

Vascular cognitive impairment, a cardiovascular complication

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Abstract

Over the past two decades, the term vascular cognitive

impairment (VCI) has been used to refer to a spectrum of cognitive decline characterized by executive dysfunction, associated with vascular pathology. With 30% of stroke survivors showing cognitive impairments, it is regarded as the most common cause of cognitive impairment. This is a narrative review of available literature citing sources from PubMed, MEDLINE and Google Scholar. VCI has a high prevalence both before and after a stroke and is associated with great economic and caregiver burden. Despite this, there is no standardized diagnostic criteria for VCI. Hypertension has been identified as a risk factor for VCI and causes changes in cerebral vessel structure and function predisposing to lacuna infarcts and small vessel haemorrhages in the frontostriatal loop leading to executive dysfunction and other cognitive impairments. Current trials have shown promising results in the use of antihypertensive medications in the management of VCI and prevention of disease progression to vascular dementia. Prevention of VCI is necessary in light of the looming dementia pandemic. All patients with cardiovascular risk factors would therefore benefit from cognitive screening with screening instruments sensitive to executive dysfunction as well as prompt and adequate control of hypertension.

Key words: Vascular dementia; Leukoaraiosis; White matter hyperintensities; Cognitive screening; Neurodegeneration

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Core tip: Vascular cognitive impairment (VCI) has recently been receiving more interest in the scientific world in terms of early identification, preventing as well as slowing down the rate of progression to vascular dementia. Majority of the risk factors for VCI are modifiable and thus amendable to treatment. This review aims to look at hypertension and its role in the early identification and prevention of VCI and dementia.

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INTRODUCTION

Over the past two decades, the concept of vascular cognitive impairment (VCI) has been regarded as a more appropriate notion in describing the spectrum of cognitive impairment caused by or associated with vascular factors^[1,2]. The concept of VCI, was proposed by Sachdev^[3] in 1999 to describe the cognitive deficit of vascular origin severe enough to meet the criteria for a diagnosable disorder. It was initially ascribed to cognitive impairment of vascular origin not significant enough to impair activities of daily living (ADL), *i.e.*, cognitive impairment that does not meet the requirements for dementia^[4]. The term now however refers to a broad spectrum of cognitive and behavioural changes associated with cerebral vascular pathology, characterized by attention and executive impairment ranging from early cognitive decline to dementia. VCI therefore encompasses all the cognitive disorders associated with cerebrovascular disease. It can be described more specifically as cognitive impairment affecting at least one cognitive domain, with evidence of a clinical stroke or subclinical cerebrovascular insult^[5-7].

VCI is not a single disorder, rather it is a spectrum of conditions with heterogeneous clinical presentations, aetiologies and treatment^[4]. VCI is characterized by deficit in executive functioning (planning, task flexibility, problem solving, *etc.*). It could however, present with a much wider range of cognitive dysfunction, non-cognitive features and behavioural changes, and currently has no universally acceptable criteria for diagnosis^[5,8]. It is a concept that, in its early stage, creates an opportunity for preventive strategies aimed at preventing the onset of dementia^[1].

It has been associated with the presence of white matter lesions on magnetic resonance imaging (MRI). The prevalence and degree of these lesions correlate negatively with cognitive function and positively with age^[9,10]. Based on the clinical and neuroimaging features, subtypes of VCI have been proffered.

Brain at risk

Presence of cardiovascular risk factors with/without neuroimaging features of subclinical brain insult and no cognitive impairment. This is the early stage of central nervous system involvement, with the presence of cardiovascular risk factors such as hypertension and white matter hyperintensity on MRI, cognitive functioning remains within normal limits following cognitive assessment.

VCI, no dementia

Impairment in at least one cognitive domain without

affectation of ADL in a patient with cardiovascular risk factors and neuroimaging features of subclinical brain insult. This follows the brain at risk but with cognitive impairment though not severe enough to affect activity of daily living.

Vascular dementia

Impairment in two or more areas of cognitive domain, severe enough to impair ADL and the presence of cardiovascular risk factors as well as neuroimaging findings of cerebral insults (white matter hyperintensities).

Mixed neurodegenerative/vascular dementia

Presence of a neurodegenerative dementia such as Alzheimer's dementia with superimposed vascular dementia^[11].

This review aims to look at current concepts of VCI, its prevalence, pathophysiology and identifiable risk factors with special attention to cardiovascular risk factors as well as possible strategies aimed at preventing VCI and halting its progression to vascular dementia.

EPIDEMIOLOGY OF VCI

Community and hospital based studies on the prevalence of cognitive impairment following a stroke have consistently shown that a significant proportion of stroke patients develop cognitive impairment. Rist *et al*^[12] showed that 30% of stroke survivors had cognitive impairment [as determined by a mini mental state examination (MMSE) score of < 27]. Other studies have also shown similar high prevalence of cognitive impairment ranging from 24% to 70%, three months to one-year post stroke^[13-15]. Douiri *et al*^[13] using the South London Stroke Register assessed the cognitive impairment of 4212 stroke patients with the MMSE and abbreviated mental test and found a prevalence of 22% at 3 mo, 22% at 5 years and 21% at 14 years post stroke. Cognitive impairment was detected within 7 d of a stroke in some of the participants but remained relatively stable after 3 mo following a stroke. The prevalence rate of cognitive impairment in this study is most likely an underestimate of the true values as the neuropsychological methods used in the assessment of cognitive function are insensitive to executive dysfunction and mild cognitive impairment^[13]. Gutiérrez Pérez *et al*^[16] studied cognitive function before and in the acute phase of a stroke. They found that cognitive impairment was frequent, being present in 52% of patients before the onset of stroke. In the post stroke period, 96% of the elderly were found to be cognitively impaired using a battery of neuropsychological tests while only 36% were cognitively impaired using the MMSE^[16].

The Canadian study on health and ageing in a prospective cohort study of 10253 community and institution dwellers aged 65 years and over found that of the different subtypes of VCI, VCI no dementia was the

most prevalent form and it was associated with higher institutionalization and mortality rate^[17]. In patients less than 74 years of age, VCI may be the commonest cause of cognitive impairment, and is associated with both an increased risk of stroke and death from stroke^[17,18].

