

## Comprehensive Review on Vascular dementia Disease: Treatment and Recommendation for future research

Upasana singh<sup>1</sup>, Dhanesh kumar<sup>2\*</sup>, Pratiksha Fulzele<sup>3</sup>, Akhilesh Kumar<sup>4</sup>

<sup>1</sup>Department of Pharmacology, Bharti College of Pharmacy, Durg, Chhattisgarh, India, pin code 491001

<sup>2</sup>Department of Pharmacology, Chhatrapati Shivaji Institute of Pharmacy, Durg, Chhattisgarh, India, pin code 491001

<sup>3</sup>Department of Pharmaceutical analysis and quality assurance, M.J. college, Kohka-Junwani Road Bhilai, Chhattisgarh, India, pin code 490023

<sup>4</sup>Department of Pharmacology, Columbia Institute of Pharmacy, Tekari, Raipur, Chhattisgarh, India, pin code 493111

Submitted: 05-08-2022

Accepted: 16-08-2022

**ABSTRACT:** Vascular dementia (VaD) is the more progressive neurological impairment which affects the unrelenting dysfunction of brain capacity and it is brought about by reduced in the blood flow mainly to the brain. Sign and symptoms of vascular dementia (VaD) are, depression, anxiety, slower thinking, forgetfulness and loss of the executive task such as working memory, reasoning, execution of assignments, judgment, planning and problem solving. VACCSS classify vascular dementia into 4 major subgroups: Multi-infarct (cortical) dementia, Mixed dementia, Post-stroke dementia and Subcortical ischemic vascular dementia. This review article has emphasis on vascular dementia, its general introduction, characteristics, risk factors, sign and symptoms, diagnostic criteria of vascular dementia by ADDTC, NINDS, ADDTC and DSM-IV (such as Passive avoidance test, object recognition test, elevated plus maze test and Y maze test etc.) prevention and current treatment by the using drugs (such as donepezil's, gallantamine, memantine or other cholinesterase inhibitors, etc.) as well as recommendation for further research. We believe that a get lot of information from the recent research or review articles related to vascular diseases it's risk, course, evaluation, treatment and understanding of conditions marked by a loss in cognitive function due to age disease history like hypertension, stroke, diabetes and Hyperlipidemia and modification of the life style, These review articles are more helpful for knowing overall about the vascular dementia but briefly emphasis on the treatment aspect and recommendation of further research along with mention the evaluation parameter and clinical assessment.

**KEYWORDS:** Vascular dementia (VaD), cognitive dysfunction, neurological impairment,

### I. INTRODUCTION:

Vascular dementia (VaD) is the more progressive neurological impairment which affects the unrelenting dysfunction of brain capacity and it is brought about by reduced in the blood flow to the brain. Vascular dementia patients may experience illness related to the effects of forgetfulness, depression, anxiety, slower thinking, and loss of the executive task such as working memory, reasoning, execution of assignments, judgment, planning and problem solving. (1.)

Vascular dementia (VaD) is one of the most regular kinds of dementia. It is additionally portrayed as a neurocognitive problem, which likewise consolidates social side effects, locomotor abnormalities like Parkinsonian-like gait problems, dysarthria and autonomic brokenness.(2)

Risk of stroke is the most dangerous factor for enhancing the vascular dementia, The most grounded proof originates from investigations of hyperlipidemia, hypertension, diabetes mellitus and the metabolic disorder all these cause dementia problems. (3)

In the Systolic Hypertension in Europe has performed, placebo treatment for controlling the initial phase of hypertension treatment in older aged people's treatment with a CCB (calcium channel blocker) and drastically effect with the decreased cognitive problems. (4)

