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ORIGINAL RESEARCH

Ninety-Day Stroke Recurrence in Minor Stroke: Systematic Review and Meta-Analysis of Trials and Observational Studies

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BACKGROUND: Risk of recurrence after minor ischemic stroke is usually reported with transient ischemic attack. No previous meta-analysis has focused on minor ischemic stroke alone. The objective was to evaluate the pooled proportion of 90-day stroke recurrence for minor ischemic stroke, defined as a National Institutes of Health Stroke Scale severity score of ≤5.

METHODS AND RESULTS: Published papers found on PubMed from 2000 to January 12, 2021, reference lists of relevant articles, and experts in the field were involved in identifying relevant studies. Randomized controlled trials and observational studies describing minor stroke cohort with reported 90-day stroke recurrence were selected by 2 independent reviewers. Altogether 14 of 432 (3.2%) studies met inclusion criteria. Multilevel random-effects meta-analysis was performed. A total of 6 randomized controlled trials and 8 observational studies totaling 45 462 patients were included. The pooled 90-day stroke recurrence was 8.6% (95% CI, 6.5–10.7), reducing by 0.60% (95% CI, 0.09–1.1; *P*=0.02) with each subsequent year of publication. Recurrence was lowest in dual antiplatelet trial arms (6.3%, 95% CI, 4.5–8.0) when compared with non-dual antiplatelet trial arms (7.2%, 95% CI, 4.7–9.6) and observational studies 10.6% (95% CI, 7.0–14.2). Age, hypertension, diabetes, ischemic heart disease, or known atrial fibrillation had no significant association with outcome. Defining minor stroke with a lower National Institutes of Health Stroke Scale threshold made no difference – score ≤3: 8.6% (95% CI, 6.0–11.1), score ≤4: 8.4% (95% CI, 6.1–10.6), as did excluding studies with n<500%–7.3% (95% CI, 5.5–9.0).

CONCLUSIONS: The risk of recurrence after minor ischemic stroke is declining over time but remains important.

Key Words: humans ■ ischemic attack, transient ■ recurrence ■ stroke

Patients with minor ischemic stroke and transient ischemic attack (TIA) have traditionally been pooled together both because treatment, prognosis, and outcome are similar and because lack of access to early imaging on patient presentation makes imaging-based differentiation challenging. Recent large antiplatelet trials have taken this approach by including both minor stroke and high-risk TIA.[1–6] Together, they are associated with a risk of recurrent stroke between 10% and 20% during the first 3 months in natural history observations.[7–9]

TIA and minor stroke are, however, not identical. Up to 38% of clinic attendees with TIA have nonischemic mimics.[10] This high proportion dilutes the estimated cohort risk of stroke recurrence because patients without ischemia effectively have a near zero rate of early

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CLINICAL PERSPECTIVE

What Is New?

- The pooled 90-day stroke recurrence after minor ischemic stroke was 8.6% using multilevel random-effects meta-analysis on data for 45 462 patients from 6 trials and 8 observational studies.
- This rate appears to be declining with each subsequent year of publication.

What Are the Clinical Implications?

- This study helps physicians understand that although the risk of recurrence after minor ischemic stroke is declining over time, this risk remains important.

Nonstandard Abbreviations and Acronyms

CATCH	CT and MRI in the Triage of TIA and Minor Cerebrovascular Events to Identify High Risk Patients
CHANCE	Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events
CHANCE-2	Clopidogrel With Aspirin in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events II
CNSR	China National Stroke Registry
CRCS-K	Clinical Research Collaboration for Stroke-Korea
DAPT	dual antiplatelet therapy
FASTER	Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence
NIHSS	National Institutes of Health Stroke Scale
NORTHSTAR	North West of England Transient Ischaemic Attack and Minor Stroke
OXVASC	Oxford Vascular Study
POINT	Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke
PRINCE	Platelet Reactivity in Acute Non-Disabling Cerebrovascular Events
SOCRATES	Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes
TARDIS	Triple Versus Guideline Antiplatelet Therapy to Prevent Recurrence After Acute Ischemic Stroke or Transient Ischemic Attack
THALES	Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death
VISION	Vascular Imaging of Acute Stroke for Identifying Predictors of Clinical Outcome and Recurrent Ischemic Events

