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New insights in the management of patients with ischaemic stroke or TIA - Level 2

TIA and mimics

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1. TIA definition and diagnosis

The concept of TIA emerged in the 1950s, with the observation by Miller Fisher, and others, that ischaemic stroke often followed transient neurological symptoms in the same arterial territory.¹

The diagnostic criteria for TIA were formulated in the first internationally accepted clinical classification for cerebrovascular disorders in 1975 by an ad hoc committee established by the Advisory Council for the American National Institute of Neurological and Communicative Disorders and Stroke (NIINDS).² TIs were defined as episodes of temporary and focal cerebral dysfunction, rapid in onset (commonly 2-15 minutes, but occasionally lasting as long as 24 hours), which are attributable to dysfunction of one arterial territory of the brain. The resolution or disappearance of each episode is swift, ordinarily a few minutes at most.

The acute loss of focal brain or monocular function in TIA is thought to be caused by inadequate cerebral or ocular blood supply as a result of arterial thrombosis, low flow or embolism associated with arterial, cardiac or haematological disease.³
The diagnosis of a TIA rests entirely on the skill with which the history is taken and in deciding the cause of symptoms.²,⁴ As the criteria represent interpretation of symptoms it can be difficult to differentiate a TIA from other disorders such as migraine, epilepsy, functional disorders and amyloid spells.⁵-¹¹ Moreover, the observer agreement for the diagnosis of TIA among physicians is poor even among stroke-trained neurologists or with rating scales.⁶,⁷,¹²,¹³

The typical history for TIA in the carotid system is a sudden onset of decrease or absence of motor or sensory function (of one extremity or of both extremities on the same side), aphasia, loss of vision in one eye or in part of one eye, or homonymous hemianopia. The typical history of a TIA in the vertebrobasilar arterial system is a sudden onset of motor or sensory defect (of any combination of extremities), loss of vision, complete or partial in both homonymous fields, ataxia (imbalance, unsteadiness, disequilibrium), vertigo, diplopia, dysphagia or dysarthria. However, the territory affected by a TIA/stroke may be difficult to ascertain clinically.¹⁴

According to the NINDS criteria, when vertigo, diplopia, dysphagia, or dysarthria occurs alone, the episode should be categorized as "uncertain TIA" and the following symptoms, transient or prolonged, were considered not to be indicative of TIAs: unconsciousness including syncope, tonic or clonic activity, march of a sensory defect, incontinence of bladder or bowel, dizziness or wooziness alone, loss of vision associated with alteration of consciousness, focal symptoms associated with migraine,
scintillating scotoma, confusion alone and amnesia alone. However, in recent decades some of those symptoms were described as of a vascular nature and were associated with an increased risk of vascular events. \(^{15-18}\)

The use of magnetic resonance (MR) with diffusion-weighted imaging (DWI), which is very sensitive to small ischaemic lesions, \(^{19}\) has shown that patients with an acute ischaemic lesion on DWI are at increased risk of recurrent stroke. \(^{20-22}\) Thus, DWI could both improve diagnosis of TIA and predict the short-term risk of stroke. Since the 24-hour time limit for TIA diagnosis is arbitrary, rather than being based on clinical, imaging or pathological criteria, a new tissue-based definition of TIA was proposed in 2002 \(^{23}\) and was incorporated into the American Heart Association guidelines in 2009. \(^{24}\) The new tissue based definition comprises a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction. \(^{24}\) Therefore, even if the tissue-based definition is used the diagnosis of TIA is still based on clinical grounds. The advantage of the tissue-based definition is that it acknowledges that the majority of TIAs last for less than 60 minutes \(^{25,26}\) and on average 34% of clinically defined TIAs show brain injury on diffusion-weighted magnetic resonance imaging (MRI). \(^{27}\) It also encourages use of neurodiagnostic investigations and emphasises the prognostic importance of cerebral infarction. \(^{28-30}\) DWI MRI is recommended by the National Institute for Health and Clinical Excellence (NICE) guidelines in TIA patients. \(^{31}\) However, the disadvantages of the new definition are that diagnosis is based on interpretation of imaging which is subject to variation between individuals and centres, diagnosis cannot be made in
centres where imaging is not available, brain imaging can be normal in clinically definite stroke and that silent infarction can occur. Furthermore, in a recent systematic review evidence was found that the DWI-positive rate varied with time between TIA and scanning.\textsuperscript{27} DWI may disappear very rapidly, for example, being present at 4 hours after symptom onset but resolving completely from DWI and other MR sequences by 24 hours, or not being visible on hyperacute imaging but becoming visible at 24 to 48 hours. The high proportion (two-thirds) of TIA patients with a negative DWI scan and the large unexplained sevenfold variation in positivity between studies (DWI findings varied from 9\% to 67\%) suggests that DWI does not provide a consistent and predictable basis for defining stroke, and researchers argued that reclassifying DWI-positive TIs as strokes was likely to increase variance in estimates of global stroke and TIA burden of disease.\textsuperscript{32}

