Chapter 3

CLINICAL ASPECTS OF VASCULAR DEMENTIA: FROM BENCH TO BEDSIDE AND BEYOND

Özge ALTINTAŞ KADIRHAN[1]
Mehmet DEMİRCİ[2]

INTRODUCTION

Dementia is characterized by a progressive and irreversible deterioration of mental capacity that aggravates maintaining the quality of independence and mobility. Advancing age is the main risk factor (1,2). Heterogeneous forms of complex pathologies such as amyloid deposits, Lewy bodies, and cerebrovascular diseases may coexist with the changes in the 'aging brain'(3).

Recent decades of etiological studies about the investigation of vascular determinants in dementia have markedly presented. The description of vascular dementia (VaD) has evolved over the centuries, however; fails to be preferred as an appropriate term for the entire spectrum of cognitive alternations caused by vascular factors. According to Vascular Impairment of Cognition Classification Consensus Study (VICCCS) guideline; vascular dementia is referred to as major clinically significant cognitive impairment (4). Severe functional impairment in at least one-cognitive domain to loss of independence in daily living is the first core clinical criteria for the disease diagnosis. And secondly, a structural neuroimaging evidence should be required, especially Magnetic Resonance Imaging (MRI) as a gold standard, for the diagnosis. The American Classification systems such as American Heart Association/ American Stroke Association (AHA/ASA) (5) and National Institute of Neurological Disorders and Stroke-Canadian Stroke Network (NINDS-CSN) (6), Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (7) have preferred the term 'the major vascular

[1] Assoc. Prof. Department of Neurology, Faculty of Medicine, Kirklareli University, dr.ozgealtintas@gmail.com
[2] Assoc. Prof. Department of Medical Microbiology, Faculty of Medicine, Kirklareli University, mdemirci1979@gmail.com

neurocognitive disorder' instead of vascular dementia, and have revised the criteria for subgroups as a major and minor vascular neurocognitive disorders (4).VaD is defined as major vascular cognitive impairment (VCI) and classified into four main groups on the basis of VICCCS consensus (4).

This specific review summarizes the occurrence of vascular dementia in the population, followed by the burden of vascular pathology in cognitive decline and the stroke-associated risk of dementia, and current VaD therapeutic treatments and future researches.

Review

Epidemiology and Risk Factors

Vascular dementia is the second most common subtype of dementia, after Alzheimer's disease, corresponding to approximately 15% to 20% of dementia cases in western countries and approximately 30 % of cases, relatively higher, in Asia and developing countries8. Studies of vascular dementia show that the risk rate of vascular dementia rises with advancing age, doubling almost every 5.3 years (9).

Stroke is presumed strongly associated with disability and cognitive impairment worldwide. Stroke critically impact factor for dementia as a twofold increase in risk (10). Despite the studies that have reported that Alzheimer disease pathology is more common rather than the pathology of vascular dementia in the poststroke patient; a long-term hospital-based study has suggested that over 75 % of postmortem findings of the demented poststroke patients aged over 75 years remarkably exhibited vascular dementia characteristics (11). Prestroke cognitive reserve, the level of education, preexisting medial temporal lobe atrophy, family history of dementia, comorbidities are consistently associated with cognitive decline, as well as might be a delay in onset of the dementia syndrome with even large strokes (12,13). In addition, around 15–30% of stroke survivors develop dementia beyond three months. A wide variety of stroke characteristics influence dementia risk after stroke, especially including stroke location and stroke severity tend to develop more poststroke dementia risk (13-16). After the transient ischemic attack, the dementia risk is 5%; whereas after severe stroke the risk relatively rises to 34% in the first year 13. Indeed, poststroke patients have been found to have the highest degree of cognitive decline in the subacute phase (14).The population-based studies have reported that the risk of dementia after stroke is 7% in cognitively intact individuals

while the risk rises to over 40% in individuals with pre-existing dementia. Also, around 20–25% of recurrent stroke patients are more vulnerable to develop a delayed dementia (17).

Clinical Features:

Vascular dementia shows heterogeneous variability in clinical presentations like memory, cognition, and behavior that are highly dependent on the affected cognitive domain by vascular injury. According to current diagnostic criteria, the presence of memory impairment is not necessary for the diagnosis (4,7). Predominantly dysfunction of frontostriatal circuits, common clinical findings appear to be a particular decline in information processing, executive function, and attention.

Standard screening tests for dementia should include the five-neurocognitive domain following as executive function, complex attention, memory, language, and perceptual-motor function. Information from learning, social cognition and neuropsychiatry domains is not required for the differential diagnosis for VaD (4,7). Cognitive assessment tests evaluating these five core neurocognitive domains are recommended and used by the VICCCS guidelines4. Common clinical findings in patients with vascular dementia include poor decision making, hypothesis generation, cognitive flexibility, slow process of initiation and planning processes, and delayed wordlist and visual content recognition (18). Standard neurocognitive assessment tests like as the mini-mental state examination have been suggested to be less sensitive to distinguish these clinical findings to detect VaD (19) rather than the Montreal Cognitive Assessment Scale (MoCA) (20) and the Vascular Dementia Assessment Scale (VADAS-cog) (21) which are especially validated for differential analyses of attention and executive function (22). Recent studies have suggested that a-low MoCA cognitive scores at the subacute phase of index event might increase the risk for neurocognitive decline (23). On the other hand, clinicians have to overcome the inability to perform valid cognitive scales in patients with delirium, severe depression, and aphasia. In this condition, detailed screening for the cognitive decline can be preferred examining the individuals three to six months after the stroke (24).

Other clinical presentations such as delusions and hallucinations are less frequently seen in VaD as which seen in Alzheimer's disease (24,25). Because of cardiovascular and cerebrovascular comorbidities, overall survival rates are much lower in vascular dementia than in other dementia subtypes (26,27).