subsequent stroke. Among meta-analyses that focus on TIA alone, the 90-day stroke risk varied from 6% to 9%.[11–13] These meta-analyses were based on studies performed more than 10 years ago. Since then, studies addressing rapid TIA pathways have reported lower risk of recurrence compared with standard care.[10,14,15] For example, a large multicenter TIA and minor stroke registry reported a 90-day recurrence risk of 3.7%, but it is not clear if this finding was dominated by cases of TIA or what the risks were in the subgroup with minor stroke.[16] Determining the risk of recurrence with TIA and minor stroke separately can be difficult as few investigators have focused on recurrence after minor stroke.[17,18] Further, recurrence rates may be reduced by treatment and therefore lower among those recruited to dual antiplatelet trials.[1–6] The aim of this meta-analysis is to determine the risk of recurrence after minor stroke. We combine the results of antiplatelet trials and observational studies, incorporating previously unpublished data on minor stroke from multiple antiplatelet trials and observational studies.

METHODS

Data Availability

This study is performed in agreement with the American Heart Association Journals' implementation of the Transparency and Openness Promotion Guidelines. This study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The authors declare that all supporting data are available within the article. This study was registered with the International Prospective Register of Systematic Reviews (2020 CRD42020203309).

Eligibility Criteria

Articles were included if a cohort with minor stroke was described along with 90-day stroke recurrence rates. Ischemic stroke was defined as a new neurologic deficit lasting at least 24 hours that was not attributable to a nonischemic cause, or a new neurologic deficit not attributable to a nonischemic cause and accompanied by neuroimaging evidence of new brain infarction. Acute minor stroke was defined by a score of 5 or

less on the National Institutes of Health Stroke Scale (NIHSS; scores range from 0 to 42, with higher scores indicating greater deficits) either at the time of randomization (for randomized controlled trials [RCTs]) or final coding (for observational studies). Studies that defined minor stroke using modified Rankin Scale criteria or disposition from the emergency department were excluded.[16,19] Stroke recurrence was defined as sudden onset of a new focal neurological deficit with clinical or imaging evidence of infarction, or a rapid worsening of an existing focal neurologic deficit. We included RCTs and observational studies. We excluded review articles, studies with follow-up duration other than 90 days, studies with narrow inclusion criteria, studies that did not report stroke recurrence or cohorts with minor stroke, study protocols, and opinion letters. If any cohorts overlapped, the larger cohort was kept, to prevent double counting of patients.[20] Studies were grouped by treatment type for the synthesis (dual antiplatelet therapy [DAPT] trial arms, non-DAPT trial arms, and observational studies).

Information Sources

PubMed and reference lists of relevant papers were searched for studies published up to December 1, 2021, using terms including "mild stroke," "minor stroke," and "recurrence." Full published papers and conference abstracts were considered. Reference lists of relevant articles and experts in the field were involved in identifying relevant studies.

Search Strategy

The actual PubMed search strategy was ("mild stroke"[All Fields] OR "minor stroke"[All Fields]) AND ("recurrence"[All Fields] OR "recurrence"[MeSH Terms] OR "recurrence"[All Fields] OR "recurrences"[All Fields] OR "recurrencies"[All Fields] OR "recurrency"[All Fields] OR "recurrent"[All Fields] OR "recurrently"[All Fields] OR "recurrents"[All Fields]). No filters nor limits were used. There was no restriction on patient ages, study settings, or geographic areas.

Selection and Data Collection Process

Two independent reviewers (A.L., T.P.) decided whether each study met inclusion criteria and extracted data into a structured Excel spreadsheet. Titles and abstracts were initially scanned for relevance. Full text articles of the selected studies were then examined for inclusion criteria. If there were missing data in a relevant paper, the authors were contacted for unpublished data.

Data Items

Data included study name, author, study type (RCT control, RCT experimental, observational), setting (single center or multicenter), cohort start and end years, publication year, NIHSS definition for minor stroke, cohort size, and number of events. The mean age of the entire study cohort was recorded. Median ages were converted to mean ages using $= \frac{a+2m+b}{4}$, where m=median and a and b are the low and high end of the range.[21] Aggregate percentage of patients with hypertension, diabetes, ischemic heart disease, and known atrial fibrillation were requested from the authors.

Study Risk of Bias Assessment

Assessment of risk of bias within studies was performed using the Joanna Briggs Institute checklist for studies reporting prevalence and cumulative incidence data[22] by an independent reviewer (S.M.).

