to determining the true prevalence of AD+CVD include variations in data collection methods, diagnostic criteria (Table 1) [21, 23–32] and assessment techniques, as well as cultural and geographical differences [4]. Additionally, the current criteria for AD or VaD do not sufficiently address AD+CVD. Furthermore, few large randomized controlled trials on AD+CVD have been conducted, and none in Asia. Nevertheless, as AD+CVD is common in clinical practice, and with increasing awareness of dementia in Asia along with greater access to neuroimaging facilities, it is important to understand the cerebrovascular contribution to dementia. Such information would

allow health planners to allocate resources to manage the vascular risk factors that contribute to dementia. Researchers will also be able to determine their research priorities to address the syndrome of AD+CVD.

Here, our aim was to review the epidemiology and diagnosis of and treatment approaches to AD+CVD in Asia and to make recommendations for the diagnosis and treatment of and research priorities for AD+CVD.

Methods

The Asia Panel for Alzheimer's disease and Cerebrovascular disease (APAC) is a group of 16 dementia specialists/experts from nine Asia Pacific countries (Hong Kong, India, Japan, the Philippines, Singapore, South Korea, Sri Lanka, Taiwan and Thailand). The members of the group completed a 30-question survey in September 2014, which was used to draft the manuscript and met on 13 November 2014 in Colombo, Sri Lanka, in conjunction with the Asian Society Against Dementia (ASAD) conference, to review the epidemiology, diagnosis and treatment of AD+CVD in Asia. During the face-to-face meeting, consensus was reached by discussion, and the manuscript was revised accordingly, with evidence provided by published studies when available. The tables and figures were prepared based on the survey results and recommendations made during the meeting.

Results

Prevalence in Asia

The findings of a recent review suggest that age-adjusted dementia prevalence estimates in persons aged 65 years and older are higher in some Asian countries (China, ≤5.0%; South Korea, 10.1%) than in others (India, 2.7%; Thailand, 3.4%; Sri Lanka, 4.0%) [2]. AD accounts for up to 60% of all dementia cases in Asia [2] and AD+CVD accounts for 10–20% of cases [33].

In a community-based survey in rural Japan, Ikejima *et al.* [34] identified 768 cases of dementia and 529 of mild cognitive impairment (MCI) amongst 3394 elderly participants. AD was the most common diagnosis (67.4%), followed by VaD (18.9%); AD+CVD was diagnosed in 4.2% of participants.

Table 1 *Current diagnostic criteria for AD+CVD*

	Clinical	Neuroimaging	Biomarkers	Neuropathology
DSM 5 [23] Aetiological subtype without separate criteria 'Due to multiple aetiologies'	None	None	None	None
Deramecourt et al. [24] Only neuropathological criteria	None	None	None	A grading system for total CVD burden was described, including the presence of atherosclerosis, dilatation of perivascular spaces, deep white matter lesions and amyloid angiopathy. Requires validation in larger samples
NIA-AA (NINCDS-ADRDA) McKhann et al [25] Mixed presentation	Clinical criteria for AD dementia, but with evidence of CVD, that is stroke related to onset of worsening cognitive impairment	The presence of multiple or extensive infarcts or severe white matter hyperintensity	Biomarkers for AD • CSF Aβ and Tau protein • Amyloid PET No biomarkers for CVD	NIA-Reagan criteria for AD • CERAD No neuropathological criteria for CVD
Gold et al. [26] Only neuropathological criteria	None	None	None	Braak NFT >II and cortical microinfarct plus thalamic and basal ganglia lacunes >2
National Institute of Neurological Disorders and Stroke–Canadian Stroke Network Hachinski et al. [27]	None	None	None	None
Newcastle criteria for mixed dementia Kalaria et al. [28] Only neuropathological criteria	None	None	None	CV strategic lesions plus AD pathology

Table 1 (*Continued*)

