Prognosis in patients with transient ischaemic attack (TIA) and minor stroke attending TIA services in the North West of England: The NORTHSTAR Study

J R Selvarajah, C J Smith, S Hulme, R F Georgiou, A Vail, P J Tyrrell, on behalf of the NORTHSTAR Collaborators

ABSTRACT

Background: The ABCD² score predicts stroke risk within a few days of transient ischaemic attack (TIA). It is not clear whether the predictive value of the ABCD² score can be generalised to UK TIA services, where delayed presentation of TIA and minor stroke are common. We investigated prognosis, and the use of the ABCD² score, in patients attending TIA services in the North West of England with a diagnosis of TIA or minor stroke.

Methods: 711 patients with TIA or minor stroke were prospectively recruited from five centres (median duration from index event to recruitment 15 days). The primary outcome was the composite of incident TIA, stroke, acute coronary syndrome or cardiovascular death at the 3 month follow-up. Prognostic factors were analysed using Cox proportional hazards regression.

Results: The primary outcome occurred in 126 (18%) patients. Overall, there were 30 incident strokes. At least one incident TIA occurred in 100 patients (14%), but only four had a subsequent stroke. In multifactorial analyses, the ABCD² score was unrelated to the risk of the primary outcome, but predicted the risk of incident stroke: score 4–5: hazard ratio (HR) 3.4 (95% CI 1.0 to 12); score 6–7: HR 4.8 (1.3 to 18). Of the components of the ABCD² score, unilateral motor weakness predicted both the primary outcome (HR 1.8 (1.2 to 2.8)) and stroke risk (HR 4.2 (1.3 to 14)).

Conclusions: In patients attending typical NHS TIA services, the risk of incident stroke was relatively low, probably reflecting delays to assessment. Current provision of TIA services, where delayed presentation to “rapid access” TIA clinics is common, does not appear to provide an appropriate setting for urgent evaluation, risk stratification or timely secondary prevention for those who may be at highest risk.

Several studies have highlighted that the early risk of stroke after transient ischaemic attack (TIA) is higher than previously thought. In population or hospital based studies of patients within a few days of TIA, the risk of stroke is approximately 5% at 2 days, 7–10% at 7 days and 10–17% at 3 months. Furthermore, patients with TIA are also at risk of subsequent cardiovascular events. When considering composite vascular end points after TIA, the risks of stroke, recurrent TIA, cardiac hospitalisation or death are as high as 25% at 3 months.

Recent studies have sought to identify predictors of early stroke risk in order to inform risk stratification and clinical decision making in the assessment of patients with TIA. The California score predicted 90 day stroke risk in patients attending the emergency room with probable TIA, of which nearly all were within 24 h of symptom onset. The ABCD² score predicted 7 day stroke risk in both a population based TIA referral service and a hospital based TIA clinic where the majority of patients were seen within a week of TIA. More recently, the ABCD² score, derived from the California and ABCD scores, has been validated in these cohorts, predicting the risk of stroke at 2, 7 or 90 days. The ABCD² score is based on five components: age (>60 years = 1 point), blood pressure (systolic ≥140 mm Hg and/or diastolic ≥90 mm Hg = 1 point), clinical features (unilateral motor weakness = 2 points; speech disturbance without weakness = 1 point), duration of symptoms in minutes (>60 = 2 points; 10–59 = 1 point) and diabetes (present = 1 point). The ABCD² score has a minimum score of 0 and a maximum score of 7.

The approach to management of TIA and minor stroke patients, either by referral to “rapid access” TIA outpatient clinics or admission to hospital for further investigation and management, remains variable and controversial. Current UK guidelines advocate specialist assessment and investigation of all TIA patients within 7 days of symptom onset. However, this is currently only achieved in 35% of UK centres and the nationwide median delay from referral to specialist TIA clinic appointment is 12 days. The ABCD² and related scores were developed in populations where the majority presented within 24 h of TIA symptom onset. It is not clear whether the predictive value of the ABCD² score can be generalised to UK TIA services, where delayed presentation of both TIA and minor stroke are common. The aim of the present study was to investigate the 3 month prognosis of patients with confirmed TIA or minor stroke assessed in a representative sample of NHS TIA services, and evaluate the use of the ABCD² score in predicting incident vascular events, specifically from the time of attendance. To achieve this aim, we performed secondary analyses of data collected prospectively in the North West of England Transient Ischaemic Attack and Minor Stroke (NORTHSTAR) study cohort.

