

SPECIAL TOPIC SECTION

# Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD)5: Guidelines for management of vascular cognitive impairment

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## Abstract

**Introduction:** Vascular disease is a common cause of dementia, and often coexists with other brain pathologies such as Alzheimer's disease to cause mixed dementia. Many of the risk factors for vascular disease are treatable. Our objective was to review evidence for diagnosis and treatment of vascular cognitive impairment (VCI) to issue recommendations to clinicians.

**Methods:** A subcommittee of the Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD) reviewed areas of emerging evidence. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to assign the quality of the evidence and strength of the recommendations.

**Results:** Using standardized diagnostic criteria, managing hypertension to conventional blood pressure targets, and reducing risk for stroke are strongly recommended.

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Intensive blood pressure lowering in middle-aged adults with vascular risk factors, using acetylsalicylic acid in persons with VCI and covert brain infarctions but not if only white matter lesions are present, and using cholinesterase inhibitors are weakly recommended.

**Conclusions:** The CCCDTD has provided evidence-based recommendations for diagnosis and management of VCI for use nationally in Canada, that may also be of use worldwide.

**KEYWORDS**

dementia, guidelines, vascular cognitive impairment, vascular dementia

## 1 | INTRODUCTION

Vascular disease is the second most common cause of dementia and is often present along with other neuropathologies in the aging brain.<sup>1</sup> Furthermore, many of the risk factors for dementia overlap with the risk factors for stroke and cardiovascular disease.<sup>2</sup> Vascular disease may be the most preventable and treatable contributor to dementia, but the clinical trial evidence to prove this is still emerging. In this setting, clinicians need evidence-based guidance on how to diagnose and manage vascular cognitive impairment (VCI), defined as any cognitive syndrome to which vascular disease contributes.

The 3rd edition of the Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD), published in 2008, included comprehensive guidelines for managing VCI.<sup>3-6</sup> A focused update was provided in 2012.<sup>7</sup> The Heart and Stroke Foundation of Canada has issued recommendations for management of VCI, but with a focus on post-stroke impairment and dementia prevention.<sup>8</sup>

In 2019-2020 the 5th CCCDTD (CCCDTD5) was conducted to comprehensively review and update guidelines for cognitive disorders.<sup>9</sup> This article reviews the development and rationale for the subset of recommendations related to medical management of VCI.

## 2 | METHODS

The CCCDTD5 Steering Committee selected a Working Group on VCI including Canadian experts representing the disciplines of neurology, psychiatry, geriatric medicine, and pharmacology. The Working Group began by reviewing prior CCCDTD guidelines to identify the ones that were still supported by current evidence and the ones that required revision. New areas for recommendations were identified by expert knowledge. Working Group members then performed targeted literature searches (Appendix) to identify new evidence, leveraging the results of high-quality recent systematic reviews. Recommendations were drafted by Working Group members and then reviewed and voted on during a teleconference. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to describe the strength of recommendation and quality of evidence (Table 1).<sup>10</sup> Working Group members were required to declare com-

peting interests, and were not allowed to vote on recommendations related to products or services in which they had a direct financial interest. The recommendations were then posted to a password-protected site online, along with background documentation and literature search, for viewing and voting by a panel of >50 Canadian experts. The threshold for acceptance of recommendations was set at 80% endorsement. The perspectives of persons with lived experience was shared and incorporated by including a member of the Heart and Stroke Foundation of Canada as a voting scientific member of the Working Group, and by having representatives of the Alzheimer Society of Canada attend the in-person conference as non-voting members.

## 3 | GUIDELINES

In the 5th edition of CCCDTD, there are nine new or revised guidelines for VCI (Table 2). All of the proposed VCI recommendations were approved by vote. The supporting literature searches are provided in Appendix 1 and the evidence tables in Appendix 2.

### 3.1 | MRI is superior to CT for investigating VCI

Magnetic resonance imaging (MRI) is preferred to computed tomography (CT) in VCI in both research<sup>11,12</sup> and clinical practice given its higher sensitivity and specificity for detecting pathological changes relevant in VCI. MRI has improved sensitivity for detecting small brain infarcts.<sup>13,14</sup> Only MRI can detect microbleeds. MRI is also the modality of choice for describing markers of cerebral small vessel disease and amyloid angiopathy by consensus criteria,<sup>15</sup> although there is a paucity of studies specifically comparing the accuracy of both modalities for most of these markers. Improved sensitivity of MRI for cortical atrophy could help to assess for concomitant additional dementia pathologies.<sup>16,17</sup> However, it is recognized that access to MRI may be limited in certain regions including in rural and remote areas, and that some patients are unable to undergo MRI due to contraindications such as metallic implants or claustrophobia. When MRI is not available or is contraindicated, then imaging with CT is a reasonable alternative.

Although there is good agreement between CT and MRI for assessment of brain atrophy and burden of white matter hyperintensities,<sup>18</sup> MRI has slightly better inter-rater reliability for both<sup>19,20</sup> and detects smaller white matter lesions.<sup>18</sup>

Imaging technique and field strength affect sensitivity for detection of microbleeds in patients with dementia.<sup>21</sup> Recommendations have been made for standardization of MRI for small vessel ischemic disease.<sup>12</sup>

There is little research comparing CT and MRI in their ability to predict symptomatic VCI. A single small study with 12-month follow-up reported that although MRI was indeed more sensitive in detecting progression of periventricular white-matter lesions, CT was more specific in predicting subsequent symptomatic cerebrovascular disease. However, cerebrovascular disease was defined according to abnormal neurological examination findings and cognition was not assessed.<sup>22</sup>

### 3.2 | Use standardized diagnostic criteria

There are multiple criteria for the diagnosis of VCI and vascular dementia. Older criteria (Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN),<sup>23</sup> Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC),<sup>24</sup> older versions of the Diagnostic and Statistical Manual of Mental Disorders [DSM]) have several limitations, including the emphasis of dementia at the exclusion of milder impairments and the requirement for memory impairments, thereby limiting use of the criteria for those with purely executive deficits or visuospatial deficits more common in earlier or milder disease states. More recent criteria attempt to address these issues, and include the Vascular Behavioral and Cognitive Disorders (VASCOG) criteria,<sup>25</sup> the Fifth Revision of the DSM (DSM-5),<sup>26</sup> the consensus statement of the American Heart Association (AHA) and American Stroke Association (ASA)<sup>27</sup> and guidelines from the Vascular Impairment of Cognition Classification Consensus Study (VICCCS).<sup>28</sup> These criteria have overlap in both content and authors. There is limited literature comparing the reliability and validity of these different criteria. One study has compared performance across multiple diagnostic criteria in 165 persons with dementia.<sup>29</sup> Agreement was high between VASCOG, DSM-5, and VICCCS criteria, and they provided comparable predictions for 5-year incident dementia and 10-year mortality. The AHA statement criteria were not included. No studies have examined these criteria compared to a neuropathological gold standard.

### 3.3 | Assess and treat hypertension

Hypertension is a risk factor for dementia, accounting for 2% of the population attributable fraction.<sup>30</sup> The relationship is complex, with a stronger association of dementia with mid-life rather compared to late-life hypertension, and evidence that blood pressure begins to fall 5 years before diagnosis of dementia.<sup>31</sup> A systematic review of nine trials (seven of pharmacological and two of lifestyle or combined approaches) found that blood pressure intervention lowered risk

#### HIGHLIGHTS

- Standardized diagnostic criteria should be used to diagnose vascular cognitive impairment (VCI), aided by neuroimaging.
- Treating risk factors for stroke should also prevent dementia, with the best evidence for treating hypertension.
- Acetylsalicylic acid may be reasonable to use in patients with VCI and silent brain infarcts on imaging, but its use for patients with white matter lesions only is not recommended.
- Cholinesterase inhibitors may be used in selected patients, based on moderate quality evidence.

