JAMA Neurology | Original Investigation

A 5-Decade Analysis of Incidence Trends of Ischemic Stroke After Transient Ischemic Attack
A Systematic Review and Meta-analysis

Shima Shahjouei, MD, MPH; Alireza Sadighi, MD; Durgesh Chaudhary, MD; Jiang Li, MD, PhD; Vida Abedi, PhD; Neil Holland, MD; Michael Phipps, MD, MHS; Ramin Zand, MD, MPH

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 τ^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.

JAMA Neurol. doi:10.1001/jamaneurol.2020.3627
Published online October 12, 2020.

Supplemental content

Author Affiliations: Department of Neurology, Geisinger Neuroscience Institute, Geisinger Health System, Danville, Pennsylvania (Shahjouei, Sadighi, Chaudhary, Holland, Zand); Department of Molecular and Functional Genomics, Geisinger Health System, Danville, Pennsylvania (Li, Abedi); Biocomplexity Institute, Virginia Tech, Blacksburg, Virginia (Abedi); Department of Neurology, University of Maryland, Baltimore (Phipps).

Corresponding Author: Ramin Zand, MD, MPH, Department of Neurology, Geisinger Neuroscience Institute, Geisinger Health System, 100 N Academy Ave, Danville, PA 17822 (rzand@geisinger.edu).

Management of transient ischemic attack (TIA) has gained significant attention during the past 25 years after several landmark studies[1-5] indicating a high rate of subsequent stroke. Although the 1994 American Heart Association guideline[6] for the management of TIA recommended a timely evaluation of patients with TIA, the 1999 supplement to the guideline[7] has emphasized different medical and surgical treatment for patients with TIAs. Furthermore, the findings from a Kaiser-Permanente Northern California study[5] and the Oxford Vascular Study group[3,8] 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.[9-12] Each study has a different cohort, recruitment interval, inclusion criteria, and outcome definition. Two reviews[9,10] have summarized studies before 2007, and 2 other reviews have limited their scope to population recruited after 2007.[11,12] In addition, Najib et al[12] used modeling and simulation to predict the cumulative rates rather than conducting the traditional meta-analysis. Valls et al[11] focused on patients with TIA receiving immediate or same-day urgent care, and Giles and Rothwell[10] and Wu et al[9] 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.

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.

Methods

Search Strategy

The study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA),[13] Meta-analysis of Observational Studies in Epidemiology (MOOSE),[14] and Enhancing the Quality and Transparency of Health Research (EQUATOR) reporting guidelines.[15] 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 intervals (2, 7, 30, and/or 90 days). We accepted both the classic definition of TIA[1] 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.[16] 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, $ABCD_2$ (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[7] and landmark studies regarding the importance of urgent TIA management and TIA clinic concept from 2005 to 2007,[3,8,17] 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 τ^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.[18] 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 (χ^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 (τ^2 statistic).[19] 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 α 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),[20] 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[3,4,21-24] and Oxford Vascular Study[1,3,24-27] were retrieved. Johnston et al[25] included these cohorts and also the cohort from Kaiser-Permanente Northern California.[5] 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,[28] Felgueiras et al,[29] Johnston et al,[25] and Rothwell et al[8]—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[30] 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[25,28-94] 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 τ^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%)[31] 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[32-36] 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[37-41] and the cohort of patients recruited from 1998 to 2000 in the study by Felgueiras et al.[29] To summarize, 66 cohorts from 58 articles[25,28-31,38,40,42-77,79-92] 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[29,30,40,42-52,85] were evaluated retrospectively and 43 studies[25,28,31,38,53-84,86-92] were collected prospectively. Only 13 studies[31,46,49-51,53-60] considered imaging results necessary for TIA diagnosis. Among the 31 studies with populations recruited after 2007, 8 (25.8%)[29,39,45,46,57,69,74,89] 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

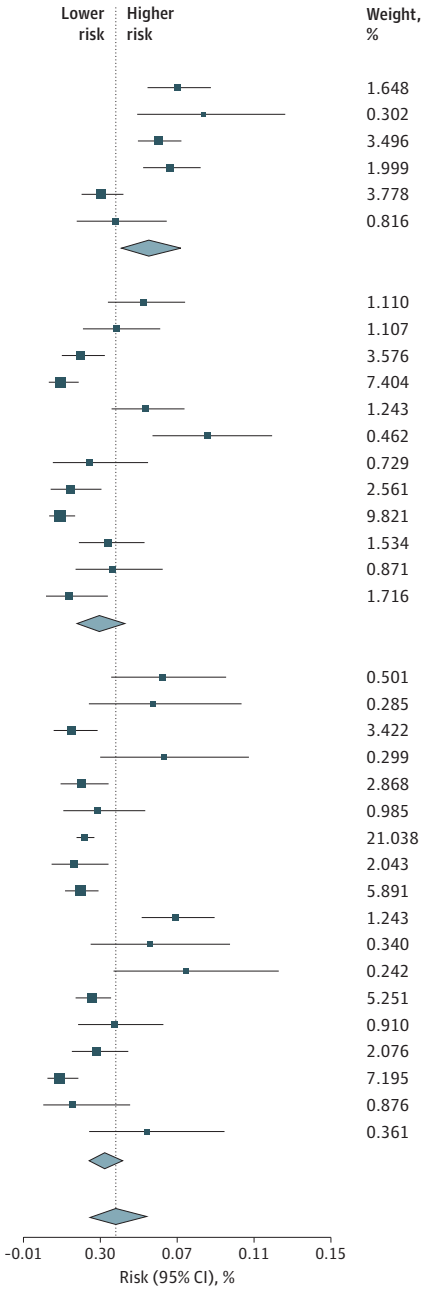
Our study demonstrated that after the index TIA, ischemic stroke had a mean incidence during the span of 1971 to 2019 equal to 2.4% (95% CI, 1.8%-3.2%) within 2 days, 3.8% (95% CI, 2.5%-5.4%) within 7 days, 4.1% (95% CI, 2.4%-6.3%) within 30 days, and 4.7% (95% CI, 3.3%-6.4%) within 90 days (Figures 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[6] 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.[7] 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