METHODS

The NORTHSTAR Study is a prospective, multi-centre, nested, case control study designed to investigate the prognostic role of peripheral and genetic inflammatory markers in patients with
The study and intention to remain resident within the area for daily living, no significant comorbidity limiting participation in cognitive impairment sufficient to interfere with independent daily living.

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics and medications at study entry (n = 711)</th>
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<tbody>
<tr>
<td><strong>Index diagnosis</strong></td>
</tr>
<tr>
<td>Cerebral TIA</td>
</tr>
<tr>
<td>Cerebral minor stroke</td>
</tr>
<tr>
<td>Retinal TIA</td>
</tr>
<tr>
<td>BRAO/CRAO</td>
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<tr>
<td><strong>Duration of symptoms (min)</strong></td>
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<tr>
<td>&gt;60</td>
</tr>
<tr>
<td>10–59</td>
</tr>
<tr>
<td>&lt;10</td>
</tr>
<tr>
<td><strong>Age (y)</strong>*</td>
</tr>
<tr>
<td><strong>Medications at study entry</strong></td>
</tr>
<tr>
<td>BP (mm Hg)*</td>
</tr>
<tr>
<td>Carotid imaging</td>
</tr>
<tr>
<td>Occlusion of at least one ICA</td>
</tr>
<tr>
<td>70–99% stenosis of at least one ICA</td>
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<tr>
<td>Medications at study entry</td>
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<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>Other antiplatelet agent</td>
</tr>
<tr>
<td>Anticoagulation</td>
</tr>
<tr>
<td>Statin</td>
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<tr>
<td>ACE-I</td>
</tr>
<tr>
<td>All RB</td>
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<tr>
<td>Other antihypertensive</td>
</tr>
<tr>
<td>Diabetes treatment</td>
</tr>
<tr>
<td><strong>Values</strong>c except <em>median (minimum, maximum) and t=mean (SD).</em>*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Values</th>
<th>Age (y)*</th>
<th>Smoking history</th>
<th>Alcohol intake (units per week)*</th>
<th>Body mass index (kg/m²)*</th>
<th>BP (mm Hg)+</th>
</tr>
</thead>
<tbody>
<tr>
<td>68 (27, 93)</td>
<td>417 (58.6)</td>
<td>77 (11.2) n = 689</td>
<td>4 (0, 126) n = 682</td>
<td>27.1 (14.8, 55.0) n = 708</td>
<td>149/81 (24/13)</td>
</tr>
</tbody>
</table>

Follow-up

At recruitment, contact details of the research team were given to patients, relatives and their general practitioner, and attached to the medical notes. Patients were requested to report any changes in their health. Prior to the 3 month follow-up assessment, a survival check was undertaken using the tracking system of the NHS Central Register, hospital records or general practitioner records. Surviving patients were contacted by telephone, or less frequently interviewed in person, using a standardised questionnaire approximately 3 months after the index event. The questionnaire comprised the mRS, BI, medical and surgical history support and vascular event screening.

Figure 1 Kaplan–Meier curves illustrating survival free from acute vascular events and stroke from time of presentation to transient ischaemic attack services.

