The Primary Care Guide of Cerebrovascular Prevention Strategies for Dementia

1. Introduction

The primary care clinician can use clinical and pathological research to recommend cardiovascular and cerebrovascular fitness as part of their cognitive wellness message. The American Heart Association predicts that 25% of the adult population is hypertensive and about one-third are undiagnosed. The clinician can develop recommendations about the role of hypertension in dementia for patients in three broad age groups: midlife (40 to 65 yrs), older (65 to 75 yrs) and very old age groups (over 75). This segment reviews the available biomedical data that defines the role of hypertension in middle-aged and older patients as a risk factor for dementia in late life (1), (2). A lay person's fact sheet (Consumer Guide) is attached to this document for use as patient education. **(Click here for Fact Sheet – 2513.15).**

The human brain is sensitive to diminished perfusion or oxygenation. Ischemic brain injury can result with as little as three minutes of diminished blood flow. Managing cerebrovascular risk factors in mid or later life may provide significant benefit to cognitive function for all individuals, especially those over age 65. The presence of metabolic syndrome in midlife may increase the risk for dementia in later life **(CLICK HERE FOR MORE INFORMATION – 2513.9)**. Chronic hypertension (3), risk factors for atherosclerosis (4), and cardiovascular disease (5), (6) are manageable risk factors in middle age that may predict cognitive decline in later life (7), (8), (9).

2. The Role of Hypertension in Cognitive Decline

A. Overview. Numerous longitudinal and cross-sectional studies have examined the rate or risk of cognitive decline in persons with untreated or under-treated hypertension. Longitudinal studies, such as those conducted in Sweden (9), England (10), Honolulu (11), (12), (13), Baltimore (14), and others report that older individuals who have a long-term history of untreated or under-treated hypertension have increased risk for dementia later in life, especially with other risk factors such as the presence of one or two APOE4 alleles (11).. Individuals with untreated hypertension may have diminished cognitive function, even in the absence of dementia (13).

Hypertension can damage both large and small caliber cerebral blood vessels in the brain. Sustained hypertension is a risk factor for accelerated atherosclerosis which is common in the large caliber cerebro-vasculature. Hypertension may damage medium and small size penetrating arterioles in hemispheric white matter producing arteriolar sclerosis in brain parenchyma. Damage to the massive plexus of penetrating arterioles that perfuse brain parenchyma is particularly apparent in white matter where the ubiquitous hyperintensities seen on MRI may be produced by hypertensive small vessel damage (15), (16), (17).

Hypertension may be a risk factor for mild cognitive impairment (MCI), Alzheimer's disease, and vascular dementia in older persons (17), (18). **(Click here for more information about MCI).**

B. Longitudinal Studies on the Role of Hypertension in Dementia. A representative sample of studies on the relationship between blood pressure during midlife and cognitive function in later life is demonstrated in **Table 1**. At least nine studies have employed cross-sectional or longitudinal methodologies to examine this issue with durations from 6 years through 30 years. The majority of studies demonstrate that sustained hypertension is associated with diminished cognitive function or increased risk for developing dementia. Each study group contained a variable mixture of individuals with a range of risk factors for atherosclerosis. The general consensus of long-term longitudinal studies supports the role of chronic hypertension in midlife as a risk factor for dementia in later life. Seven studies are cited that examine the rate of cognitive decline for older individuals based on a pre-existing history of hypertension **(See Table 2).** The study durations ranged from 3 years to 20 years. Location of these studies included the United States and Europe. Study groups were large, ranging from 600 to 4,000 older individuals. In general, studies of older individuals demonstrated more variation of cognitive outcomes for blood pressure levels than studies in midlife.

