FEATURED EDITORIAL

Transient ischaemic attacks: time to wake up

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''The risk of stroke in the week after a transient ischaemic attack or minor stroke is high and relatively predictable. Emergency investigation and treatment are justified.''

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Stroke is the most common cause of neurological disability in adults in developed countries, and in at least some areas the incidence of stroke is higher than that of acute coronary syndromes.[1] Primary prevention strategies have resulted in a fall in age-adjusted incidence of the first stroke over the past few decades,[2] but major improvements are required in secondary prevention after a transient ischaemic attack (TIA) and minor stroke.[3]

About 15–20% of patients who have a stroke report a preceding TIA,[4] and a similar proportion have a preceding minor stroke. These ''warning'' events provide an opportunity for prevention, but owing to methodological problems in early studies of prognosis the immediate risk of stroke after a TIA was underestimated for many years.[5] Recent hospital-based and population-based cohort studies have reported risks of up to 10% at 7 days and 15% at 30 days[6 7]—not dissimilar to the risks of myocardial infarction in patients with unstable angina. A study of the timing of TIAs preceding ischaemic stroke also showed that the time-window for prevention is short, with 17% of TIAs occurring on the day of the stroke, and 43% during the 7 days before the stroke.[4]

There is considerable international variation in the way in which patients with a suspected TIA and minor stroke are managed, with some healthcare systems providing immediate emergency inpatient care and others offering only semi-urgent outpatient clinic assessment.[8] North American and UK guidelines simply state that all patients in whom a diagnosis of TIA is suspected should be assessed and investigated within 7 days, although this is often not achieved in practice. The potential consequences of non-emergency assessment of a TIA were illustrated by an audit of 210 consecutive patients with suspected TIA referred to a standard weekly specialist clinic in the UK, in which all patients who did not attend the clinic appointment were traced to ensure inclusion of all follow-up strokes.[9] Although the median delay from referral to the clinic appointment (9 days) was less than the UK average, 11 (5.3%) patients had a stroke after referral but before their scheduled appointment, nine of whom had major disabling strokes requiring admission to hospital and so did not attend the clinic appointment. The fact that physicians who do non-emergency TIA clinics may never be aware of the poor outcomes in such patients perhaps partly explains why this mode of service provision has persisted for so long in so many countries.

If some of these early strokes could be prevented, then more urgent investigation and treatment would be justified. However, not all patients with a suspected TIA would necessarily need to be seen urgently. Only about 50% of patients referred with a suspected TIA have the diagnosis confirmed by their neurologist and so even with a 10% 7-day stroke risk in confirmed TIAs, 95% of all referrals of suspected TIA will not have an early stroke.

Validated models are now available to predict the early risk of stroke after a TIA,[9 10] such that front-line physicians can identify which patients with suspected TIA should be referred onwards for emergency assessment. The six-point ABCD score (age $\geq$60 years = 1, blood pressure (systolic $>$140 mm Hg and/or diastolic $\geq$90 mm Hg = 1), clinical features (unilateral weakness = 2, speech disturbance without weakness = 1, other = 0) and duration of symptoms in minutes ($\geq$60 = 2, 10–59 = 1, $<$10 = 0)) is a useful predictor of the 7-day risk of stroke after a TIA. For example, in the original validation cohort, 95% of early strokes occurred in 27% of the patients with a score $\geq$5, with a 7-day risk in 12.1% of patients with a score of 5 and 31.4% in those a score of 6.[9] Subsequent independent validations of the ABCD score have shown similar predictive power,[10 11] and the score has been refined by the addition of a point for diabetes (ABCD^2 score).

Several treatments are likely to reduce the early risk of stroke after a TIA and minor stroke. Aspirin reduces the risk of recurrence after acute ischaemic stroke, and there is some evidence that addition of clopidogrel to aspirin might be beneficial in the acute phase, at least in patients with carotid atherosclerosis.[12] Benefit from combination antiplatelet therapy and from treatment with statins in the acute phase would be expected by extrapolation from trials in acute coronary syndromes, and anticoagulation is indicated in the acute phase after a TIA in patients with atrial fibrillation. Further research is required to determine the risks and benefits of blood pressure lowering in the acute phase.