Effect Measures

The primary outcome measure was the risk of 90-day stroke recurrence (inclusive of both progression and recurrence). This was calculated as a proportion $\left(\frac{\text{number of events}}{\text{cohort size}}\right)$ and reported as a percentage. Ninety days was chosen as the follow-up duration in line with major clinical trials.[1–4,23]

Statistical Analysis

Statistical analysis was performed in R with the help of the metafor[24] package. DAPT trial arms, non-DAPT trial arms, and observational studies were analyzed both separately and pooled. Meta-analysis was performed using the random effects model. Random effects was chosen over fixed effects to account for expected interstudy variability given the inclusion of observational studies in this meta-analysis.[25] Raw proportions were used rather than inexact methods that can be challenging to interpret.[26] Three-level meta-analysis was chosen given the presumed dependency between each pair of effect sizes extracted per RCT.[20] The restricted maximum-likelihood estimator method was used to estimate the amount of heterogeneity. DAPT trial arms, non-DAPT trial arms, and observational studies were analyzed both separately and pooled. The inconsistency I^2 index,[27] the sum of the squared deviations from the overall effect and weighted by study size, was used to measure heterogeneity.[27] Metaregression was planned regardless of evidence for statistical heterogeneity; this decision was made to justify the inclusion of observational studies.[25] Three-tiered study type (RCT experimental, RCT control, observational), 2-tiered study type (RCT, observational), and time of onset to recruitment cutoff (12 hours, 24 hours, 48 hours, or none) were used as categorical moderators. Publication year was chosen as a covariate given reports of improving outcomes with contemporary management of minor

stroke and TIA[15] and TIA alone.[11,14,28] Age, hypertension, diabetes, ischemic heart disease, and known atrial fibrillation were also tested as continuous moderators. Sensitivity analysis to compare various minor stroke definitions (NIHSS score ≤3, NIHSS score ≤4, and NIHSS score ≤5) and the exclusion of studies with n<500 to minimize the potential overestimating effect of studies with small sample sizes[29] was conducted to assess the robustness of the synthesized results.

RESULTS

Study Selection

The search yielded 14 eligible studies (6 RCTs and 8 observational studies) describing 45 462 patients. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart is shown in Figure S1. Regarding notable exclusions, only the largest Oxford Vascular Study (OXVASC) cohort was retained,[30] with previous overlapping cohorts excluded.[15,31] One major trial (THALES [Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and ASA (Aspirin) for Prevention of Stroke and Death]) was excluded as the follow-up ended at 30 days.[32] One major registry (tiaregistry.org)[16] and 1 observational study (NORTHSTAR [North West of England Transient Ischaemic Attack and Minor Stroke][19]) chose a modified Rankin Scale score of ≤1 as the definition of minor stroke. The FASTER (Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence) trial, although using NIHSS score ≤3, was excluded as the minor stroke subset data could not be obtained from the authors.[33] One observational study defined minor stroke at discharge, that is, "any ischemic stroke (*International Classification of Diseases, Tenth Revision, Canadian Version* [*ICD-10-CA*] codes H341, I63* [except I636], I64*, I676) that was discharged home with or without support directly from the emergency department"[34] and was excluded due to not meeting the NIHSS score ≤5 on admission criteria and unavailability of minor stroke subset data.

Study Characteristics

The data contain 45 462 patients. Characteristics are summarized in the Table.

Three observational studies were single center, and all other studies were multicenter. Most studies chose to define minor stroke as NIHSS score ≤3 (9/14=64%). Less common definitions were NIHSS score ≤5 (2/14=14%), NIHSS score ≤4 (1/14=7%), or NIHSS score ≤2 (1/14=7%). The mean NIHSS score was 3.3±0.8. The TARDIS (Triple Versus Guideline Antiplatelet Therapy to Prevent Recurrence After Acute Ischemic Stroke or Transient Ischemic Attack) trial did not have an NIHSS upper limit for recruitment,[5] but the authors were able to provide data for NIHSS score ≤3. For the purposes of the subgroup analysis, the TARDIS experimental arm (aspirin, clopidogrel, and dipyridamole) was classified as a DAPT arm and the control arm (clopidogrel alone or aspirin and dipyridamole) a non-DAPT arm. For 9 studies, additional unpublished data were obtained from the authors to clarify outcomes for minor stroke in isolation. This included data obtained from the National Institute of Neurological Disorders and Stroke and from AstraZeneca. The minor stroke data from SOCRATES (Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes)[2] were provided with the requirement that Chinese patients were removed.