Studies done in sub-Saharan Africa have shown incidence and prevalence rates of cognitive impairment and dementia to be on the increase due to the increasing elderly population. Studies carried out in Benin, Botswana, the Central African Republic, the Congo and Nigeria determined that the prevalence of dementia ranges from 0% to 10.1% (95%CI: 8.6-11.8), and the prevalence of cognitive impairment ranged from 6.3%, in Nigeria, to 25% (95%CI: 21.2-29.0), in the Central African Republic^[19]. These studies used various neuropsychological batteries in the assessment of cognitive impairment. Akinyemi *et al*^[20] (2014) assessed the baseline cognitive profile and factors associated with VCI three months after stroke in the Cognitive Function after Stroke Nigerian Study. The study comprised 217 subjects of which 143 were stroke survivors. Standard neuropsychological tests including the Vascular Neuropsychological Battery, which assessed executive function/mental speed, memory, language, and visuospatial/visuoconstructive functioning were used. Among the stroke survivors, 39.9% had cognitive impairment no dementia while 8.4% had dementia at baseline. They associated pre-stroke cognitive decline as a risk factor for cognitive impairment with an odds ratio of 4.51, and educational level and dietary factors as modifiable risk factors^[20]. The different prevalence values from these studies can be attributed to the different neuropsychological tests used for screening cognitive impairment, with some tests being more sensitive to the cognitive impairment profile seen in VCI than others. This buttresses the need for a standardized battery for cognitive assessment for both research and clinical use. Despite these differences in approaches to cognitive screening, these studies found high prevalence of VCI prior to and after a stroke.

Knowledge about the economic implications of VCI is valuable but insufficient. The health cost of the VCI spectrum has to be seen from a societal perspective for the true burden of disease to be appreciated as well as from the impact of cardiovascular co-morbidities on the cost and utilization of health care. The health cost of vascular dementia (VaD) (a subtype of VCI) has been found to be 23% higher than that of Alzheimer's dementia^[21]. The presence of VCI superimposed on a stroke increases the economic burden as well as the burden of care. A community based study on health care utilization and cost in patients with VaD, Alzheimer's dementia, other dementias, cerebrovascular accident without dementia and control group found that the highest annual cost of health care of \$14387 was in VaD compared to \$7839 for Alzheimer's dementia ($P < 0.0001$). VaD had the highest cost for hospital admissions and had a three times increase in hospital days compared to cerebrovascular disease

no dementia^[22]. In the Sub-Saharan setting where the burden of care (physical, emotional and financial) lies heavily on the immediate and extended family, it creates and opportunity for caregiver burden/fatigue and elder abuse.

Data has shown that VCI is common irrespective of the neuropsychological test used for the screening of cognitive impairment and in the older population may be the commonest form of cognitive impairment. VCI is associated with increased mortality and higher institutionalization rates in the elderly. From an economic stand point, it carries a larger financial burden than Alzheimer's dementia and Stroke. With the looming dementia pandemic, the incidence and prevalence is expected to increase in the near future and with this increase, an increase in the financial and care giver burden.

RISK FACTORS FOR VCI

Several cardiovascular risk factors including hypertension, diabetes mellitus, dyslipidaemia, smoking and obesity have been identified as modifiable risk factors for cognitive decline. In this review, emphasis will be placed on blood pressure and its association with VCI.

Blood pressure (both lowered and elevated) has been linked with decline in cognitive function (especially in concentration). Epidemiological studies have shown an inverted "U" shaped relationship between blood pressure and cognitive performance in the elderly^[23].

Zuccalà *et al*^[24] studied 13635 patients without cerebrovascular disease or Alzheimer's dementia; 1583 of the subjects had heart failure. He found cognitive impairments in 26% of patients with heart failure and in 19% of the remaining subjects. Systolic blood pressure less than 130 mmHg predicted cognitive impairment among patients with heart failure. No association with specific types of heart failure was found. They concluded that systolic blood pressure was specifically associated with cognitive impairment in elderly patients with heart failure and that early treatment of low output cardiac states can reverse this cognitive state. They also buttressed the need for systematic assessment of cognitive function in the management of patients with heart failure^[24]. Recent studies have supported this finding that hypotension causes reduced cognitive function (demonstrated by neuropsychological tests) and activity^[25,26]. Orthostatic dysregulation has been associated with an increased tendency of white matter hyperintensities (WMH)^[27]. Yamamoto *et al*^[28], however disagreed with this. They found that nighttime dip in blood pressure was protective against cognitive impairment and patients who were non-dippers had a higher prevalence of cognitive impairment and vascular dementia. There is however, the need for further studies to investigate if controlling night time blood pressure would reduce the risk of cognitive impairment and dementia.

Hypertension has often been observed to be a risk

factor for vascular dementia and even Alzheimer's dementia^[29]. Hypertension has been shown to cause damage to the cerebral tissues resulting in subcortical white matter lesions (leukoaraiosis), which contribute to the risk of stroke and vascular dementia. Increase in blood pressure has been associated with more severe periventricular and subcortical white matter lesions (ischaemic damage), and poorly controlled hypertension has an even higher risk of white matter lesions and thus cognitive impairment than those without hypertension, controlled hypertension or untreated hypertension^[30]. In the system Europe Study, treatment of hypertensive subjects with calcium channel blockers was associated with a decrease in the incidence of dementia^[31].