1.2. Atypical TIs and non-specific Transient Neurological Attacks (TNAs)

In 1989 the Oxfordshire Community Stroke Project (OCSP) investigators published an observation study of patients with lone bilateral blindness (n=14) lasting under 24 hours without associated symptoms of focal cerebral ischaemia, epilepsy, or reduction in consciousness.\textsuperscript{33} In OCSP, investigators found that those patients with lone bilateral blindness had the same prevalence of vascular risk factors and that their age was close to that of patients who presented with transient ischaemic attacks (n=184). During a mean follow-up of 2.4 years, patients with lone bilateral blindness had a 16 times higher risk of stroke than expected. It was
concluded that lone bilateral blindness should be included, for practical purposes, under the diagnostic heading of TIA.

In 1991 a retrospective study was published of 64 patients with a mean age of 55 years and admitted to a neurology ward in Rotterdam, with cardiovascular risk factors and atypical transient cerebral or visual symptoms that could not be classified as unequivocal TIs nor migraine, epilepsy or neurosis. Those patients had a low risk of stroke but a high risk of major cardiac events when followed-up for a mean of 3.75 years. Patients with an unequivocal TIA or a minor stroke were used as a control group. Since then, additional data about atypical TIs or nonspecific Transient Neurological Attacks (TNAs) has been published. In addition, a recent study has shown that isolated transient brainstem symptoms are common in the 3 months preceding a vertebrobasilar TIA. All these findings indicate that the clinical definition of TIA might need to be broaden.

2. Incidence of TIA

The total incidence of TIA has been estimated as ranging from 20,000 to 90,000 in the UK, and from 200,000 to 500,000 in the USA. The true incidence and prevalence of TIA are difficult to determine as many patients who experience TIA do not present to medical attention. The annual incidence of TIA from population-based studies has ranged from 0.16 per 1000 in Novosibirsk, Russia to 0.80 in Segovia, Spain. However, in these studies, the stringent definition of ‘first ever in a
lifetime,’ definite, TIA, may underestimate the overall burden of TIA, which includes those with non-vascular diagnoses (TIA mimics) that present to medical attention. More recent data from a comparison with a previous population-based study in Oxfordshire has shown the standardized incidence of any definite or probable TIA is approximately 1.08 (95% confidence interval (CI) 0.95–1.21) per 1000 population, almost double the rate calculated according to the definition of ‘first ever in a lifetime’, definite TIA, as used in previous incidence studies.48

3. Prognosis after a TIA

3.1 Short-term prognosis and risk prediction after a TIA

The early risk of recurrent stroke after a TIA has been underestimated for many years. Approximately 15-20% of ischaemic strokes are preceded by a TIA49 and the appropriate detection and urgent diagnostic work-up for patients with TIA can potentially avoid further disabling stroke if the correct treatment is indicated. A retrospective study of consecutive patients attending emergency departments (EDs) within 24 hours of TIA demonstrated that the stroke risk after the index event was higher than previously thought: 10.5% at 90 days, with 5.3% occurring within two days of symptom onset.50 Several studies have been published since this publication. Different studies have reported conflicting stroke rates after TIA, and cohorts from Oxford, UK and northern Portugal have reported very high risks of stroke at 7 days (11% to 13%) and 90 days (17% to 21%), respectively. A systematic review and meta-analysis identified 53 studies
providing data on stroke risk at 7 days, 90 days, or > 90 days. The rate of recurrent stroke at all points assessed varied widely from 0% to 22.4% at seven days, 0.6% to 23.7% at 90 days, and 4.7% to 27% at > 90 days. A further meta-analysis showed the pooled risk of recurrent stroke at seven days to be 5.2%, at 90 days to be 6.7%, and at > 90 days to be 11.3%. A decrease of risk of stroke after a TIA was demonstrated in a recent systematic review and meta-analysis of recent intervention studies which showed that the pooled stroke risk was 3.42% (95% CI 3.14-3.74) at 90 days, 2.78% (95% CI 2.47-3.12) at 30 days, 2.06% (95% CI 1.83-2.33) at 7 days and 1.36% (95% CI 1.15-1.59) at 2 days.

