

# The inclusion of cognition in vascular risk factor clinical practice guidelines

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**Background:** People with vascular risk factors are at increased risk for cognitive impairment as well as vascular disease. The objective of this study was to evaluate whether vascular risk factor clinical practice guidelines consider cognition as an outcome or in connection with treatment compliance.

**Methods:** Articles from PubMed, EMBASE, and the Cochrane Library were assessed by at least two reviewers and were included if: (1) Either hypertension, high cholesterol, diabetes, or atrial fibrillation was targeted; (2) The guideline was directed at physicians; (3) Adult patients (aged 19 years or older) were targeted; and (4) The guideline was published in English. Of 91 guidelines, most were excluded because they were duplicates, older versions, or focused on single outcomes.

**Results:** Of the 20 clinical practice guidelines that met inclusion criteria, five mentioned cognition. Of these five, four described potential treatment benefits but only two mentioned that cognition may affect compliance. No guidelines adequately described how to screen for cognitive impairment.

**Conclusion:** Despite evidence that links cognitive impairment to vascular risk factors, only a minority of clinical practice guidelines for the treatment of vascular risk factors consider cognition as either an adverse outcome or as a factor to consider in treatment.

**Keywords:** clinical practice guidelines, evidence-based medicine, vascular risk, cognition, target organ damage

As people age, they are more susceptible to dementia and as populations age, the dementias generally become more common.<sup>1,2</sup> These particularly burdensome illnesses have important public health consequences.<sup>2,3</sup> As a result, new effort has focused on whether dementia is preventable, and in particular whether vascular risk factor control might yield this additional benefit.<sup>4,5</sup>

The idea that vascular risk factor control might prevent dementia is not new. Our understanding of the relationship between vascular risk factors and dementia evolved from the ancient view that Alzheimer's disease arose from 'hardening of the arteries.' That idea gave way in the 1970s to a hard-won conceptual distinction between neurodegenerative dementias on the one hand and dementias from vascular causes on the other.<sup>6</sup> Later, we came again to understand that the two are related,<sup>7</sup> as it was appreciated that vascular risk factors are not only important for vascular dementias but are also risk factors for Alzheimer's disease.<sup>8</sup> Neuropathological studies indicate that cerebrovascular pathology and neurodegenerative pathology uncommonly appear

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in isolation in elderly people,<sup>9,10</sup> and that they can have synergistic effect on cognitive impairment,<sup>11,12</sup> although this need not always be the case.<sup>13,14</sup> In addition, dementia and atherosclerosis share both risk factors (hypertension, elevated cholesterol, diabetes) and pathologic features (inflammatory markers, protein mis-folding).<sup>15</sup>

Given the importance now accorded to vascular risk factors in dementia, there is new interest in whether the treatment of vascular risk factors might reduce or prevent the incidence of dementia. Of note, treatment of hypertension, both in midlife and in old age, appears to reduce the risk of cognitive impairment in later life.<sup>16–19</sup> Statin therapy is also associated with a reduced cognitive decline in patients with elevated serum cholesterol, although this relationship has been inconsistent.<sup>20</sup> Physical activity and a mediterranean diet, often advocated to lessen risk of vascular disease, are also associated with a reduced risk of dementia and cognitive decline.<sup>21–24</sup> In consequence, the treatment of vascular risk factors prescribed to prevent outcomes such as myocardial infarction or renal insufficiency may also prevent adverse cognitive outcomes, although whether this should be a matter of public health policy is debated.<sup>3,4</sup>

Against this background, it seems reasonable that clinical practice guidelines for the treatment of vascular risk factors should include cognition as an aspect of target organ damage, even if prevention of damage is not always be possible. Our cursory impression was that this is not the case. In consequence, we investigated the extent to which cognition is included as an aspect of end-organ damage in clinical practice guidelines for the treatment for vascular risk factors. We considered cognition in the context of other attributes of the guidelines, such as their search strategy and description of the search methods.

## Methods

### Data sources

PubMed, EMBASE, and the Cochrane Library were searched for items published between January 1st, 2001 and August 30th, 2008.

