

# A 5-Decade Analysis of Incidence Trends of Ischemic Stroke After Transient Ischemic Attack

## A Systematic Review and Meta-analysis

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 Supplemental content

**IMPORTANCE** Management of transient ischemic attack (TIA) has gained significant attention during the past 25 years after several landmark studies indicated the high incidence of a subsequent stroke.

**OBJECTIVE** To calculate the pooled event rate of subsequent ischemic stroke within 2, 7, 30, and 90 days of a TIA and compare this incidence among the population with TIA recruited before 1999 (group A), from 1999 to 2007 (group B), and after 2007 (group C).

**DATA SOURCES** All published studies of TIA outcomes were obtained by searching PubMed from 1996, to the last update on January 31, 2020, irrespective of the study design, document type, or language.

**STUDY SELECTION** Of 11 516 identified citations, 175 articles were relevant to this review. Both the classic time-based definition of TIA and the new tissue-based definition were accepted. Studies with a combined record of patients with TIA and ischemic stroke, without clinical evaluation for the index TIA, with diagnosis of index TIA event after ischemic stroke occurrence, with low suspicion for TIA, or duplicate reports of the same database were excluded.

**DATA EXTRACTION AND SYNTHESIS** The study was conducted and reported according to the PRISMA, MOOSE, and EQUATOR guidelines. Critical appraisal and methodological quality assessment used the Quality in Prognosis Studies tool. Publication bias was visualized by funnel plots and measured by the Begg-Mazumdar rank correlation Kendall  $\tau^2$  statistic and Egger bias test. Data were pooled using double arcsine transformations, DerSimonian-Laird estimator, and random-effects models.

**MAIN OUTCOMES AND MEASURES** The proportion of the early ischemic stroke after TIA within 4 evaluation intervals (2, 7, 30, and 90 days) was considered as effect size.

**RESULTS** Systematic review yielded 68 unique studies with 223 866 unique patients from 1971 to 2019. The meta-analysis included 206 455 patients (58% women) during a span of 4 decades. The overall subsequent ischemic stroke incidence rates were estimated as 2.4% (95% CI, 1.8%-3.2%) within 2 days, 3.8% (95% CI, 2.5%-5.4%) within 7 days, 4.1% (95% CI, 2.4%-6.3%) within 30 days, and 4.7% (95% CI, 3.3%-6.4%) within 90 days. There was a significant risk reduction of 3.4% among group A in comparison with 2.1% in group B or 2.1% in group C within 2 days; 5.5% in group A vs 3.2% in group B or 2.9% in group C within 7 days; 6.3% in group A vs 3.4% in group B or 2.9% in group C within 30 days, and 7.4% in group A vs 3.9% in group B or 3.9% in group C within 90 days.

**CONCLUSIONS AND RELEVANCE** These findings suggest that TIA continues to be associated with a high risk of early stroke; however, the rate of post-TIA stroke might have decreased slightly during the past 2 decades.

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**M**anagement of transient ischemic attack (TIA) has gained significant attention during the past 25 years after several landmark studies<sup>1-5</sup> indicating a high rate of subsequent stroke. Although the 1994 American Heart Association guideline<sup>6</sup> for the management of TIA recommended a timely evaluation of patients with TIA, the 1999 supplement to the guideline<sup>7</sup> has emphasized different medical and surgical treatment for patients with TIAs. Furthermore, the findings from a Kaiser-Permanente Northern California study<sup>5</sup> and the Oxford Vascular Study group<sup>3,8</sup> from 2000 to 2007 confirmed the importance of urgent TIA management, especially among patients with vascular risk factors.

Thus far, 4 systematic reviews of the subsequent cerebral ischemia after TIA have been performed.<sup>9-12</sup> Each study has a different cohort, recruitment interval, inclusion criteria, and outcome definition. Two reviews<sup>9,10</sup> have summarized studies before 2007, and 2 other reviews have limited their scope to population recruited after 2007.<sup>11,12</sup> In addition, Najib et al<sup>12</sup> used modeling and simulation to predict the cumulative rates rather than conducting the traditional meta-analysis. Valls et al<sup>11</sup> focused on patients with TIA receiving immediate or same-day urgent care, and Giles and Rothwell<sup>10</sup> and Wu et al<sup>9</sup> reported significant heterogeneity.

We aim to estimate the risk of stroke after TIA through a more inclusive design, consider all published studies from 1971 to 2019, and observe trends. We calculated the pooled incidence of subsequent stroke within 2, 7, 30, and 90 days of TIA and compared the risk among studies with research study population recruitment before 1999, from 1999 to 2007, and after 2007. We also conducted subgroup meta-analyses based on the time of patients' recruitments to be through vs after 2007 and retrospective vs prospective study designs.