The risk of recurrent stroke after TIA is high, especially during the first week after the event, as mentioned above. The benefit of medical therapy to prevent recurrent stroke after a TIA is greatest if given as early as possible after the event. Likewise, the benefit of endarterectomy for symptomatic carotid stenosis is highest when performed within two weeks of the index event and falls rapidly with increasing delay. Consequently, patients with TIA need a rapid comprehensive assessment to reduce the short- and long-term risks of recurrent stroke and other vascular conditions. Numerous clinical risk prediction scores have been developed to identify patients at high risk of stroke to prioritise services. In 2000, a northern California study demonstrated that simple clinical variables (age > 60, symptom duration greater than 10 minutes, diabetes mellitus, weakness and speech impairment during the episode) were associated with a high risk of stroke at 90 days. The estimated risk of further stroke was 34% in patients presenting with all five predictors. In
addition, a population-based study from Canada\textsuperscript{57} showed that age, and diabetes mellitus together with hypertension, were associated with a high risk of stroke one year after TIA. Subsequently the ABCD score was created to predict the stroke risk during the first week after TIA using those clinical variables that have been independent predictors for stroke.\textsuperscript{58} The score includes age, blood pressure elevation on first assessment after TIA, unilateral weakness, speech disturbance and duration of symptoms as clinical variables. The score was able to predict with accuracy the risk of stroke at seven days after TIA. By combining the components of the California score and the ABCD score, the ABCD2 score was generated in 2007,\textsuperscript{59} which includes as clinical variables age, blood pressure elevation on the first assessment after TIA, unilateral weakness, speech disturbance, duration of symptoms and diabetes. The score classifies TIA or minor stroke patients as low, moderate or high risk using cut-off points of $< 4$, $4-5$ and $> 5$. Recently other variants of the ABCD2 score have been generated (ABCD2-I, ABCD3, ABCD3-I),\textsuperscript{60,61} which add either more clinical or brain or carotid variables. Ideally all suspected TIA patients should be seen urgently.

The TIA registry study showed a lower risk of cardiovascular events than previously reported. The Kaplan-Meier estimates of the stroke rate at days 2, 7, 30, 90, and 365 were 1.5\%, 2.1\%, 2.8\%, 3.7\%, and 5.1\%, respectively. In multivariable analyses, multiple infarctions on brain imaging, large-artery atherosclerosis, and an ABCD(2) score of 6 or 7 were each associated with more than a doubling of the risk of stroke.\textsuperscript{62}
3.2 Long-term prognosis after TIA

Data on the medium- (one to five years) and long- (five years and beyond) term prognosis after a TIA/minor stroke are fundamental to advise patients and direct secondary prevention. Many studies have addressed the question of medium-term prognosis, although many were undermined by non-standardised diagnostic criteria, a small number of cases, retrospective case identification and incomplete follow-up.63 Three prospective, population-based studies of the medium-term prognosis of TIA have been published from Söderhamn, Sweden,64 Oxfordshire,65 UK, and Perugia, Italy.66 In the Söderhamn cohort, the risk of stroke was approximately 5% per year and the overall mortality was 24.7% over a mean of three years. In the Oxfordshire cohort, the annual stroke risk was 4.4%, although this was highest in the first year after TIA. The risk of death at five years was 31.3% and the annual risk of death was 6.3%. The risk of either fatal or non-fatal MI was 12.1% at five years and the approximate annual risk was 2.4%. In the Perugia cohort, the annual risk of stroke after TIA was 2.4%. The cumulative risk of death was 28.6% at five years and 49.5% at 10 years with roughly equal numbers of cerebrovascular, cardiovascular and non-vascular deaths. Thus, the risks of stroke and other vascular events after TIA are significant in the medium term. However, data on vascular risk in the longer term is limited. There are two studies providing reliable data on prognosis up to fifteen years after the initial event. In a study of 290 patients with TIA who had participated either in the Oxfordshire Community Stroke Project (OCSP) or a contemporaneous hospital referred cohort study followed-up over ten years from 1988, the risk of stroke was 18.8%.65 The risk of MI or death
from coronary heart disease was 27.8% and the risk of death from any cause was 50.7%. The risk of any first stroke, MI or vascular death was 42.8%. The risk of major vascular events was found to be constant throughout the follow-up. In this study, the median length of follow-up after TIA was 3.8 years and mean age at baseline was 69 years.

The Life Long After Cerebral Ischaemia (LILAC) study reported near complete follow-up on 2473 participants from the Dutch TIA Trial. Mean age was 65 and 759 patients had a TIA while the remainder had a minor stroke (defined as mRS score ≤3) at enrolment. At ten years the cumulative risk of recurrent stroke was 18.4% and the risk of death was 46.6%.

3.3 Prognosis after TIA mimic

Approximately half of the patients who attend neurovascular clinics in the UK with transient or mild neurological symptoms do not have a final diagnosis of a cerebrovascular disease event; less is known about the prognosis of these patients, although non-cerebrovascular events are considered a benign condition.\textsuperscript{67,68}

After expert clinical assessment, a significant number of patients referred with the diagnosis of suspected TIA have a final diagnosis of a non-cerebrovascular event or mimic.\textsuperscript{13,68} In a survey of stroke prevention clinics in 2011 in the UK, half of the centres indicated that the proportion of patients with a final diagnosis of TIA or minor stroke was between 11% and 60%.\textsuperscript{69} Accurate diagnosis of cerebrovascular disease compared with non-cerebrovascular causes of symptoms is essential to ensure appropriate
management. Brain imaging is useful in identifying an acute ischaemic lesion or some non-vascular imaging (e.g. brain tumour, MS); however, a normal CT or MRI is still compatible with the diagnosis of both TIA and non-cerebrovascular mimic.

