significance, particularly those that do not have a clear and unambiguous biological rationale, should be viewed with caution.[9]

The presumption in dose-finding is that a specific threshold dose will show optimum efficacy, with fewer side-effects at lower doses.[10] The usual reason to assess multiple doses is to find the dose with the highest potential efficacy but that is still within an acceptable range regarding side-effects. Dose–response curves are generally sigmoidal, but U-shaped curves have also been reported, whereby the therapeutic effect at one dose is attenuated at a higher dose. However, evidence for such a dose–response would need to be robust, and a dose–response in a narrow therapeutic range raises concerns about the actual clinical application of such treatment. The pharmacokinetics of a drug generally means that target tissues are not exposed to one static dose of drug and exposure varies across patients.

The importance of oligodendrocyte precursor cell differentiation as a means of achieving remyelination remains very relevant, despite the intrinsic limitations of opicinumab and its therapeutic failure in relapsing multiple sclerosis[1] and acute optic neuritis.[8] The negative findings are likely to be a reflection of the antibody-based approach or that LINGO-1 might not be an appropriate biological target to achieve remyelination. Although it might be impossible to know exactly why the SYNERGY trial was unsuccessful, the field will benefit from recognising that the therapeutic approach investigated here is not a path forward. Regardless, remyelination remains a promising tactic for preventing disability and restoring function for patients with multiple sclerosis.

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Blood pressure in intracerebral haemorrhage: which variables matter?

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Blood pressure reduction in patients with acute intracerebral haemorrhage is an important, unresolved issue in stroke management. Two large clinical trials have shown inconsistent results, but are now combined for further analyses. The main phase of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2) with 2839 patients found that intensive systolic blood pressure reduction (target <140 mm Hg within 1 h, cessation of treatment at <130 mm Hg) within 6 h of onset of intracerebral haemorrhage improved functional recovery on a number of secondary outcomes, although the primary outcome (death or major disability at 90 days post-randomisation) was not significant. By contrast, the second Antihypertensive Treatment of Acute Cerebral Hemorrhage Trial (ATACH-II) with 1000 patients used a more intensive strategy (target 110–139 mm Hg

within 2 h) within 4·5 h of symptom onset and reported no benefit and an excess of renal adverse events.[1,2] Analysis of blood pressure variability as a prognostic indicator in INTERACT2 participants found that maximum systolic blood pressure in the hyperacute phase (first 24 h) and variability of systolic blood pressure in the acute phase (days 2–7) were the strongest predictors of death or major disability at 90 days.[3] Smaller studies have provided some evidence of a benefit of minimising blood pressure variability around target levels,[4,5] whereas meta-analyses have shown no overall benefit of early intensive blood pressure lowering compared with guideline target levels.[6–9]

In *The Lancet Neurology*, Tom Moullaali and colleagues[10] report findings from a pooled individual patient-level data analysis from INTERACT2 and ATACH-II, evaluating three summary statistics of observed systolic blood pressure: mean achieved systolic blood pressure, magnitude of reduction in the first hour after randomisation, and variability (SD). This unified analysis begins to clarify the complexity of the blood pressure reduction problem. In the prespecified adjusted primary analysis, the combined measure of these three summary measures as continuous variables suggests that systolic blood pressure control seems safe and efficacious. Achieved systolic blood pressure and variability in systolic blood pressure were significantly associated with good outcomes, whereas magnitude of reduction was not. For their secondary assessments, the authors report significant linear trends for magnitude of systolic blood pressure reduction associated with functional independence at 90 days post-randomisation, neurological deterioration over 24 h, and death within 90 days, whereas achieved systolic blood pressure was significantly associated with neurological deterioration over 24 h, and variability with death. The U-shaped relationship for magnitude revealed some evidence for significant associations between reductions up to 60 mm Hg with functional independence, whereas greater reductions were significantly associated with lower odds of good outcome. The associations between magnitude of systolic blood pressure reduction and poor outcomes were significant for the first hour post-randomisation, but not over 24 h.

This analysis adds important evidence to the controversy over optimal blood pressure control in patients with acute intracerebral haemorrhage, confirming the INTERACT2 results that some degree of blood pressure lowering is beneficial and that more variability in systolic blood pressure could be deleterious. Large reductions in systolic blood pressure over the first hour after onset of symptoms might also be harmful. Unfortunately, the combined measure used for the primary analyses is complex and a does not provide a quantifiable target for acute stroke care teams. Thus, the current findings should be considered hypothesis-generating rather than practice changing.

This study did not find any interaction with study treatment group, but showed an association between both achieved systolic blood pressure and variability in systolic blood pressure with serious adverse events within 90 days post-randomisation. In addition, magnitude of systolic blood pressure reduction from 15 min to 24 h post-randomisation was associated with adverse events within 90 days post-randomisation (odds ratio 1·05 [95% CI 1·00–1·10]; p=0·0434). The potential for harm exists both for hypertensive patients with shifted autoregulatory curves and abnormal vessels, who might have relative cerebral hypoperfusion with rapid systolic blood pressure lowering, and patients with large intracerebral haemorrhage, or intraventricular haemorrhage with obstructive hydrocephalus, in whom cerebral perfusion pressure is compromised. In these patients, avoidance or limitation of blood pressure reduction might be beneficial. Similarly, patients with large (>30 mL) haematoma volumes and other poor prognostic criteria (eg, intraventricular extension and oedma causing mass effect) might also have higher peak systolic blood pressure and more variability, although post-hoc analyses adjusting for intracerebral haemorrhage location (deep *vs* other) and intracerebral haemorrhage volume reported consistent associations with harmful outcomes. Given the well established presence of vascular disease in the patient population with intracerebral haemorrhage, additional rigourous evaluations for vascular harms from blood pressure lowering are needed in future trials.

Although lower achieved systolic blood pressure and less systolic blood pressure variability were associated with reduction in haematoma expansion as continuous variables, categorised systolic blood pressure summary measures were not associated with haematoma expansion, consistent with results of INTERACT2.[1] Beneficial effects of early reduction of blood pressure might be driven by non-haematoma growth mechanisms, including autonomic dysfunction and systemic stress reactions.[11]

Because both INTERACT2 and ATACH-II excluded patients with large haematomas and high clinical severity (ie, a low score on the Glasgow Coma Scale or an intracerebral haemorrhage volume of >60 mL), associations between magnitude of blood pressure reduction and outcomes by haematoma size, obstructive hydrocephalus, and large volume cerebral oedema, which are all markers of mass effect or elevated intracranial pressure, were unlikely to be identified in the current study. These results suggest that physicians should consider an individualised approach to systolic blood pressure management that avoids abrupt, uneven, and large drops in systolic blood pressure. Such an approach might be a reasonable objective in patients with acute intracerebral haemorrhage for small and medium size lesions. Future randomised controlled trials of blood pressure lowering and control of blood pressure variability will be needed to better understand benefit and harm, especially with large reductions when harm might occur. More data are needed if current guideline targets or other approaches are to be more helpful given the incomplete evidence now available. We look forward to variability and magnitude of reduction targets being used in trials of blood pressure lowering now underway and in a meta-analysis of all bood pressure lowering trials.

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