#### RESEARCH IN CONTEXT

- Systematic review: Using expert knowledge and review of previous guidelines published in the English language, the writing committee identified clinical questions for guideline development. For each question, a search strategy was created and the Medline database was searched on September 3, 2019, using PubMed.
- Interpretation: Guidelines are offered for diagnosis of vascular cognitive impairment (VCI), choice of neuroimaging modality, prevention of VCI by managing stroke risk factors, use of acetylsalicylic acid for patients with VCI and neuroimaging signs of previously unrecognized cerebrovascular disease, and use of cholinesterase inhibitors.
- Future directions: Research will be needed to determine how these guidelines influence clinical practice. The supporting evidence is of only moderate or low quality, so future research may change these guidelines.

of dementia by 7% (not statistically significant), with no evidence of greater risk reduction with greater blood pressure reduction.<sup>32</sup>

This systematic review did not include the results of the MIND sub-study of the Systolic Blood Pressure Intervention Trial (SPRINT), which randomly assigned patients (mean age 68) to intensive (<120 mmHg) or standard (<140 mmHg) blood pressure targets. To be included, patients had to be >50 years of age, hypertension with systolic blood pressure  $\geq$ 130 mmHg, and at least one risk factor for heart disease including the presence of clinical or subclinical cardiovascular disease (but not stroke), chronic kidney disease, a Framingham Risk Score for 10-year myocardial infarction risk  $\geq$ 15%, or age >75 years. Because of insufficient numbers of cognitive events, the cognitive follow-up was extended beyond the randomization period (median intervention period 3.34 years, median overall follow-up 5.11 years). Compared with the standard treatment arm, intensive blood pressure lowering

**TABLE 1** Evidence grading system

Strength of recommendation	1	Strong: benefits clearly outweigh undesirable effects
	2	Weak, or conditional: either lower quality evidence or desirable and undesirable effects are more closely balanced
Quality of evidence	A	High: "further research is unlikely to change confidence in the estimate of effect"
	B	Moderate: "further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate"
	C	Low: "further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate"

Legend: Strength and quality levels are based on the GRADE system.<sup>10</sup>

reduced the incidence of mild cognitive impairment (MCI) (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.69 to 0.95) and the combined end point of MCI or dementia (HR, 0.85; 95% CI, 0.74 to 0.97), with a similar effect on dementia alone (the prespecified substudy end point) but without statistical significance (HR 0.83, 95% CI, 0.67 to 1.04). In an MRI substudy, intensive blood pressure lowering compared to standard treatment reduced the progression of white matter hyperintensities (between-group difference in change,  $-0.54 \text{ cm}^3$  [95% CI,  $-0.87$  to  $-0.20$ ]).<sup>33</sup> Compared to prior trials,<sup>32</sup> the SPRINT MIND substudy<sup>34</sup> aimed for a lower target pressure and included older patients (mean age 68 vs 60 years).

It is important to note that patients with stroke, dementia, and diabetes were excluded and therefore it is uncertain whether the SPRINT MIND results can be generalized to patients with history of stroke or with neurodegenerative disorders. Patients being treated with intensive blood pressure lowering should be monitored for signs of cerebral hypoperfusion which could include presyncope, syncope, or falls. One of the concerns with the generalizability of the SPRINT findings is that office measurements are probably biased to be higher than SPRINT, which took the average of three measurements after 5 minutes of quiet rest using an automated device. One systematic review suggests that routine office blood pressure readings are on average 14.5 mmHg higher than automated office blood pressure readings of the kind used in SPRINT (contributing to the "white coat effect"), whereas automated blood pressure readings were no different than ambulatory blood pressure monitoring (the gold standard).<sup>35</sup> The consequence of this routine overestimation of blood pressure could be over-aggressive treatment and increased risk for complications from hypotension.

Hypertension Canada (<https://guidelines.hypertension.ca/>) offers guidelines for hypertension management.<sup>36</sup> The 2018 iteration strongly recommends starting antihypertensive therapy for patients with average diastolic blood pressure measurements of  $\geq 100$  mmHg or average systolic measurements of  $\geq 160$  mmHg in patients without clinical or subclinical cardiovascular disease or cardiovascular risk

**TABLE 2** CCCDTD5 recommendations for vascular cognitive impairment

Recommendation	Grade
Magnetic resonance imaging (MRI) is recommended over computed tomography (CT) for investigating vascular cognitive impairment	2C
Use of standardized criteria (one of: the Vascular Behavioral and Cognitive Disorders [VAS-COG] Society criteria, Diagnostic and Statistical Manual of Mental Disorders [DSM5], Vascular Impairment of Cognition Classification Consensus Study, or the American Heart Association consensus statement) are recommended for the diagnosis of vascular mild cognitive impairment and vascular dementia	1C
Because treatment of hypertension may reduce risk of dementia, clinicians should assess, diagnose, and treat hypertension according to guidelines from Hypertension Canada	1B
For patients with cognitive disorders in which a vascular contribution is known or suspected, antihypertensive therapy should be strongly considered for average diastolic blood pressure readings $\geq 90$ mmHg and for average systolic blood pressure readings $\geq 140$ mmHg.	1B
In middle-aged and older persons being treated for hypertension who have associated vascular risk factors a systolic BP treatment target of $< 120$ mmHg may be associated with a decreased risk of developing mild cognitive impairment (MCI) and should be considered when deciding on the intensity of their therapy	2C
All patients with cognitive symptoms or impairment should receive guideline-recommended treatments to prevent first-ever or recurrent stroke, as appropriate	1B
The use of aspirin is not recommended for patients with MCI or dementia who have brain imaging evidence of covert white matter lesions of presumed vascular origin without history of stroke or brain infarcts	2C
The effects of aspirin on cognitive decline in patients with MCI or dementia who have covert brain infarcts detected on neuroimaging without history of stroke has not been defined. The use of aspirin in this setting is reasonable, but the benefit is unclear	2C
Cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine may be considered for the treatment of vascular cognitive impairment in selected patients	2B

Abbreviations: CCCDTD, Canadian Consensus Conference on Diagnosis and Treatment of Dementia; BP, blood pressure; GRADE, Grading of Recommendations Assessment, Development, and Evaluation

factors. For patients with clinical or subclinical cardiovascular disease (including stroke) it recommends that antihypertensive therapy should be strongly considered for average DBP readings  $\geq 90$  mmHg (high-quality evidence) or for average SBP readings  $\geq 140$  mmHg (moderate-quality evidence for 140 to 160 mmHg; high quality evidence for  $> 160$  mmHg). Although not stated as such by Hypertension Canada, it would be reasonable to consider the presence of VCI as equivalent to clinical evidence of stroke or cardiovascular

disease. There are no high-quality data to indicate which classes of antihypertensive should be preferred for the purpose of reducing the risk of dementia. The Syst-Eur trial reported that a calcium-channel blocker, nitrendipine (with or without the addition of other classes as needed to achieve systolic blood pressure <150 mmHg), reduced the risk of dementia (7.7 cases to 3.8 cases per 1000 patient-years).<sup>37</sup> Based on observational studies and pathophysiological consideration, angiotensin receptor blockers might be preferred.<sup>38</sup>

