

# Early Risk of Stroke After Transient Ischemic Attack

## A Systematic Review and Meta-analysis

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**Background:** Recent observational studies suggest that the risk for stroke may be high in the first 90 days after transient ischemic attack (TIA). This finding may, however, not be consistent across existing studies assessing stroke risk after TIA. The objectives of our study were to conduct a systematic review and meta-analysis of observational studies estimating the risk of stroke at 2, 30, and 90 days after TIA and to explore clinical and methodological factors that may explain variability in findings across studies.

**Methods:** Articles were obtained by searching the Cochrane Database of Systematic Reviews (1996 to present), MEDLINE (1966 to present), EMBASE (1980 to present), CINAHL (1982 to present), and BIOSIS previews (1980 to present). Searches were supplemented by scanning bibliographies of included articles, review articles, and conference proceedings and by contacting an expert in the field. Abstracts were retained if they reported original data and addressed early risk of stroke in patients with TIA. We identified 51 candidate studies reporting early risk of stroke after TIA. Two reviewers independently extracted information from 11 selected studies. Indicators of study quality were collected and in-

cluded consecutive enrollment, losses to follow-up, explicit criteria used to define TIA and stroke, and method of ascertainment. Pooled early risk of stroke was estimated using fixed and random effects models, and meta-regression was used to assess the association between clinical and methodological factors and the reported early risk of stroke.

**Results:** Based on a random effects model, the pooled early risk of stroke was 3.5%, 8.0%, and 9.2% at 2, 30, and 90 days after TIA, respectively. Studies reported higher risks when the methodology involved active ascertainment of stroke outcome compared with passive ascertainment. Early risk of stroke was 9.9%, 13.4%, and 17.3% at 2, 30, and 90 days, respectively, when only studies with active outcome ascertainment were considered.

**Conclusions:** Transient ischemic attack is associated with high early risk of stroke. The methodological design of studies accounts for some of the variability seen in previous reports of early stroke risk after TIA.

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**T**RANSIENT ISCHEMIC ATTACK (TIA), defined classically as a brief episode of neurological dysfunction caused by a focal disturbance of brain or retinal ischemia lasting less than 24 hours and without evidence of infarction,<sup>1</sup> heralds future stroke. Previous data suggest that approximately 15% of ischemic strokes are preceded by TIA.<sup>2</sup>

Previously, the risk of stroke in the early period after TIA was thought to be low, quoted as 1% to 2% at 7 days and 2% to 4% at 30 days.<sup>3</sup> More recent data, however, suggest a higher incidence of stroke after TIA, especially in the first few months following the event, with the greatest risk of stroke occurring in the first week. In recent years, several new observational studies have estimated the early risk of stroke

after TIA,<sup>4,6</sup> and an informal review of these studies suggests a wide range of risk estimates. As such, the estimation of the early risk of stroke after TIA is uncertain, as are the reasons for the disparity in estimates from the various studies.

Current stroke prevention practice guidelines advise that evaluation and management of patients with TIA should occur within 1 to 2 weeks of a TIA to reduce the risk of a future stroke.<sup>7,8</sup> This can be achieved through rapid access clinics or through admission to hospital for rapid evaluation. These strategies, particularly patient admission for rapid evaluation, increase health care resource utilization and have been a topic of controversy in the literature,<sup>9,10</sup> particularly with respect to the cost-effectiveness of rapid evaluation. An accurate estimate of the early risk of stroke

after TIA is important because it is the most crucial and uncertain variable when evaluating the cost-effectiveness of early management of TIA.

To our knowledge, there has been no systematic review addressing the early risk of stroke after TIA, an important gap in the literature given that systematic review and meta-analysis are effective tools for summarizing existing evidence and for exploring clinical and methodological factors that underlie study findings. Therefore, the primary objective of this study was to provide a systematic review of the literature in this area to refine our understanding of the early risk of stroke at 2, 30, and 90 days following TIA. A secondary objective was to identify those study factors that may explain the variability in reported early risk of stroke following TIA.

