Voice of Stroke — July 2026

Episode 6: Small Vessels, Big Questions – Biomarkers, Cerebrovascular Autoregulation and Emerging Therapeutic Targets in Cerebral Small Vessel Disease

Introduction: Welcome to Voice of Stroke – your rapid, reliable update on the science advancing stroke care – brought to you by the European Stroke Organisation.

Cerebral small vessel disease or cSVD is increasingly recognised as one of the major contributors to stroke, cognitive impairment and dementia worldwide. Yet despite its enormous clinical impact, treatment remains largely limited to controlling conventional vascular risk factors, while disease-modifying therapies are still lacking.

In this episode of Voice of Stroke, we discuss five recent publications illustrating how the field is evolving. Together, these studies highlight two major themes: first, how biomarkers are helping us to understand the biology of cerebral small vessel disease; and second, how advances in cerebral vascular physiology are pointing towards new therapeutic strategies.

- First, we briefly highlight a systematic review and meta-analysis published in the *International Journal of Stroke*, providing an updated overview of the global burden of cerebral small vessel disease.
- Next, we discuss two translational studies published in *Nature Aging* and *Alzheimer's Research & Therapy*, exploring cerebrospinal fluid and blood biomarkers.
- Finally, we discuss a state-of-the-art review on cerebral autoregulation, followed by a systematic review and meta-analysis evaluating phosphodiesterase-5 inhibitors as a potential therapeutic strategy.

Let's begin with the global burden of cerebral small vessel disease.

Cerebral small vessel disease remains substantially under-recognised despite its enormous clinical and societal

impact.

A recent systematic review and meta-analysis published in the *International Journal of Stroke* summarises the current epidemiological evidence on the global burden. Pooling data from 88 cohorts across 17 regions, the authors found that MRI markers of cerebral small vessel disease were common. Perivascular spaces affected almost one in four people, moderate-to-severe white matter hyperintensities almost one in five, and both lacunes and cerebral microbleeds around one in ten. However, there were also regional, age, and sex differences. For example, lacune was less common in patients from Europe compared to Asia, whilst perivascular space was more common in Asia. Moreover, males tended to have more lacunes and microbleeds compared with females. Perhaps unsurprisingly, advancing age was the strongest risk factor, reinforcing the view that cerebral small vessel disease is, at least in part, a disease of ageing.

Better understanding of the pathological processes underlying cSVD will therefore be essential for developing future disease-modifying therapies.

This brings us to our next two studies.

Although MRI has transformed the diagnosis of cerebral small vessel disease, conventional imaging provides relatively limited information about the biological processes driving disease progression.

Our next two studies take an important step towards addressing this gap.

The first study, published in *Nature Aging*, used large-scale cerebrospinal fluid or CSF proteomics to characterize the molecular pathways associated with MRI markers of cSVD.

Using the Swedish BioFINDER 2 cohort, the investigators analysed CSF protein levels for approximately 3000 proteins in near 1,700 participants, ranging from cognitively unimpaired individuals to patients with mild cognitive impairment and dementia, and related these to white matter hyperintensities, cerebral microbleeds, and subcortical infarcts or lacunes. They validated their results in two additional datasets, using both CSF and plasma.

Here are some findings that stood out.

Several biological pathways were consistently associated with cerebral small vessel disease, including extracellular matrix remodelling and changes in vascular structure. Cell-type enrichment analyses further highlighted vascular-associated cells, particularly arterial smooth muscle cells, as key cellular contributors to cSVD. At the same time, different MRI markers demonstrated partially distinct molecular signatures, suggesting

that different biological mechanisms may contribute to different imaging phenotypes.

Beyond biomarker discovery, this study challenges the traditional view of cSVD as an umbrella term by providing a broader molecular framework for understanding the biological heterogeneity of cerebral small vessel disease.

Our second biomarker study, a multicentre cross-sectional and longitudinal study published in ***Alzheimer's Research & Therapy***, complements these findings by investigating extracellular vesicle-derived blood biomarkers in patients with cSVD with and without cognitive impairment, alongside healthy controls and patients with Alzheimer's disease.

So, what did they find?

The investigators identified three extracellular vesicle proteins that were associated with cSVD severity and cognitive impairment, with combinations of these biomarkers showing good diagnostic performance for identifying both cSVD and cSVD-related cognitive impairment. In addition, several biomarkers were also associated with subsequent disease progression, suggesting that blood biomarkers may eventually complement MRI for risk stratification, disease monitoring and patient selection in future intervention trials.

Together, these two studies illustrate how contemporary cSVD research is moving beyond describing structural MRI lesions towards understanding the molecular biology underlying distinct cerebral small vessel diseases.

Let's now move to our final two papers, focusing on cerebral vascular function.