Leukoaraiosis has been found to be more prevalent and severe in stroke patients (both ischaemic and haemorrhagic) compared to normal people. The presence of leukoaraiosis (from its different pathophysiological processes) has more than doubles the odds of stroke and increases the odds of subsequent dementia by a factor of four^[32]. Leukoaraiosis is seen on MRI as WMH in the periventricular and subcortical white matter regions of the brain. These WMH have been associated with cognitive impairment, increased risk of stroke and dementia^[33]. Studies have shown that there might be a genetic basis to the development leukoaraiosis. The Genetic Epidemiology Network of Arteriopathy estimated the heritability of leukoaraiosis at 0.82 ± 0.102 (SE) $P (< 0.0001)$, showing a strong genetic influence on the susceptibility of leukoaraiosis and thus the risk to cognitive impairment and dementia^[34]. It is a prominent feature of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) and is associated with increased vulnerability of the brain to ischaemic injury^[35]. CADASIL is an inheritable cause of vascular dementia. Leukoaraiosis also has a sporadic form which is also associated with stroke risk factors such as hypertension and diabetes^[32]. Patients with silent brain infarcts and leukoaraiosis at baseline are at an increased long-term risk for recurrent stroke, cognitive decline, and dementia^[36]. A family based study design in generally healthy individuals found the heritability of WMH in individuals aged 55 years of age and over to be 0.68 ($P < 0.0001$) with heritability being higher in females than males^[37]. There is a significant evidence that a gene influencing WMH is located on chromosome 4p^[38]. This implies that the tendency of the cerebrovascular system to damaging changes by the cardiovascular risk factors such as hypertension may be inherited and therefore may serve as a non-modifiable risk factor or predisposing factor to VCI, with hypertension acting on this predisposition and making the brain more vulnerable to damage. Strategies that aim to prevent the onset of VCI by early identification and prompt and adequate treatment of such factors would go a long way in reducing the incidence, prevalence, economic and care giver burden of VCI.

PATHOPHYSIOLOGY OF VCI

Within the brain, there are control mechanisms that ensure adequate perfusion to meet its metabolic demands. At times of increased brain activity and metabolism, cerebral blood flow increases to meet metabolic demands and to clear metabolic waste. This is termed functional hyperaemia^[39]. Cerebral autoregulation is another mechanism in which cerebral blood vessels are able to maintain a relatively stable cerebral blood flow despite changes in arterial blood pressure. These above mechanisms are able to regulate cerebral blood flow within 60 and 150 mmHg mean arterial blood pressure^[40]. Aging and hypertension act independently on these mechanisms, altering the range of mean arterial pressure at which cerebral blood flow is regulated.

Aging brings with changes in cerebral blood flow, with decreased numbers of capillaries, thickened fibrotic basal membrane, some degenerative processes which contributes to decrease in cerebral perfusion, depletion of cerebrovascular reserve, and susceptibility of the brain to vascular insufficiency and ischaemic injury^[41,42].

Hypertension acts on the aging brain and generates significant changes in the structure of cerebral blood vessels. It promotes atherosclerosis in cerebral arteries, promotes lipohyalinosis (a pathologic process of fibrinoid necrosis of vascular wall) of penetrating small cerebral arteries and arterioles leading to small white matter strokes (lacunas) or haemorrhages and causes adaptive remodeling of cerebral vessels leading to narrowing of the lumen and decrease cerebral blood flow with impaired cerebrovascular reactivity and functional hyperaemia. It shifts the cerebrovascular autoregulation to the right requiring higher blood pressure to maintain cerebral perfusion and increased the vulnerability of the brain to low blood pressure, predisposing to hypoperfusion during hypotension^[41]. These changes may lead to cerebrovascular dysfunction through amyloid and enzyme mediated pathways. Long-term decrease in mean arterial pressure has been associated with increase tau phosphorylated at threonine 181 (p-tau 181) and thus related to decline in episodic memory^[43]. Hypertension causes alteration of the blood brain barrier compromising cerebral microenvironment and increasing the vulnerability of regions of the brain critical for cognition (subcortical white matter, hippocampus and neocortex) to ischaemic hypoxic brain damage and ultimately leads to neuronal dysfunction and cognitive deficit^[44]. These multiple small infarcts and small vessel disease are more often related to VaD than single major infarcts. Esiri, in his study on the neuropathological lesions seen in VaD concluded that microvascular disease, not macroscopic infarction, was the chief substrate of vascular dementia^[45]. These microvascular diseases (hypoxic ischaemia and lacunar infarcts) are the processes that kick start VCI. Their appearance on neuroimaging techniques are referred to as leukoaraiosis [bilateral patchy or diffuse areas seen as hypodense areas on computer tomography (CT)

scan], and hyperintense areas on T2 weighted MRI in the subcortical regions of the brain^[46].

NEUROPSYCHOLOGICAL PROFILE OF VCI

An understanding of the pattern of neurocognitive impairment in the early stages of VCI [brain at risk and vascular cognitive impairment, no dementia (VCIND)] is advantageous in the clinical detection of cognitive impairment and prevention of the progression to dementia (VaD). Cognitive function mediated by the frontostriatal loop has been shown to be susceptible to the damaging effects of subcortical disease and thus leads to impairment in frontal lobe executive function. This has been shown to occur in VCIND and VaD. The different spectrums of VCI (brain at risk, VCIND and VaD) have been proposed to have different neurocognitive patterns. While the brain at risk exhibits no clinical or functional impairment, VCIND was associated with decreased information processing speed, reduced cognitive flexibility, deficit in the ability to hold and manipulate memory, impaired verbal retrieval, and impaired verbal cognition memory and poor learning efficiency^[47,48]. Therefore, in choosing a neuropsychological test for the assessment of VCI, the test in question has to be sensitive to a wide range of cognitive abilities and be especially attuned to the assessment of executive function. Using timed executive function tests may be especially sensitive to VCI (due to the slow information processing)^[49].

A cross sectional study of four groups (normal control, risk of cerebrovascular disease, VCIND and VaD) was carried out to find the neuropsychological cognitive pattern using a combination of tests (trail making test, controlled oral word associated test, Boston naming test, California verbal naming test). They found that the brain at risk group was similar in their cognitive profile to the normal control as they did not fall into the cognitive impairment range of any of the tests used. VCIND group on the other hand had mild impairment in cognitive flexibility, subtle difficulty in total learning and long delay free recall. The VaD group performed uniformly well below normative expectation (moderate to severe range) in all measures of cognitive functioning^[50]. Sachdev *et al*^[51] in 2004 had similar findings and was able to differentiate VCI from unimpaired patients in areas of abstraction, mental flexibility, information processing speed and working memory. Cognitive impairment was also significantly correlated with deep WMH. Reed *et al*^[52] however found no significant difference in memory and executive dysfunction scores in VCI and Alzheimer's disease. They concluded that cognitive effects of small vessel cerebrovascular disease were variable and not especially distinct and their use as diagnostic markers of VaD were not reliable^[50]. This however is in contrast with the predominant view from research on the cognitive pattern of VCI.