Classification of Vascular Dementia

VICCCS phase-1 (VICCCS-1) supported the same protocols with AHA/ASA and NINDS-CSN (27). And then VICCCS phase 2 (VICCCS-2) included the contributions of (the International Society of Vascular Behavioral and Cognitive Disorders (VASCOG) and DSM-V guidelines (4). According to the VICCCS-1, VaD is defined as major vascular cognitive impairment (VCI) and classified into four main subgroups: (i) post-stroke dementia (PSD); (ii) subcortical ischemic vascular dementia (SIVaD); (iii) multi-infarct (cortical) dementia (MID); and (iv) mixed dementias (further subdivided according to additional neurodegenerative pathologies). According to the consensus report, poststroke dementia (PSD) has referred to as the onset of cognitive decline within 6 months after the index stroke event4. VICCCS-2 consensus is recommended MRI measurements to support the evidence of vascular injury (4). Highlights of the VICCCS-2 consensus are summarized in Figure-1.

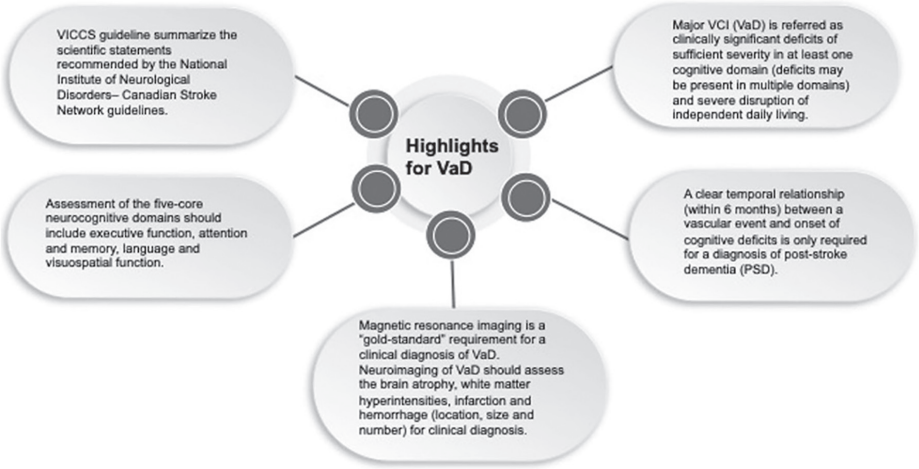

Figure 1. Highlights for vascular dementia

Highlights of the VICCCS-2 consensus (4) are summarized in Figure-1. Abbreviations: VICCCS, Vascular Impairment of Cognition Classification Consensus Study,VaD, vascular dementia; VCI, vascular cognitive impairment; PSD, post-stroke dementia.

Unraveling the Risk Factors

Long-term population based researches make suggestions to outline the key areas to characterize and explain the underlying neuropathologic mechanisms. Cardiovascular risk factors, genetically determined forms of microangiopathies, neuroimaging core measurements, and serum biomarkers might be summarized as the four-cardinal area to unravel the cause. The potential pathophysiological pathways are demonstrated in Figure 2.

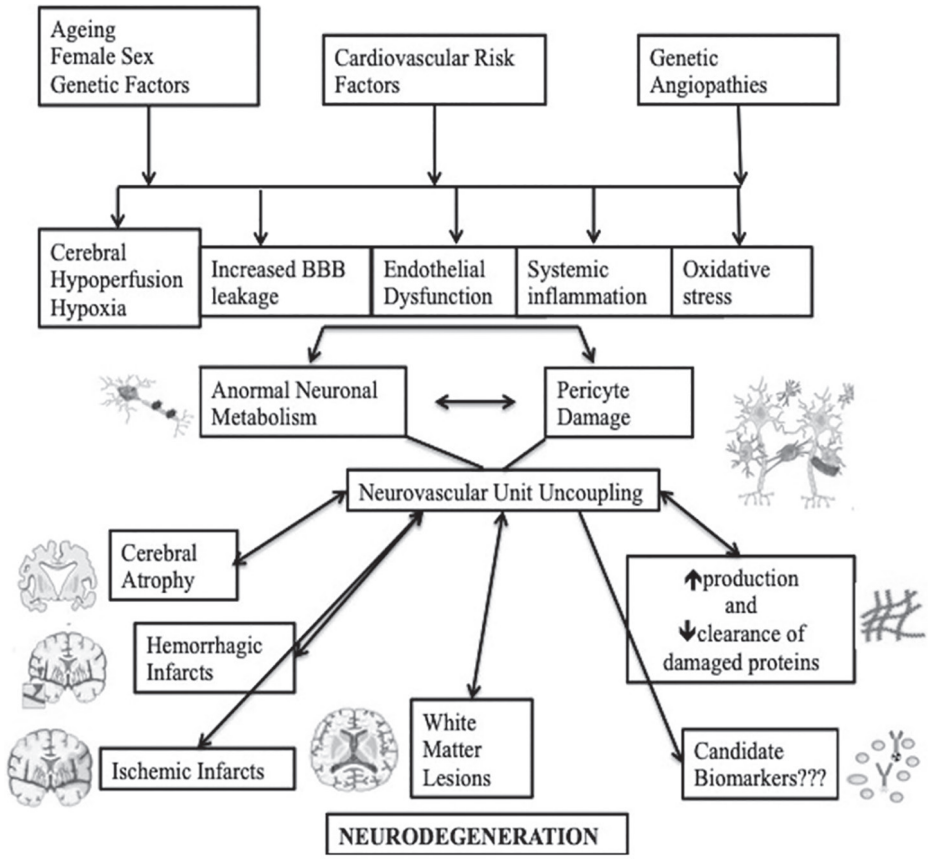

Figure 2. The potential pathophysiological pathways of vascular dementia

Medical Images (icons) are obtained from Server Medical Art (smart.servier.com). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (28)

Firstly, cardiovascular risk factors not only cause cognitive decline via cerebrovascular disease as well may also directly contribute to the neurodegeneration process. In this field, various researches have revealed several potential mechanisms underlying VaD such as hypoperfusion and hypoxia, blood-brain barrier (BBB) leakage, endothelial dysfunction, systemic inflammation, and oxidative stress, and neurovascular unit uncoupling (29-31). High blood pressure changes cause cerebral micro/microangiopathies via losing elasticity in large blood vessels (30,32,33). Blood-brain barrier (BBB) leakage, pericyte damage, and endothelial dysfunction contribute to alternations on neuronal metabolism, local cerebral perfusion to maintain neurovascular unit coupling (34,35). Furthermore, to these potential mechanisms linking vascular dysfunction with cognitive decline, vascular dysfunction independently could also contribute neurodegeneration process due stimulating the production and limiting the clearance of proteinopathies (36).

