

## Recent advances in management of transient ischaemic attacks and minor ischaemic strokes

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The risk of recurrent stroke during the first few days after a transient ischaemic attack or minor stroke is much higher than previously estimated. However, there is substantial variation worldwide in how patients with suspected transient ischaemic attack or minor stroke are investigated and treated in the acute phase: some health-care systems provide immediate emergency inpatient care and others provide non-emergency outpatient clinical assessment. This review considers what is known about the early prognosis after transient ischaemic attack and minor ischaemic stroke, what factors identify individuals at particularly high early risk of stroke, and what evidence there is that urgent preventive treatment is likely to be effective in reducing the early risk of stroke.

### Introduction

Stroke is a leading cause of death and the most common cause of neurological disability in adults in developed countries and is also a major cause of falls, epilepsy, depression, and dementia. In some Western populations the incidence of stroke is higher than that of acute coronary syndromes.<sup>1</sup> Without more effective prevention, the risk of stroke will increase because of ageing populations in developed and developing countries.<sup>1,2</sup> There is evidence that primary prevention strategies are reducing the age-adjusted incidence of first stroke,<sup>3</sup> but improvements in secondary prevention after transient ischaemic attack and stroke are also needed.<sup>4</sup>

About 15–20% of patients with stroke have a preceding transient ischaemic attack.<sup>5</sup> A similar proportion of major strokes are also preceded by minor strokes. These “warning” events provide an opportunity for prevention, and some clinical guidelines highlight the need for urgent assessment of patients with transient ischaemic attack and minor stroke. However, until recently there was little information on the early prognosis after transient ischaemic attack or minor stroke, risk factors for early recurrence, optimum investigation, or the effectiveness of early intervention.<sup>4</sup> Therefore there is uncertainty about how quickly patients with minor stroke or transient ischaemic attack should be seen for secondary prevention to be most effective. North American and UK guidelines suggest that assessment should be completed within one week of a transient ischaemic attack or minor stroke.<sup>6,7</sup> However, there is substantial variation worldwide regarding how patients with suspected transient ischaemic attack are managed in the acute phase: some health-care systems provide immediate emergency inpatient care and others provide non-emergency outpatient clinic assessment<sup>8,9</sup> with little consensus about which strategy is most cost-effective.<sup>10,11</sup> In this review we will discuss early prognosis after transient ischaemic attack and minor ischaemic stroke and what might be gained by early investigation and treatment.

### What is the early risk of major stroke after a minor stroke or transient ischaemic attack?

The urgency of treatment of minor stroke or transient ischaemic attack should depend on the early risk of major

stroke. Although one early retrospective study did suggest that the risk of stroke was high after a transient ischaemic attack,<sup>12</sup> the risk has generally been considered to be relatively low (approximately 1–2% at one week and 2–4% at one month)<sup>10,13–15</sup> and many clinical services have been organised accordingly. However, these risks are underestimates because they were determined in cohort studies and clinical trials of transient ischaemic attack or minor stroke in which patients were recruited several weeks or months after their initial event, and patients who had major strokes before recruitment were excluded.<sup>16</sup> Moreover, the definition of recurrent stroke in many studies excluded either all events within 30 days of the initial transient ischaemic attack or stroke, or all events within 21 days in the same vascular territory.<sup>17</sup> However, several studies report reliable estimates of the true early risk of stroke after transient ischaemic attack or minor ischaemic stroke.

The first reliable study of prognosis after transient ischaemic attack was in patients presenting to emergency departments of 16 hospitals in a health maintenance organisation in northern California, USA.<sup>18</sup> Of 1707 patients with physician-diagnosed transient ischaemic attack in 1997–1998, 180 (10.5%) returned within 90 days of the index transient ischaemic attack with a stroke, half of which happened in the first 2 days after the transient ischaemic attack. Strokes were fatal in 38 patients and disabling in another 115 patients; within the first 90 days, 2.6% of patients were hospitalised for cardiovascular events, 2.6% of patients died, and 12.7% had recurrent transient ischaemic attacks.

A subsequent emergency department-based study in Alberta, Canada, identified all patients presenting with physician-diagnosed transient ischaemic attack and stroke in four publicly funded administrative health-care databases between April 1999 and March 2000.<sup>19</sup> Among 2285 patients with transient ischaemic attack the estimated risk of stroke at 30 days was 6.7% (95% CI 5.7–7.7) and at 90 days was 9.5% (8.3–10.7). The risk of stroke, myocardial infarction, or death at 1 year was 21.8% (20.0–23.6). Unlike the study from northern California, diagnosis relied on administrative data alone because patients were not reviewed by a neurologist and stroke

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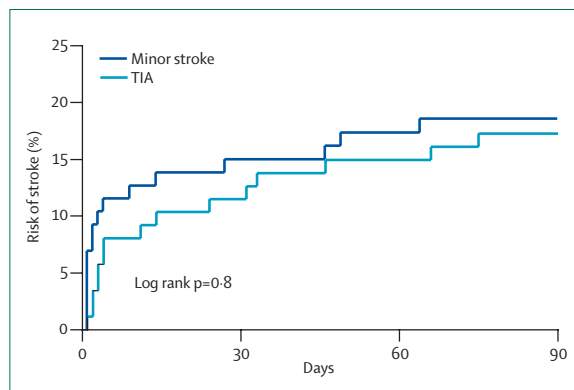


Figure 1: Cumulative risk of stroke following a transient ischaemic attack or minor stroke in the Oxford Vascular Study<sup>21</sup>

risk was probably underestimated because there was no follow-up of individual patients. Strokes within 24 h of the initial transient ischaemic attack were also excluded.