## METHODS

### SEARCH STRATEGY

We performed this systematic review using a predetermined protocol and in accordance with the quality of reporting of meta-analysis (QUOROM)<sup>11</sup> and meta-analysis of observational studies (MOOSE) statements.<sup>12</sup> We identified relevant articles in any language by searching the Cochrane Database of Systematic Reviews (1996 to present), MEDLINE (1966 to present), EMBASE (1980 to present), CINAHL (1982 to present), and BIOSIS previews (1980 to present). Searches were supplemented by scanning bibliographies of included articles, review articles, and conference proceedings and by contacting experts in the field. The literature search was originally performed in March 2006. An updated search was performed in December 2006 and revealed no new relevant studies.

For searching electronic databases, we used the strategy recommended for systematic reviews of observational studies.<sup>13</sup> We derived 4 comprehensive search themes that were then combined using the Boolean operator "and." The first theme, *transient ischemic attack*, was created using the Boolean operator "or" to combine exploded versions of the specific Medical Subject Heading (*ischemic attack*, *transient*) or text words (*TIA* or *transient*). The second theme, *stroke*, was created using the Boolean operator "or" to combine exploded versions of subject headings (*cerebrovascular accident*) or text words (*stroke* or *CVA*). The third theme, *early*, was created using the Bool-

ean operator "or" to combine text words (*early* or *short-term*). The fourth theme, identifying studies that provide information on *prognosis*, was created using the Boolean operator "or" to combine exploded versions of subject headings (*cohort studies* or *incidence* or *mortality* or *follow-up studies*) or subject heading (*mortality*) or text words (*prognos* or *predict* or *course* or *risk* or *incident* or *mortality* or *follow-up* or *cohort*).

### SCREENING OF ABSTRACTS FOR ELIGIBILITY

Abstracts identified from online literature searches were screened by 2 reviewers (C.M.W. and K.M.) to determine eligibility for further review. Abstracts were retained if they reported original data and if the article appeared to address the issue of early risk of stroke in patients with TIA. The reviewers were liberal in retaining abstracts on this initial screen and only discarded those that clearly did not meet the aforementioned criteria. The 2 reviewers agreed on inclusion and exclusion status of 78% of abstracts reviewed, and articles were retained for further review whenever they disagreed.

### FULL-TEXT REVIEW OF ARTICLES

The same 2 reviewers then reviewed full-text versions of all retained articles and all additional articles identified by searching bibliographies and by contacting an expert in the field (M.D.H.). Full-text articles were retained if they met inclusion criteria (ie, they were studies of original cohort data that report the early risk of stroke at 2 days and/or 30 days and/or 90 days after TIA). Exclusion criteria were applied as follows: studies with noncohort design (case series and randomized controlled trial) and studies that did not present original data or did not address the incidence of early stroke. The 2 reviewers agreed on inclusion and exclusion assignment for 100% of the full-text articles reviewed.

### DATA EXTRACTION

The 2 reviewers independently extracted the following information from all studies: number of patients; cohort demographics; community vs hospital-based cohort; first-ever vs recurrent TIA; symptoms (motor, sensory, and speech); comorbidities (previous cerebrovascular events, hypertension, diabetes, hyperlipidemia, smoking, atrial fibrillation, ischemic heart disease, and cardiac failure); treatment at presentation (antiplatelet agents, warfarin sodium, and

lipid-lowering therapy); treatment initiated (medical, surgical, and endovascular); and outcome data (stroke at 2, 30, and 90 days). We also collected information on the following key indicators of study quality: whether consecutive patients were studied; whether study follow-up began immediately after TIA; whether explicit criteria were used to define TIA and stroke; data source for cohort identification (administrative data vs prospective cohort study or registry); data source for stroke identification (administrative data vs prospective cohort study or registry); losses to follow-up within 90 days; and method of outcome ascertainment (active vs passive).