	Clinical	Neuroimaging	Biomarkers	Neuropathology
DSM IV [29] Mixed dementia	• Multiple cognitive deficits • One or more cognitive disturbances (apraxia, agnosia, aphasia or executive function) Plus clinical criteria of VaD, that is the presence of focal neurological signs related to the disturbance	Evidence indicative of CVD	None	None
NINDS-AIREN Román *et al.* [21] AD+CVD	Typical AD, with clinical evidence of stroke based on: • History • Presence of focal signs Temporal relationship between the occurrence of dementia and stroke	• Multiple or single dominant hemisphere stroke • Strategically placed infarct (angular gyrus, thalamus, basal forebrain or posterior or anterior cerebral artery) • Multiple basal ganglia and white matter lacunes • Extensive periventricular white matter lesions	None	Neuropathological criteria only for VaD, not AD+CVD

Table 1 (*Continued*)

	Clinical	Neuroimaging	Biomarkers	Neuropathology
ICD 10 [30] Atypical/mixed dementia	Deficits in higher cognitive functions Clinical evidence of focal brain damage	Evidence of cerebral infarction	None	None
Hachinski Ischemic score [31] No criteria for AD+CVD	Use of an intermediate score of 5–6 has been suggested	None	None	None
ADDTC Chui *et al.* [32] Mixed dementia	Presence of ischaemic vascular disease and a second brain pathology	Two or more ischaemic strokes with at least one infarct outside the cerebellum	None	None

AA, Alzheimer's association; Aβ, amyloid-β peptide; AD, Alzheimer's disease; ADDTC, Alzheimer's Disease Diagnosis and Treatment Center; CERAD, Consortium to Establish a Registry for Alzheimer Disease; CSF, cerebrospinal fluid; CVD, cerebrovascular disease; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; NFT, neurofibrillary tangle; NIA, National Institute on Aging; NINCDS-ADRDA, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; NINDS-AIREN, National Institute of Neurological Disorders and Stroke/the Association Internationale pour la Recherché et l'Enseignement en Neurosciences; PET, positron emission tomography; VaD, vascular dementia.

The prevalence estimates of dementia and MCI in Korea were 8.1% (95% CI 6.9–9.2) and 24.1% (95% CI 21.0–27.2), respectively, in a representative nationwide sample of elderly adults above 65 years of age [35]. AD was the most prevalent type of dementia (5.7%) followed by VaD (2.0%). More recently, a systematic review and meta-analysis showed a dementia prevalence of 9.2% amongst individuals aged 65 years or older [36], whilst an earlier study demonstrated a prevalence of 6.8–13.0% [37]. Na *et al.* [38] found that 30.7% of patients with AD in Korea also had cerebrovascular lesions (diagnosed by MRI).

The overall weighted prevalence of dementia in an elderly Hong Kong Chinese population ($n = 1034$) was estimated to be $6.1 \pm 0.7\%$, which is low in comparison with Caucasian populations [39]. AD accounted for 64.6% of cases and VaD for 29.3%. Lam *et al.* [40] reported prevalence rates for very mild and mild dementia of 8.5% and 8.9%, respectively. In a recent study amongst Hong Kong Chinese patients with consecutive stroke/transient ischaemic stroke, concurrent AD-like amyloid plaques were detected in about 30% of individuals with incident early poststroke dementia [8].

In a recent study in a Singaporean Chinese population (≥60 years of age), the overall prevalence of cognitive impairment and dementia was 15.2%, which is similar to rates in Caucasian populations [41]. Analysis by ethnicity using data from the Singapore National Mental Health Survey (Elderly) demonstrated that dementia prevalence was 4.2% in Chinese adults, 9.4% in Malays and 8.8% in Indians [42]. Meanwhile, in a study comparing healthy elderly subjects and patients with MCI, mild AD and moderate-to-severe AD, Kandiah *et al.* [22] found that total white matter hyperintensity increased with increasing severity of AD (6.7%, 9.7%, 28.4% and 39.7%, respectively). In another study investigating the role of CVD in the pathogenesis of AD, participants with MCI who had concomitant CVD had a greater risk of progression to AD compared to those without CVD [43]. These findings clearly demonstrate the importance of identifying individuals with MCI and CVD as they are at increased risk of incident dementia.

