Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis

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Summary

Background Stroke is often preceded by transient ischaemic attack (TIA), but studies of stroke risk after TIA are logistically difficult and have yielded conflicting results. However, reliable estimation of this risk is necessary for planning effective service provision, clinical trials, and public education. We therefore did a systematic review of all studies of stroke risk early after TIA.

Methods All studies of stroke risk within 7 days of TIA were identified by use of electronic databases and by hand searches of reference lists, relevant journals, and conference abstracts. Stroke risks at 2 days and 7 days after TIA were calculated overall and analyses for heterogeneity were done, if possible, after categorisation by study method, setting, population, and treatment.

Findings 18 independent cohorts were included, which reported stroke risk in 10 126 TIA patients. The pooled stroke risk was 5·2% (95% CI 3·9–6·5) at 7 days, but there was substantial heterogeneity between studies ($p<0·0001$), with risks ranging from 0% to 12·8%. However, the risks reported in individual studies over different durations of follow-up were highly correlated (0–7 days *vs* 8–90 days, $r=0·89$, $p<0·0001$), and the heterogeneity between studies was almost fully explained by study method, setting, and treatment. The lowest risks were seen in studies of emergency treatment in specialist stroke services (0·9% [95% CI 0·0–1·9], four studies) and the highest risks in population-based studies without urgent treatment (11·0% [8·6–13·5], three studies). Results were similar for stroke risk at 2 days.

Interpretation The reported early risks of stroke after TIA were highly heterogeneous, but this could be largely accounted for by differences in study method, setting, and treatment, with lowest risks in studies of emergency treatment in specialist stroke services.

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Introduction

Up to 23% of strokes are preceded by transient ischaemic attack (TIA),[1] and there is substantial research interest in improving prevention during the short window between TIA and stroke.[2] However, the prospective estimation of the early risk of stroke is logistically difficult and studies have yielded inconsistent results,[3] with 7-day risks ranging from 0% to 12·8%.[4,5] Nevertheless, reliable estimation of this risk is essential to allow us to understand the potential absolute benefits of early treatment and the likely cost-effectiveness of different methods of service provision, to inform future clinical trial design, and to justify investment in public education.

The measured risk will depend on several factors. First, study method is important, particularly the delay from TIA to study entry, the inclusion or exclusion of patients having a stroke during this interval, and the thoroughness of follow-up used to identify subsequent stroke.[6] Second, the clinical setting (population, emergency department, clinic, or specialist stroke service) and study population may influence the measured risk. Third, the intensity and timing of secondary preventive treatment may reduce stroke risk after TIA.[4,7,8] Fourth, the stroke risk after TIA has been shown to vary according to characteristics of the patient (age, blood pressure, diabetes),[9,10] clinical features of the event (focal weakness, speech deficit, and symptom duration),[9–11] and underlying aetiology.[12] Thus, differences in study method, setting and population, treatment, and case mix must all be considered when interpreting heterogeneity in measured risk between studies.

We therefore systematically reviewed studies of the risk of stroke within 7 days after a TIA, to estimate stroke risk overall and to determine the influence of study method, setting, population, treatment, and case mix.

Methods

We aimed to identify all studies reporting the risk of stroke within 7 days of TIA, irrespective of the study design, setting, or language, in accordance with the MOOSE guidelines[13] for meta-analysis of observational studies in epidemiology. Ovid Medline (1950 to June, 2007) and Embase (1980 to June, 2007) were searched by use of both the medical subject heading (MESH) terms and text words: [TIA OR amaurosis fugax OR transient isch(a)emic attack] AND [outcome OR prognosis OR follow-up OR cohort OR randomized control trial OR risk OR natural history]. We hand searched the reference lists of all included studies, any relevant review articles, and the contents pages of the three journals from which most eligible papers were identified in the electronic search. To identify recent studies not yet published as full

***Panel:* Data extracted from eligible reports**

Study method
Country
Start date and end date
Population studied and the clinical setting (population based *vs* emergency department *vs* clinic *vs* specialist stroke service)
Method for ascertaining patients
By whom the diagnosis was made (neurologist or stroke physician *vs* non-specialist)
Inclusion criteria (incident *vs* incident and recurrent TIA; or definite *vs* definite and probable TIA)
Delay from qualifying event to study inclusion
How patients with stroke were analysed before seeking medical attention or study inclusion
Method (face-to-face review *vs* notes review *vs* database search) and completeness of follow-up
How follow-up stroke events were adjudicated

Characteristics of patients and events
Basic demographic data
Vascular risk factors
Frequency of high-risk features for early stroke (weakness, longer symptom duration, speech deficit)[9,10]
Underlying aetiology

Treatment
Delay from event to treatment
Setting (specialist *vs* non-specialist unit; inpatient *vs* outpatient)
Treatment given (antiplatelet and antihypertensive agents, statins, carotid endarterectomy)
Frequency of hospital admission

Outcome
Number of strokes occurring at 2 days, 7 days, and 90 days after TIA

TIA=transient ischaemic attack.

papers, we searched books of abstracts from the following recent conferences: Joint World Congress on Stroke 2006, American Heart Association International Stroke Conferences 2006 and 2007, and the European Stroke Conferences 2006 and 2007. The final electronic search was done on June 11, 2007.