## Methods

### Search Strategy

The study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA),<sup>13</sup> Meta-analysis of Observational Studies in Epidemiology (MOOSE),<sup>14</sup> and Enhancing the Quality and Transparency of Health Research (EQUATOR) reporting guidelines.<sup>15</sup> We searched PubMed for any studies published from 1996 to January 31, 2020, irrespective of the study design, document type, or language. We used the following keywords in addition to Medical Subject Headings terms to build up the search protocol: *transient ischemic attack, ischemic attack, transient, TIA, early outcome, early ischemic stroke, early occurrence of ischemic stroke, early ischemic stroke outcome, stroke risk, risk of stroke, short-term prognosis, short term prognosis, prognosis of short-term, prognosis of short term, and follow up*. We used forward and backward citation tracking and communication with the corresponding authors to enhance the results.

### Eligibility Criteria

We considered retrospective or prospective cohort studies with original data on recurrent cerebral ischemia at 4 evaluation in-

## Key Points

**Question** What is the incidence of subsequent ischemic stroke after a transient ischemic attack (TIA)?

**Findings** In this systematic review and meta-analysis of 206 455 unique patients in 68 unique studies during 5 decades, the subsequent risk of ischemic stroke was 2.4% within 2 days, 3.8% within 7 days, 4.1% within 30 days, and 4.7% within 90 days. The incidence among the study population recruited before 1999 was significantly higher.

**Meaning** These findings suggest that TIA is associated with a high risk of early stroke, although the rate of post-TIA stroke might have decreased slightly during the past 2 decades.

tervals (2, 7, 30, and/or 90 days). We accepted both the classic definition of TIA<sup>1</sup> and the new tissue-based definition considering TIA as a transient episode of neurological dysfunction caused by the focal cerebral, spinal cord, or retinal ischemia, without acute infarction.<sup>16</sup> We excluded studies (1) with a combined record of patients with TIA and ischemic stroke, (2) without clinical encounter evaluation for the index TIA event, (3) with the diagnosis of index TIA event after ischemic stroke occurrence, (4) with low suspicion of TIA after clinical evaluation, and (5) that were duplicate reports of the same data set.

### Outcome Measure

The proportion of the early ischemic stroke after index TIA within 4 evaluation intervals (2, 7, 30, and 90 days) was considered as effect size. We extracted these data from the summary statistics of each study.

### Data Abstraction and Management

Two reviewers (S.S. and A.S.) independently evaluated the titles and abstracts of retrieved articles and screened the full texts based on the predefined inclusion and exclusion criteria. In case of any disagreement, the final decision was made through consultation with a third reviewer (R.Z.).

We collected the following data elements for this study: demographic data, study design, population recruitment interval, inclusion or exclusion of imaging in TIA definition, TIA and stroke risk factors (diabetes, hypertension, atrial fibrillation, coronary artery disease, dyslipidemia, carotid stenosis), smoking history, large-artery diseases, ABCD<sub>2</sub> (age, blood pressure, clinical features, duration of symptoms, and diabetes) score, history of the previous stroke, use of antiplatelet or anticoagulation medicine, use of medication to lower lipid levels before recurrent cerebral ischemia, and subsequent event rate for stroke after the index TIA at 4 different time intervals (2, 7, 30, and 90 days). When the articles presented 2 or more cohorts of patients with different demographic profiles or study design or management settings, we reported and analyzed the cohorts separately. In the case of multiple reports from the same data set, the most recent or most comprehensive report was selected.

### Subgroup Analysis

Based on many significant advances in medical therapy and surgical management for patients with TIAs leading to the

supplement to the American Heart Association guidelines in 1999<sup>7</sup> and landmark studies regarding the importance of urgent TIA management and TIA clinic concept from 2005 to 2007,<sup>3,8,17</sup> we divided the included studies into 3 groups: the patients' recruitment years (not study publication year) before 1999 (group A), from 1999 to 2007 (group B), and after 2007 (group C). To be able to compare our results with previous meta-analyses, we provided the recurrent cerebral ischemia at each evaluation interval (2, 7, 30, and 90 days) by considering all patients recruited through 2007 (groups A and B) and after 2007 (group C). To evaluate the influence of observation type on heterogeneity and reported rates of subsequent ischemic stroke, we compared retrospective and prospective studies at each evaluation interval.

### Publication Bias Assessment

Publication bias was visualized by funnel plots. Asymmetry was measured by the Begg-Mazumdar rank correlation Kendall  $\tau^2$  statistic and the Egger bias test. The trim and fill method was used to adjust the effect size and deal with the bias if needed.

### Risk of Bias Assessment

Critical appraisal and methodological quality assessment used the Quality in Prognosis Studies tool.<sup>18</sup> Accordingly, we evaluated the potential bias for each study based on the study population, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, and analysis and reporting. We summarized the outcomes (eTable 1 in the [Supplement](#)) as low, medium, or high risk of bias.