Several prospective population-based cohort studies have also reported high early risk of stroke after transient ischaemic attack.<sup>20–22</sup> Reanalysis of data from the Oxfordshire Community Stroke Project—which was done in the 1980s—found stroke risks from the date of onset of first-ever transient ischaemic attack of 8.6% (4.8–12.4) at 7 days and 12% (7.6–16.4) at 30 days.<sup>20</sup> Given a median delay to recruitment of 6 days (interquartile range 2–48 days), the equivalent risks from the date of recruitment were 1.9% (0.1–3.8) and 4.4% (1.6–7.2), respectively, therefore indicating the importance of methodology in reliably determining risk. Another population-based prospective cohort study in the same population<sup>21</sup> showed that the early risk of stroke after transient ischaemic attack was still high in 2002–2004, with recurrent stroke risks at 7 days, 1 month, and

3 months of 8.0% (2.3–13.7), 11.5% (4.8–18.2), and 17.3% (9.3–25.3), respectively. This study also reported the prognosis after minor ischaemic stroke (National Institute of Health Stroke Scale Score  $\leq 3$ ) and found very similar risks of early recurrent stroke; 11.5% (4.8–11.2), 15.0% (7.5–22.5), and 18.5% (10.3–26.7), respectively (figure 1).<sup>21</sup>

These latter two studies had the advantages of being population-based, all patients being assessed and diagnosed by a neurologist, and all patients having prospective follow-up. However, there is still one potential bias; some patients who have a transient ischaemic attack do not seek medical attention unless they go on to have a stroke.<sup>12–15</sup> There are two ways around this problem. First, in order to exclude any possibility of bias, the two Oxfordshire studies excluded any patients who had a transient ischaemic attack or minor stroke during the study period but did not seek medical attention until they had a subsequent stroke. These exclusions did not substantially reduce the early risk of recurrence. In the Oxford Vascular study,<sup>21</sup> for example, of the 31 patients who had a recurrent stroke within 3 months of the initial event, only 8 patients did not seek medical attention before the stroke. If these patients were excluded for more conservative estimates, the risks of stroke were 7.6% (3.5–11.7) at 7 days, 10.1% (5.4–14.8) at 1 month, and 14.6% (9.1–20.1) at 3 months. The second approach is to retrospectively determine the timing and frequency of preceding transient ischaemic attacks in patients with major ischaemic stroke. Unlike the risk of stroke after a transient ischaemic attack, the temporal association between preceding transient ischaemic attacks and stroke can be estimated reliably, at least over a short period, because most patients who have a major stroke do seek medical attention. The timing of preceding transient ischaemic attacks in patients with stroke was reported in four independent studies.<sup>3,23–25</sup> Findings in the four studies were very similar and so the data on 2416 patients who had ischaemic stroke were pooled.<sup>5</sup> Of these, 549 patients (23%) gave a history of a preceding transient ischaemic attack, the timings of which were highly consistent across the studies, with 17% happening the day of the stroke, 9% on the previous day, and 43% at some point in the previous 7 days.<sup>5</sup> Figure 2 shows the timing of all transient ischaemic attacks that happened during the 2 weeks before stroke.

Thus, however the question is addressed, there is consistent evidence that the early risk of stroke after a transient ischaemic attack or minor stroke is much higher than was previously supposed and that the time window for prevention is short.

### Identification of high-risk patients

Patients with transient ischaemic attack and minor ischaemic stroke are a very heterogeneous group in terms of symptoms, risk factors, underlying pathology, and early prognosis. The key question might therefore not be

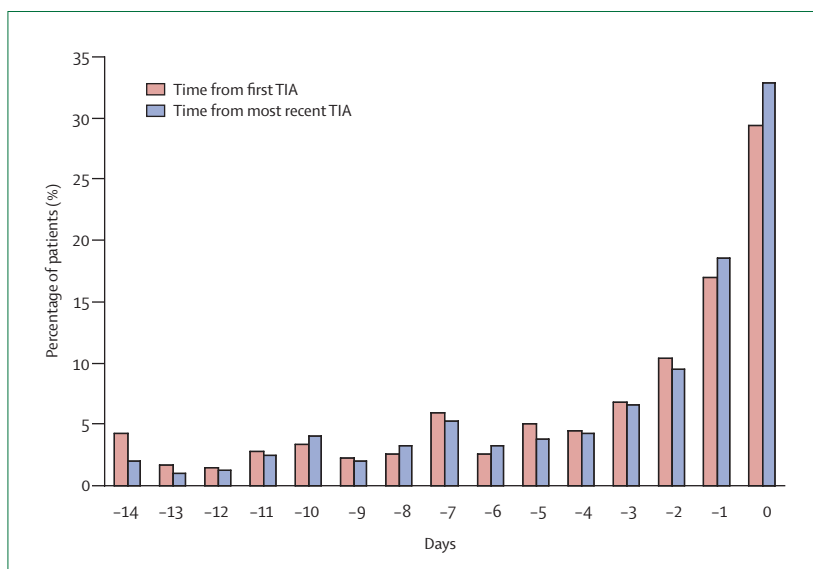


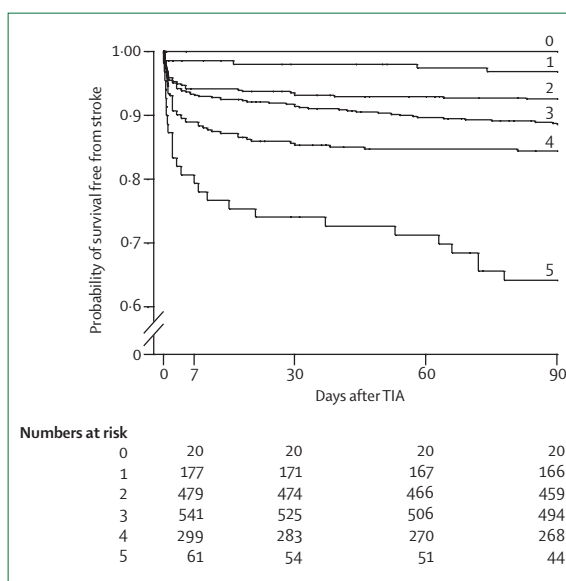
Figure 2: Distribution of time from preceding transient ischaemic attack to stroke for patients suffering a stroke who reported a transient ischaemic attack within the previous 14 days<sup>5</sup>

whether emergency inpatient care or non-emergency outpatient care is most appropriate, but for which patients is emergency assessment needed and which patients can be appropriately managed in a non-emergency outpatient setting? Only about 50% of patients referred for specialist assessment with suspected transient ischaemic attack have the diagnosis confirmed and so even if the 7-day stroke risk after a transient ischaemic attack is as high as 10%, 95% of referrals will not have a stroke in that time period. Effective secondary prevention depends on reliable identification of those at high risk and targeting treatment appropriately. Validated models are available for long-term risk of stroke after transient ischaemic attack or minor stroke,<sup>22,26-28</sup> but there has, until recently, been no work on predictors of early recurrent stroke. However, there is now increasing evidence that the early risk of stroke after a transient ischaemic attack is highly predictable.