### 3.4 | Follow guidelines to prevent first-ever or recurrent stroke

As stated in the Berlin Manifesto<sup>39</sup>: “Because stroke doubles the chances of developing dementia and 90% of strokes are preventable, mitigating stroke risk at the population level, and for those at increased individual risk, provides the most immediate and promising opportunity to reduce the rates of both stroke and dementia through the same international and national policies.” For patients with a prior history of symptomatic stroke, the Canadian Stroke Best Practices provided evidence-based recommendations for diagnostic workup and secondary prevention, along with clinical considerations and performance measures.<sup>40</sup> For patients without a prior history of symptomatic stroke, the American Stroke Association provides guidelines for primary prevention of stroke including lifestyle and behavioral modification.<sup>41</sup>

### 3.5 | Acetylsalicylic acid for patients with white matter lesions only

White matter lesions of presumed vascular origin, visible as hypodensities on CT or hyperintensities on MRI, are associated with a 2.45-fold increased risk of future symptomatic stroke and a 1.84-fold increased risk of future dementia according to population-based studies.<sup>42</sup> The presence of confluent white matter lesions is a supporting criterion for the presence of vascular cognitive impairment.<sup>25</sup> Although cerebral white matter lesions have an ischemic basis, the pathophysiology is complex, probably multifactorial, and may not be strongly related to thrombosis.<sup>43</sup> Other pathways to generate white matter lesions may include venous collagenosis, blood–brain barrier disruption, clasmotodendrosis, and inflammation. There is little evidence, including no large clinical trials, on whether treatment with acetylsalicylic acid (ASA), or other preventive strategies, reduces the risk of cognitive decline or stroke associated with white matter lesions.<sup>44</sup> ASA is therefore of uncertain benefit in these patients. In addition, secondary analysis of two clinical trials suggests that patients with extensive cerebral white matter lesions may be at increased risk of bleeding complications from anti-thrombotics. In the Stroke Prevention in Reversible Ischemia (SPIRIT) trial of patients with non-cardioembolic ischemic stroke, the patients with confluent white matter lesions who were randomly assigned to warfarin were at increased risk of intracranial hemorrhage.<sup>45</sup> In the Evaluation of Vascular Care in Alzheimer’s Disease study (EVA), patients with dementia and either confluent

white matter lesions or infarcts were randomized to ASA or placebo, and there was an excess risk of intracranial hemorrhage in the ASA group, although not statistically significant.<sup>46</sup> For these reasons we recommend against the use of ASA for confluent white matter lesions only. However, if there is an independent evidence-based indication for ASA (such as history of prior ischemic stroke or myocardial infarction) then white matter lesions should not be considered a contraindication to ASA treatment.

### 3.6 | Acetylsalicylic acid for patients with brain infarcts without a history of stroke

Covert brain infarcts are defined as those detected on neuroimaging, including in the setting of cognitive impairment, in the absence of a clinical history of symptomatic stroke. Vas-Cog criteria suggest that the presence of three or more brain infarcts on neuroimaging, or one or more infarcts in strategic locations, supports the diagnosis of vascular cognitive impairment.<sup>25</sup> Although aspirin is an effective therapy for preventing recurrent symptomatic ischemic stroke,<sup>47</sup> it is not known whether aspirin prevents new or recurrent covert infarcts.<sup>44</sup> In addition, it is not known whether aspirin prevents VCI in patients with covert infarcts.<sup>48</sup> There are no large clinical trials that have addressed these issues. Based on the effectiveness of aspirin for preventing symptomatic ischemic stroke, it can be hypothesized that it would also have some effectiveness for preventing new covert infarcts in persons at risk.

Studies in the general population have failed to find that aspirin prevents dementia. The Aspirin in Reducing Events in the Elderly (ASPREE) trial found no effect of aspirin on dementia incidence in persons in the general community without history of symptomatic stroke.<sup>49</sup> Although patients in ASPREE were not screened with MRI, population-based studies indicate that some of the participants would have had covert brain infarcts.

Potential harm from ASA also needs to be considered. The most common serious complication of ASA is bleeding. Pooled data from primary and secondary prevention trials found an excess absolute risk increase for major extracranial bleeding of 0.03% per year (0.07% per year without ASA compared with 0.10% per year with ASA,  $P < .0001$ ).<sup>47</sup> The risks of major extracranial and intracranial bleeding in patients with vascular cognitive impairment specifically have not been defined.

Contemporary randomized controlled trials in older persons without a history of stroke confirm the excess bleeding risks with ASA, and fail to consistently show that ASA prevents first-ever cardiovascular events.<sup>50</sup> Consequently, a recent guideline from the Heart and Stroke Foundation of Canada recommends against using ASA for primary prevention of first-ever stroke while finding that “the net benefit of ASA in individuals with asymptomatic atherosclerosis is uncertain.”<sup>50</sup>

Therefore, at this time there is insufficient evidence to determine whether ASA is effective at preventing cognitive decline in patients with VCI and brain infarcts. Clinical trials have not addressed the specific question of ASA or other anti-thrombotics for secondary pre-

vention after covert brain infarcts. It seems reasonable to investigate and treat individuals with covert brain infarcts and VCI as one would with symptomatic brain infarcts and VCI, including providing ASA.<sup>40</sup> However, in the absence of evidence for this patient group, clinical approaches will be conditional on physician preference, patient preference, and acceptable risk. The use of ASA should be reserved for patients who are likely to tolerate it and who do not have excessive risks of bleeding.

### 3.7 | Cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine

The 4th CCCDTD stated that cholinesterase inhibitors (and memantine as noted in the text) were treatment options for dementia due to AD with cerebrovascular disease but concluded there was insufficient evidence to make a recommendation for or against cholinesterase inhibitors in the treatment of vascular dementia (VaD).<sup>7</sup> Since the 4th CCCDTD, no new, high-quality primary research has been published on the utility of cholinesterase inhibitors or memantine for VCI, but a recent systematic review and network meta-analysis examined the available evidence and concluded that although there was evidence of modest efficacy in the cognitive domain (and global status for memantine), use of cholinesterase inhibitors was associated with more adverse events.<sup>51</sup> International guidelines published since 2012 support the use of these agents (in particular cholinesterase inhibitors) for VCI when AD is also present,<sup>52-54</sup> with two also stating they could be a consideration for VaD.<sup>27,55</sup> The 2019 *Canadian Stroke Best Practice Recommendations* concluded that cholinesterase inhibitors and memantine could be considered for individuals with either a vascular or mixed dementia following a stroke.<sup>8</sup> If prescribed, no contraindication to the use of the chosen drug must be present. The patient (or their agent) should be fully informed as to the likely benefit and potential risks, especially as cholinesterase inhibitors and memantine are not currently approved by Health Canada for the treatment of VCI. Consent to treatment should be documented. Follow-up of treated patients is necessary to ensure safety and determine the relative benefits and harms of continued use. Finally, it should be noted that reimbursement of these drugs through publicly funded drug benefit programs are generally tied to the dementia being due to AD, either solely or in combination with another brain pathology.