The National Institute for Neurological Disorders and Stroke and the Canadian Stroke Network recommended three neuropsychological battery to diagnose VCI based on epidemiological, clinical, neuroimaging, neuropsychological and neuropathological profiles of VCI in an attempt to aid the identification of early stages of cognitive impairment, make studies comparable, and by integrating knowledge, accelerate the pace of progress^[48]. They are: (1) the sixty (60) minute protocol for research studies, which assesses four cognitive domains (executive/activation, language, visuospatial, memory \pm neurobehavioral changes and depression); The thirty (30) minute protocol for clinical screening of suspected VCI. This assesses Semantic Fluency (Animal Naming), Phonemic Fluency (Controlled Oral Word Association Test), Digit Symbol-Coding from the Wechsler Adult Intelligence Scale, Hopkins Verbal Learning Test, Center for Epidemiologic Studies Depression Scale, Neuropsychiatric Inventory, Questionnaire Version (NPI-Q), Supplemental: MMSE, Trail Making Test; and (3) The five (5) minute protocol for potential use by primary care physicians, nurses and other allied health professionals as well as in large epidemiological studies. This protocol contains 5-Word Memory Task (registration, recall, and recognition), 6-Item Orientation and 1-Letter Phonemic Fluency^[48].

This neuropsychological battery has been validated in several countries in stroke and transient ischaemic attack patients^[53]. It has also been used in studies for the identification of VCI^[20]. Further validation of this neuropsychological battery for diagnosis of VCI might aid in the formulation of a diagnostic criteria for the different subtypes of VCI that would adequately capture the neuropsychological profile of VCI.

MANAGEMENT AND PREVENTION OF VCI

The role of vascular disease as a cause of cognitive impairment is evident either alone or in combination with Alzheimer's disease. The main management strategy for VCI is the symptomatic treatment of VaD, management of risk factors as well non-pharmacological approaches aimed at preventing progression to VaD. The initial assessment should include a medical history, assessment of functioning (global functioning and ADL), cognitive screening, and assessment for behavioural and psychological symptoms as well as neuroimaging techniques.

Randomized control trials for the use of cholinesterase inhibitors for the treatment of VaD have shown moderate statistical but modest clinical benefits in the treatment of VaD. Cholinesterase inhibitors (donepezil, galantamine and rivastigmine) show significant improvement in cognitive function, ADL and behaviour after 24 wk of use^[49,54]. Memantine has been found to improve function and decrease care dependency when compared to controls in mild to moderately demented patients^[55]. A randomized double blind placebo control

Table 1 Research studies on antihypertensive use and cognitive impairment

| Ref. | Sample size | Treatment option | Primary outcome | Treatment period | Result |
|--------------------------------------|-------------|---|---|------------------|---|
| Tzourio <i>et al</i> ^[64] | 6108 | Participants were assigned to either active treatment (perindopril and indapamide) or matching placebo(s) | Dementia (using DSM-IV criteria) and cognitive decline (a decline of 3 or more points in the Mini-Mental State Examination score) | 3.9 yr | Dementia was documented in 193 (6.3%) of the 3051 randomized participants in the actively treated group and 217 (7.1%) of the 3054 randomized participants in the placebo group [relative risk reduction, 12% (95%CI: -8% to 28%); $P = 0.2$]. Cognitive decline occurred in 9.1% of the actively treated group and 11.0% of the placebo group [risk reduction, 19% (95%CI: 4% to 32%); $P = 0.01$]. The risks of the composite outcomes of dementia with recurrent stroke and of cognitive decline with recurrent stroke were reduced by 34% (95%CI: 3% to 55%) ($P = 0.03$) and 45% (95%CI: 21% to 61%) ($P < 0.001$), respectively, with no clear effect on either dementia or cognitive decline in the absence of recurrent stroke |
| Dufouil <i>et al</i> ^[65] | 192 | Participants were assigned to a combination of perindopril plus indapamide or their placebos or to single therapy with perindopril or placebo | Cerebral MRI both at baseline and after a mean follow-up time of 36 mo WMHs were graded with a visual rating scale from A (no WMH) to D (severe WMH) | 36 mo | Twenty-four subjects (12.5%) developed new WMHs at follow-up. The risk of new WMH was reduced by 43% (95%CI: -7% to 89%) in the active treatment group compared with the placebo group ($P = 0.17$). The mean total volume of new WMHs was significantly reduced in the active treatment group [0.4 mm^3 (SE = 0.8)] compared with the placebo group [2.0 mm^3 (SE = 0.7); $P = 0.012$] |
| Hajjar <i>et al</i> ^[62] | 53 | Lisinopril, candesartan, or hydrochlorothiazide | Cerebral blood flow velocity (BFV; transcranial Doppler ultrasonography during rest, sitting, standing, hypercapnia, and hypocapnia), cognition (trail making test), and blood pressure | 12 mo | There was a tendency toward an increase in BFV in the candesartan group and a decrease in the lisinopril and hydrochlorothiazide groups (between-group $P = 0.57$) that was significant in those with low BFV at baseline ($< \text{median } 27.6 \text{ cm/s}$, between-group $P = 0.03$). The candesartan group also had the greatest improvement in executive function (Trail Making Test Part B improved by 17.1 s, <i>vs</i> hydrochlorothiazide improved by 4.2 s and lisinopril worsened by 14.4 s, $P = 0.008$). Carbon dioxide vasoreactivity and vasomotor range declined significantly in the lisinopril (within-group $P = 0.001$ for vasoreactivity and 0.02 for vasomotor range) and hydrochlorothiazide groups (within-group $P = 0.10$ and 0.009, respectively) but not in the candesartan group (within-group $P = 0.25$ and 0.38, respectively; between-group $P = 0.30$ and 0.46, respectively) |
| Gelber <i>et al</i> ^[61] | 2197 | Different classes of antihypertensive medication | Cognitive function was assessed at 7 standardized examinations using the CASI | 5.8 yr | 854 men developed cognitive impairment (median follow-up, 5.8 yr). β -blocker use as the sole antihypertensive drug at baseline was consistently associated with a lower risk of cognitive impairment (IRR 0.69; 95%CI: 0.50-0.94), as compared with men not taking any antihypertensive medications. The use of diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, or vasodilators alone was not significantly associated with cognitive impairment |