As might again be expected from our knowledge of the natural history of acute coronary syndromes, the subgroup of patients with TIA and minor stroke who have the highest risk of early stroke are those with large-artery atherosclerosis (usually carotid bifurcation stenosis). In a meta-analysis of data from 1709 patients in four population-based studies, although large-artery disease was present in only 14% of patients, this group had 37% of early recurrent strokes.[13] A population-based study

of prognosis of patients with TIA and ⩾50% symptomatic carotid stenosis reported risks of stroke in the region of 20% during the 2 weeks before endarterectomy,[14] and other studies have highlighted the high risk of stroke if endarterectomy is delayed.[15] A pooled analysis of individual patient data from 5893 patients in randomised controlled trials of carotid endarterectomy versus medical treatment alone showed that benefit from surgery was greatest in patients randomised within 2 weeks after their last ischaemic event and fell rapidly with increasing delay. For patients with ⩾50% stenosis, the number of patients needed to undergo surgery to prevent one ipsilateral stroke in 5 years was five for patients randomised within 2 weeks after their last ischaemic event versus 125 for patients randomised at >12 weeks.[16] This trend was due, in part, to the fact that the operative risk of endarterectomy in the trials (a 1% risk of death and a 5–6% risk of stroke) was not increased in patients operated on within a week of their last event. A systematic review of all published surgical case series came to the same conclusion, although the operative stroke risk was unacceptably high (around 20%) in unstable patients with fluctuating or evolving symptoms.[17] Thus, for neurologically stable patients with a TIA and minor stroke, benefit from endarterectomy is greatest if performed within a few days of the event.

Further research is required to determine the balance of risk and benefit for emergency surgery or stenting. However, there is currently little scope for large-scale trials of emergency intervention in the UK, where the median time to endarterectomy for severe symptomatic carotid stenosis is about 3 months.[14]

More widespread adoption of urgent assessment and treatment of a TIA and minor stroke is hampered by a lack of evidence proving that acute intervention is effective. However, two studies of treatment in the acute and subacute phases will report in 2007. The FASTER Trial (**F**ast **A**ssessment of **S**troke and **T**ransient Ischemic Attack to prevent **E**arly **R**ecurrence)[18] is a 2×2 factorial design trial comparing aspirin plus clopidogrel with aspirin alone, and simvastatin 40 mg with placebo in about 400 patients who have had a TIA or minor ischaemic stroke within the previous 24 hours. Treatment is for 1 month and the main outcome is recurrent stroke. The EXPRESS Study (**E**arly use of E**X**isting **PRE**ventive **S**trategies for **S**troke) is a new population-based prospective study of the impact of early intervention after a TIA and minor ischaemic stroke, in which 30 months of a standard semi-urgent TIA clinic service is compared with a second 30 months of a daily open-access emergency clinic where all appropriate preventive treatment is started immediately.[19] Although this is not a randomised comparison, near-complete ascertainment of all TIAs and stroke in the population will ensure that the patients recruited during the two periods are comparable and, of particular importance, that any effect of the introduction of a policy of early treatment is generalisable—at least to similar healthcare systems.

There is debate in the UK as to whether the 20–30% 7-day risk of stroke in patients who have had a TIA with an ABCD score of 6 necessitates admission to hospital. Even if acute prevention were ineffective, admission would allow thrombolysis to be given within minutes of any subsequent stroke that did occur. More speculative, but worthy of trials, would be the prophylactic use of neuroprotective agents, such that patients are pretreated before any stroke occurs, thereby mimicking the animal models of stroke, in which many agents are highly effective.[20]

In conclusion, the risk of stroke in the 7 days after a TIA or minor stroke is high and relatively predictable. Emergency investigation and treatment are justified, and data on the effectiveness of currently available treatments will be available later this year. However, further trials are required to determine the most effective strategies for acute prevention. The improvements in outcome after acute coronary syndromes that have been achieved over the past few decades suggest that more intensive and timely investigation of TIA and minor stroke is also likely to be highly effective.