Source	Recruitment	No. with stroke/ No. with TIA	Risk (95% CI), %	Weight, %
Group A before 1999				
Kleindorfer et al,[40] 2005	1993-1994	65/927	0.070 (0.055-0.087)	1.648
Johnston et al,[25] 2007	1981-1986	17/203	0.084 (0.049-0.126)	0.302
Johnston et al,[25] 2007	1997-1998	103/1707	0.060 (0.050-0.072)	3.496
Johnston et al,[25] 2007	1998-1999	71/1069	0.066 (0.052-0.082)	1.999
Johnston et al,[25] 2007	1998-1999	29/962	0.030 (0.020-0.042)	3.778
Gladstone et al,[61] 2004	2000	10/265	0.038 (0.018-0.065)	0.816
RE model for group, $Q=0.01$; $P=.81$; $I^2=0.0\%$			0.055 (0.041-0.072)	
Group B 1999-2007				
Ay et al,[50] 2009	2000-2006	25/479	0.052 (0.034-0.074)	1.110
Nguyen et al,[43] 2010	2006-2008	14/363	0.039 (0.021-0.061)	1.107
Lisabeth et al,[62] 2004	2000-2002	12/612	0.020 (0.010-0.032)	3.576
Stead et al,[63] 2011	2001-2006	6/637	0.009 (0.003-0.019)	7.404
Johnston et al,[25] 2007	2002-2005	29/545	0.053 (0.036-0.074)	1.243
Johnston et al,[25] 2007	2002-2005	27/315	0.086 (0.057-0.119)	0.462
Cucchiara et al,[64] 2009	2002-2007	4/164	0.024 (0.005-0.055)	0.729
Calvet et al,[53] 2009	2003-2007	5/343	0.015 (0.004-0.031)	2.561
Ghia et al,[65] 2011	2004-2006	7/789	0.009 (0.003-0.017)	9.821
Sheehan et al,[66] 2010	2005-2008	15/443	0.034 (0.019-0.053)	1.534
Sciolla et al,[67] 2008	2006	10/274	0.036 (0.017-0.062)	0.871
Ovbiagele et al,[58] 2008	NA	3/222	0.014 (0.002-0.034)	1.716
RE model for group, $Q=0.00$; $P=.95$; $I^2=0.0\%$			0.029 (0.018-0.043)	
Group C after 2007				
Arsava et al,[85] 2011	2003-2009	16/257	0.062 (0.036-0.095)	0.501
Gon et al,[46] 2015	2006-2013	8/139	0.058 (0.024-0.103)	0.285
Fujinami et al,[45] 2014	2008-2009	7/464	0.015 (0.006-0.029)	3.422
Felgueiras et al,[29] 2020	2009-2011	10/158	0.063 (0.030-0.107)	0.299
Bonifati et al,[44] 2011	NA	10/502	0.020 (0.009-0.034)	2.868
Purroy et al,[89] 2011	2006-2009	7/247	0.028 (0.011-0.053)	0.985
Perry et al,[68] 2014	2006-2011	86/3906	0.022 (0.018-0.027)	21.038
von Weitzel–Mudersbach et al,[69] 2011	2007-2008	5/306	0.016 (0.005-0.034)	2.043
Wasserman et al,[70] 2010	2007-2009	19/982	0.019 (0.012-0.029)	5.891
Kiyohara et al,[71] 2014	2007-2012	48/693	0.069 (0.051-0.089)	1.243
Cancelli et al,[72] 2011	2007-2009	9/161	0.056 (0.025-0.097)	0.340
Tsivgoulis et al,[73] 2010	2008-2009	11/148	0.074 (0.037-0.123)	0.242
Purroy et al,[74] 2014	2008-2009	29/1137	0.026 (0.017-0.036)	5.251
Jové et al,[75] 2015	2008-2012	11/293	0.038 (0.018-0.063)	0.910
Lim et al,[57] 2015	2010-2012	14/500	0.028 (0.015-0.045)	2.076
Ildstad et al,[76] 2019	2012-2014	5/577	0.009 (0.002-0.018)	7.195
Sadighi et al,[59] 2019	2016-2018	2/131	0.015 (0.000-0.045)	0.876
Delgado et al,[38] 2012	NA	15/166	0.054 (0.024-0.095)	0.361
RE model for group, $Q=0.83$; $P=.36$; $I^2=0.0\%$			0.032 (0.024-0.042)	
Overall estimate				
RE model for total, $Q=0.83$; $P=.36$; $I^2=0.0\%$			0.038 (0.025-0.054)	



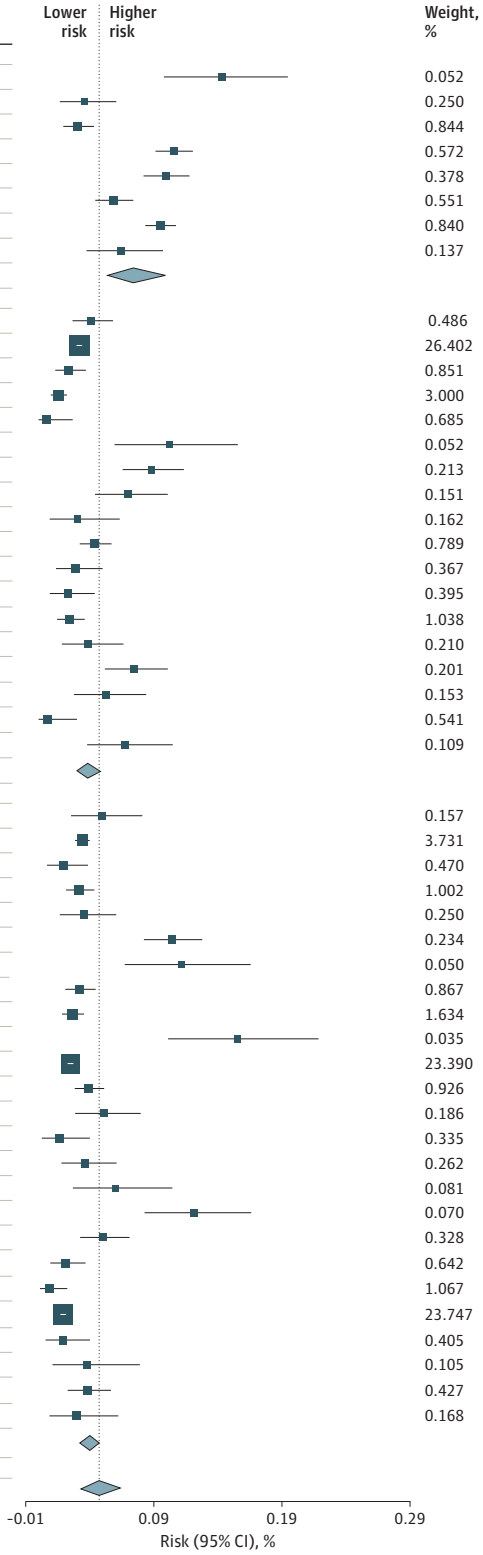
Data are stratified by population recruitment intervals. The boxes illustrate the effect estimates from each single study; the horizontal lines through the boxes, length of the 95% CI; and the diamonds, the overall estimates. NA indicates not available; RE, random effects.