## 4 | CONCLUSIONS

Using standardized diagnostic criteria, neuroimaging with MRI instead of CT, where it is available, management of hypertension to conventional blood pressure targets, and risk reduction for stroke are strongly recommended. Intensive blood pressure lowering in middle-aged adults with vascular risk factors, using ASA in persons with VCI and covert brain infarcts but not if only white matter lesions are present,

and use of cholinesterase inhibitors are weakly or conditionally recommended. However, these recommendations are based on moderate- or low-quality evidence and not high-quality evidence from multiple randomized controlled trials.

Additional recommendations for screening and diagnosing cognitive impairment, primary prevention, supportive care, and management of other conditions, many of which are also relevant to comprehensive care for persons with VCI, are found in the main article summarizing all CCCDTD5 recommendations.<sup>56</sup>

Other organizations have also provided consensus recommendations for prevention and treatment of vascular contributions to cognitive impairment and dementia. Prior iterations of the CCCDTD in 2008<sup>3-6</sup> and 2014<sup>7</sup> provided recommendations for using the diagnostic criteria available at the time, neuroimaging with either CT or MRI, treating vascular risk factors with the best evidence for lowering blood pressure, and using cholinesterase inhibitors in AD with a cerebrovascular component, with insufficient evidence for or against use of ASA and cholinesterase inhibitors or memantine in patients with pure vascular dementia. The Heart and Stroke Foundation of Canada has issued guidelines for treatment of mood, cognition, and fatigue following stroke,<sup>8</sup> which includes recommendations to screen for cognitive impairment after stroke or transient ischemic attack, use neuroimaging as an adjunct to diagnosis (with MRI more sensitive than CT), management of vascular risk factors, and for rehabilitation. The National Institute for Health and Care Excellence in the United Kingdom (NICE) recommends NINDS-AIREN criteria to diagnose vascular dementia, using MRI in suspected cases, and use of cholinesterase inhibitors only in persons with vascular dementia suspected of also having AD.<sup>53</sup> For primary prevention, NICE recommends public health efforts to reduce smoking, increase physical activity, reduce alcohol consumption, adopt healthier diets, and achieve or maintain healthy weight, all of which are also stroke risk factors. Australian guidelines recommend that cholinesterase inhibitors could be considered for persons with vascular dementia, and generally avoiding use of antipsychotics.<sup>55</sup> A scientific statement from the AHA recommends MRI with T2\*-weighted sequences, genetic testing for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in patients with suggestive features, smoking cessation, moderating alcohol intake, treating hypertension, and, based on moderate strength of evidence, use of cholinesterase inhibitors for vascular dementia.<sup>27</sup> An American Academy of Neurology practice guideline for MCI contained no recommendations specific to VCI.<sup>57</sup>

The CCCDTD guidelines on VCI are in accordance with others in recommending use of standardized criteria, the superiority of MRI over CT, and addressing vascular risk factors. Other guidelines are split on the usefulness of cholinesterase inhibitors for vascular dementia. Some guidelines recommend them only for patients with concomitant AD, whereas others recommend that they could be considered for all patients; however, they are consistent in finding that the level of evidence is weak. Uniquely, in CCCDTD we addressed the controversial question of whether ASA is indicated for persons with VCI and signs of silent cerebrovascular disease. We recognize that there is insufficient evidence to make a strong recommendation. However, this topic was

prioritized based on our expert's experience that it was commonly on the minds of clinicians and a frequent question in referrals.

There are limitations to these recommendations. They are based on evidence of moderate or low quality, and not on large, randomized trials. More research is needed to validate diagnostic criteria by neuropathology, and to determine the effect of vascular risk reduction on incidence and progression of VCI. Newer, better treatments are also needed<sup>48,58</sup> because VCI remains common even though there are preventive strategies for many of its risk factors.

These recommendations should be useful for clinicians looking for evidence-based guidance on diagnosing, treating, and preventing VCI, a common cause of cognitive decline. Future research will be needed to learn how these guidelines are incorporated into clinical practice and their impact on costs, quality of care, and patient outcomes.

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## APPENDIX

## SEARCH STRATEGIES

Searches were conducted using the PubMed search engine on September 3, 2019

1. Magnetic resonance imaging (MRI) is recommended over computed tomography (CT) for investigating vascular cognitive impairment

("Cerebrovascular Disorders/Diagnostic Imaging"[mesh] OR "Dementia, Vascular/Diagnostic Imaging"[mesh] OR "Cerebral Hemorrhage/Diagnostic Imaging"[mesh] OR "Intracranial Hemorrhages/Diagnostic Imaging"[mesh] OR ("microbleeds"[tiab] OR "microbleeds"[nm] OR "microbleeds"[mh] OR "microbleeds"[tt] OR "microbleeds"[pmid]) OR "Cerebral Small Vessel Diseases/Diagnostic Imaging"[mesh]) AND (("Magnetic Resonance Imaging"[mesh] AND "Tomography, X-Ray Computed"[mesh]) OR "Neuroimaging/methods"[MAJR]) NOT ("case reports"[Publication Type] OR "Clinical Conference"[pt] OR "Case Reports"[pt]) NOT (("Animals"[Mesh] OR animal\*[tiab] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR dog[tiab] OR dogs[tiab]) NOT "Humans"[Mesh])

Limit to publication date 1980/01/01 or later

2. Use of standardized criteria (one of: the Vascular Behavioral and Cognitive Disorders [VAS-COG] Society criteria, Diagnostic and Statistical Manual of Mental Disorders [DSM5], Vascular Impairment of Cognition Classification Consensus Study, or the American Heart Association consensus statement) are recommended for the diagnosis of vascular mild cognitive impairment and vascular dementia (vascular dementia[MeSH Major Topic]) AND criteria[Title/Abstract] OR ("vascular behavioral") AND criteria[Title/Abstract] OR (dsm AND vascular[Title/Abstract] AND criteria[Title/Abstract]) OR (vsccs AND criteria[Title/Abstract]) OR ("Vascular Impairment of Cognition Classification Consensus Study") OR ("American Heart Association" AND vascular[Title/Abstract] AND criteria[Title/Abstract])