Secondly, recent studies have provided neurobiological clues to outline the genetic linkage between the cardiovascular and cerebrovascular disease processes underlying neurodegeneration (37). CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) (38), CARASIL (a cerebral autosomal recessive variant of CADASIL, MAEDA syndrome) (39,40), Trex-1 gene related microangiopathies (HERNS- hereditary endotheliopathy retinopathy nephropathy with stroke/ stroke-like episodes) (40,41), CARASAL (cathepsin-A related arteriopathy with strokes and leukoencephalopathy) (42) and familial forms of cerebral amyloid angiopathy (CAA) (43) are genetically determined forms of microangiopathies according to genetic data (especially GWAS analysis). Briefly, these entities are usually associated with infarcts (microinfarcts or lacunar infarcts) whereas; classic stroke signs and symptoms may not be presented, generally the patients have progressive cognitive decline (37).

Thirdly, neuroimaging research studies have emphasized the vasculopathies largely responsible for VaD, suggested novel markers clinically relevant with prognosis, treatment and prevention strategies. MRI is a "gold-standard" requirement for a clinical diagnosis of VaD (4). Computed tomography imaging would be an appropriate diagnostic tool if the MRI method were unavailable or contraindicated. Neuroimaging of VaD should assess the brain atrophy, white matter hyperintensities, infarction, and hemorrhage (location, size, and number) for clinical diagnosis (4). Neuroimaging studies have shown that

both generalized and hippocampal atrophy as strongly as vascular injury could contribute to the dementia process. Imaging studies have shown that atrophy, both generalized and hippocampal is at least as strongly associated with dementia as the extent of vascular pathology (44). As mentioned previously, many lacunar infarcts, strategic infarcts, white matter lesions, dilated perivascular spaces, or their combinations can be identified in support of VaD (12,45). However, the specificity of the findings has been questioned. At the recent neuroimaging study, the researchers enrolled the patients aged over 65 years to study and investigated that neuroimaging findings have shown at least 30% have silent infarcts and approximately 90% have white matter degenerations (46,47). And then the Leukoaraiosis And DISability (LADIS) study has reported that study individuals aged 65 and older years without any cognitive decline, the presence of severe white matter lesions at baseline could be cause progressive disability and cognitive impairment within 3 years period (48). On the other hand, cerebral perfusion, cerebrovascular otoreactivity, BBB permeability can be added to further analysis to monitor the course of the structural alternations over time and distinguish characteristic patterns of VaD. As a result, effective strategies of neuroimaging findings are needed to investigate for prevention of VaD, reducing future disability in patients even if not accompanied by symptoms and disability.

Fourth, assessment of biomarkers of vascular dementia, apart from neuroimaging findings, are less well developed than for Alzheimer's disease but candidates have been proposed, including albumin, metalloproteinases, and inflammatory markers. As an inflammatory biomarker, the researchers have found that C-reactive protein levels are elevated in VaD patients49. Indeed, high homocysteine level and lipoprotein- a level found to be correlated as a vascular risk factor in VaD patients (50,51). Also, the researchers found that the level of prothrombotic and endothelial dysfunction markers have increased indicating the pathologic link between stroke and VaD (49). Although cerebrospinal fluid (CSF) biomarkers basically serum/albumin ratio, CSF total protein, and CSF index are used to identifying the maintenance of blood-brain barrier and microvascular injury are not specify the dementia subtypes (52). Otherwise, the cytoskeletal organelle, neurofilament, and the matrix metalloproteases (MMPs) in the CSF could be used to specify white matter degeneration in VaD patients due to identify demyelination and axonal damage (53).

miRs are important epigenetic regulators of cellular pathways including neurodegenerative diseases, curious knowledge on omic biotechnology would

provide candidate biomarkers in VaD patients. Recent studies have shown that the expression level of miR-132, miR-134, miR-491-5p, and miR-370 could be changed in mild cognitive impairment patients (54). Indeed, the lowered expression level of miR126 is found to detect the vascular inflammatory process in early VCI (55). All these biomarkers lack specificity to distinguish VaD patients from other dementia subtypes and large prospective studies are needed to enhance their diagnostic utility. With new validated circulating and cerebrospinal fluid markers would be established stratification schemes to adequately prevent the clinical course of the disease.

Several investigations are suggested that vascular risk factor modification might prevent neurocognitive impairment with associated neuropathology. According to the Framingham Heart Study and other long-term trials have shown that the risk of age-specific dementia has lowered over the past 3-4 decades (56). Better treatment methodologies of vascular risk factors especially hypertension, hyperlipidemia, and smoking could be explained this decline. These studies found that these risk factors are associated with dementia in mid-life (age 40–65 years) (57). These findings implicate that prevention or treatment of vascular risk factors plays a crucial role to preserve or enhance cognitive functioning in the younger populations. The unmodifiable risk factors are increasing age, female sex, and Apolipoprotein E13. Although Apolipoprotein E plays a crucial risk factor in Alzheimer's disease pathology especially in women, the pathologic link between stroke and VaD should require more investigations (58). Modifiable risk factors such as obesity, hypertension, smoking, and diabetes mellitus are account for approximately 25% of dementia in the population1. Indeed hypertension and diabetes are recognized as the strongest modifiable risk factors for VaD (1,59,60). Hypertension appears to predispose cerebral vessel (61). The high blood pressure level is found to be associated with increased white matter degenerations and smaller brain volumes (62). Affecting both small and large arteries, diabetes is biochemically closely linked to vascular dementia and cerebrovascular disorders (63,64). Diabetes directly damages the maintenance of BBB permeability that contributes to cognitive decline. Thus, diabetes causes secondary neuroinflammation, which leads nervous system damage. Several studies have revealed that diabetic patients showed cognitive impairment and lowering of cortical volumes on MRI scans (65,66). There is supportive evidence about increased education level, cognitive reserve, Mediterranean diet, and active physical-mental exercise could be prevent or

delay the progression of cognitive impairment (67). The spectrum of vascular risk factor involved in vascular dementia is shown in Figure 3.

