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Title: Longer time windows, refining benefit, and prevention targets lifestyle.

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Commentary

2018 was a busy year. Advances included extended time windows for recanalisation therapies in acute ischaemic stroke, more ingenious devices to improve outcomes, refining the use of antiplatelet drugs in secondary prevention, and greater awareness of adverse environmental and lifestyle exposure impacts on brain health and of cerebrovascular disease on cognition.

Recanalisation therapy finally broke the 4.5 hour barrier in the carotid circulation to reach 16[1] or 24[2] hours, or unknown time of onset,[3] using thrombectomy[1,2] or intravenous thrombolytic therapy;[3] These trials all used some form of imaging to select patients, either perfusion imaging with a perfusion lesion-to-infarct core ratio of 1.8 or more,[1] or with an acute ischaemic lesion on diffusion but not FLAIR magnetic resonance imaging (MRI),[2] or a mismatch between the severity of the clinical neurological deficit and the infarct volume on CT or MR,[2,3] these providing a range of less to more pragmatic approaches to use in clinical practice. The trials stopped early, through greater benefit with active trial treatment without excess hazard. Attention should now turn to optimising delivery. World Stroke Congress (WSO) presentation of a trial of vertebrobasilar thrombectomy suggests that this may too be effective. While delivering thrombectomy remains problematic in many places, patients who undergo it without general anaesthetic have better outcomes than those who have a general anaesthetic.[4] Current licence criteria for intravenous alteplase treatment, the workhorse for acute ischaemic stroke, are long overdue for change. An individual patient data meta-analysis demonstrated that removing the 80 years upper age limit (Europe) and relaxing the time window from three to 4.5 hours (USA) would allow substantially more patients to benefit from alteplase (around

17% and 36% respectively) without additional harm.[5] Every acute stroke patient arriving at hospital should be considered for recanalisation therapy unless a hard contraindication is identified; 'time every brain'[1] should be the new maxim.

Gadgets aimed at improving outcomes, in various ingenious ways, are achieving prominence and reaching the Large Trials sessions at international conferences. In patients requiring tracheostomy for impaired swallowing, three days of pharyngeal electrical stimulation increased the number of patients ready for decanulation.[6] WSO presentation of a trial of sphenopalatine ganglion stimulation to enhance collateral flow around the infarct suggest that this may become a new reperfusion approach.

In secondary prevention, the issue of how many antiplatelet drugs and for how long is becoming clearer. In the POINT trial, 90 days of clopidogrel plus aspirin prevented more recurrent ischaemic vascular events (1.5% less) but caused more major haemorrhages (0.5% more) than aspirin alone when given after TIA or minor ischaemic stroke.[7] Even more intensive antiplatelet treatment was given in the TARDIS trial where one month of three agents after TIA or minor ischaemic stroke caused more major haemorrhages although there was no net hazard once ischaemic events were subtracted.[8] Reassuringly, the beneficial effects of randomised intensive lipid and blood pressure lowering given for 3-6 years in the ASCOT trial lasted much longer with reduced mortality out to 16 years.[9]

For primary prevention, and more importantly for brain health, the focus is firmly on lifestyle, environment and education.[10] The American Heart Association's 'Life's Simple 7' (https://www.heart.org/en/healthy-living/healthy-lifestyle/be-healthy-for-good-with-lifes-simple-7-infographic) includes diet, exercise and weight control as well as blood pressure, blood sugar, cholesterol management and smoking cessation, but estimates that only 0.5% of USA citizens meet the targets. Simple devices, such as mobile phone apps, such as the World Stroke Organisation's Stroke Riskometer, that help individuals monitor their activities may help people adjust their lifestyles. These approaches are important, since an analysis of over 300,000 people in the UK identified that high versus low adverse lifestyles increased the risk of stroke far more (by 66%) than did high versus low polygenic risk for stroke (by 35%).[11]

Brain health is a vascular issue. Cognitive impairment and dementia are arguably the commonest manifestations of cerebrovascular disease. Despite this, vascular disease is still low on the horizon amongst Alzheimer's disease researchers, which is unfortunate since vascular disease is preventable and treatable, while so far, Alzheimer's disease is not. Conversely, cognitive consequences of stroke still do not receive enough research or clinical

attention. It may help that finally, as of 2018, stroke no longer masquerades as a brain disease on the pages of this journal, but is officially a 'Neurological Disease' according to the World Health Organisation; but, arguably, given the diversity and size of its health burden, stroke should be in a category of its own.

Declarations

PB: TARDIS: CI. PHAST-TRAC: Chair TSC, received honoraria from Phagenesis

JMW: thrombolysis IPD, academic grants for research in stroke

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