


# Cerebrovascular disease in patients with cognitive impairment: A white paper from the ESO dementia committee – A practical point of view with suggestions for the management of cerebrovascular diseases in memory clinics

European Stroke Journal  
2021, Vol. 6(2) 111–119  
© European Stroke Organisation  
2021  
Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/2396987321994294  
journals.sagepub.com/home/eso  


Ana Verdelho<sup>1</sup> , Geert Jan Biessels<sup>2</sup>, Hugues Chabriat<sup>3</sup>,  
Andreas Charidimou<sup>4,5</sup>, Marco Duering<sup>6,7</sup>, Olivier Godefroy<sup>8</sup>,  
Leonardo Pantoni<sup>9</sup> , Aleksandra Pavlovic<sup>10</sup> and  
Joanna Wardlaw<sup>11</sup> 

## Abstract

**Purpose:** Practical suggestions on clinical decisions about vascular disease management in patients with cognitive impairment are proposed.

**Methods:** The document was produced by the Dementia Committee of the European Stroke Organisation (ESO) based on the evidence from the literature where available and on the clinical experience of the Committee members. This paper was endorsed by the ESO.

**Findings:** Vascular risk factors and cerebrovascular disease are frequent in patients with cognitive impairment. While acute stroke treatment has evolved substantially in last decades, evidence of management of cerebrovascular pathology beyond stroke in patients with cognitive impairment and dementia is quite limited. Additionally, trials to test some daily-life clinical decisions are likely to be complex, difficult to undertake and take many years to provide sufficient evidence to produce recommendations. This document was conceived to provide some suggestions until data from field trials are available. It was conceived for the use of clinicians from memory clinics or involved specifically in cognitive disorders, addressing practical aspects on diagnostic tools, vascular risk management and suggestions on some therapeutic options.

**Discussion and conclusions:** The authors did not aim to do an exhaustive or systematic review or to cover all current evidence. The document approach in a very practical way frequent issues concerning cerebrovascular disease in patients with known cognitive impairment.

<sup>1</sup>Department of Neurosciences and Mental Health, CHLN-Hospital de Santa Maria, Instituto de Medicina Molecular – IMM e Instituto de Saude Ambiental-ISAMB, Faculdade de Medicina. University of Lisbon, Lisbon, Portugal

<sup>2</sup>Department of Neurology, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, the Netherlands

<sup>3</sup>Department of Neurology, FHU NeuroVasc, Hôpital Lariboisiere, University of Paris and INSERM U1141, Paris, France

<sup>4</sup>Hemorrhagic Stroke Research Program, J. Philip Kistler Stroke Research Center, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

<sup>5</sup>Department of Neurology, Boston Medical Center, Boston University School of Medicine, Boston, MA, USA

<sup>6</sup>Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Germany

<sup>7</sup>Medical Image Analysis Center (MIAC AG) and qbig, Department of Biomedical Engineering, University of Basel, Basel, Switzerland

<sup>8</sup>Departments of Neurology, Amiens University Hospital, and Laboratory of Functional Neurosciences I,6 (UR UPJV 4559), Jules Verne Picardy University, Amiens, France

<sup>9</sup>Stroke and Dementia Lab, “Luigi Sacco” Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy

<sup>10</sup>Faculty for Special Education and Rehabilitation, University of Belgrade, Belgrade, Serbia

<sup>11</sup>Centre for Clinical Brain Sciences, UK Dementia Research Institute, University of Edinburgh, Edinburgh, UK

## Corresponding author:

Ana Verdelho, Department of Neurosciences, Hospital de Santa Maria, University of Lisbon, Av Prof. Egas Moniz, Lisbon, Portugal.  
Email: averdelho@medicina.ulisboa.pt

## Keywords

Cerebrovascular disease, cognitive impairment, dementia, small vessel disease, stroke

Date received: 9 October 2020; accepted: 19 January 2021

## Introduction

Dementia and stroke share several modifiable vascular risk factors and are risk factors for each other.<sup>1–3</sup> Hence, patients with cognitive impairment (CI) who are seen at memory clinics frequently present with vascular risk factors and cerebrovascular disease. Furthermore, cerebrovascular disease contributes to clinical symptoms that may aggravate or anticipate the clinical expression of underlying degenerative brain pathology. There is a lack of evidence on the treatment of cerebrovascular disease in patients with CI.<sup>4,5</sup> Uncertainty about management of vascular risk factors and cerebrovascular disease in people affected by CI might lead to heterogeneity in the treatment of those patients. In addition, professionals from memory clinics may have less experience in the recognition and in the appropriate management of cerebrovascular disease. The aim of this paper is to help reducing this potential knowledge gap, while waiting for appropriate field trials.