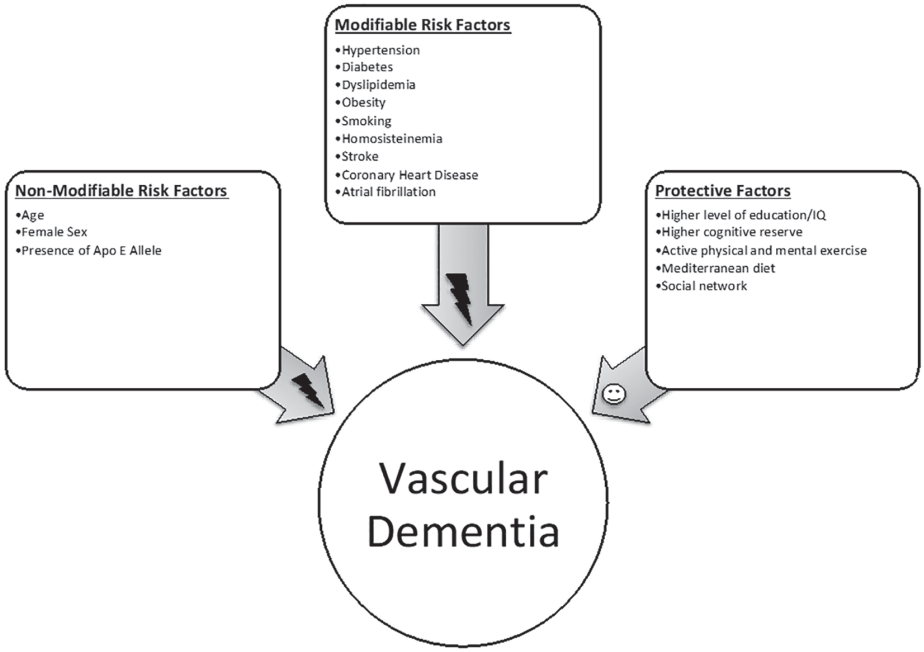

Figure 3. The spectrum of vascular risk factors involved in vascular dementia

Neuropathological changes of Vascular Dementia:

Clinical and neuroimaging criteria for discrimination of vascular dementia have been clearly set and suggested the heterogeneous forms of cerebral lesions, but neuropathological criteria in vascular dementia is restrictive and involve autopsy examinations. The Newcastle group has proposed a practical, new categorization with six subtypes associated with vascular cognitive impairment. These six subgroups (i) Large infarcts including cortical infarcts, (ii) Multiple small infarcts or lacunes, (iii) Strategic infarcts or lacunes, (iv) Hypoperfusive brain injury/lesions and/or hippocampal sclerosis, (v) Cerebral hemorrhages, and (vi) cerebrovascular pathologic change with Alzheimer disease alterations. According to the classification; subtypes (i)–(iii) are referred the post stroke survivors and the individuals with massive white matter degenerations without other pathologies are subclassed under lacunar infarcts68.

Management of vascular Dementia

Treatment schemes should include preventing further cognitive decline, preserving or enhancing current cognitive, behavioral status, decrease morbidity and mortality. Also, caregiver training should be supported to provide the necessary knowledge to enable caregivers to navigate through the progression of dementia.

Currently, there is no authorized treatment approach and methodology for VaD. The treatment methodology used in VaD is only suitable for symptomatic treatment and cannot prevent or reduce the occurrence and progression of VaD. As mentioned above there are modifiable vascular risk factors associated with VaD neuropathology. Targeting proactive management of these vascular risk factors might decline the prevalence of VaD patients. The primary prevention of stroke could prevent cognitive impairment and mortality69. According to updated information provided in 2014 the AHA/ASA guidelines for the primary prevention of stroke70 and the 2019 American College of Cardiology/ American Heart Association (ACC/AHA) Guideline on the primary prevention of cardiovascular disease71, intensive medical management of these vascular risk factors especially hypertension, diabetes, dyslipidemia, smoking cessation plays a crucial role in primary stroke prevention. Also controlling the vascular risk factors in patients with silent brain infarcts, white matter degeneration, and cerebral microbleeds who have not shown cognitive decline symptoms could be associated with reducing future incident cognitive decline and stroke72. Moreover, improving these vascular risk factors in patients with a mild degree of cognitive impairment could slow the disease progression and daily living independence5. The Atherosclerosis Risk in Communities (ARIC) cohort showed that in mid-life having high blood pressure noticeably increased the risk of cognitive impairment progression within 20 years73. Moreover, the Honolulu Heart Program or Honolulu Asia Aging Study demonstrated that patients diagnosed with prehypertension less than 50 years of age had an increased risk of dementia without under any antihypertensive therapy74. Abell et al. reported that diagnosed with high systolic blood pressure in patients over 50 years of age elevation is linked with increased risk of dementia75. Also, a target systolic blood pressure level of 130 mmHg or lower has been shown to significantly improve cognitive decline progression at age 5075. On the other hand, the Hypertension In the Very Elderly Trial-COGnitive function assessment (HYVETCOG) trial has suggested that antihypertensive therapy

did not significantly reduce the incidence of dementia in late-life76. Also, the HYVET cohort study revealed that the presence of orthostatic hypotension contributed to the cognitive impairment progression76. As a result, especially at the mid-life, the new guideline lower the target for blood pressure treatment to 130/80 mm Hg. Adults with diabetes have an approximately 1.5- to 2.5-fold increased risk of cognitive63,77. On the basis of a long-term prospective cohort study, onset of diabetes in mid-age was appeared to affect cognitive function over 20 years78. The Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) trial has suggested that a hypoglycemic attack in diabetic patients was associated with cognitive decline78. The consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)79 recommended that the glycemic goals (HbA1c, glycosylated hemoglobin as a marker of glucose control) can be 7.5%, in patients with mild-to-moderate cognitive dysfunction the goal of 8% and in patients with severe cognitive dysfunction the goal of 8.5% is recommended80,81. The meta-analysis of 25 studies proposed that the use of statins might reduce the risk of all types of dementia and mild cognitive impairment, but not of incident vascular dementia82. Although the lack of effective studies, for patients aged between 20-75 years, a target of LDL-C level 190 mg/dl or lower could be recommended by using high-intensity statin therapy to reduce LDL level by 50% or more83. Cognitive impairment is defined as one of the major long-term effects of stroke. The lower the potential risk secondary prevention is essential. Focus on proactive best medical management of vascular risk factors should be supported in patients after first ever stroke. The 2021 AHA/ASA secondary stroke prevention guidelines state that the components of best-medical therapy should include antiaggregants and anticoagulants, blood pressure–lowering medications, cholesterol-lowering medications, carotid revascularization, cessation of cigarette smoking, diet, and exercise84.