There is good evidence that the clinical features of a transient ischaemic attack provide substantial prognostic information. Johnston and colleagues<sup>18</sup> identified five risk factors independently associated with a high risk of recurrent stroke at 3 months in a large emergency-department-based cohort of patients with transient ischaemic attack: age over 60 years (OR 1.8; 95% CI 1.4-2.9), symptom duration greater than 10 min (2.3, 1.3-4.2), motor weakness (1.9, 1.4-2.6), speech impairment (1.5, 1.1-2.1), and diabetes mellitus (2.1, 1.1-2.7). A simple index with 1 point for each risk factor was useful in estimating risk at 3 months, which varied from 0% in patients with no risk factors to 34% in those with five risk factors. The index also differentiated between risk groups during the first few days after the transient ischaemic attack (figure 3).<sup>1</sup> Isolated sensory or visual symptoms were associated with a low risk of stroke and the other factors—sex, ethnicity, previous diagnoses of coronary artery disease or hypertension, smoking, antiplatelet or anticoagulant use at presentation, and blood pressure—did not predict early stroke.<sup>18,29</sup>

Rothwell and colleagues<sup>30</sup> studied predictors of stroke during the first 7 days after a transient ischaemic attack in two independent population-based studies and derived and validated a prognostic score specifically for this very early risk. Table 1 compares the regression model for the 7-day stroke risk derived from the population-based studies<sup>30</sup> with the similar model for 90-day risk of stroke by Johnston and colleagues.<sup>18</sup> The independent predictors are remarkably similar; the main difference is in the size of the hazard ratios for 7-day risk versus 90-day risk.

These risk models clearly show that the early risk of stroke after a transient ischaemic attack is highly predictable. The models will be further refined, but the simple scores developed so far can already be used in routine clinical practice. Rothwell and colleagues<sup>30</sup> developed the 6-point ABCD (age, blood pressure, clinical factors, duration of symptoms) score (table 2) which was highly predictive of the 7-day risk of stroke in two



**Figure 3: Kaplan-Meier survival free from stroke after a transient ischaemic attack (TIA) stratified by number of independent risk factors<sup>18</sup>**

Observations were indexed to the time of TIA symptom resolution. Risk factors included age >60 years, duration of symptoms >10 min, diabetes mellitus, weakness associated with the TIA, and speech impairment associated with the TIA. Follow-up was censored at the time of death or endarterectomy, so numbers do not reflect the total number of patients with TIA at risk during the entire period.

independent validation cohorts. Using this 6 point score in a population-based cohort of all patients referred with suspected transient ischaemic attack, 19 out of 20 early recurrent strokes occurred in the 27% of the patients with

Risk factor	Hazard ratio (95% confidence interval)	P
<b>Oxfordshire model</b>		
Age ≥60 years	2.57 (0.75-8.81)	0.133
Systolic BP >140mm Hg or diastolic blood pressure ≥90mm Hg	9.67 (2.23-41.94)	0.002
Clinical features		
Unilateral weakness	6.61 (1.53-28.50)	0.016
Speech disturbance without weakness	2.59 (0.50-13.56)	
Other	1	
Duration of symptoms		
≥ 60 min	6.17 (1.43-26.62)	0.019
10-59 min	3.08 (0.64-14.77)	
< 10 min	1	
Diabetes mellitus	4.39 (1.36-14.22)	0.014
<b>California model</b>		
Age ≥60 years	1.8 (1.1-2.7)	0.01
Clinical features		
Unilateral weakness	1.9 (1.4-2.6)	<0.001
Speech disturbance	1.5 (1.1-2.1)	0.01
Duration of Symptoms		
>10 min	2.3 (1.3-4.2)	0.005
Diabetes mellitus	2.0 (1.4-2.9)	<0.001

**Table 1: Prognostic model for the 7-day risk of stroke in patients with transient ischaemic attack derived from population-based studies of transient ischaemic attack in Oxfordshire, UK (Oxfordshire model)<sup>30</sup> and equivalent model for the 90-day risk of stroke derived from an emergency-department cohort of patients with transient ischaemic attack in the USA (California model)<sup>18</sup>**

	Risk factor	Points
<b>ABCD score</b>		
Age	≥60 years	1
Blood pressure	Systolic >140 mm Hg and/or diastolic ≥90 mm HG	1
Clinical features	Unilateral motor weakness	2
	Speech disturbance without weakness	1
	Other	0
Duration of symptoms	≥60 min	2
	10–59 min	1
	<10 min	0
<b>California Score</b>		
Age	>60 years	1
Motor weakness		1
Speech disturbance		1
Duration of symptoms	>10 minutes	1
Diabetes mellitus		1

**Table 2: The ABCD prognostic score for the 7-day risk of stroke in patients with transient ischaemic attack derived from population based studies of transient ischaemic attack in Oxfordshire, UK<sup>29</sup> and the equivalent score for the 90-day risk of stroke derived from an emergency-department cohort of patients with transient ischaemic attack in the USA (California Score)<sup>18</sup>**

a score ≥5 points: 7-day risk was 0.4% (95% CI 0–1.1) in 274 (73%) patients with a score <5 points, 12.1% (4.2–20.0) in 66 patients (18%) with a score of 5 points, and 31.4% (16.0–46.8) in 35 patients (9%) with a score of 6. In a hospital-referred weekly clinic cohort, all patients (n=14, 7.5%) who had a stroke before their scheduled appointment had a score ≥4 points.<sup>30</sup>

In another study,<sup>31</sup> motor weakness or speech disturbance was associated with an increased risk of stroke at 3 months after transient ischaemic attack. Another study of predictors of stroke during the first year after transient ischaemic attack identified hypertension, diabetes, and increasing age as independent risk factors but did not collect data on the nature of the presenting symptoms.<sup>19</sup>

Early risk of stroke after a transient ischaemic attack or minor stroke is also associated with the vascular territory of the presenting event. For example, in keeping with the lower long-term risk of stroke after monocular transient ischaemic attacks versus carotid territory cerebral transient ischaemic attacks,<sup>13,22</sup> the early risk of stroke after monocular events is also low. Posterior circulation territory events, which account for about 25% of all transient ischaemic attacks, have been thought to have a good prognosis and are commonly investigated and treated less rigorously than carotid territory events. However, recent evidence suggests that there are no major differences in long-term prognosis, and that the early risk of stroke is higher after posterior circulation territory events.<sup>32</sup> In a meta-analysis of cohort studies in which risks were compared, studies that recruited patients during the acute phase after the presenting event reported

a higher risk of subsequent stroke in patients with posterior circulation events (OR 1.47, 95%CI 1.1–2.0, p=0.014), whereas studies mainly recruiting patients after the acute phase found a lower risk (OR 0.74, 0.7–0.8, p=0.00001).<sup>32</sup> Further research is needed to determine the predictors of early stroke, specifically in patients with posterior circulation transient ischaemic attack, and to determine overall prognosis in patients with isolated transient ischaemic attack-like presentations, such as transient isolated diplopia and transient speech arrest.<sup>4</sup>