Abstracts of all identified studies were reviewed and any study reporting the stroke risk within 6 months of TIA was included for full-text review. We aimed to include any study that reported data on the risk of stroke within 7 days after a TIA. We included studies that only reported from the time that the patients sought medical attention or were seen in secondary care, but excluded studies that reported only outcomes beyond 7 days. To maximise the generalisability of our results, we also excluded studies that were confined to patients with specific underlying pathologies (eg, severe carotid stenosis, capsular warning syndrome, atrial fibrillation) and studies nested within randomised controlled trials (due to generally stringent inclusion and exclusion criteria in trials).[14] In cases of multiple publications from the same cohort, the most recent report was generally chosen. Cohorts including both stroke and TIA were excluded if stroke risk after TIA was not described separately. The data extracted from eligible reports are shown in the panel.

Statistical analysis

The percentage risks of stroke and 95% CIs at 2 days, 7 days, and 90 days were calculated for individual studies, and pooled estimates were derived. The 95% CIs of the pooled risk estimates were calculated to allow for extra-binomial variation,[15] since standard methods of calculating CIs produce artificially narrow intervals if there is heterogeneity of risk between different studies. Analyses of heterogeneity of risks across studies were done with χ^2 tests.

Further analyses were done to explore the heterogeneity of reported stroke risk. First, consistency of stroke risk within individual studies was assessed by comparing stroke risk between 0–7 days with that between 8–90 days by correlation and also by regression weighted according to study size. Second, studies were categorised according to method, setting, population, case mix, and urgency of treatment, and analyses of heterogeneity were repeated within categories. Third, the proportion of the overall heterogeneity of risk across all studies that could be accounted for by the above subcategorisation was determined by an inverse-variance weighted regression of log(risk) against study type. Analyses were done with Microsoft Excel 2003.

Role of the funding source

The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The search of electronic databases yielded 11 350 publications. After initial screening, 69 reports were identified for full-text review. 15 additional reports were identified by searching relevant reference lists and abstract books from recent conferences. No further studies were identified by hand searches of the three journals from which most eligible studies were identified electronically (*Stroke*, *The Lancet*, and *Cerebrovascular Diseases*). Of the resulting 84 reports that were reviewed in full text, 18 independent studies were identified that reported the risk of stroke within 7 days after TIA in non-trial cohorts of patients, unselected on the basis of underlying pathology. Three studies that reported outcomes at 1 month or 3 months,

but not within 7 days, were excluded.[16–18] Four separate studies (Johnston and colleagues,[10,19] Oxfordshire Community Stroke Project (OCSP),[9,10,20,21] Oxford Vascular Study,[4,9,10,22] and Purroy and colleagues[23,24]) were described in multiple reports, so the most relevant report was included for each study. Observed stroke risks from the first 2 years of the Oxford Vascular Study were extracted from the report on the derivation and validation of the ABCD score[9] rather than the report on phase I of the EXPRESS study.[4] However, phase II of the EXPRESS study was included as a separate study because of the different nature of the clinical service and treatment in phase II compared with phase I.[4] One report in Spanish was translated;[23] all other reports were in English.

The methods of the studies included in this review are summarised in table 1. Two studies included only patients with incident, first-in-a-lifetime TIA.[5,21] Two studies included patients with possible and definite TIA, and those with possible TIA were excluded from further analysis.[25,33]

