influenced their treatment decisions. There was no change in the HR after adjustment.

A series of subgroup and sensitivity analyses provide additional reassurance that the findings are consistent with the conclusion that antithrombotics might be protective in these patients. In each analysis, the estimates were in the same direction, with a clinically relevant effect, although not statistically significant, possibly because of the small sizes of the groups or the small number of events. These analyses included patients taking anticoagulants (none of 10 patients), individuals with intracerebral haemorrhage at presentation (adjusted HR 0·41, in 52 patients), and when antithrombotic therapy was analysed as a time-dependent covariate (adjusted HR 0·30). Importantly, when the outcome was restricted to intracerebral haemorrhage only, the direction of effect was similar but not significant (one [2%] of 62 patients *vs* 18 [8%] of 238; log-rank p=0·070). Furthermore, a systematic review of six other published and unpublished studies showed similar findings, with fewer intracerebral haemorrhages in the patients on antithrombotics.[1]

Are these findings plausible on the basis of current knowledge of the pathophysiology of CCMs? Histologically, these lesions consist of dilated thin-walled vascular channels lined by endothelium, with no or minimal intervening brain tissue, surrounded by gliosis and haemosiderin.[6] Thrombi within these channels are seen in about a half to three-quarters of cases.[7,8] It is plausible that thrombosis could impair venous drainage or trigger inflammation, with expression of metalloproteinases, leading to increased pressure and breakdown of the extracellular matrix, with consequent bleeding.

The findings from this study provide some reassurance that clinicians can use antithrombotics safely, if clearly indicated, in patients with CCMs—particularly when the patient is asymptomatic and excision or radiosurgery is not indicated or not possible.[9] Perhaps antithrombotics could even be used as a treatment for CCMs, although it would be presumptuous to do so based only on uncontrolled observational evidence. A clinical trial of antithrombotics is well justified by the findings of this observational study, and hopefully will be done.

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Blood pressure control as an intervention to prevent dementia

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Observational findings of a relationship between blood pressure during midlife and cognitive brain outcomes have been replicated in different populations, but negative findings have also been reported.[1] Often based on cross-sectional studies or on data from very old people (ie, >80 years of age), interpretations of these negative studies have not accounted for issues such as reverse causation.[2] As a consequence of inconsistencies in the published literature, blood pressure lowering has not been accepted as a candidate for intervention against cognitive impairment or dementia—a trial was needed.

The SPRINT MIND trial detected a cognitive benefit of blood pressure lowering in a large cohort of people aged 50 years and older with diverse ethnic origins.[3] This

trial strengthens the observational study conclusions that blood pressure is involved in modulating risk for dementia and underlines the importance of linking findings in risk factors during middle age with outcomes in older people.

In *The Lancet Neurology*, Lane and colleagues[4] bring new insights into blood pressure–cognitive-related outcomes, drawing from data collected on a subsample of the 1946 British birth cohort, in a design that controls for reverse causation. With data on multiple measures done at around 8-year intervals between the ages of 36 years and 70 years, the authors examined the associations of levels and changes in blood pressure with brain structure and function and with amyloid load, a biomarker for Alzheimer's disease pathology. The study addresses windows of opportunity for prevention of dementia and provides data testing the hypothesis that vascular damage contributes to Alzheimer's disease pathology.

This study showed that the window of opportunity spans middle age, peaking in the 40s. During this period, both heightened and increases in systolic and diastolic blood pressure were associated with more white matter lesions, an indicator of vascular damage. Higher diastolic blood pressure and change in diastolic blood pressure in the period of 36–43 years of age were associated with smaller whole-brain volume later in life. These results were robust to correction for other cardiovascular risk factors at 70 years of age.

However, blood pressure was not associated with cognition but, as the authors note, there might not have been enough variability to detect differences in cognition. Absence of association might also reflect life course differences. The authors adjusted their findings for early life cognitive performance, a factor that has been shown previously to be significantly correlated with later life cognitive performance in this cohort;[5] at older ages, changes in cognition might lag behind changes in brain structure.

This new study finds no association between high blood pressure and amyloid pathology measured on PET. As the authors note, this negative finding suggests that high blood pressure more likely affects dementia through small vessel disease than through amyloid-related pathways. However, a negative finding does not necessarily provide evidence against a vascular contribution to Alzheimer's disease pathology. For instance, PET amyloid imaging cannot identify precursors to amyloid deposition or be used to investigate the interaction between neurodegenerative and vascular processes on a micro level.