There is also evidence that the early risk of stroke depends on the underlying causal pathology. For example, a recent meta-analysis of data from 1709 patients in four population-based studies of stroke showed that the risks of recurrent stroke were 4% (95% CI 0.2–7.8) at 7 days and 12.6% (5.9–19.3) at 30 days in patients with large-artery atherosclerosis compared with 0% and 2% (0–4.2), respectively, in patients with lacunar stroke.<sup>33</sup> Although large-artery atherosclerosis accounted for only 14% of the 1709 initial strokes, this group represented 37% of the recurrences at 7 days (figure 4). It should be emphasised, however, that subtype differences are probably smaller in patients with only transient ischaemic attack, where, for example, some patients with small-vessel disease can have a very high early risk of stroke.<sup>34</sup> Nevertheless, the high risk of stroke in patients with large-artery atherosclerosis is likely to be generalisable to routine clinical practice. A recent population-based study of prognosis of patients with transient ischaemic attack and ≥50% symptomatic carotid-artery stenosis reported risks of stroke of about 20% during the 2 weeks before endarterectomy (figure 5),<sup>35</sup> and other studies have highlighted the high risk of stroke if endarterectomy is delayed,<sup>36</sup> and hence the rapid decrease in benefit from surgery with increasing time since event.<sup>37</sup>

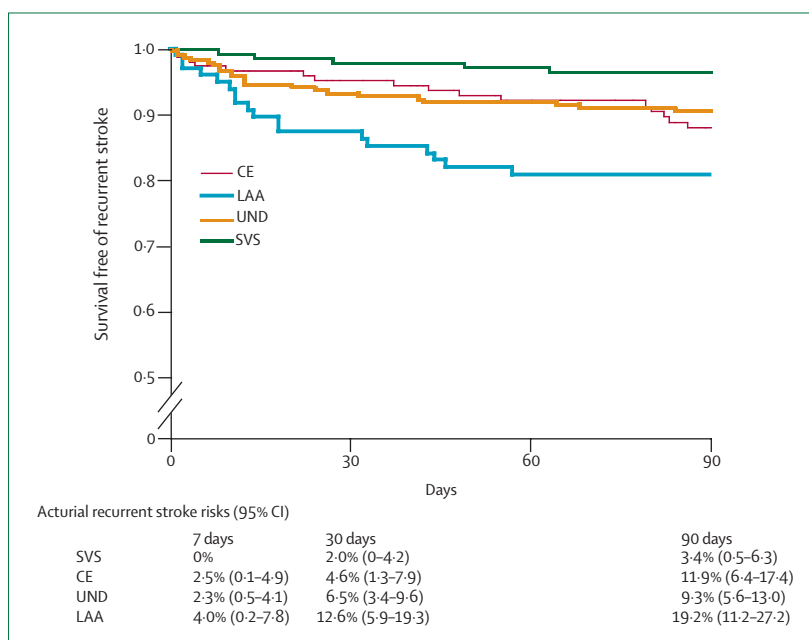
Brain imaging also seems to be of prognostic value. The presence of infarction on CT brain scans in patients with transient ischaemic attack or minor stroke is associated with an increased risk of stroke recurrence in the medium and long term.<sup>38,39</sup> A study of patients with transient ischaemic attack who had CT scans within 48 h of their clinical event showed that new infarction on CT could be highly predictive of recurrent stroke (OR 4.06; 95% CI 1.16–14.14; p=0.028).<sup>40</sup> However, diffusion-weighted MRI is of greater clinical usefulness,<sup>41</sup> and seems to be of similar prognostic value.<sup>42–45</sup> In one study of diffusion-weighted MRI of patients with transient ischaemic attack, the combination of abnormalities on diffusion-weighted MRI and symptoms that lasted longer than 1 h was an independent predictor of further cerebral ischaemic events (OR 5.02, CI, 1.37–18.3; p=0.015).<sup>43</sup> Another study, in which patients were scanned within 24 h of a transient ischaemic attack, reported a higher risk of recurrence in the presence of an acute lesion on diffusion-weighted MRI and also an interaction with vessel occlusion, with a 32.6% risk of recurrent stroke at 90 days in those patients with both an ischaemic lesion

and an occlusion.<sup>44</sup> Another study of 119 patients with non-disabling stroke who had diffusion-weighted MRI within 24 h of symptom onset showed that multiple acute cerebral infarcts was an independent predictor of recurrence of stroke, vascular events, and death compared with only a single acute infarct.<sup>45</sup>

Brain imaging with CT or diffusion-weighted MRI could therefore be a useful prognostic method, but further studies are needed to determine whether the presence of an acute ischaemic lesion predicts stroke independently of the simple clinical characteristics in the risk scores. For example, focal motor weakness, speech disturbance, and symptoms lasting longer than 1 h have all been associated with acute ischaemic lesions on diffusion-weighted MRI in patients with transient ischaemic attack.<sup>42</sup> Large prospective studies are needed in which detailed data on the clinical characteristics, event characteristics, time since event, and results of brain and vascular imaging are combined, and the optimum prognostic strategy is determined. Experience with prognostic modelling in patients with recently symptomatic carotid stenosis suggests that all of these different factors might be independently predictive of outcome.<sup>28</sup> Detection of cerebral microemboli might also be of value in certain subgroups,<sup>46</sup> and research is needed to determine whether newer technologies, such as biomarkers of cerebral ischaemia and molecular imaging of the cerebral vessels, can add additional prognostically useful information by defining a clinical phenotype in terms of parenchymal injury and vascular pathology.