## Methods

This document is a white paper produced by the Dementia Committee members, and endorsed by the European Stroke Organization, aiming to give practical clinical suggestions for the management and treatment of cerebrovascular disease in patients with cognitive disorders. It was meant for the use of professionals involved in the management of patients with CI, including medical specialists, general practitioners, but also non-medical professionals interested in CI and dementia, in order to help clinical decisions. Content is not a result of a systematic review, but rather based on relevant literature and on the clinical experience of the authors.

In this paper an effort was made to incorporate differences of approach and access to ancillary investigations, keeping in mind the standard usual best practice from a cerebrovascular disease perspective. For a practical use, cognitive impairment (CI) include patients with objective cognitive impairment regardless of having or not criteria for dementia. Subjective cognitive impairment refers to subjective complaints of decline in cognition without confirmation of decline on objective cognitive assessment.

## Findings

### *Clinical expression of cerebrovascular contribution in CI*

**Cognitive and behavioral manifestations.** Once a patient is seen in a memory clinic and the diagnosis of CI has been confirmed, the possible presence, coexistence, or relevance of a cerebrovascular component in the etiology of CI should be considered. Identification of cerebrovascular disease through neuroimaging is quite straightforward (see below). However, identification of symptoms and signs of cerebrovascular disease on clinical grounds might be less obvious. A synthetic approach is given in Text Box 1. Over the last years, there has been much discussion about the potential role of neuropsychology in order to differentiate the vascular from the degenerative component of CI.<sup>6</sup> Although there is consensus that compromise of some cognitive domains (such as memory) may be more prominent in Alzheimer disease (AD) than in cerebrovascular diseases,<sup>7</sup> and executive dysfunctions are thought to be more typical of cerebrovascular pathology, in fact all major cognitive domains are affected in small vessel disease<sup>8</sup> and neuropsychological testing cannot *per se* differentiate between vascular CI and AD at the

Text Box 1. Clinical symptoms/signs which should raise possibility of concomitant cerebrovascular disease

|                                                   |                                                                                                                                                                                                 |
|---------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cognitive symptoms                                | Slowness of processing speed<br>Attention deficits<br>Reasoning problems<br>Decision-making difficulties<br>Apathy                                                                              |
| Behavioral and psychological symptoms             | Mood changes (namely depressive symptoms)<br>Emotional control problems<br>Lack of initiative<br>Apparent change in personality<br>Informant report of cognitive decline and behavioral changes |
| Motor and other non-cognitive/behavioral symptoms | Gait changes<br>Urinary problems<br>Finger tapping changes                                                                                                                                      |

individual level,<sup>9</sup> nor clearly outline the presence of a vascular contribution in patients with CI of degenerative origin.<sup>10</sup> Nevertheless, the combination of the information driven by neuropsychological testing (and remaining clinical evaluation) with brain imaging is the best clue to support a likely cerebrovascular contribution.

Behavioral and psychological symptoms are highly frequent among cerebrovascular disease manifestations<sup>11,12</sup> and might be different according to the nature of cerebrovascular lesions.<sup>13</sup> Those symptoms might be undervalued by relatives (and interpreted for instance as due to ageing) or overlooked due to other concomitant cognitive symptoms. Depressive symptoms, lack of emotion expression control and emotionalism, apathy and lack of initiative and change in personality traits are among those symptoms. There is no ideal short battery for the identification of deficits in patients with cerebrovascular disease. We should keep in mind that less exhaustive neuropsychological study might fail to put in evidence few cognitive deficits and behavioral changes<sup>14</sup>

**Evolution over time.** Apart from detailed evaluation of cognitive testing, there might be other clinical hints that suggest the presence of a vascular component in a patient with CI.

Historically, one clinical tool to differentiate the vascular component of the cognitive decline is to apply the so-called ischemic score published by Hachinski and co-authors, aiming to differentiate AD from multi-infarct dementia.<sup>15</sup> The score is today considered partly out-of-date and is more rarely used than in the past; however, it may serve to outline and discuss some aspects. According to the original paper, a few characteristics of the clinical course of the cognitive deterioration may indicate the presence of a vascular component (or cause); these are the abrupt onset, the stepwise deterioration, and a fluctuating course. However, it should be kept in mind that the original paper was referring to patients with multiple strokes. Today, we know that a good proportion of patients whose CI recognizes a vascular cause - or at least a vascular component of it -, have small vessel disease (SVD),<sup>16</sup> and the course of their cognitive decline is not usually stepwise but rather progressive and with insidious onset. Other items of the original scale, given the current knowledge, appear of limited utility as they are scarcely discriminative and are also a risk factor for AD (more information concerning Hachinski's score is provided in supplementary material).