The prevalence of dementia in India ranges from 2.4% to 4.9% [44–48] and community- and clinic-based studies have shown that AD is the most common type of dementia (38.3–48.7%) followed by VaD (22.0–25.4%); AD+CVD has been found in 8.6–15.0% of patients [49–51]. In a regional survey in Sri Lanka, the prevalence of dementia was 3.98% (95% CI 2.6–5.7%) [52]. The rates for AD, VaD and mixed dementia were 71.4%, 14.3% and 7.1%, respectively. In Taiwan, the prevalence of suspected dementia was 13.6% and the prevalence rates of MCI and dementia were 18.8%, with a female predominance of 73.0% [53, 54]. AD was the most common cause of dementia [55].

A survey conducted in northern Thailand showed that the prevalence of dementia was 2.35% amongst participants aged 45 years and older. AD was the most common type of dementia (75.0%), followed by VaD (12.5%) [56]. A Thai national survey demonstrated a dementia prevalence of 3.3% (95% CI, 2.7–3.8) amongst adults aged 60 years and older [57]. Age-specific prevalence increased dramatically from 1.0% in the age group 60–64 years to 31.3% in those aged 90 years and above. Senanarong *et al.* found a dementia prevalence of 9.9% in Thailand [58], and moderate-to-severe white matter lesions in 38.6% of elderly Thais who had undergone MRI of the brain [59].

Alzheimer's disease and cerebrovascular disease is thought to be underdiagnosed in Asia (and worldwide), primarily due to a lack of awareness as a result of a lack of diagnostic criteria. Other reasons for underdiagnosis include misdiagnosis as VaD or AD, lack of diagnostic facilities, resource constraints and cost of investigations. Of note, there are no specific clinical practice guidelines for diagnosis and treatment of AD+CVD in Asia.

It is possible that Asian studies are affected by 'survivor bias'. In research on early life exposures and health in old age, a large proportion of patients are likely to die before reaching old age, so there could be a high degree of survivor bias [60]. As most patients with AD+CVD have more medical comorbidities and a greater level of disability compared to patients with AD alone, prevalence rates in this group may be affected by survivor bias.

Table 2 shows the prevalence of dementia in Asia by country [8, 20, 22, 36–39, 44–55, 58, 59, 61–63]. Caution should be used when interpreting these results, as the same methodologies and diagnostic criteria may not have been used in studies from different countries.

Table 2 *Epidemiology of dementia in Asia by country*

Country	Prevalence of dementia (% in population >60 years)	Dementia patients with AD+CVD (%)	References
Hong Kong	6.0[a]	30	Chiu *et al.* [39]
			Yang *et al.* [8]
Japan	11.0–12.4	31.3–50.0	Asada [61]
			Meguro *et al.* [20]
India	2.4–4.8	8.6–15.0	Vas *et al.* [44]
			Rajkumar *et al.* [45]
			Shaji *et al.* [46]
			Shaji *et al.* [47]
			Mathuranath *et al.* [48]
			Alladi *et al.* [49]
			Nair *et al.* [50]
			Das *et al.* [51]
Singapore	2.0–10.0	48.0	Hilal *et al.* [62]
		28.4 for mild patients with AD	Kandiah *et al.* [22]
		39.7 for moderate-to-severe patients with AD[b]	
South Korea	6.8–13.0	30.7	Kim *et al.* [36]
			Youn *et al.* [37]
			Na *et al.* [38]
Sri Lanka	4.0	7.1	de Silva *et al.* [52]
Taiwan	6.0–18.8[c]	7.1–15.0	Sun *et al.* [54]
			National Health Insurance database
			Guideline Subcommittee
			of the Taiwan Dementia
			Society [55]
Thailand	9.9	40.0	Senanarong *et al.* [58]
			Senanarong *et al.* [59]
Asia (range)	2.0–18.8	7.1–50.0	
Asia	4.7[d]	NR	Alzheimer's Disease
			International [1]

AD, Alzheimer's disease; CVD, cerebrovascular disease; NR, not reported.
[a]Patients older than 70 years.
[b]90% by magnetic resonance imaging-based mild white matter disease [22].
[c]Suspected mild cognitive impairment or dementia [53, 54, 63].
[d]Crude estimated prevalence.

Diagnosis

Advances in neuroimaging techniques have led to better understanding of the high prevalence and increased recognition of the features of AD+CVD. However, the current diagnostic methods may not always distinguish pure AD and VaD from AD+CVD [64]. Accurate diagnosis is needed for

preventive and therapeutic strategies [4]. Taking into consideration both AD and CVD in patients with cognitive decline is important as populations age and develop increasingly more chronic comorbidities [15].