### Investigations of Heterogeneity, Data Synthesis, and Sensitivity Analyses

We assessed the heterogeneity among the studies with the Cochran Q test ( $\chi^2$  test for heterogeneity). The percentage of total heterogeneity to total variability was quantified by  $I^2$  and its 95% CI. Significant statistical heterogeneity was defined as a Q test with  $P < .10$  or an  $I^2$  statistic greater than 60%. To minimize the heterogeneity of the included studies in the systematic review for meta-analysis, we conducted the following measures: we screened the outliers and studies with substantial influence on heterogeneity by studentized residuals greater than 2 in absolute value, Baujat plot, or a set of leave-one-out diagnostic tests including the difference in fits values, Cook distances, and leave-one-out estimates for the amount of heterogeneity ( $\tau^2$  statistic).<sup>19</sup> We used bubble plots to indicate the moderators and performed meta-regression models (study design, diabetes, and hypertension as the modifiers) and subclassification analyses to consider the effect of the moderators on the outcome. We also excluded the studies with less than 100 patients in the meta-analyses. We visualized subsequent stroke risk (with 95% CIs) after TIA in individual and pooled studies, as well as the weight of each study in the meta-analyses by forest plots. Random-effects models with double arcsine transformations and DerSimonian-Laird estimator were used. Except for the  $I^2$  statistic, 2-sided  $P < .05$  was considered statistically significant. To evaluate the significance of the

difference in proportions among groups of each analysis, we calculated the between-group  $P$  value; when significant, we ran pairwise comparisons and adjusted the  $\alpha$  level when applicable. We conducted meta-analyses of high-quality studies at each evaluation time interval (2, 7, 30, and 90 days) after excluding the studies with less than 100 patients, moderate or high risk of bias according to the Quality in Prognosis Studies tool, or retrospective study design or that were recognized as outliers by the abovementioned tests. Meta-analyses were performed using the R, version 3.5.0, metafor package (R Institute),<sup>20</sup> which allows for the inclusion of moderator variables (study-level covariates) in the random-effects models.

## Results

### Literature Review

Of 11 516 identified citations, 175 articles were relevant to our study and were further evaluated by full-text screening (flowchart in eFigure 1 in the [Supplement](#)). Based on the predefined criteria, 107 articles were excluded (eTable 2 in the [Supplement](#)). Most of the excluded articles (43 articles) had unspecified timing of the stroke occurrence. Five articles produced guidelines or study design descriptions, and 14 were review articles. In 4 articles, TIA was retrospectively diagnosed after the admission for ischemic stroke. In 18 articles, the outcomes were reported for patients with both TIA and stroke, and 9 articles did not include the outcome of interest. Several reports of the Oxfordshire Community Stroke Project<sup>3,4,21-24</sup> and Oxford Vascular Study<sup>1,3,24-27</sup> were retrieved. Johnston et al<sup>25</sup> included these cohorts and also the cohort from Kaiser-Permanente Northern California.<sup>5</sup> We excluded the redundant reports among these publications. Similarly, we identified the most recent or more comprehensive data set of multiple reports and thereby excluded 16 articles (eTable 2 in the [Supplement](#)). Among the 68 articles included for systematic review, 4—Al-Khaled et al,<sup>28</sup> Felgueiras et al,<sup>29</sup> Johnston et al,<sup>25</sup> and Rothwell et al<sup>8</sup>—presented multiple cohorts of patients. Because the population, timing, and inclusion and exclusion criteria for patients' recruitments were different among these cohorts, we considered them as separate reports in the meta-analysis. Sundararajan et al<sup>30</sup> provided annual details of stroke occurrence; therefore, for our subgroup analysis, we split their results into 2 separate cohorts (2001-2007 and 2008-2011) (eTable 3 in the [Supplement](#)). To summarize, 77 patient cohorts from 68 articles<sup>25,28-94</sup> met the eligibility criteria of this study and were included in this systematic review.

### Publication Bias Assessment

Funnel plots for studies reporting subsequent stroke within 2, 7, 30, or 90 days are available in eFigure 2 in the [Supplement](#). Neither the Egger bias test nor Begg-Mazumdar rank correlation Kendall  $\tau^2$  statistic could detect publication bias among studies reporting the risk within 2, 7, or 90 days (eTable 4 in the [Supplement](#)). The Egger bias test but not the Begg-Mazumdar test showed significant publication bias among

studies reporting the recurrent cerebral ischemia within 30 days ( $z = 2.23$ ;  $P = .03$ ).

### Risk of Bias Assessment

Based on the Quality in Prognosis Studies tool, the overall risk of bias assessment of 66 included cohorts in the meta-analysis was low in 56 (84.8%) and medium in 10 (15.2%). We measured medium risk of bias regarding study population (9 [13.6%]), study attrition (5 [7.6%]), prognostic factor measurement (10 [15.2%]), confounding measurement and account (12 [18.2%]), and analysis and reporting (1 [1.5%]). One cohort (1.5%)<sup>31</sup> had a high risk of bias regarding prognostic factor measurement (eTable 1 in the [Supplement](#)).