**Motor and non-motor manifestations.** More relevant in this sense are the history of strokes and the presence of

focal neurological symptoms and signs. These latter should be always searched for, systematically, as they are highly indicative of a cerebrovascular contribution.

CI phenotype usually reflects more than one pathological mechanism. Biomarkers (namely imaging for vascular pathology) are able to put in evidence cerebrovascular disease. The knowledge of the clinical expression of vascular pathology leads to the possibility of addressing better the specific trigger for CI in a specific person. Some neurological signs may help in the identification of the etiology of the clinical picture. One relevant aspect to be outlined is the possibility to suspect a vascular component of CI by assessing physical performance with simple and clinically friendly tools.<sup>17</sup> Patients with cerebrovascular disease have frequently gait disturbances with balance difficulties, small steps, and bradykinesia. Besides those affected by the sequelae of previous stroke such as hemiparesis, patients with SVD have typically a slowed, short-stepped, wide-based gait. These patients also have an increased rate of falls. More sophisticated tools for assessing gait performance maybe better but also difficult to implement in memory clinics on a large scale.<sup>18</sup>

Finally, there have been data supporting that changes in other non-cognitive symptoms (as for instance urinary troubles early in the course of the disease) since these are common in patients with vascular contributions to CI and have an adverse effect on their daily lives. Cerebral SVD is associated with urinary problems<sup>19</sup> and also with abnormalities on neurological examination, such as slowness of finger tapping.<sup>20</sup> Despite the possibility that these features might direct the attention of the treating physician towards the presence of a vascular contribution, other degenerative pathologies may present with similar findings<sup>21,22</sup>. It might be reasonable however to search for all these aspects in each patient arriving at a memory clinic.

**Subjective cognitive impairment.** One last word concerning subjective CI, that usually is associated with higher risk of dementia, usually of the Alzheimer type (and not with SVD).<sup>12</sup> However, among community cohorts, may represent an increase in the relative risk for, particularly, CI of vascular origin.<sup>23</sup> Clinicians should keep in mind that patients with subjective complaints living in the community are an opportunity to identify vascular risk factors in people otherwise well, and reinforce preventive actions concerning those vascular risk factors.

**What investigation/complementary investigation(s) are important?**

Patients presenting to memory clinics should have brain imaging that includes assessment for vascular

and neurodegenerative or other brain lesions. They should be assessed for common modifiable vascular and lifestyle risk factors to minimize their impact on brain and general health (Table 1).

### Neuroimaging

**General considerations.** On neuroimaging, vascular lesions include cortical or subcortical infarcts or old haemorrhages, signs of SVD including white matter hyperintensities (WMH), lacunes and microbleeds, and cortical superficial siderosis (cSS).<sup>24</sup> Perivascular spaces are common in cerebrovascular disease, but their clinical relevance is currently less clear.<sup>25,26</sup> Brain atrophy occurs in the common neurodegenerative dementias including AD (particularly of medial temporal lobes), fronto-temporal dementia (of frontal and temporal lobes), dementia with Lewy Bodies (of parietal lobes), but also occurs diffusely in SVD<sup>27</sup> and focally after infarcts and haemorrhages. The pattern of atrophy may provide clues of the dementia type,

but many patients have global brain atrophy, so in practice, atrophy patterns may have limited specificity.

**MRI and CT scan applications.** Brain imaging can be performed with computerized tomography (CT) scanning or magnetic resonance imaging (MRI). MRI might not always be available, or not applicable for every patient, so clear knowledge about limitations and advantages of each technique is needed. Moreover, CT is of quick realization, which is quite relevant for instance in patients with behavioral changes, fear of closed environments or with MRI contraindications (pacemaker or some prostheses, for instance). CT is equally accurate as MRI for pathologies such as brain tumours, subdural haematomas, many larger infarcts, acute haemorrhages, and can show brain atrophy, moderate to severe white matter lesions (leukoaraiosis), and lacunes.<sup>28</sup> Nevertheless, differentiation of old haemorrhages from old infarcts, identification of microbleeds and cSS and some small acute infarcts is not reliable on CT. MRI is much more