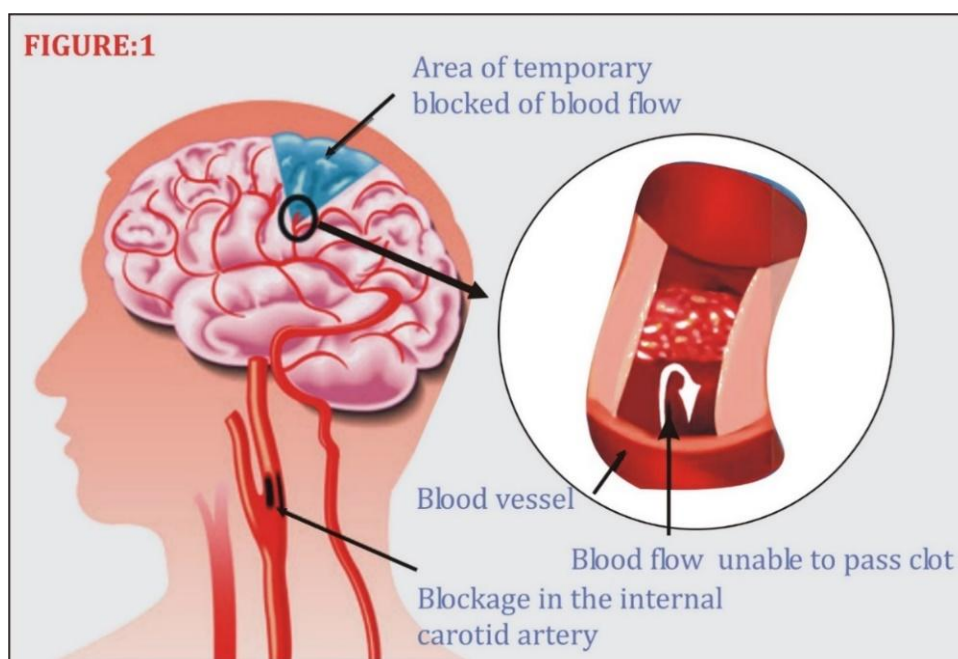
Perindopril in the treatment of Recurrent Stroke Studies has performed that the preclinical treatment of hypertension along with the blood

pressure after stroke decrease in the cognitive problems (5)

Both “diabetes mellitus” (DM) and the “metabolic disorder” enhance the risk of dementia (6), Raised cholesterol seems to anticipate dementia right off the bat throughout everyday life, except an example of dropping cholesterol further down the

road additionally is related with the beginning of dementia. (7)

Estrogen use in postmenopausal ladies has been related with both an expanded danger of stroke and increased cognitive decline and dementia (8,9) As a rule, most stroke chance elements are likewise chance components for dementia and cognitive impairment.



### SIGNS AND SYMPTOMS

**Early phase:** In the earlier phase symptoms occur are combination of memories, space and time confusion and forgetfulness