	Study period	Category	Setting	Ascertainment method (details)	TIA diagnosed by	Proportion of patients attending ED	Follow-up
Johnston et al[19]	1997–98	Population based with administrative follow-up without exclusions	Multiple EDs	Retrospective (screening of computerised database)	ED physician	100%	Notes
OCSP[21]	1981–86	Population based with active follow-up methods	Population based	Prospective (multiple search methods)	Stroke specialist (in person)	..	In person
Gladstone et al[25]	2000	Population based with administrative follow-up with exclusions	Multiple EDs	Prospective (screening of ED databases)	ED physician	100%	Coding data
Hill et al[11]	1999–2000	Population based with administrative follow-up with exclusions	Multiple EDs	Retrospective (screening of computerised databases)	ED physician	100%	Coding data
BASIC[26]	2000–02	Population based with administrative follow-up with exclusions	Population based	Prospective (multiple search methods)	Neurologist (note review)	93%	Notes
Whitehead et al[27]	2002–04	Ascertainment via routine clinic attendance	Clinic	Prospective (consecutive referrals to TIA clinic)	Stroke specialist (in person)	0%	Notes
Kleindorfer et al[28]	1993–94	Population based with administrative follow-up without exclusions	Multiple EDs	Retrospective (multiple search methods)	Neurologist (note review)	82%	Notes
ABCD[9]	2002–05	Population based with active follow-up methods	Population based	Prospective (multiple search methods)	Stroke specialist (in person)	18%	In person
Correia et al[5]	1998–2000	Population based with active follow-up methods	Population based	Prospective (multiple search methods)	Neurologist (in person)	48%	In person
Cucchiara et al[29]	2002–05	Ascertainment through specialist stroke service offering emergency treatment	Specialist service	Prospective (admissions to neurology ward)	Neurologist (in person)	100%	In person
Tsivgoulis et al[30]	2000–04	Ascertainment via single ED	Single ED	Prospective (consecutive ED attenders)	Neurologist (in person)	100%	In person
Johnston et al[10]							
ED cohort	2004–06	Population based with administrative follow-up without exclusions	Multiple EDs	Retrospective (screening of computerised database)	ED physician	100%	Notes
Clinic cohort	2004–06	Ascertainment via routine clinic attendance	Clinic	Retrospective (consecutive referrals to TIA clinic)	Neurologist (in person)	0%	Notes
Bray et al[31]	2004	Ascertainment via single ED	Single ED	Retrospective (screening ED database)	ED physician	100%	Telephone and notes
Purroy et al[24]	2002–04	Ascertainment via single ED	Single ED	Prospective (consecutive ED attenders)	Neurologist (in person)	100%	In person
Calvet et al[32]	2003–05	Ascertainment through specialist stroke service offering emergency treatment	Specialist service	Prospective (admissions to neurology ward)	Neurologist (in person)	80%	In person
EXPRESS[4]	2004–07	Ascertainment through specialist stroke service offering emergency treatment	Specialist service	Prospective (consecutive referrals to specialist unit)	Stroke specialist (in person)	0%	In person
SOS-TIA[33]	2003–05	Ascertainment through specialist stroke service offering emergency treatment	Specialist service	Prospective (consecutive referrals to specialist unit)	Neurologist (in person)	0%	Telephone

ED=emergency department. TIA=transient ischaemic attack. ..=not reported.

Table 1: **Study design and settings**

	Number of patients	Mean (SD) age (years)	Number (%) of men	Stroke risk (%)		
				2 days	7 days	90 days
Johnston et al[19]	1707	72 (..)	808 (47·3%)	5·3%	6·0%	10·5%
OCSP[21]	209	69·4 (12·3)	112 (53·6%)	4·3%	8·6%	14·3%
Gladstone et al[25]	265	71 (..)	138 (52·0%)	2·6%	3·8%	6·4%
Hill et al[11]	2285	71·4 (13·8)	1117 (48·9%)	1·4%	..	9·5%
BASIC[26]	362	72·3 (12·1)	143 (39·1%)	1·9%	2·5%	5·8%
Whitehead et al[27]	121	..	..	..	5·8%	..
Kleindorfer et al[28]	1023	70·4 (12·6)	476 (46·5%)	3·9%	7·0%	14·6%
ABCD[9]	190	73·7 (12·5)	79 (42·0%)	6·8%	10·5%	16·8%
Correia et al[5]	141	69·9 (..)	61 (43·3%)	9·9%	12·8%	20·6%
Cucchiara et al[29]	117	63 (14)	51 (43·6%)	1·7%	1·7%	1·7%
Tsivgoulis et al[30]	226	63·9 (12·3)	133 (58·8%)	..	8·0%	..
Johnston et al[10]						
ED cohort	1084	..	525 (48·4%)	4·7%	6·6%	14·3%
Clinic cohort	962	..	455 (47·3%)	1·7%	3·0%	14·3%
Bray et al[31]	98	73 (14·5)	49 (50%)	3·1%	4·1%	7·1%
Purroy et al[24]	345	71·4 (12·1)	173 (55·6%)	..	6·4%	..
Calvet et al[32]	201	61·2 (16)	124 (61·7%)	2·0%	2·5%	3·5%
EXPRESS[4]	160	71·4 (12·8)	82 (45·1%)	0·6%	0·6%	0·6%
SOS-TIA[33]	629	66·0 (14·6)	365 (56·1%)	0·0%	0·3%	1·9%

..=not reported.