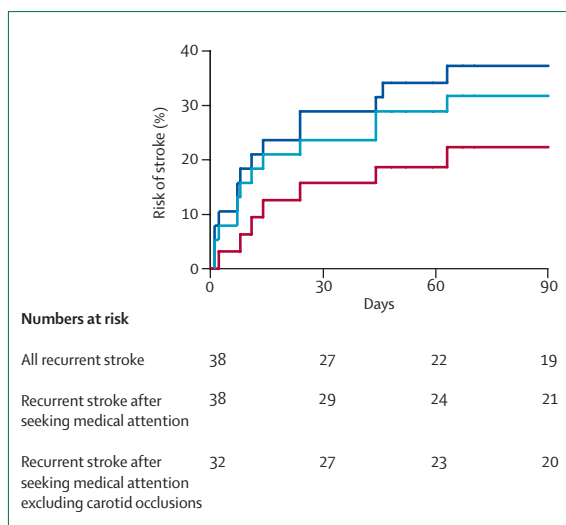
### Early treatment after transient ischaemic attack and minor stroke

To justify treating transient ischaemic attack and minor stroke as an emergency, it needs to be shown that urgent treatment could prevent some of the early recurrent strokes, or at least that there is a reasonable potential that future research will identify effective preventive treatments. There are several treatments that are likely to be effective in preventing stroke in the acute phase after a transient ischaemic attack or minor ischaemic stroke including aspirin,<sup>47</sup> possibly in combination with clopidogrel,<sup>48–50</sup> anticoagulation in patients with atrial fibrillation,<sup>51</sup> and possibly statins.<sup>52</sup> Endarterectomy for patients with  $\geq 50\%$  symptomatic carotid stenosis is safe and highly effective in neurologically stable patients 1–2 weeks after a transient ischaemic attack or non-disabling stroke.<sup>37,53</sup> Further research is needed to determine the risks and benefits of lowering blood pressure acutely after transient ischaemic attack or minor stroke, and of the prophylactic use of neuroprotective drugs; patients could be pretreated before any stroke happens, thereby mimicking studies in animal models of stroke in which many drugs are highly effective.<sup>54</sup> Finally, given that patients with transient ischaemic attack and high-risk scores have a 30% risk of major stroke,<sup>18,30</sup> even if acute prevention is ineffective, admission to hospital



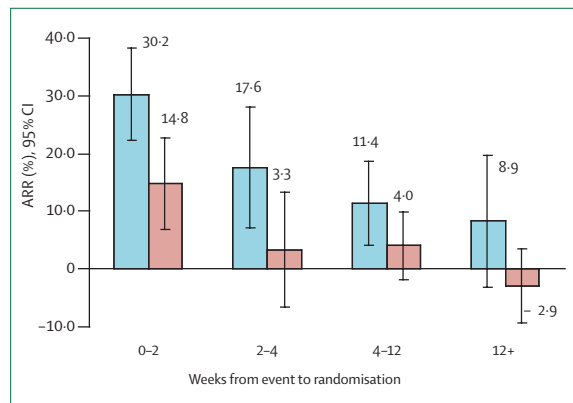
**Figure 4: Cumulative risk of recurrent stroke by aetiological subtype of the presenting stroke in a pooled analysis of data from the Oxford Vascular Study and the Oxfordshire Community Stroke Project<sup>33</sup>** LAA=large-artery atherosclerosis; SVS=small vessel stroke; CE=cardioembolic; UND=undetermined. The corresponding actuarial risks of recurrent stroke in each subtype are given below the figure with 95% confidence intervals.

would probably still be cost-effective because of the potential for immediate thrombolysis in the event of subsequent stroke. A recent cost-utility analysis found that 24 h hospitalisation for transient ischaemic attack



**Figure 5: The risk of recurrent stroke in all patients with transient ischaemic attack (TIA) or non-disabling ischaemic stroke in the Oxford Vascular Study population**

The dark blue line shows those who were found to have  $\geq 50\%$  symptomatic carotid stenosis prior to any endarterectomy.<sup>35</sup> The light blue line shows this same risk excluding strokes that occurred prior to the patient seeking medical attention after the initial TIA or minor stroke. The red line shows this latter risk excluding cases in whom carotid imaging was performed after the recurrence and showed a complete occlusion at that time.



**Figure 6:** The absolute reduction with surgery in the 5 year risk of stroke and operative death in patients with 50–69% stenosis (red bar) and  $\geq 70\%$  stenosis without near-occlusion (blue bar) stratified by the time from last symptomatic event to randomisation in a pooled analysis of data from randomised trials of endarterectomy for recently symptomatic carotid stenosis<sup>37</sup>

The numbers above the bars indicate the actual absolute risk reduction (ARR).

was borderline cost-effective simply on the basis of providing thrombolysis more consistently.<sup>55</sup> The benefits of thrombolysis within 1 h of stroke onset are substantial,<sup>56</sup> and the benefits of treatment within a few minutes of stroke could be dramatic.

Given the benefits of aspirin after major ischaemic stroke,<sup>47,57</sup> aspirin is likely to reduce the early risk of stroke after transient ischaemic attack and minor ischaemic stroke. The relative reduction in the risk of recurrent ischaemic stroke with aspirin in the pooled data from the International Stroke Trial and the Chinese Acute Stroke Trial was 30% at 14 days ( $p < 0.00001$ ).<sup>44,57</sup> There is also some evidence that the combination of aspirin and clopidogrel might be effective in the acute phase. In the MATCH trial,<sup>58</sup> only 21% of patients had transient ischaemic attack (as opposed to stroke) at entry and median time to randomisation was 15 days (range 0 to 119 days). However, in patients randomised within the first week after the qualifying event there was a borderline significant trend towards benefit from combination treatment with aspirin and clopidogrel. Although the risk of life-threatening haemorrhage was significantly higher in the combination antiplatelet group at 18 months than the clopidogrel only group, this difference did not become apparent until 3 to 4 months after randomisation.<sup>58</sup> These observations suggest that the risk-benefit ratio of aspirin and clopidogrel compared with monotherapy might be greatest when initiated early and continued only for a few weeks or months after the initial event. This treatment option was associated with promising results in the CARESS trial in patients with recently symptomatic carotid stenosis.<sup>50</sup>

In patients with unstable angina or non-Q wave myocardial infarction, the MIRACL trial<sup>52</sup> reported an approximate 50% reduction in risk of ischaemic stroke at 16 weeks in patients treated with a statin within 24–96 h

of the initial event compared with placebo. However, there is no specific evidence from randomised controlled trials for the use of statins in the very early treatment of minor stroke or transient ischaemic attack. The Heart Protection Study<sup>59</sup> included 3280 patients with previous stroke or transient ischaemic attack, in whom simvastatin (40 mg) resulted in a non-significant reduction in ischaemic stroke risk (6.1% vs 7.5%,  $p = 0.2$ ) and an increase in haemorrhagic stroke risk (1.3% vs 0.7%,  $p = 0.03$ ), but few if any patients were randomised in the acute phase.

