Four-Year Follow-Up of Transient Ischemic Attacks, Strokes, and Mimics
A Retrospective Transient Ischemic Attack Clinic Cohort Study

Dipankar Dutta, FRCP; Emily Bowen, MRCP; Chris Foy, MSc

Background and Purpose—There is limited information on outcomes from rapid access transient ischemic attack (TIA) clinics. We present 4-year outcomes of TIAs, strokes, and mimics from a UK TIA clinic database.

Methods—All patients referred between April 2010 and May 2012 were retrospectively identified and outcomes determined. End points were stroke, myocardial infarction, any vascular event (TIA, stroke, or myocardial infarction), and all-cause death. Data were analyzed by survival analysis.

Results—Of 1067 patients, 31.6% were TIAs, 18% strokes, and 50.4% mimics. Median assessment time was 4.5 days from onset and follow-up was for 34.9 months. Subsequent strokes occurred in 7.1% of patients with TIA, 10.9% of patients with stroke, and 2.0% of mimics at the end of follow-up. Stroke risk at 90 days was 1.3% for patients diagnosed as TIA or stroke. Compared with mimics, hazard ratios for subsequent stroke were 3.88 (1.90–7.91) for TIA and 5.84 (2.81–12.11) for stroke. Hazard ratio for any subsequent vascular event was 2.91 (1.97–4.30) for TIA and 2.83 (1.81–4.41) for stroke. Hazard ratio for death was 1.68 (1.10–2.56) for TIA and 2.19 (1.38–3.46) for stroke.

Conclusions—Our results show a lower 90-day stroke incidence after TIA or minor stroke than in earlier studies, suggesting that rapid access daily TIA clinics may be having a significant effect on reducing strokes. (Stroke. 2015;46:1227-1232. DOI: 10.1161/STROKEAHA.114.008632.)

Key Words: follow-up study ■ prognosis ■ transient ischemic attack

Transient ischemic attacks (TIAs) have a very high early stroke risk1,2 and predispose to myocardial infarction (MI)3 and vascular death.4,5 Rapid assessment and treatment of TIA reduces the risk of early recurrent stroke,6,7 fatal or disabling recurrent strokes, and disability at 6 months.8 Rapid access TIA clinics, using the ABCD2 score9 to risk stratify patients, have been widely established in the United Kingdom to manage TIA and minor stroke with a dramatic reduction in time to assessment.10

Several studies have described the prognosis of TIAs and minor strokes. Some are population based,11-14 whereas others have reported on patients presenting to hospitals and emergency departments.15-19 Most outpatient studies were conducted before the establishment of daily rapid access TIA clinics based on the EXPRESS study4 model. They do not, therefore, take into account the influence of early secondary prevention on prognosis. Many recent TIA studies have reported 90-day outcomes.11,20,21 Ten-year results of the OXVASC Study are also available.22

Up to 60% of patients referred to TIA clinics by nonspecialists turn out to be TIA mimics.23,24 The prognosis of mimics is also of interest; studies suggest that transient neurological symptoms, particularly isolated brain stem symptoms, that do not fit the conventional diagnostic criteria for TIA may be associated with posterior circulation strokes, coronary events, and dementia.25-27 Other mimics may have a more benign prognosis. A recent study comparing TIAs and mimics followed up a small number of patients for 90 days.24 We present the results of 4-year follow-up of a larger cohort of patients, including TIAs, minor strokes, and mimics, referred to the daily TIA clinics of a UK general hospital.

Methods

Study Population
All patients referred to the daily (Monday to Friday) TIA clinics of Gloucestershire Royal Hospital between April 2010 and May 2012 were included and identified from our TIA clinic database. The catchment area for Gloucestershire Royal Hospital has a population of 560,000 of predominantly white origin. All stroke services for the county of Gloucestershire are centralized at Gloucestershire Royal Hospital, and no other hospitals or clinics in our area provide a TIA service. Referrals are accepted from Emergency Departments, General Practitioners, paramedics, and other departments.