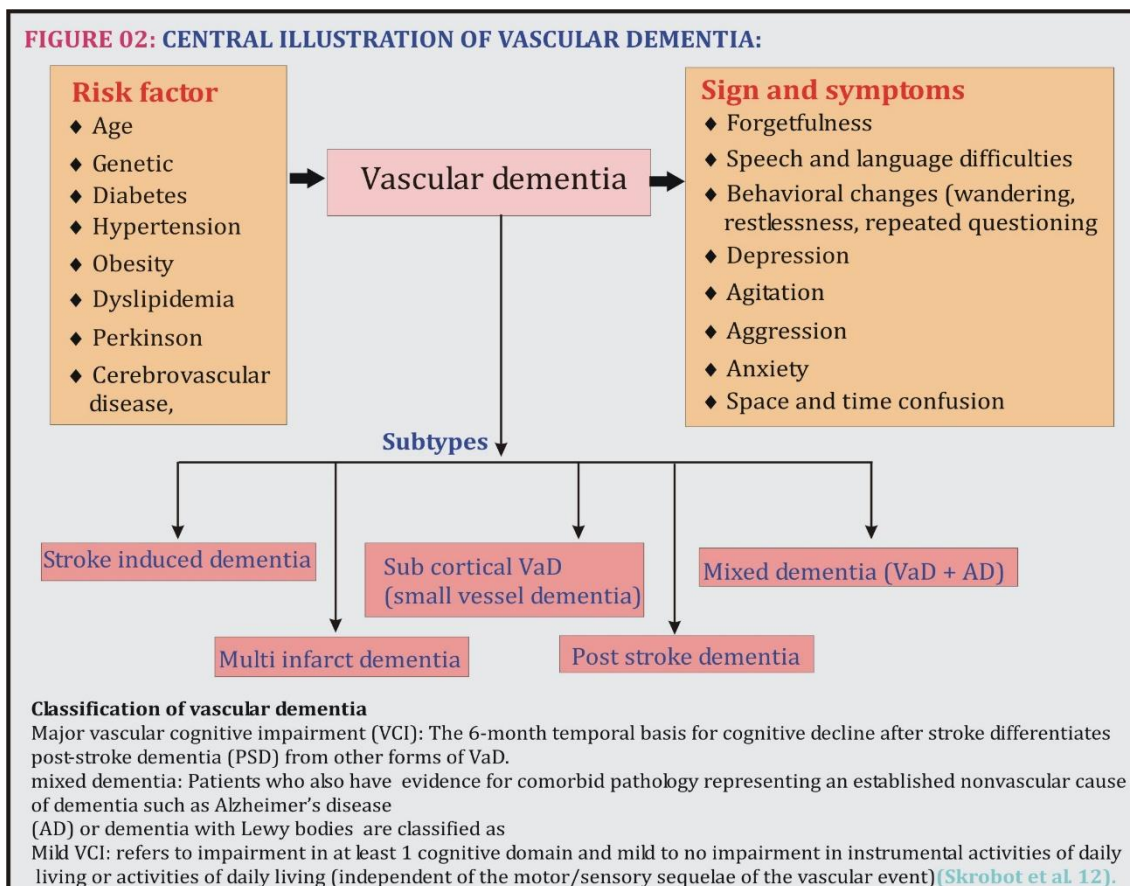
**Middle phase:** In middle stage of vascular dementia having trouble eating, balance problems, behavioral changes like wandering, restlessness, swallowing, tremors, speech and language difficulties, and other difficulties are (problem-solving, communication, attention, repeated questioning); and memory problems (combination of memories, sequence of events, confusion of people etc.) (10,11)

**Late phase:** Marked by the most severe memory problems (such as not being able to recognize family members and acquaintances) behavioral changes (such as aggression, crying, anger) more physical issues, almost complete dependency and inactivity, unawareness of time and place, sadness, and anxiety, In all the forms of vascular dementia nearly invariably include behavioural and

psychological symptoms such as agitation, delusions, irritability imbalance, sleep disturbances and motor behaviour. (12,13)

### CLASSIFICATION:

“Vascular Impairment of Cognition Classification Consensus Study” (VICCCS) has been classified vascular dementia into mainly 4 subgroups: “Mixed dementia, multi-infarct (cortical) dementia, post-stroke dementia (PSD) and Subcortical ischemic vascular dementia (SIVaD)” (14). VICCCS provide the guidelines regarding for diagnosis of Vascular dementia with the help of Magnetic resonance imaging (MRI) and identification of vascular lesions that meet the criteria for identify the diagnosis of subtypes of VaD. Central illustration related to risk factor, sign and symptoms along with times sub-types of vascular dementia are given in below (Figure 1)



## EPIDEMIOLOGY

Epidemiological studies also lack consensus due to the issues in agreeing on clinical criteria for diagnosis and the variety of sources of cases mentioned above. determination of the frequency of vascular dementia in people over 65 in Europe and North America from population-based research range from 1.2 to 4.2 percent (15). However, compared to Alzheimer's disease, this rise in risk with ageing is far less pronounced. Pathological research on a few populations also suggests that the prevalence of pure vascular dementia is really much lower than these epidemiological studies suggest (figure 3).

The risk of hypertension is lower than stroke and Alzheimer's disease found that it was only a risk factor for females studied by Canadian journals (16), Other risk factors for vascular dementia such as “cardiac disease, diabetes, orthostatic hypotension, elevated blood homocysteine levels smoking, obesity, major surgery and hyperlipidemia”.

