cysteine, which chelates and deposits iron in the cells of the globus pallidus.[7] Cysteine is ordinarily metabolised in the biosynthetic pathway of coenzyme A; however, the first step of this pathway, the phosphorylation of dietary pantothenate to 4-phosphopantothenate, is prevented in PKAN by a mutation in PANK2.[2] Cysteine concentrations rise as a result and coenzyme A is depleted, and both are major regulators of the iron-dependent cell death pathway (eg, ferroptosis). Cysteine is the rate-limiting substrate for glutathione synthesis, which is the necessary cofactor for glutathione peroxidase 4, the master regulator of ferroptosis.[8] Coenzyme A is required to produce phosphatidylethanolamine, which is the main target for iron-induced peroxidation in ferroptosis.[9] Although it could be hypothesised that neuronal death in this disorder of neurodegeneration with brain iron accumulation is caused by ferroptotic cell death, patients with PKAN should be protected from ferroptosis because of these biochemical changes.

Given the challenges in implementing clinical trials in this population, we must glean as much information as possible from this trial about the efficacy of deferiprone. The uncertain role of iron in causing toxicity and the limitations of the primary outcome measure used in this study notwithstanding, there are certainly hints that deferiprone was beneficial: the treatment seemed to slow deterioration in patients with atypical PKAN; the extension phase showed evidence of slowed disease progression; and secondary analyses of the placebo-controlled phase provided evidence that deferiprone might reduce the use of dystonia medication, freezing of gait, and cognitive impairment. Therefore, these results support the possibility that brain iron accumulation is indeed at least a component of pathogenesis. The tolerability of deferiprone in this study supports conservative iron chelation as a therapy in patients with PKAN, given that there are no other treatment options. However, other potential biochemical consequences of the mutation also warrant investigation.

*Scott Ayton, *Ashley I Bush*
Melbourne Dementia Research Centre, Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, VIC 3052, Australia
ashley.bush@florey.edu.au

SA and AIB report research grants from the Australian National Health and Medical Research Council and the **US** National Institutes of Health, relevant to this work. AIB is a shareholder in Alterity Ltd, Cogstate Ltd, Brighton Biotech LLC, Grunbiotics Pty Ltd, Eucalyptus Pty Ltd, and Mesoblast Ltd. He is a paid consultant for, and has a profit share interest in, Collaborative Medicinal Development Pty Ltd.

1 Hogarth P, Kurian MA, Gregory A, et al. Consensus clinical management guideline for pantothenate kinase-associated neurodegeneration (PKAN). *Mol Genet Metab* 2017; **120:** 278–87.
2 Arber CE, Li A, Houlden H, Wray S. Review: insights into molecular mechanisms of disease in neurodegeneration with brain iron accumulation: unifying theories. *Neuropathol Appl Neurobiol* 2016; **42:** 220–41.
3 Hare D, Ayton S, Bush A, Lei P. A delicate balance: iron metabolism and diseases of the brain. *Front Aging Neurosci* 2013; **5:** 34.
4 Klopstock T, Tricta F, Neumayr L, et al. Safety and efficacy of deferiprone for pantothenate kinase-associated neurodegeneration: a randomised, double-blind, controlled trial and an open-label extension study. *Lancet Neurol* 2019; **18:** 631–42.
5 Sohn YS, Breuer W, Munnich A, Cabantchik ZI. Redistribution of accumulated cell iron: a modality of chelation with therapeutic implications. *Blood* 2008; **111:** 1690–99.
6 Devos D, Moreau C, Devedjian JC, et al. Targeting chelatable iron as a therapeutic modality in Parkinson's disease. *Antiox Redox Signal* 2014; **21:** 195–210.
7 Perry TL, Norman MG, Yong VW, et al. Hallervorden-Spatz disease: cysteine accumulation and cysteine dioxygenase deficiency in the globus pallidus. *Ann Neurol* 1985; **18:** 482–89.
8 Dixon SJ, Lemberg KM, Lamprecht MR, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell* 2012; **149:** 1060–72.
9 Doll S, Proneth B, Tyurina YY, et al. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. *Nat Chem Biol* 2017; **13:** 91–98.

Antiplatelets after intracerebral haemorrhage: treat the patient, not the brain imaging

Clinicians underestimate harms and overestimate benefits from medical interventions.[1] However, according to a report by Rustam Al-Shahi Salman and colleagues[2] published in *The Lancet Neurology*, the perceived risk from restarting antiplatelet therapy after intracerebral haemorrhage in patients with cerebral microbleeds has been substantially overestimated on the basis of observational data. Use of antiplatelet therapy in patients with intracerebral haemorrhage is common,[3] a conservative estimate is one in four patients, so more certainty in making decisions regarding restarting such therapy is highly relevant.