Table 1. The Relationship Between Blood Pressure During Midlife and Cognitive Function in Later Life

	Location	Duration	Study Size	Relationship to HBP	Refs.
1.	NIH	30 yrs.	392	⇩ Cognitive function	3
2.	Sweden	21	1449	⇧ Risk for dementia	9
3.	New Mexico	30	717	⇩ Cognitive function	68
4.	Honolulu	26	3605	⇩ Cognitive function	11
5.	England	14	5838	Small but significant ⇩ Cognitive function	10
6.	Finland	21	1449	⇧ Risk for MCI but related to other vascular risk factors	69
7.	Japan	25 to 30	1660	Associated with Vascular dementia	70
8.	USA	30+ yrs	8845	Hypertension and multiple other cardiovascular risk factors ⇧ risk for dementia	5
9.	Multi-site/USA	6 yrs.	10,963	⇧ Risk and ⇧ rate of dementia	71

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Among studies that include older subjects, a single study **(See Table 2, Line 1)** demonstrated no significant association while the remainder of the studies demonstrated diminished cognition of varying severity. Several studies **(See Table 3)** in elderly subjects cited loss of cognitive function with extremes of blood pressure and negative effect from low pressure as well as high pressure **(19)**. In general, the relationship between hypertension in the older individual, i.e., over age 65, seems less clear, especially for individuals with mild hypertension. Five longitudinal studies examine the relationship

between cognitive function and blood pressure in very old individuals, i.e., over age 75 **(See Table 3).** The duration of studies ranged from 3 to 6 years and the population sizes ranged from 377 to 4, 937. The role of hypertension in the very old seemed more obscure than in studies in older individuals (20). Lower blood pressure appeared problematic, as well as significant hypertension (21) and some studies suggest that hypertensive individuals with dementia demonstrate normalization of blood pressure over time (5). Sympathetic autonomic regulation is partially mediated by the right insular cortex which often sustains damage in Alzheimer's disease. Hypertensive demented patients have a steeper rate of cognitive decline than normotensive individuals (22).

Table 2. Rate of Cognitive Decline for Older Individuals Based on Blood Pressure

	Age	Location	Duration	Study Size	Relationship to HBP	Refs
1.	Over 65	Chicago	3-6 years	4284	No Association	72
2.	69-74	Sweden	20 yrs.	502	↓ cognitive function	73
3.	Over 65	Medicare Population	7 yrs.	1259	May ↑risk of dementia, especially with other CV diseases	74
4.	Over 65	Duke, NC	3 yrs.	4136	Decline associated with extremes of BP	75
5.	Over 65	East Boston	6 yrs.	3657	Complex relationship between BP and cognition	76
6.	Over 65	East Boston	13 yrs	634	Not associated with AD	77
7.	Over 65	Baltimore	11	847	↓ Cognition	14

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Table 3. Relationship Between Cognitive Function and Blood Pressure in the Very Old

	Age	Location	Duration (years)	n	Relations to HBP	Refs
1.	Over 75	Australia	6	377	Unclear relations	78
2.	75-101	Sweden	3.5	1736	Lower BP may be problematic Very high BP is problematic	79
3.	> 75	Sweden	3	924	↓ Cognitive Function	80
4.	70-89	*SCOPE	3.7	4937	Elders with HBP and mild impairment have greater risk for dementia	87
5.	70+	Sweden	15	382	↑ risk for dementia	6

n= study size *SCOPE: Study on Cognition and Prognosis in the Elderly

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Results of studies in individuals with mild cognitive impairment (MCI) appear less consistent for hypertension as a risk factor for persons with MCI progressing to dementia (23), (24), (25). Cardiovascular risk factors may be associated with the risk of developing MCI and the likelihood of transition from MCI into dementia; however, few studies have carefully examined this relationship **(See Table 4).**

Table 4. A Summary on Studies About the Role of Treating Hypertension in Preventing Dementia