Patient Evaluation and Management
The traditional definition of TIA as an acute loss of focal cerebral or ocular function lasting <24 hours presumed to be caused by embolic or thrombotic vascular disease was used.15 However, patients with resolution of symptoms within 24 hours but with recent infarcts

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From the Stroke Service (D.D., E.B.) and Research Design Service (C.F.), Gloucestershire Royal Hospital, Gloucester, UK.
Correspondence to Dipankar Dutta, FRCP, Stroke Service, Gloucestershire Royal Hospital, Great Western Rd, Gloucester GL1 3NN, UK. E-mail dipankar.dutta@glos.nhs.uk
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on imaging were reclassified as a stroke. The diagnoses were made by consultant stroke physicians with >7 to 10 years stroke experience. The traditional National Institute of Neurological Disorders and Stroke diagnostic criteria for TIA were used in most cases with a few exceptions at the discretion of the diagnosing stroke specialist. The diagnosis made was broadly classed as TIA, stroke, or mimic. Vascular events were classified as cerebral or retinal. Data entered into the database included demographic information, past history, risk factors (previous cerebrovascular disease, hypertension, diabetes mellitus, atrial fibrillation (AF), other vascular disease, and smoking), history, and examination. Investigations included a same day CT scan, carotid duplex ultrasound electrocardiogram, and blood tests. Magnetic resonance imaging scans, echocardiograms, Holter monitoring, CT or MR angiograms were not done the same day but obtained subsequently as required. All treatment, typically antiplatelets, statins, antihypertensives, and oral anticoagulants in AF, was prescribed and supplied to patients after the consultation.

Outcome Events
All subsequent outcome events were prespecified and defined. Stroke was defined as a clinically defined syndrome of rapidly developing symptoms or signs of focal loss of cerebral function with no apparent cause other than that of vascular origin with symptoms lasting >24 h or leading to death. Acute MI was defined as elevation of cardiac troponins with either symptoms of ischemia or presumed new electrocardiogram changes. Outcomes of interest were stroke, MI, any vascular event (TIA, stroke, or MI), and all-cause mortality.

Data Collection
Follow-up was electronic and did not involve patient contact. Several databases linked by the patients’ Medical Records Numbers were accessed to record further events. These included the hospital Infoflex database (Chameleon Information Management Services), which records details of all admissions to hospital, discharge summaries, outpatient referrals, and death. This database directly records deaths in hospital and has robust links with general practices, county registration officers, and funeral directors for capturing deaths occurring in the community. Outpatient clinic correspondence databases, Patient Administration Services, and radiology Picture Archival and Communication Systems were accessed. Death certification data were available only for people who died in hospital because we did not have the necessary funding to request this information for deaths in the community.

Data collection was done by 4 authorized clinicians and admin staff. It was not possible to blind them to the diagnosis made in TIA clinic because search of the TIA clinic database for recurrent events was essential for our data collection. We ensured that no patients included in our data analysis were lost to follow-up.

Statistical Analysis
Univariate comparison of TIAIs, strokes, and mimics were performed with the chi-squared and Kruskal–Wallis test as appropriate. The Kaplan–Meier product limit method was performed to determine the cumulative probability of outcome events after the index TIA clinic assessment. The log-rank test was used for comparison of event-free survival between groups. Cox proportional hazards regression was used to identify variables associated with the occurrence of end points and hazard ratios and 95% confidence intervals obtained. The statistical software R was used for analysis.