Recent TIA or minor stroke. The primary analyses of the NORTHSTAR Study will be reported separately. The study was conducted in TIA services at five UK centres (see appendix) in Greater Manchester and Liverpool. Local research ethics committee approval for the study was obtained for each centre. Four centres each operated a weekly TIA clinic, and one operated twice weekly clinics. Referrals to clinics were from primary care, accident and emergency, and other hospital specialties, including ophthalmology services. In addition, some patients were recruited directly from the accident and emergency unit or the acute stroke unit at Hope Hospital, Salford. The eligibility criteria for inclusion were diagnosis of TIA or minor stroke confirmed by a consultant stroke physician or neurologist, symptom onset within the preceding 6 weeks, age ≥18 years, modified Rankin Scale (mRS) ≤1, no known cognitive impairment sufficient to interfere with independent daily living, no significant comorbidity limiting participation in the study and intention to remain resident within the area for the duration of the study, with access to a telephone. TIA was defined as a clinical syndrome of acute loss of focal cerebral or monocular function, of vascular origin, with symptoms resolving within 24 h. Minor stroke was defined as a clinical syndrome of rapidly developing symptoms and signs of focal loss of cerebral function, of vascular origin, lasting more than 24 h, with minimal residual functional impairment (mRS ≤1).

Patients with a confirmed diagnosis of TIA or minor stroke were screened for eligibility by a member of the research team. Written informed consent was obtained in all cases. Baseline data, including date and duration of symptoms, past medical history, vascular risk factors, current medications, mRS, Barthel Index (BI), blood pressure (BP) and ECG were recorded at study entry. A history of atrial fibrillation was defined by current atrial fibrillation on ECG using standard criteria or previously documented atrial fibrillation. Left ventricular hypertrophy was assigned using the Minnesota guidelines (codes 3-1 and/or 3-5). TIA and minor stroke were classified as either cerebral or retinal. Cerebral events were further classified as anterior or posterior circulation, based on the clinical features, supplemented by imaging findings where possible. Following recruitment, investigation and secondary prevention were initiated at the discretion of the clinician responsible for the patient. The study entry ABCD² score was assigned retrospectively using clinical information collected at the time of recruitment.

Follow-up

At recruitment, contact details of the research team were given to patients, relatives and their general practitioner, and attached to the medical notes. Patients were requested to report any changes in their health. Prior to the 3 month follow-up assessment, a survival check was undertaken using the tracking system of the NHS Central Register, hospital records or general practitioner records. Surviving patients were contacted by telephone, or less frequently interviewed in person, using a standardised questionnaire approximately 3 months after the index event. The questionnaire comprised the mRS, BI, medical and surgical history support and vascular event screening.
questionnaire, including stroke-free status. For consistency, all follow-up interviews were conducted by the same research physician. Information obtained directly from patients and/or relatives was supplemented, wherever possible, by hospital records, general practitioner records and death certification. Follow-up was continued until death, or 3 months from the date of the index event.

Definition of outcome events
The primary outcome was time to the predefined composite end point of first verified incident TIA, fatal or non-fatal stroke, acute coronary syndrome or cardiovascular death during follow-up. Acute coronary syndromes were defined according to WHO guidelines. Cardiovascular death was defined by acute coronary syndrome certified as the cause of death or contributing directly to death. Fatal stroke was defined as incident stroke as the cause of death or contributing directly to death. All suspected outcome events were adjudicated by a panel (see appendix) of experienced consultant physicians (one stroke physician, one vascular neurologist and one elderly care physician) appointed prior to study commencement, and required agreement of all three panel members. In patients with more than one verified outcome event, the first incident event during follow-up was assigned the primary outcome. Incident strokes occurring during follow-up were analysed separately.

Statistical analysis
Time from recruitment until primary outcome event, stroke or end of follow-up was analysed using Cox proportional hazards regression in SPSS version 13.0. The assumption of proportionality was checked using the complementary log-log plot and found to be acceptable for the risk factors of interest. It was assumed that the hazard of further acute vascular events would be highest immediately following TIA or minor stroke and then decrease. Therefore, all analyses controlled for whether participants had experienced an acute cerebrovascular event in the month preceding the index event and for the time from the index event until recruitment. Analyses of risk factors for subsequent stroke were adjusted only for these two confounders because of the low number of strokes observed. Analyses of risk factors for the primary outcome were adjusted simultaneously for other putative risk factors.