In a real-world multicentre study of 107 neurologists, geriatricians and psychiatrists, there was substantial variability in the tools used to diagnose patients with AD+CVD [65]. Clinical history was most frequently used by psychiatrists (100%) and geriatricians (97%), but less often by neurologists (85%) ($P = 0.015$). Neuroimaging was most frequently used by neurologists (99%) and geriatricians (96%), but less often by psychiatrists (84%) ($P < 0.0001$). Therefore, specific clinical practice guidelines are needed for the diagnosis of AD+CVD.

Diagnostic criteria

The most commonly used clinical diagnostic criteria in Asia are the National Institute of Neurological and Communicative Diseases and Stroke/ Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [25] and the NINDS-AIREN [21] criteria (Table 1). The NINCDS-ADRDA criteria are used to diagnose pure AD and AD+CVD (clinical criteria for AD and evidence of CVD). Neuroimaging features include the presence of multiple or extensive infarcts or severe white matter hyperintensity. Biomarkers for AD include cerebrospinal fluid amyloid-β peptide and tau protein, and amyloid PET.

The NINDS-AIREN criteria are used to diagnose AD+CVD or VaD. Clinical criteria for AD+CVD include typical AD with evidence of stroke based on history and presence of focal signs, such as hemiparesis, neglect or hemianopia, with a temporal relationship between the occurrence of dementia and stroke. Neuroimaging criteria include multiple

or single-vessel stroke, strategically located infarcts (angular gyrus, thalamus, basal forebrain or posterior or anterior cerebral artery), multiple basal ganglia and white matter lacunes and extensive periventricular white matter lesions. The NINDS-AIREN guidelines highlight the value of neuropsychological testing, the importance of brain imaging to support the clinical findings and the need to establish the relationship between stroke and dementia onset [21]. The NINDS-AIREN criteria are detailed and reliable, whilst remaining easy to use.

It is difficult to diagnose AD+CVD solely on the symptomatology or clinical presentation without the aid of neuroimaging. Table 3 shows the differences between AD, AD+CVD and VaD for diagnostic purposes. The extent of vascular pathology and the ischaemic nature of white matter lesions need clarification, and further research is recommended.

>The APAC consensus was that the diagnosis of AD+CVD should therefore be performed in a stepwise manner of clinical evaluation followed by neuroimaging. The history of CVD should prompt a clinician to explore the presence of cognitive deficits; however, the usual clinical process is that the cognitive disorder suggested by the concern of a patient or informant is established first and then its aetiology is investigated.

Neuropsychological evaluation

A comprehensive clinical approach would be to assess dementia symptoms in the following domains: cognition, behavioural and psychological symptoms, functional staging of the disease, assessment of motor and process skills, disability, activities and instrumental activities of daily living [66]. In Asia, the AD8 test [67], Community Screening Instrument for Dementia [68], Consortium to Establish a Registry for Alzheimer's

Table 3 *Diagnosis of AD, AD+CVD and VaD*

Diagnosis	Onset	Progression	Neurological signs	MRI/CT findings
AD	Insidious	Gradual	None	None
AD+CVD	Insidious/sudden	Gradual/stepwise	None/focal and nonfocal signs	Vascular lesions
VaD[a]	Sudden	Stepwise	Focal/nonfocal signs	Vascular lesions

AD, Alzheimer's disease; CT, computed tomography; CVD, cerebrovascular disease; MRI, magnetic resonance imaging; VaD, vascular dementia.
[a]The clinical course and progression of VaD may not always be sudden and stepwise and is not always distinctive.

Disease battery [69] and Early Assessment Self Inventory [70] are widely used in primary care. In secondary and tertiary care, local language versions of the Mini-Mental State Examination (MMSE), such as Chinese [71] or Hindi [72], General Practitioner assessment of Cognition [73], Montreal Cognitive Assessment [74], Mini-Cognitive Assessment Instrument [75], Neuropsychiatric Inventory (NPI) [76], Disability Assessment for Dementia [77], Addenbrooke's Cognitive Examination Revised [78], Activities of Daily Living [79], Assessment of Motor and Process Skills [80] and Clinical Dementia Rating [81] have been used. More recently, the neuropsychological instruments proposed by the National Institute of Neurological Disorders and Stroke–Canadian Stroke Network [27] for assessment of vascular cognitive impairment have been utilized in Hong Kong [82] and Korea [83].