### Diabetes:

Diabetes contributed to virtually all of the dementia risk (17). Patients who are pre-diabetes and diabetes also typically cause risk factor of transitioning from mild to severe neurological impairment to dementia (18) Diabetes enhances the risk of vascular dementia, mainly when it develops in people throughout their middle years, such as between the ages of 65 and 80. (18)

### Hypertension:

Ageing is a risk factor for hypertension, which increases the likelihood that someone may develop vascular dementia (19). Hypertension in middle age (mean age 54 years) might increase the risk of vascular dementia in old age (approximately 25 to 30 years later), in particular. A few systems central on white matter (WM) damage might help explain how hypertension affects vascular dementia: Raised blood pressure has been linked to White matter lesions in the ageing non-demanded population; uncontrolled and untreated hypertension is a significant risk factor for white matter lesions and accelerates the progression of vascular dementia disease.

**Metabolic disorder (MetS)**

In any case, three of the most common cardiovascular risk factors, such as stomach/focal obesity, hypertension, large waistline, dyslipidemia, with low high-density lipoprotein (HDL) or high triglycerides cholesterol, and insulin resistance, such as high fasting blood glucose levels, combine to cause MetS. (Grundy et al., 2004 Feb 3). Metabolic disorder appears to have a large influence on cognitive impairments, but only in individuals younger than 70 years old (20, 21).

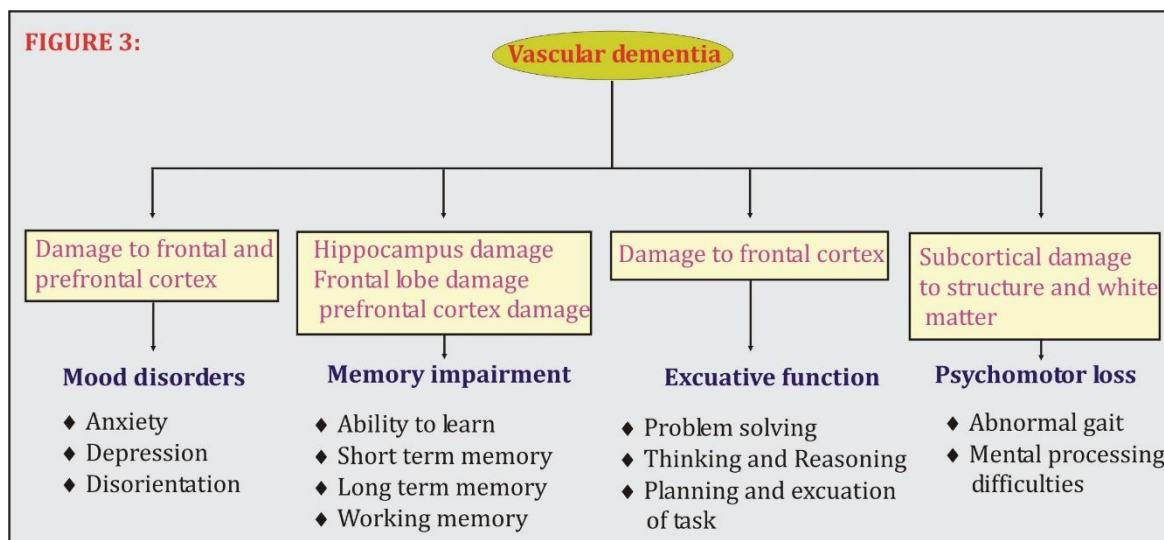
**Evaluation of cognitive dysfunction**

“The clinical diagnostic criteria for vascular dementia by the following include Association International pour la Recherche et l'Enseignement en Neurosciences (AIREN), ADDTC (Alzheimer's Disease Diagnostic and Treatment Centers, National

Institute of Neurological Disorders and Stroke (NINDS), DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) and ), ICD-10 (10<sup>th</sup> revision of the International Classification of Diseases)”(22,23), diagnostic criteria for the vascular dementia are given below:

- 1) “Novel object recognition test to test short/long term (1 h–24 h), visual learning and memory based on animal bias to explore new objects”. (24)
- 2) “Elevated plus maze test for anxiety related responses” (25)
- 3) “Open field test for anxiety problems” (25)
- 4) “Odor test for olfactory learning based on animal mostly preference for new smells” (26)
- 5) “Morris water maze or Barnes maze tests for spatial and visual learning and memory” (27)
- 6) “Y maze test to evaluate spontaneous alternation capacity of animals.” (28)

Different aspects of cognitive failure that Vascular patients suffer from symptoms summarize in the (figure 2).