Table 2: **Characteristics of patients and risk of stroke, by study**

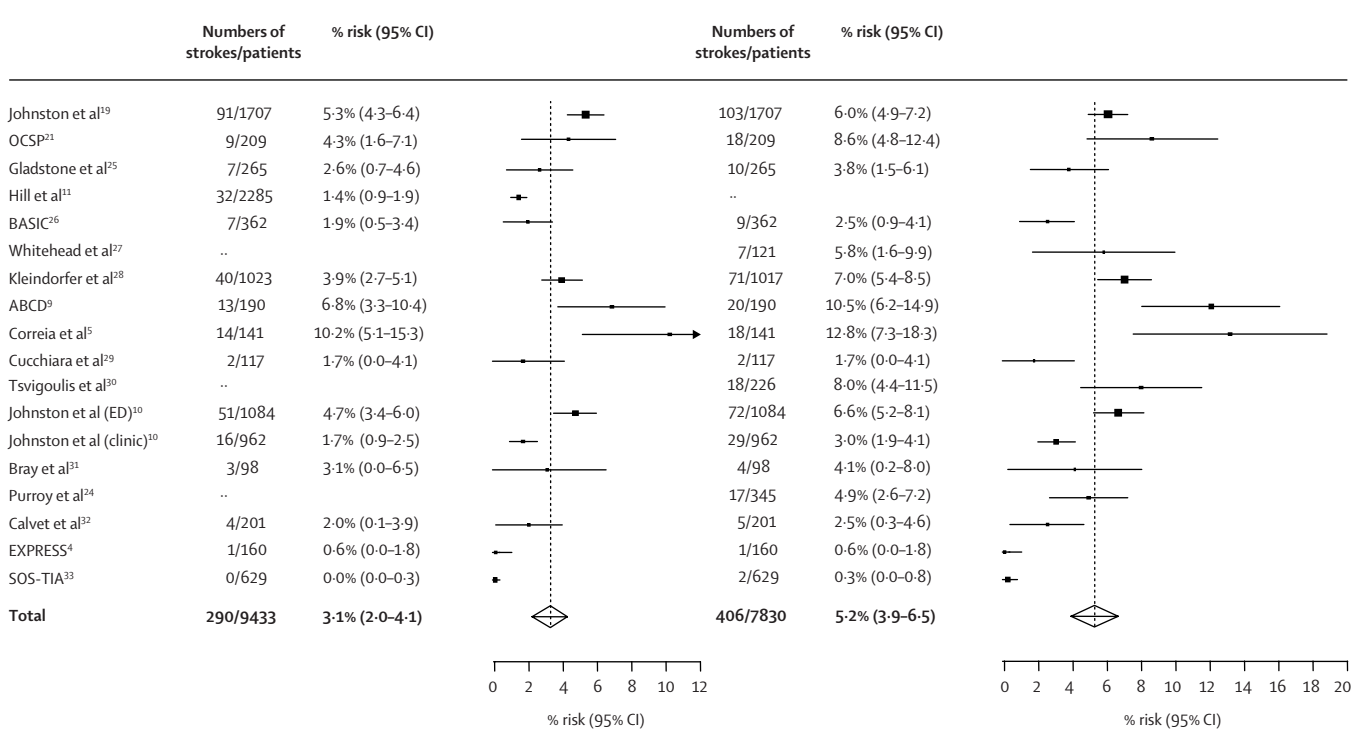

Figure 1: **Stroke risk at 2 days and 7 days for all studies**
There was significant heterogeneity in both analyses (p<0·0001). Each symbol for stroke-risk estimate is proportional to study size. ED=emergency department. ..=not reported.

10 126 patients in 18 cohorts were studied (table 2). Mean ages ranged from 61 years to 73 years (p<0·0001) and the proportion of men ranged from 39% to 62% (p<0·0001; table 2). 15 studies reported 290 strokes among 9433 patients at 2 days after TIA, and 17 studies reported 406 strokes among 7830 patients at 7 days after TIA. The corresponding pooled risks of stroke were 3·1% (95% CI 2·0–4·1) at 2 days and 5·2% (3·9–6·5) at 7 days (figure 1). However, there was substantial heterogeneity across studies for both pooled risk estimates (p<0·0001).

To explore the heterogeneity of reported stroke risk across studies, we first determined the consistency of stroke risk within individual studies by comparing the stroke risk between 0–7 days with that between 8–90 days. Of the 17 studies reporting stroke risk at 7 days, 15 also reported stroke risk at 90 days (table 2). One of these studies was solely outpatient based and underestimated the earliest stroke risk due to non-attendance of patients with stroke before their appointment and was therefore excluded.[10] In the remaining 14 studies, the correlation coefficient (r) for 0–7 day risk *vs* 8–90 day risk was 0·89 (p<0·0001; figure 2). In a weighted regression analysis, the corresponding r^2 value was 0·66. The consistent pattern of heterogeneity between studies in the reported stroke risk during these different time periods suggests that the overall heterogeneity was due to systematic differences between studies rather than due to chance alone.

We therefore stratified the analysis of stroke risk by study methods and setting to further explore the heterogeneity in reported risk. Three population-based studies intentionally used identical methods, with multiple means of ascertainment to prospectively identify all TIA patients from a well-defined population, irrespective of their mode of presentation, with all patients being assessed and followed up in person by a study neurologist.[5,9,21] In each of these studies, patients ascertained with a stroke but who had had a preceding TIA that they had not brought to medical attention were included. Six population-based studies ascertained patients predominantly through attendance at multiple emergency departments,[10,11,19,25] although two used some additional methods,[26,28] and relied on diagnosis by the emergency-department physician or notes review by a neurologist. Subsequent strokes were identified by administrative follow-up methods, including notes review and searches of diagnostic coding data from hospital or other sources (individual patients were not followed up face-to-face). Of these, three had important exclusions, such as patients who were admitted to hospital,[25] patients with persistent symptoms at discharge from emergency department,[26] and follow-up strokes occurring on the same day as the TIA.[11] Three studies ascertained consecutive patients attending single emergency departments and used active methods of face-to-face or telephone follow-up.[24,30,31] Two studies ascertained patients by attendance at outpatient services and used administrative methods of follow-up.[10,27] Four studies described the outcome of cohorts of TIA patients treated on an emergency basis by specialist stroke services, two of which were in inpatient settings[29,32] and two were in outpatient settings,[4,33] where diagnosis and follow-up were done in person.