Neuroimaging evaluation

The usual imaging modalities are computed tomography (CT) and MRI. Single-photon emission computed tomography (SPECT) or PET is only required if specifically indicated.

Cerebrovascular disease should be preferentially evaluated by MRI (if available) to determine the presence of relevant lesions in regions such as the cortex, and subcortical structures such as the thalamus. CVD in the white matter, particularly when located in the networks of the frontosubcortical circuits or cholinergic fibres from the nucleus basalis of Meynert, may also be considered relevant [84]. However, although MRI is generally superior to CT in assessing CVD, it is less readily available and its use is contraindicated in about 10% of patients.

A variety of visual rating scales are available to quantify cerebrovascular burden in patients with cognitive impairment, the most useful of which are the Scheltens' scale, the scale for age-related white matter changes or the Fazekas scale for white matter lesions. Microhaemorrhage scales are also available (the Brain Observer MicroBleed Scale and the Moss Attention Rating Scale).

Even in patients with AD without neuroimaging evidence of CVD, vascular risk factors should be screened for and treated. Similarly, cognitive impairment and dementia should be screened for in patients with CVD. Biomarkers, as proposed by NIA-AA [25], may assist the diagnosis of AD.

More information, including clinical and imaging features, is needed to better define the diagnostic criteria for AD+CVD. However, regardless of the diagnostic criteria used, the most important steps are review of the clinical history and physical examination, neuropsychological evaluation and neuroimaging (Fig. 1) [27, 67–75, 78, 81–83]. If this careful evaluation yields evidence of both AD and CVD from the history or from imaging, a diagnosis of AD+CVD should be made.

Management of AD+ CVD

The goals of treatment of AD+CVD are to stabilize or slow progression, reduce behavioural and psychological symptoms, improve quality of life and reduce family and caregiver burden.

Cholinergic deficits are known to occur in VaD independently of AD and may result in cognitive impairment or dementia [85]. Additionally, brain ischaemia may worsen cognitive defects in AD. Results from randomized clinical trials have indicated that treatment with acetylcholinesterase inhibitors (AChEIs) has similar beneficial effects on cognitive and functional outcomes in patients with AD+CVD compared to those with AD [64]. Wilkinson *et al.* [86] reported that treatment with donepezil (5 or 10 mg) resulted in significant improvements in cognition and global function compared with placebo in a randomized controlled study of 616 patients with possible or probable VaD. Both donepezil-treated groups showed improvements on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), compared with placebo, of approximately two points (donepezil 5 mg -1.65, $P = 0.003$; donepezil 10 mg -2.09; $P = 0.0002$). Greater improvements on the Clinician's Interview-Based Impression of Change–plus Caregiver Input (CIBIC-plus) were observed in both donepezil groups compared with the placebo group (overall donepezil versus placebo, $P = 0.008$); 25% of the placebo group showed improvement compared with 39% ($P = 0.004$) and 32% ($P = 0.047$) of the donepezil 5 and 10 mg groups, respectively.