The RESTART trial,[4] which is published in *The Lancet*, randomly assigned 537 survivors of intracerebral haemorrhage that occurred while taking antithrombotic therapy to start or avoid antiplatelet therapy. The investigators

Published **Online** May 22, 2019 http://dx.doi.org/10.1016/S1474-4422(19)30189-9

See **Articles** page 643

reported no significant differences in risk of recurrent intracerebral haemorrhage but a reduced risk, albeit not reaching statistical significance, of both haemorrhagic and ischaemic stroke was observed consistently in subgroups in patients allocated to start antiplatelet therapy.[4] The neuroimaging substudy[2] of the RESTART trial, published in *The Lancet Neurology*, focused on the 254 patients with MRI performed before randomisation. By contrast with previous observational data, there were no indications that starting antiplatelet therapy increased risk of recurrent intracerebral haemorrhage in patients with cerebral microbleeds or superficial siderosis. The number of microbleeds did not seem to affect risk of recurrent intracerebral haemorrhage.

RESTART is the first randomised trial to address this subject; until now, data were based on observational hospital cohorts that suggested excess risk of recurrent intracerebral haemorrhage from reintroduction of antiplatelets, with the highest risk in patients with cerebral microbleeds.[5] Uncertainty remains in relation to the precision of these findings. RESTART was underpowered: a sample size of 2200 is suggested by the investigators as needed for a potentially conclusive study. However, findings were consistent across prespecified subgroups. Selection bias towards small haematomas was present: median intracerebral haemorrhage volume was 3·7 mL in the intervention group and 4·3 mL in the control group, and few participants had high numbers of microbleeds. There was a predominance of men in the MRI substudy and entire cohort. Also, all MRI field strengths were accepted and gradient-recalled echo was used for bleeding detection, which most likely led to lower detection rates of cerebral microbleeds than what would have been the case if based on high field strengths or susceptibility weighted imaging, or both.[6]

Consequently, the results could be substantially different in an adequately powered trial and therefore the external validity of the results of the current substudy in relation to the overall intracerebral haemorrhage population is unclear—for example, these results cannot be directly extrapolated to patients with larger haematoma volumes or large numbers of microbleeds. However, the investigators have succeeded in recruiting a high-risk population; the proportion of recurrent intracerebral haemorrhage was 4·9% in the start antiplatelet therapy group versus 9·1% in the control group during an average follow-up of 2 years.[2] Furthermore, consideration of reinitiation of antiplatelet therapy is most pertinent in patients with small haematomas and good outcome.

These data are indeed surprising because most stroke clinicians would have expected that presence of cerebral microbleeds heralds higher risk of recurrent intracerebral haemorrhage on starting antiplatelet therapy, because the higher risk of intracerebral haemorrhage in patients with microbleeds has been well documented,[7] and observational data support further increase in risk with use of antithrombotic drugs.[5,8]

That antiplatelet therapy increases risk of intracerebral haemorrhage overall and that patients after intracerebral haemorrhage have high risk of recurrence do not necessarily imply that antiplatelet therapy will increase risk of intracerebral haemorrhage in this patient population. Furthermore, imaging findings such as the presence of microbleeds can often arouse concern, which can be worrying even in the absence of intracerebral haemorrhage—but possibly more for the clinician than for the patient's prognosis. These findings underline that our pathophysiological understanding remains incomplete and we should not rely on observational data, but always aim for randomised controlled data. More data are certainly needed in this field, including data on specific antiplatelet drugs and specific combinations of antiplatelet drugs that are frequently used—eg, standard regimens for acute coronary syndrome. Data from randomised controlled trials are also needed for oral anticoagulants, for which a parallel discussion is ongoing.

My clinical interpretation of these results is that physicians can be less restrictive in prescribing antiplatelets to patients with minor intracerebral haemorrhage. Decisions cannot be made on the basis of MRI findings such as cerebral microbleeds; according to these data, there is no excess risk attributed to the antiplatelet intervention in this population, so the focus of a therapeutic decision should rest not on the reasons to prescribe antiplatelets, but on the reasons not to prescribe them. However, the best evidence remains to be from randomised trials when available: RESTART-Fr (NCT02966119) and STATICH (NCT03186729) are ongoing and might settle any remaining uncertainty.

For more on the **RESTART-Fr trial** see https://clinicaltrials.gov/ct2/show/NCT02966119

For more on the **STATICH trial** see https://clinicaltrials.gov/ct2/show/NCT03186729

Hanne Christensen
Department of Neurology, Bispebjerg Hospital and University of Copenhagen, 2400 Copenhagen NV, Denmark
hanne.krarup.christensen@regionh.dk

I declare no competing interests.

Copyright © 2019 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY-NC-ND 4.0 license.