Our fourth paper is a state-of-the-art review published in the *International Journal of Stroke*, summarising current evidence on cerebral autoregulation in cerebral small vessel disease.

Cerebral autoregulation is the physiological mechanism that maintains relatively stable cerebral blood flow despite fluctuations in systemic blood pressure. Most contemporary studies assess dynamic autoregulation using continuous blood pressure monitoring combined with transcranial Doppler ultrasound, while MRI-based techniques and near-infrared spectroscopy are emerging as complementary research tools for assessing cerebral perfusion and cerebrovascular function.

Overall, the review highlights increasing evidence that autoregulation becomes impaired in patients with cerebral small vessel disease and is associated with disease severity, either as a consequence of microvascular injury or as a contributor to disease progression. Although current clinical studies are very limited, and any causative role for autoregulation remains unclear, the authors conclude that cerebral

autoregulation represents an increasingly important physiological biomarker and a promising therapeutic target but more needs to be done to understand this potential.

Maintaining autoregulation depends on healthy cerebral vascular function. This raises another question: could drugs that improve vascular function also slow disease progression?

This leads to our last paper, which is a systematic review and meta-analysis evaluating phosphodiesterase-5 PDE5 inhibitors in patients with cerebral small vessel disease. PDE5 inhibitors enhance the body's natural nitric oxide signalling pathway, helping blood vessels remain relaxed for longer. In theory, this could then improve cerebral vascular function and ultimately cerebral blood flow.

In this meta-analysis, the investigators pooled data from four small randomised placebo-controlled trials involving 236 participants, evaluating both sildenafil and tadalafil.

So, what were the results?

PDE5 inhibitors improved several cerebral haemodynamic measures, including cerebral blood flow within white matter hyperintensities. However, convincing improvements in cognition were not observed, and the available evidence remains limited by relatively small sample sizes, short treatment duration and the use of predominantly physiological and imaging endpoints rather than clinical outcomes.

Overall, the available evidence suggests that pharmacological targeting of cerebral vascular function is biologically plausible, but the available trials have been too small to determine whether this translates into meaningful clinical benefit.

The next step will be to address this question in larger trials. The ongoing phase III LACI-3 trial is evaluating whether isosorbide mononitrate and cilostazol- two agents targeting cerebral vascular function - can reduce cognitive decline and recurrent vascular events after lacunar stroke. In addition, the forthcoming phase III SILENCE trial will evaluate sildenafil versus placebo in patients with symptomatic cerebral small vessel disease, using a hierarchical composite outcome including stroke, dementia, functional dependence and death. Together, these studies will provide important evidence on whether targeting cerebral vascular function can modify disease progression and improve clinically meaningful outcomes.

So, to wrap up:

- Cerebral small vessel disease remains a major and growing contributor to stroke, cognitive impairment and dementia, highlighting the urgent need for disease-modifying therapies

- Recent biomarker studies are improving our understanding of the molecular pathways underlying cerebral small vessel disease and may facilitate future biological classification and patient stratification.
- Finally, growing evidence suggests that impaired cerebral vascular function, including autoregulation, may represent an important therapeutic target, with large clinical trials now underway

Full references and links to all studies discussed are available in the episode notes.

Ending: That's all for this episode of Voice of Stroke, brought to you by the European Stroke Organisation. You can listen to Voice of Stroke on all your favourite podcast channels, including Spotify and Apple. Visit the European Stroke Organisation for more information about our organisation, mission and our key activities. I'm Linxin Li. Thanks for listening.

Credit: This episode was written by Voice of Stroke Podcast editor Annemijn Algra and editor-in-chief Linxin Li.

References

1. Lam BYK, et al. Global burden of cerebral small vessel disease determined from large MRI studies: A systematic review and meta-analysis. *International Journal of Stroke* 2026. https://doi.org/10.1177/17474930261441916

2. Hristovska I, et al. Identification of distinct and shared biomarker panels in different manifestations of cerebral small-vessel disease through proteomic profiling. *Nature Aging* 2026; 6: 703–721. https://doi.org/10.1038/s43587-026-01081-7

3. Yang D, et al. Plasma extracellular vesicle proteins biomarker for cerebral small vessel disease related cognitive impairment. *Alzheimer's Research & Therapy* 2026. https://doi.org/10.1186/s13195-026-02078-5

4. Webb AJS, et al. The role of impaired autoregulation in cerebral small vessel disease and vascular cognitive impairment. *International Journal of Stroke* 2026. https://doi.org/10.1177/17474930261456372

5. Yan L, et al. Phosphodiesterase-5 inhibitors for cerebral small vessel disease-related ischemic stroke and cognitive decline: Systematic review and meta-analysis. *Frontiers in Neurology* 2026; 17: 1776589. https://doi.org/10.3389/fneur.2026.1776589