**Table 1.** Investigations to avoid missing modifiable vascular risk factors.

| Measure                                                                    | To detect                                                                                                                                                                                       |                                                                                                                                      |
|----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| <i>Modifiable vascular risk factors</i>                                    |                                                                                                                                                                                                 |                                                                                                                                      |
| Blood pressure                                                             | Hypertension                                                                                                                                                                                    | May need multiple measures, or ambulatory monitoring                                                                                 |
| Blood glucose                                                              | Diabetes                                                                                                                                                                                        |                                                                                                                                      |
| Blood lipids                                                               | Hyperlipidaemia                                                                                                                                                                                 |                                                                                                                                      |
| Body mass index                                                            | Overweight and obesity                                                                                                                                                                          |                                                                                                                                      |
| Lifestyle history                                                          | Excessive alcohol intake, smoking, poor diet, inadequate exercise and sedentary habit                                                                                                           |                                                                                                                                      |
| Other proxy-risk factors, as obstructive sleep apnea, homocysteine levels  | Different factors associated with higher vascular risk                                                                                                                                          | If not actively searched be a missed opportunity to be identified                                                                    |
| <i>Sources of emboli and evidence of ischaemic cardiovascular disease:</i> |                                                                                                                                                                                                 |                                                                                                                                      |
| ECG                                                                        | Cardiac arrhythmias, particularly atrial fibrillation; ischaemic heart disease                                                                                                                  | May need ambulatory monitoring, to detect paroxysmal arrhythmias or even an ECG-T (cardiac event recorder)                           |
| Echocardiogram                                                             | Heart valve disease, atrial septal defects (ASDs) Aortic cross atheroma                                                                                                                         | Transoesophageal echo with iv echo-contrast is more sensitive to ASDs than transthoracic                                             |
| Doppler Ultrasound, CT or MR angiography                                   | Carotid or vertebral artery extra- or intracranial stenosis                                                                                                                                     | CT or MR angiography for suspected intracranial stenosis                                                                             |
| <i>Evidence of cerebrovascular disease</i>                                 |                                                                                                                                                                                                 |                                                                                                                                      |
| MR or CT brain imaging <sup>a</sup>                                        | Acute or old cortical infarcts; Acute or old subcortical infarcts; acute or old brain haemorrhage; WMH, lacunes, microbleeds, cortical siderosis; brain atrophy including regional distribution | T1-weighted, T2-weighted, FLAIR, SWI and DWI sequences are all essential to assess for the range of cerebrovascular disease lesions. |

<sup>a</sup>MRI preferred, as more sensitive for detecting vascular changes. CT will detect non vascular causes and brain atrophy, many infarcts, acute haemorrhage, and moderate to severe WMH and lacunes, but not microbleeds, differentiate old infarct from haemorrhage, and is much less sensitive to SVD lesions than is MRI. CT possibilities discriminated in main text.

WMH: white matter hyperintensities; FLAIR: fluid attenuated inversion recovery; SWI: susceptibility-weighted imaging; DWI: diffusion-weighted imaging or diffusion imaging.



sensitive to vascular lesions, particularly WMH, microbleeds and cSS. MRI is also better for detecting and differentiating sporadic vascular lesions from multiple sclerosis, vasculitis, some infections and familial genetic causes of dementia and cerebrovascular disease such as CADASIL. However, when using MRI, the correct MRI sequences are required to identify key vascular pathologies. Many memory clinics use MRI protocols including 3D T1 and T2, which detect brain atrophy, some cortical infarcts, lacunes and can exclude tumours and subdural haematomas, for instance. However, to detect key vascular lesions, a fluid attenuated inversion recovery (FLAIR) sequence is required for WMH and small cortical infarcts, a susceptibility-weighted imaging (SWI or Gradient Echo or T2\*) sequence is essential to detect microbleeds, cSS, and old macrohaemorrhages, and diffusion-weighted imaging (DWI) is important to detect small acute infarcts.

**Specific hints from neuroimaging.** WMH, lacunes, microbleeds and atrophy all increase with age.<sup>24,25</sup> However, a higher than expected burden of WMH for age, and any lacunes or microbleeds, should trigger a search for modifiable risk factors.<sup>29</sup> Smith et al. provided a practical schema of WMH severities according to age groups, based on MRI, in a recent publication (see Figure 7 in).<sup>29</sup> Large numbers of WMH and lacunes in a young patient should raise the possibility of a monogenic SVD such as CADASIL. Multiple cortical infarcts especially in multiple arterial territories, should trigger a search for proximal embolic sources. Microbleeds are associated with hypertension, where they typically occur mainly in deep grey and white matter, and commonly found in patients with cerebral amyloid angiopathy (CAA) where they typically have a lobar distribution and are seen at the cortical-subcortical junction, although mixed distributions of microbleeds are common. Microbleeds plus cSS are likely to indicate CAA.<sup>30</sup>

#### *Vascular risk management*

**Vascular risk factors assessment.** The main modifiable vascular risk factors are hypertension, hyperlipidemia, diabetes, and sources of emboli or altered cerebral perfusion such as atrial fibrillation or other cardiac arrhythmias, heart valve disease, and atheromatous internal carotid artery stenosis. Modifiable lifestyle risk factors include tobacco smoking, lack of regular physical exercise and poor diet including excess dietary sodium and alcohol.