### DATA ANALYSIS

The study methods included in the systematic review was sufficiently similar to permit meta-analysis. The proportion of patients experiencing a stroke at the predefined times after TIA was recorded for each study along with the exact 95% confidence intervals. The *Q* statistic was calculated to assess for significant heterogeneity between the included studies. This statistic tests the null hypothesis that the underlying risk of stroke following TIA for the pooled studies is equivalent. Since the *Q* statistic indicated significant heterogeneity, we used a random effects model to combine the risk of stroke following TIA for the studies included in the meta-analysis. In light of the heterogeneity observed, we also performed meta-regression to explore clinical and methodological factors that might contribute to the heterogeneity. We performed a sensitivity analysis to test the robustness of our findings. In this analysis, the study by Gladstone et al,<sup>5</sup> in which only outcomes of patients discharged from the emergency department were reported, was removed and the meta-analysis repeated. We then extended this sensitivity analysis to perform a series of pooled analyses for which individual constituent studies were removed 1 at a time to assess whether any one study significantly affected the pooled estimates of stroke rates. All statistical tests were performed using STATA version 8.0 (Stata-Corp, College Station, Texas). *P* ≤ .05 was considered statistically significant.

## RESULTS

### LITERATURE SEARCH

**Figure 1** shows the progress through the systematic review. A search of online databases yielded

679 unique articles. After the initial screening of abstracts, 36 abstracts warranted further full-text review and 15 additional articles were identified from bibliographies and by contacting an expert and qualified for further review, yielding a total of 51 articles for full-text review. Forty studies were excluded after full-text review, leaving 11 articles for detailed study. Reasons for exclusion of reviewed studies were nonoriginal data ( $n=14$ ), noncohort study design ( $n=5$ ), patients in the cohort did not fulfill the definition criteria for TIA ( $n=4$ ), and early risk of stroke was not reported ( $n=17$ ). Two studies (Dennis et al<sup>14</sup> and Lovett et al<sup>15</sup>) described the same cohort of patients. Although the report by Dennis et al<sup>14</sup> preceded that by Lovett et al,<sup>15</sup> we selected the latter study for inclusion in the meta-analysis because it included the risk of stroke from the time of TIA, whereas the former study reported only the risk from time of assessment by a neurologist.

#### DETAILS OF INCLUDED STUDIES

The publication dates of the 11 studies that reported the early risk of stroke after TIA ranged from 1973 to 2006, and the number of patients per study ranged from 62 to 2285. Three studies included only patients with first-ever TIA and 8 included either first-ever or recurrent TIA. None of the included studies restricted patient entry on the basis of the cause or clinical presentation of TIA. Ten studies reported outcomes for consecutive patients with TIA, with the exception being the study by Gladstone et al,<sup>5</sup> which only reported the outcomes for patients discharged from the emergency department. Of the 11 studies, 7 reported the risk of stroke at 2 days, 9 reported the risk of stroke at 30 days, and 9 reported the risk of stroke at 90 days. All of the 11 studies followed patients for at least 90 days after TIA, although only 5 specifically reported whether patients were lost to follow-up during this period. In 3 studies, patients had a face-to-face encounter with medical or nursing staff at 3 months after TIA. These studies were deemed to have an “active” out-

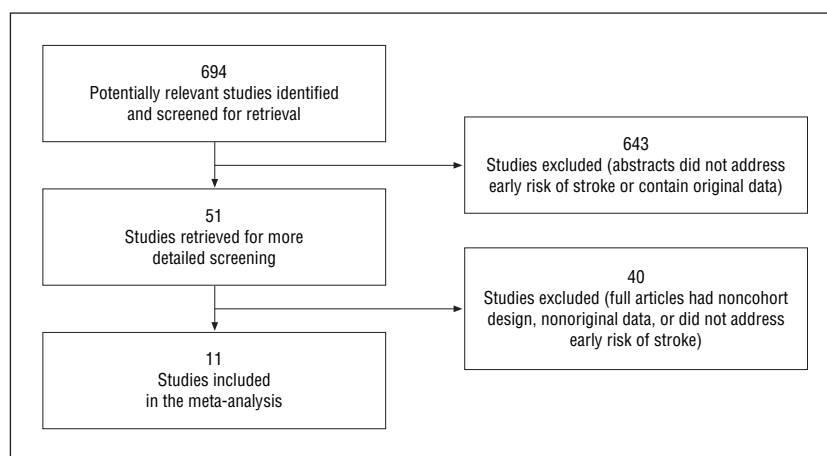


Figure 1. Progress through the systemic review.