Limit to publication date 2011/01/01 or later

3. Because treatment of hypertension may reduce risk of dementia, clinicians should assess, diagnose, and treat hypertension according to guidelines from Hypertension Canada (((("Dementia"[Mesh] OR dement\*[tiab] OR alzheimer\*[tiab]))) AND (((("Antihypertensive Agents"[Mesh] OR "Antihypertensive Agents" [Pharmacological Action] OR "Hypertension/drug therapy"[Mesh] OR "Hypertension/prevention and control"[Mesh] OR "Hypertension/therapeutic use"[Mesh] OR "Hypertension/therapy"[Mesh] OR "Hypertension/diet therapy"[Mesh] OR "Hypertension/drug effects"[Mesh] OR "Nutrition Therapy"[Mesh] OR "Diet, Food, and Nutrition"[Mesh] OR "Diet"[Mesh] OR "Alcohol Drinking"[Mesh] OR "Exercise"[Mesh] OR "Exercise Therapy"[Mesh] OR "Exercise Movement Techniques"[Mesh] OR "Sports"[Mesh] OR "Physical Fitness"[Mesh] OR "Body Weight"[MeSH] OR "Life Style"[Mesh] OR "Tobacco Use"[Mesh] OR "Tobacco Use Cessation"[Mesh] OR "Smoking Cessation"[MeSH] OR exercis\*[tiab] OR aerobic\*[tiab] OR physical activit\*[tiab] OR sport\*[tiab] OR physical fitness\*[tiab] OR diet\*[tiab] OR nutrition\*[tiab] OR nutrient\*[tiab] OR food[tiab] OR feeding[tiab] OR weigh\*[tiab] OR overweigh\*[tiab] OR obes\*[tiab] OR smok\*[tiab] OR life style\*[tiab] OR lifestyle\*[tiab]))) OR (((pharmacolog\*[tiab] OR nonpharmacolog\*[tiab] OR non-pharmacolog\*[tiab]) AND (intervention\*[tiab] OR treatment\*[tiab] OR therap\*[tiab] OR management[tiab] OR strateg\*[tiab]))) OR (((("Sodium Potassium Chloride Symporter Inhibitors"[Mesh] OR "Sodium Potassium Chloride Symporter Inhibitors" [Pharmacological Action] OR "Bumetanide"[Mesh] OR "Ethacrynic Acid"[Mesh] OR "Furosemide"[Mesh] OR "torsemide" [Supplementary Concept] OR "Sodium Chloride Symporter Inhibitors"[Mesh] OR "Sodium Chloride Symporter Inhibitors" [Pharmacological Action] OR "Hydrochlorothiazide"[Mesh] OR "Chlorothiazide"[Mesh] OR "Bendroflumethiazide"[Mesh] OR "Xipamide"[Mesh] OR "Indapamide"[Mesh] OR "Chlorthalidone"[Mesh] OR "Metolazone"[Mesh] OR "Diuretics, Potassium Sparing"[Mesh] OR "Amiloride"[Mesh] OR "Triamterene"[Mesh] OR "Dihydropyridines"[Mesh] OR "Amlodipine"[Mesh] OR "cilnidipine" [Supplementary Concept] OR "Felodipine"[Mesh] OR "Isradipine"[Mesh] OR "lercanidipine" [Supplementary Concept] OR "Nicardipine"[Mesh] OR "Nifedipine"[Mesh] OR "Nimodipine"[Mesh] OR "Nitrendipine"[Mesh] OR "mepirodipine" [Supplementary Concept] OR "lacidipine" [Supplementary Concept] OR "aranidipine" [Supplementary Concept] OR "azelnidipine" [Supplementary Concept] OR "benidipine hydrochloride" [Supplementary Concept] OR "clevudipine" [Supplementary Concept] OR "darodipine" [Supplementary Concept] OR "efonidipine" [Supplementary Concept] OR "manidipine" [Supplementary Concept] OR "niguldipine" [Supplementary Concept] OR "nilvadipine" [Supplementary Concept] OR "Nisoldipine"[Mesh] OR "Nitrendipine"[Mesh] OR "oxodipine" [Supplementary Concept] OR "pranidipine" [Supplementary Concept] OR "Diltiazem"[Mesh] OR "Verapamil"[Mesh] OR "Angiotensin-Converting Enzyme Inhibitors"[Mesh] OR "Captopril"[Mesh] OR "Enalapril"[Mesh] OR "Fosinopril"[Mesh] OR "Lisinopril"[Mesh] OR "Perindopril"[Mesh] OR "quinapril" [Supplementary Concept] OR "Ramipril"[Mesh] OR "trandolapril" [Supplementary Concept] OR "benazepril" [Supplementary Concept] OR "zofenopril" [Supplementary Concept] OR "imidapril" [Supplementary Concept] OR "Cilazapril"[Mesh] OR "Angiotensin Receptor Antagonists"[Mesh] OR "candesartan" [Supplementary Concept] OR "eprosartan" [Supplementary Concept] OR "irbesartan" [Supplementary Concept] OR "Losartan"[Mesh] OR "olmesartan" [Supplementary Concept] OR "telmisartan" [Supplementary Concept] OR "Valsartan"[Mesh] OR "azilsartan" [Supplementary Concept] OR "fimasartan" [Supplementary Concept] OR "Atenolol"[Mesh] OR "Metoprolol"[Mesh] OR "Nadolol"[Mesh] OR "Nebivolol"[Mesh] OR "Oxprenolol"[Mesh] OR "Pindolol"[Mesh] OR "Propranolol"[Mesh] OR "Timolol"[Mesh] OR "Bisoprolol"[Mesh] OR "Acebutolol"[Mesh] OR "Celiprolol"[Mesh] OR "esmolol" [Supplementary Concept] OR "Sotalol"[Mesh] OR "Doxazosin"[Mesh] OR "Phentolamine"[Mesh] OR "Indoramin"[Mesh] OR "Phenoxybenzamine"[Mesh] OR "Prazosin"[Mesh] OR "Terazosin" [Supplementary Concept] OR "Ketanserin"[Mesh] OR "urapidil" [Supplementary Concept] OR "Phentolamine"[Mesh] OR "carvedilol" [Supplementary Concept] OR "Labetalol"[Mesh] OR "Hydralazine"[Mesh] OR "Minoxidil"[Mesh] OR "aliskiren" [Supplementary Concept] OR "Mineralocorticoid Receptor Antagonists"[Mesh] OR "eplerenone" [Supplementary Concept] OR "Spironolactone"[Mesh] OR "Clonidine"[Mesh] OR "Guanabenz"[Mesh] OR "Guanfacine"[Mesh] OR "Methyldopa"[Mesh] OR "moxonidine"