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[5] and the Oxford Vascular Study group[3,8] 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[95] and mortality.[96] 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.[97] This could be due to an increase in the use of antihypertensive medications (63% to 77%), mostly multiple antihypertensive agents (37% to 48%).[98] By 2010,

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

Source	Recruitment	No. with stroke/ No. with TIA	Risk (95% CI), %	Weight, %
Group A before 1999				
Johnston (OCSP) et al,[25] 2007	1981-1986	29/203	0.143 (0.098-0.195)	0.052
Bos et al,[77] 2007	1990-1993	10/282	0.035 (0.017-0.061)	0.250
Harrison et al,[47] 2010	1992-2004	24/795	0.030 (0.019-0.043)	0.844
Johnston et al,[25] 2007	1997-1998	180/1707	0.105 (0.091-0.120)	0.572
Johnston et al,[25] 2007	1998-1999	106/1069	0.099 (0.082-0.118)	0.378
Johnston et al,[25] 2007	1998-1999	56/962	0.058 (0.044-0.074)	0.551
Hill et al,[52] 2004	1999-2000	217/2285	0.095 (0.083-0.107)	0.840
Gladstone et al,[61] 2004	2000	17/265	0.064 (0.037-0.097)	0.137
RE model for group, $Q = 0.01$; $P = .93$; $I^2 = 0.0\%$			0.074 (0.053-0.099)	
Group B 1999-2007				
Lisabeth et al,[62] 2004	2000-2002	25/612	0.041 (0.026-0.058)	0.486
Sundararajan et al,[30] 2014	2001-2007	817/25 689	0.032 (0.030-0.034)	26.402
Stead et al,[63] 2011	2001-2006	15/637	0.024 (0.013-0.037)	0.851
Weimar et al,[78] 2009	2002-2006	22/1448	0.015 (0.009-0.022)	3.000
Rothwell (OXVASC−Ph2) et al,[8] 2007	2002-2005	1/160	0.006 (0.000-0.027)	0.685
Rothwell (OXVASC−Ph1) et al,[8] 2007	2002-2005	16/156	0.103 (0.059-0.156)	0.052
Johnston (OXVASC) et al,[25] 2007	2002-2005	48/545	0.088 (0.066-0.113)	0.213
Johnston et al,[25] 2007	2002-2005	22/315	0.070 (0.044-0.101)	0.151
Cucchiara et al,[64] 2009	2002-2007	5/164	0.030 (0.009-0.063)	0.162
Lavallée (SOS−TIA) et al,[55] 2017	2003-2008	46/1052	0.044 (0.032-0.057)	0.789
Calvet et al,[53] 2009	2003-2007	10/343	0.029 (0.014-0.050)	0.367
Sanders et al,[79] 2012	2004-2007	7/301	0.023 (0.009-0.044)	0.395
Ghia et al,[65] 2011	2004-2006	19/789	0.024 (0.014-0.036)	1.038
Correia et al,[54] 2015	2004-2009	10/258	0.039 (0.018-0.066)	0.210
Sheehan et al,[66] 2010	2004-2008	33/443	0.074 (0.052-0.101)	0.201
Engelter et al,[80] 2012	2006-2008	13/248	0.052 (0.028-0.084)	0.153
Nahab et al,[42] 2012	2008-2009	1/142	0.007 (0.000-0.030)	0.541
Ovbiagele (WASID) et al,[58] 2008	NA	15/222	0.068 (0.038-0.105)	0.109
RE model for group, $Q = 0.00$; $P = .95$; $I^2 = 0.0\%$			0.039 (0.030-0.048)	
Group C after 2007				
Purroy et al,[89] 2011	2006-2009	12/242	0.050 (0.025-0.081)	0.157
Perry et al,[74] 2014	2006-2011	132/3883	0.034 (0.029-0.040)	3.731
von Weitzel−Mudersbach et al,[69] 2011	2007-2008	6/306	0.020 (0.007-0.039)	0.470
Wasserman et al,[70] 2010	2007-2009	31/982	0.032 (0.021-0.043)	1.002
Palomeras Soler et al,[31] 2015	2007-2012	10/282	0.035 (0.017-0.061)	0.250
Kiyohara et al,[71] 2014	2007-2012	72/693	0.104 (0.082-0.128)	0.234
Cancelli et al,[72] 2011	2007-2009	18/161	0.112 (0.067-0.166)	0.050
Al-Khaled (QugSS2) et al,[28] 2013	2007-2010	27/853	0.032 (0.021-0.045)	0.867
Al-Khaled (QugSS2) et al,[28] 2013	2007-2010	35/1335	0.026 (0.018-0.036)	1.634
Tsivgoulis et al,[73] 2010	2008-2009	23/148	0.155 (0.101-0.219)	0.035
Sundararajan et al,[30] 2014	2008-2011	446/17 933	0.025 (0.023-0.027)	23.390
Purroy et al,[74] 2014	2008-2009	43/1105	0.039 (0.028-0.051)	0.926
Jové et al,[75] 2014	2008-2012	15/293	0.051 (0.029-0.080)	0.186
Griffiths et al,[81] 2014	2008-2010	3/188	0.016 (0.002-0.040)	0.335
De Marchis et al,[82] 2014	2009-2011	11/302	0.036 (0.018-0.061)	0.262
Arhami Dolatabadi et al,[51] 2013	2010-2011	9/150	0.060 (0.027-0.104)	0.081
Song et al,[60] 2013	2010-2011	29/239	0.121 (0.083-0.166)	0.070
Lim et al,[57] 2015	2010-2012	25/500	0.050 (0.032-0.071)	0.328
Guarino et al,[83] 2015	2010-2013	9/433	0.021 (0.009-0.037)	0.642
Dutta et al,[56] 2015	2010-2012	3/337	0.009 (0.001-0.022)	1.067
Appelros et al,[37] 2017	2011-2012	272/14 157	0.019 (0.017-0.022)	23.747
Vigen et al,[49] 2018	2013	5/261	0.019 (0.005-0.040)	0.405
Sadighi et al,[59] 2019	2016-2018	5/131	0.038 (0.011-0.079)	0.105
Bonifati et al,[44] 2011	NA	19/502	0.038 (0.023-0.057)	0.427
Raser et al,[84] 2012	NA	5/167	0.030 (0.008-0.062)	0.168
RE model for group, $Q = 3.47$; $P = .18$; $I^2 = 42.3\%$			0.039 (0.032-0.047)	
Overall estimate				
RE model for total, $Q = 3.59$; $P = .31$; $I^2 = 16.5\%$			0.047 (0.033-0.064)	



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; OCSP, 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 Schlaganfallver- sorgung in Schleswig-Holstein"; WASID, Warfarin-Aspirin Symptomatic Intracranial Disease Study.