#	t	a	n	Treatment Effect on Dementia Risk and Cognition	Ref.
1	39 m	60+	2902	Reduction of 55% by treatment	32
2	6 m	69+	69	Lowering blood pressure did not lower cognition	66
3	6 wks	25-55	98	No adverse effect on cognition	33
4	22 m	65+	7046	Slight ⇩ risk for dementia, probably vascular	34
5	6yrs	55+	1979	Impaired cognition predicts poor compliance	36
6	5 yrs	60+	4736	No adverse effect from treating hypertension, unclear benefit on cognition	67
7	5 yrs	65+	1900	Antihypertensive treatment reduces odds of increased cognitive impairment by 38%	27
8	2 yrs	55-89	1993	Cognitive impairment may ⇩ compliance	54
9	3 yrs	65+	3308	⇩ AD with potassium sparing diuretics	91

t=duration of study a=age of subjects m=months n=number of subjects

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Meta-analyses are not available that examine the role of hypertension and cognition in longitudinal studies. A meta-analysis would be limited by the size and variability of the study populations as well as the techniques used to examine the relationship between hypertension and cognition. Substantial, longitudinal data suggests that early onset hypertension may be more damaging to cognitive function than late-life onset hypertension and treatment of early onset hypertension may diminish the risk for developing cognitive impairment in later life.

Brain infarction is a major complication that can result from hypertension and cardiovascular disease. Stroke substantially increases the risk for dementia in persons over the age of 65 (29), (30). Twenty percent of all older individuals have silent strokes which are most commonly lacunar infarcts in the basal ganglia (80%). This often unrecognized cerebrovascular disease doubles the risk for developing dementia in later life (31). Stroke risk factors include hypertension, atherosclerotic vascular disease, and elevated homocysteine.

C. Cognitive Effects of Pharmacological Interventions for Hypertension

Antihypertensive therapy may reduce the risk of cognitive decline in persons with chronic hypertension (26), (27) and treatment should not worsen cognitive function. No specific class of antihypertensive medication is consistently identified as more beneficial to cognition **(See Table 4),** (32), (33), (34). The first step in reducing hypertensive risk factors for cognitive decline is adequate, safe control of hypertension. Sustained compliance by the demented patient may become problematic, as dementia increases the likelihood of non-compliance (35), (36). Neurodegenerative changes such as senile plaques and neurofibrillary tangles begin to develop in some persons over age 50 and aggressive cardiovascular preventive interventions could be reviewed at this point in the

patient's life. Protection of left ventricular function and reduction of atherosclerotic risk factors would appear prudent for cognitive as well as cardiac health. Appropriate control of homocysteine in all age groups may diminish the risk of cognitive decline. Long-term folic acid and B-Complex vitamin supplementation appear to reduce the homocysteine level in many older individuals. Demented persons receiving appropriate antihypertensive therapy may have enhanced benefit from cholinesterase therapy (28). (Click here for additional information on the role of folic acid and homocysteine in cognitive function – DETA 2513.41).

Older persons with atrial fibrillation have increased risk of cognitive decline, as well as stroke and white matter damage (37), (38), (39). The cognitive benefit of prophylactic anticoagulants or anti-arrhythmic agents in older persons with atrial fibrillation has not been adequately studied. Conventional wisdom suggests prudent but aggressive therapy of atrial fibrillation as protection of cognitive and neurological function (40). Demented persons treated with antihypertensive medications may have better response to cholinesterase inhibitor therapy (28).

The majority of studies that examine the role of statins in dementia suggest a protective effect in some individuals, although several studies dispute this beneficial effect (41). The beneficial effect of statins on cardiovascular function suggests a possible reduction of vascular burden in the brain (42). Other putative roles for statin therapy include the reduction of amyloid burden. The risk-benefit ratio for statins supports the aggressive use of these medications in persons with hyperlipidemia; however, the prophylactic use of these drugs in at-risk populations for dementia is not recommended (41). The prophylactic use of low dose aspirin therapy for cognition has not been adequately studied. Click here for additional information on the role of statin therapy and cognition – DETA 2513.91.