come ascertainment, while the remaining 8 studies, which determined stroke after TIA from administrative data, were deemed to have a “passive” outcome ascertainment. Details of the individual studies are given in **Table 1**.

#### EARLY RISK OF STROKE AFTER TIA

The early risk of stroke reported across studies ranged from 1.4% to 9.9% at 2 days, from 3.2% to 17.7% at 30 days, and from 3.9% to 17.3% at 90 days (**Table 2**). When the individual studies were combined in a meta-analysis, there was significant heterogeneity for all periods considered ( $P<.001$ ). The pooled estimate of risk using the random effects model was 3.5% (95% confidence interval [CI], 2.1%-5.0%), 8.0% (95% CI, 5.7%-10.2%), and 9.2% (6.8%-11.5%) at 2, 30, and 90 days, respectively. The early risk of stroke after TIA at 2, 30, and 90 days is presented graphically in forest plots in **Figure 2**.

#### SOURCES OF HETEROGENEITY

##### Clinical Sources of Heterogeneity

Clinical factors assessed through meta-regression as potential contributors to heterogeneity were population-based vs hospital-based cohorts, studies including only first-ever TIA vs studies including first-ever and recurrent TIA, and North American vs European stud-

ies. There was no significant heterogeneity associated with any of these factors ( $P>.05$  for all  $\beta$  coefficients assessed through meta-regression). We did not assess presenting clinical features or treatment because only 5 of 13 studies reported these data and reporting in these studies was inconsistent.

##### Methodological Sources of Heterogeneity

Methodological factors assessed in meta-regression were the method of cohort identification (administrative data vs entry into a prospective study/registry), time of study entry (immediately following TIA or delayed entry), and method of outcome ascertainment (passive vs active). There was no significant heterogeneity associated with method of cohort identification or time of study entry ( $P>.05$  for all variables), but there was significant heterogeneity associated with method of outcome ascertainment. The 2 and 30 days risk of stroke after TIA was higher for studies with active outcome ascertainment ( $\beta=6.78$  [ $P=.02$ ] and  $\beta=7.19$  [ $P=.004$ ], respectively). The difference at 90 days did not reach statistical significance ( $\beta=8.59$  [ $P=.11$ ]).

Given the apparent importance of the outcome ascertainment method, we then performed an analysis stratified on this variable (**Table 3**). The pooled risk of stroke was higher in studies with active outcome ascertainment. The reported risk of stroke at 2 and 30 days after TIA for studies with active outcome ascertain-