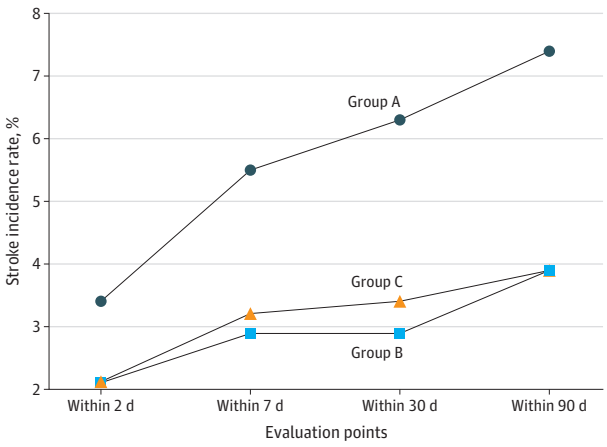
Table. Associated Comorbidities in Patients With Transient Ischemic Attack in Systematic Review and Meta-analysis

	Systematic review (n = 223 866)			Meta-analysis (n = 206 455)		
Index item	No. (%) of patients[a]	Mean (SD), %	Median (IQR), %	No. (%) of patients[a]	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.

[a] 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.[98] The same trend can be observed for the use of statins through 1996 to 2015 (62-fold increase)[99] and oral medications for diabetes from 2006 to 2013.[100]

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."[101(p1713)] After the introduction of magnetic resonance imaging in clinical medicine in 1988[102] 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.[103] The wide implementation of magnetic resonance imaging—from 28% in 1999 to 57% in 2005[104,105]—resulted in rapid changes in diagnosis and management protocols. The introduction of magnetic resonance imaging disclosed infarction in as many as 50% of the proposed TIAs with this definition.[16] 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."[16(p2281)] 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.[106] Although there has been significant improvement in vascular risk factor control,[107] the aging population and diabetes prevalence[108] are increasing worldwide. A review of European studies[109] 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[9-12] (eTable 5 in the Supplement). Wu et al[9] and Giles and Rothwell[10] reviewed the studies published before 2006 and 2007, respectively. Valls et al[11] and Najib et al[12] 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[9,10] (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[11] (eTable 5 in the Supplement). The results of Najib et al,[12] 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[12] used modeling and simulation to predict the cumulative rates. Valls et al[11] 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[10] and Wu et al[9] 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.[9,10] To overcome this issue, Giles and Rothwell[10] 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.

ARTICLE INFORMATION

Accepted for Publication: July 26, 2020.

Published Online: October 12, 2020. doi:10.1001/jamaneurol.2020.3627

Author Contributions: Dr Zand had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Shahjouei, Sadighi, Abedi, Holland, Zand.
Acquisition, analysis, or interpretation of data: Shahjouei, Sadighi, Chaudhary, Li, Abedi, Phipps, Zand.
Drafting of the manuscript: Shahjouei, Sadighi, Abedi, Zand.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Shahjouei, Sadighi, Chaudhary, Li, Abedi, Zand.
Obtained funding: Zand.
Administrative, technical, or material support: Shahjouei, Sadighi, Abedi, Zand.
Supervision: Shahjouei, Sadighi, Abedi, Holland, Zand.

Conflict of Interest Disclosures: Dr Zand reported receiving grants from Genentech, Geisinger Health Plan, and Bucknell University outside the submitted work. No other disclosures were reported.

Funding/Support: This study was supported in part by the Geisinger Health Plan Quality (Dr Zand) and grant R56HL116832 from National Institutes of Health (Dr Abedi and Sutter Health).

Role of the Funder/Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Coull AJ, Lovett JK, Rothwell PM; Oxford Vascular Study. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. *BMJ*. 2004;328(7435):326-328. doi:10.1136/bmj.37991.635266.44

2. Amarenco P, Lavallée PC, Labreuche J, et al; TIAregistry.org Investigators. One-year risk of stroke after transient ischemic attack or minor stroke. *N Engl J Med*. 2016;374(16):1533-1542. doi:10.1056/NEJMoa1412981

3. Rothwell PM, Giles MF, Flossmann E, et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet*. 2005;366(9479):29-36. doi:10.1016/S0140-6736(05)66702-5

4. Dennis M, Bamford J, Sandercock P, Warlow C. Prognosis of transient ischemic attacks in the Oxfordshire Community Stroke Project. *Stroke*. 1990;21(6):848-853. doi:10.1161/01.STR.21.6.848

5. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA*. 2000;284(22):2901-2906. doi:10.1001/jama.284.22.2901

6. Feinberg WM, Albers GW, Barnett HJ, et al; From the Ad Hoc Committee on Guidelines for the Management of Transient Ischemic Attacks of the Stroke Council of the American Heart Association. Guidelines for the management of transient ischemic attacks. *Circulation*. 1994;89(6):2950-2965. doi:10.1161/01.CIR.89.6.2950

7. Albers GW, Hart RG, Lutsep HL, Newell DW, Sacco RL. AHA Scientific Statement: supplement to the guidelines for the management of transient ischemic attacks: a statement from the Ad Hoc Committee on Guidelines for the Management of Transient Ischemic Attacks, Stroke Council, American Heart Association. *Stroke*. 1999;30(11):2502-2511. doi:10.1161/01.STR.30.11.2502

8. Rothwell PM, Giles MF, Chandratheva A, et al; Early use of Existing Preventive Strategies for Stroke (EXPRESS) study. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet*. 2007;370(9596):1432-1442. doi:10.1016/S0140-6736(07)61448-2

