probably require many groups to collaborate to achieve the ambitious goals outlined by the InTBIR investigators. We anticipate that the CENTER-TBI efforts will be combined with those of ongoing studies, including the Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) study[5], the Italian Creactive study, several Canadian studies of mild TBI in children, along with many other clinical and research efforts worldwide to generate data that will help us understand how to care for the myriad external injuries that can occur so commonly to the most complicated organ in the human body. Perhaps the foresight of the InTBIR organisers has launched a wonderful decade, or *mirum decennium*, for TBI.

Michael J Bell, Patrick M Kochanek
Division of Critical Care Medicine, Children's National Medical Center, George Washington University School of Medicine, Washington DC 20010, WA, USA (MJB); and Department of Critical Care Medicine and the Safar Center for Resuscitation Research, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA (PMK)
mbell@childrensnational.org

PMK reports a stipend from the Society of Critical Care Medicine as editor-in-chief of the journal *Pediatric Critical Care Medicine*, which published the Guidelines for the Management of Severe TBI in Children in 2019, on which he was the first author. MJB declares no competing interests.

1 Renn J, Hoffman D. 1905—a miraculous year. *J Phys B: At Mol Ot Phys* 2005; **38:** S437–48.
2 Steyerberg EW, Weigers E, Sewalt C, et al. The contemporary landscape of traumatic brain injury in Europe: case-mix, care pathways, and outcomes from the CENTER-TBI study. *Lancet Neurol* 2019; **18:** 923–34.
3 Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol* 2017; **16:** 987–1048.
4 Lingsma HF, Roozenbeek B, Perel P, Roberts I, Maas AI, Steyerberg EW. Between-centre differences and treatment effects in randomized controlled trials: a case study in traumatic brain injury. *Trials* 2011; **12:** 201.
5 Manley GT, Maas AI. Traumatic brain injury: an international knowledge-based approach. *JAMA* 2013; **310:** 473–74.

Antithrombotics and bleeding risk: paradoxical findings

Published **Online**
August 7, 2019
http://dx.doi.org/10.1016/S1474-4422(19)30280-7

See **Articles** page 935

Can an antithrombotic drug prevent bleeding? For cerebral cavernous malformations (CCMs), a study in *The Lancet Neurology* by Susanna Zuurbier and colleagues[1] suggests that, paradoxically, it might.

CCMs, also called cavernous angiomas or cavernomas, are small vascular lesions that are detected in up to 0·2% of the general population[2] and can cause focal neurological deficits or seizures. Clinicians typically avoid antithrombotics in these patients because CCMs are prone to bleeding, with an approximate risk of bleeding of 0·8–1·6% per year for asymptomatic lesions and 3·6–6·2% per year for symptomatic lesions, depending on location.[3] However, avoiding antithrombotics is becoming increasingly difficult because of expanding indications for their use and an ageing population.[4]

In this cohort study, systematic review, and meta-analysis, the authors used data from the Scottish Audit of Intracranial Vascular Malformations and the published literature to establish whether antithrombotic use was associated with new focal neurological deficits or bleeding.[1] Patients were identified by screening of all radiology reports within a defined geographical area (Scotland, UK) for diagnosed CCMs. Active surveillance was then used to identify patients who had either new episodes of documented bleeding or new focal neurological deficits in the absence of new bleeding, as well as treatment with antithrombotics.

Despite the widely held clinical concern that antithrombotic drugs could increase the risk of bleeding, the findings from the study suggested the opposite. There were fewer episodes of new bleeding or new focal neurological deficits over a mean follow-up of 11·6 years in the patients given antithrombotics (one [2%] of 61 patients) than in those who did not take antithrombotics (29 [12%] of 239).

The adjusted hazard ratio (HR) of 0·12 (95% CI 0·02–0·88) was remarkably low, given that HRs that small are rarely seen in clinical research. In secondary prevention trials, for example, aspirin prevents recurrent stroke with an HR of 0·83.[5] Therefore, potential sources of bias should be considered. The most plausible source of bias could be confounding by indication. That is, if clinicians mostly use antithrombotics in patients at lower risk for haemorrhage, but not in patients at higher risk, then a spurious association might be detected between antithrombotic use and lower recurrence of haemorrhages. To mitigate this risk for bias, the authors adjusted for type of presentation and brainstem location,[3] the two factors that influence bleeding risk that would also be known to the treating clinician and might have

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.

Eric E Smith
Health Sciences Centre, University of Calgary, Calgary, AB T2N 4N1, Canada
eesmith@ucalgary.ca

EES reports personal fees from Portola Pharmaceuticals and Alnylam Pharmaceuticals, outside the submitted work.

1 Zuurbier SM, Hickman CR, Tolias CS, et al. Association between long-term antithrombotic therapy and risk of intracranial haemorrhage from cerebral cavernous malformations: a population-based cohort study, systematic review, and meta-analysis. *Lancet Neurology* 2019; **18:** 935–41.
2 Morris Z, Whiteley WN, Longstreth WT Jr, et al. Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ* 2009; 339: b3016.
3 Horne MA, Flemming KD, Su IC, et al. Clinical course of untreated cerebral cavernous malformations: a meta-analysis of individual patient data. *Lancet Neurology* 2016; **15:** 166–73.
4 Adelborg K, Grove EL, Sundboll J, Laursen M, Schmidt M. Sixteen-year nationwide trends in antithrombotic drug use in Denmark and its correlation with landmark studies. *Heart* 2016; **102:** 1883–89.
5 Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; **373:** 1849–60.
6 Raychaudhuri R, Batjer HH, Awad IA. Intracranial cavernous angioma: a practical review of clinical and biological aspects. *Surg Neurol* 2005; **63:** 319–28.
7 Frischer JM, Pipp I, Stavrou I, Trattnig S, Hainfellner JA, Knosp E. Cerebral cavernous malformations: congruency of histopathological features with the current clinical definition. *J Neurol Neurosurg Psychiatry* 2008; **79:** 783–88.
8 Abe M, Fukudome K, Sugita Y, Oishi T, Tabuchi K, Kawano T. Thrombus and encapsulated hematoma in cerebral cavernous malformations. *Acta Neuropathologica* 2005; **109:** 503–09.
9 Akers A, Al-Shahi Salman R, A Awad I, et al. Synopsis of guidelines for the clinical management of cerebral cavernous malformations: consensus recommendations based on systematic literature review by the Angioma Alliance Scientific Advisory Board Clinical Experts Panel. *Neurosurgery* 2017; **80:** 665–80.

Blood pressure control as an intervention to prevent dementia

Published **Online** August 20, 2019
http://dx.doi.org/10.1016/S1474-4422(19)30288-1

See **Articles** page 942

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