**Table 1. Characteristics of Studies Reporting the Early Risk of Stroke After Transient Ischemic Attack**

Source	Cohort Details			Demographics		Study Quality					
	No. of Patients	Community-Based vs Hospital-Based Cohort	Recurrent TIA Included	Male, %	Age, Mean, y	Consecutive Patients	Explicit Event Criteria	Losses to Follow-up	Method of Cohort Identification	Immediate vs Delayed Entry Into Study	Method of Outcome Ascertainment
Whisnant et al, <sup>16</sup> 1973	198	Community	No	44	70	Yes	Yes	No	Administrative	Immediate	Passive
Calandre and Molina, <sup>17</sup> 1985	62	Hospital	Yes	74	56	Yes	Yes	No	Administrative	Delayed	Passive
Lovett et al, <sup>15</sup> 2003	209	Community	No	54	69	Yes	Yes	NR	Prospective	Immediate	Active
Kleindorfer et al, <sup>18</sup> 2005	927	Community	Yes	47	70	Yes	Yes	No	Administrative	Immediate	Passive
Johnston et al, <sup>4</sup> 2000	1707	Hospital	Yes	47	72	Yes	Yes	NR	Prospective	Immediate	Passive
Correia et al, <sup>19</sup> 2006	141	Community	No	43	70	Yes	Yes	NR	Prospective	Immediate	Active
Hill et al, <sup>6</sup> 2004	2285	Community	Yes	49	71	Yes	Yes	NR	Administrative	Delayed	Passive
Lisabeth et al, <sup>20</sup> 2004	612	Community	Yes	39	74	Yes	Yes	No	Prospective	Immediate	Passive <sup>a</sup>
Gladstone et al, <sup>5</sup> 2004	371 <sup>b</sup>	Hospital	Yes	52	71	No	Yes	Yes	Prospective	Delayed	Passive
Wu <sup>c</sup>	639	Hospital	Yes	42	70	Yes	Yes	NR	Administrative	Immediate	Passive
Coull et al, <sup>21</sup> 2004	87	Community	Yes	44	75	Yes	Yes	NR	Prospective	Immediate	Active

Abbreviations: NR, not reported; TIA, transient ischemic attack.

<sup>a</sup>Ascertainment active for admitted patients.

<sup>b</sup>Reports only data for patients discharged from emergency department (n=265).

<sup>c</sup>Unpublished data (C.M.W.), January 1 to December 31, 2000.

**Table 2. Early Risk of Stroke After Transient Ischemic Attack**

Source	No. of Patients	Patients With Stroke at Follow-up Time, No. (%)		
		2 Days	30 Days	90 Days
Whisnant et al, <sup>16</sup> 1973	198	NR	15 (7.6)	20 (10.1)
Calandre and Molina, <sup>17</sup> 1985	62	NR	NR	5 (8.1)
Lovett et al, <sup>15</sup> 2003	209	NR	25 (12.0)	NR
Kleindorfer et al, <sup>18</sup> 2005	927	36 (3.9)	104 (11.2)	135 (14.6)
Johnston et al, <sup>4</sup> 2000	1707	90 (5.3)	NR	179 (10.5)
Correia et al, <sup>19</sup> 2006	141	14 (9.9)	25 (17.7)	NR
Hill et al, <sup>6</sup> 2004	2285	32 (1.4)	153 (6.7)	217 (9.5)
Lisabeth et al, <sup>20</sup> 2004	612	10 (1.6)	20 (3.2)	24 (4.0)
Gladstone et al, <sup>5</sup> 2004	371 <sup>a</sup>	11 (2.6)	19 (4.9)	22 (6.4)
Wu <sup>b</sup>	639	24 (3.8)	32 (5.0)	45 (7.0)
Coull et al, <sup>21</sup> 2004	87	NR	10 (11.5)	15 (17.3)

Abbreviation: NR, not reported.

<sup>a</sup>Reports only data for patients discharged from the emergency department (n=265).

<sup>b</sup>Unpublished data (C.M.W.), January 1 to December 31, 2000.

ment was more than double that of studies with passive ascertainment.

### SENSITIVITY ANALYSES

The exclusion of the study by Gladstone et al<sup>5</sup> resulted in a nonsignificant increase in the pooled estimate of risk of stroke at each period after TIA (3.6% [95% CI, 2.0%-5.3%], 8.5% [95% CI, 6.1%-11.0%], and 9.6% [95% CI, 7.0%-

12.2%] at 2, 30, and 90 days, respectively). When we extended this analysis to sequentially remove each of the individual constituent studies from the analysis 1 at a time, we found that the pooled event rates at 2, 30, and 90 days were not substantively altered (range of pooled event rates across sensitivity analyses: 3.0%-3.9% at 2 days; 7.2%-8.6% at 30 days; and 8.3%-9.9% at 90 days).