Results
Between April 2010 and May 2012, 1103 patients with suspected TIA were referred to the TIA clinic. Twenty-one patients were visitors or left Gloucestershire permanently and were excluded, leaving 1082 patients. Fifteen patients did not attend (DNA) their TIA appointment, leaving 1067 patients. Median age was 72 years (interquartile range, 60–80), and 546 (51.2%) were female. Median time to assessment from onset of symptoms was 4.5 days (interquartile range, 2.0–9.3). TIAs were diagnosed in 337 (31.6%) patients, strokes in 189 (18%), and mimics in 538 (50.4%). The brain was involved in 81.3% (430/539) of strokes and TIAIs while 18.7% (99/539) were retinal events. Mimics included migraine (139/538), transient global amnesia (17/538), brain tumors (10/538), and others (comprising partial seizures, syncope/ presyncope, labyrinthitis, neuropathy, subdural hematomas, anxiety, myasthenia, Bell’s palsy, and other nonspecific transient symptoms with no firm diagnosis) in 373 of 538 mimics. Median follow-up was for 34.9 months (interquartile range, 27.7–41.6) and maximum follow-up just over 4 years. Table 1 shows the baseline characteristics of patients by diagnosis. Patients with ABCD2 score ≥4 numbered 284, 26.6% of the sample. Significant carotid stenosis (symptomatic or asymptomatic) of >50% (NASCET criteria) by duplex ultrasound was found in 14.8% of the confirmed TIAs and 8.3% of strokes. Mimics were younger, had lower ABCD2 scores, and a lower proportion of preexisting vascular disease, hypertension, and AF.

Of the 15 DNAs, 2 were admitted to hospital with stroke and 4 (26%) were dead by the end of the study. Table 2 shows the number of outcome events, proportions, and 95% confidence interval of the proportions stratified by diagnosis (excluding DNAs) at different time points during follow-up. At 90 days, 0.9% of TIAs had a stroke, 2.1% of patients with strokes had a subsequent stroke, and 0.2% of mimics had suffered a stroke. Subsequent strokes occurred in 7.1% of patients with TIA, 10.9% of patients with stroke, and 2.0% of mimics by the 50-month period of follow-up.

Kaplan–Meier plots of stroke, MI, any vascular event (stroke, TIA, or MI), and all-cause death stratified by diagnosis (TIA, stroke, and mimic) are shown in Figure 1. All patients in Table 1 are included in the Kaplan–Meier survival data. The statistical software R was used for analysis.
outcomes were more likely in patients with stroke or TIA than in mimics. The mimics who had strokes (all infarcts) included 1 patient with a subdural hematoma, 4 patients diagnosed as migraine, 3 with presyncope, 1 diagnosed as partial seizure, and 3 mimics with an uncertain diagnosis. All of these patients had hypertension or previous vascular disease.

Figure 2 shows Kaplan–Meier plots of mimics (transient global amnesia, migraine, and others) and stroke/TIA for the outcomes of subsequent stroke and all-cause death. Brain tumors were excluded from this analysis. No patient with transient global amnesia had any outcome events. Six patients with migraine out of 138 and 21 of 372 other unclassified mimics had strokes or TIAs and 3 of 139 migraines and 43 of 373 other unclassified mimics died.