9. Wu CM, McLaughlin K, Lorenzetti DL, Hill MD, Manns BJ, Ghali WA. Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis. *Arch Intern Med*. 2007;167(22):2417-2422. doi:10.1001/archinte.167.22.2417

10. Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol*. 2007;6(12):1063-1072. doi:10.1016/S1474-4422(07)70274-0

11. Valls J, Peiro-Chamarro M, Cambray S, Molina-Seguin J, Benabdelhak I, Purroy F. A current estimation of the early risk of stroke after transient ischemic attack: a systematic review and meta-analysis. *Cerebrovasc Dis*. 2017;43(1-2):90-98. doi:10.1159/000452978

12. Najib N, Magin P, Lasserson D, et al. Contemporary prognosis of transient ischemic attack patients: a systematic review and meta-analysis. *Int J Stroke*. 2019;14(5):460-467. doi:10.1177/1747493018823568

13. Moher D, Shamseer L, Clarke M, et al; PRISMA-P Group. Preferred Reporting Items for Systematic Review and Meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1. doi:10.1186/2046-4053-4-1

14. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA*. 2000;283(15):2008-2012. doi:10.1001/jama.283.15.2008

15. Equator Network. Enhancing the quality and transparency of health research. University of Oxford. Published 2019. Accessed January 31, 2020. https://www.equator-network.org

16. Easton JD, Saver JL, Albers GW, et al; American Heart Association; American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Interdisciplinary Council on Peripheral Vascular Disease. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. *Stroke*. 2009;40(6):2276-2293. doi:10.1161/STROKEAHA.108.192218

17. Lavallée PC, Meseguer E, Abboud H, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. *Lancet Neurol*. 2007;6(11):953-960. doi:10.1016/S1474-4422(07)70248-X

18. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med*. 2013;158(4):280-286. doi:10.7326/0003-4819-158-4-201302190-00009

19. Wang N. How to conduct a meta-analysis of proportions in R: a comprehensive tutorial conducting meta-analyses of proportions in R. *John Jay Coll Crim Justice*. 2018;1(June):1-62. doi:10.13140/RG.2.2.27199.00161

20. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw*. 2010;36(3):1-48. doi:10.18637/jss.v036.i03

21. Dennis MS, Bamford JM, Sandercock PAG, Warlow CP. Incidence of transient ischemic attacks in Oxfordshire, England. *Stroke*. 1989;20(3):333-339. doi:10.1161/01.STR.20.3.333

22. Lovett JK, Dennis MS, Sandercock PAG, Bamford J, Warlow CP, Rothwell PM. Very early risk of stroke after a first transient ischemic attack. *Stroke*. 2003;34(8):e138-e140. doi:10.1161/01.STR.0000080935.01264.91

23. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Long-term risk of recurrent stroke after a first-ever stroke: the Oxfordshire Community Stroke Project. *Stroke*. 1994;25(2):333-337. doi:10.1161/01.STR.25.2.333

24. Rothwell PM, Warlow CP. Timing of TIAs preceding stroke: time window for prevention is very short. *Neurology*. 2005;64(5):817-820. doi:10.1212/01.WNL.0000152985.32732.EE

25. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet*. 2007;369(9558):283-292. doi:10.1016/S0140-6736(07)60150-0

26. Gulli G, Marquardt L, Rothwell PM, Markus HS. Stroke risk after posterior circulation stroke/transient ischemic attack and its relationship to site of vertebrobasilar stenosis: pooled data analysis from prospective studies. *Stroke*. 2013;44(3):598-604. doi:10.1161/STROKEAHA.112.669929

27. Chandratheva A, Geraghty OC, Luengo-Fernandez R, Rothwell PM; Oxford Vascular Study. ABCD2 score predicts severity rather than risk of early recurrent events after transient ischemic attack. *Stroke*. 2010;41(5):851-856. doi:10.1161/STROKEAHA.109.570010

28. Al-Khaled M, Matthis C, Eggers J. The prognostic impact of the stroke unit care versus conventional care in treatment of patients with transient ischemic attack: a prospective population-based German study. *J Vasc Interv Neurol*. 2013;5(2):22-26.

29. Felgueiras R, Magalhães R, Silva MR, Silva MC, Correia M. Transient ischemic attack: incidence and early risk of stroke in northern Portugal from 1998-2000 to 2009-2011. *Int J Stroke*. 2020;15(3):278-288. doi:10.1177/1747493019830322

30. Sundararajan V, Thrift AG, Phan TG, Choi PM, Clissold B, Srikanth VK. Trends over time in the risk of stroke after an incident transient ischemic attack. *Stroke*. 2014;45(11):3214-3218. doi:10.1161/STROKEAHA.114.006575

31. Palomeras Soler E, Fossas Felip P, Cano Orgaz AT, Sanz Cartagena P, Casado Ruiz V, Muriana Batista D. Rapid assessment of transient ischaemic attack in a hospital with no on-call neurologist. *Neurologia*. 2015;30(6):325-330. doi:10.1016/j.nrl.2013.12.021

32. Mendelowitz DS, Kimmins S, Evans WE. Prognosis of patients with transient ischemic attacks and normal angiograms. *Arch Surg*. 1981;116(12):1587-1591. doi:10.1001/archsurg.1981.01380240067010

33. Coutts SB, Hill MD, Campos CR, et al; VISION study group. Recurrent events in transient ischemic attack and minor stroke: what events are happening and to which patients? *Stroke*. 2008;39(9):2461-2466. doi:10.1161/STROKEAHA.107.513234

34. Ricci S, Celani MG, La Rosa F, et al. A community-based study of incidence, risk factors and outcome of transient ischaemic attacks in Umbria, Italy: the SEPIVAC study. *J Neurol*. 1991;238(2):87-90. doi:10.1007/BF00315687

35. Ferro JM, Crespo M. Prognosis after transient ischemic attack and ischemic stroke in young adults. *Stroke*. 1994;25(8):1611-1616. doi:10.1161/01.STR.25.8.1611

36. Geil K, González-Concepción JJ, Jiménez-Velázquez IZ, Medina B, Velazco X. Management and outcome of transient ischemic attacks in Ponce, Puerto Rico. *Bol Asoc Med P R*. 2008;100(3):11-14.