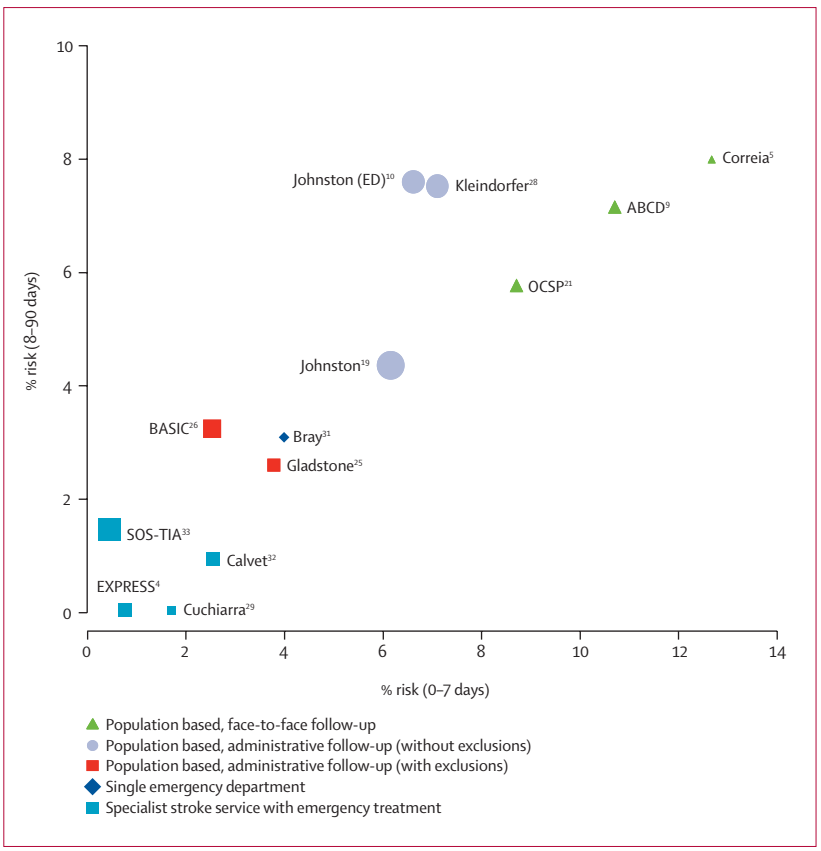

Figure 2: **Percentage stroke risks at 0–7 days against percentage stroke risks at 8–90 days for all studies reporting relevant data**
Two outpatient cohorts were excluded,[10,27] and data were unavailable in three studies.[11,24,29] Each symbol area is proportional to study size. ED=emergency department.

Studies were grouped according to study method and setting into the following categories: population based with active follow-up, population based with administrative follow-up without exclusions, population based with administrative follow-up with exclusions, single-centre emergency-department based, routine clinic based, and specialist stroke services based (table 1). After stratification of 2-day and 7-day stroke risks by the above classification, heterogeneity between cohorts was substantially reduced (figure 3). This classification accounted alone for 78·6% and 85·6%, respectively, of the overall heterogeneity of the pooled estimates of risk at 2 days and 7 days in an inverse-variance weighted regression analysis of log(risk) against study type.