[Supplementary Concept] OR "Guanethidine"[Mesh] OR "Mecamylamine"[Mesh] OR "Magnesium Sulfate"[Mesh] OR antihypertensive[tiab] OR anti-hypertensive[tiab] OR beta-blocker\*[tiab] OR betablocker\*[tiab] OR angiotensin\*[tiab] OR loop diuretic\*[tiab] OR bumetanide[tiab] OR ethacrynic acid[tiab] OR furosemide[tiab] OR torsemide[tiab] OR thiazide diuretic\*[tiab] OR epitizide[tiab] OR hydrochlorothiazide[tiab] OR chlorothiazide[tiab] OR bendroflumethiazide[tiab] OR xipamide[tiab] OR indapamide[tiab] OR chlorthalidone[tiab] OR metolazone[tiab] OR amiloride[tiab] OR triamterene[tiab] OR amlodipine[tiab] OR cilnidipine[tiab] OR felodipine[tiab] OR isradipine[tiab] OR lercanidipine[tiab] OR levamlodipine[tiab] OR nicardipine[tiab] OR nifedipine[tiab] OR nimodipine[tiab] OR nitrendipine[tiab] OR barnidipine[tiab] OR lacidipine[tiab] OR arandipine[tiab] OR azelnidipine[tiab] OR benidipine[tiab] OR clevidipine[tiab] OR darodipine[tiab] OR efonidipine[tiab] OR manidipine[tiab] OR niguldipine[tiab] OR nilvadipine[tiab] OR nisoldipine[tiab] OR nitrendipine[tiab] OR oxodipine[tiab] OR pranidipine[tiab] OR diltiazem[tiab] OR verapamil[tiab] OR ACE-inhibitor\*[tiab] OR captopril[tiab] OR enalapril[tiab] OR fosinopril[tiab] OR lisinopril[tiab] OR perindopril[tiab] OR quinapril[tiab] OR ramipril[tiab] ORtrandolapril[tiab] OR benazepril[tiab] OR zofenopril[tiab] OR imidapril[tiab] OR cilazapril[tiab] OR candesartan[tiab] OR eprosartan[tiab] OR irbesartan[tiab] OR losartan[tiab] OR olmesartan[tiab] OR telmisartan[tiab] OR valsartan[tiab] OR azilsartan[tiab] OR fimasartan[tiab] OR atenolol[tiab] OR metoprolol[tiab] OR nadolol[tiab] OR nebivolol[tiab] OR oxprenolol[tiab] OR pindolol[tiab] OR propranolol[tiab] OR timolol[tiab] OR bisoprolol[tiab] OR acebutolol[tiab] OR celiprolol[tiab] OR esmolol[tiab] OR sotalol[tiab] OR doxazosin[tiab] OR phentolamine[tiab] OR indoramin[tiab] OR phenoxybenzamine[tiab] OR prazosin[tiab] OR terazosin[tiab] OR tolazolin[tiab] OR ketanserin[tiab] OR urapidil[tiab] OR fentolamin[tiab] OR carvedilol[tiab] OR labetalol[tiab] OR hydralazine[tiab] OR minoxidil[tiab] OR aliskiren[tiab] OR eplerenone[tiab] OR spironolactone[tiab] OR clonidine[tiab] OR guanabenz[tiab] OR guanfacine[tiab] OR methyldopa[tiab] OR moxonidine[tiab] OR guanethidine[tiab] OR mecamylamine[tiab] OR magnesium sulfate[tiab] AND ("Blood Pressure"[Mesh] OR "Blood Pressure Determination"[Mesh] OR "Blood Flow Velocity"[Mesh] OR "Hypertension"[Mesh] OR "Cardiovascular Diseases"[Mesh] OR "Cardiovascular Physiological Processes"[Mesh] OR antihypertens\*[tiab] OR antihypertens\*[tiab] OR blood pressur\*[tiab] OR systolic[tiab] OR diastolic[tiab] OR blood flow[tiab] OR (blood[tiab] AND lower\*[tiab]) OR hypertens\*[tiab] OR vascular[tiab] OR cardiovascular[tiab])) AND (("Randomized Controlled Trial" [Publication Type] OR "Random Allocation"[Mesh] OR "Double-Blind Method"[Mesh] OR "Single-Blind Method"[Mesh] OR "Placebos"[Mesh] OR "Meta-Analysis" [Publication Type] OR "Clinical Trials as Topic"[MeSH Terms] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Controlled Clinical Trial" [Publication Type] OR random\*[tiab] OR trial\*[tiab] OR RCT[tiab] OR RCTs[tiab] OR systematic review[tiab] OR meta-anal\*[tiab] OR metaanal\*[tiab])) NOT (("Animals"[Mesh] OR animal\*[tiab] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR dog[tiab] OR dogs[tiab]) NOT "Humans"[Mesh])

4. For patients with cognitive disorders in which a vascular contribution is known or suspected, antihypertensive therapy should be strongly considered for average diastolic blood pressure readings  $\geq 90$  mmHg and for average systolic blood pressure readings  $\geq 140$  mmHg. 1B

((("Dementia"[Mesh] OR dement\*[tiab] OR alzheimer\*[tiab])) AND (((("Antihypertensive

Agents"[Mesh] OR "Antihypertensive Agents" [Pharmacological Action] OR "Hypertension/drug therapy"[Mesh] OR "Hypertension/prevention and control"[Mesh] OR "Hypertension/therapeutic use"[Mesh] OR "Hypertension/therapy"[Mesh] OR "Hypertension/diet therapy"[Mesh] OR "Hypertension/drug effects"[Mesh] OR "Nutrition Therapy"[Mesh] OR "Diet, Food, and Nutrition"[Mesh] OR "Diet"[Mesh] OR "Alcohol Drinking"[Mesh] OR "Exercise"[Mesh] OR "Exercise Therapy"[Mesh] OR "Exercise Movement Techniques"[Mesh] OR "Sports"[Mesh] OR "Physical Fitness"[Mesh] OR "Body Weight"[MeSH] OR "Life Style"[Mesh] OR "Tobacco Use"[Mesh] OR "Tobacco Use Cessation"[Mesh] OR "Smoking Cessation"[MeSH] OR exercis\*[tiab] OR aerobic\*[tiab] OR physical activit\*[tiab] OR sport\*[tiab] OR physical fitness\*[tiab] OR diet\*[tiab] OR nutrition\*[tiab] OR nutrient\*[tiab] OR food[tiab] OR feeding[tiab] OR weigh\*[tiab] OR overweight[tiab] OR obes\*[tiab] OR smok\*[tiab] OR life style\*[tiab] OR lifestyle\*[tiab])) OR ((pharmacolog\*[tiab] OR nonpharmacolog\*[tiab] OR non-pharmacolog\*[tiab]) AND (intervention\*[tiab] OR treatment\*[tiab] OR therap\*[tiab] OR management[tiab] OR strateg\*[tiab])) OR ((("Sodium Potassium Chloride Symporter Inhibitors"[Mesh] OR "Sodium Potassium Chloride Symporter Inhibitors" [Pharmacological Action] OR "Bumetanide"[Mesh] OR "Ethacrynic Acid"[Mesh] OR "Furosemide"[Mesh] OR "torsemide" [Supplementary Concept] OR "Sodium Chloride Symporter Inhibitors"[Mesh] OR "Sodium Chloride Symporter Inhibitors" [Pharmacological Action] OR "Hydrochlorothiazide"[Mesh] OR "Chlorothiazide"[Mesh] OR "Bendroflumethiazide"[Mesh] OR "Xipamide"[Mesh] OR "Indapamide"[Mesh] OR "Chlorthalidone"[Mesh] OR "Metolazone"[Mesh] OR "Diuretics, Potassium Sparing"[Mesh] OR "Amiloride"[Mesh] OR "Triamterene"[Mesh] OR "Dihydropyridines"[Mesh] OR "Amlodipine"[Mesh] OR "cilnidipine" [Supplementary Concept] OR "Felodipine"[Mesh] OR "Isradipine"[Mesh] OR "lercanidipine" [Supplementary Concept] OR "Nicardipine"[Mesh] OR "Nifedipine"[Mesh] OR "Nimodipine"[Mesh] OR "Nitrendipine"[Mesh] OR "mepirodipine" [Supplementary Concept] OR "lacidipine" [Supplementary Concept] OR "arandipine" [Supplementary Concept] OR "azelnidipine" [Supplementary Concept] OR "benidipine hydrochloride" [Supplementary Concept] OR "clevidipine" [Supplementary Concept] OR "darodipine" [Supplementary Concept] OR "efonidipine" [Supplementary Concept] OR "manidipine" [Supplementary Concept] OR "niguldipine" [Supplementary Concept] OR "nilvadipine" [Supplementary Concept] OR "Nisoldipine"[Mesh] OR "Nitrendipine"[Mesh] OR "oxodipine" [Supplementary Concept] OR "pranidipine" [Supplementary Concept] OR "Diltiazem"[Mesh] OR "Verapamil"[Mesh] OR "Angiotensin-Converting Enzyme Inhibitors"[Mesh] OR "Captopril"[Mesh] OR

