Introduction to the ACNR Stroke Series

A key aspect of the revolution in the approach to stroke medicine in recent years has been increased awareness of the very high early risk of ischaemic stroke after TIA, with realization that a TIA syndrome is thus a unique and golden opportunity to avert future disaster by early investigation and treatment. As part of this revolution, risk scores have been developed and widely enshrined in national guidelines and stroke care pathways, especially the ABCD² score. Such scores may have a very useful role in patient triage, but are subject to misunderstanding of their intended purpose (e.g. they are not diagnostic instruments), and to misuse in clinical practice. In this next article in the Stroke series, Aine Merwick and Peter Kelly give an excellent clear and comprehensive insight into the development and implementation of TIA risk prediction scores, with elegant explanation of the statistical approaches needed, as well as a summary of their limitations and a look to the future of such instruments.

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Predicting ischaemic stroke risk after TIA: promise and pitfalls

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Summary

• Stroke risk following TIA is highest in the days immediately following a TIA.
• Risk prediction tools can identify patients at low and high risk of stroke in the short term following TIA.
• Urgent brain and vessel imaging improves risk prediction following TIA.
• External validation and cost effectiveness studies of clinical prediction tools such as the ABCD³ may help demonstrate their utility in everyday clinical practice.

Introduction

Transient ischaemic attack (TIA) is associated with high risk of early stroke, with stroke rates of 10-15% reported in population studies with routine treatment. Early recognition and treatment of TIA provides an ideal opportunity for rapid intervention to prevent stroke and related sequelae. TIA is also an important marker of risk of late stroke recurrence, coronary events and cognitive impairment. When combined with clinical assessment by a trained physician, clinical prediction scores for stroke risk after TIA have the potential to be valuable aids, particularly for identification of patients at highest stroke risk.

In practice identifying which patient may be most high risk is a challenge, and therefore clinical prediction tools can be helpful for answering patient’s questions regarding likelihood of stroke after a TIA.

Clinical prediction tools and ABCD² score

The ideal characteristics of a predictive score include transportability (also termed generalisability and demonstrated by external validation), good calibration (defined as comparison of observed and predicted event rates for groups of patients) and discrimination (the ability of the risk prediction models to distinguish those who go on to experience an outcome event from those who do not). Epidemiological studies have shown that older age, hypertension, diabetes mellitus, and multiple recent TIs are associated with stroke risk. Further clinical features including motor weakness, speech disturbance, and symptom duration >60 minutes were associated with increased stroke risk.

Based on the features identified in studies of stroke risk following TIA, a simple clinical prediction tool was devised for triage purposes. The ABCD² clinical prediction score was originally intended for use at the initial evaluation of patients with suspected TIA by primary care and emergency department physicians to aid triage decisions for hospital admission and urgent referral to specialist stroke services. The ABCD² score (age ≥60 years [1 point]; blood pressure ≥140/90mmHg [1 point]; clinical features of weakness [2 points] or speech impairment [1 point]; duration of symptoms ≥60 min [2 points] or 10-59 min [1 point]; diabetes mellitus [1 point])) has been developed based on information obtained on basic clinical examination and history taking. The score was deliberately designed not to include information frequently obtained after initial investigations have been performed, as it was designed for use by general practitioners and emergency department doctors. The score was designed with the aim of helping to accurately triage patients and specifically to identify which patients may be managed in an outpatient/clinic setting (low risk patients) and identify high risk patients, who may benefit most from hospitalisation and/or prioritised diagnostic investigations and treatments. Ideally prediction scores for TIA patients would have high sensitivity.
and high specificity. To determine the validity of a prediction score, its discriminative ability to predict stroke is usually evaluated by receiver-operating characteristic (ROC) analysis and the c-statistic (corresponding to area under the ROC curve) calculated. Ideal discrimination produces a c-statistic of 1.0 whereas discrimination which is no better than chance produces a c-statistic of 0.5.4,11