### Heterogeneity Assessment

As described in the Methods, to increase the validity of the risk assessment and reduce the heterogeneity among the cohorts that were included in the systematic review, we further considered the following steps to select the cohorts for meta-analyses. First, we excluded 5 studies<sup>32-36</sup> with less than 100 patients. Second, based on studentized residual and leave-one-out analyses, we identified the outliers and fully reviewed the design and risk of bias in each of these cohorts. Accordingly, we excluded 5 articles<sup>37-41</sup> and the cohort of patients recruited from 1998 to 2000 in the study by Felgueiras et al.<sup>29</sup> To summarize, 66 cohorts from 58 articles<sup>25,28-31,38,40,42-77,79-92</sup> were included in the meta-analysis (eFigure 1 in the [Supplement](#)).

The overall estimates for all 4 evaluation intervals (2, 7, 30, and 90 days) showed low heterogeneity ( $I^2 < 50\%$  and  $P > .10$ ) (Figure 1 and Figure 2). Subgroup analyses by considering the study recruitment intervals (groups A, B, and C) yielded moderate heterogeneity for group C at 2-day (Figure 1A) and 30-day (Figure 2A) assessments and low heterogeneity for other estimates at all other evaluation intervals. Grouping of studies with populations recruited through or after 2007 resulted in minimal heterogeneity for all estimates except for strata of recurrent cerebral ischemia within 2 days among patients recruited after 2007 (group C) (eFigure 3 in the [Supplement](#)). When meta-analyses were conducted based on study design, there was insignificant or minimal heterogeneity in each stratum for retrospective or prospective studies, but significant heterogeneity in cumulative data in 2 ( $I^2 = 85.5\%$ ;  $P < .001$ ), 7 ( $I^2 = 87.2\%$ ;  $P < .001$ ), 30 ( $I^2 = 93.9\%$ ;  $P < .001$ ), and 90 ( $I^2 = 94.4\%$ ;  $P < .001$ ) days (eFigure 4 in the [Supplement](#)). Meta-analyses of high-quality studies were conducted under minimal heterogeneity (eFigure 5 in the [Supplement](#)).

### Characteristics of Included Studies in Meta-analysis

We reviewed 68 studies encompassing a publication time frame of almost 5 decades from 1971 to 2019. A total of 206 455 patients with TIA (42% men and 58% women) were included in the systematic review. In the meta-analysis, we included 206 455 patients in a time frame of almost 4 decades from 1981 to 2018. The number of patients with TIA in the meta-analysis at 2 days was 22 231; at 7 days, 21 086; at 30 days, 139 620; and at 90 days, 86 675. The included studies were from 25 countries in North America, Europe, Asia, and Oceania and

Australia, with a large range in population size (131-122 063). Fifteen studies<sup>29,30,40,42-52,85</sup> were evaluated retrospectively and 43 studies<sup>25,28,31,38,53-84,86-92</sup> were collected prospectively. Only 13 studies<sup>31,46,49-51,53-60</sup> considered imaging results necessary for TIA diagnosis. Among the 31 studies with populations recruited after 2007, 8 (25.8%)<sup>29,39,45,46,57,69,74,89</sup> used the tissue-based definition. The most prevalent reported comorbidities among patients with TIA were hypertension (55.54%), diabetes (21.78%), large artery diseases (18.56%), and dyslipidemia (17.30%). Atrial fibrillation (14.21%), previous incidence of stroke (13.01%), current tobacco use (9.47%), and carotid artery stenosis (5.19%) were other frequently reported comorbidities (Table). Details of all cohorts are presented in eTable 3 in the [Supplement](#).