<table>
<thead>
<tr>
<th>Table 2. Subsequent Outcome Events by Diagnosis (TIA, Stroke, and Mimic) at 90 Days, 1 Year, 2 Years, and End of Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA (n=337) Stroke (n=192) Mimic (n=538)</td>
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<tr>
<td><strong>Subsequent outcome events at 90 days</strong></td>
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<tr>
<td>Stroke                                                                                      3 (0.89%, 0.2%–2.8%) 4 (2.1%, 0.7%–5.6%) 1 (0.19%, 0.1%–1.2%)</td>
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<tr>
<td>MI                                                                                         3 (0.89%, 0.2%–2.8%) 3 (1.6%, 0.4%–4.9%) 3 (0.6%, 0.1%–1.8%)</td>
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<td>Any vascular event                                                                        10 (3.0%, 1.5%–5.6%) 6 (3.1%, 1.3%–7.0%) 4 (0.7%, 0.2%–2.0%)</td>
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<td>All cause death                                                                            4 (1.2%, 0.4%–3.2%) 5 (2.6%, 1.0%–6.3%) 3 (0.6%, 0.1%–1.8%)</td>
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<tr>
<td><strong>Subsequent outcome events at 1 y</strong></td>
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<tr>
<td>Stroke                                                                                      8 (2.4%, 1.1%–4.8%) 9 (4.7%, 2.3%–9.0%) 6 (1.1%, 0.5%–2.5%)</td>
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<tr>
<td>MI                                                                                         6 (1.8%, 0.7%–4.0%) 6 (3.1%, 1.3%–7.0%) 7 (1.3%, 0.6%–2.8%)</td>
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<td>Any vascular event                                                                        22 (6.5%, 4.2%–9.9%) 14 (7.3%, 4.2%–12.2%) 13 (2.4%, 1.3%–4.2%)</td>
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<td>All cause death                                                                            11 (3.3%, 1.7%–5.9%) 9 (4.7%, 2.3%–9.0%) 17 (3.2%, 1.9%–5.1%)</td>
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<td><strong>Subsequent outcome events at the end of follow-up</strong></td>
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<td>Stroke                                                                                      15 (4.5%, 2.6%–7.4%) 13 (6.8%, 3.8%–11.5%) 10 (1.9%, 0.9%–3.5%)</td>
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<td>MI                                                                                         9 (2.7%, 1.3%–5.2%) 8 (4.2%, 2.0%–8.3%) 8 (1.5%, 0.7%–3.0%)</td>
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<td>Any vascular event                                                                        39 (11.6%, 8.5%–15.6%) 21 (10.9%, 7.1%–16.4%) 26 (4.8%, 3.2%–7.1%)</td>
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<td>All cause death                                                                            32 (9.5%, 6.7%–13.3%) 23 (12.0%, 7.9%–17.6%) 29 (5.4%, 3.7%–7.7%)</td>
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</table>

The risk of subsequent stroke (1.3%) at 90 days in TIA and minor stroke patients in our cohort is lower than many older studies in the literature. The 90-day stroke risk after TIA in a study from 1999 to 2000 was 9.4%. Similarly, Wu found a pooled risk of stroke after TIA at 90 days of 9.2%.

Discussion

Our study is one of the first to report outcomes of daily rapid access TIA clinics based on the EXPRESS study model. The incidence of MI at 50 months for TIAs (4.7%) and stroke (7.3%) in our cohort is broadly similar to previously reported annual risk of MI after TIA of 0.95% and an annual risk of MI of 2.2% in patients with TIA or stroke.

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Hazard ratios for association between clinical diagnosis (TIA, stroke, or mimic) and subsequent stroke, any vascular event, and all-cause death at the end of follow-up are shown in Table 3. Variables used in our Cox proportional hazards model were age, sex, history of hypertension, diabetes mellitus, vascular disease, AF, significant carotid stenosis, and ABCD2 score ≥4. Both unadjusted and hazard ratios adjusted for other covariates are shown. Although age and previous vascular disease were independent predictors for subsequent vascular events or death in our multivariate model, ABCD2 score ≥4 or significant carotid stenosis (≥50%, NASCET) were not.

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Discussion

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The incidence of MI at 50 months for TIAs (4.7%) and stroke (7.3%) in our cohort is broadly similar to previously reported annual risk of MI after TIA of 0.95% and an annual risk of MI of 2.2% in patients with TIA or stroke. The mortality of 12.8% of TIAs and 16.7% for strokes in our cohort at 50 months seems lower than that in other studies; results from OXVASC showed that 27% of TIAs and 47% of strokes had died by 5 years. A 5-year mortality of 49.6% for TIA and 60% for hospitalized acute ischemic stroke was found in a 1995 study and a 10-year mortality of 32% for minor strokes in 1998. In a large cohort of hospitalized TIA patients, 10% had died by 1 year.