Main Analysis

The pooled 90-day stroke recurrence for minor stroke was 8.6% (95% CI, 6.5–10.7)—see Figure. Recurrence was lowest in DAPT arms (6.3%, 95% CI, 4.5, 8.0) when compared with non-DAPT arms (7.2%, 95% CI, 4.7–9.6) and observational studies 10.6% (95% CI, 7.0–14.2) (Figure). Test of moderators using study type as a 3-tiered categorical moderator (RCT experimental, RCT control, observational) demonstrated significant difference between study types (Q_M=21.59, df=2, P<0.001). Study type as a 2-tiered categorical moderator (RCT, observational) trended to significant (Q_M=3.24, df=1, P=0.07). Time of onset to recruitment as a categorical moderator (12 hours, 24 hours, 48 hours, or none) was not significant (Q_M=2.42, df=3, P=0.49). Metaregression with continuous variables demonstrated a significant reduction in the estimate with each subsequent year of publication 0.60% (95% CI, 0.09–1.1, P=0.02). No significant trend was observed with age (β=−0.003, 95% CI, −0.009 to 0.02, P=0.23), hypertension (β=−0.001, 95% CI, −0.003 to 0.001, P=0.48), diabetes (β=0.001, 95% CI, −0.002 to 0.005, P=0.51), ischemic heart disease (β=−0.001, 95% CI, −0.007 to 0.005, P=0.63), known atrial fibrillation (β=0.001, 95% CI, −0.002 to 0.004, P=0.35), or percentage antiplatelet treatment (redundant predictor). Defining minor stroke with a lower NIHSS threshold made no difference—NIHSS score ≤3: 8.6% (95% CI, 6.0–11.1), NIHSS score ≤4: 8.4% (95% CI, 6.1–10.6), as did excluding studies with n<500%–7.3% (95% CI, 5.5–9.0). Assessment of individual study bias demonstrated low risk overall, with none of the selected studies scoring a "no" on any of the 9 domains assessed. This is provided in the Table S1.

DISCUSSION

The major finding of this analysis was that the pooled 90-day stroke recurrence rate for minor stroke is 8.6%, and this appears to be declining by 0.60% per year.