All patients attending memory clinics should have their blood pressure measured using an approved and well maintained sphygmomanometer device. Blood pressure should be assessed sitting after at least five minutes of rest, and in both arms to avoid falsely low

reading due to a subclavian artery stenosis. More detailed repeated measures of BP in clinic or home monitoring may be required but this is out of scope for this paper. Loss of adherence to hypertension treatment should be prevented (namely patients might stop medication when values get normal due to treatment), hence, any attendance at a clinic is a good opportunity to check that vascular risk management is under control. Patients should also have their blood glucose and blood lipids (cholesterol, LDL, HDL) measured if these have not been performed recently elsewhere, and appropriate management implemented whenever necessary.<sup>31</sup>

**Ancillary investigations concerning vascular risk factors.** As cholinesterase inhibitors may delay atrial-ventricular conduction, an electrocardiogram (ECG) is usually requested in memory clinics. When there is evidence of cerebrovascular disease, an ECG will be helpful to identify arrhythmias, and signs of ischaemic heart disease or left or right chamber hypertrophy. Special attention must be given to patients with recent focal neurological symptoms or evidence of cerebrovascular lesions on scanning, especially if in multiple vascular territories: in those patients, ambulatory monitoring may be required to detect paroxysmal arrhythmias and further investigations such as echocardiography, and neck or intracranial artery imaging e.g. with Doppler ultrasound, CT or MR angiography<sup>32</sup> may be needed. Patients with more complex cerebrovascular disease as recurrent strokes despite adequate management and adequate secondary prevention, rare causes of stroke (as genetic diseases as CADASIL) and patients with recent acute stroke or suspected TIA should be considered for referral to a stroke clinic.

**Other life-style and global measures.** Tobacco smoking<sup>33</sup> and excess alcohol consumption damage the brain,<sup>34</sup> so cessation of those habits should be suggested. Exercise helps to maintain brain vascular health,<sup>35</sup> and a well-balanced diet including recommended amounts of fruit and vegetables,<sup>36</sup> avoiding excess sodium<sup>37</sup> and processed meats, is advisable. Lifestyle advice encourages patient awareness of their vascular risk and is part of comprehensive risk management.

A synopsis of suggested investigations is given in Table 1, and a summary of relevant suggestions in Text Box 2.

#### *Treatment*

**Primary and secondary prevention of stroke.** Prevention of new vascular events in people with symptomatic cardiovascular disease is one of the real success stories of

Text Box 2. Summary of suggestions for the management of cerebrovascular disease in patients with CI.

- Clinical appointments due to CI should be considered as an opportunity to check and better control of vascular risk factors
- Brain imaging (made in the context of CI) should be reviewed to verify existence of cerebrovascular disease
- In the case of cerebrovascular component highly suspected/not clear after CT, an MRI should be considered (namely if doubt about hemorrhagic component including microbleeds and cSS, small acute lesions, specific profiles as familiar -e.g.CADASIL, or extension of WMC and SVD)
- Specific investigations should be considered in acute lesions, recurrent and multiple strokes (namely neck and intracranial artery imaging and cardiac study)

preventive medicine. In patients who experienced a ischaemic stroke, or transient ischaemic attack, the risk of future vascular events can be reduced by 30–50% through guideline-based treatments and lifestyle recommendations.<sup>38</sup> Of note, the evidence on which these guidelines are built is largely derived from studies on atherosclerotic (large artery) disease. By comparison, the available evidence specifically concerning treatment of cerebral SVD, the commonest form of vascular brain injury encountered in people with CI, is quite limited.<sup>29,39</sup>

There clearly is an important potential for vascular prevention strategies in patients with CI. Yet, physicians should be careful to apply guidelines for secondary prevention after stroke to people with CI and so-called “silent cerebrovascular disease”. In this setting, some treatments that are cornerstones in secondary prevention, in particular antithrombotic agents, may be ineffective, or sometimes even harmful. Although some recommendations are published,<sup>29</sup> we try to summarize few practical points in the next lines.

In all patients with CI and vascular brain injury, guidelines for primary prevention of cardiovascular disease apply.<sup>40</sup> This includes lifestyle recommendations, and encouraging cessation of smoking, if applicable, as mentioned above. To determine if additional treatment is needed, or existing treatments should be modified, a pragmatic approach is the following:

First, determine if the patient had a previous ischaemic vascular event or other ischemic vascular disease elsewhere in the body. If this is the case, this previous cardiovascular disease generally determines the choice of antithrombotic agents and blood pressure and cholesterol targets, according to available guidelines.<sup>38,40</sup> Nevertheless, the memory clinic visit should be taken as an opportunity to double check if this treatment is appropriately installed.

