Voice of Stroke — March 2026

Episode 2: What's New In The Field Of Lipids, And Can It Help Us Prevent Stroke?

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

Body: Managing lipids is part of the daily routine of stroke physicians. Yet many questions remain, including adherence, drug selection and who benefits most from intensive therapy.

In this episode of Voice of Stroke, we discuss a Lancet individual participant-level meta-analysis that reframes concerns regarding statin side effects, a major NEJM (read as *N-E-J-M*) trial of a PCSK9 (read as *P-C-S-K nine*) inhibitor, and new long-term data linking lipids and inflammation to stroke risk decades later, plus a quick overview of oral PCSK-9 drugs in development.

We will focus on three key questions:

- First: are most adverse events listed on statin labels truly caused by statins?
- Second: in patients without previous symptomatic vascular disease, does the PCSK9 inhibitor Evolocumab (read *E- vo - lu - q - mab*) reduce major vascular events, including stroke?
- And finally: can LDL (read as *L-D-L*), lipoprotein(a) (read *lipoprotein A)*, and high-sensitivity CRP (read as *C-R-P*) predict stroke risk 30 years into the future?

Let's start.

Statins reduce the risk of death and vascular events but they remain underused, in part due to concerns about side effects. However, much of the concern comes from observational data, which can't prove causation. A new individual participant data meta-analysis from the Cholesterol Treatment Trialists' Collaboration, published in *The Lancet* addresses this using randomised blinded trial data.

Previous reports from this group have established that statins mildly increase the risk of myopathy and of newly diagnosed diabetes, and this study extends the analysis to the other side effects included in statin product labels.

In the current analysis, over 150,000 participants from 23 large double-blind randomised controlled trials were included. The median follow-up was about 5 years. The mean age was 63 years and about half of the participants had known vascular disease.

What did they find?

Across 19 placebo-controlled, blinded trials, only four of the 66 side effects listed in statin product labels were confirmed as being caused by statins, and the absolute increases were very small - well under one additional case per thousand patients per year. These four side effects were mild liver enzyme elevations, other minor liver test abnormalities, a small increase in protein in the urine, and oedema. Among four double-blind trials where higher-dose statins were compared with lower-dose statins, only liver test abnormalities were clearly more frequent in the higher-dose groups. Again, with low absolute rates. For the other 62 side effects, such as cognitive impairment or sleep disorders, there was no evidence of a causal association with statins.

Together with earlier evidence showing that only 1 in 15 muscle symptoms in randomised controlled trials are truly statin-related, this study reinforces that genuine statin side effects appear to be uncommon. This has important implications for clinical practice, particularly when counselling patients who are hesitant to start or continue treatment or who develop symptoms of uncertain cause.

If statins are safer than many fear, the next question is whether adding non-statin options can safely lower LDL even further. We know from secondary prevention trials that PCSK-9 inhibitors, such as Evolocumab, reduce the risk of vascular events in addition to statin therapy, but are these agents beneficial in individuals without previous symptomatic vascular disease?

The VESALIUS-CV trial, published in the *New England Journal of Medicine* , aimed to answer this question. This industry-sponsored double-blind randomised controlled trial enrolled participants without a previous myocardial infarction or stroke who were at increased risk of vascular disease due to atherosclerosis or high-risk diabetes.

Over 12,000 participants were randomised to Evolocumab or placebo, on top of background lipid-lowering treatment. The median age was 66 years and the baseline median LDL was 3.16 millimole per litre.

After a median follow-up of 4.6 years, Evolocumab reduced the rate of death from coronary heart disease, myocardial infarction, or ischaemic (read as *is-ki-mic*) stroke by 25%, with a number needed to treat of 56 over 5 years. All secondary endpoints were in the direction of benefit, with a 21% reduction in ischaemic stroke and a 36% reduction in myocardial infarction. Results were consistent in all key subgroups, including by age, sex, qualifying disease, LDL cholesterol at baseline, and intensity of previous statin therapy. Serious adverse events did not vary between groups, although rates of intracranial haemorrhage were not reported.

In a lipid substudy that included a random subset of the trial population, Evolocumab led to a 55% decrease in LDL cholesterol and a 27% decrease in lipoprotein (a).

VESALIUS-CV extends the evidence supporting PCSK-9 inhibitors in high-risk populations for primary prevention. These findings may therefore help to inform the management of patients with asymptomatic intracranial or extracranial artery stenosis. However, cost-effectiveness remains a key consideration.

Looking ahead, oral PCSK-9 inhibitors are now moving through phase-3 development and some have shown substantial LDL reductions in phase-2 trials, raising the possibility of having a daily pill option in the future. However, we're still awaiting definitive cardiovascular outcome data, including effects on stroke, before these drugs can enter routine practice.

Indeed, identifying who will benefit most from early and intensive lipid lowering remains a key challenge in primary stroke prevention, particularly in younger individuals whose short-term risk appears low.

A recent study published in *The Lancet Neurology* evaluated whether LDL cholesterol, lipoprotein(a), and high-sensitivity CRP can predict 30-year risk of stroke in women without known vascular disease.

The analysis included nearly 28,000 participants from the Women's Health Study, which was a randomised controlled trial of aspirin and vitamin E for the primary prevention of vascular disease that was conducted in the USA starting from 1993.

The median age at enrolment was 53 years. During a median of 28 years of follow-up, over 1,300 women developed a stroke. High-sensitivity CRP showed the strongest association with future stroke risk, while LDL

cholesterol and lipoprotein(a) showed more modest associations with ischaemic stroke only. Notably, women with an elevation in all of these three biomarkers had the highest long-term risk.

These findings indicate that simple blood tests may be useful to predict the future risk of stroke, and these estimates may be helpful for the design of future trials targeting inflammation or lipoprotein(a).

So in summary:

- Statin side effects are uncommon and often overstated.
- PCSK-9 inhibitors further reduce major vascular events in high-risk patients, with oral agents on the horizon.
- And emerging biomarker data may help us think beyond short-term risk towards lifetime stroke prevention.

Finally, a very brief guideline update: the 2026 American guideline on management of dyslipidaemia was published this month in Circulation. This is an update from the 2018 American Heart Association and American College of Cardiology guideline. Key updates include recommendations of wider use of tests such as lipoprotein A, CRP and coronary artery calcium scoring to personalise lifetime risk, and the return of LDL and non-HDL cholesterol treatment goals, with lower targets for higher-risk groups.

Links to the guideline and to all the studies discussed are available in the episode notes.

To explore this topic further, including LDL management after lobar ICH and ongoing trials, please see the recent International Journal of Stroke review, “Dyslipidemia Management in Stroke Prevention: An Individualized Approach.”

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 E-S-O-dash-stroke-dot-org 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 Ahmad Nehme and Editor-in-chief Linxin Li.