### Review methods

Search terms included the medical subject headings *hypertension*, *diabetes mellitus*, *diabetes mellitus – type 2*, *hypercholesterolemia*, *hypercholesterolemia – familial*, and *atrial fibrillation*.

### Inclusion criteria

Articles were included if they met the following criteria:

1. Hypertension, high cholesterol, diabetes, and/or atrial

fibrillation was targeted; 2. The guideline was directed at physicians; 3. Adult patients (aged 19 years or older) were targeted; and 4. The guideline was published in English. In the case of duplicated or updated guidelines, only the most recent clinical practice guideline from a given organization or group of authors was considered. Only the unabridged versions of duplicated guidelines were reviewed.

Studies were independently evaluated for inclusion by two reviewers. Where disagreement arose, a third reviewer came to a resolution. We performed an independent assessment of both the processes by which guidelines were developed and their content with respect to the assessment of end-organ damage. To evaluate the process, a quality assessment instrument (Supplementary Material A) was developed, based on a more general instrument for evaluating the quality of consensus guidelines.<sup>25</sup> Here, we also noted the composition of the review teams and specifically whether they included physicians likely to have an interest in cognition. To evaluate the content, we developed another standardized assessment (Supplementary Material B). We evaluated how commonly cognition was mentioned and how frequently it was mentioned in comparison with other outcomes. In addition to renal disease and claudication, pheochromocytoma was included to compare the inclusion of cognition to another disorder that is much less common than cognitive impairment but which is traditionally considered in people with hypertension.

## Results

The initial database search revealed 321 articles for further consideration of which only 91 were clinical practice guidelines. Once guidelines that were targeted to nonadult populations, not aimed at physicians, focused on few or only one specific outcomes, or were joint/older versions of publications were eliminated, 20 relevant clinical practice guidelines remained (Table 1).<sup>26–45</sup>

Of the 20 clinical practice guidelines that met all criteria, five mentioned cognition. Of these five, four discussed cognition as an aspect of target organ damage and suggested that cognition may benefit from treatment. Two discussed cognitive impairment with respect to treatment compliance but no guideline thoroughly discussed the assessment of cognition. Of the guidelines that mentioned cognition, four focused on hypertension and one targeted diabetes.

Guidelines that mentioned cognitive impairment as an outcome of uncontrolled vascular risk factors were more likely to have mentioned claudication and renal function.

**Table 1** Characteristics of clinical practice guidelines included in the review

Association	Year	Vascular risk factor	Target population
American College of Chest Physicians <sup>36</sup>	2004	Atrial fibrillation	Not specified
American Academy of Family Physicians, American College of Physicians <sup>38</sup>	2003	Atrial fibrillation: First-detected	Adults with first-detected atrial fibrillation
American College of Cardiology, American Heart Association, European Society of Cardiology <sup>37</sup>	2001	Atrial fibrillation	Not specified
California Healthcare Foundation, American Geriatrics Society <sup>26</sup>	2003	Diabetes	Older persons
US Preventive Services Task Force <sup>41</sup>	2003	Diabetes: diabetes mellitus	Adults (diabetes mellitus)
Agence Nationale d'Accréditation et d'Évaluation en Santé <sup>28</sup>	2000	Diabetes: type 2 diabetes	Type 2 diabetics without complications
Canadian Cardiovascular Society <sup>42</sup>	2006	Cholesterol: dyslipidemia	
American Diabetes Association <sup>23</sup>	2004	Cholesterol: dyslipidemia	Adults with diabetes
National Cholesterol Education Program <sup>30</sup>	2002	Cholesterol: high blood cholesterol	Adults
American Diabetes Association <sup>24</sup>	2004	Hypertension	Adults with diabetes
American Hypertension Association <sup>33</sup>	2008	Hypertension	Adults
Canadian Hypertension Education Program <sup>29</sup>	2007	Hypertension therapy	Adults
Canadian Hypertension Education Program <sup>32</sup>	2007	Hypertension: diagnosis and risk	Adults
European Society of Hypertension <sup>39</sup>	2007	Hypertension: arterial	Not specified
Joint National Committee-7 <sup>27</sup>	2003	Hypertension: high blood pressure	Not specified
National Collaborating Centre for Chronic Conditions <sup>31</sup>	2006	Hypertension	Not specified
South African Hypertension Society <sup>34</sup>	2006	Hypertension	Adults
US Preventative Services Task Force <sup>40</sup>	2003	Hypertension: high blood pressure	Adults
Agence Nationale d'Accréditation et d'Évaluation en Santé <sup>25</sup>	2005	Hypertension	Adults
American Geriatrics Society <sup>35</sup>	2001	Anticoagulants (Warfarin)	Older people