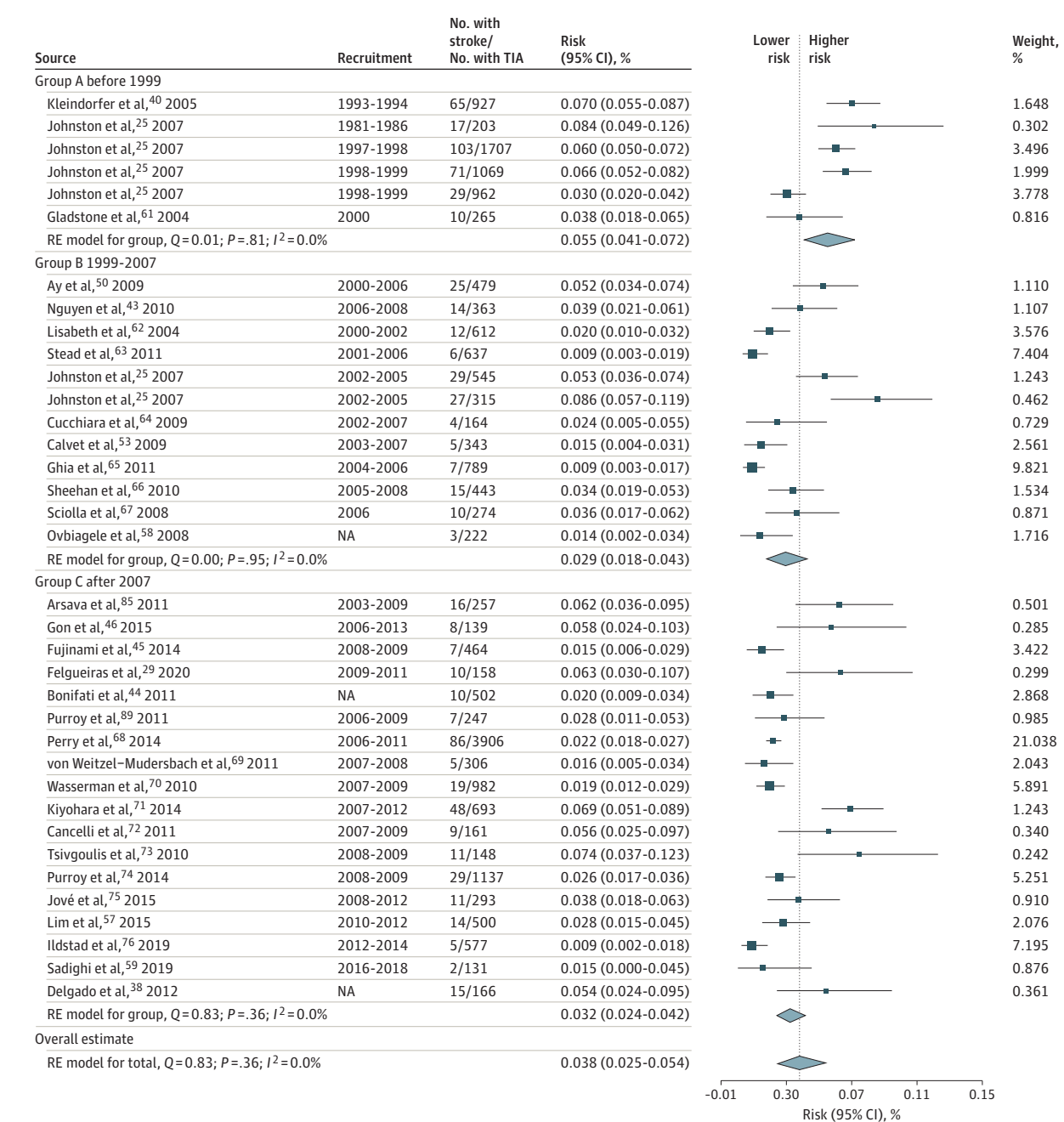
### Outcome of Meta-analysis

Our study demonstrated that after the index TIA, ischemic stroke had a mean incidence during the span of 1971 to 2019 equal to 2.4% (95% CI, 1.8%-3.2%) within 2 days, 3.8% (95% CI, 2.5%-5.4%) within 7 days, 4.1% (95% CI, 2.4%-6.3%) within 30 days, and 4.7% (95% CI, 3.3%-6.4%) within 90 days (Figures 1 and 2). The group incidences for groups within 2 days (3.4% for A, 2.1% for B, and 2.1% for C), within 7 days (5.5% for A, 2.9% for B, and 3.2% for C), within 30 days (6.3% for A, 2.9% for B, and 3.4% for C), and within 90 days (7.4% for A, 3.9% for B, and 3.9% for C) showed substantial decrease in recurrent cerebral ischemia after 1999 compared with group A (eTable 5 in the [Supplement](#)). When comparing the population recruited through 2007 (groups A plus B) and after 2007 (group C), the decreasing trend was observed within 2, 7, and 90 days (eTable 5 in the [Supplement](#)). However, except at the 30-day evaluation (2.9% vs 3.4%;  $P = .004$ ), comparing groups B (1999-2007) and C (after 2007) could not reveal a significant decrease in subsequent ischemic stroke events (eTable 5 in the [Supplement](#)), highlighting the more prominent decrease in stroke rate around 1999. Comparing the result of studies with retrospective vs prospective study population recruitment showed a significantly different proportion rate at 7-day (4.4% vs 3.3%;  $P = .002$ ), 30-day (5.0% vs 3.0%;  $P < .001$ ), and 90-day (3.6% vs 4.6%;  $P = .003$ ) intervals but not within 2 days (eTable 5 in the [Supplement](#)).