As discussed above, the subgroup of patients with large-artery atherosclerosis (usually carotid bifurcation stenosis) accounts for the largest proportion of early recurrent strokes. A meta-analysis of individual patient data from 5893 patients in randomised controlled trials of carotid endarterectomy versus medical treatment showed that benefit from surgery was highly dependent on the time from the last symptomatic event to randomisation (figure 6).<sup>37</sup> 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  $\geq 50\%$  stenosis, the number of patients needed to undergo surgery to prevent one ipsilateral stroke in 5 years was 5 for patients randomised within 2 weeks after their last ischaemic event versus 125 for patients randomised  $> 12$  weeks.<sup>37</sup> This trend was due, in part, to the fact that 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 that reported data on operative risk by time since presenting event found that emergency carotid endarterectomy for patients with evolving symptoms had a much higher risk (19.2%, 10.7–27.8) than surgery in patients with stable symptoms (OR 3.9, 2.7–5.7,  $p < 0.001$ , 13 studies), but that there was no difference between early ( $< 3$ –6 weeks) and late ( $> 3$ –6 weeks) surgery for stroke in stable patients (OR=1.13, 0.79–1.62,  $p = 0.62$ , 11 studies).<sup>53</sup> Thus, for neurologically stable patients with transient ischaemic attack and minor stroke, benefit from endarterectomy is greatest if done within 2 weeks of the event.

### Ongoing studies of treatment in the acute and subacute phases

The FASTER trial (Fast Assessment of Stroke and Transient Ischaemic Attack to prevent Early Recurrence) is the only ongoing randomised trial of treatment of patients in the hyperacute phase after transient ischaemic attack.<sup>60</sup> FASTER is a two by two factorial-design trial comparing aspirin and clopidogrel versus aspirin alone, and simvastatin (40 mg) versus placebo in patients who have had a transient ischaemic attack or minor ischaemic stroke within the previous 24 h. Treatment is for 1 month and the main outcome is recurrent stroke. The initial pilot phase aims to recruit 500 patients and should report findings in early 2007.

The CASTIA trial (Clopidogrel in Acute Stroke and Transient Ischaemic Attack) will shortly start to randomise patients with acute transient ischaemic attack or minor ischaemic stroke within 24 h of symptom onset to clopidogrel (300 mg load followed by 75 mg/day) or placebo. All patients will be treated with aspirin 75 mg day. The composite outcome will include clinical stroke, new MRI infarction, myocardial infarction, and vascular death at 90 days.

The EXPRESS study (Early Use of Existing Preventive Strategies for Stroke) is a novel population-based prospective audit of the consequences of the introduction of early intervention after transient ischaemic attack and minor ischaemic stroke within the Oxford vascular study. For the first 30 months of this population-based cohort study most patients with transient ischaemic attack and minor stroke were seen and investigated in an appointment-based daily clinic in which there was often a delay of 1 or 2 days to assessment and advice about preventive treatment (usually antiplatelet treatment, a statin, and a blood pressure lowering drug as appropriate) was faxed to the family physician after the clinic but was often not initiated until after a further delay of several days. In October 2004, a daily open-access emergency clinic was introduced which aimed to see patients on the same day as they sought medical attention and to initiate all appropriate preventive treatment immediately after assessment and investigation in the clinic. The risk of recurrent ischaemic events during the two periods will be compared. Although this will not be a randomised comparison, the Oxford vascular study is a population-based study with near-complete ascertainment of all transient ischaemic attack and stroke, which ensures 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 health-care systems.

### Optimum service provision

Optimum service provision for transient ischaemic attack and minor ischaemic stroke has yet to be determined, but will certainly be influenced by the recent development of reliable risk assessment and the results of future therapeutic studies. Health-care systems that provide emergency inpatient care for nearly all patients<sup>61</sup> might consider rapid-access outpatient clinics for those with low risk scores. In countries, such as the UK, where patients with transient ischaemic attack are usually seen in weekly outpatient clinics, commonly after a delay of 2 weeks or more, the risk of stroke in those with high risk scores should lead to immediate changes in policy. Such patients need to be assessed, investigated, and treated as an emergency, a point perhaps best made by the high rates of stroke before scheduled clinic appointments seen in audits of weekly clinics. For example, among 210 consecutive referrals with suspected transient ischaemic attack to a weekly transient ischaemic attack clinic in

Oxford, UK, the median time from referral to clinic and the appointment was 9 (4–16) days, with 42% seen within 7 days of referral. During this delay between referral and scheduled clinic appointment 11 (5.2%) patients had a stroke, of whom nine patients were admitted to hospital with disabling events.<sup>30</sup>

As discussed above, optimum service provision should include urgent carotid-artery imaging and rapid referral of appropriate patients for carotid endarterectomy. Current practice in many countries is too slow to allow effective prevention of stroke. For example, in a population-based study of all patients having carotid imaging for retinal or cerebral transient ischaemic attack or stroke, of the 85 patients found to have 50–99% symptomatic stenosis, 49 had endarterectomy, but in only three (6%) patients was surgery done within 2 weeks of their presenting event and only 21 (43%) had surgery within 12 weeks.<sup>35</sup>

These audits indicate the enormous improvements that are needed in service provision in some countries before prevention of stroke during the immediate days and weeks after a transient ischaemic attack or minor ischaemic stroke can be made effective.

### Public education

The emergency treatment of minor stroke and transient ischaemic attack depends on the swift presentation of patients to specialist services and the capacity of specialist services to assess, investigate, and treat patients appropriately. However, public awareness of the symptoms of transient ischaemic attack and the need to seek medical attention urgently is poor.<sup>62–64</sup> A nationwide telephone survey of adults in the USA revealed widespread ignorance of the symptoms of transient ischaemic attack and implied a lack of understanding of the severity of the condition.<sup>62</sup> Using randomly generated telephone numbers, 11 400 households were contacted and 10 112 interviews were done to investigate public knowledge of transient ischaemic attack. Only 8.7% correctly understood the definition of transient ischaemic attack and only 8.6% could correctly identify a symptom of a transient ischaemic attack. Increasing age was associated with better knowledge of definition and symptoms as was female sex, white ethnicity, high income, and high educational level. Of the 2.3% of people who reported a physician-diagnosed transient ischaemic attack, 36% did not recall seeing a physician in the first 24 h. An additional 3.2% recalled symptoms typical of transient ischaemic attack that were not brought to medical attention.<sup>62</sup>

Data from Oxfordshire suggest that the picture is similar in the UK. Of 377 consecutive patients attending specialist transient ischaemic attack and stroke clinics, 40% with minor stroke and 50% with transient ischaemic attack delayed seeking medical attention for over 24 h.<sup>64</sup> Moreover, only 10% attended the emergency department, 90% seeking medical attention via their primary care physician. Only 41% of patients with minor stroke and

### Search strategy and selection criteria

This non-systematic review is based on material known to the authors or identified by searches of MEDLINE (up to January 2006) for original research using combinations of the terms "transient ischaemic attack", "ischaemic stroke", "prognosis", and "treatment". Selection of material for inclusion was based on quality and relevance.