**Prevention of Vascular Dementia:**

The important significant part of the preventative management of vascular dementia and evasion of further movement, is the aggressive management of risk factors. On the off chance that one needs to anticipate dementia, the best guidance is to complete a similar preventive way of life and medical estimates prevent to cardiovascular disease like strokes, heart attack and other heart problem and adopting work out, healthy diet plan, stop smoking, and keep away from the risk factor of diabetes, cholesterol level and blood pressure and all

of them factor are more helpful for preventing vascular dementia (29,30) Statin users were shown to have a 71 percent lower risk of developing dementia, according to a situation control research. A productive field of current study is the prevention of vascular dementia by risk factor treatments.

**Clinical assessment:**

Clinical evaluations for patients with vascular cognitive impairment aim to diagnose the condition and identify particular therapy targets for each patient (Figure no. 05).

### FIGURE 5: CLINICAL ASSESSMENT FOR VASCULAR DEMENTIA

#### History

History of the following disease are necessary to identify which is more helpful in the specific treatment for vascular dementia

- Relation to stroke,
- Transient ischemic attack,
- Myocardial infarction.
- Diabetes, hypertension, hyperlipidemia.
- Family history of cardiovascular or neurological disease.

#### Psychiatric disorders:

- Depression may affect the diagnostic assessment and require treatment in its own right.
- Psychosis, whether chronic or acute, can produce cognitive impairment.

#### Neuropsychological testing:

• To establish breadth and depth of cognitive impairment. Sometimes the diagnosis will be apparent with only very limited testing such as with the Mini-Mental State Examination (Folstein 19751) but in cerebrovascular disease there may well be significant breadth of impairment requiring more extensive testing. (Hachinski et al 2006) recommended a 5-minute screening test based on subscales of the Montreal Cognitive Assessment as a quick and useful instrument that can be used by telephone if necessary. Screening tests for depression such as the Cornell Scale for Depression in Dementia (Alexopoulos 1988) may be useful.

#### Physical examination:

- Focal neurological signs, asymmetries of power, tone, reflexes and sensation, tremor, and balance and gait abnormalities.
- Cardiovascular system, signs of relevant systemic disease such as diabetes mellitus.
- Other associated degenerative disorders such as Parkinson's disease
- Extrapyramidal signs could be a feature of cerebrovascular disease

#### Investigations:

- Blood screen, including vitamin B12, and folate.
- Growing evidence that homocysteine is a risk factor for dementia, and may prove to be a useful treatment target (Smith 2010).
- Chest X-ray and electrocardiogram should be considered, if relevant, Neuroimaging is recommended.
- Computed tomography is widely available, economical and helpful
- MRI provides more information, although it is more expensive and may be less well tolerated because each MRI scan takes much longer (20-40 min) than CT.

#### Treatment

##### Treatment of cognitive changes:

Only limited efficacy was discovered in two preliminary randomized controlled trials that looked at donepezil's effectiveness in treating vascular dementia (31, 32). A trial with galantamine in individuals who had both Alzheimer's disease and cerebrovascular disease found minimal benefit overall (33), although benefit was shown in the subgroup with probable vascular dementia. Memantine's effects on vascular dementia have been investigated in two randomized controlled trials, and both found it to be only marginally effective. (34, 35)

The National Institute for Health and Clinical Excellence (NICE) does not recommend the

use of memantine or other cholinesterase inhibitors for the signs and symptoms of vascular dementia because neither drug is approved for such a condition (National Institute for Health and Clinical Excellence 2011). Other medications, such as calcium channel blockers (such as nimodipine), nootropics (such as piracetam and citicoline), xanthenes (such as pentoxifylline), vasodilators, ergot derivatives, and antithrombotic agents, have been attempted for vascular dementia (for example ibuprofen, ginkgo). Most don't seem to be doing anything, and none are doing much more than modest things (36, 37)

### Symptomatic treatment

Regardless of whether there is a causal relationship between depression and cognitive impairment, depression is a normal disease that needs to be treated. Vascular dementia is a growing issue, and while there are acceptable treatments for it, they may not be as successful in treating other types of depression (38). Dementia is especially susceptible to depression. As with any kind of dementia, patients and caregivers must have access to the right assistance and information. These appear to have a more positive impact on prosperity than currently available medications.