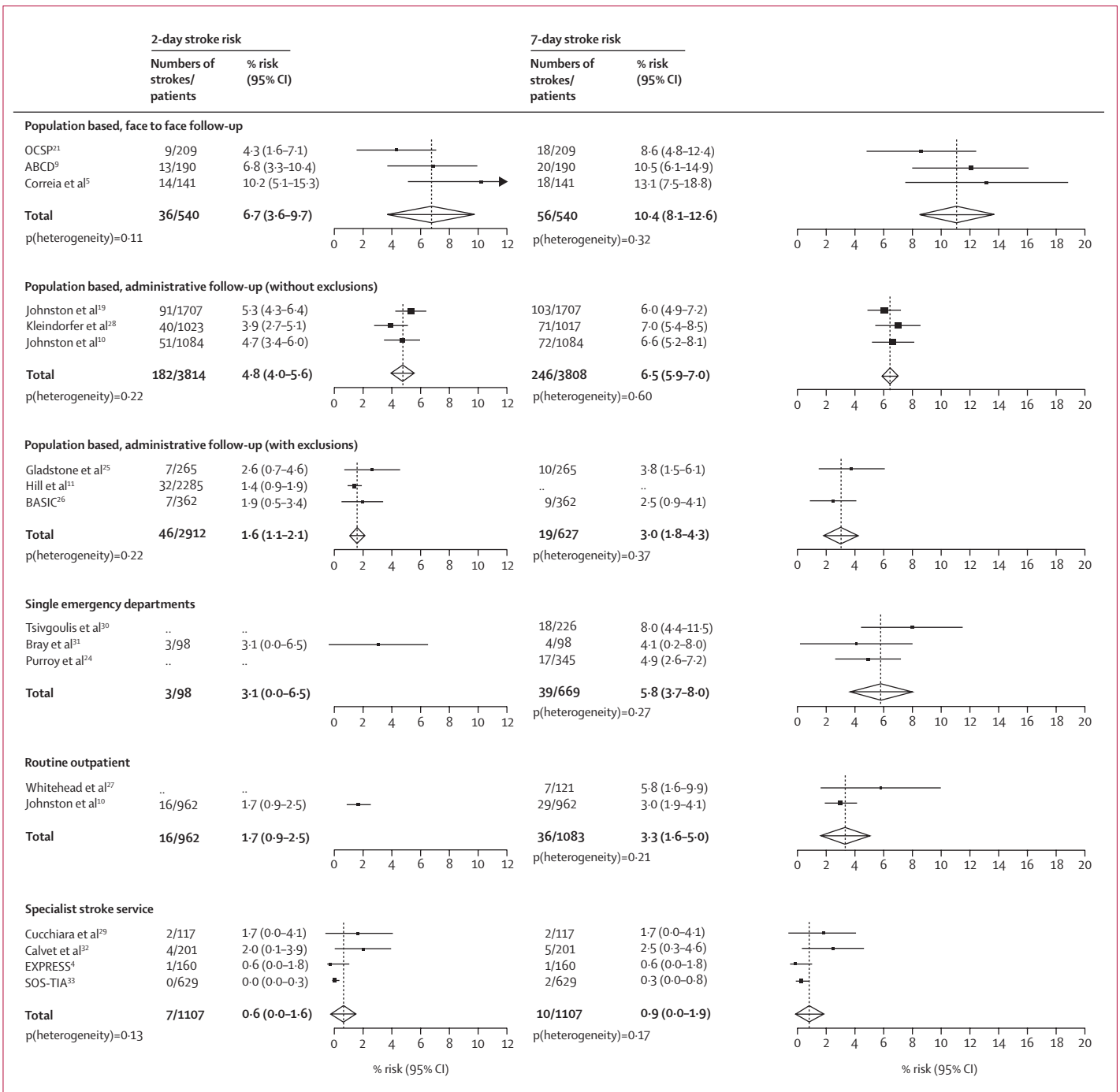

Figure 3: **Stroke risks at 2 days and 7 days stratified by study method and setting**
Each symbol for stroke-risk estimate is proportional to study size. ED=emergency department. ..=not reported.

In relation to treatment provision and intensity, four studies reported stroke outcomes in cohorts treated solely as an emergency by specialist stroke services, two of which were in outpatient settings[4,33] and two of which were in inpatient settings.[29,32] A further five studies reported outcomes in cohorts mainly managed by specialists but not on an emergency basis (eg, TIA or neurology clinics).[5,9,10,21,27] Among the remaining eight studies that recruited patients mostly from emergency departments (table 1), neurology consultation varied from 4%[4] to 100%.[24] Hospital admission ranged from 0%[27] to 100%[29,32] in the 15 studies that reported this information,

	Previous vascular risk factors							High-risk features				Treatment		
	Hypertension	CHD	Stroke	Hypercholesterolaemia	Current smoker	Diabetes mellitus	Atrial fibrillation	Motor deficit	Symptom duration (mins)			Aspirin	Anticoagulant	Admitted to hospital
									Mean	Median	Other			
Johnston et al[19]	58%	24%	23%	15%	14%	19%	9%	46%	207	..	..	68%	14%	14%
OCSP[21]	38%	24%	0%	..	29%	4%	14%	54%	..	..	>60 (37%), 10–59 (30%), <10 (33%)	47%	5%	6%
Gladstone et al[25]	56%	17%	22%	26%	39%	20%	15%	65%	..	..	..	63%	7%	0%
Hill et al[11]	62%	..	..	..	..	18%	..	..	..	..	..	..	..	26%
BASIC[26]	65%	31%	..	19%	23%	31%	10%	67%	..	..	..	67%	15%	64%
Whitehead[27]	..	..	..	..	..	..	..	..	..	..	..	..	..	0%
Kleindorfer et al[28]	..	..	..	..	..	..	..	..	..	..	..	..	..	64%
ABCD[9]	53%	22%	18%	22%	13%	11%	16%	50%	..	10–60	..	83%	8%	10%
Correia et al[5]	..	..	0%	..	..	..	..	..	..	30–59	..	..	..	..
Cucchiara et al[29]	55%	18%	27%	32%	16%	24%	20%	..	..	60	..	71%	30%	..
Tsivgoulis et al[30]	65%	14%	..	..	13%	15%	..	36%	..	0–60	..	..	..	100%
Johnston et al[10]														
ED cohort	56%	13%	..	51%	26%	25%	12%	47%	..	..	>60 (46%), 10–59 (36%), <10 (16%)	85%	15%	100%
Clinic cohort	57%	..	..	..	..	19%	7%	44%	..	>60	..	67%	6%	15%
Bray et al[31]	54%	..	12%	..	18%	18%	6%	33%	..	>60	..	82%	7%	3%
Purroy et al[24]	54%	..	..	32%	..	18%	12%	57%	..	..	>60 (79%), 10–59 (9%), <10 (12%)	..	..	46%
Calvet et al[32]	45%	13%	8%	45%	33%	10%	5%	54%	30	..	..	85%	28%	100%
EXPRESS[4]	54%	7%	13%	..	14%	14%	9%	35%	..	..	>60 (42%), 10–59 (34%), <10 (24%)	90%	8%	0%
SOS-TIA[33]	52%	25%	14%	47%	20%	12%	4%	39%	..	15	..	90%	9%	0%