1 Hoffmann TC, Del Mar C. Clinicians' expectations of the benefits and harms of treatments, screening, and tests: a systematic review. *JAMA Intern Med* 2017; **177:** 407–19.
2 Al-Shahi Salman R, Minks DP, Mitra D, et al. Effects of antiplatelet therapy on stroke risk by brain imaging features of intracerebral haemorrhage and cerebral small vessel diseases: subgroup analyses of the RESTART randomised, open-label trial. *Lancet Neurol;* **18:** 643-52.
3 Thompson BB, Béjot Y, Caso V, et al. Prior antiplatelet therapy and outcome following intracerebral hemorrhage: a systematic review. *Neurology* 2010; **75:** 1333–42.
4 RESTART Collaboration. Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART): a randomised, open-label trial. *Lancet* 2019; published online May 22. http://dx.doi.org/10.1016/S0140-6736(19)30840-2.
5 Biffi A, Halpin A, Towfighi A, et al. Aspirin and recurrent intracerebral hemorrhage in cerebral amyloid angiopathy. *Neurology* 2010; **75:** 693–98.
6 Nandigam RN, Viswanathan A, Delgado P, et al. MR imaging detection of cerebral microbleeds: effect of susceptibility-weighted imaging, section thickness, and field strength. *AJNR Am J Neuroradiol* 2009; **30:** 338–43.
7 Charidimou A, Boulouis G, Roongpiboonsopit D, et al. Cortical superficial siderosis and recurrent intracerebral haemorrhage risk in cerebral amyloid angiopathy: large prospective cohort and preliminary meta-analysis. *Int J Stroke* 2019: published online Feb 20. DOI:10.1177/1747493019830065.
8 Charidimou A, Karayiannis C, Song TJ, et al. Brain microbleeds, anticoagulation, and hemorrhage risk: meta-analysis in stroke patients with AF. *Neurology* 2017; **89:** 2317–26.

Can cerebral microbleeds predict stroke recurrence?

Published **Online** May 23, 2019 http://dx.doi.org/10.1016/S1474-4422(19)30194-2

See **Articles** page 653

Should patients with a history of ischaemic stroke or transient ischaemic attack be treated with antithrombotic drugs? The answer to this question has been considered to be clear and straightforward for more than two decades.[1,2] However, the question regarding the balance of future intracranial bleeding risk compared with risk of recurrent ischaemic stroke in patients with high burden of cerebral microbleeds remains one of the most complicated problems of modern stroke medicine.[3]

In *The Lancet Neurology*, Duncan Wilson and colleagues[4] aim to elucidate the association between cerebral microbleed burden in baseline neuroimaging and the risk of recurrent stroke. The study was a pooled analysis of individual patient data from 20 322 patients (mean age 70 years [SD 13]) with history of ischaemic stroke or transient ischaemic attack from 38 cohort studies.[4] After a cumulative follow-up of 35 225 patient-years (median 1·34 years [IQR 0·19–2·44]) the investigators documented that cerebral microbleed presence in baseline neuroimaging was associated with increased risk for both ischaemic stroke and intracranial haemorrhage. Despite the fact that the adjusted hazard ratio (aHR) for intracranial haemorrhage was nearly five times higher than that for ischaemic stroke for patients with five or more or ten or more cerebral microbleeds and nearly eight times higher for patients with 20 or more cerebral microbleeds, the absolute rate of ischaemic stroke exceeded that of intracranial haemorrhage even in patients with high (≥20) cerebral microbleed burden.[4] Notably, all associations were independent from cerebral microbleed anatomical distribution (lobar *vs* mixed *vs* deep), antithrombotic treatment (antiplatelet or anticoagulant), ethnicity (white *vs* non-white), age (>80 years *vs* ≤80 years), and the presence of white-matter hyperintensities on baseline neuroimaging or the diagnosis of probable cerebral amyloid angiopathy.[4]

The main strengths of this study are the large sample size, including almost all available findings from published and unpublished cohort studies of adults with recent ischaemic stroke or transient ischaemic attack using appropriate MRI sequence sensitive to magnetic susceptibility, the prospective study design with strict inclusion and exclusion criteria, and the comprehensive, prespecified, and robust statistical analysis plan. This study offers novel and clinically relevant information that in patients with recent ischaemic stroke or transient ischaemic attack the absolute risk of ischaemic stroke is higher than that of intracranial haemorrhage, regardless of cerebral microbleed presence, burden, or pattern and independently of their secondary prevention treatment with antiplatelets or oral anticoagulants. Notably, the individual-patient-data meta-analysis credibly contradicts the findings of a previous meta-analysis that did not detect any association between cerebral microbleed presence or burden and recurrent ischaemic stroke in patients with ischaemic stroke treated with oral anticoagulants.[5]

However, the observational study design is prone to residual confounding, and selection and indication biases. Furthermore, the investigators were unable to adjust for other cofounders in their multivariable models,