D. Neuropathological Correlates to Hypertension

The role of hypertension and cerebrovascular disease in the pathogenesis of dementia or age-related cognitive decline remains vague because neuropathologist lacks precise methodologies to quantitate the extent of vascular damage to the brain. Longitudinal studies suggest that brains from decedents with chronic hypertension exhibit increased Alzheimer's pathology. Senile plaque counts in brains of non-demented older subjects correlate to severity of coronary artery stenosis by atherosclerosis (15), (16), (43), but not premortem cholesterol levels (89). Hypertensive individuals have diminished brain volume in comparison to normotensive and increased microscopic pathology, as well as increased numbers of white matter lucencies (21), (44), (45), (46), (47), (48), (49). White matter damage is present in brains of intact and demented elders but this damage may worsen cognition in Alzheimer patients (50).

Microscopic examination of white matter blood vessels in persons with chronic hypertension demonstrate thickening of vascular media and loss of brain parenchyma around the vessel along with evidence of old perivascular microscopic bleeding as detected by hemosiderin laden macrophages around arterioles (45), (46), (47), (17). This non-specific finding can be seen in other disorders that produce neuropsychiatric symptoms including Systemic Lupus Erythematosis. White matter blood vessels are susceptible to hypertensive injury because they have diminished pressure regulating capacity in comparison to arborizing blood vessels in the cerebral cortex. This hypertensive arteriolar damage is associated with lacunar or slit-like infarcts in the white matter as well as in the basal ganglia and thalamus. Small vessel disease in white matter may correlate with cognitive decline (51).

E. Conclusion about the Role of Chronic Hypertension on Cognition

Mild, chronic hypertension in midlife may produce greater cognitive morbidity in later life than similar elevations of blood pressure in the very old. Hypotension in the elderly person may be as problematic as moderately severe hypertension. Severe hypertension appears problematic in all groups. A further confounding issue is the role of multiple cardiovascular risk factors. The vague, imprecise neuropathological definitions used to diagnose "vascular dementia" incorporate only discrete quantities of infarcted brain parenchyma despite the fact that diffuse white matter hypertensive small vessel disease can produce wide-spread injury (17). In fact, neuroscientists have no accurate method of measuring total vascular damage in the human brain.

3. The Role of Cerebrovascular Disease in Dementia

Most strokes are produced by extracranial cerebrovascular disease originating in the left ventricle of the heart, the carotid system or the Circle of Willis. Older individuals have a significantly increased risk for developing dementia following a stroke and efforts to reduce risk factors for stroke may reduce risk for cognitive decline (17). Individuals with low left ventricular ejection fraction and atrial fibrillation have increased risk for cognitive decline with aging (40), (52).

The role of atherogenic medical conditions, such as hyperlipidemia, in the pathogenesis of cognitive decline remains contradictory, as some studies dispute the relationship between dyslipidemia and dementia. The protective role of statin medications also remains unclear. Elevated homocysteine and decreased folic acid are known risk factors for accelerated atherosclerosis (55). Folic acid supplementation may reduce the serum level of homocysteine and benefit cognition through cerebral vascular benefits or other undetermined mechanisms (56), (57). Click here for more information about risk factors for atherosclerosis – DETA 2513.91).

Data from the Nun Study suggests that vascular pathology is an important benchmark for cognitive decline in aging members of well-characterized populations, such as the clergy

(58). Individuals with microscopic features of Alzheimer's disease may retain intellectual function into later life; however, those individuals with both Alzheimer pathology and vascular damage were more likely to demonstrate cognitive deficits before death. Mixed dementias often include both vascular damage and Alzheimer's disease.

The concept of cognitive reserve remains controversial; however, the newest science supports this principle. Cognitive reserve may reflect redundancy of synapses, redundancy of strategic cognitive functions through interconnected neural networks or enhanced neural plasticity. Dementia may occur when the cumulative burden of brain damage exceeds a threshold value required to sustain normal intellectual function. ***Click here for more information about cognitive reserve – 2513.51.*** Vascular damage to the brain may occur through several mechanisms including direct loss of neurons, disruption of vascular permeability, damage to vital white matter pathways carrying ascending fibers, such as cholinergic systems or disruption of cortical to cortical pathways that run through the hemispheric white matter (17). The addition of vascular damage to Alzheimer pathology may accelerate the onset of intellectual loss.