Table. Study Characteristics

Study	Study type	DAPT arm?	Cutoff time (onset to recruitment in hours)	Setting	Cohort years	Publication year	NIHSS	Mean age*	Hypertension (%)	Diabetes (%)	IHD (%)	Known AF (%)	Antiplatelet treatment (%)	n	Event	%
CHANCE[1]	RCT control	FALSE	24	Multicenter	2009–12	2013	3	62.2	1188 (63.9)	370 (19.9)	NA	32 (1.7)	100	1858	215	11.57
CHANCE[1]	RCT experimental	TRUE	24	Multicenter	2009–12	2013	3	63.2	1208 (64.7)	395 (21.2)	NA	37 (2.0)	100	1867	153	8.19
SOCRATES[2]	RCT control	FALSE	24	Multicenter	2014–15	2016	5	65.9	3259 (74.4)	1001 (22.9)	570 (13.0)	8 (0.2)	100	4378	302	6.90
SOCRATES[2]	RCT experimental	FALSE	24	Multicenter	2014–15	2016	5	65.8	3196 (73.8)	1081 (25.0)	536 (12.4)	12 (0.3)	100	4330	261	6.03
POINT[3]	RCT control	FALSE	12	Multicenter	2010–17	2018	3	65.0	938 (67.1)	365 (26.1)	126 (9.0)	9 (0.6)	100	1397	105	7.52
POINT[3]	RCT experimental	TRUE	12	Multicenter	2010–17	2018	3	64.8	948 (68.8)	371 (27.0)	128 (9.3)	18 (1.3)	100	1376	72	5.23
TARDIS[5]	RCT control	FALSE	48	Multicenter	2009–16	2018	3	68.9	345 (54.7)	129 (20.5)	82 (13.0)	0 (0.0)	100	629	15	2.38
TARDIS[5]	RCT experimental	TRUE	48	Multicenter	2009–16	2018	3	69.1	350 (55.6)	103 (16.4)	77 (12.2)	0 (0.0)	100	630	24	3.81
PRINCE[4]	RCT control	TRUE	24	Multicenter	2015–17	2019	3	60.5	178 (61.5)	71 (24.6)	19 (6.5)	4 (1.4)	100	289	28	9.69
PRINCE[4]	RCT experimental	TRUE	24	Multicenter	2015–17	2019	3	61.1	169 (61.4)	66 (24.0)	23 (8.4)	0 (0.0)	100	275	16	5.82
CHANCE-2[6]	RCT control	TRUE	24	Multicenter	2019–21	2021	3	64.3	1587 (61.5)	603 (23.4)	NA	NA	100	2581	198	7.67
CHANCE-2[6]	RCT experimental	TRUE	24	Multicenter	2019–21	2021	3	64.7	1566 (60.8)	657 (25.5)	NA	NA	100	2577	151	5.86
VISION[7]	Observational	NA	12	Single center	2002–06	2008	3	65.6	NA	NA	NA	NA	100	85	19	22.35
Barcelona Registry[9]	Observational	NA	None	Single center	2004–07	2008	3	71.7	319 (68.2)	150 (32.1)	67 (14.3)	71 (15.1)	100	468	69	14.74
CATCH[35]	Observational	NA	24	Single center	2008–10	2012	3	66.0	143 (60.3)	40 (16.9)	NA	20 (8.4)	100	237	33	13.92
CNSR-I Registry[17]	Observational	NA	None	Multicenter	2007–08	2015	3	64.8	3438 (73.6)	1274 (27.3)	600 (12.9)	270 (5.7)	100	4669	459	9.83
Ontario Registry[36]	Observational	NA	None	Multicenter	2008–11	2016	2	74.3	2082 (68.6)	799 (26.3)	607 (20.0)	NA	NA	3033	110	3.63
Austrian Stroke Unit Registry[37]	Observational	NA	24	Multicenter	2010–15	2016	3	71.4	1002 (79.4)	294 (23.3)	NA	263 (20.8)	NA	1262	74	5.86
CRCS-K Registry[18]	Observational	NA	24	Multicenter	2011–18	2021	5	65.5	6453 (52.7)	3249 (26.6)	NA	1105 (9.0)	NA	12 234	1666	13.62

(*Continued*)

Table. Continued

Study	Study type	DAPT arm?	Cutoff time (onset to recruitment in hours)	Setting	Cohort years	Publication year	NIHSS	Mean age*	Hypertension (%)	Diabetes (%)	IHD (%)	Known AF (%)	Antiplatelet treatment (%)	n	Event	%
Oxford Vascular Study[30]	Observational	NA	None	Multicenter	2002–18	2021	4	72.4	715 (55.6)	183 (14.2)	250 (19.4)	219 (17.0)	100	1287	93	7.23

CATCH indicates CT and MRI in the Triage of TIA and Minor Cerebrovascular Events to Identify High Risk Patients; CHANCE, Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events; CHANCE-2, Clopidogrel With Aspirin in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events II; CNSR, China National Stroke Registry; CRCS-K, Clinical Research Collaboration for Stroke-Korea; DAPT, dual antiplatelet therapy; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institute of Neurological Disorders and Stroke; POINT, Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke; PRINCE, Platelet Reactivity in Acute Non-Disabling Cerebrovascular Events; RCT, randomized controlled trial; SOCRATES, Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes; TARDIS, Triple Versus Guideline Antiplatelet Therapy to Prevent Recurrence After Acute Ischemic Stroke or Transient Ischemic Attack; and VISION, Vascular Imaging of Acute Stroke for Identifying Predictors of Clinical Outcome and Recurrent Ischemic Events.

*Mean age of entire study cohort with exceptions (Austrian registry: admitted patients only; Oxford: minor stroke only). Median ages were converted to mean ages using $= \frac{a+2m+b}{4}$, where m=median and a and b are the low and high end of the range.[21]

This finding is new as it both contains previously unpublished data on minor stroke and focuses on minor stroke alone. Furthermore, the risk is lowest among those in the DAPT arms compared with the non-DAPT arms or observational studies. The lower risk of recurrence after minor stroke in the DAPT arms compared with non-DAPT arms of RCTs is consistent with overall findings of these trials showing a benefit of DAPT after TIA or minor stroke. It is possible that the higher rate of recurrence from observational studies is due to combination of factors including comorbidities and rapid assessment pathways leading to administration of medications within 24 hours.