37. Appelros P, Håls Berglund M, Ström JO. Long-term risk of stroke after transient ischemic attack. *Cerebrovasc Dis*. 2017;43(1-2):25-30. doi:10.1159/000451061

38. Delgado P, Chacón P, Penalba A, et al. Lipoprotein-associated phospholipase A_2 activity is associated with large-artery atherosclerotic etiology and recurrent stroke in TIA patients. *Cerebrovasc Dis*. 2012;33(2):150-158. doi:10.1159/000334193

39. Ohara T, Uehara T, Toyoda K, et al. Early stroke risk after transient ischemic attack in patients without large-artery disease or atrial fibrillation. *J Stroke Cerebrovasc Dis*. 2015;24(7):1656-1661. doi:10.1016/j.jstrokecerebrovasdis.2015.03.039

40. Kleindorfer D, Panagos P, Pancioli A, et al. Incidence and short-term prognosis of transient ischemic attack in a population-based study. *Stroke*. 2005;36(4):720-723. doi:10.1161/01.STR.0000158917.59233.b7

41. Ois A, Gomis M, Rodríguez-Campello A, et al. Factors associated with a high risk of recurrence in patients with transient ischemic attack or minor stroke. *Stroke*. 2008;39(6):1717-1721. doi:10.1161/STROKEAHA.107.505438

42. Nahab F, Leach G, Kingston C, et al. Impact of an emergency department observation unit transient ischemic attack protocol on length of stay and cost. *J Stroke Cerebrovasc Dis*. 2012;21(8):673-678. doi:10.1016/j.jstrokecerebrovasdis.2011.02.017

43. Nguyen H, Kerr D, Kelly AM. Comparison of prognostic performance of scores to predict risk of stroke in ED patients with transient ischaemic attack. *Eur J Emerg Med*. 2010;17(6):346-348. doi:10.1097/MEJ.0b013e328337b1c6

44. Bonifati DM, Lorenzi A, Ermani M, et al. Carotid stenosis as predictor of stroke after transient ischemic attacks. *J Neurol Sci*. 2011;303(1-2):85-89. doi:10.1016/j.jns.2011.01.005

45. Fujinami J, Uehara T, Kimura K, et al. Incidence and predictors of ischemic stroke events during hospitalization in patients with transient ischemic attack. *Cerebrovasc Dis*. 2014;37(5):330-335. doi:10.1159/000360757

46. Gon Y, Sakaguchi M, Okazaki S, Mochizuki H, Kitagawa K. Prevalence of positive diffusion-weighted imaging findings and ischemic stroke recurrence in transient ischemic attack. *J Stroke Cerebrovasc Dis*. 2015;24(5):1000-1007. doi:10.1016/j.jstrokecerebrovasdis.2014.12.023

47. Harrison JK, Sloan B, Dawson J, Lees KR, Morrison DS. The ABCD and ABCD2 as predictors of stroke in transient ischemic attack clinic outpatients: a retrospective cohort study over 14 years. *QJM*. 2010;103(9):679-685. doi:10.1093/qjmed/hcq108

48. Ong MEH, Chan YH, Lin WP, Chung WL. Validating the ABCD(2) score for predicting stroke risk after transient ischemic attack in the ED. *Am J Emerg Med*. 2010;28(1):44-48. doi:10.1016/j.ajem.2008.09.027

49. Vigen T, Thommessen B, Rønning OM. Stroke risk is low after urgently treated transient ischemic attack. *J Stroke Cerebrovasc Dis*. 2018;27(2):291-295. doi:10.1016/j.jstrokecerebrovasdis.2017.08.037

50. Ay H, Arsava EM, Johnston SC, et al. Clinical- and imaging-based prediction of stroke risk after transient ischemic attack: the CIP model. *Stroke*. 2009;40(1):181-186. doi:10.1161/STROKEAHA.108.521476

51. Arhami Dolatabadi A, Meisami A, Hatamabadi H, et al. Improving the prediction of stroke or death after transient ischemic attack (TIA) by adding diffusion-weighted imaging lesions and TIA etiology to the ABCD2 score. *J Stroke Cerebrovasc Dis*. 2013;22(7):e25-e30. doi:10.1016/j.jstrokecerebrovasdis.2012.03.007

52. Hill MD, Yiannakoulias N, Jeerakathil T, Tu JV, Svenson LW, Schopflocher DP. The high risk of stroke immediately after transient ischemic attack: a population-based study. *Neurology*. 2004;62(11):2015-2020. doi:10.1212/01.WNL.0000129482.70315.2F

53. Calvet D, Touzé E, Oppenheim C, Turc G, Meder JF, Mas JL. DWI lesions and TIA etiology improve the prediction of stroke after TIA. *Stroke*. 2009;40(1):187-192. doi:10.1161/STROKEAHA.108.515817

54. Correia M, Fonseca AC, Canhão P. Short-term outcome of patients with possible transient ischemic attacks: a prospective study. *BMC Neurol*. 2015;15(1):78. doi:10.1186/s12883-015-0333-1

55. Lavallée PC, Sissani L, Labreuche J, et al. Clinical significance of isolated atypical transient symptoms in a cohort with transient ischemic attack. *Stroke*. 2017;48(6):1495-1500. doi:10.1161/STROKEAHA.117.016743

56. Dutta D, Bowen E, Foy C. Four-year follow-up of transient ischemic attacks, strokes, and mimics: a retrospective transient ischemic attack clinic cohort study. *Stroke*. 2015;46(5):1227-1232. doi:10.1161/STROKEAHA.114.008632

57. Lim J-S, Hong K-S, Kim G-M, et al. Cerebral microbleeds and early recurrent stroke after transient ischemic attack: results from the Korean Transient Ischemic Attack Expression Registry. *JAMA Neurol*. 2015;72(3):301-308. doi:10.1001/jamaneurol.2014.3958

58. Ovbiagele B, Cruz-Flores S, Lynn MJ, Chimowitz MI; Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study Group. Early stroke risk after transient ischemic attack among individuals with symptomatic intracranial artery stenosis. *Arch Neurol*. 2008;65(6):733-737. doi:10.1001/archneur.65.6.733

59. Sadighi A, Abedi V, Stanciu A, et al. Six-month outcome of transient ischemic attack and its mimics. *Front Neurol*. 2019;10:294. doi:10.3389/fneur.2019.00294

60. Song B, Fang H, Zhao L, et al. Validation of the ABCD3-I score to predict stroke risk after transient ischemic attack. *Stroke*. 2013;44(5):1244-1248. doi:10.1161/STROKEAHA.113.000969