### COMMENT

#### SOURCES OF HETEROGENEITY IN COHORT STUDIES REPORTING EARLY RISK OF STROKE AFTER TIA

In this meta-analysis, we found significant heterogeneity among the 11 observational cohort studies reporting the early risk of stroke after TIA. Using meta-regression, we observed that at least some of this heterogeneity was related to study methodology. The reported early risk of stroke after TIA was more than doubled for studies with active outcome ascertainment compared with studies with passive outcome ascertainment. That active ascertainment of outcome increases the estimate of early stroke risk is certainly a plausible finding. Studies with passive outcome ascertainment may underestimate the early risk of stroke because they may only document strokes that are recorded in their administrative data set. Some patients with stroke may not present to a hospital or may present to a health care facility that does not provide data to the administrative database. These events may, however, be detected by



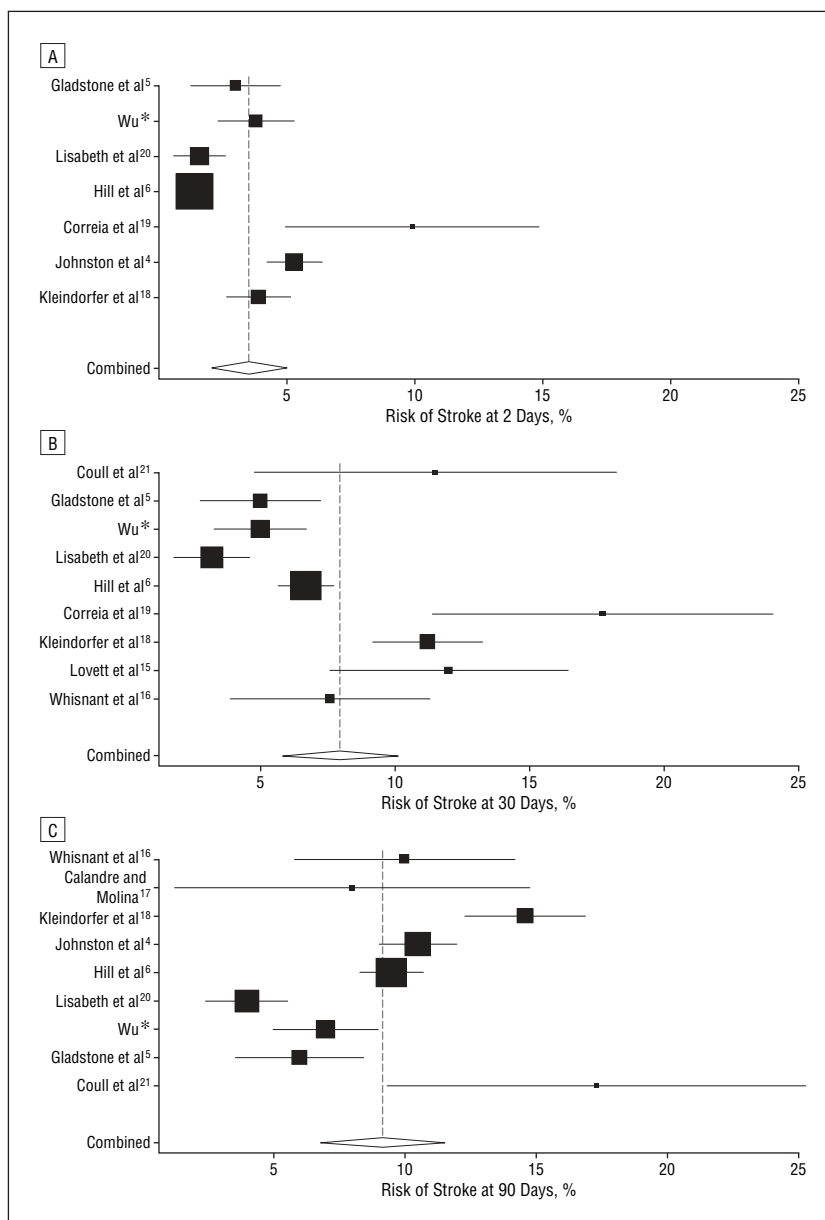
active ascertainment. While it could be argued that active ascertainment may be detecting milder strokes that do not require admission to hospital, these strokes may still be of considerable relevance to patients, health care providers, and the health care system.