RESULTS
A total of 711 patients meeting the eligibility criteria were recruited between June 2003 and January 2006. Baseline characteristics are presented in table 1. Median (range) duration from the index TIA or minor stroke to study entry was 15 (0–42) days. Seventy-eight patients (11%) were inpatients when recruited; the remainder were recruited from TIA outpatient clinics. Clinical features of the index event were as follows: unilateral weakness (54%), speech disturbance (42%), hemisensory disturbance (38%), monocular visual loss (14%), binocular visual loss (11%), ataxia (15%) and vertigo (5%). Subtypes were classified as follows: anterior circulation 611 (86%), posterior circulation 100 (14%). Brain imaging was undertaken in 481 (68%) patients and carotid duplex, with or without magnetic resonance angiography, in 656 (92%). Two patients were lost to follow-up immediately after recruitment. The other 709 patients had known status through to at least 6 weeks following recruitment. Forty-seven patients (7%) underwent carotid endarterectomy during follow-up.

The primary outcome occurred in 126 patients (18%) (fig 1, table 2), of whom 28 were hospitalised. A further 59 outcome events in 39 participants occurred (table 2). Overall, there were 30 fatal or non-fatal incident strokes in 29 (4%) of the cohort (fig 1) and stroke accounted for nearly 20% of the primary outcome events. In contrast, at least one incident TIA occurred in 100 (14%) of the cohort, but only four of these patients went on to have a stroke during follow-up. There were three deaths during follow-up, two of which were vascular deaths (a perioperative fatal stroke at carotid endarterectomy and an acute coronary syndrome). Of 706 survivors followed-up to 3 months, 508 (72%) were mRS grade 0 and 188 (27%) mRS grade 1. Six hundred and eighty-eight (97%) patients scored 95 or 100 on the BI.

In multivariable analyses, the ABCD$^2$ score was unrelated to the risk of the primary outcome, despite significant association with the risk of incident stroke (fig 2, table 3). Hazard ratios (95% CI) for the individual components of the ABCD$^2$ score for stroke were: age $\geq$ 60 years, 0.95 (0.41 to 2.1); BP $\geq$ 140/90, 0.89 (0.43 to 1.9); speech disturbance without weakness, 1.9 (0.38 to 9.3); unilateral weakness, 4.2 (1.3 to 14); symptom duration at least 1 h, 4.5 (1.5 to 14); and diabetes, 0.80 (0.28 to 2.3). Thus the relationship between ABCD$^2$ score and stroke risk appeared to be driven by the presence of unilateral weakness and symptom duration of 1 h or more. Of all components, only unilateral weakness was found to significantly increase the risk of the subsequent primary outcome event (HR 1.8 (95% CI 1.2 to 2.8)).

DISCUSSION
We evaluated prognosis in a large prospective cohort of patients attending TIA services in the North West of England with confirmed TIA or minor stroke, where the majority of patients were assessed in “rapid access” TIA outpatient clinics. The median delay from onset of the index event to assessment was 15 days, which is representative of current UK practice. Our eligibility criteria were pragmatic, but excluded patients with pre-existing significant physical disabilities and/or cognitive impairment. Despite this, we believe our findings can be generalised to TIA services across the UK, because all are likely
to include many similar patients to ours, recruited with similar delays.

Our estimate of 3 month stroke risk is less than half that reported in most studies where patients were assessed within the first few days of TIA onset.\(^1\)\(^-\)\(^3\) In these studies, around half of the strokes at 3 months had occurred within 2 days of the index TIA, at a time before most of the present cohort were recruited. Despite this, the 3 month stroke risk in the present study was still comparable with some studies assessing patients soon after the index TIA.\(^2\)\(^-\)\(^3\) Furthermore, the risk of composite vascular end points in our study was still relatively high at 3 months, which accords with previous studies.\(^1\)\(^-\)\(^4\) A high proportion of our patients had a TIA or minor stroke in the month preceding the index event. However, we did not ascertain the proportion of patients initially referred to TIA services who then had a stroke, and subsequently did not attend. It is noteworthy that the majority of our patients were already taking at least one antiplatelet agent, or anticoagulants, and approximately 54% were taking statins at study entry, which may have influenced incident stroke rates. We did not collect data on the duration of these therapies prior to study entry, but following study entry, additional antiplatelet agents were prescribed in a further 37% and statins in a further 55% (data not shown).

