Stroke

CLINICAL AND POPULATION SCIENCES

P2Y12 Inhibitors Plus Aspirin Versus Aspirin Alone in Patients With Minor Stroke or High-Risk Transient Ischemic Attack

Zi-Xiao Li, MD, PhD*; Yunyun Xiong, MD, PhD*; Hong-Qiu Gu, PhD*; Marc Fisher, MD; Ying Xian, MD, PhD; S. Claiborne Johnston, MD, PhD; Yong-Jun Wang, MD

BACKGROUND AND PURPOSE: We performed a systemic review and meta-analysis to elucidate the effectiveness and safety of dual antiplatelet (DAPT) therapy with P2Y12 inhibitors (clopidogrel/ticagrelor) and aspirin versus aspirin monotherapy in patients with mild ischemic stroke or high-risk transient ischemic attack.

METHODS: Following Preferred Reported Items for Systematic Review and Meta-Analysis standards for meta-analyses, Medline, Embase, Cochrane Central Register of Controlled Trials, and the Cochrane Library were searched for randomized controlled trials that included patients with a diagnosis of an acute mild ischemic stroke or high-risk transient ischemic attack, intervention of DAPT therapy with clopidogrel/ticagrelor and aspirin versus aspirin alone from January 2012 to July 2020. The outcomes included subsequent stroke, all-cause mortality, cardiovascular death, hemorrhage (mild, moderate, or severe), and myocardial infarction. A DerSimonian-Laird random-effects model was used to estimate pooled risk ratio (RR) and corresponding 95% CI in R package meta. We assessed the heterogeneity of data across studies with use of the Cochran Q statistic and I^2 test.

RESULTS: Four eligible trials involving 21 493 participants were included in the meta-analysis. DAPT therapy started within 24 hours of symptom onset reduced the risk of stroke recurrence by 24% (RR, 0.76 [95% CI, 0.68–0.83], I^2=0%) but was not associated with a change in all-cause mortality (RR, 1.30 [95% CI, 0.90–1.89], I^2=0%), cardiovascular death (RR, 1.34 [95% CI, 0.56–3.17], I^2=0%), mild bleeding (RR, 1.25 [95% CI, 0.37–4.29], I^2=94%), or myocardial infarction (RR, 1.45 [95% CI, 0.62–3.39], I^2=0%). However, DAPT was associated with an increased risk of severe or moderate bleeding (RR, 2.17 [95% CI, 1.16–4.08], I^2=41%); further sensitivity tests found that the association was limited to trials with DAPT treatment duration over 21 days (RR, 2.86 [95% CI, 1.75–4.67], I^2=0%) or ticagrelor (RR, 2.17 [95% CI, 1.16–4.08], I^2=37%) but not within 21 days or clopidogrel.

CONCLUSIONS: In patients with noncardioembolic mild stroke or high-risk transient ischemic attack, DAPT with aspirin and clopidogrel/ticagrelor is more effective than aspirin alone for recurrent stroke prevention with a small absolute increase in the risk of severe or moderate bleeding.

Key Words: clopidogrel ■ ischemic stroke ■ meta-analysis ■ randomized controlled trial ■ ticagrelor

Acute mild ischemic stroke or transient ischemic attack (TIA) accounts for 65% of all ischemic cerebrovascular events.[1] A recent large prospective study revealed that the risk of subsequent ischemic stroke in mild stroke and high-risk TIA within 1 week was 8%,[2] with a risk of 10.5% within 3 months after the index event.[3]

Based on the CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events)[4] and the POINT trial (Platelet-Oriented

Correspondence to: Yongjun Wang, MD, China National Clinical Research Center for Neurological Diseases, Vascular Neurology, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China. Email yongjunwang@ncrcnd.org.cn

*Z.-X. Li, Y. Xiong, and H.-Q. Gu contributed equally.

This manuscript was sent to Emmanuel Touzé, Guest Editor, for review by expert referees, editorial decision, and final disposition.

The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.120.033040.

For Sources of Funding and Disclosures, see page 2256.

Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

CHANCE	Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Event
DAPT	dual antiplatelet
FASTER	Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence
HR	hazard ratio
POINT	Platelet-Oriented Inhibition in New TIA
RD	risk difference
RR	risk ratio
THALES	The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death
TIA	transient ischemic attack

Inhibition in New TIA and Minor Ischemic Stroke),[5] recent acute stroke management guidelines recommended initiating dual antiplatelet (DAPT) with aspirin and clopidogrel within 24 hours after symptom onset and continuing it for 21 days in patients with noncardioembolic high-risk TIA and minor stroke (National Institutes of Health Stroke Scale score ≤3).[6] However, clopidogrel requires hepatic conversion to its active form and a substantial percentage of patients have clopidogrel resistance because of a genetic predisposition to reduced conversion.[7] Ticagrelor rapidly and reversibly binds and inhibits the P2Y12 receptor on platelets without the need for conversion to an active form.[8,9] Recently, the THALES trial (The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death) demonstrated that patients with acute mild ischemic stroke or high-risk TIA randomized to receive ticagrelor and aspirin had a lower risk of a subsequent stroke or death as compared to aspirin alone during 30 days follow-up.[10]

We performed an updated systematic review and meta-analysis of randomized, placebo-controlled trials that enrolled patients with mild ischemic stroke or high-risk TIA within 3 days of presentation and elucidated the effectiveness and safety of DAPT therapy with clopidogrel or ticagrelor and aspirin versus aspirin alone.

METHODS

We adhere to the AHA Journals' implementation of the Transparency and Openness Promotion Guidelines (available online at https://www.ahajournals.org/top-guidelines). Detailed data, analytic methods, and study materials for the purposes of reproducing the results or replicating procedures can be made available on request to the corresponding author, who manages the information. We did not have a review protocol. We conducted the systematic review and meta-analysis following the Preferred Reported Items for Systematic Review and Meta-Analysis guidelines.

Eligibility Criteria

Trials were selected based on the following inclusion criteria: (1) placebo-controlled trials that included patients with a diagnosis of an acute mild ischemic stroke with National Institutes of Health Stroke Scale score ≤5 or high-risk TIA; (2) treatment onset within 3 days; (3) intervention of DAPT therapy with clopidogrel or ticagrelor and aspirin versus aspirin alone; and (4) the trials also had to report at least one of the following outcomes up to 90 days: all-cause mortality, cardiovascular death, subsequent ischemic or hemorrhagic stroke, intracranial hemorrhage, extracranial hemorrhage (mild, moderate, or severe), TIA, and myocardial infarction. Exclusion criteria were (1) studies of cardioembolic ischemic stroke; (2) studies published only in abstract form; and (3) studies published in languages other than English.

Search Strategies

We identified a 2018 meta-analysis addressing aspirin + clopidogrel versus single antiplatelet therapy for acute ischemic stroke or TIA and judged that the search, up to July 2018, was comprehensive. We evaluated all 3 studies included in that review for eligibility. And we conducted a comprehensive search for aspirin plus clopidogrel or aspirin plus ticagrelor relevant studies from January 2012 to July 2020.

Medline, Embase, Cochrane Central Register of Controlled Trials, Cochrane Library, and grey literature (https://www.opengrey.eu/) were searched. The search strategy included the keywords "antiplatelet therapy," "aspirin," "acetylsalicylic acid," "ASA," "clopidogrel," "Plavix," "Iscover," "thienopyridines," "ADP receptor inhibitors," "ticagrelor," "stroke," "cerebral ischemia," "cerebral infarction," "transient ischemic attack," "TIA," and "randomized controlled trial."

To identify trials that may not have been published in full or were missed through the electronic search, the investigators manually searched all references from the included studies and relevant previous systematic reviews.

Data Collection

Two reviewers (Y. Xiong and Z.-X. Li) independently screened the title and abstract and full-text levels of potentially eligible studies. A third team member (H.-Q. Gu) reviewed all final decisions, and a consensus was reached after group discussion.

Data Extraction and Management

Two reviewers (Y. Xiong and H.-Q. Gu) independently extracted data for the eligible studies using a predesigned data extraction form characteristics of enrolled patient population, description of intervention and control, and events of key outcomes.

Disagreement on a data element was resolved by group discussion.

Assessment of Risk of Bias

To address risk of bias, we used version 2 of the Cochrane tool for assessing risk of bias in randomized trials.[11] We assessed bias due to randomization, deviations from intended intervention, missing data, measurement of the outcome, and selection of

reported result. Bias in each domain and overall bias were classified into low risk of bias, some concerns, or high risk of bias.

Statistical Analysis

We abstracted information about the following outcomes from the main trial publications, supplemental appendices, and relevant subsequent analyses: stroke, ischemic stroke, hemorrhagic stroke, all-cause mortality, severe bleeding, moderate bleeding, mild bleeding (definition details are listed in Table I in the Data Supplement) and composite outcome of stroke, myocardial infarction, or cardiovascular death. When possible, we did analyses with the intention-to-treat population for each outcome, and the analyses were stratified according to the treatment.