Using Cholinesterase inhibitors and memantine therapy options in VaD patients is alternate therapy derived from Alzheimer's disease treatment methodology are shown not to be appropriate although sharing similar neurochemical mechanism. Two cross-sectional studies enrolled patients with mild to moderate cognitive impairment to evaluate memantine therapy, for 28 weeks follow-up period. The report showed a significantly higher ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive subscale) score was established in the treatment group compared to the placebo group85. According to this

finding, Memantine might be beneficial to cognitive performance. Two large-scale randomized clinical studies enrolled patients with probable or possible vascular cognitive impairment (diagnosed according to NINCDS-AIREN (National Institute of Neurological Disorders and Stroke and the Association International pour la Recherche et l' Enseignement en Neurosciences) criteria) to evaluate the efficacy of donepezil over 24 weeks. Data analysis showed that donepezil had a superior beneficial effect on cognitive improvement, daily independence and motor functions compared to the control group86,87. The data about Rivastigmine's efficacy in VaD is not sufficient to suggest any benefits on cognitive impairment88. In summary, there are no data about the effects of the combination of acetylcholinesterase inhibitors or memantine as beneficial to cognitive functions; but further studies is required to confirm these findings.

New potential medications are investigated as putative candidates in current clinical trials. Preliminary studies of nicardipine as a calcium channel blocker showed a decrease in cognitive deterioration in patients with cerebrovascular disease89. In VaD animal models have shown that Edaravone, resveratrol, chotosan, and dextromethorphan as neuroprotective agents could inhibit oxidative stress, improve the antioxidant capability to prevent neurodegeneration90. Mostly in the basic researches have been proposed that potential neuroprotective drugs could be beneficial to VaD and the underlying molecular mechanisms, but the agents should be re-investigated under large community based prospective studies in the future to be used therapeutic treatments.

Future Directions and Conclusions

In this review, we subsequently address the occurrence of vascular dementia in the population, followed by the burden of vascular pathology in cognitive decline and the stroke-associated risk of dementia, and current VaD therapeutic treatments and future researches.

In the multifactorial cause of cognitive decline at old age, we could suggest the addition of a vascular component score (including white matter hyperintensities, lacunar infarcts, microbleeds, and perivascular spaces) and a biomarker component score to the current classification system can be powered the valid scoring system. Increasing evidence provided by technological advances in genetics, metabolomics, proteomics, and (preclinical) models of disease, we could overcome the absence of disease-modifying treatments,

prevent cerebrovascular disease, and related-cognitive impairment in the coming years.

Author contributions

OAK analyzed the data. OAK and MD wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors have no conflicts of interest to disclose.

Funding

This work was not supported external funding.

REFERENCES

1. Wolters FJ, Ikram MA. Epidemiology of Vascular Dementia. Arterioscler Thromb Vasc Biol.2019,39:1542-1549. (https://dx.doi.org/10.1161/ATVBAHA.119.311908)
2. O'Brien JT, Thomas A: Vascular dementia Lancet. 2015, 386:1698-706. (https://dx.doi.org/10.1016/S0140-6736(15)00463-8)
3. Power MC, Mormino E, Soldan A, James BD, Yu L, Armstrong NM, et al. Combined neuropathological pathways account for age-related risk of dementia. Ann Neurol. 2018,84:10-22. (https://dx.doi.org/10.1002/ana.25246)
4. Skrobot OA, Black SE, Chen C, et al. Progress toward standardized diagnosis of vascular cognitive impairment: Guidelines from the Vascular Impairment of Cognition Classification Consensus Study Alzheimers Dement. 2018,14:280-292. (https://dx.doi.org/10.1016/j.jalz.2017.09.007)
5. Gorelick PB, Scuteri A, Black SE, et al. American Heart Association Stroke Council,Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/ american stroke association. Stroke. 2011, 42:2672-713. (https://dx.doi.org/10.1161/STR.0b013e3182299496)
6. Hachinski V, Iadecola C, Petersen RC, et al. National Institute of Neurological Disorder and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke. 2006, 37:2220-41. (https://dx.doi.org/10.1161/01.STR.0000237236.88823.47)
7. American Psychiatric Association: Diagnostic and statistical manual of mental disorders,Fifth Edition. American Psychiatric Publishing, Arlington, VA; 2013. (https://doi.org/10.1176/appi.books.9780890425596.dsm17)
8. Kalaria RN, Maestre GE, Arizaga R, et al; World Federation of Neurology Dementia Research Group. Alzheimer's disease and vascular dementia in developing countries:

prevalence, management, and risk factors. Lancet Neurol. 2008;7:812–826. (https://dx.doi.org/10.1016/S1474-4422(08)70169)
9. Jorm AF, Jolley D: The incidence of dementia: a meta-analysis. Neurology. 1998, 51:728-33. (https://dx.doi.org/10.1212/wnl.51.3.728)
10. Kuźma E, Lourida I, Moore SF, et al. Stroke and dementia risk: A systematic review and meta-analysis. Alzheimers Dement. 2018, 14:1416-1426. (https://dx.doi.org/10.1016/j.jalz.2018.06.3061)
11. Allan LM, Rowan EN, Firbank MJ, Thomas AJ, Parry SW, Polvikoski TM, et al. Long term incidence of dementia, predictors of mortality and pathological diagnosis in older stroke survivors. Brain. 2011;134(Pt 12):3716-27. (https://dx.doi.org/10.1093/brain/awr273)
12. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with prestroke and post-stroke dementia: a systematic review and meta-analysis. 2009, 8:1006- (https://dx.doi.org/10.1016/S1474-4422(09)70236-4)
13. Pendlebury ST, Rothwell PM; Oxford Vascular Study. Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based oxford vascular study. Lancet Neurol. 2019;18:248–258. (https://dx.doi.org/10.1016/S1474-4422(18)30442-3)
14. Munsch F, Sagnier S, Asselineau J, et al. Stroke location is an independent predictor of cognitive outcome. Stroke. 2016;47:66–73. (https://dx.doi.org/10.1161/STROKEAHA.115.011242)
15. Tatemichi TK, Desmond DW, Prohovnik I, et al. Confusion and memory loss from capsular genu infarction: a thalamocortical disconnection syndrome? Neurology. 1992;42:1966–1979. (https://dx.doi.org/10.1212/wnl.42.10.1966)
16. Mok VC, Lam BY, Wong A, et al. Early-onset and delayed-onset poststroke dementia - revisiting the mechanisms. Nat Rev Neurol. 2017;13:148–159. (https://dx.doi.org/10.1038/nrneurol.2017.16)
17. Ballard, C, Rowan, E, Stephens, S, et al. Prospective follow-up study between 3 and 15 months after stroke: improvements and decline in cognitive function among dementia-free stroke survivors >75 years of age. Stroke 2003; 34:2440 4. (https://dx.doi.org/10.1161/01.STR.0000089923.29724.CE).
18. Looi JC, Sachdev PS. Differentiation of vascular dementia from AD on neuropsychological tests. Neurology 1999;53:670–8. (https://dx.doi.org/10.1212/wnl.53.4.670).
19. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–198.
20. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695–699. (https://dx.doi.org/10.1016/0022-3956(75)90026-6)
21. Ylikoski R, Jokinen H, Andersen P, et al, and the LADIS Study Group. Comparison of the Alzheimer's Disease Assessment Scale Cognitive Subscale and the Vascular Dementia Assessment Scale in diff erentiating elderly individuals with diff erent degrees of white matter changes. The LADIS Study. Dement Geriatr Cogn Disord 2007; 24: 73–81. (https://dx.doi.org/10.1159/000103865)

22. Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. MoCA, ACE-R, and MMSE versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards neuro-psychological battery after TIA and stroke. Stroke 2012;43:464–9. (https://dx.doi.org/10.1161/STROKEAHA.111.633586).
23. Zietemann V, Georgakis MK, Dondaine T, et al. Early MoCA predicts long-term cognitive and functional outcome and mortality after stroke. Neurology. 2018 Nov 13;91(20):e1838-e1850. (https://dx.doi.org/10.1212/WNL.0000000000006506)
24. Gupta M, Dasgupta A, Khwaja GA, Chowdhury D, Patidar Y, Batra A. Behavioural and psychological symptoms in poststroke vascular cognitive impairment. Behav Neurol. 2014;2014:430128. doi: 10.1155/2014/430128. (https://dx.doi.org/10.1155/2014/430128)
25. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. JAMA 2002; 288: 1475–83. (https://dx.doi.org/10.1001/jama.288.12.1475)
26. Kua EH, Ho E, Tan HH, Tsoi C, Thng C, Mahendran R. The natural history of dementia. Psychogeriatrics 2014; 14: 196–201. (https://dx.doi.org/10.1111/psyg.12053)
27. Skrobot OA, O'Brien J, Black S, et al. The Vascular Impairment of Cognition Classification Consensus Study. Alzheimers Dement. 2017 Jun;13(6):624-633. (https://dx.doi.org/10.1016/j.jalz.2016.10.007)
28. Server Medical ART (https://smart.servier.com). (2021). Accessed: December 12: https://smart.servier.com (https://smart.servier.com).
29. Iadecola C. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. Neuron 2017;96:17–42. (https://dx.doi.org/10.1016/j.neuron.2017.07.030).
30. Iadecola C, Duering M, Hachinski V, Joutel A, Pendlebury ST, Schneider JA, Dichgans M. Vascular Cognitive Impairment and Dementia: JACC Scientific Expert Panel. J Am Coll Cardiol. 2019 Jul 2;73(25):3326-3344. (https://dx.doi.org/10.1016/j.neuron.2017.07.030)
31. Zlokovic BV, Gottesman RF, Bernstein KE, et al. Vascular contributions to cognitive impairment and dementia (VCID): A report from the 2018 National Heart, Lung, and Blood Institute and National Institute of Neurological Disorders and Stroke Workshop. Alzheimers Dement. 2020 Dec;16(12):1714-1733. doi: 10.1002/alz.12157. (https://dx.doi.org/10.1002/alz.12157)
32. Kalaria RN. Vascular basis for brain degeneration: faltering controls and risk factors for dementia. Nutr Rev. 2010 Dec;68 Suppl 2(Suppl 2):S74-87. (https://dx.doi.org/10.1111/j.1753-4887.2010.00352.x)
33. Lacolley P, Regnault V, Segers P, Laurent S. Vascular smooth muscle cells and arterial stiffening: relevance in development, aging, and disease. Physiol Rev 2017;97:1555–617. (https://dx.doi.org/10.1152/physrev.00003.2017)
34. Nation DA, Sweeney MD, Montagne A, et al. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. Nat Med 2019;25:270–6. (https://dx.doi.org/10.1038/s41591-018-0297-y)