A larger portion of the guidelines that mentioned cognition also included descriptive studies in the evidence and provided a description of the authors. Studies that cited cognition were also less likely to describe the search strategy and explicitly link evidence to the strength of the guidelines (Table 2).

## Discussion

The number of people diagnosed with dementia is expected to surge in the upcoming decades largely because of more people living to an age where dementia is common.<sup>1,2</sup> As a result, the prevention of dementia has emerged as a major public health focus<sup>46</sup> and vascular risk factor control is one of the most promising factors for the prevention of dementia.<sup>47</sup> Despite the strong association between vascular risk factors and dementia, this review of current clinical practice guidelines

for vascular risk factor management indicated that only a minority (four of 20) discussed cognition either as an aspect of target organ damage or as a consideration in treatment. The mention of cognition tended to be idiosyncratic, and unrelated to most other measures of the completeness of the guidelines or to the processes by which they were achieved.

Our data must be interpreted with caution. Language bias could be present because only guidelines published in English were included. However, a guideline from South Africa was included along with guidelines from North America and Europe and a systematic strategy was followed. In addition, our search ended prior to the publication of the Hypertension in the Very Elderly Trial data and its analyses of the impact of hypertension treatment on cognition.<sup>18</sup> While the study was not entirely conclusive, the results favored hypertension

**Table 2** A comparison of the vascular risk factor clinical practice guidelines that mentioned cognition (n = 5) to those that did not (n = 15)

Questions	Answer	Mentioned cognition?	
		Yes	No
Is there a description of the individuals who were involved in the guidelines development?	Yes	4	1
	No	5	10
Were there representatives of all relevant disciplines?	Yes	3	2
	No	3	3
Is the search strategy described?	Yes	2	3
	No	6	9
Are descriptive studies included?	Yes	3	0
	No	7	2
Is there a description of the methods used to interpret and assess the strength of the evidence?	Yes	2	3
	No	12	3
Is there an explicit link between the recommendations and the level of supporting evidence?	Yes	3	2
	No	14	1
Are recommendations made for ongoing monitoring of condition and complications?	Yes	5	0
	No	10	5
Does the guideline discuss compliance?	Yes	3	2
	No	4	11
Does the guideline mention claudication?	Yes	4	1
	No	2	13
Does the guideline mention renal function?	Yes	5	0
	No	12	3
Is pheochromocytoma mentioned?	Yes	2	3
	No	2	13

treatment for the benefit of cognition when combined into a meta-analysis.<sup>18</sup> Future clinical practice guidelines targeting hypertension may include cognition in consequence to these results.

There is substantial evidence to suggest that people who have vascular risk factors are at elevated risk for cognitive impairment.<sup>15</sup> In addition, there is preliminary evidence to suggest that lifestyle modification through diet and exercise and the treatment of vascular risk factors, particularly hypertension, may partially reduce this risk.<sup>16–19,23,24</sup> Even so, our study found that few guidelines for vascular risk factors mention cognition and even fewer make clear recommendations for the screening and evaluation of cognitive impairment as an adverse outcome of vascular risk factors. As a result, physicians are likely to underestimate the cognitive impact of vascular disease. Even stroke neurologists have been urged to better recognize cognitive impairment in patients with cerebrovascular disease.<sup>48</sup>

Review procedures that emphasize randomized control trials and downgrade evidence from epidemiological studies often overlook the weaknesses of these trials, such as poor validity to clinical populations. In particular, stroke guidelines have been criticized for being derived from

study populations that do not adequately reflect those seen in primary care.<sup>49</sup> If the outcomes that are important for inclusion in clinical practice guidelines are those that most impact patients' lives and well-being, as has been suggested,<sup>30</sup> then cognition is of utmost importance even if the treatment evidence is primarily observational and preliminary in controlled trials.<sup>16–20</sup> That some guidelines described the evaluation of pheochromocytoma, but not cognition, suggests that the population burden of illness has not always been considered of primary importance when developing vascular risk factor guidelines.