CASI: Cognitive Abilities Screening Instrument; MRI: Magnetic resonance imaging; WMH: White matter hyperintensities; IRR: Incidence rate ratio.

trial of 404 patients with moderate to severe Alzheimer's dementia was performed to compare the efficacy and safety of memantine in patients already receiving donepezil in 24 wk. Memantine resulted in significantly better outcome compared to placebo on measures of cognition, ADL, goal outcome and behavior and was well tolerated. This showed that memantine can be used in combination with cholinesterase inhibitors^[56]. A Cochrane review of available studies support the benefit of donepezil in improving cognitive function, clinical global impression and ADL in patients with probable or possible mild to moderate VCI after 6 mo treatment^[57].

Long standing hypertension has been continuously

linked to the development of cognitive impairment and dementia in later life^[58]. Population attributable risk for dementia is the highest for hypertension and therefore, should be regarded as a potential major target for the prevention of dementia^[7]. Observational studies suggest that administration of antihypertensive medication in younger age group with hypertension has preventive effects on cognitive decline in later life^[59,60]. β blocker use has been associated with lower risk of developing cognitive impairment (assessed using cognitive ability screening instrument) in a prospective community based cohort study examining 2197 elderly hypertensive participants. After a median follow up of 5.8 years, 854

subjects developed cognitive impairment. This study showed that β -blocker use as the sole antihypertensive medication was associated with a lower risk of VCI (incidence risk ratio of 0.69, 95%CI: 0.45-0.94) when compared to patients not taking any antihypertensive medication. Use of other antihypertensives were not significantly associated with VCI^[61]. Setbacks of this study includes the fact that only hypertensive men were examined and no neuroimaging techniques were used at any point of the study to rule out subjects at early stages of cognitive impairment that may not have been captured with the tool used to screen cognitive function. Hajjar *et al*^[62] conducted 12-mo double blind randomized control trial comparing candesartan, Lisinopril and hydrochlorothiazide in hypertensive patients with early executive dysfunction. The study recruited 53 participants 60 years of age and older with hypertension and executive dysfunction. Cerebral blood flow, cognition and blood pressure were measured at baseline, 6 mo and 12 mo. The candesartan group had greatest improvement in executive dysfunction (trail making test) and less improvement was seen in the hydrochlorothiazide group. The Lisinopril group showed worsened executive dysfunction. They showed that angiotensin receptor blocking group may preferentially preserve cerebral haemodynamics and executive function in individuals with executive dysfunction^[62]. Various randomized controlled trials (RCT) investigated the effect of antihypertensive treatment on the incident of dementia. Majority of these RCT showed that antihypertensive treatment decrease the incidence of stroke but only a few have shown a significant positive effect on the incidence of dementia^[63]. A randomized treatment trial of an angiotensin converting enzyme inhibitor, Perindopril showed that active treatment significantly decreased the risk of dementia and cognitive impairment and delayed progression of WMH on MRI. The Perindopril Protection Against Recurrent Stroke Study, was a randomized double blind placebo - control trial conducted on 6105 subjects with prior stroke or transient ischaemic attack with primary outcome of development of dementia using (DSM-IV diagnostic criteria) and cognitive decline (MMSE decline of 3 or more points). During the follow-up period (mean of 3.9 years) 193 (6.3%) of the treatment group compared to 217 (7.1%) of randomized placebo group developed dementia (Relative Risk Reduction of 12%). Cognitive decline was recorded in 9.1% of actively treated group and 11.0% of placebo (risk reduction of 19%). The risk of dementia and cognitive impairment with recurrent stroke were reduced by 35% and 45% respectively in the treatment group^[64,65] (Table 1). Meta-analysis of randomized trials of antihypertensive on prevention of dementia showed an overall reduction of risk of dementia ranged from 11%-20%^[7]. There is however no general consensus or standardized clinical guidelines on antihypertensive use in the prevention of VCI.

CONCLUSION

The full spectrum of VCI has been consistently linked to cardiovascular risk factors. There are constant evidences from research that hypertension is associated with the development of VCI through overt clinical stroke and small cerebral arteries and arteriole pathologies leading to subcortical infarcts (lacuna) and haemorrhages. The clinical outcome of which is cognitive impairment with predominant affectation of executive dysfunction as well as other areas of functioning.

Preventive strategies aimed at controlling hypertension have been shown to significantly reduce the incidence of vascular dementia, with antihypertensive of the angiotensin receptor blocker and angiotensin converting enzyme inhibitor to be at the forefront of research. However, more research works on preventing VCI and decreasing its progression to dementia are required as vascular dementia is one of the dementia complexes in which prevention is possible. Prevention is necessary in light of the looming dementia pandemic in order to not only decrease the burden of disease on the patient but also the economic burden on the government and care giver.