35. Lulita MF, Noriega de la Colina A, Girouard H. Arterial stiffness, cognitive impairment and dementia: confounding factor or real risk? J Neurochem 2017;144:527–48. (https://dx.doi.org/10.1111/jnc.14235)
36. Iadecola C. The pathobiology of vascular dementia. Neuron. 2013;80(4):844-66. (https://dx.doi.org/10.1016/j.neuron.2013.10.008)
37. Vinters HV, Zarow C, Borys E, et al. Review: Vascular dementia: clinicopathologic and genetic considerations. Neuropathol Appl Neurobiol. 2018;44(3):247-266. (https://dx.doi.org/10.1111/nan.12472)
38. Chabriat H, Joutel A, Dichgans M, Tournier-Lasserve E, Bousser M-G. CADASIL. Lancet Neurol 2009; 8: 643–53. (https://dx.doi.org/10.1016/S1474-4422(09)70127-9)
39. Tikka S, Baumann M, Siitonen M, et al. CADASIL and CARASIL. Brain Pathol 2014; 24: 524–44. (https://dx.doi.org/10.1111/bpa.12181)
40. Jen J, Cohen AH, Yue Q, et al. Hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS). Neurology 1997; 49: 1322–30. (https://dx.doi.org/10.1212/wnl.49.5.1322)
41. Kavanagh D, Spitzer D, Kothari PH, et al. New roles for the major human 3'-5' exonuclease TREX1 in human disease. Cell Cycle 2008; 7: 1718–25. (https://dx.doi.org/10.4161/cc.7.12.6162.)
42. Bugiani M, Kevelam SH, Bakels HS, et al. Cathepsin A-related arteriopathy with strokes and leukoencephalopathy (CARASAL). Neurology 2016; 87: 1777–86. (https://dx.doi.org/10.1212/WNL.0000000000003251).
43. Verbeek MM, deWaal RMW, Vinters HV (editors). Cerebral Amyloid Angiopathy in Alzheimer's Disease and Related Disorders. Dordrecht/Boston: Kluwer Academic, 2000. (https://books.google.com.tr/books?hl= tr&lr= &id=RUQ4PFzDixwC&oi=fnd&pg=PR9&dq=Cerebral+Amyloid+Angiopathy+in+Alzheimer's+Disease+and+Related+Disorders.+Dordrecht/Boston:+Kluwer+Academic,+2000.&ots=wRXAYC6H40&sig=Ok1pQJYVKQR2wdpGyoXz13vBa1A&redir_esc=y#v=onepage&q=Cerebral%20Amyloid%20Angiopathy%20in%20Alzheimer's%20Disease%20and%20Related%20Disorders.%20Dordrecht%2FBoston%3A%20Kluwer%20Academic%2C%202000.&f=false).
44. Fein G, Di Sclafani V, Tanabe J, et al. Hippocampal and cortical atrophy predict dementia in subcortical ischemic vascular disease. Neurology 2000; 55: 1626–35. (https://dx.doi.org/10.1212/wnl.55.11.1626)
45. Price CC, Jefferson AL, Merino JG, Heilman KM, Libon DJ. Subcortical vascular dementia: integrating neuropsychological and neuroradiologic data. Neurology 2005; 65: 376–82. (https://dx.doi.org/10.1212/01.wnl.0000168877.06011.15)
46. Longstreth WT Jr, Bernick C, Manolio TA, Bryan N, Jungreis CA, Price TR. Lacunar infarcts defi ned by magnetic resonance imaging of 3660 elderly people: the Cardiovascular Health Study. Arch Neurol 1998; 55: 1217–25. (https://dx.doi.org/10.1001/archneur.55.9.1217)
47. de Leeuw FE, de Groot JC, Achten E, et al. 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. (https://dx.doi.org/10.1136/jnnp.70.1.9)

48. Inzitari D, Pracucci G, Poggesi A, Carlucci G, Barkhof F, Chabriat H, et al, and the LADIS Study Group. Changes in white matter as determinant of global functional decline in older independent outpatients: three year follow-up of LADIS (leukoaraiosis and disability) study cohort. BMJ 2009; 339: b2477. (https://dx.doi.org/10.1136/bmj.b2477)
49. Jagtap A, Gawande S, Sharma S. Biomarkers in vascular dementia: A recent update. Biomarkers and Genomic Medicine (2015); 7 (2): 43-56. (https://dx.doi.org/10.1016/j.bgm.2014.11.001)
50. Malaguarnera M, Ferri R, Bella R, Alagona G, Carnemolla A, Pennisi G. Homocysteine, vitamin B12 and folate in vascular dementia and in Alzheimer disease. Clin Chem Lab Med. 2004;42(9):1032-5. (https://dx.doi.org/10.1515/CCLM.2004.208)
51. Tsimikas S, Hall JL. Lipoprotein (a) as a potential causal genetic risk factor of cardiovascular disease: a rationale for increased efforts to understand its pathophysiology and develop targeted therapies. J Am Coll Cardiol. 2012;60: 716e721. (https://dx.doi.org/10.1016/j.jacc.2012.04.038).
52. Wardlaw JM, Sandercock PA, Dennis MS, Starr J. Is breakdown of the blood-brain barrier responsible for lacunar stroke, leukoaraiosis, and dementia? Stroke. 2003;34(3):806-12. (https://dx.doi.org/10.1161/01.STR.0000058480.77236.B3)
53. Wallin A, Sjogren M. Cerebrospinal fluid cytoskeleton proteins in patients with subcortical white-matter dementia. Mech Ageing Dev. 2001;122:1937e1949. (https://dx.doi.org/10.1016/s0047-6374(01)00306-2)
54. Sheinerman KS, Tsivinsky VG, Mullan MJ, Abdullah L, Umansky SR. Plasma microRNA biomarkers for detection of mild cognitive impairment. Aging. 2012;4:590e605. (https://dx.doi.org/10.18632/aging.100486.)
55. Yamacuchi M. MicroRNAs in vascular biology. Int J Vasc Med. 2012:1e12. (https://dx.doi.org/10.1155/2012/794898)
56. Satizabal C, Beiser AS, Seshadri S. Incidence of Dementia over Three Decades in the Framingham Heart Study. N Engl J Med. 2016;375(1):93-4. (https://dx.doi.org/10.1056/NEJMc1604823)
57. Malik R, Georgakis MK, Neitzel J, et al. Midlife vascular risk factors and risk of incident dementia: Longitudinal cohort and Mendelian randomization analyses in the UK Biobank. Alzheimers Dement. 2021;17(9):1422-1431. (https://dx.doi.org/10.1002/alz.12320)
58. Markus HS, Schmidt R. Genetics of vascular cognitive impairment. Stroke 2019;50:765–72. (https://dx.doi.org/10.1161/STROKEAHA.118.020379)
59. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. Lancet. 2017;390: 2673–734. (https://dx.doi.org/10.1016/S0140-6736(17)31363-6)
60. Mogi M. Could Management of Blood Pressure Prevent Dementia in the elderly? Clin Hypertens. 2019;25:27. (https://dx.doi.org/10.1186/s40885-019-0135-7)
61. Faraco G, Iadecola C. Hypertension: a harbinger of stroke and dementia. Hypertension. 2013;62:810–7. (https://dx.doi.org/10.1161/HYPERTENSIONAHA.113.01063)
62. Alateeq K, Walsh EI, Cherbuin N. Higher Blood Pressure is Associated with Greater White Matter Lesions and Brain Atrophy: A Systematic Review with Meta-Analysis. J Clin Med. 2021;10(4):637. (https://dx.doi.org/10.3390/jcm10040637)

63. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: the RotterdamStudy. Neurology 1999;53:1937–1942. (https://dx.doi.org/10.1212/wnl.53.9.1937)
64. Gregg EW, Sattar N, Ali MK. The changing face of diabetes complications. Lancet Diabetes Endocrinol. 2016;4:537-547. 19 (https://dx.doi.org/10.1016/S2213-8587(16)30010-9)
65. Roberts RO, Knopman DS, Przybelski SA, et al. Association of type 2 diabetes with brain atrophy and cognitive impairment. Neurology. 2014;82:1132-1141. (https://dx.doi.org/10.1212/WNL.0000000000000269)
66. Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA. 2004;292:2237-2242. (https://dx.doi.org/10.1001/jama.292.18.2237)
67. Stern Y, Chételat G, Habeck C, et al. Mechanisms underlying resilience in ageing. Nat Rev Neurosci. 2019;20(4):246. (https://dx.doi.org/10.1038/s41583-019-0138-0)
68. Kalaria RN. Neuropathological diagnosis of vascular cognitive impairment and vascular dementia with implications for Alzheimer's disease. Acta Neuropathol. 2016;131(5):659-85. (https://dx.doi.org/10.1007/s00401-016-1571-z)
69. Douiri A, McKevitt C, Emmett ES, Rudd AG, Wolfe CD. Long-term effects of secondary prevention on cognitive function in stroke patients. Circulation. 2013;128(12):1341-8. (https://dx.doi.org/10.1161/CIRCULATIONAHA.113.002236)
70. Meschia JF, Bushnell C, Boden-Albala B, et al. ; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(12):3754-832. (https://dx.doi.org/10.1161/STR.0000000000000046)
71. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;140(11):e596-e646. (https://dx.doi.org/10.1161/CIR.0000000000000678)
72. Kalaria RN, Akinyemi R, Ihara M. Stroke injury, cognitive impairment and vascular dementia. Biochim Biophys Acta. 2016;1862(5):915-25. (https://dx.doi.org/10.1016/j.bbadis.2016.01.015)
73. Gottesman RF, Schneider AL, Albert M, et al. Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study. JAMA Neurol. 2014;71:1218–27. (https://dx.doi.org/10.1001/jamaneurol.2014.1646)
74. Launer LJ, Hughes T, Yu B, et al. Lowering midlife levels of systolic blood pressure as a public health strategy to reduce late-life dementia: perspective from the Honolulu heart program/ Honolulu Asia aging study. Hypertension. 2010;55:1352–9. (https://dx.doi.org/10.1161/HYPERTENSIONAHA.109.147389)
75. Abell JG, Kivimaki M, Dugravot A, et al. Singh-Manoux a. association between systolic blood pressure and dementia in the Whitehall II cohort study: role of age, duration, and threshold used to define hypertension. Eur Heart J. 2018;39:3119–25. (https://dx.doi.org/10.1093/eurheartj/ehy288)

76. Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the hypertension in the very elderly trial cognitive function assessment (HYVET-COG): a doubleblind, placebo controlled trial. Lancet Neurol. 2008;7:683–9. (https://dx.doi.org/10.1016/S1474-4422(08)70143-1)
77. Peila R, Rodriguez BL, Launer LJ; Honolulu- Asia Aging Study. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: the Honolulu-Asia Aging Study. Diabetes 2002;51:1256–1262. (https://dx.doi.org/10.2337/diabetes.51.4.1256)
78. Rawlings AM, Sharrett AR, Schneider AL, et al. Diabetes in midlife and cognitive change over 20 years: a cohort study. Ann Intern Med 2014;161:785–793. (https://dx.doi.org/10.7326/M14-0737)
79. Punthakee Z, Miller ME, Launer LJ, et al.; ACCORD Group of Investigators; ACCORDMIND Investigators. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care 2012;35:787–793. (https://dx.doi.org/10.2337/dc11-1855)
80. Buse JB, Wexler DJ, Tsapas A, et al. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020;43(2):487-493. (https://dx.doi.org/10.2337/dci19-0066)
81. Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB, et al. Diabetes in older adults. Diabetes Care. 2012;35(12):2650-64. (https://dx.doi.org/10.2337/dc12-1801)
82. Chu CS, Tseng PT, Stubbs B, Chen TY, Tang CH, Li DJ, et al. Use of statins and the risk of dementia and mild cognitive impairment: A systematic review and meta-analysis. Sci Rep. 2018; 8(1): 5804. (https://dx.doi.org/10.1038/s41598-018-24248-8)
83. Poly TN, Islam MM, Walther BA,et al. Association between Use of Statin and Risk of Dementia: A Meta-Analysis of Observational Studies. Neuroepidemiology. 2020;54(3):214-226. (https://dx.doi.org/10.1159/000503105)
84. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. Stroke. 2021;52(7):e364-e467. (https://dx.doi.org/10.1161/STR.0000000000000375)
85. Areosa SA, Sherriff F, McShane R. Memantine for dementia. Cochrane Database Syst Rev. 2005;(2):CD003154. (https://dx.doi.org/10.1002/14651858.CD003154.pub3)
86. Malouf R, Birks J. Donepezil for vascular cognitive impairment. Cochrane Database Syst Rev. 2004;(1):CD004395. (https://dx.doi.org/10.1159/000088494)
87. Román GC, Wilkinson DG, Doody RS, Black SE, Salloway SP, Schindler RJ. Donepezil in vascular dementia: combined analysis of two large-scale clinical trials. Dement Geriatr Cogn Disord. 2005;20(6):338-44. (https://dx.doi.org/10.1159/000088494)
88. Baskys A, Hou AC. Vascular dementia: pharmacological treatment approaches and perspectives. Clin Interv Aging. 2007;2(3):327-35. (https://www.dovepress.com/articles.php?article_id=178).
89. Amenta F, Lanari A, Mignini F, Silvestrelli G, Traini E, Tomassoni D. Nicardipine use in cerebrovascular disease: a review of controlled clinical studies. J Neurol Sci. 2009;283(1-2):219-23. (https://dx.doi.org/10.1016/j.jns.2009.02.335)

90. Kuang H, Zhou ZF, Zhu YG, et al. Pharmacological Treatment of Vascular Dementia: A Molecular Mechanism Perspective. Aging Dis. 2021;12(1):308-326. (https://dx.doi.org/10.14336/AD.2020.0427)