Less is known about the prognosis of patients with TIA mimic, although these are generally considered to be benign in most cases and given less attention. Several medical conditions can imitate a TIA or minor stroke, and require different approaches from cerebrovascular events. Furthermore, previous studies reported a considerable proportion of patients with miscellaneous or unclassifiable events, probably including entities with different pathophysiology and unknown prognosis. In a recent systematic review and meta-analysis of frequency, differential diagnosis, and prognosis of TIA/minor stroke mimics among 16 studies identified, only two were population-based (OCSP and a community register in Segovia, Spain). The proportion of TIA mimics was 40% for TIA clinics and 40% for population-based studies and 32% for hospital-/emergency department-based studies. The risk of stroke and other vascular events was described in five studies. None of the studies were population-based. The reported stroke risk up to 90 days was lower for mimics than TIs (three studies, zero events vs 1.5-5.2%, respectively). In summary, there is a paucity of good quality data comparing the prognosis of patients with TIA mimic and TIA in the general population. Therefore, the prognosis for any transient neurological event other than TIA has not yet been fully delineated and long-term follow up of these patients is required.
4. Secondary prevention after a TIA

The aim of treatment after TIA and minor stroke is the secondary prevention of a disabling stroke. Prevention of recurrent ischaemic stroke is by rapid identification of underlying risk factors (such as ipsilateral tight carotid artery stenosis, atrial fibrillation (AF), hypertension and hypercholesterolaemia) and implementation of optimal medical (antiplatelet agents, statins, antihypertensive drugs or anticoagulant drugs when necessary)\textsuperscript{53,76-79} and surgical (endarterectomy for symptomatic moderate to severe carotid stenosis)\textsuperscript{80} treatment. In the acute phase, antiplatelets reduces the risk of recurrent stroke after TIA and minor stroke. The evidence of the decrease risk of stroke after a TIA with the use of antiplatelets in the acute phase was found in two non-randomised studies of a combination of preventative treatments started urgently in specialist units,\textsuperscript{81} the Early Use of Existing Preventative Strategies for Stroke (EXPRESS) and SOS-TIA studies.\textsuperscript{53,54} A recent pooled data analysis for 15,778 participants from 12 trials of aspirin versus control in secondary prevention showed that Aspirin reduced the 6 week risk of recurrent ischaemic stroke by about 60% (84 of 8452 participants in the aspirin group had an ischaemic stroke vs 175 of 7326 in the control group, hazard ratio [HR] 0·42, 95% CI 0·32-0·55, p<0·0001) and disabling or fatal ischaemic stroke by about 70% (36 of 8452 vs 110 of 7326; 0·29, 0·20-0·42, p<0·0001), with greatest benefit noted in patients presenting with TIA or minor stroke (at 0-2 weeks, two of 6691 participants in the aspirin group with TIA or minor stroke had a disabling or fatal ischaemic stroke vs 23 of 5726 in the control group, HR 0·07, 95% CI 0·02-0·31, p=0·0004; at 0-6 weeks, 14 vs 60
participants, 0.19, 0.11-0.34, p<0.0001). In a Chinese randomized-controlled study in patients with TIA or minor stroke treated within 24 hours after the onset of symptoms, the combination of clopidogrel and aspirin was superior to aspirin alone for reducing the risk of stroke in the first 90 days and did not increase the risk of hemorrhage.\(^8\)

Initiation of BP therapy is indicated for previously untreated patients with ischemic stroke or TIA who, after the first several days, have an established BP ≥140 mm Hg systolic or ≥90 mm Hg diastolic.\(^8\) A meta-analysis of randomized trials confirmed that antihypertensive medications reduced the risk of recurrent stroke after stroke or TIA.\(^8\) It included 10 randomized trials published through 2009 that compared hypertension therapy with placebo or no therapy. Together, these trials included participants with transient ischemic stroke, TIA, or intracerebral hemorrhage randomized days to months after the index event and followed up for 2 to 5 years. No trials tested nonpharmacological interventions. Overall, treatment with antihypertensive drugs was associated with a significant reduction in recurrent strokes (RR, 0.78; 95% CI, 0.68-0.90). Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic with or without evidence for other clinical atherosclerotic cerebrovascular disease.\(^8\) After a TIA or ischemic stroke, all patients should probably be screened for DM with testing of fasting plasma glucose, HbA1c, or an oral glucose tolerance test.\(^8\)
References