## Discussion

The present systematic review and meta-analysis summarize the incidence proportion of subsequent ischemic stroke after TIA in the past 4 decades. A decremental trend can be observed in every evaluation interval (2, 7, 30, and 90 days) before 1990 and through 2007 (Figure 3 and eFigure 6 in the [Supplement](#)). Although the 1994 American Heart Association guideline<sup>6</sup> recommended the timely evaluation of TIA, the introduction of several significant advances in medical and surgical therapy in 1999 prompted a supplement to the 1994 guidelines.<sup>7</sup> This amendment can be considered as a consequential statement from the Ad Hoc Committee on Guidelines for the Management of Transient Ischemic Attacks, Stroke Council, American Heart Association. A reduction in the rate

Figure 1. Forest Plots of Pooled Incidence Rates of Subsequent Ischemic Stroke Incidence After Transient Ischemic Attack (TIA) Within 7 Days

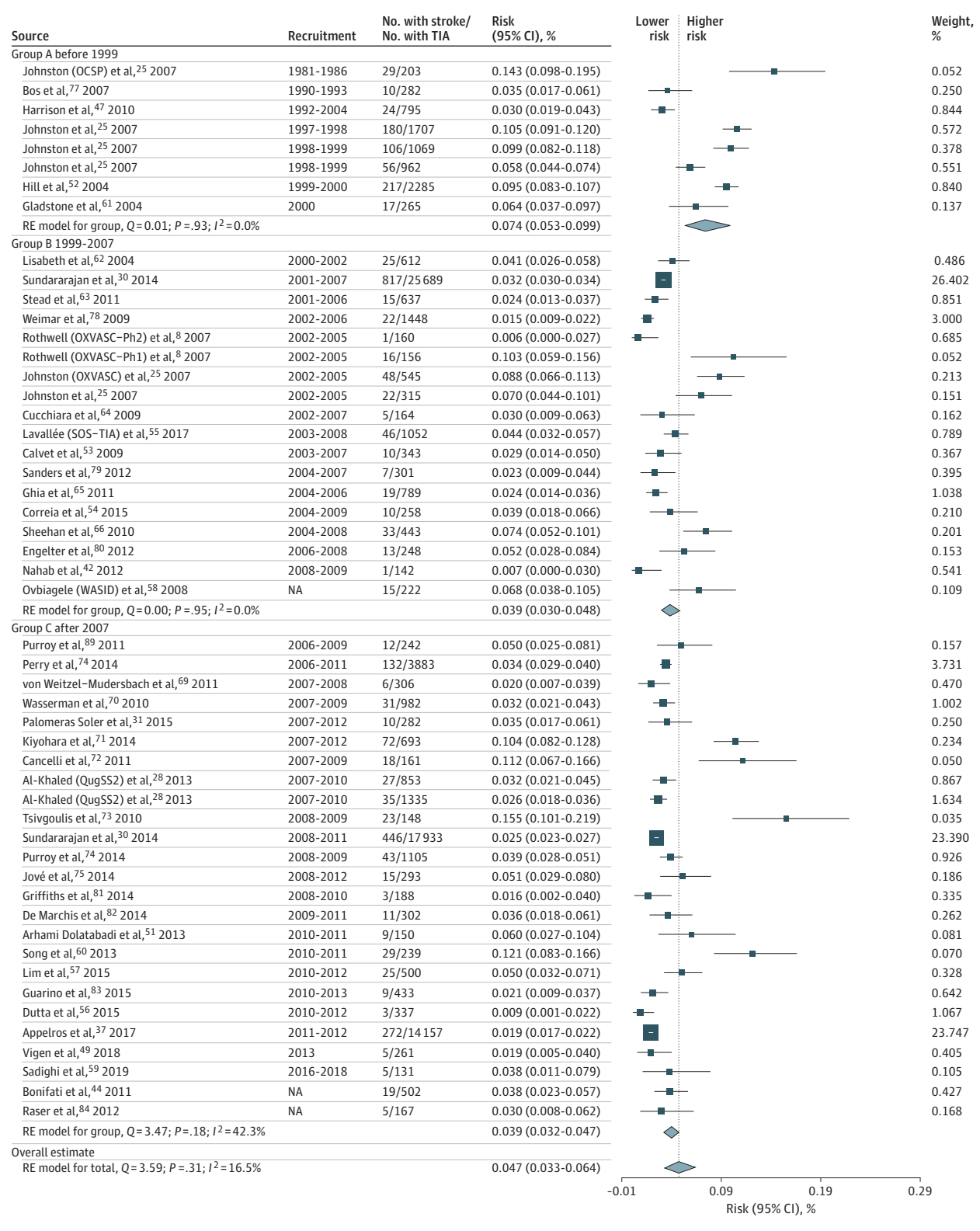


Data are stratified by population recruitment intervals. The boxes illustrate the effect estimates from each single study; the horizontal lines through the boxes, length of the 95% CI; and the diamonds, the overall estimates. NA indicates not available; RE, random effects.

of subsequent cerebral ischemic incidence after a TIA, as we observed in our study, can be partially associated with this practice guideline change. Other landmark studies such as Kaiser Permanente Northern California<sup>5</sup> and the Oxford Vascular Study group<sup>3,8</sup> further highlighted the importance of urgent TIA management in the early and late 2000s. However, our results do not indicate any rapid or decremental changes in the incidence of subsequent cerebral ischemia after a TIA after 2007.