### Control of vascular risk factors

There is no lack of possible areas of attention for the therapy of vascular cognitive impairment risk factors, but the evidence that slows the rate of illness progression is lacking. In individuals with hypertension who have no prior cerebrovascular disease, a Cochrane review failed to find convincing evidence that lowering blood pressure avoids a development of dementia or psychological impediment (39). Despite the Syst-Eur and PROGRESS studies showing modest but significant reductions in dementia from treating hypertension (40).

A few studies have failed to demonstrate a benefit of statins in the treatment of vascular dementia. According to Bowler(41), this may be due to the fact that hypertension is the most well-established treatable risk factor for vascular dementia and that cholesterol has little association with small vessel disease. Subcortical vascular subjective impedance is the most common form of vascular dementia disability. Most doctors would eventually consider it appropriate to treat vascular risk factors despite them.

### Recommendations for future research:

Moving toward a comprehensive strategy for vascular dementia diagnosis, treatment, and prevention We believe that there are many takeaways from the above review of recent research on the role of vascular diseases related to the risk, course, evaluation, treatment, and conceptualization of disorders characterized by aging-related cognitive impairment decline history of disease like hypertension, stroke, diabetes, and hyperlipidemia, as well as modification of lifestyle. Therefore, we believe that more research is necessary on vascular dementia for the development of effective treatments and a healthy lifestyle.

### a. Most dementias are occur with combinations of risk factors

In any cases, the readily available data demonstrates that the majority of dementia cases are characterized by a mixed phenotype, both throughout life and at the time of evaluation after death. The diseases associated with AD and vascular dementias are the most well-known co-occurring conditions. Following the post--mortem brain examination, aging-related diseases including hypertension, diabetes, obesity, hyperlipidemia, etc. are exacerbated while being accompanied with evidence of vascular dementia. Accordingly, it would seem to be more pertinent to focus research efforts on identifying the mechanisms through which vascular and neurodegenerative systems mutually contribute to the progression and movement of maturing-related cognitive disorder than to see them as separate illnesses.

### b. Translational and implementation research

Clinical practice seldom changes quickly in response to research findings on the efficacy of a particular treatment (42). There are various separable components that contribute to this hole, and each call for specific techniques. (43) An ongoing study has shown that a 10% drop in the prevalence of major modifiable risk factors, including some of those mentioned in this article (such as diabetes, hypertension, and obesity), might significantly lower the rate of Alzheimer's disease (ADs) (44).

### c. Applying rising standards, techniques, and discoveries of frameworks science and system prescription to utilize existing information and create models of disease forms that will prompt testable theories about the effect of intercessions for which adequate proof doesn't yet exist

Given the level of interrelatedness among the frameworks embroiled in and affecting metabolic and vascular failure (45), a numerical biologic methodology can significantly educate the explanation regarding the important pathophysiologic processes that add to the movement of the sickness procedure after some time. For example, hypertension and T2DM are both distinguished before in the content as risk factors for vascular illness interceded cognitive disease; notwithstanding, hypertension is related with insulin resistance, which thusly is risk factor for T2DM. Correspondingly, obesity is a risk factor for both insulin resistance (and subsequently T2DM) and hypertension. A numerical biologic way to deal with evaluating the net effect of risk factors and their part

pathophysiologic components after some time would coordinate realized information utilizing measurable models of the dynamic and intelligent procedures required, just as recognizing regions where information are deficient and further research is required.

## II. CONCLUSIONS

This review has focused on vascular dementia, its characteristics, risk factors, sign and symptoms, evaluation of vascular dementia, prevention and current treatment as well as recommendation for further research. Without this knowledge, we have so far been unable to identify a solution and are instead forced to rely only on symptomatic therapies that have little to no value for vascular dementia and This review articles are more helpful for knowing overall about the vascular dementia but briefly emphasis on the treatment aspect and recommendation of further research along with mention the evaluation parameter, In the future, it will be necessary to adopt a set of normative criteria for cognitive evaluation, including testing kinds and timing, and evaluation must include tests to gauge learning and memory as well as behavioural, motor, and emotional deficiencies.