REFERENCES

- 1 **Bowler JV.** The concept of vascular cognitive impairment. *J Neurol Sci* 2002; **203-204**: 11-15 [PMID: 12417350 DOI: 10.1016/S0022-510X(02)00253-8]
- 2 **Bowler JV.** Modern concept of vascular cognitive impairment. *Br Med Bull* 2007; **83**: 291-305 [PMID: 17675645]
- 3 **Sachdev P.** Vascular cognitive disorder. *Int J Geriatr Psychiatry* 1999; **14**: 402-403 [PMID: 10389048 DOI: 10.1002/(SICI)1099-1166(199905)14]
- 4 **Suvarna A.** Vascular cognitive impairment. *Indian J Psychiatry* 2009; **51** Suppl 1: S61-S64 [PMID: 21416020]
- 5 **O'Brien JT.** Vascular cognitive impairment. *Am J Geriatr Psychiatry* 2006; **14**: 724-733 [PMID: 16943169]
- 6 **Moorhouse P, Rockwood K.** Vascular cognitive impairment: current concepts and clinical developments. *Lancet Neurol* 2008; **7**: 246-255 [PMID: 18275926 DOI: 10.1016/S1474-4422(08)70040-1]
- 7 **Gorelick PB, Scuteri A, Black SE, DeCarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW, Seshadri S.** Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011; **42**: 2672-2713 [DOI: 10.1161/STR.0b013e3182299496]
- 8 **Román GC, Sachdev P, Royall DR, Bullock RA, Orgogozo JM, López-Pousa S, Arizaga R, Wallin A.** Vascular cognitive disorder: a new diagnostic category updating vascular cognitive impairment and vascular dementia. *J Neurol Sci* 2004; **226**: 81-87 [PMID: 15537526 DOI: 10.1016/j.jns.2004.09.016]
- 9 **de Leeuw FE, de Groot JC, Achten E, Oudkerk M, Ramos LM, Heijboer R, Hofman A, Jolles J, van Gijn J, Breteler MM.** Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. *J Neurol Neurosurg Psychiatry* 2001; **70**: 9-14 [PMID: 11118240 DOI: 10.1136/jnnp.70.1.9]
- 10 **Debette S, Bombois S, Bruandet A, Delbeuck X, Lepoittevin S, Delmaire C, Leys D, Pasquier F.** Subcortical hyperintensities are associated with cognitive decline in patients with mild cognitive impairment. *Stroke* 2007; **38**: 2924-2930 [PMID: 17885256 DOI: 10.1161/STROKEAHA.107.136199]