Conflicts of interest: None.

REFERENCES

1 **Rothwell PM**, Coull AJ, Silver LE, for the Oxford Vascular Study, *et al*. Population-based study of event-rate, incidence, case fatality and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). *Lancet* 2005;**366**:1773–83.
2 **Rothwell PM**, Coull A, Giles MF, for the Oxford Vascular Study, *et al*. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet* 2004;**363**:1925–33.
3 **Rothwell PM**. Lack of epidemiological data on secondary stroke prevention. *Lancet Neurology* 2005;**4**:518–9.
4 **Rothwell PM**, Warlow CP. Timing of transient ischaemic attacks preceding ischaemic stroke. *Neurology* 2005;**64**:817–20.
5 **Coull A**, Rothwell PM. Under-estimation of the early risk of recurrence after first stroke by the use of restricted definitions. *Stroke* 2004;**35**:1925–9.
6 **Johnston SC**, Gress DR, Browner WS, *et al*. Short-term prognosis after emergency department diagnosis of TIA. *JAMA* 2000;**284**:2901–6.
7 **Coull A**, Lovett JK, Rothwell PM, on behalf of the Oxford Vascular Study. Early risk of stroke after a TIA or minor stroke in a population-based incidence study. *BMJ* 2004;**328**:326–8.
8 **Johnston SC**, Smith WS. Practice variability in management of transient ischaemic attacks. *Eur Neurol* 1999;**42**:105–8.
9 **Rothwell PM**, Giles MF, Flossmann E, *et al*. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet* 2005;**366**:29–36.
10 **Johnston SC**, Rothwell PM, Nguyen-Huynh MN, *et al*. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet* 2007;**369**:283–92.
11 **Tsivgoulis G**, Spengos K, Manta P, *et al*. Validation of the ABCD score in identifying individuals at high early risk of stroke after a transient ischemic attack. A Hospital-Based Case Series Study. *Stroke* 2006;**37**:2892–7.
12 **Markus HS**, Droste DW, Kaps M, *et al*. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. *Circulation* 2005;**111**:2233–40.
13 **Lovett JK**, Coull A, Rothwell PM, on behalf of the Oxford Vascular Study. Early risk of recurrent stroke by aetiological subtype: implications for stroke prevention. *Neurology* 2004;**62**:569–74.
14 **Fairhead JF**, Mehta Z, Rothwell PM. Population-based study of delays in carotid imaging and surgery and the risk of recurrent stroke. *Neurology* 2005;**65**:371–5.
15 **Blaser T**, Hofmann K, Buerger T, *et al*. Risk of stroke, transient ischaemic attack, and vessel occlusion before endarterectomy in patients with symptomatic severe carotid stenosis. *Stroke* 2002;**33**:1057–62.
16 **Rothwell PM**, Eliasziw M, Gutnikov SA, for the Carotid Endarterectomy Trialists Collaboration, *et al*. Effect of endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and to the timing of surgery. *Lancet* 2004;**363**:915–24.
17 **Bond R**, Rerkasem K, Rothwell PM. A systematic review of the risks of carotid endarterectomy in relation to the clinical indication and the timing of surgery. *Stroke* 2003;**34**:2290–301.
18 **Kennedy J**, Eliasziw M, Hill MD, *et al*. The Fast Assessment of Stroke and Transient Ischemic Attack to prevent Early Recurrence (FASTER) Trial. *Semin Cerebrovasc Dis Stroke* 2003;**3**:25–30.
19 **Rothwell PM**. Observational comparisons of different clinical services. *Lancet* 2007;**369**:254–5.
20 **Gladstone DJ**, Black SE, Hakim AM. Toward wisdom from failure: lessons from neuroprotective stroke trials and new therapeutic directions. *Stroke* 2002;**33**:2123–36.