The ABCD\(^2\) score predicted the 3 month stroke risk in our cohort, despite the relatively low rate of stroke and delay from index event to assessment. Our findings suggest that it may be reasonable to apply the ABCD\(^2\) score in patients with minor stroke, not only in those with TIA, although we did not analyse the two groups separately. From a practical point of view, this is relevant as the risk of incident stroke is comparable in patients with TIA and minor stroke,\(^2\) and patients with minor stroke accounted for around half of our cohort. When analysing the components of the ABCD\(^2\) score separately, only unilateral motor weakness and symptom duration predicted stroke. This accords with recent evidence suggesting that these clinical features, along with dysphasia or dysarthria, are more likely to be associated with underlying cerebral ischaemic lesions on diffusion weighted imaging.\(^22\) We used clinical information collected at the time of presentation to TIA services to assign the ABCD\(^2\) score, which is useful if patients did not initially seek medical attention soon after their event. However, this may explain why BP, recorded following delayed presentation, was not associated with stroke risk in our study. It is not clear why age, speech disturbance or diabetes mellitus were not associated with stroke risk, but there was a lack of statistical power given the low number of incident strokes. It is possible that at risk older patients had their stroke prior to attending TIA services. However, several other studies have also not identified associations between diabetes,\(^3\)\(^-\)\(^3\)\(^2\) age\(^1\)\(^-\)\(^4\)\(^\)\(^2\)\(^3\) or certain clinical features and risk of stroke 3 months after TIA.\(^2\)\(^3\)

As the ABCD\(^2\) score was designed to predict early stroke risk after TIA, it is therefore perhaps not surprising that it was unrelated to the risk of the composite primary outcome in the present study. However, unilateral weakness did predict

![Figure 2](image)  
**Figure 2**  
Kaplan–Meier curves illustrating survival free from (A) stroke and (B) acute vascular events from time of presentation to transient ischaemic attack services, stratified according to ABCD\(^2\) score.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Risk factors for the primary outcome or stroke from Cox regression models</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factor</strong></td>
<td><strong>Level</strong></td>
</tr>
<tr>
<td>Time since index event</td>
<td>Per day</td>
</tr>
<tr>
<td>TIA or minor stroke in preceding month</td>
<td>Yes</td>
</tr>
<tr>
<td>ABCD(^2) score</td>
<td>0 to 3</td>
</tr>
<tr>
<td></td>
<td>4 or 5</td>
</tr>
<tr>
<td></td>
<td>6 or 7</td>
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<tr>
<td>Smoking</td>
<td>Ex</td>
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<td></td>
<td>Current</td>
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</table>

*Separate multifactorial models each containing the first two factors (HR (95% CI)).

**Table 3**  
Risk factors for the primary outcome or stroke from Cox regression models.

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incident stroke or the composite primary outcome, but we did not examine factors predicting risk of incident TIA as a separate outcome. In contrast with the risk of stroke at 3 months, the risk of one or more incident TIA following the index event was considerably higher, but comparable with previous studies. Only a minority of these patients went on to have a subsequent stroke, suggesting that a subset of patients with recent TIA presenting to TIA services have a relatively benign short term outcome. Further studies are required to refine risk stratification of patients presenting with recurrent TIA, to differentiate those at risk of stroke from those with a more benign prognosis.