## REFERENCE:

- [1]. Plassman, B.L., et al., 2007. Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology* 29 (1–2), 125–132
- [2]. Wardlaw, J.M., Smith, C., Dichgans, M., 2013. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet Neurol.* 12, 483e497.
- [3]. Knopman D, Boland LL, Mosley T, et al.: for the Atherosclerosis Risk in Communities (ARIC) Study Investigators: Cardiovascular risk factors and cognitive decline in middleagedadults. *Neurology* 2001, 56:42–48.
- [4]. Forette F, Seux ML, Staessen JA, et al.: Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet* 1998, 352:1347–1351.
- [5]. Hanon O, Forette F: Prevention of dementia: lessons from SYST-EUR and PROGRESS. *J NeurolSci*2004, 226:71–74.
- [6]. Yaffe K, Kanaya A, Lindquist K, et al.: The metabolic syndrome, inflammation, and rise of cognitive decline. *JAMA* 2004, 292:2237–2242.
- [7]. Solomon A, Kareholt I, Ngandu T: Serum cholesterol changes after mid-life and late-life cognition: twenty-one year follow-up. *Neurology* 2007, 68:751–756.
- [8]. Shumaker SA, Legault C, Rapp SR, et al.: Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. The Women’s Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003, 289:2651–2652.
- [9]. Rapp SR, Espeland MA, Shumaker SA: Effect of estrogen plus progestin on global cognitive function in post menopausal women. The Women’s Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003, 289:2663–2672.
- [10]. Dougall NJ, Bruggink S, Ebmeier KP. Systematic review of the diagnostic accuracy of 99mTc-HMPAO-SPECT in dementia. *The American Journal of Geriatric Psychiatry* 2004;12(6):554-70.
- [11]. Steen JT, Radbruch L, Hertogh CM. White paper defining optimal palliative care in older people with dementia: A Delphi study and recommendations from the European Association for Palliative Care. *Palliative medicine.* 2014;28(3):197-209.
- [12]. Fink HA, Jutkowitz E, McCarten, JR. Computerized cognitive training in cognitively healthy older adults: a systematic review and metaanalysis of effect modifiers. *PLoS Medicine* 2017;11(11):e1001756.
- [13]. Fymat AL. Epilepsy: A review. *Journal of Current Opinions on Neurological Science* 2017;1(5):240-54.
- [14]. 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: 280–92.
- [15]. Hebert R, Brayne C (1995) Epidemiology of vascular dementia. *Neuroepidemiology* 14: 240–57.
- [16]. Hebert R, Lindsay J, Verreault R, et al (2000) Vascular dementia: incidence and risk factors in the Canadian study of health and aging. *Stroke* 31: 1487
- [17]. Ott, A., et al., 1999. Diabetes mellitus and the risk of dementia: the Rotterdam Study. *Neurology* 53 (9), 1937–1942.
- [18]. Xu,W., et al., 2010. Accelerated progression from mild cognitive impairment to dementia

