



## Voice of Stroke — May 2026

### Episode 4: Intracerebral Haemorrhage - From Blood Pressure Control to Secondary Brain Injury

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

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**Body:** Intracerebral haemorrhage remains one of the most severe forms of stroke worldwide, but evidence-based treatment options are still relatively limited. However, the field is evolving rapidly.

In this episode of Voice of Stroke, we focus on two themes that are currently driving ICH research forward: first, improving implementation of effective treatments we already know - particularly blood pressure control - and second, developing new therapeutic targets aimed at limiting secondary injury after the initial bleed.

We will discuss three important recent studies:

- First, the TRIDENT trial published in the New England Journal of Medicine, evaluating strategies for long-term blood pressure lowering after ICH.
- Second, an individual participant data meta-analysis published in Stroke, examining peri-haematoma oedema growth, as a marker of secondary injury and clinical outcome.
- And finally, a translational study published in Annals of Neurology, exploring inflammatory signalling directly within the haematoma cavity after ICH.

We will also briefly highlight the award-winning projects presented at the ESO ICH Academy Meeting in Maastricht early this month.

Let's begin with the TRIDENT trial.

Although hypertension is the most important modifiable risk factor for recurrent ICH, the benefits of intensive blood pressure lowering and the optimal treatment strategy remain uncertain.

The TRIDENT trial, recently published in the *New England Journal of Medicine*, evaluated the efficacy and safety of a fixed low dose combination antihypertensive regimen, referred to as the “triple pill”, in addition to standard care, among patients with a history of intracerebral haemorrhage. The triple pill contains telmisartan 20 mg, amlodipine 2.5 mg, and indapamide 1.25 mg in a single formulation.

Nearly 1,700 patients were randomized to receive either the “triple pill” or placebo on top of usual care. Most participants were recruited in Asian populations, particularly Sri Lanka, and the mean age was relatively young, around 58 years. Randomization occurred relatively early, at a median of 54 days after the index ICH. An important design feature was the pre-randomization run-in phase, during which patients unable to tolerate treatment were excluded before entering the blinded study.

So, what did they find?

During a median follow up of two and a half years, the triple-pill group achieved a mean systolic blood pressure of 127 mm Hg, compared with 138 mm Hg in the placebo group. Recurrent stroke occurred in 4.6% of patients receiving the triple pill, versus 7.3% in the placebo group. This corresponded to an absolute risk reduction of approximately 3%, numbers need to treat of 37, and a relative risk reduction approaching 40%. Much of the benefit appeared to be driven by fewer recurrent ICH.

Importantly, the low-dose triple combination was generally well tolerated, without an increase in serious adverse events. However, excluding treatment-intolerant patients before randomization likely improved tolerability estimates, and it remains uncertain whether the same strategy would be equally safe in older or more frail patients commonly encountered in routine practice.

Still, TRIDENT builds on signals previously seen in the PROGRESS trial and provides some of the strongest contemporary evidence that sustained intensive blood pressure control after ICH can substantially reduce recurrent stroke risk.

It is worth noting that although the triple pill approach improved blood pressure control overall, only around half of the patients in this group achieved the target systolic blood pressure of less than 130 at 6 months. This suggests that whilst a simplified low-dose combination strategy may improve long-term adherence, maintaining good control will still require close follow-up and lifestyle interventions alongside medication.

Interestingly, secondary analyses presented at ESOC 2026 showed that despite the reduction in recurrent stroke, no significant differences were observed in dementia, cognitive outcomes, or MRI markers of cerebral

small vessel disease between the triple-pill and placebo groups after three years. These findings suggest that any cognitive benefits of long-term blood pressure lowering after ICH may require longer follow-up or larger dedicated studies to detect.

Let's now move on to our second study, published in *Stroke*, focusing on perihematoma oedema - or P-H-E.

Perihematoma oedema develops rapidly after intracerebral haemorrhage and is considered an important marker of secondary brain injury. However, there has been ongoing debate about which oedema measures are clinically most relevant.

Rather than focusing on static oedema volume, this study assessed oedema growth over time.