"Enalapril"[Mesh] OR "Fosinopril"[Mesh] OR "Lisinopril"[Mesh] OR "Perindopril"[Mesh] OR "quinapril" [Supplementary Concept] OR "Ramipril"[Mesh] OR "trandolapril" [Supplementary Concept] OR "benazepril" [Supplementary Concept] OR "zofenopril" [Supplementary Concept] OR "imidapril" [Supplementary Concept] OR "Cilazapril"[Mesh] OR "Angiotensin Receptor Antagonists"[Mesh] OR "candesartan" [Supplementary Concept] OR "eprosartan" [Supplementary Concept] OR "irbesartan" [Supplementary Concept] OR "Losartan"[Mesh] OR "olmesartan" [Supplementary Concept] OR "telmisartan" [Supplementary Concept] OR "Valsartan"[Mesh] OR "azilsartan" [Supplementary Concept] OR "fimasartan" [Supplementary Concept] OR "Atenolol"[Mesh] OR "Metoprolol"[Mesh] OR "Nadolol"[Mesh] OR "Nebivolol"[Mesh] OR "Oxprenolol"[Mesh] OR "Pindolol"[Mesh] OR "Propranolol"[Mesh] OR "Timolol"[Mesh] OR "Bisoprolol"[Mesh] OR "Acebutolol"[Mesh] OR "Celiprolol"[Mesh] OR "esmolol" [Supplementary Concept] OR "Sotalol"[Mesh] OR "Doxazosin"[Mesh] OR "Phentolamine"[Mesh] OR "Indoramin"[Mesh] OR "Phenoxybenzamine"[Mesh] OR "Prazosin"[Mesh] OR "Terazosin" [Supplementary Concept] OR "Ketanserin"[Mesh] OR "urapidil" [Supplementary Concept] OR "Phentolamine"[Mesh] OR "carvedilol" [Supplementary Concept] OR "Labetalol"[Mesh] OR "Hydralazine"[Mesh] OR "Minoxidil"[Mesh] OR "aliskiren" [Supplementary Concept] OR "Mineralocorticoid Receptor

Antagonists"[Mesh] OR "eplerenone" [Supplementary Concept] OR "Spironolactone"[Mesh]

OR "Clonidine"[Mesh] OR "Guanabenz"[Mesh] OR "Guanfacine"[Mesh] OR "Methyldopa"[Mesh] OR "moxonidine" [Supplementary Concept] OR "Guanethidine"[Mesh] OR "Mecamylamine"[Mesh] OR "Magnesium Sulfate"[Mesh] OR antihypertensive[tiab] OR anti-hypertensive[tiab] OR beta-blocker\*[tiab] OR betablocker\*[tiab] OR angiotensin\*[tiab] OR loop diuretic\*[tiab] OR bumetanide[tiab] OR ethacrynic acid[tiab] OR furosemide[tiab] OR torsemide[tiab] OR thiazide diuretic\*[tiab] OR epitizide[tiab] OR hydrochlorothiazide[tiab] OR chlorothiazide[tiab] OR bendroflumethiazide[tiab] OR xipamide[tiab] OR indapamide[tiab] OR chlorthalidone[tiab] OR metolazone[tiab] OR amiloride[tiab] OR triamterene[tiab] OR amlodipine[tiab] OR cilnidipine[tiab] OR felodipine[tiab] OR isradipine[tiab] OR lercanidipine[tiab] OR levamlodipine[tiab] OR nicardipine[tiab] OR nifedipine[tiab] OR nimodipine[tiab] OR nitrendipine[tiab] OR barnidipine[tiab] OR lacidipine[tiab] OR aranidipine[tiab] OR azelnidipine[tiab] OR benidipine[tiab] OR clevidipine[tiab] OR darodipine[tiab] OR efonidipine[tiab] OR manidipine[tiab] OR niguldipine[tiab] OR nilvadipine[tiab] OR nisoldipine[tiab] OR nitrendipine[tiab] OR oxodipine[tiab] OR pranidipine[tiab] OR diltiazem[tiab] OR verapamil[tiab] OR ACE-inhibitor\*[tiab] OR captopril[tiab] OR enalapril[tiab] OR fosinopril[tiab] OR lisinopril[tiab] OR perindopril[tiab] OR quinapril[tiab] OR ramipril[tiab] ORtrandolapril[tiab] OR benazepril[tiab] OR zofenopril[tiab] OR imidapril[tiab] OR cilazapril[tiab] OR candesartan[tiab] OR eprosartan[tiab] OR irbesartan[tiab] OR losartan[tiab] OR olmesartan[tiab] OR telmisartan[tiab] OR valsartan[tiab] OR azilsartan[tiab] OR fimasartan[tiab] OR atenolol[tiab] OR metoprolol[tiab] OR nadolol[tiab] OR nebivolol[tiab] OR oxprenolol[tiab] OR pindolol[tiab] OR propranolol[tiab] OR timolol[tiab] OR bisoprolol[tiab] OR acebutolol[tiab] OR celiprolol[tiab] OR esmolol[tiab] OR sotalol[tiab] OR doxazosin[tiab] OR phentolamine[tiab] OR indoramin[tiab] OR phenoxybenzamine[tiab] OR prazosin[tiab] OR terazosin[tiab] OR tolazolin[tiab] OR ketanserine[tiab] OR urapidil[tiab] OR fentolamin[tiab] OR carvedilol[tiab] OR labetalol[tiab] OR hydralazine[tiab] OR

minoxidil[tiab] OR aliskiren[tiab] OR eplerenone[tiab] OR spironolactone[tiab] OR clonidine[tiab] OR guanabenz[tiab] OR guanfacine[tiab] OR methyldopa[tiab] OR moxonidine[tiab] OR guanethidine[tiab] OR mecamylamine[tiab] OR magnesium sulfate[tiab])))) AND ((("Blood Pressure"[Mesh] OR "Blood Pressure Determination"[Mesh] OR "Blood Flow Velocity"[Mesh] OR "Hypertension"[Mesh] OR "Cardiovascular Diseases"[Mesh] OR "Cardiovascular Physiological Processes"[Mesh] OR antihypertens\*[tiab] OR antihypertens\*[tiab] OR blood pressur\*[tiab] OR systolic[tiab] OR diastolic[tiab] OR blood flow[tiab] OR (blood[tiab] AND lower\*[tiab]) OR hypertens\*[tiab] OR vascular[tiab] OR cardiovascular[tiab])))) AND (((("Randomized Controlled Trial" [Publication Type] OR "Random Allocation"[Mesh] OR "Double-Blind Method"[Mesh] OR "Single-Blind Method"[Mesh] OR "Placebos"[Mesh] OR "Meta-Analysis" [Publication Type] OR "Clinical Trials as Topic"[MeSH Terms] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Controlled Clinical Trial" [Publication Type] OR random\*[tiab] OR trial\*[tiab] OR RCT[tiab] OR RCTs[tiab] OR

systematic review[tiab] OR meta-anal\*[tiab] OR metaanal\*[tiab])))) NOT ((("Animals"[Mesh] OR

animal\*[tiab] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR dog[tiab] OR dogs[tiab]) NOT "Humans"[Mesh])

5. In middle-aged and older persons being treated for hypertension who have associated vascular risk factors a systolic BP treatment target of < 120 mmHg may be associated with a decreased risk of developing mild cognitive impairment and should be considered when deciding on the intensity of their therapy (((("Dementia"[Mesh] OR dement\*[tiab] OR alzheimer\*[tiab])))) AND ((((((("Antihypertensive