An overall downtrend in stroke recurrence rate of 0.60% per year seems consistent with improving outcomes with contemporary management of minor stroke and TIA[15] and TIA alone.[10,11,14] This may simply reflect increasing attention to urgent assessment and early initiation of preventive treatments.[15] This effect of decreasing risk of recurrence was seen among those in RCT and observational studies. The one exception was the Korean registry, which had collected data from 2011 to 2018.[18] It is possible that newer studies or updates of recent clinical registries may lead to lower rate of recurrence. Another potential explanation is that reclassification of TIA to minor stroke on the basis of diffusion weighted imaging can affect recurrence rate being present in 34.3% of "TIA."[38] We consider this less likely as the mean NIHSS score was 3.3 rather than approaching 0 if more cases of TIA with positive diffusion restricted lesions were classified as minor stroke. It would not be credible. However. to assume this downward trend to continue indefinitely, and one would expect an eventual plateau of baseline risk. The late increase may be the effect of the Korean registry on the overall curve, acknowledging again the addition of patients as early as 2011 to the 2021 data point.[18]

The observed variability in the definition of minor stroke is consistent with previous published observations,[39] and unsurprising given the lack of consensus with diagnostic criteria. There is no *ICD* code for minor stroke whereas *ICD* codes are available for TIA. Previously, the National Institute of Neurological Disorders and Stroke attempted to define minor stroke in a post hoc analysis of the NINDS rt-PA (National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator) Stroke Study.[40] The 5 proposed National Institute of Neurological Disorders and Stroke definitions have not been adopted in stroke research.[39] Recently, major clinical trials[1–4,23] have chosen to use NIHSS criteria, but even then, the chosen score cutoff varied, with the SOCRATES trial choosing to include NIHSS score 4 and 5 patients,[2] compared with the standard choice of NIHSS score ≤3. Choosing NIHSS score ≤5 as the cutoff for this meta-analysis meant relevant studies were