In the original ABCD2 score derivation study the clinically based score predicted stroke by two days after TIA (c-statistic: 0.62-0.70) and by seven days after TIA (c-statistic: 0.63-0.83).5 Based on clinical outcome events risk categories were assigned (0.3 low risk, 4-5 moderate risk, 6-7 high risk).9 Current international guidelines for use of the ABCD2 prediction tool, have mostly adopted either a greater than or equal to 4 threshold.11,11

Evaluation of the ABCD2 score has been demonstrated in a meta-analysis of 11 independent TIA cohorts (ie. excluding the original samples in which the score was derived and validated). On receiver operating characteristic analysis, the pooled area-under-curve (AUC) for seven day stroke was 0.69 (CI 0.64-0.74).12

Carotid stenosis, neurovascular imaging and risk prediction after TIA

Imaging evidence of carotid stenosis (≥50% lumen narrowing) has also been linked with high risk of early recurrence in several studies. In a population based study of 633 TIA patients the hazard ratio (HR) of 90-day stroke recurrence associated with any carotid stenosis ≥50% was 2.6 (95% CI, 1.28 to 5.20) and with >70% carotid stenosis was 3.3 (95% CI, 1.5 to 7.4, P=0.002).13 The risk of 90-day stroke was seen to rise in a linear fashion with increasing severity of carotid stenosis, ranging from 5.4% (≥50% stenosis) to 17.2% (≥70% stenosis or occlusion) (P=0.002). Carotid stenosis had moderate sensitivity (43.8%) but high specificity (77.9%) for identification of TIA patients who subsequently developed 90-day stroke. In the OXVASC study patients with posterior circulation TIA, 50% vertebral and basilar stenosis was also associated with 90-day risk of recurrent stroke/TIA (OR 3.2, P=0.006), with rates of 22% for stroke and 46% for TIA or stroke recurrence.14

Several groups have demonstrated that addition of brain imaging, especially magnetic resonance imaging (MRI) data may enhance the predictive utility of existing clinical scores.15-18 Diffusion weighted imaging (DWI) is particularly important, and remains an ongoing area of clinical relevance. Several techniques may have a future role in TIA risk prediction. Lipoprotein-associated phospholipase A2 (LP-PLA2), a serum marker of plaque macrophage activation was independently associated with a combined outcome measure of stroke, death, large artery or cardioembolic mechanism in 147 acute TIA patients.21 Other substances have also been suggested as biomarkers for stroke risk prediction but validation and determination of the utility of serum biomarkers remains to be verified.

Combining follow-up imaging after TIA with novel imaging modalities such as perfusion weighted imaging (PWI), or arterial spin label imaging may help better characterise stroke risk.22,23

Stroke prediction in patients with carotid stenosis is an area where risk prediction is particularly important, and remains an ongoing area of clinical relevance. An online calculator of stroke risk based on data from the European Carotid Surgery Trial is available, and is a further adjunct to clinical decision making (http://www.stroke.ox.ac.uk/model/form1.html).

Figure 1: DWI image showing acute restricted diffusion in the left parietal lobe in a 45-year-old patient who presented with a TIA.

While not intended to replace clinical judgement in the assessment of individual patients, clinically useful risk stratification by prediction tools provide the clinician with an easy to use method of estimating stroke risk
Transcranial Doppler (TCD) may provide prognostic information based on detection of intracranial stenosis, occlusion or micro-embolic signals (MES). In 1,881 TIA patients followed for one year, increased risk of intracranial recanalisation, stroke, myocardial infarction, or vascular death was associated with intracranial stenosis or occlusion detected on TCD, compared to none (adjusted hazard ratio 2.25). Use of 18F fluorodeoxyglucose positron-emission tomography (FDG PET) in large artery stroke may identify high-risk TIA patients based on carotid plaque metabolic activity. A study of TIA and minor stroke patients with symptomatic carotid stenosis showed FDG PET uptake predicted early stroke recurrence, independently of stenosis severity. Long-term presence of stroke risk after TIA is an area that less data is available for, however a Japanese group has recently shown some predictive ability of the ABCD3-I score (c-statistic 0.61) at three years. However, a limitation of prognostic tools in general is that the majority of outcome events occur in the low or medium risk groups, since the absolute number of events is greater in the low or medium risk group than in the high risk group – the prevention paradox.