In a parallel study, Black *et al.* [87] showed significant improvement in cognitive functioning in the donepezil 5 and 10 mg treatment groups versus placebo. At week 24, the mean changes from
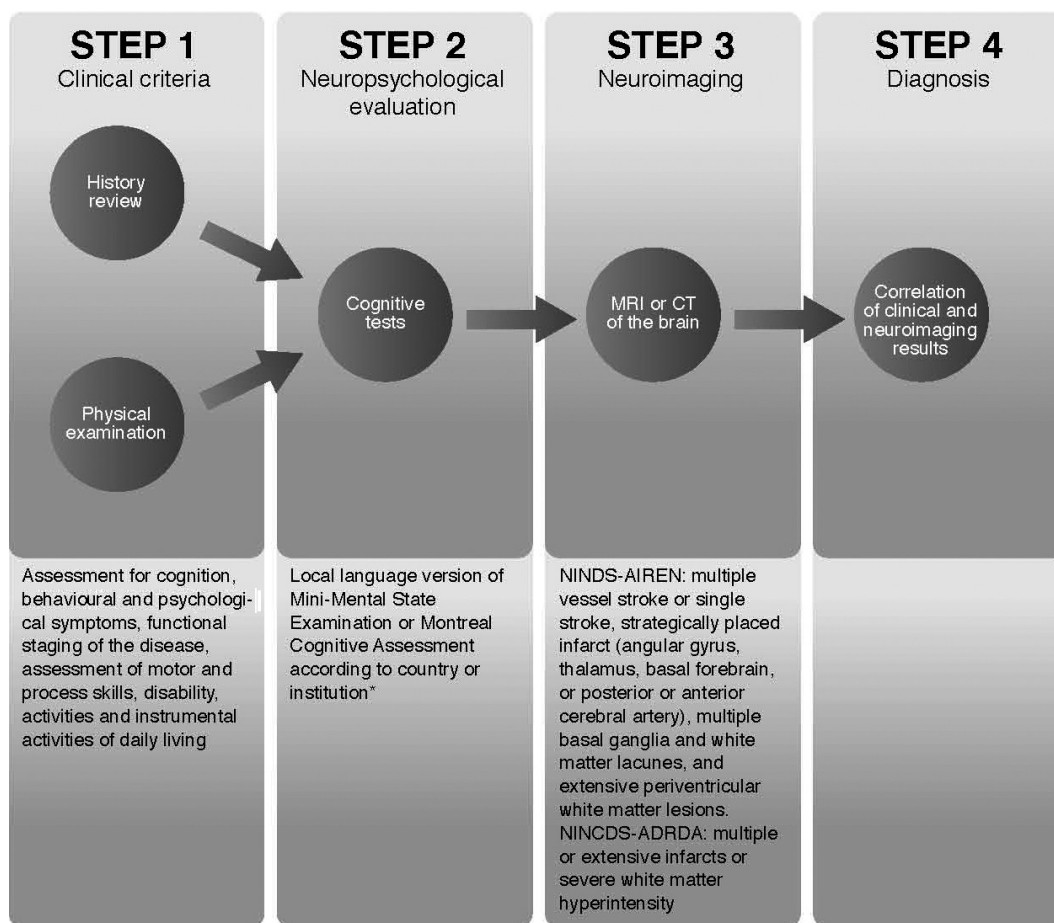
STEP 1
Clinical criteria

History review

Physical examination

Assessment for cognition, behavioural and psychological symptoms, functional staging of the disease, assessment of motor and process skills, disability, activities and instrumental activities of daily living

STEP 2
Neuropsychological evaluation

Cognitive tests

Local language version of Mini-Mental State Examination or Montreal Cognitive Assessment according to country or institution*

STEP 3
Neuroimaging

MRI or CT of the brain

NINDS-AIREN: multiple vessel stroke or single stroke, strategically placed infarct (angular gyrus, thalamus, basal forebrain, or posterior or anterior cerebral artery), multiple basal ganglia and white matter lacunes, and extensive periventricular white matter lesions. NINCDS-ADRDA: multiple or extensive infarcts or severe white matter hyperintensity

STEP 4
Diagnosis

Correlation of clinical and neuroimaging results

Fig. 1 *Stepwise diagnosis of AD+CVD. AD+CVD, Alzheimer's disease and cerebrovascular disease; CT, computed tomography; MRI, magnetic resonance imaging; NINCDS-ADRDA, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; NINDS-AIREN, National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherché et l'Enseignement en Neurosciences. *In primary care, the AD8 [67], Community Screening Instrument for Dementia [68], Consortium to Establish a Registry for Alzheimer's Disease battery [69] and Early Assessment Self Inventory [70] may be used. In secondary and tertiary care, local language versions of the Mini-Mental State Examination [71, 72], General Practitioner assessment of Cognition [73], Montreal Cognitive Assessment [74], Mini-Cognitive Assessment Instrument [75], Addenbrooke's Cognitive Examination Revised [78], Clinical Dementia Rating [81] and National Institute of Neurological Disorders and Stroke–Canadian Stroke Network [27, 82, 83] may be used.*

baseline scores for the ADAS-cog were -1.90 ($P = 0.001$) for donepezil 5 mg and -2.33 ($P < 0.001$) for donepezil 10 mg; the mean change from baseline scores for activities of daily living on the Alzheimer's Disease Functional Assessment and Change Scale was -1.31 ($P = 0.02$) for both donepezil-treated groups. Significant improvement in global function for donepezil versus placebo at week 24 (CIBIC-plus) was observed only in the donepezil 5 mg group ($P = 0.014$).