61. Gladstone DJ, Kapral MK, Fang J, Laupacis A, Tu JV. Management and outcomes of transient ischemic attacks in Ontario. *CMAJ*. 2004;170(7):1099-1104. doi:10.1503/cmaj.1031349

62. Lisabeth LD, Ireland JK, Risser JMH, et al. Stroke risk after transient ischemic attack in a population-based setting. *Stroke*. 2004;35(8):1842-1846. doi:10.1161/01.STR.0000134416.89389.9d

63. Stead LG, Suravaram S, Bellolio MF, et al. An assessment of the incremental value of the ABCD2 score in the emergency department evaluation of transient ischemic attack. *Ann Emerg Med*. 2011;57(1):46-51. doi:10.1016/j.annemergmed.2010.07.001

64. Cucchiara BL, Messe SR, Sansing L, et al. Lipoprotein-associated phospholipase A_2 and C-reactive protein for risk-stratification of patients with TIA. *Stroke*. 2009;40(7):2332-2336. doi:10.1161/STROKEAHA.109.553545

65. Ghia D, Thomas P, Cordato D, et al. Low positive predictive value of the ABCD2 score in emergency department transient ischaemic attack diagnoses: the South Western Sydney transient ischaemic attack study. *Intern Med J*. 2012;42(8):913-918. doi:10.1111/j.1445-5994.2011.02564.x

66. Sheehan OC, Kyne L, Kelly LA, et al. Population-based study of ABCD2 score, carotid stenosis, and atrial fibrillation for early stroke prediction after transient ischemic attack: the North Dublin TIA study. *Stroke*. 2010;41(5):844-850. doi:10.1161/STROKEAHA.109.571844

67. Sciolla R, Melis F; SINPAC Group. Rapid identification of high-risk transient ischemic attacks: prospective validation of the ABCD score. *Stroke*. 2008;39(2):297-302. doi:10.1161/STROKEAHA.107.496612

68. Perry JJ, Sharma M, Sivilotti MLA, et al. A prospective cohort study of patients with transient ischemic attack to identify high-risk clinical characteristics. *Stroke*. 2014;45(1):92-100. doi:10.1161/STROKEAHA.113.003085

69. von Weitzel-Mudersbach P, Johnsen SP, Andersen G. Low risk of vascular events following urgent treatment of transient ischaemic attack: the Aarhus TIA study. *Eur J Neurol*. 2011;18(11):1285-1290. doi:10.1111/j.1468-1331.2011.03452.x

70. Wasserman J, Perry J, Dowlatshahi D, et al. Stratified, urgent care for transient ischemic attack results in low stroke rates. *Stroke*. 2010;41(11):2601-2605. doi:10.1161/STROKEAHA.110.586842

71. Kiyohara T, Kamouchi M, Kumai Y, et al; Fukuoka Stroke Registry Investigators. ABCD3 and ABCD3-I scores are superior to ABCD2 score in the prediction of short- and long-term risks of stroke after transient ischemic attack. *Stroke*. 2014;45(2):418-425. doi:10.1161/STROKEAHA.113.003077

72. Cancelli I, Janes F, Gigli GL, et al. Incidence of transient ischemic attack and early stroke risk: validation of the ABCD2 score in an Italian population-based study. *Stroke*. 2011;42(10):2751-2757. doi:10.1161/STROKEAHA.110.612705

73. Tsivgoulis G, Stamboulis E, Sharma VK, et al. Multicenter external validation of the ABCD2 score in triaging TIA patients. *Neurology*. 2010;74(17):1351-1357. doi:10.1212/WNL.0b013e3181dad63e

74. Purroy F, Jiménez Caballero PE, Gorospe A, et al. How predictors and patterns of stroke recurrence after a TIA differ during the first year of follow-up. *J Neurol*. 2014;261(8):1614-1621. doi:10.1007/s00415-014-7390-z

75. Jové M, Mauri-Capdevila G, Suárez I, et al. Metabolomics predicts stroke recurrence after transient ischemic attack. *Neurology*. 2015;84(1):36-45. doi:10.1212/WNL.0000000000001093

76. Ildstad F, Ellekjær H, Wethal T, et al. Stroke risk after transient ischemic attack in a Norwegian prospective cohort. *BMC Neurol*. 2019;19(1):2-9. doi:10.1186/s12883-018-1225-y

77. Bos MJ, van Rijn MJE, Witteman JCM, Hofman A, Koudstaal PJ, Breteler MM. Incidence and prognosis of transient neurological attacks. *JAMA*. 2007;298(24):2877-2885. doi:10.1001/jama.298.24.2877

78. Weimar C, Benemann J, Huber R, et al; German Stroke Study Collaboration. Long-term mortality and risk of stroke after transient ischemic attack: a hospital-based cohort study. *J Neurol*. 2009;256(4):639-644. doi:10.1007/s00415-009-0150-9

79. Sanders LM, Srikanth VK, Jolley DJ, et al. Monash transient ischemic attack triaging treatment: safety of a transient ischemic attack mechanism-based outpatient model of care. *Stroke*. 2012;43(11):2936-2941. doi:10.1161/STROKEAHA.112.664060

80. Engelter ST, Amort M, Jax F, et al. Optimizing the risk estimation after a transient ischaemic attack - the ABCDE⊕ score. *Eur J Neurol*. 2012;19(1):55-61. doi:10.1111/j.1468-1331.2011.03428.x

81. Griffiths D, Sturm J, Heard R, et al. Can lower risk patients presenting with transient ischaemic attack be safely managed as outpatients? *J Clin Neurosci*. 2014;21(1):47-50. doi:10.1016/j.jocn.2013.02.028

82. De Marchis GM, Weck A, Audebert H, et al. Copeptin for the prediction of recurrent cerebrovascular events after transient ischemic attack: results from the CoRisk study. *Stroke*. 2014;45(10):2918-2923. doi:10.1161/STROKEAHA.114.005584

83. Guarino M, Rondelli F, Favaretto E, et al. Short-and long-term stroke risk after urgent management of transient ischaemic attack: the Bologna TIA clinical pathway. *Eur Neurol*. 2015;74(1-2):1-7. doi:10.1159/000430810

84. Raser JM, Cucchiara BL. Modifications of the ABCD2 score do not improve the risk stratification of transient ischemic attack patients. *J Stroke Cerebrovasc Dis*. 2012;21(6):467-470. doi:10.1016/j.jstrokecerebrovasdis.2010.11.005