- in people with diabetes. *Diabetes* 59 (11), 2928–2935.
- [19]. Tzourio C, Anderson C (2003) Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Archives of Internal Medicine* 163: 1069–75.
- [20]. Frisardi, V., 2014. Impact of metabolic syndrome on cognitive decline in older age: protective or harmful, where is the pitfall? *J. Alzheimers Dis.* 4, 4.
- [21]. Siervo, M., et al., 2014. Metabolic syndrome and longitudinal changes in cognitive function: a systematic review and meta-analysis. *J. Alzheimers Dis.* 27, 27. Rouch, I., et al., 2014. Metabolic syndrome is associated with poor memory and executive performance in elderly community residents: the PROOF study. *Am. J. Geriatr. Psychiatry* 25 (14), 00032–00033.
- [22]. Lee, A.Y., 2011. Vascular dementia. *Chonnam. Med. J.* 47 (2), 66–71.
- [23]. Wetterling, T., Kanitz, R.D., Borgis, K.J., 1996. Comparison of different diagnostic criteria for vascular dementia (ADDTC, DSM-IV, ICD-10, NINDS-AIREN). *Stroke* 27 (1), 30–36.
- [24]. Stuart, S.A., et al., 2013. Chronic pravastatin but not atorvastatin treatment impairs cognitive function in two rodent models of learning and memory. *PLoS One* 8 (9), e75467.
- [25]. Brown, R., Corey, S., Moore, A., 1999. Differences in measures of exploration and fear in MHC-congenic C57BL/6J and B6-H-2K mice. *Behav. Genet.* 29 (4), 263–271.
- [26]. Spinetta, M.J., et al., 2008. Alcohol-induced retrograde memory impairment in rats: prevention by caffeine. *Psychopharmacology* 201 (3), 361–371.
- [27]. Ohno, M., et al., 2006. Differential effects of alphaCaMKII mutation on hippocampal learning and changes in intrinsic neuronal excitability. *Eur. J. Neurosci.* 23 (8), 2235–2240.
- [28]. Weiss, C., Shroff, A., Disterhoft, J.F., 1998. Spatial learning and memory in aging C57BL/6 mice. *Neurosci. Res. Commun.* 23 (2), 77–92.
- [29]. Gorelick PB, Erkinjuntti T, Hofman A, et al.: Prevention of vascular dementia. *Alzheimer Dis Assoc Disord* 1999, 13(Suppl 3):S131–S139.
- [30]. Jick H, Zornberg GL, Jick SS, et al.: Statins and the risk of dementia. *Lancet* 2000, 356:1627–1631.
- [31]. Wilkinson D, Doody R, Helme R, et al (2003) Donepezil in vascular dementia: a randomized, placebo-controlled study. *Neurology* 61: 479–86.
- [32]. Black S, Roman GC, Geldmacher DS, et al (2003) Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. *Stroke* 34: 2323–32.
- [33]. Erkinjuntti T, Kurz A, Gauthier S, et al (2002) Efficacy of galantamine in probable vascular dementia and Alzheimer’s disease combined with cerebrovascular disease: a randomised trial. *Lancet* 359: 1283–90.
- [34]. Orgogozo J, Rigaud A, Stoffler A, et al (2002) Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). *Stroke* 33: 1834–9.
- [35]. Wilcock G, Möbius HJ, Stöfler A (2002) A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). *International Clinical Psychopharmacology* 17: 297–305.
- [36]. Erkinjuntti T, Roman G, Gauthier S, et al (2004) Emerging therapies for vascular dementia and vascular cognitive impairment. *Stroke* 35: 1010.
- [37]. Román G (2005) Therapeutic strategies for vascular dementia. In *Dementia* (3rd edn) (eds A Burns, J O’Brien, D Ames): 574–600. Hodder Arnold.
- [38]. Sheline YI, Pieper CF, Barch DM, et al (2010) Support for the vascular depression hypothesis in late-life depression: results of a 2-site, prospective, antidepressant treatment trial. *Archives of General Psychiatry* 67: 277–85.
- [39]. McGuinness B, Todd S, Passmore P, et al (2009) Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. *Cochrane Database of Systematic Reviews* issue 4: CD004034 (doi: 10.1002/14651858.CD004034.pub3).
- [40]. Forette F, Seux ML, Staessen JA, et al (2002) The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Archives of Internal Medicine* 162: 2046–52.





- 
- [41]. Bowler JV (2007) Modern concept of vascular cognitive impairment. *British Medical Bulletin* 83: 291–305.
- [42]. Winner B, Kohl Z, Gage FH. Neurodegenerative disease and adult neurogenesis. *Eur J Neurosci* 2011;33:1139–51.
- [43]. Dancause N, Nudo RJ. Shaping plasticity to enhance recovery after injury. *Prog Brain Res* 2011;192:273–95.
- [44]. Negash S, Bennett DA, Wilson RS, Schneider JA, Arnold SE. Cognition and neuropathology in aging: multidimensional perspectives from the Rush Religious Orders Study and Rush Memory and Aging Project. *Curr Alzheimer Res* 2011;8:336–40.
- [45]. Eichner JE, Dunn ST, Perveen G, Thompson DM, Stewart KE, Stroehla BC. Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. *Am J Epidemiol* 2002;155:487–95.