Potential pitfalls in the use of prediction tools includes delay in presenting with a TIA and inter-rater variability in assigning the score components of the prediction tool e.g. using incorrect value for blood pressure.

Summary
While not intended to replace clinical judgement in the assessment of individual patients, clinically useful risk stratification by prediction tools provide the clinician with an easy to use method of estimating stroke risk. The ABCD2 clinical prediction tool is a well validated triage tool in TIA management. Risk prediction in the post-investigation phase of TIA management benefits from the incorporation of information gained from imaging e.g. presence of imaging abnormalities on parenchymal imaging or detection of large vessel stenosis. The ABCD3-I score which incorporates imaging information has been shown to improve prediction when compared to the ABCD2 score. Future work may also need to examine the cost effectiveness and safety of using the ABCD2 score predictive tool in clinical decision making in patients with transient neurological symptoms, as well as determine the external validity of the use of the score by non-specialists or non-physicians and via telemedicine. Robust external validation of ABCD3-I score, investigation of the safety and use of acute TIA management algorithms based on ABCD3-I, and research on clinical scenarios in which the utility of prediction tools are unclear (e.g. posterior circulation TIA or TIA in young adults) may be useful next steps for refining risk prediction in TIA.

REFERENCES
The MS Society comments on NICE clinical guidelines for MS

Recent National Institute of Health and Care Excellence Guidelines for multiple sclerosis (MS) will block access to important treatments for the condition, the MS Society has warned.

The MS Society welcomed the publication of the guidelines but continues to express concern over access to medication for people with MS. The guidelines reject Sativex and Fampyra because they have not been considered cost-effective. Sativex is a cannabis based medicine proven to relieve painful muscles spasms and stiffness, while Fampyra has been shown to improve mobility. This is particularly disappointing for people with progressive MS as these drugs represent two of only three MS specific treatments available to them.

The MS Society believes the decision to reject Sativex and Fampyra was based on a flawed assessment completed within an inappropriate process. The MS Society has urged NICE to take into account the wider cost benefit of the treatments, such as potential savings in social care costs and called on them to conduct a full technology appraisal of these medicines.

The guidelines also fail to include vital references on the use of disease modifying treatments (DMTs) for MS—a significant omission, particularly given the changing landscape in this area with three new treatments licensed last year alone. However, the MS Society has welcomed significant elements of the guidelines and recognises that NICE have listened to the MS community. For example, the guidelines now recommend that people with MS have an annual review of their treatment and care and stress that people with MS should have access to coordinated care within a team of health and care professionals. These recommendations could significantly improve the treatment, care and support that people with MS receive.

The MS Society believes that this is a significant but important step and the NHS and local authorities should commit the necessary resources to make co-ordinated, reliable care a reality. At a time of already stretched NHS budgets, delivering the guideline recommendations on patient care will be challenging without a commitment to additional investment and resource.

MS Society Chief Executive Michelle Mitchell said, “There is encouraging and disappointing news in these guidelines. Making sure that people with MS are able to access a team of health and care professionals, with a minimum annual review of their treatment and support are important steps and should not be underestimated. It is vital that these recommendations are implemented without delay.

However, NICE’s decision to reject Sativex and Fampyra as treatment options is really disappointing. Surely we should be striving for the most innovative treatment and care to be made available to people with MS, not limiting options even further? The guidelines also fail to stress the importance of the many treatments now available for relapsing forms of MS. This will increase the risk of people with MS not receiving the right treatment at the right time.”

MS Society’s ‘Treat Me Right’ campaign found that access to treatments licensed specifically to help people manage the symptoms of MS is abysmally low; just one in 50 people with MS take these. Through the campaign, people with MS are fighting for the right treatment, at the right time, wherever they live.

New evidence on demand for Sativex
A survey of nearly 4,000 people with MS showed the huge gap between people with MS experience of muscle stiffness and spasms with their access to Sativex. 82% of those who currently take it consider Sativex to be essential or a high priority, but 54% of those who have experienced muscle stiffness and spasms and have never taken it.