In a trial by Román *et al.* [88], 974 patients with VaD diagnosed according to the NINDS-AIREN criteria were randomly assigned to receive donepezil 5 mg or placebo. Donepezil-treated patients had significantly greater improvement from baseline to study end on the Vascular ADAS-cog (-1.156, 95% CI -1.98 to -0.33; $P < 0.01$), but not the CIBIC-plus, compared to placebo-treated patients. In a subanalysis of 681 patients undergoing MRI analysis, 369 (54%) had hippocampal atrophy

(presumably patients with AD+CVD) and 312 (46%) had normal hippocampal size. Baseline scores for measures of dementia, except CIBIC-plus, were significantly better in patients without compared to those with hippocampal atrophy. In patients with normal hippocampal size, there was a significant treatment difference in the Vascular ADAS-cog for donepezil (-2.11 ± 0.42) versus placebo (-0.80 ± 0.53, $P = 0.04$). In patients with hippocampal atrophy, there was worsening with placebo (1.44 ± 0.67) and improvement with donepezil (-0.56 ± 0.50, $P = 0.01$).

Another AChEI, galantamine, has been shown to cause significantly greater cognitive and functional improvements than placebo in patients with AD+CVD [89]. The proportions of responders demonstrating improved or maintained cognition at 6 months on the ADAS-cog were 60.5% for galantamine and 46.0% for placebo ($P = 0.013$), and the proportions of patients responding by at least four points on the ADAS-cog were 33.6% for galantamine and 17.2% for placebo ($P = 0.003$). For the CIBIC-plus, 75.0% of galantamine-treated patients improved or remained stable compared with 53.6% of those receiving placebo ($P = 0.0006$). Significantly higher responder rates were observed with galantamine (64.9%) than with placebo (56.6%, $P = 0.024$).

A long-term (48-week) open-label trial of donepezil was conducted at nine medical centres in South Korea. A total of 114 patients with mild-to-moderate AD were enrolled, of whom 35 (30.7%) had concomitant cerebrovascular lesions on MRI [38]. At week 24, patients with and without cerebrovascular lesions showed improvements in MMSE scores (both $P < 0.05$) and slight increases in ADAS-cog scores (both $P > 0.05$). At week 48, both groups continued to show non-significant improvements in MMSE and ADAS-cog scores, with no significant differences between groups.

Results from a real-world study (tertiary dementia clinic) in Singapore showed that cognitive enhancers (AChEIs or memantine) reduce annual cognitive decline to a greater extent in patients with AD+CVD compared to those with pure AD [90]. Although there was a slight decrease in MMSE scores over time in the AD+CVD patients (-0.04, $P = 0.007$), this difference was not significantly different between AD+CVD or pure AD patients (-0.03, $P = 0.246$).

The findings of a 26-week open-label pilot study from the USA have suggested that the AChEI rivastigmine may be beneficial for patients with AD+VaD. More than 25% of patients treated with rivastigmine (6–12 mg day^{-1}) had a clinically significant improvement of at least four points on the ADAS-cog at 26 weeks [91].

AChEIs are the preferred first-line drugs for AD+CVD in Asia, of which the most commonly used is donepezil. The main reasons for prescribing donepezil as first-line therapy are its proven benefit and tolerability, as shown by the greater number of trials of donepezil for patients with VaD. AChEIs are reimbursed in most, but not all, Asian countries, so there may be some treatment differences within the region. The possibilities for second-line therapy include optimizing the dose of donepezil, switching to another AChEI or adding memantine (only for moderate-to-severe dementia). Treatment is usually given long term, and only stopped for disease progression, hospitalization or death, or for adverse reactions or perceived lack of benefit.