85. Arsava EM, Furie KL, Schwamm LH, Sorensen AG, Ay H. Prediction of early stroke risk in transient symptoms with infarction: relevance to the new tissue-based definition. *Stroke*. 2011;42(8):2186-2190. doi:10.1161/STROKEAHA.110.604280

86. Al-Khaled M, Eggers J. Early hospitalization of patients with TIA: a prospective, population-based study. *J Stroke Cerebrovasc Dis*. 2014;23(1):99-105. doi:10.1016/j.jstrokecerebrovasdis.2012.10.001

87. Eliasziw M, Kennedy J, Hill MD, Buchan AM, Barnett HJM; North American Symptomatic Carotid Endarterectomy Trial Group. Early risk of stroke after a transient ischemic attack in patients with internal carotid artery disease. *CMAJ*. 2004;170(7):1105-1109. doi:10.1503/cmaj.1030460

88. Ottaviani M, Vanni S, Moroni F, Peiman N, Boddi M, Grifoni S. Urgent carotid duplex and head computed tomography versus ABCD2 score for risk stratification of patients with transient ischemic attack. *Eur J Emerg Med*. 2016;23(1):19-23. doi:10.1097/MEJ.0000000000000165

89. Purroy F, Begué R, Gil MI, et al. Patterns of diffusion-weighted magnetic resonance imaging associated with etiology improve the accuracy of prognosis after transient ischaemic attack. *Eur J Neurol*. 2011;18(1):121-128. doi:10.1111/j.1468-1331.2010.03080.x

90. Ohara T, Uehara T, Sato S, et al; PROMISE-TIA Study Investigators. Small vessel occlusion is a high-risk etiology for early recurrent stroke after transient ischemic attack. *Int J Stroke*. 2019;14(9):871-877. doi:10.1177/1747493019840931

91. Rothwell PM, Giles MF, Chandratheva A, et al; Early use of Existing Preventive Strategies for Stroke (EXPRESS) study. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet*. 2007;370(9596):1432-1442. doi:10.1016/S0140-6736(07)61448-2

92. Lichtman JH, Jones SB, Watanabe E, et al. Elderly women have lower rates of stroke,

cardiovascular events, and mortality after hospitalization for transient ischemic attack. *Stroke*. 2009;40(6):2116-2122. doi:10.1161/STROKEAHA.108.543009

93. Akijian L, Ní Chróinín D, Callaly E, et al. Why do transient ischemic attack patients have higher early stroke recurrence risk than those with ischemic stroke? Influence of patient behavior and other risk factors in the North Dublin Population Stroke Study. *Int J Stroke*. 2017;12(1):96-104. doi:10.1177/1747493016669851

94. Amort M, Fluri F, Schäfer J, et al. Transient ischemic attack versus transient ischemic attack mimics: Frequency, clinical characteristics and outcome. *Cerebrovasc Dis*. 2011;32(1):57-64. doi:10.1159/000327034

95. Zheng S, Yao B. Impact of risk factors for recurrence after the first ischemic stroke in adults: a systematic review and meta-analysis. *J Clin Neurosci*. 2019;60:24-30. doi:10.1016/j.jocn.2018.10.026

96. Redon J, Olsen MH, Cooper RS, et al. Stroke mortality and trends from 1990 to 2006 in 39 countries from Europe and Central Asia: implications for control of high blood pressure. *Eur Heart J*. 2011;32(11):1424-1431. doi:10.1093/eurheartj/ehr045

97. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet*. 2017;389(10064):37-55. doi:10.1016/S0140-6736(16)31919-5

98. Gu Q, Burt VL, Dillon CF, Yoon S. Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension: the National Health and Nutrition Examination Survey, 2001 to 2010. *Circulation*. 2012;126(17):2105-2114. doi:10.1161/CIRCULATIONAHA.112.096156

99. Mortensen MB, Falk E, Schmidt M. Twenty-year nationwide trends in statin utilization and expenditure in Denmark. *Circ Cardiovasc Qual Outcomes*. 2017;10(7):e003811. doi:10.1161/CIRCOUTCOMES.117.003811

100. Lipska KJ, Yao X, Herrin J, et al. Trends in drug utilization, glycemic control, and rates of severe hypoglycemia, 2006-2013. *Diabetes Care*. 2017;40(4):468-475. doi:10.2337/dc16-0985

101. Albers GW, Caplan LR, Easton JD, et al; TIA Working Group. Transient ischemic attack—proposal for a new definition. *N Engl J Med*. 2002;347(21):1713-1716. doi:10.1056/NEJMsb020987

102. Kleindorfer D, Khoury J, Alwell K, et al. The impact of magnetic resonance imaging (MRI) on ischemic stroke detection and incidence: minimal impact within a population-based study. *BMC Neurol*. 2015;15:175. doi:10.1186/s12883-015-0421-2

103. van Everdingen KJ, van der Grond J, Kappelle LJ, Ramos LMP, Mali WPTM. Diffusion-weighted magnetic resonance imaging in acute stroke. *Stroke*. 1998;29(9):1783-1790. doi:10.1161/01.STR.29.9.1783

104. Kleindorfer D, Broderick J, Khoury J, et al. The unchanging incidence and case-fatality of stroke in the 1990s: a population-based study. *Stroke*. 2006;37(10):2473-2478. doi:10.1161/01.STR.0000242766.65550.92

105. Kissela BM, Khoury JC, Alwell K, et al. Age at stroke: temporal trends in stroke incidence in a large, biracial population. *Neurology*. 2012;79(17):1781-1787. doi:10.1212/WNL.0b013e318270401d

106. Feigin VL, Krishnamurthi RV, Parmar P, et al; GBD 2013 Writing Group; GBD 2013 Stroke Panel Experts Group. Update on the Global Burden of Ischemic and Hemorrhagic Stroke in 1990-2013: the GBD 2013 Study. *Neuroepidemiology*. 2015;45(3):161-176. doi:10.1159/000441085

107. Lackland DT, Roccella EJ, Deutsch AF, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; Council on Functional Genomics and Translational Biology. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(1):315-353. doi:10.1161/01.str.0000437068.30550.cf

108. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract*. 2019;157:107843. doi:10.1016/j.diabres.2019.107843

109. Béjot Y, Bailly H, Durier J, Giroud M. Epidemiology of stroke in Europe and trends for the 21st century. *Presse Med*. 2016;45(12, pt 2):e391-e398. doi:10.1016/j.lpm.2016.10.003