37% of patients with transient ischaemic attack correctly identified the cause of their symptoms, and only 45% of patients thought that the event was a medical emergency. Data from the Asymptomatic Carotid Atherosclerosis Study showed significant delays in reporting transient ischaemic attack even in a high-risk patient population participating in a clinical trial with asymptomatic carotid stenosis and even after prior encouragement and education about the need to seek medical attention urgently.<sup>63</sup> Only 32% of patients experiencing transient ischaemic attack and 44.9% experiencing stroke within the study period reported symptoms to medical attention within 3 days of onset and fewer than 25% of events were reported within 24 h.

Part of the problem with public education about transient ischaemic attack and minor stroke has been the difficulty in conveying a succinct message about how to recognise an event because of the wide variety and the sometimes non-specific nature of the potential clinical manifestations. However, the data now available on the association between the nature of the clinical event and the early risk of stroke should allow public education to be simple and effectively focussed.<sup>21,30</sup> Most early strokes happen after transient ischaemic attacks with specific and clearly definable characteristics. For example, in referrals to the Oxford Vascular Study all of the strokes in the first 7 days occurred in the 51% of patients who had focal motor weakness or speech disturbance.<sup>27</sup> If the event also lasted  $\geq 60$  min, the subset was reduced to 30% of referrals but still included 90% of the strokes that occurred within 7 days.

### Conclusion

The risk of recurrent stroke during the first few days after a transient ischaemic attack or minor stroke is much higher than previously estimated. Risk scores can identify patients at particularly high risk of stroke and there is increasing evidence that early preventive treatment is effective. Further research is needed to determine the effect of emergency prevention targeted on the basis of reliable clinical diagnosis, prognosis, and detailed brain and vascular imaging.

#### Authors' contributions

PMR did the literature search and drafted the initial version of the review. SCJ and AB made detailed comments on subsequent versions of the manuscript and added material.

#### Conflicts of interest

We have no conflicts of interest.

### References

- Rothwell PM, Coull AJ, Silver LE, 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.
- Elkins JS, Johnston SC. Thirty-year projections for deaths from ischemic stroke in the United States. *Stroke* 2003; **34**: 2109–12.
- Rothwell PM, Coull A, Giles MF, 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.
- Rothwell PM. Lack of epidemiological data on secondary stroke prevention. *Lancet Neurol* 2005; **4**: 518–19.
- Rothwell PM, Warlow CP. Timing of transient ischaemic attacks preceding ischaemic stroke. *Neurology* 2005; **64**: 817–20.
- Wolf PA, Clagett GP, Easton JD, et al. Preventing ischemic stroke in patients with prior stroke and transient ischemic attack: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Stroke* 1999; **30**: 1991–94.
- The Intercollegiate Working Party for Stroke. National Clinical Guidelines for Stroke. London: RCPL, 2002.
- Johnston SC, Smith WS. Practice variability in management of transient ischemic attacks. *Eur Neurol* 1999; **42**: 105–108.
- Goldstein LB, Bian J, Bonito AJ, Lux LJ, Matchar DB. New transient ischemic attack and stroke: outpatient management by primary care physicians. *Arch Intern Med* 2000; **160**: 2941–46.
- Gubitz G, Phillips S, Dwyer V. What is the cost of admitting patients with transient ischaemic attacks to hospital? *Cerebrovasc Dis* 1999; **9**: 210–14.
- Ovbiagele B, Saver JL, Fredieu A, et al. In-hospital initiation of secondary stroke prevention therapies yield high rates of adherence at follow-up. *Stroke* 2004; **35**: 2879–83.
- Whisnant JP, Matsumoto N, Elveback LR. Transient cerebral ischemic attacks in a community: Rochester, Minnesota, 1955 through 1969. *Mayo Clin Proc* 1973; **48**: 194–48.
- Hankey GJ, Slattery JM, Warlow CP. The prognosis of hospital-referred transient ischaemic attacks. *J Neurol Neurosurg Psychiatry* 1991; **54**: 793–802.
- Warlow CP, Dennis MS, van Gijn J, Sandercock PAG, Bamford JM, Wardlaw JM. Preventing recurrent stroke and other serious vascular events. In: *Stroke: a practical guide to management*; 2001. Blackwell Science Ltd, Oxford.
- Gubitz G, Sandercock P. Prevention of ischaemic stroke. *BMJ* 2000; **321**: 1455–59.
- Rothwell PM. Incidence, risk factors and prognosis of stroke and transient ischaemic attack: the need for high-quality large-scale epidemiological studies. *Cerebrovascular Disease* 2003; **16** (suppl 3): 2–10.
- Coull A, Rothwell PM. Under-estimation of the early risk of recurrence after first stroke by the use of restricted definitions. *Stroke* 2004; **35**: 1925–29.
- Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA* 2000; **284**: 2901–06.
- Hill MD, Yiannakoulis N, Jeerakathil T, Tu JV, Svenson LW, Schopflocher DP. The high risk of stroke immediately after transient ischemic attack: a population-based study. *Neurology* 2004; **62**: 2015–20.
- Lovett J, Dennis M, Sandercock PAG, Bamford J, Warlow CP, Rothwell PM. The very early risk of stroke following a TIA. *Stroke* 2003; **34**: e138–40.
- 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**: 326–28.
- Hankey GJ, Slattery JM, Warlow CP. Transient ischaemic attacks: Which patients are at high (and low) risk of serious vascular events? *J Neurol Neurosurg Psychiatry* 1992; **55**: 640–52.
- Bamford J, Sandercock P, Dennis M, et al. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981–86: methodology, demography and incident cases of first-ever stroke. *J Neurol Neurosurg Psychiatry* 1988; **51**: 1373–80.