4. The Role of Cardiac Disease and Bypass Surgery in Cognitive Decline

Severe left ventricular dysfunction as measured by low ejection fracture (below 30%) is correlated to poor cognitive function (52). Specific kinds of cardiac or peripheral vascular disease, such as past myocardial infarction (90) or thickened carotid arteries may increase the likelihood of cognitive decline in later life (51). Increased left ventricular mass is associated with diminished cognitive function over five years (93). The role of coronary artery bypass grafting (CABG) as a precipitant for cognitive decline in older persons is problematic for the primary care physician who may recommend bypass surgery. Multiple studies have suggested the adverse effect of CABG on the brain (59), (60), (61), (62); however, recent studies dispute this observation (53), (63). Post-operative functional brain imaging studies suggest diminished metabolic activity in persons undergoing CABG procedure, although obvious variables such as pump time, clamp time and gender do not seem to impact cognition. Post-operative delirium continues to be a major issue and these symptoms may persist for up to six months. CABG surgery can sustain left ventricular function and theoretically reduce other risk factors associated with dementia. The clinician must weigh risk benefits to each patient comparing the severity of cardiac morbidity to cognitive and functional status. Available data will not provide guidance for which patients might suffer greater cognitive loss following CABG surgery.

5. Future Directions for Crafting Preventive Recommendations on Vascular Risk Factors and Cognition

A prospective study that randomizes hypertensive individuals into treated versus non-treated groups to assess the impact of long-term antihypertensive therapy on cognitive decline will not be done for ethical and legal issues. Available data suggests diminished

risk for dementia with treatment by potassium sparing diuretics (91) and others (88). The best available science indicates that midlife choices determine later life cardiovascular, cerebrovascular, and cognitive wellness. Hypertension, heart disease or metabolic syndromes are linked to cognitive decline; providing additional incentives to patients for compliance with medications and lifestyle changes (67). The potential impact of a cerebrovascular fitness program on the cognitive function for individuals over the age of 65 is unclear, although conventional, clinical wisdom would encourage the use of these interventions in persons of all age groups.

The concept of a "brain screen" has been proposed that includes prospective assessment of vascular risk factors in the older patient that may identify a substantial yield of disorders that respond to therapy (65). The role of preventive interventions in older persons remains unclear; however, conventional wisdom suggests that cerebrovascular risk reduction will likely benefit middle age and older individuals (92).

Table 5. The Possible Role Of Cardiovascular Preventive Interventions In Midlife And Later Life For Dementia

	Intervention	40-60 Midlife	>60 Older	Recommendation to Clinician	Refs.
1	Weight Control	Obesity correlated to cognitive decline	Unclear	Weight management in midlife	9
2.	Control HBP	Correlated to later cognitive decline	Unclear, except for severe HBP	1. control all severe HBP 2. ↓ BP in midlife to ↓ risk	78, 26, 82, 88, 91
3.	Statin Therapy	Unclear but probably beneficial	Unclear	Treat dyslipidemia	41
4.	Reduce Plasma Homocysteine	Correlated to ↓ cognitive function in late life	Correlated to dementia	Vitamin supplementation	83, 84, 85
5.	Exercise Program	Correlated to ↓ CV disease and ↓ dementia	Correlated to ↓dementia	Promote regular exercise	86

HBP – hypertension **CV**-cardiovascular

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Recommendations to the Primary Care Providers

1. Monitor BP and treat hypertension as per published national guidelines.
2. Educate patients that cardiovascular fitness protects the aging brain.
3. Monitor for the metabolic syndrome and treat each component.
4. Maximize ejection fraction to optimize cognitive function.
5. Screen cognitive function for all bypass candidates.
6. Empower patients to control their cognitive aging by managing vascular risk factors.
7. Use dementia risk reduction as another compliance tool for medications, diet, and health behaviors.

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