Next, determine the nature of the vascular brain injury. Assess the different lesion types and burden as indicators of risk of future vascular injury. Of note, lesions that are typically considered to be ischemic, such as WMH and lacunes, not only convey an increased risk of future ischemic stroke, but also of

intracerebral haemorrhage (ICH).<sup>41</sup> Similarly, lesions that are typically considered to be haemorrhagic, in particular, microbleeds, also convey an increased risk of ischaemic stroke. For example, in patients who previously experienced a TIA or ischaemic stroke it has been established that presence of multiple microbleeds is associated with a much higher relative hazard ratio for future ICH than for ischaemic stroke.<sup>42</sup> Yet, because the overall rate of ischaemic stroke in these patients is several fold higher than that of ICH, even in patients with multiple microbleeds the absolute risk of ischaemic stroke is higher than that of ICH.<sup>42</sup> These observations illustrate how difficult it can be to base indications for antithrombotic agents on patients with these lesions. Practical hints are given in Text Box 3.

*Specific issues in the use of antithrombotic therapy.* It is also important to consider if the vascular brain injury, as seen on the scan, provides an indication to initiate or modify antithrombotic therapy. As a general principle “silent” ischemic lesions, in particular WMH, do not provide a clear indication for prescription of antithrombotic agents.<sup>29</sup> By contrast, it is also questionable if presence of a few microbleeds should be a reason to withhold antithrombotic agents in patients in whom such agents are otherwise indicated for presence of symptomatic ischaemic vascular disease. An exception may be people with high (e.g. >10) numbers of microbleeds and also people with cSS, particularly if disseminated (detected in more than 3 sulci). cSS is an indicator of CAA and conveys an absolute risk of future ICH of 11% per year when disseminated.<sup>43,44</sup>

In all cases, particularly for prescribing or discontinuing antithrombotic agents, an individualized approach is needed. Where possible this should be based on weighing the patients estimated absolute risk (and not relative risk which might often be misleading) of both future ischaemic and haemorrhagic events. The challenge is that such estimates are still imprecise and are largely derived from studies that did not specifically include patients from memory clinics. This clearly is an area for further study.

Text Box 3. Practical suggestions concerning treatment of cerebrovascular disease in patients with CI.

- Implement primary and secondary prevention of stroke; primary prevention applies to all patients. Patients who experienced a stroke should be treated according to secondary prevention guidelines.
- No evidence base to support application of secondary stroke prevention treatment strategies for WMH alone.
- Individualized approach to initiate or modify antithrombotic agents based on weighing the individual patients estimated absolute risk of future ischaemic or haemorrhagic events.

## Conclusion and suggestions for future research

The interplay between vascular and neurodegenerative pathologies in patients with CI and dementia remains an active area of research. In recent years, the notion of potentially significant vascular contributions to CI and dementia in different patient settings is becoming better appreciated by clinicians. However, the mechanisms of how cerebrovascular pathophysiology reciprocally interacts with neurodegeneration in producing or contributing to cognitive symptoms and decline are complex and currently elusive. For example, there are many strong epidemiological links between traditional vascular risk factors and CI, and also a plethora of theoretical pathophysiological crosstalk mechanisms between brain vessels pathologies and  $\beta$ -amyloid, a hallmark of neurodegeneration pathobiology. Often, age-related CI and dementia represent really a mix of neurodegenerative and vascular pathologies. Despite the details and trajectories being largely unknown, this realization gives a reason for hope, in that more contributions to CI in patients translates to more targets and opportunities to intervene. Such targets might include protection of the endothelium, the blood-brain barrier, other components of the neurovascular unit, or targeting CAA. It will also be of interest to assess the independent benefit on cognition of commonly used medications for primary and secondary stroke prevention, including antithrombotics in different stroke patient cohorts.

Ongoing and future research should focus on human- and animal-based studies of these interactions and on multidisciplinary consortia exploring potential biomarkers and clinical targets for intervention. Another relevant issue is the need to learn how to best evaluate and qualify cognitive performance as to outline cognitive components that are more specific of the vascular contribution<sup>45</sup> and whether this approach would be clinically meaningful. In the meanwhile, it is reasonable for all patients being assessed or managed for CI, to also be assessed for vascular brain injury and risk for it, and follow relevant published guidelines for primary or secondary prevention of cardio-cerebrovascular disease as applicable.

## Acknowledgements

We thank Professor Franz Fazekas, from the Medical University of Graz, Austria, for his contribution on this paper and we thank the European Stroke Organisation for supporting and for endorsing this initiative.

## Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Olivier Godefroy during the last five years has served on scientific advisory boards and speaker (Biogen, Astra Zeneca, Novartis) and received funding for travel and meetings from Bristol-Myers Squibb, Roche, Biogen, Teva-santé, Boehringer-Ingelheim, Covidien, Ipsen. The remaining authors declare that there are no conflict of interest concerning the paper.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## Informed consent

Informed consent is not applicable to this manuscript.