Agents"[Mesh] OR "Antihypertensive Agents" [Pharmacological Action] OR "Hypertension/drug therapy"[Mesh] OR "Hypertension/prevention and control"[Mesh] OR "Hypertension/therapeutic use"[Mesh] OR "Hypertension/therapy"[Mesh] OR "Hypertension/diet therapy"[Mesh] OR "Hypertension/drug effects"[Mesh] OR "Nutrition Therapy"[Mesh] OR "Diet, Food, and Nutrition"[Mesh] OR "Diet"[Mesh] OR "Alcohol Drinking"[Mesh] OR "Exercise"[Mesh] OR "Exercise Therapy"[Mesh] OR "Exercise Movement Techniques"[Mesh] OR "Sports"[Mesh] OR "Physical Fitness"[Mesh] OR "Body Weight"[MeSH] OR "Life Style"[Mesh] OR "Tobacco Use"[Mesh] OR "Tobacco Use Cessation"[Mesh] OR "Smoking Cessation"[MeSH] OR exercis\*[tiab] OR aerobic\*[tiab] OR physical activit\*[tiab] OR sport\*[tiab] OR physical fitness\*[tiab] OR diet\*[tiab] OR

nutrition\*[tiab] OR nutrient\*[tiab] OR food[tiab] OR feeding[tiab] OR weigh\*[tiab] OR overweigh\*[tiab] OR obes\*[tiab] OR smok\*[tiab] OR life style\*[tiab] OR lifestyle\*[tiab])))) OR (((pharmacolog\*[tiab] OR nonpharmacolog\*[tiab] OR non-pharmacolog\*[tiab]) AND (intervention\*[tiab] OR treatment\*[tiab] OR therap\*[tiab] OR management[tiab] OR strateg\*[tiab])))) OR ((("Sodium Potassium Chloride Symporter Inhibitors"[Mesh] OR "Sodium Potassium Chloride Symporter Inhibitors" [Pharmacological Action] OR "Bumetanide"[Mesh] OR "Ethacrynic Acid"[Mesh] OR "Furosemide"[Mesh] OR "torsemide" [Supplementary Concept] OR "Sodium Chloride Symporter Inhibitors"[Mesh] OR "Sodium Chloride Symporter Inhibitors" [Pharmacological Action] OR "Hydrochlorothiazide"[Mesh] OR "Chlorothiazide"[Mesh] OR "Bendroflumethiazide"[Mesh] OR "Xipamide"[Mesh] OR "Indapamide"[Mesh] OR "Chlorthalidone"[Mesh] OR "Metolazone"[Mesh] OR "Diuretics, Potassium Sparing"[Mesh] OR "Amiloride"[Mesh] OR "Triamterene"[Mesh] OR "Dihydropyridines"[Mesh] OR "Amlodipine"[Mesh] OR "cilnidipine" [Supplementary Concept] OR "Felodipine"[Mesh] OR "Isradipine"[Mesh] OR "lercanidipine" [Supplementary Concept] OR "Nicardipine"[Mesh] OR "Nifedipine"[Mesh] OR "Nimodipine"[Mesh] OR "Nitrendipine"[Mesh] OR "mepirodipine" [Supplementary Concept] OR "lacidipine" [Supplementary Concept] OR "aranidipine" [Supplementary Concept] OR "azelnidipine" [Supplementary Concept] OR "benidipine hydrochloride" [Supplementary Concept] OR "clevidipine" [Supplementary Concept] OR "darodipine" [Supplementary Concept] OR "efonidipine" [Supplementary Concept] OR "manidipine" [Supplementary Concept] OR "niguldipine" [Supplementary Concept] OR "nilvadipine" [Supplementary Concept] OR "Nisoldipine"[Mesh] OR "Nitrendipine"[Mesh] OR "oxodipine" [Supplementary Concept] OR "pranidipine" [Supplementary Concept] OR "Diltiazem"[Mesh] OR "Verapamil"[Mesh] OR "Angiotensin-Converting Enzyme Inhibitors"[Mesh] OR "Captopril"[Mesh] OR

"Enalapril"[Mesh] OR "Fosinopril"[Mesh] OR "Lisinopril"[Mesh] OR "Perindopril"[Mesh] OR "quinapril" [Supplementary Concept] OR "Ramipril"[Mesh] OR "trandolapril" [Supplementary Concept] OR "benazepril" [Supplementary Concept] OR "zofenopril" [Supplementary Concept] OR "imidapril" [Supplementary Concept] OR "Cilazapril"[Mesh] OR "Angiotensin Receptor Antagonists"[Mesh] OR "candesartan" [Supplementary Concept] OR "eprosartan" [Supplementary Concept] OR "irbesartan" [Supplementary Concept] OR "Losartan"[Mesh] OR "olmesartan" [Supplementary Concept] OR "telmisartan" [Supplementary Concept] OR "Valsartan"[Mesh] OR "azilsartan" [Supplementary Concept] OR "fimasartan" [Supplementary Concept] OR "Atenolol"[Mesh] OR "Metoprolol"[Mesh] OR "Nadolol"[Mesh] OR "Nebivolol"[Mesh] OR "Oxprenolol"[Mesh] OR "Pindolol"[Mesh] OR "Propranolol"[Mesh] OR "Timolol"[Mesh] OR "Bisoprolol"[Mesh] OR "Acebutolol"[Mesh] OR "Celiprolol"[Mesh] OR "esmolol" [Supplementary Concept] OR "Sotalol"[Mesh] OR "Doxazosin"[Mesh] OR "Phentolamine"[Mesh] OR "Indoramin"[Mesh] OR "Phenoxybenzamine"[Mesh] OR "Prazosin"[Mesh] OR "Terazosin" [Supplementary Concept] OR "Ketanserin"[Mesh] OR "urapidil" [Supplementary Concept] OR "Phentolamine"[Mesh] OR "carvedilol" [Supplementary Concept] OR "Labetalol"[Mesh] OR "Hydralazine"[Mesh] OR "Minoxidil"[Mesh] OR "aliskiren" [Supplementary Concept] OR "Mineralocorticoid Receptor

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6. All patients with cognitive symptoms or impairment should receive guideline-recommended treatments to prevent first-ever or recurrent stroke, as appropriate

Not applicable.

7. The use of aspirin is not recommended for patients with MCI or dementia who have brain imaging evidence of covert white matter lesions of presumed vascular origin without history of stroke or brain infarcts

("silent" OR "covert" OR "vascular") AND (brain OR cerebra\* OR cerebro\*) AND (MRI

OR computed tomography) OR (((white matter) AND (hyperintens\* OR

lesion\* OR disease\* or change\*)) OR (leukoaraiosis)) AND (MRI

OR computed tomography) NOT (multiple sclerosis)) AND (clinical trial OR aspirin OR acetylsalicylic) AND Random\*

Limit to 1980-01-01 or later

8. The effects of aspirin on cognitive decline in patients with MCI or dementia who have covert brain infarcts detected on neuroimaging without history of stroke has not been defined. The use of aspirin in this setting is reasonable, but the benefit is unclear

((“silent” OR “covert” OR “vascular”) AND (brain OR cerebra\* OR cerebro\*) AND (MRI

OR computed tomography) OR (((white matter) AND (hyperintens\* OR

lesion\* OR disease\* or change\*)) OR (leukoaraiosis)) AND (MRI

OR computed tomography) NOT (multiple sclerosis)) AND (clinical trial OR aspirin OR acetylsalicylic) AND Random\*

Limit to 1980-01-01 or later

9. Cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine may be considered for the treatment of vascular cognitive impairment in selected patients

((“vascular dementia”) OR (“vascular cognitive impairment”)) AND ((donepezil) OR (rivastigmine) OR (galantamine) OR (memantine))