Dementia guidelines indicate that people with hypertension, hyperlipidemia, and diabetes are at high risk for dementia and indicate that for hypertension, treatment will reduce this risk.<sup>50,51</sup> It follows that clinical practice guidelines for the management of vascular risk factors, and particularly hypertension, should similarly recommend that practitioners consider patients with vascular risk factors to be at high risk for cognitive impairment, particularly with patients who are at an age (>65 years) where cognitive impairment is common. Cognitive screening by general practitioners, cardiologists and other physicians has the potential to detect more patients in the earliest stages of cognitive impairment and dementia, where early detection is important for treatment

and will become increasingly important as more preventative therapies are identified.<sup>52</sup>

Magnetic resonance imaging (MRI) can provide a detailed image of the brain and cerebrovascular system. However, the structural changes detected with MRI do not accurately predict the clinical manifestation<sup>53</sup> of cognitive impairment so cognitive testing is imperative. With the development of new cognitive testing guidelines,<sup>48</sup> which include a 30 minute and a 5–10 minute standardized cognitive battery, it is now relatively straightforward to administer cognitive testing that is more sensitive to vascular cognitive impairment than the traditionally used Mini-Mental State Examination (MMSE),<sup>54</sup> which is relatively insensitive to the executive dysfunction and subtle memory changes that are important to the diagnosis of vascular cognitive impairment.<sup>55</sup> Since the five-minute battery can be administered by study personnel with minimal training, including a version that can be administered by telephone, it is feasible to include the brief battery for clinical screening of patients with vascular risk factors and as a measure of cognition in research studies.

Two recent guideline updates offer contrasting evidence of progress. The 2007 guidelines for the management of arterial hypertension, created jointly by the European Society of Hypertension and the European Society of Cardiology,<sup>42</sup> thoroughly describes the evidence linking hypertension to the risk of cognitive impairment, unlike its 2003 predecessor. Screening for memory impairment is also suggested, though the testing procedures are not described (unlike for renal disease and pheochromocytoma). The National Collaborating Centre for Chronic Conditions, in updating the British Society for Hypertension guidelines, however, removed the mention of dementia in its 2006 update of the hypertension guideline.<sup>34</sup> Instead, it describes cerebrovascular disease without reference to cognitive impairment as an adverse outcome.

Despite the worldwide burden of cardiovascular risk factors and their traditionally understood adverse outcomes, under-treatment remains an important problem.<sup>56</sup> Whether realizing that these also increase the risk of dementia will prompt people to modify their lifestyles or to seek treatment or physicians to initiate treatment is not clear, but on a worldwide basis it might provide enough additional motivation to make a difference.

## Contributions

Kenneth Rockwood, Sandra Black, and Ingmar Skoog conceptualized this paper. Laura Middleton, who was a PhD student at Dalhousie University when we started the review,

and Paige Moorhouse did much of the retrieving of papers and inter-rater reliability reviews. Dr Sandra, Dr Skoog, and I each reviewed one third of the papers. Dr Middleton, Dr Moorhouse, and Dr Rockwood wrote the first draft, everyone else has revised it. We all approve the submitted version.