- 10.1161/STROKEAHA.107.488403]
- 11 **Rockwood K**, Black SE, Song X, Hogan DB, Gauthier S, MacKnight C, Vandrope R, Guzman A, Montgomery P, Kertesz A, Bouchard RW, Feldman H. Clinical and radiographic subtypes of vascular cognitive impairment in a clinic-based cohort study. *J Neurol Sci* 2006; **240**: 7-14 [PMID: 16212979]
- 12 **Rist PM**, Chalmers J, Arima H, Anderson C, Macmahon S, Woodward M, Kurth T, Tzourio C. Baseline cognitive function, recurrent stroke, and risk of dementia in patients with stroke. *Stroke* 2013; **44**: 1790-1795 [PMID: 23686974 DOI: 10.1161/STROKEAHA.111.680728]
- 13 **Douiri A**, Rudd AG, Wolfe CD. Prevalence of poststroke cognitive impairment: South London Stroke Register 1995-2010. *Stroke* 2013; **44**: 138-145 [PMID: 23150656 DOI: 10.1161/STROKEAHA.112.670844]
- 14 **Rasquin SM**, Lodder J, Ponds RW, Winkens I, Jolles J, Verhey FR. Cognitive functioning after stroke: a one-year follow-up study. *Dement Geriatr Cogn Disord* 2004; **18**: 138-144 [PMID: 15211068 DOI: 10.1159/000079193]
- 15 **Ihle-Hansen H**, Thommessen B, Wyller TB, Engedal K, Øksengård AR, Stenset V, Løken K, Aaberg M, Fure B. Incidence and subtypes of MCI and dementia 1 year after first-ever stroke in patients without pre-existing cognitive impairment. *Dement Geriatr Cogn Disord* 2011; **32**: 401-407 [PMID: 22311341 DOI: 10.1159/000335361]
- 16 **Gutiérrez Pérez C**, Sävborg M, Pålman U, Cederfeldt M, Knopp E, Nordlund A, Astrand R, Wallin A, Fröjd K, Wijk H, Tarkowski E. High frequency of cognitive dysfunction before stroke among older people. *Int J Geriatr Psychiatry* 2011; **26**: 622-629 [PMID: 20922768 DOI: 10.1002/gps.2573]
- 17 **Rockwood K**, Wentzel C, Hachinski V, Hogan DB, MacKnight C, McDowell I. Prevalence and outcomes of vascular cognitive impairment. Vascular Cognitive Impairment Investigators of the Canadian Study of Health and Aging. *Neurology* 2000; **54**: 447-451 [PMID: 10668712 DOI: 10.1212/WNL.54.2.447]
- 18 **Ferrucci L**, Guralnik JM, Salive ME, Pahor M, Corti MC, Baroni A, Havlik RJ. Cognitive impairment and risk of stroke in the older population. *J Am Geriatr Soc* 1996; **44**: 237-241 [PMID: 8600190 DOI: 10.1111/j.1532-5415.1996.tb00908.x]
- 19 **Mavrodaris A**, Powell J, Thorogood M. Prevalences of dementia and cognitive impairment among older people in sub-Saharan Africa: a systematic review. *Bull World Health Organ* 2013; **91**: 773-783 [PMID: 24115801 DOI: 10.2471/BLT.13.118422]
- 20 **Akinyemi RO**, Allan L, Owolabi MO, Akinyemi JO, Ogbale G, Ajani A, Firbank M, Ogunniyi A, Kalaria RN. Profile and determinants of vascular cognitive impairment in African stroke survivors: the CogFAST Nigeria Study. *J Neurol Sci* 2014; **346**: 241-249 [PMID: 25238666 DOI: 10.1016/j.jns.2014.08.042]
- 21 **Wimo A**, Winblad B. Societal burden and economics of vascular dementia: preliminary results from a Swedish-population-based study. *Int Psychogeriatr* 2003; **15** Suppl 1: 251-256 [PMID: 16191249 DOI: 10.1017/S1041610203009281]
- 22 **Hill J**, Fillit H, Shah SN, del Valle MC, Futterman R. Patterns of healthcare utilization and costs for vascular dementia in a community-dwelling population. *J Alzheimers Dis* 2005; **8**: 43-50 [PMID: 16155348]
- 23 **Waldstein SR**, Giggey PP, Thayer JF, Zonderman AB. Nonlinear relations of blood pressure to cognitive function: the Baltimore Longitudinal Study of Aging. *Hypertension* 2005; **45**: 374-379 [PMID: 15699446 DOI: 10.1161/01.HYP.0000156744.44218.74]
- 24 **Zuccalà G**, Onder G, Pedone C, Carosella L, Pahor M, Bernabei R, Cocchi A. Hypotension and cognitive impairment: Selective association in patients with heart failure. *Neurology* 2001; **57**: 1986-1992 [PMID: 11739814 DOI: 10.1212/WNL.57.11.1986]
- 25 **Duschek S**, Schandry R. Reduced brain perfusion and cognitive performance due to constitutional hypotension. *Clin Auton Res* 2007; **17**: 69-76 [PMID: 17106628]
- 26 **Duschek S**, Meinhardt J, Schandry R. Reduced cortical activity due to chronic low blood pressure: an EEG study. *Biol Psychol* 2006; **72**: 241-250 [PMID: 16460867 DOI: 10.1016/j.biopsycho.2005.06.011]
- 27 **Oh YS**, Kim JS, Lee KS. Orthostatic and supine blood pressures are associated with white matter hyperintensities in Parkinson disease. *J Mov Disord* 2013; **6**: 23-27 [PMID: 24868422 DOI: 10.14802/jmd.13006]
- 28 **Yamamoto Y**, Akiguchi I, Oiwa K, Hayashi M, Ohara T, Ozasa K. The relationship between 24-hour blood pressure readings, subcortical ischemic lesions and vascular dementia. *Cerebrovasc Dis* 2005; **19**: 302-308 [PMID: 15775671 DOI: 10.1159/000084498]
- 29 **Moretti R**, Torre P, Antonello RM, Manganaro D, Vilotti C, Pizzolato G. Risk factors for vascular dementia: hypotension as a key point. *Vasc Health Risk Manag* 2008; **4**: 395-402 [PMID: 18561514]
- 30 **van Dijk EJ**, Breteler MM, Schmidt R, Berger K, Nilsson LG, Oudkerk M, Pajak A, Sans S, de Ridder M, Dufouil C, Fuhrer R, Giampaoli S, Launer LJ, Hofman A. The association between blood pressure, hypertension, and cerebral white matter lesions: cardiovascular determinants of dementia study. *Hypertension* 2004; **44**: 625-630 [PMID: 15466662 DOI: 10.1161/01.HYP.0000145857.98904.20]
- 31 **Forette F**, Seux ML, Staessen JA, Thijs L, Birkenhäger WH, Babarskiene MR, Babeanu S, Bossini A, Gil-Extremera B, Girerd X, Laks T, Lilov E, Moiseyev V, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Fagard R. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet* 1998; **352**: 1347-1351 [PMID: 9802273 DOI: 10.1016/S0140-6736(98)03086-4]
- 32 **Smith EE**. Leukoaraiosis and stroke. *Stroke* 2010; **41**: S139-S143 [PMID: 20876490 DOI: 10.1161/STROKEAHA.110.596056]
- 33 **Breteler MM**, van Swieten JC, Bots ML, Grobbee DE, Claus JJ, van den Hout JH, van Harskamp F, Tanghe HL, de Jong PT, van Gijn J. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. *Neurology* 1994; **44**: 1246-1252 [PMID: 8035924]
- 34 **Turner ST**, Jack CR, Fornage M, Mosley TH, Boerwinkle E, de Andrade M. Heritability of leucoaraiosis in hypertensive sibships. *Hypertension* 2004; **43**: 483-487 [PMID: 14718359 DOI: 10.1161/01.HYP.0000112303.26158.92]
- 35 **Iadecola C**, Hachinski V, Rosenberg GA. Vascular cognitive impairment: introduction. *Stroke* 2010; **41**: S127-S128 [PMID: 20876487 DOI: 10.1161/STROKEAHA.110.595488]
- 36 **Norrving B**. Leucoaraiosis and silent subcortical infarcts. *Rev Neurol (Paris)* 2008; **164**: 801-804 [PMID: 18760430 DOI: 10.1016/j.neurol.2008.07.009]
- 37 **Atwood LD**, Wolf PA, Heard-Costa NL, Massaro JM, Beiser A, D'Agostino RB, DeCarli C. Genetic variation in white matter hyperintensity volume in the Framingham Study. *Stroke* 2004; **35**: 1609-1613 [PMID: 15143299 DOI: 10.1161/01.STR.0000129643.77045.10]
- 38 **DeStefano AL**, Atwood LD, Massaro JM, Heard-Costa N, Beiser A, Au R, Wolf PA, DeCarli C. Genome-wide scan for white matter hyperintensity: the Framingham Heart Study. *Stroke* 2006; **37**: 77-81 [PMID: 16322484 DOI: 10.1161/01.STR.0000196987.68770.b3]
- 39 **Iadecola C**. Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nat Rev Neurosci* 2004; **5**: 347-360 [PMID: 15100718 DOI: 10.1038/nrn1387]
- 40 **Paulson OB**, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* 1990; **2**: 161-192 [PMID: 2201348]
- 41 **Iadecola C**, Park L, Capone C. Threats to the mind: aging, amyloid, and hypertension. *Stroke* 2009; **40**: S40-S44 [PMID: 19064785 DOI: 10.1161/STROKEAHA.108.533638]
- 42 **Andresen J**, Shafi NI, Bryan RM. Endothelial influences on cerebrovascular tone. *J Appl Physiol* (1985) 2006; **100**: 318-327 [PMID: 16357085]
- 43 **Głodzik L**, Rusinek H, Pirraglia E, McHugh P, Tsui W, Williams S, Cummings M, Li Y, Rich K, Randall C, Mosconi L, Osorio R, Murray J, Zetterberg H, Blennow K, de Leon M. Blood pressure decrease correlates with tau pathology and memory decline in hypertensive elderly. *Neurobiol Aging* 2014; **35**: 64-71 [PMID: 23969178 DOI: 10.1016/j.neurobiolaging.2013.06.011]
- 44 **Levine DA**, Langa KM. Vascular cognitive impairment: disease