Why was the stroke risk in our cohort so low? This may represent a true effect of improved awareness combined with urgent TIA clinic assessment and treatment; 38.8% of our patients were already on aspirin by the time they arrived at the clinic. All subsequent treatments were prescribed and handed to the patients after the consultation. Median time to assessment from...
Symptom onset was 4.5 days, however, which is higher than the median delay of 1 day in the EXPRESS study, reflecting actual practice in the typical hospital in England where delays are caused by slow response from patients or primary care and limited clinic capacity. It is possible that a proportion of patients had completed strokes before they could be referred to our TIA clinic. A paradox referred to as the Will Rodgers phenomenon must also be considered in TIA prognostic studies. In the context of cerebrovascular disease, this refers to the reclassification of diffusion-weighted positive TIAs (which have a worse prognosis) as strokes. Although we did not use diffusion-weighted magnetic resonance imaging routinely, we reclassified patients with visible infarcts on CT as stroke even if their symptoms had resolved within 24 hours. The tissue-based definition of TIA has been shown to reduce the incidence of subsequent stroke in diffusion-weighted negative TIA to \( \approx 1\% \) at 90 days irrespective of ABCD2 score. The incidence of stroke at 90 days after TIA (with normal CT) in our cohort was 0.9%.

Another possibility is that we failed to ascertain all outcomes because of limitations in our methodology. We feel this is unlikely as current guidelines strongly recommend urgently referring all suspected TIAs to TIA clinics. In addition, public education campaigns, such as the Face, Arm, Speech, Time (FAST) campaign, are increasing awareness of TIA symptoms and encouraging patients to seek urgent help. All patients who attend our clinics receive TIA and FAST education. The centralized nature of stroke services in our county and results of local audits mean that we can be fairly confident that the majority of patients with strokes are admitted to our stroke units. Calculations based on expected TIA incidence suggest most suspected TIAs are referred to our service. The possibility that we are over diagnosing TIAs, that is, labeling mimics as TIAs, seems unlikely given that 50% of our cohort was identified as stroke mimics, a figure consistent with the literature.

Mimics in our cohort were a heterogeneous group comprising migraine, syncope, seizures, tumors, transient global

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Figure 1. Kaplan–Meier plots of outcomes stratified by diagnosis (mimic, stroke, and TIA). \( P \) values for the overall comparison of difference between the 3 groups by the log rank test. TIA indicates transient ischemic attack.
amnesia, and other undiagnosed transient events. Unlike earlier studies 25–27 which suggested that transient neurological symptoms (not meeting the diagnostic criteria for TIA) are associated with posterior circulation strokes, MI, and dementia, our cohort of mimics seemed to have fewer vascular events. Our study, however, may not be directly comparable to these earlier reports. Overall, 0.2% of mimics had suffered a stroke by 90 days, 2% had strokes, and 8% had died by the end of the study. All these rates were significantly lower than those for strokes and TIA.

Other limitations are those of a retrospective hospital-based cohort study. Case ascertainment, however, was by confirmation of the diagnosis by experienced stroke clinicians rather than through coding or administrative databases. All the outcome events were defined and prespecified to minimize reporting bias. It was, however, not possible to blind the data collectors to the diagnosis made in TIA clinic. We made every effort to minimize missing data and ensured that no patients included in our analysis were lost to follow-up. Although we are confident that we were able to record all deaths, funding restrictions meant we were unable to determine the cause of death in people who died out of hospital. It is well known that many patients do not realize the significance of transient neurological symptoms and are never referred to secondary care. However, for reasons recorded earlier, the current trend is for immediate referral of all suspected TIAs and minor strokes to secondary care. Overall, we feel that our results can be generalized to similar TIA services and support their effectiveness.

In summary, our data suggest that TIA clinics based on the EXPRESS model may be having a significant effect on reducing strokes after TIAs. There seems to be no effect in preventing MI after TIA or stroke. Given the limitations of our methodology, further work will be needed before any firm conclusion can be reached.

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Disclosures
None.

References


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