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## Disclosures

Within the past five years, Kenneth Rockwood has participated in the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia, and served as a paid consultant to the Centers for Disease Control on the role of exercise in dementia prevention, and to Pfizer, Eisai, Elan/Wyeth, GlaxoSmithKline, Janssen-Ortho, Myriad, Numico and Novartis on dementia treatment. He is a consultant to a study of dementia treatment for Pfizer. Sandra Black has participated in guidelines for stroke and dementia and has, within the past five years, served as a paid consultant to Pfizer, Janssen-Ortho, Novartis, Lundbeck, Myriad Pharmaceuticals, Epix Pharmaceuticals, GlaxoSmithKline, Schering-Plough, Elan and Wyeth Pharmaceuticals. She has also received research funds from Novartis Pharmaceuticals, Myriad Pharmaceuticals, Eisai-Pfizer, Sanofi-Aventis, Boehringer Ingelheim, Novo Nordisk and AstraZeneca and speaker's honoraria from Janssen-Ortho, Novartis Pharmaceutical, Lundbeck, Pfizer and Myriad Pharmaceuticals. Ingmar Skoog was co-chairman on the SCOPE study and received honoraria from AstraZeneca for this. Ingmar Skoog has also been on speakers' bureaus for AstraZeneca, Lundbeck, Shire, Esai, Pfizer, Novartis, JansenCilag, Bayer, and Organon. None of the authors hold stocks in any pharmaceutical company. None of these sponsors had any input into the decision to write or the content of the paper.



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## Supplementary materials

### Supplementary material A

	Quality of the guideline	Y	N	N/A
1	Are the guidelines peer-reviewed? If no, eliminate from further review.			
2	Is the agency responsible for the development of the guidelines clearly identified?			
3	Was external support received?			
4	Did it include pharmaceutical support? If no, skip to 5			
4a	<ul style="list-style-type: none"> <li>If pharmaceutical support was received, did the company(s) who provided support manufacture or distribute drugs that treat cognitive impairment?</li> </ul>			
5	Is there a description of the individuals who were involved in the guidelines development? If no, skip to 6			
5a	<ul style="list-style-type: none"> <li>If so, were there representatives of all relevant disciplines? <b>Comments:</b></li> </ul>			
6	Is there a description of the search strategy used to select the studies on which the recommendations are based? If no, skip to 7			
6a	<ul style="list-style-type: none"> <li>If so, does the evidence include descriptive studies as well as randomized controlled trials?</li> </ul>			
7	Is there a description of the method(s) used to interpret and assess the strength of the evidence? <b>Comments:</b>			
8	Is there an explicit link between the major recommendations and the level of supporting evidence? <b>Comments:</b>			
9	Is there a description of the patients to whom the guidelines are meant to apply? <b>Comments:</b>			

### Supplementary material B

	Content of the guideline	Y	N	N/A
1	Does the guideline mention claudication?			
2	Does the guideline mention cognitive impairment? If no, skip to 3.			
2a	<ul style="list-style-type: none"> <li>If yes to 2, does the guideline discuss how to screen for cognitive impairment?</li> </ul>			
3	Does the guideline mention renal function? If no, skip to 4.			
3a	<ul style="list-style-type: none"> <li>If yes to 3, does the guideline discuss how to screen for renal function?</li> </ul>			
4	Does the guideline discuss target organ damage? If no, skip to 5.			
4a	<ul style="list-style-type: none"> <li>If yes to 4, does the guidelines mention cognitive impairment as an aspect of target organ damage?</li> </ul>			
5	Does the guidelines include outcomes? If no, skip to 6.			
5a	<ul style="list-style-type: none"> <li>If yes to 5, does the guideline mention claudication as an outcome?</li> </ul>			

(Continued)



**Supplementary material B** (Continued)

	Content of the guideline	Y	N	N/A
	<ul style="list-style-type: none"> <li>• If yes to 5, does the guideline mention cognitive impairment as an outcome?</li> <li>• If yes to 5, does the guideline mention renal function as an outcome?</li> </ul>			
6	Does the guideline cite evidence for outcomes that are likely to benefit from the recommended management? If no, skip to 7.			
6a	<ul style="list-style-type: none"> <li>• If so, does the guideline cite evidence or otherwise suggest that cognition is likely to benefit from the recommended management?</li> </ul>			
7	Are recommendations made for ongoing monitoring of the principle condition and complications? If no, skip to 8.			
7a	<ul style="list-style-type: none"> <li>• If so, do these recommendations include assessment of cognition?</li> </ul>			
8	Was cognition mentioned as a risk factor (exposure) for any vascular outcome? If no, skip to 9.			

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