- mechanisms and therapeutic implications. *Neurotherapeutics* 2011; **8**: 361-373 [PMID: 21556678 DOI: 10.1007/s13311-011-0047-z]
- 45 **Esiri MM**, Wilcock GK, Morris JH. Neuropathological assessment of the lesions of significance in vascular dementia. *J Neurol Neurosurg Psychiatry* 1997; **63**: 749-753 [PMID: 9416809 DOI: 10.1136/jnnp.63.6.749]
 - 46 **Inzitari D**. Leukoaraiosis: an independent risk factor for stroke? *Stroke* 2003; **34**: 2067-2071 [PMID: 12829859 DOI: 10.1161/01.str.0000080934.68280.82]
 - 47 **Waldstein SR**, Jennings JR, Ryan CM, Muldoon MF, Shapiro AP, Polefrone JM, Fazzari TV, Manuck SB. Hypertension and neuropsychological performance in men: interactive effects of age. *Health Psychol* 1996; **15**: 102-109 [PMID: 8681917]
 - 48 **Hachinski V**, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, Powers WJ, DeCarli C, Merino JG, Kalra RN, Vinters HV, Holtzman DM, Rosenberg GA, Wallin A, Dichgans M, Marler JR, Leblanc GG. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. *Stroke* 2006; **37**: 2220-2241 [PMID: 16917086 DOI: 10.1161/01.STR.0000237236.88823.47]
 - 49 **Black S**, Román GC, Geldmacher DS, Salloway S, Hecker J, Burns A, Perdomo C, Kumar D, Pratt R. Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. *Stroke* 2003; **34**: 2323-2330 [PMID: 12970516]
 - 50 **Garrett KD**, Browndyke JN, Whelihan W, Paul RH, DiCarlo M, Moser DJ, Cohen RA, Ott BR. The neuropsychological profile of vascular cognitive impairment--no dementia: comparisons to patients at risk for cerebrovascular disease and vascular dementia. *Arch Clin Neuropsychol* 2004; **19**: 745-757 [PMID: 15288328]
 - 51 **Sachdev PS**, Brodaty H, Valenzuela MJ, Lorentz L, Looi JC, Wen W, Zagami AS. The neuropsychological profile of vascular cognitive impairment in stroke and TIA patients. *Neurology* 2004; **62**: 912-919 [PMID: 15037692]
 - 52 **Reed BR**, Mungas DM, Kramer JH, Ellis W, Vinters HV, Zarow C, Jagust WJ, Chui HC. Profiles of neuropsychological impairment in autopsy-defined Alzheimer's disease and cerebrovascular disease. *Brain* 2007; **130**: 731-739 [PMID: 17267522]
 - 53 **Chen X**, Wong A, Ye R, Xiao L, Wang Z, Lin Y, Yang F, Li H, Feng T, Duan L, Han Y, Dai Q, Du J, Xu G, Mok V, Xiong Y, Liu X. Validation of NINDS-CSN neuropsychological battery for vascular cognitive impairment in Chinese stroke patients. *BMC Neurol* 2015; **15**: 20 [PMID: 25886571 DOI: 10.1186/s12883-015-0270-z]
 - 54 **Erkinjuntti T**, Román G, Gauthier S, Feldman H, Rockwood K. Emerging therapies for vascular dementia and vascular cognitive impairment. *Stroke* 2004; **35**: 1010-1017 [PMID: 15001795]
 - 55 **Görtelmeyer R**, Erbler H. Memantine in the treatment of mild to moderate dementia syndrome. A double-blind placebo-controlled study. *Arzneimittelforschung* 1992; **42**: 904-913 [PMID: 1418054]
 - 56 **Tariot PN**, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA* 2004; **291**: 317-324 [PMID: 14734594 DOI: 10.1001/jama.291.3.317]
 - 57 **Malouf R**, Birks J. Donepezil for vascular cognitive impairment. *Cochrane Database Syst Rev* 2004; **(1)**: CD004395 [PMID: 14974068 DOI: 10.1002/14651858.cd004395.pub2]
 - 58 **Sharp SI**, Aarsland D, Day S, Sonnesyn H, Ballard C. Hypertension is a potential risk factor for vascular dementia: systematic review. *Int J Geriatr Psychiatry* 2011; **26**: 661-669 [PMID: 21495075 DOI: 10.1002/gps.2572]
 - 59 **Peila R**, White LR, Masaki K, Petrovitch H, Launer LJ. Reducing the risk of dementia: efficacy of long-term treatment of hypertension. *Stroke* 2006; **37**: 1165-1170 [PMID: 16601212 DOI: 10.1161/01.STR.0000217653.01615.93]
 - 60 **Haag MD**, Hofman A, Koudstaal PJ, Breteler MM, Stricker BH. Duration of antihypertensive drug use and risk of dementia: A prospective cohort study. *Neurology* 2009; **72**: 1727-1734 [PMID: 19228584 DOI: 10.1212/01.wnl.0000345062.86148.3f]
 - 61 **Gelber RP**, Ross GW, Petrovitch H, Masaki KH, Launer LJ, White LR. Antihypertensive medication use and risk of cognitive impairment: the Honolulu-Asia Aging Study. *Neurology* 2013; **81**: 888-895 [PMID: 23911753 DOI: 10.1212/WNL.0b013e3182a351d4]
 - 62 **Hajjar I**, Hart M, Chen YL, Mack W, Milberg W, Chui H, Lipsitz L. Effect of antihypertensive therapy on cognitive function in early executive cognitive impairment: a double-blind randomized clinical trial. *Arch Intern Med* 2012; **172**: 442-444 [PMID: 22412114 DOI: 10.1001/archinternmed.2011.1391]
 - 63 **Dichgans M**, Zietemann V. Prevention of vascular cognitive impairment. *Stroke* 2012; **43**: 3137-3146 [PMID: 22935401 DOI: 10.1161/STROKEAHA.112.651778]
 - 64 **Tzourio C**, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, Chalmers J. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med* 2003; **163**: 1069-1075 [PMID: 12742805 DOI: 10.1001/archinte.163.9.1069]
 - 65 **Dufouil C**, Chalmers J, Coskun O, Besançon V, Bousser MG, Guillon P, MacMahon S, Mazoyer B, Neal B, Woodward M, Tzourio-Mazoyer N, Tzourio C. Effects of blood pressure lowering on cerebral white matter hyperintensities in patients with stroke: the PROGRESS (Perindopril Protection Against Recurrent Stroke Study) Magnetic Resonance Imaging Substudy. *Circulation* 2005; **112**: 1644-1650 [PMID: 16145004 DOI: 10.1161/CIRCULATIONAHA.104.501163]

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