Moreover, comorbidities such as hypertension, diabetes mellitus, atrial fibrillation, and coronary heart disease substantially contribute to the risk of stroke recurrence<sup>95</sup> and mortality.<sup>96</sup> Awareness and proper management of these comorbidities may lead to a better prognosis for TIA. There is a worldwide downturn of the prevalence of raised blood pressure from 1975 to 2015.<sup>97</sup> This could be due to an increase in the use of antihypertensive medications (63% to 77%), mostly multiple antihypertensive agents (37% to 48%).<sup>98</sup> By 2010,

Figure 2. Forest Plots of Pooled Incidence Rates of Subsequent Ischemic Stroke Incidence After Transient Ischemic Attack (TIA) Within 90 Days



Data are stratified by population recruitment intervals. The boxes illustrate the effect estimates from each single study; the horizontal lines through the boxes, length of the 95% CI; and the diamonds, the overall estimates. NA indicates not available; RE, random effects; OCSF, Oxfordshire Community Stroke Project; OXVASC-Ph1, Oxford Vascular Study Phase 1; OXVASC-Ph2, Oxford Vascular Study Phase 2; QugSS2, Quality of Treatment of Stroke in Schleswig-Holstein "Qualitätsgemeinschaft Schlaganfallversorgung in Schleswig-Holstein"; WASID, Warfarin-Aspirin Symptomatic Intracranial Disease Study.

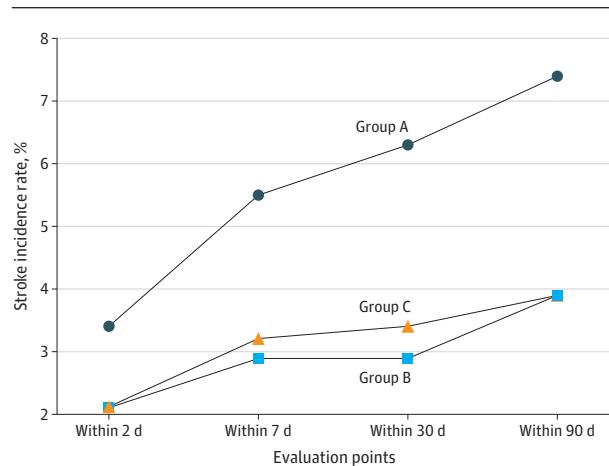
Table. Associated Comorbidities in Patients With Transient Ischemic Attack in Systematic Review and Meta-analysis

Index item	Systematic review (n = 223 866)			Meta-analysis (n = 206 455)		
	No. (%) of patients <sup>a</sup>	Mean (SD), %	Median (IQR), %	No. (%) of patients <sup>a</sup>	Mean (SD), %	Median (IQR), %
Age, y	80.8	68 (5)	69 (67-72)	73.2	69 (4)	69 (68-72)
Men	100 226 (44.97)	55 (21)	52 (47-60)	91 214 (44.39)	55.2 (9)	52 (48-60)
Hypertension	126 063 (56.70)	61 (16)	64 (54-71)	114 467 (55.54)	61 (16)	64 (56-70)
Diabetes mellitus	48 305 (21.83)	21 (11)	19 (15-25)	44 667 (21.78)	21 (11)	19 (14-26)
Coronary artery disease	22 468 (11.80)	18 (10)	16 (12-24)	22 213 (11.76)	19 (13)	16 (12-24)
Dyslipidemia	13 312 (17.97)	40 (18)	39 (31-51)	12 539 (17.30)	40 (18)	39 (32-53)
Atrial fibrillation	32 146 (15.06)	14 (6)	14 (10-17)	28 110 (14.21)	14 (6)	14 (10-17)
Carotid artery stenosis	2860 (5.33)	22 (16)	18 (14-28)	2773 (5.19)	21 (13)	17 (14-24)
Large artery disease	1151 (18.68)	21 (23)	15 (11-23)	1113 (18.56)	23 (24)	15 (13-23)
Smoking	20 064 (9.57)	23 (12)	21 (15-29)	18 383 (9.47)	23 (12)	21 (15-26)
Stroke	22 773 (11.99)	20 (12)	17 (10-24)	19 126 (13.01)	20.6 (12)	19 (11-26)

Abbreviation: IQR, interquartile range.

<sup>a</sup> Data presented as number and percentage unless otherwise indicated. Percentages are estimated.

Figure 3. Trend of Subsequent Ischemic Stroke Incidence After Transient Ischemic Attack



Data were stratified by recruitment intervals before 1999 (group A), from 1999 to 2007 (group B), and after 2007 (group C).

almost 47% of all patients with hypertension and 60% of those receiving treatment had controlled blood pressure.<sup>98</sup> The same trend can be observed for the use of statins through 1996 to 2015 (62-fold increase)<sup>99</sup> and oral medications for diabetes from 2006 to 2013.<sup>100</sup>