Our findings have relevance when considering current UK practice. Although patients attending typical TIA services are generally at low risk of incident stroke in the short term, the ABCD² score can be used to identify patients at risk of stroke, and might be applied to inform targeted expedited investigation and secondary prevention in those individuals. However, our data suggest that current provision of TIA services where delayed presentation to “rapid access” TIA clinics is common, does not appear to provide an appropriate setting for urgent evaluation or timely secondary prevention in those who may be at the highest risk of stroke. Our findings therefore support the argument that patients with TIA or minor stroke require more urgent evaluation and risk stratification, requiring major improvements in public awareness and prompt primary care/accident and emergency triage. In high risk patients triaged acutely using the ABCD² score, more effective stroke prevention might be achieved by admission to hospital or by provision of daily open access TIA clinics, but these strategies require further evaluation and may prove challenging to implement. Traditional “rapid access” TIA clinics would still continue to play a valuable role in the differential diagnosis and management of TIA presentations, perhaps with more focus on management of lower risk patients triaged acutely using the ABCD² score, who would still require specialist assessment within 7 days, and patients with delayed presentations to medical attention.

The present study has several limitations. The analyses presented here were secondary analyses of a prospective cohort, with the ABCD² score assigned retrospectively. As patient assessments were generally delayed following the index event, recall of symptoms and durations may have been less reliable in some cases. Not all patients underwent brain imaging, which was at the discretion of individual treating stroke physicians and neurologists. This variation reflects current UK practice and the lack of specific guidelines regarding brain imaging following TIA or minor stroke. Finally, although we did not perform face-to-face follow-up interviews in all instances, telephone follow-up was attempted in all patients. However, we did use a single interviewer, a validated questionnaire and independently verified vascular events.

CONCLUSION

In patients with TIA or minor stroke presenting to typical UK TIA services, the risk of incident stroke at 3 months was relatively low, probably reflecting delays in patient assessment. The ABCD² score predicted the incident 3 month stroke risk, but not composite vascular end points. Incident TIA occurred more frequently, and generally followed a benign course. Current provision of TIA services, where delayed presentation to “rapid access” TIA clinics is common, does not appear to provide an appropriate setting for urgent evaluation, risk stratification or timely secondary prevention in those who may be at the highest risk of stroke.

Acknowledgements: We are extremely grateful to Professor Nancy J Rothwell and Dr Stephen J Hopkins for their intellectual input during the design and analyses of the NORTHSTAR study, and our colleagues and the staff in the collaborating TIA services for their assistance throughout the study (see appendix).

P J Tyrrell is the Principal Investigator of the NORTHSTAR study and designed the study with CJS, AV and RFG. AV was responsible for the statistical analyses. JRS, SH and CJS collected the data. JRS, CJS and AV analysed the data. All authors contributed to writing the manuscript.

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Competing interests: None.

REFERENCES

Elongated styloid process (Eagle’s syndrome) as a cause of atypical craniocervical pain

A 48-year-old Caucasian woman presented with a long term history of oropharyngeal intermittent pain associated with foreign body sensation in her throat, and difficulty swallowing. The pain radiated to the right mastoid area and increased with neck rotation. Introral palpation triggered a painful sensation in the right tonsillar fossa. Three dimensional CT bone window mode volume-rendered reconstruction of the upper cervical region showed bilaterally elongated styloid processes, measuring 46 mm and 43 mm on the right and left, respectively (fig 1). The patient underwent a successful intra-oral styloidectomy and 3 years later she remains pain free.

Eagle’s syndrome is characterised by an elongated styloid process or a calcified stylohyoid ligament which causes craniocervical and recurrent throat pain.\(^1\) Clinicians should consider this entity in the differential workup of a patient with atypical craniocervical pain. Three dimensional CT is a valuable diagnostic tool in Eagle’s syndrome to make accurate length measurements of the styloid process.\(^2\)

**Figure 1** Three dimensional CT bone window mode volume-rendered reconstruction of the upper cervical region shows bilaterally elongated styloid process/consistent with Eagle’s syndrome.

**REFERENCES**


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**Competing interests:** None.

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**APPENDIX**

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**Advisory Committee**

GA Ford, HS Markus.

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- Aintree University Hospitals NHS Foundation Trust, UK: AK Sharma.
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