The findings from this study motivate a deeper dive into the role of blood pressure components and brain health. For example, most studies have examined the level of blood pressure in relation to brain outcomes, but other components of blood pressure might be physiologically important, such as pulse wave velocity, or other manifestations of hypertension, such as isolated high systolic or diastolic blood pressure. Additionally, besides macro structure changes in the brain, data are scarce, particularly from cohort studies, on the contribution of elevated blood pressure to cerebral microstructural damage and cerebral blood flow and metabolism, or to disturbances in the blood brain barrier, autoregulation, and clearance of toxic substances from the brain. Whether there are phases and dependencies in which these brain pathologies emerge that are differentially related to vascular and haemodynamic changes is also unknown. Several clinical questions also remain. For example, should treatment options be the same for cardiovascular disease or are specific regimes or drugs more effective than others in reducing risk of cognitive impairment; and should different protocols be developed depending on age, comorbidity, and ethnicity, as cardiovascular guidelines propose?

Although there are several major translational efforts to more completely understand the complexity of blood pressure–cognitive-related outcomes, the association between blood pressure and vascular brain pathology is unlikely to be a chance finding. Millions of individuals have unhealthy blood pressure. Immediate attention should be given to efforts to control blood pressure through clinical services and public health interventions, and to alleviate the barriers to delivery and uptake of these public-health messages.[6]

Life in View/SPL

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Should plasma GFAP guide the management of patients with traumatic brain injury and a negative CT scan?

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The ability to accurately diagnose the severity of traumatic brain injury (TBI) to establish the consequent need for treatment still eludes modern emergency care systems. Every year, millions of patients worldwide present to emergency departments after head injury,[1] most with debilitating TBI symptoms including impaired consciousness and cognition, amnesia, vomiting, and headache. Currently, the sole standard diagnostic tool is the CT brain scan, which accurately detects TBI in the small minority of patients requiring neurosurgery or neurocritical care for life-threatening injury.[1] However, the CT brain scan is negative in more than 90% of patients with TBI symptoms,[2] leading to uncertainty as to the extent of TBI and likely need for further treatment. The role of MRI after a negative CT finding is currently unclear and not part of routine care in conscious patients (without neurological signs).[1] Adding a routine MRI scan to the pathway of all CT-negative patients (before discharge from the emergency department) could be prohibitively expensive, because an additional stay of some hours or a ward admission would occur.

In children and adults (aged <65 years) injured by high-energy mechanisms, such as motor vehicle collisions and sport, these presenting symptoms could be reasonably attributed to TBI after a negative CT scan, but the recovery trajectory and advice on return to work, participation in sport, and driving is not currently based on precise assessment of TBI severity. The presenting conscious level and duration of amnesia do not provide a reliable guide as to who is at risk of developing disabling post-concussion symptoms.[3] In patients with low-energy falls causing loss of consciousness or amnesia, the diagnostic challenge is greater still, because TBI symptoms can be contiguous with those of intoxication or pre-existing illness causing falls.[4]

Most patients with a negative CT scan are discharged from emergency departments with safety net advice to revisit emergency departments or seek primary care if their post-injury symptoms are disabling. The numbers of CT-negative patients are deemed too great for routine follow-up.[1] However, up to 60% of these patients with so-called mild TBI have clinically significant depression at 10 weeks post injury.[3] It would undoubtedly be cost-effective to have a biomarker of the severity of TBI when the CT scan is negative, because this could direct the need for follow-up clinics, early rehabilitation, and the use of MRI for better injury characterisation, and facilitate advice on return to contact sports.

An analysis of the TRACK-TBI study, reported by John Yue and colleagues[5] in *The Lancet Neurology,* addresses these diagnostic and therapeutic uncertainties; an accurate blood biomarker for TBI in patients with a negative CT scan could be transformative. Glial fibrillary acidic protein (GFAP) is attractive in this regard; it is a specific marker of astrocyte injury. In 2018, the US Food and Drug Administration licensed its use to guide the initial need for CT scan in patients with suspected TBI.[6]

The TRACK-TBI Investigators did a rigorous study of 1234 patients in US trauma centres receiving head CT scan for investigation of TBI whose conscious level was full or minimally impaired (Glasgow Coma Scale score 13–15). 450 of the 794 patients with TBI and negative head CT scans completed follow-up with a head MRI scan. This cohort mainly comprised young people (mean age 36 years) injured by high-energy mechanisms. A quarter (120 [27%]) of these patients had positive findings on MRI scan—most of these (65 [54%]) showing traumatic axonal injury. GFAP concentration at 9–16 h post injury discriminated well between patients with MRI-positive