Some other factors may also contribute to the decreasing trend in subsequent ischemic stroke incidence throughout the decades. Transient ischemic attack was primarily defined as “a sudden, focal neurological deficit lasting less than 24 hours.”<sup>101(p1713)</sup> After the introduction of magnetic resonance imaging in clinical medicine in 1988<sup>102</sup> and the diffusion-weighted imaging modality later, magnetic resonance imaging became a reliable modality compared with computed tomographic scanning for evaluation of acute cerebral ischemic diseases.<sup>103</sup> The wide implementation of magnetic resonance imaging—from 28% in 1999 to 57% in 2005<sup>104,105</sup>—resulted in rapid changes in diagnosis and management protocols. The introduction of magnetic resonance imaging disclosed infar-

tion in as many as 50% of the proposed TIAs with this definition.<sup>16</sup> Later, TIA was defined as “a brief episode of neurological dysfunction caused by the focal cerebral, spinal cord, or retinal ischemia in the absence of acute infarction.”<sup>16(p2281)</sup> The decreased incidence of TIA and its subsequent cerebral ischemia might be due to this more stringent definition and excluding patients with minor stroke.

We did not observe a further decrease in the post-TIA risk of stroke after 2007. Although this observation is interesting, it is not unexpected. The age-standardized stroke mortality rates have declined worldwide during the last decades, although the number of new strokes is increasing every year.<sup>106</sup> Although there has been significant improvement in vascular risk factor control,<sup>107</sup> the aging population and diabetes prevalence<sup>108</sup> are increasing worldwide. A review of European studies<sup>109</sup> further discusses the problem of the increasing prevalence of stroke as the elderly population grows larger and stroke incidence stays stable. Nevertheless, defining the reasons behind this observation is beyond the scope of this systematic review.

To our knowledge, 4 systematic reviews and meta-analyses similar to the current study have been published<sup>9-12</sup> (eTable 5 in the Supplement). Wu et al<sup>9</sup> and Giles and Rothwell<sup>10</sup> reviewed the studies published before 2006 and 2007, respectively. Valls et al<sup>11</sup> and Najib et al<sup>12</sup> limited their literature review to 2007 to 2014 and 2008 to 2015, respectively. To provide a better comparison of our results with previous meta-analyses under the same condition, we split the included cohorts between those with population recruitment through 2007 (groups A and B) and after 2007 (group C) (eTable 5 and eFigure 5A in the Supplement). The stroke recurrence rates through 2007 in our study are relatively lower than those of the other 2 studies before 2007<sup>9,10</sup> (eTable 5 in the Supplement). When considering the studies with population ascertainment after 2007, our results appeared to be similar but slightly higher than those of Valls et al<sup>11</sup> (eTable 5 in the Supplement). The results of Najib et al,<sup>12</sup> when compared with our results, varied from lower rates at day 2 to almost the same at day 7 and higher at days 30 and 90. We believe that the dif-

ferences among the above results might be partially due to different inclusion and exclusion criteria and the methods for dealing with modifiers and meta-analysis. For instance, instead of a traditional meta-analysis of the actual reported incidence rates, Najib et al<sup>12</sup> used modeling and simulation to predict the cumulative rates. Valls et al<sup>11</sup> focused on patients with TIA who received urgent care (immediate or same-day), and it is logical that they report lower recurrence rates than more comprehensive reviews. Of notice, overall proportions provided by Giles and Rothwell<sup>10</sup> and Wu et al<sup>9</sup> are reported with significant heterogeneity.

Wide methodological and clinical diversity, management protocols, and settings of outcome measure were recognized as the source of the heterogeneity.<sup>9,10</sup> To overcome this issue, Giles and Rothwell<sup>10</sup> stratified the included cohorts, but no more than 3 studies were analyzed in each subgroup. In addition, their subgroup analysis yielded a wide range of recurrence rates of 1.6% to 6.7% within 2 days and 3% to 10.4% within 7 days. In our study, besides the time of recruitment (which reflects the protocol of care), prospective or retrospective study design was taken into consideration (eFigure 4 in the Supplement). By this subgrouping, the heterogeneity in all strata of retrospective or prospective studies could be reduced, but there was a significant heterogeneity when calculating the cumulative rates under each evaluation time interval (2, 7, 30, and 90 days).

## Limitations

The present review is unique for considering a wide range of studies to depict a big picture of early trends of TIA outcomes during the past 5 decades. The included studies vary significantly in terms of methods and demographic characteristics, but we reduced the heterogeneity by applying a restricted protocol. However, some fundamental differences between the studies, such as the definition of the TIA or whether the study was limited to first-ever TIA or included the patients with a history of TIA or stroke, should be considered when interpreting the results. Although the present study focused on the outcome of patients with TIA, further studies considering patients with minor stroke may be warranted, because the early assessment of these 2 entities is similar. Despite the comprehensive review of literature, the current review may not reflect a global trend, because the incidences of TIA and subsequent ischemic stroke reviewed in this study are mostly from industrialized countries, and the incidences are not available in many developing countries.

## Conclusions

This systematic review and meta-analysis found that transient ischemic attack continues to be associated with a high risk of early stroke. However, the rate of post-TIA stroke might have decreased slightly during the past 2 decades.

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