In this individual participant data meta-analysis, the investigator included over 1,500 patients from 12 studies. All patients had spontaneous ICH who underwent baseline CT imaging within 72 hours, and had repeat imaging within 14 days. Surgical patients and patients receiving interventions likely to alter oedema evolution were excluded.

The key finding was remarkably consistent.

Greater PHE growth at both 24 and 72 hours independently predicted worse functional outcome at 90 days, even after adjustment for haematoma volume and other major prognostic factors. The effect sizes were modest but clinically relevant. Each 1-milliliter increase in oedema growth was associated with approximately a 2-4% increase in the odds of death or dependency at 90 days, depending on the timing of oedema measurement.

So, what are the implications?

Perhaps the most important implication is that PHE growth may represent a useful imaging biomarker for future ICH trials. CT imaging is rapid, inexpensive, and widely available, making serial oedema assessment feasible across many stroke systems. Several ongoing drug trials targeting perihematoma oedema are already incorporating repeat imaging within 72 hours, potentially allowing PHE growth to be evaluated as an intermediate treatment outcome. Moreover, a better understanding of the mechanisms driving PHE growth may also help identify new therapeutic targets for future drug development.

Our final study takes us from imaging into translational neuroimmunology.

This study, published in *Annals of Neurology* explored inflammatory signalling directly within the haematoma cavity after intracerebral haemorrhage.

This was a prospective substudy nested within the MISTIE III trial. Patients undergoing minimally invasive catheter evacuation had serial haematoma fluid samples collected over the first week after ICH, allowing investigators to study inflammatory pathways directly inside the haematoma itself.

What makes this study particularly interesting is that the investigators examined inflammation across multiple biological compartments - including haematoma fluid, peripheral blood, and cellular transcriptomic analyses from haematoma-derived immune cells. The focus was on cytokines within the interleukin-1 pathway, including IL1 beta, IL-6, and IL-1 receptor antagonist - or I-L-1-R-A.

Several findings stood out.

Higher haematoma concentrations of IL-1 receptor antagonist were linked to better functional outcome at one year. Interestingly, higher IL-6 levels were also associated with favourable long-term outcome, challenging the traditional view of IL-6 as purely harmful and supporting the idea that post-ICH inflammation may contribute to both injury and repair.

The study also identified monocyte and macrophages within the haematoma as key sources of IL-1 beta, IL-6, and IL-1Ra. In contrast, peripheral blood biomarkers correlated poorly with intracerebral inflammation, highlighting how differently inflammation behaves within the brain compared with the systemic circulation.

Finally, IL-1 related cytokines remained detectable within the haematoma fluid throughout the first week after haemorrhage, suggesting a potential longer therapeutic window for anti-inflammatory interventions than previously thought.

Although exploratory and relatively small, this study advances understanding of post-ICH inflammation and strengthens interest in therapies targeting the IL-1 pathway, including anakinra and other immunomodulatory approaches.

Before we finish, we should also highlight the award-winning projects presented at the annual ESO ICH Academy Meeting in Maastricht, which is becoming an increasingly important forum for ICH research.

This year, the Clinical Science Award went to Umberto Pensato from Milan for the SPOTMAP project, an international multicenter study using multiphase CTA to improve prediction of haematoma expansion. The Basic Science Award was presented to Gözde Caan from Edinburgh for ICH-SOLES, a machine-learning platform to integrate evolving clinical and preclinical ICH research to help accelerate drug development.

So, to wrap up:

- The TRIDENT trial reminds us that rigorous blood pressure control after intracerebral haemorrhage remains one of the most effective strategies we currently have to reduce recurrent stroke risk.
- Dynamic perihematoma oedema growth appears to be an important marker of secondary brain injury and poor functional outcome.
- And translational studies of inflammatory signalling continue to improve our understanding of post-ICH biology and potential therapeutic targets.

Together, these studies show how contemporary ICH research is evolving on two parallel fronts: improving implementation of established preventive strategies while simultaneously developing new mechanistic targets for future intervention trials.

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 [E-S-O-dash-stroke-dot-org](https://www.euro-stroke.org) for more information about our organisation, mission and our key activities. I'm Linxin Li. Thanks for listening.

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

## References

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4. ICH Academy Meeting: <https://eso-stroke.org/resources/eso-ich-academy-meeting-iam/>