CHD=coronary heart disease. ED=emergency department. ..=not reported.

Table 3: **Treatment of patients, previous vascular risk factors, and high-risk features for early recurrent stroke, by study**

as shown in table 3, although admitted patients were excluded in one study.[25] Table 3 shows the wide variation in the proportions of patients receiving antiplatelet agents and anticoagulation after TIA. Five, six, and seven studies reported percentages of patients treated with antihypertensive treatment,[4,10,21,30,33] statin therapy,[4,9,24,25,30,33] and carotid endarterectomy after TIA,[4,9,10,11,24,32,33] respectively (table 3).

The risks of stroke observed in patients treated by specialist stroke services on an emergency basis were 0·6% (95% CI 0·0–1·6) at 2 days and 0·9% (0·0–1·9) at 7 days compared with 3·6% (2·4– 4·7) at 2 days and 6·0% (4·7–7·3) at 7 days from other cohorts. No further analyses of the influence of treatment on the observed risk of stroke were done due to non-reporting of data.

Vascular risk factors and clinical characteristics of TIA that carry a higher risk of early stroke are shown in table 3.[9] Ten studies reported the proportions of patients with high-risk TIA characteristics, which indicated substantial variation between studies. For instance, the frequency of weakness at TIA onset ranged from 33% to 67%, and there was considerable variation in the distribution of the duration of symptoms (table 3). No further analyses of the influence of vascular risk factors or high-risk characteristics were done due to non-reporting of data.

Discussion

This review showed an overall risk of stroke at 2 days after TIA of 3·1% (95% CI 2·0–4·1) in 15 cohorts including 9433 patients, and 5·2% (3·9–6·5) at 7 days in 17 cohorts including 7830 subjects, but with significant heterogeneity ($p<0·0001$) between studies for both results. This degree of heterogeneity, the high correlation between stroke risks at 0–7 days and 8–90 days in individual studies, and the reduction in heterogeneity by stratification of studies by common methods and setting suggest that observed differences between studies were unlikely to be due to chance. Moreover, the plausible trend in pooled risks after stratification, with lowest risks reported in cohorts treated urgently by specialist stroke services, suggests that most of the observed heterogeneity was due to study method, setting, and treatment. Analyses of the influence of vascular risk factors and characteristics of TIA that carry a high risk of early stroke were not

possible due to non-reporting of data in many studies.[9] Of historical interest, a few earlier studies of prognosis after TIA reported high risks of stroke in the subacute phase,[16,17,18,34,35] but their findings were not widely recognised, and all studies included in this review have been published since 2000.

The three studies that intentionally used identical methods reported highly consistent risk estimates, despite being done over three decades and in different countries.[5,9,21] All studies defined TIA according to the standard WHO definition of symptom resolution within 24 h and independently of imaging results.[36] When applied in everyday clinical practice, the exact distinction between TIA and minor stroke is not precise, and therefore some studies may have included patients with minor stroke; however, the existing evidence suggests that the early risk of recurrence after minor stroke (National Institutes of Health stroke scale score <3) is the same as that after TIA.[22] The extent to which differing stringencies of the definition of events at inception (definite *vs* possible, incident *vs* incident and recurrent) would influence measured stroke risk is uncertain. There were no significant changes to measured stroke risk when possible TIAs were excluded from the two studies that included them,[19,26] whereas previous TIA has not been shown to predict early risk.[9] The inclusion of patients who had a stroke after TIA but before they sought medical attention undoubtedly increases measured risk, but this issue was only addressed in three studies.[5,9,21] In addition to inception, methods of follow-up may also influence measured risk; face-to-face follow-up is more sensitive than administrative methods in identifying subsequent stroke, as shown by the higher rates of stroke measured by population-based studies that used the former method,[5,9,21] compared with those that used the latter.[10,11,19,25,26,28] Indeed, a low rate of stroke at 2 days was reported by Hill and colleagues[11] in a cohort that was followed up by administrative methods that were not designed to detect stroke on the same day as TIA. However, face-to-face follow-up is labour intensive, and can therefore limit the potential size of studies.