Additional treatment for stroke and management of vascular disease risk factors is required to slow or prevent progression of AD+CVD. However, there is no standard approach to treatment of silent stroke and more evidence is needed to clarify the factors that increase the risks or benefits of treatment.

In a recent meta-analysis, several potentially modifiable risk factors for AD, including diet, metabolic disease and lifestyle, were identified [92]. Dementia support groups remain important for reducing the burden of AD+CVD for patients and their families and caregivers.

Summary

The true prevalence of AD+CVD in Asia is uncertain, although it is thought to be higher than is currently recognized, and is likely to be underdiagnosed. The reasons for the possible underdiagnosis of AD+CVD include lack of awareness as the clinical presentations of pure AD and AD+CVD are similar in the absence of a clear history of stroke, the high cost of diagnostic imaging and financial constraints preventing its use, misdiagnosis as VaD or AD, survivor bias and lack of diagnostic criteria. Because of these diagnostic limitations, most evidence for AD+CVD comes from autopsy studies. However, making the diagnosis earlier during the course of the disease would provide a more accu-

Table 4 *Proposed Asia Panel for Alzheimer's and Cerebrovascular disease clinical criteria for AD+CVD*

	Clinical	Neuroimaging[a]	Biomarkers[b]	Neuropathology
AD+CVD	Clinical criteria for AD dementia, with evidence of CVD (i.e. stroke related to onset of worsening cognitive impairment)	The presence of multiple or extensive infarcts or severe white matter hyperintensity, multiple microbleeds and microinfarcts Atrophy of cortical and subcortical brain regions	Decreased CSF Aβ1-42 and increased Tau protein Positive amyloid PET	Pathological criteria of AD and more than two lacunes, or cortical infarction that is correlated with clinical symptoms, or severe subcortical small vessel disease that is sufficient to cause dementia
VaD+AD	Clinical criteria for VaD, with evidence of AD (e.g. progressive decline before or after stroke)			

Aβ1–42, amyloid β-peptide 1–42; AD, Alzheimer's disease; CSF, cerebrospinal fluid; CVD, cerebrovascular disease; PET, positron emission tomography; VaD, vascular dementia.
[a]Computed tomography may be more readily available than magnetic resonance imaging (MRI) and can be used to exclude some treatable conditions such as subdural haematoma, tumour and normal pressure hydrocephalus. MRI may be more sensitive for studying brain morphology, white matter and vascular pathology.
[b]CSF biomarkers and amyloid PET may not be readily available.

rate prevalence pattern and enable more targeted treatment and, ultimately, prevention.

Although there is a lack of guidelines for AD+CVD, a similar approach to diagnosis and treatment of AD+CVD is followed throughout Asia by dementia experts; the NINDS-AIREN and NINCDS-ADRDA guidelines are the most commonly used objective clinical criteria, brain imaging is frequently performed in countries in which cost is not a constraint and MRI is the usual imaging modality. If there is evidence of AD and stroke from the history and neuroimaging results, whether 'silent' or 'eloquent', a diagnosis of AD+CVD should be made.

In all Asian countries, first-line therapy is usually an AChEI, the most common of which is donepezil. Second-line therapy involves optimizing the first-line AChEI, switching to another AChEI or adding memantine.

Vascular disease risk factors should be taken into consideration and treated to prevent or slow progression of dementia. Given that the risk factors for stroke such as atrial fibrillation, hypertension, diabetes mellitus and hypercholesterolaemia are similar to those for vascular cognitive impairment and may also be risk factors for AD, and their detection and control could be effective for prevention of these types of dementia [93].

AD+CVD is a major problem in Asia, which is likely to be under-recognized. Epidemiological studies show the huge burden of AD+CVD both globally and in Asia. There are distinct clinical differences, affecting diagnosis and treatment, between AD and AD+CVD. Therefore, further research using a common standard for case ascertainment is needed to establish the true prevalence of, and to better define the criteria for, this treatable and potentially preventable disease. Table 4 illustrates suggested clinical criteria; these require operationalization as well as clinicopathological studies for validation, but represent a step forward in this important area.

Conflict of interest statement

Christopher Chen has served on the advisory boards of Allergan, Novartis, Pfizer, Eisai, Danone

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