## Ethical approval

Ethical approval is not applicable for this manuscript.




## Guarantor

AV.

## Contributorship

All authors contributed equally to conceive the manuscript, the structure of paper, literature research and writing of the manuscript. All authors contributed to the different stages of the manuscript, reviewed and edited and finally approved the final version of the manuscript.

## ORCID iDs

Ana Verdelho  <https://orcid.org/0000-0003-4945-4946>  
 Leonardo Pantoni  <https://orcid.org/0000-0001-7357-8530>  
 Joanna Wardlaw  <https://orcid.org/0000-0002-9812-6642>

## Supplemental material

Supplementary material for this article is available online.

## References

1. Rostamian S, Mahinrad S, Stijnen T, et al. Cognitive impairment and risk of stroke: a systematic review and meta-analysis of prospective cohort studies. *Stroke* 2014; 45: 1342–1134.
2. Pendlebury S, Rothwell P and Study OV. Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based oxford vascular study. *Lancet Neurol* 2019; 18: 248–258.
3. Hachinski V. Stoop to conquer: preventing stroke and dementia together. *Lancet* 2017; 389: 1518.
4. Deschaintre Y, Richard F, Leys D, et al. Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. *Neurology* 2009; 73: 674–680.
5. Frederiksen KS, Cooper C, Frisoni GB, et al. A European academy of neurology guideline on medical management issues in dementia. *Eur J Neurol* 2020; 27: 1805–1820.
6. Salvadori E and Pantoni L; on behalf of the Società Italiana di NeuroGeriatrics (SINEG). The role of the neuropsychologist in memory clinics. *Neurol Sci* 2020; 41: 1483–1488.
7. Lamar M, Price CC, Giovannetti T, et al. The dysexecutive syndrome associated with ischaemic vascular disease and related subcortical neuropathology: a Boston process approach. *Behav Neurol* 2010; 22: 53–62.
8. Hamilton O, Kl Blackhouse EV, Janssen E, et al. Cognitive impairment in sporadic cerebral small vessel disease: a systematic review and meta-analysis. *Alzheimers Dement*. Epub ahead of print 13 November 2020. DOI: 10.1002/alz.12221.
9. Andriuta D, Roussel M, Barbay M, et al. Differentiating between Alzheimer's disease and vascular cognitive impairment: is the "memory versus executive function" contrast still relevant? *J Alzheimers Dis* 2018; 63: 625–633.
10. Mathias JL and Burke J. Cognitive functioning in Alzheimer's and vascular dementia: a meta-analysis. *Neuropsychology* 2009; 23: 411–423.
11. O'Brien J. Behavioral symptoms in vascular cognitive impairment and vascular dementia. *Int Psychogeriatr* 2003; 15 Suppl 1: 133–138.
12. Clancy U, Jochems ACC, Doubal FN, et al. Neuropsychiatric symptoms associate with cerebral small vessel disease: systematic review and Meta-analysis. *Lancet Psychiatry* (In press).
13. Tiel C, Sudo FK, Alves GS, et al. Neuropsychiatric symptoms in vascular cognitive impairment: a systematic review. *Dement Neuropsychol* 2015; 9: 230–236.
14. Salvadori E, Brambilla M, Cova I, et al. Cognitive evaluation in cerebral small vessel disease: towards an evidence-based identification of the reference standards. Part 1. A systematic review and qualitative data synthesis. *J Neurol*. Epub ahead of print 13 October 2020. DOI: 10.1007/s00415-020-10262-2. Epub ahead of print.
15. Hachinski VC, Iliff LD, Zilhka E, et al. Cerebral blood flow in dementia. *Arch Neurol* 1975; 32: 632–637.
16. Wardlaw JM, Smith C and Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol* 2019; 18: 684–696.
17. Verwer JH, Biessels GJ, Heinen R, et al.; Utrecht Vascular Cognitive Impairment (VCI) study group. Occurrence of impaired physical performance in memory clinic patients with cerebral small vessel disease. *Alzheimer Dis Assoc Disord* 2018; 32: 214–219.
18. Mc Ardle R, Morris R, Wilson J, et al. What can quantitative gait analysis tell us about dementia and its subtypes? A structured review. *J Alzheimers Dis* 2017; 60: 1295–1312.
19. Poggesi A, Pracucci G, Chabriat H, et al.; on behalf of the LADIS Study Group. Urinary complaints in nondisabled elderly people with age-related white matter changes: the leukoaraiosis and DISability (LADIS) study. *J Am Geriatr Soc* 2008; 56: 1638–1643.
20. Poggesi A, Gouw A, van der Flier W, et al. Cerebral white matter changes are associated with abnormalities on neurological examination in non-disabled elderly: the LADIS study. *J Neurol* 2014; 261: 1160–1169.
21. Jeppesen Kragh F, Bruun M, Budtz-Jørgensen E, et al. Quantitative measurements of motor function in Alzheimer's disease, frontotemporal dementia, and dementia with lewy bodies: a proof-of-concept study. *Dement Geriatr Cogn Disord* 2018; 46: 168–179.
22. Kim KJ, Jeong SJ and Kim JM. Neurogenic bladder in progressive supranuclear palsy: a comparison with Parkinson's disease and multiple system atrophy. *Neurol Urodyn* 2018; 37: 1724–1730.
23. Slot RER, Sikkens SAM, Berkhof J, et al.; SCD-I Working Group. Subjective cognitive decline and rates of incident Alzheimer's disease and non-Alzheimer's disease dementia. *Alzheimers Dement* 2019; 15: 465–476.
24. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration: a united approach. *Lancet Neurol* 2013; 12: 822–838.
25. Debette S, Schilling S, Duperron M, et al. Clinical significance of magnetic resonance imaging markers of vascular brain injury: a systematic review and meta-analysis. *JAMA Neurol* 2019; 76: 81–94.
26. Francis F, Ballerini L and Wardlaw JM. Perivascular spaces and their associations with risk factors, clinical disorders and neuroimaging features: a systematic review and Meta-analysis. *Int J Stroke* 2019; 14: 359–371.
27. Ter Telgte A, van Leijsen EMC, Wiegertjes K, et al. Cerebral small vessel disease: from a focal to a global perspective. *Nat Rev Neurol* 2018; 14: 387–398.
28. Pasi M, Poggesi A and Pantoni L. The use of CT in dementia. *Int Psychogeriatr* 2011; 23 Suppl 2: S6–S12.
29. Smith EE, Saposnik G, Biessels GJ, et al.; American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Functional Genomics and Translational Biology; and Council on Hypertension. Prevention of stroke in patients with silent cerebrovascular disease: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2017; 48: e44–e71.
30. Wollenweber FA, Baykara E, Zedde M, et al. Cortical superficial siderosis in different types of cerebral small vessel disease. *Stroke* 2017; 48: 1404–1407.