Study setting affects measured risk in several ways. In the UK, TIA patients with high-risk features for early stroke (particularly motor deficit and increased symptom duration) are more likely to attend emergency medical services than primary-care services.[37] Although health-care provision and behaviour vary from country to country, cohorts ascertained mainly via emergency departments are found to be at high risk. The three population-based cohort studies that used administrative follow-up, recruited mainly from emergency departments, and reported the lowest risks all had important exclusions, including patients who were admitted to hospital,[25] patients with persistent symptoms at discharge from the emergency department,[26] and strokes occurring on the same day as TIA.[11] Stroke risks measured in patients who attended non-emergency outpatient services were found to be lower, presumably due to the non-attendance of patients who had a stroke before the appointment.[10,27]

The FASTER pilot trial,[7] a 2×2 factorial multicentre randomised controlled trial of clopidogrel or simvastatin versus placebo in patients with TIA and non-disabling stroke who attended emergency departments, was excluded from this analysis in common with other randomised trials because of its stringent eligibility criteria and selective recruitment (87·2% of potential patients screened for the trial were excluded). However, the high rate of stroke reported in the trial (35 [8·9%] of 392 patients had a stroke within 90 days of randomisation) is not inconsistent with the low early risk of stroke in other studies in the setting of urgent treatment by specialist services included in our review.[4,29,32,33] Although patients in the FASTER trial were generally managed in a specialist setting and other standard treatments were instituted early, a high risk of stroke would be expected for several reasons. First, the very short delay from qualifying event to study entry in patients attending emergency departments means that the very high risk of recurrence in the first 24 h of a TIA is fully included. Indeed, half of all of the 90-day recurrent strokes in the FASTER trial occurred within 24 h of randomisation. Second, the inclusion criteria required a TIA or stroke manifest as weakness or speech disturbance lasting longer than 5 min. In the Oxford Vascular Study of all TIAs in the study population, all 7-day recurrent strokes occurred in the 45% of patients with these features who had a 7-day risk of over 12%.[9] Finally, partly for these same reasons, TIA patients who present to emergency departments usually have higher ABCD scores than do patients who present via family doctors.[9,37]

No single study method or setting is ideal for all purposes. Outcome based on administrative data gathered in secondary-care settings are more relevant to health-care providers, whereas those based on face-to-face follow-up, which might identify mild strokes that do not result in hospital admission, would be more relevant to patients. Studies that include patients who did not seek medical attention until after a subsequent stroke would be relevant to public education schemes. Outcomes in the acute and subacute phases may also represent different pathophysiological processes and may require different treatment approaches.

Despite the relative paucity of direct clinical trial evidence for therapeutic interventions given specifically in the few days after TIA, the extension of trial data from secondary prevention studies in acute stroke suggests that several treatments started early after TIA are likely to be effective in the reduction of subsequent stroke risk.[4] The influence of specific treatments on outcome was impossible to determine from this analysis, because neither the timing nor the extent of treatments initiated

were reported uniformly. However, stroke risks in the four studies in which patients were treated as emergency cases by specialist stroke services were consistently low.[4,29,32,33] This finding is in contrast to the three studies with longest delays (median delay from TIA, 3–4 days) to mainly outpatient-based assessment that report the highest rates of stroke at 7 days, despite both groups of studies using similar methods of face-to-face follow-up.[5,9,21] The former results may therefore represent outcome in so-called "urgently treated" TIA, whereas the latter represents the natural course of the condition and supports the argument for TIA to be managed on an emergency basis in specialist units.

Some limitations of our study must be acknowledged. Meta-analysis of observational studies done in several countries, using multiple methods, over a 20-year period is liable to be confounded by many factors. However, most heterogeneity in reported risk between studies seemed to be accounted for by basic differences in methods, setting, and treatment. Only a few studies reported the racial mix of their study populations,[4,9,21,26,28] and only one was not predominantly white.[26] Caution is therefore required in extrapolating our results to non-white populations. The selection of stroke risk within 7 days of TIA excluded some studies that reported outcomes only at 30 days or 90 days.[16–18] However, risk of stroke within a week of TIA is clinically most relevant to acute service provision and clinical trials, and this was the basis for the choice.

In summary, we have shown that the risk of stroke at 2 days and 7 days after TIA is substantial. Heterogeneity between studies can be largely accounted for by study method, setting, and treatment, with lowest risks in cohorts treated as emergency cases in specialist units.

Contributors

Both authors contributed to the data collection, analysis, and writing of the manuscript.

Conflicts of interest

We have no conflicts of interest.

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