- 24 UK-TIA Study Group. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry* 1991; **54**: 1044–54.
- 25 European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998; **351**: 1379–87.
- 26 Kernan WN, Viscoli CM, Brass LM, et al. The stroke prognosis instrument II (SPI II): a clinical prediction instrument for patients with transient ischaemia and non-disabling ischaemic stroke. *Stroke* 2000; **31**: 456–62.
- 27 Rothwell PM, Warlow CP. Prediction of benefit from carotid endarterectomy in individual patients: a risk modeling study. *Lancet* 1999; **353**: 2105–10.
- 28 Rothwell PM, Z Mehta, SC Howard, SA Gutnikov, CP Warlow. From subgroups to individuals: general principles and the example of carotid endarterectomy. *Lancet* 2005; **365**: 256–65.
- 29 Johnston SC, Sidney S, Bernstein AL, Gress DR. A comparison of risk factors for recurrent TIA and stroke in patients diagnosed with TIA. *Neurology* 2003; **60**: 280–85.
- 30 Rothwell PM, Giles MF, Flossmann E, et al. A simple score (ABCD) to identify individuals at high early risk of stroke after a transient ischaemic attack. *Lancet* 2005; **366**: 29–36.
- 31 Gladstone DJ, Kapral MK, Fang J, Laupacis A, Tu JV. Management and outcomes of transient ischaemic attacks in Ontario. *CMAJ* 2004; **170**: 1099–104.
- 32 Flossman E, Rothwell PM. Prognosis of vertebrobasilar TIA and minor ischaemic stroke. *Brain* 2003; **126**: 1940–54.
- 33 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.
- 34 Donnan GA, O'Malley HM, Quang L, Hurler S, Bladin PF. The capsular warning syndrome: pathogenesis and clinical features. *Neurology* 1993; **43**: 957–62.
- 35 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**: 371–75.
- 36 Rantner B, Pavelka M, Posch L, Schmidauer C, Fraedrich G. Carotid endarterectomy after ischemic stroke: is there a justification for delayed surgery? *Eur J Vasc Endovasc Surg* 2005; **30**: 36–40.
- 37 Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJM. Effect of endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and to the timing of surgery. *Lancet* 2004; **363**: 915–24.
- 38 van Swieten JC, Kappelle LJ, Algra A, van Latum JC, Koudstaal PJ, van Gijn J. Hypodensity of cerebral white matter in patients with transient ischaemic attack or minor stroke: influence on the rate of subsequent stroke: Dutch TIA Study Group. *Ann Neurol* 1992; **32**: 177–183.
- 39 Evans GW, Howard G, Murros KE, Rose LA, Toole JF. Cerebral infarction verified by cranial computed tomography and prognosis for survival following transient ischemic attack. *Stroke* 1991; **22**: 431–36.
- 40 Douglas CD, Johnston CM, Elkins J, Sidney S, Gress DR, Johnston SC. Head computed tomography findings predict short-term stroke risk after transient ischemic attack. *Stroke* 2003; **34**: 2894–99.
- 41 Schulz UGR, Briley D, Meagher T, Molyneux A, Rothwell PM. Diffusion Weighted MR-Imaging in 300 consecutive patients presenting late with subacute TIA or minor stroke. *Stroke* 2004; **35**: 2459–65.
- 42 Crisostomo RA, Garcia MM, Tong DC. Detection of diffusion-weighted MRI abnormalities in patients with transient ischemic attack: correlation with clinical characteristics. *Stroke* 2003; **34**: 932–37.
- 43 Purroy F, Montaner J, Rovira A, Delgado P, Quintana M, Alvarez-Sabin J. Higher risk of further vascular events among transient ischaemic attack patients with diffusion-weighted imaging acute lesions. *Stroke* 2004; **35**: 2313–19.
- 44 Coutts SB, Simon JE, Eliasziw M, et al. Triaging transient ischemic attack and minor stroke patients using acute magnetic resonance imaging. *Ann Neurol* 2005; **57**: 848–54.
- 45 Wen HM, Lam WWM, Rainer T, Fan YH, Leung TWH, Chan YL, Wong KS. Multiple acute cerebral infarcts on diffusion-weighted imaging and risk of recurrent stroke. *Neurology* 2004; **63**: 1317–19.
- 46 Markus HS, MacKinnon A. Asymptomatic embolization detected by Doppler ultrasound predicts stroke risk in symptomatic carotid artery stenosis. *Stroke* 2005; **36**: 971–75.
- 47 International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both or neither among 19435 patients with acute ischaemic stroke. *Lancet* 1997; **349**: 1569–81.
- 48 Hankey GJ. Ongoing and planned trials of antiplatelet therapy in acute and long term management of patients with ischaemic brain syndromes: setting a new standard of care. *Cerebrovasc Dis* 2004; **17** (suppl 3): 11–16.
- 49 Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345**: 494–502.
- 50 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.
- 51 European Atrial Fibrillation Trial Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 1993; **342**: 1255–62.
- 52 Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. The MIRACL Study: a randomized controlled trial. *JAMA* 2001; **285**: 1711–18.
- 53 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.
- 54 Gladstone DJ, Black SE, Hakim AM. Toward wisdom from failure: lessons from neuroprotective stroke trials and new therapeutic directions. *Stroke* 2002; **33**: 2123–36.
- 55 Nguyen-Huynh MN, Johnston SC. Is hospitalization after TIA cost-effective on the basis of treatment with tPA? *Neurology* 2005; **65**: 1799–1801.
- 56 Hacke W, Donnan G, Fieschi C, JP et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 2004; **363**: 768–74.
- 57 CAST (Chinese Acute Stroke Trial) Collaborative Group. CAST: randomised placebo-controlled trial of early aspirin use in 20 000 patients with acute ischaemic stroke. *Lancet* 1997; **349**: 1641–49.
- 58 Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischemic stroke or transient ischemic attack in high-risk patients (MATCH): randomised double-blind, placebo-controlled trial. *Lancet* 2004; **364**: 331–337.
- 59 Heart Protection Study Collaborative Group. Effects of cholesterol lowering with Simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high risk conditions. *Lancet* 2004; **363**: 757–67.
- 60 Kennedy J, Eliasziw M, Hill MD, Buchan AM. The Fast Assessment of Stroke and Transient Ischemic Attack to prevent Early Recurrence (FASTER) Trial. Seminars in Cerebrovascular Diseases and Stroke 2003 Vol 3; 25–30.
- 61 Weimar C, Kraywinkel K, Rodl J, et al. Etiology, duration, and prognosis of transient ischemic attacks: an analysis from the German Stroke Data Bank. *Arch Neurol* 2002; **59**: 1584–88.
- 62 Johnston SC, Fayad PB, Gorelick PB, Hanley DF, Shwayder P, van Husen D, Weiskopf T. Prevalence and knowledge of transient ischemic attack among US adults. *Neurology* 2003; **60**: 1429–34.
- 63 Castaldo JE, Nelson JJ, Reed JF, Longenecker JE, Toole JF. The delay in reporting symptoms of carotid artery stenosis in an at-risk population: the asymptomatic carotid atherosclerosis study experience, a statement of concern regarding watchful waiting. *Arch Neurol* 1997; **54**: 1267–71.
- 64 Giles MF, Rothwell PM. Determinants of delay in seeking medical attention after a TIA or minor stroke. *Cerebrovasc Dis* 2004; **17** (suppl 5): 6.