31. Norrving B, Barrick J, Davalos A, et al. Action plan for stroke in Europe 2018–2030. *Eur Stroke J* 2018; 3: 309–336.
32. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2019; 50: e344–e418.
33. Karama S, Ducharme S, Corley J, et al. Cigarette smoking and thinning of the brain's cortex. *Mol Psychiatry* 2015; 20: 778–785.
34. Makin SD, Doubal FN, Shuler K, et al. The impact of early-life intelligence quotient on post stroke cognitive impairment. *Eur Stroke J* 2018; 3: 145–156.
35. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multi-domain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (finger): a randomised controlled trial. *Lancet* 2015; 385: 2255–2263.
36. Luciano M, Corley J, Cox SR, et al. Mediterranean-type diet and brain structural change from 73 to 76 years in a Scottish cohort. *Neurology* 2017; 88: 449–455.
37. Heye AK, Thrippleton MJ, Chappell FM, et al. Blood pressure and sodium: association with MRI markers in cerebral small vessel disease. *J Cereb Blood Flow Metab* 2016; 36: 264–274.
38. Kernan WN, Ovbiagele B, Black HR, et al.; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014; 45: 2160–2236.
39. Smith EE and Markus HS. New treatment approaches to modify the course of cerebral small vessel diseases. *Stroke* 2020; 51: 38–46.
40. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation* 2019; 140: e596–e646.
41. Kaffashian S, Tzourio C, Zhu YC, et al. Differential effect of white-matter lesions and covert brain infarcts on the risk of ischemic stroke and intracerebral hemorrhage. *Stroke* 2016; 47: 1923–1925.
42. Wilson D, Ambler G, Lee KJ, et al. Cerebral microbleeds and stroke risk after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies. *Lancet Neurol* 2019; 18: 653–665.
43. Charidimou A, Boulouis G, Greenberg SM, et al. Cortical superficial siderosis and bleeding risk in cerebral amyloid angiopathy: a meta-analysis. *Neurology* 2019; 93: e2192–e2202.
44. Wollenweber FA, Opherck C, Zedde M, et al. Prognostic relevance of cortical superficial siderosis in cerebral amyloid angiopathy. *Neurology* 2019; 92: e792–e801.
45. Salvadori E, Dieci F, Caffarra P, et al. Qualitative evaluation of the immediate copy of the Rey-Osterrieth complex figure: comparison between vascular and degenerative MCI patients. *Arch Clin Neuropsychol* 2019; 34: 14–23.