## EARLY RISK OF STROKE AFTER TIA

Our finding regarding the importance of the method of outcome ascertainment as a determinant of study findings is notable on 2 fronts. First, it provides an at least partial explanation for the discrepancy in findings reported in the existing literature. Perhaps more importantly, though, it also provides insight into the most accurate risk of stroke after TIA. We would assert that the studies with active outcome ascertainment are providing better risk estimates than studies with passive outcome ascertainment and accordingly would conclude that the risk of stroke within 3 months of TIA is likely between 15% and 20% (Table 3).

## STUDY LIMITATIONS

Our study has limitations. Risk estimates from observational studies have inherent biases and are subject to known and unknown confounders. This is already evident with the differences seen in the risk estimates reported in studies with active vs passive identification of outcome. Nevertheless, we sought to identify potential sources of bias and confounding within and between studies. Unfortunately, many of the factors that we attempted to extract from studies were not available or not explicitly stated by many of the authors of the studies. For example, we were unable to test for differences among study populations for factors such as differences in prevalence of comorbidities such as diabetes or differences in treatments received such as antiplatelet therapy. In addition, given that the number of studies is small, analyses such as the meta-regression are likely underpowered and unable to detect the significance of some of the moderate sources of heterogeneity.



**Figure 2.** Forest plots of early stroke risk after transient ischemic attack at 2 days (A), 30 days (B), and 90 days (C) (random effects model). The boxes represent the mean risk or percentage of patients incurring stroke after transient ischemic attack for the time frame specified for each individual study. The lines represent the 95% confidence intervals for these values. The area of the boxes represents the weight given to an individual study with respect to the calculation of the pooled estimate for risk. \*Unpublished data (C.M.W.), January 1 to December 31, 2000.

**Table 3. Stratified Meta-analysis of the Early Risk of Stroke Following Transient Ischemic Attack for Passive vs Active Ascertainment of Outcome (Random Effects Models)**

Risk of Stroke at Follow-up, d	Passive Ascertainment, % (95% CI)	Active Ascertainment, % (95% CI)	P Value
2	3.1 (1.7-4.6)	9.9 (4.9-14.9)	.02
30	6.4 (4.2-8.5)	13.4 (9.8-17.1)	.004
90	8.7 (6.3-11.1)	17.3 (9.3-25.3)	.11

Abbreviation: CI, confidence interval.

## CONCLUSIONS

Despite these limitations, our study summarizes a large and somewhat inconsistent body of literature reporting on stroke risk after TIA. Based on studies with active outcome ascertainment, however, the early risk of stroke after TIA is likely in the order of 15% to 20% at 90 days. This prognostic information is valuable to patients and health care providers. The high risk of stroke after TIA also heightens the need for timely research into the early management strategies for patients presenting with TIA. While admission to hospital and/or rapid access outpatient clinics may appear to be reasonable strategies in light of this risk, these strategies are, as yet, of unproven benefit. Further studies are needed to evaluate strategies designed to reduce the early risk of stroke after TIA.

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**Author Contributions:** *Study concept and design:* Wu, McLaughlin, Lorenzetti, Manns, and Ghali. *Acquisition of data:* Wu and McLaughlin. *Analysis and interpretation of data:* Wu, McLaughlin, Hill, and Ghali. *Drafting of the manuscript:* Wu and McLaughlin. *Critical revision of the manuscript for important intellectual content:* Wu, McLaughlin, Lorenzetti, Hill, Manns, and Ghali. *Statistical analysis:* Wu, McLaughlin, Hill, and Ghali. *Administrative, technical, and material support:* Lorenzetti and

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