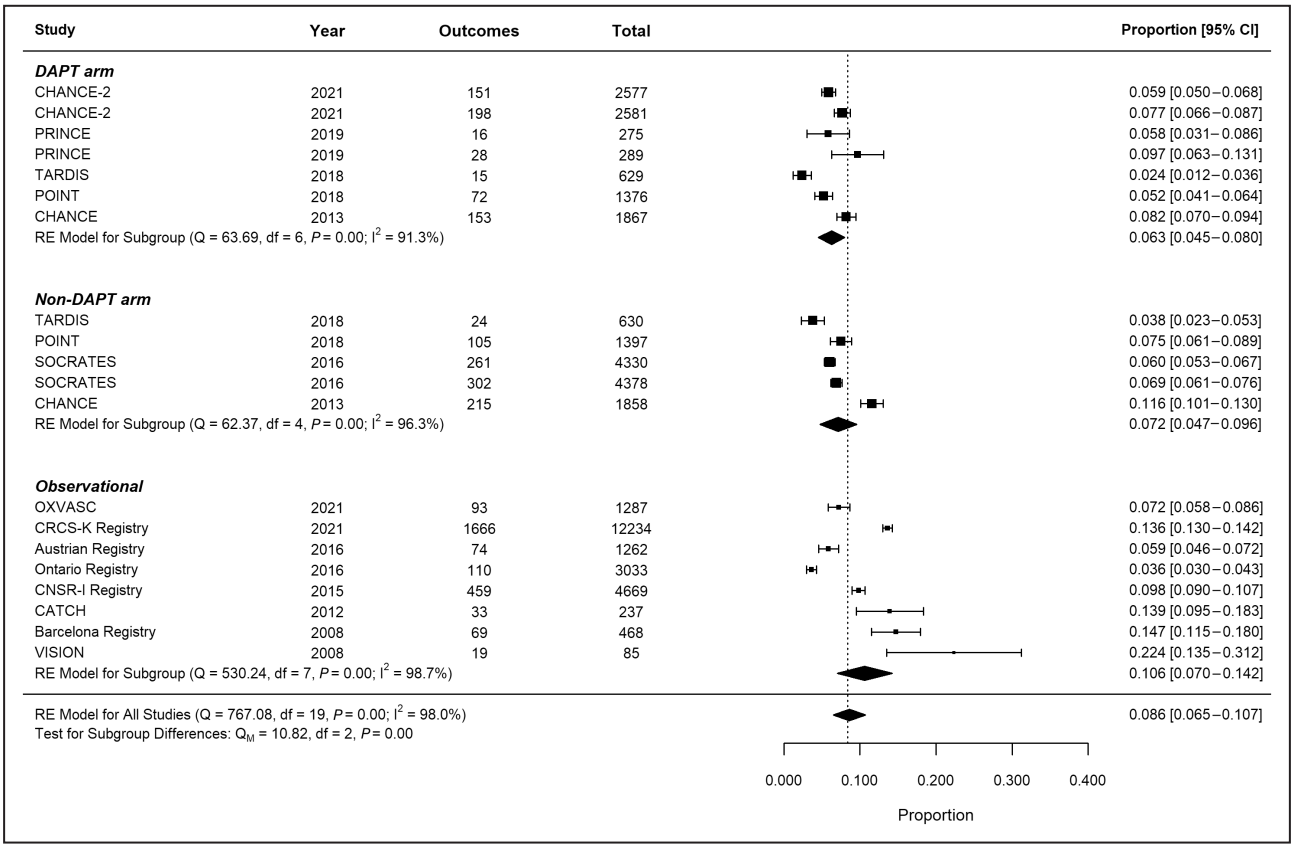

Figure. Forest plot of randomized trials and observational studies measuring 90-day stroke recurrence in minor stroke. CATCH indicates CT and MRI in the Triage of TIA and Minor Cerebrovascular Events to Identify High Risk Patients; CHANCE, Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events; CHANCE-2, Clopidogrel With Aspirin in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events II; CNSR, China National Stroke Registry; CRCS-K, Clinical Research Collaboration for Stroke-Korea; DAPT, dual antiplatelet therapy; OXVASC, Oxford Vascular Study; POINT, Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke; PRINCE, Platelet Reactivity in Acute Non-Disabling Cerebrovascular Events; SOCRATES, Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes; TARDIS, Triple Versus Guideline Antiplatelet Therapy to Prevent Recurrence After Acute Ischemic Stroke or Transient Ischemic Attack; and VISION, Vascular Imaging of Acute Stroke for Identifying Predictors of Clinical Outcome and Recurrent Ischemic Event.

excluded from this quantitative pooling of results due to alternative criteria—for example modified Rankin Scale score ≤1,[16,19] or the pragmatic definition of "any ischemic stroke (*ICD-10-CA* codes H341, I63* [except I636], I64*, I676) that was discharged home with or without support directly from the emergency department."[34] This was to minimize heterogeneity when generating pooled estimates. A unified definition is required, perhaps NIHSS score ≤3 as adopted by the major antiplatelet trials, to achieve greater consistency for future studies.

Limitations

Our study was made possible through the generous release of previously unpublished data from randomized trials. However, a caveat is that the data on minor stroke from SOCRATES[2] trial did not contain information on Chinese patients, and the FASTER data could not be obtained. As such our study does not contain all possible data. Selection bias between trials and observational studies exist due to trials having stringent inclusion and exclusion criteria compared with observational studies. Furthermore, not all minor strokes are the same, as those with large vessel occlusion having thrombectomy or thrombolysis are generally excluded from these studies.[41] In addition, the use of penumbral imaging to select candidates for reperfusion (and therefore exclude from the cohorts described in this paper) was not reported, adding a further unmeasured confounder. Another potential source of bias is measurement bias with regard to diagnosis of stroke recurrence, which can differ between RCTs and observational studies. Finally, it would be ideal to perform this analysis with individual patient data.[42] However, this would prove difficult, as some of the authors contacted stated that the data were no longer accessible due to expiry of ethics approval or archiving.

CONCLUSIONS

The overall 90-day recurrence rate of minor ischemic stroke is estimated to be 8.6% with the lowest recurrence rate seen among those randomized to the DAPT arms of RCTs. A downtrend in stroke recurrence rate of 0.60% per year suggests improving outcomes with advances in evaluation and treatment.

ARTICLE INFORMATION

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Disclosures

Philip M. Bath has consulted for DiaMedica, Moleac, Phagenesis, and Roche. The remaining authors have no disclosures to report.

Supplemental Material

Table S1
Figure S1

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