As primary outcomes varied from trial to trial, our primary analyses were based on the number of events with similar definitions across studies in each intervention and control group. We used DerSimonian-Laird random-effects model to estimate pooled risk ratio (RR) and corresponding 95% CI in R package meta. We assessed the heterogeneity of data across studies with use of the Cochran Q statistic and I^2 test.

Effect size can also be estimated based on a generalized estimate equation model to account for the intrahospital effect. Therefore, we performed a sensitivity analysis based on reported relative risk (hazard ratio [HR] or RR) directly.

RESULTS

Figure I in the Data Supplement summarizes our search for eligible studies. All the 3 identified studies in the 2018 systematic review were eligible for our review. Our search of an electronic database retrieved 1675 records, of which 341 were duplicates. We excluded 1317 records based on title and abstract and assessed 17 full-text articles, of which 4 were eligible for our review.

Characteristics of Included Studies

The characteristics of the 4 eligible trials[4,5,10,12] involving 21 493 participants are presented in Table 1. All 4 studies enrolled patients with acute minor ischemic stroke or high-risk TIA with 3 enrolling within 24 hours after symptom onset and one enrolling within 12 hours. One study used a factorial design, also including a comparison between simvastatin and placebo; the other 3 studies each included 2 treatment arms. One study added ticagrelor to aspirin with a treatment duration of 30 days and a follow-up of 30 days; the other 3 studies added clopidogrel to aspirin with treatment duration ranged from 21 to 90 days and a follow-up of 90 days. All eligible studies reported the risk of a recurrent of stroke (ischemic or hemorrhagic) and severe or moderate bleeding events. Other reported outcomes are summarized in Table 2.

Risk of Bias

Figure 1 summarizes the risk of bias assessment for stroke and severe or moderate bleeding. All judgments concluded a low risk of bias. POINT was halted after 84% of the anticipated number of patients had been enrolled,[5,13] as interim analyses for efficacy were prespecified, therefore, we also classified it into low risk of other bias. FASTER[12] trial (Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence) was discontinued because of an increase in major hemorrhage, however, the discontinuation was not assessed in the new risk of bias tool.

Outcomes

Stroke Recurrence Within 90 Days

Four studies including 21 463 patients reported stroke recurrence within 90 days after randomization (THALES[10] at 30 days). Pooled analysis indicated that DAPT therapy started within 24 hours of symptom onset reduced the risk of stroke recurrence by 24% (RR, 0.76 [95% CI, 0.68–0.83], I^2=0%) and with an absolute reduction of 2% (95% CI, −0.032 to −0.008, I^2=57%; Figure 2, Figure II in the Data Supplement). The number needed to treat for a stroke outcome is 46, with a 95% CI of 35 to 48 (Table II in the Data Supplement). Results stratified by P2Y12 inhibitor type showed similar results (Figure 2). Sensitivity analysis based on effect size reported by individual study showed a similar result (HR, 0.75 [95% CI, 0.67–0.83], I^2=0%; Figure III in the Data Supplement).

Three studies reported ischemic or hemorrhagic stroke directly in their reports. We calculated the events number based on published results for one study. Ischemic stroke dominated all stroke outcome events, and the pooled results of ischemic stroke within 90 days showed a nearly identical effect size as total stroke events (RR, 0.74 [95% CI, 0.67–0.82], I^2=0%; absolute reduction of 2.2% [95% CI, −0.034 to −0.010], I^2=58%; Figure 2, Figure II in the Data Supplement). The number needed to treat for an ischemic stroke outcome is 44, with 95% CI of 35 to 63 (Table II in the Data Supplement). Results stratified by P2Y12 inhibitor type showed similar results (Figure 2). Sensitivity analysis showed similar results as well (HR, 0.73 [95% CI, 0.66–0.82], I^2=0%; Figure III in the Data Supplement). With respect to hemorrhagic stroke, DAPT was not significantly associated increased risk (RR, 1.83 [95% CI, 0.83–4.03]). Analysis for intracranial hemorrhage also showed that DAPT was not associated with an increased risk (RR, 2.02 [95% CI, 0.91–4.50]; Figure 2).

All-Cause Mortality

Three studies including 21 067 patients reported all-cause mortality. Pooled analysis showed that DAPT was not associated with increased risk of all-cause mortality (RR, 1.30 [95% CI, 0.90–1.89], I^2=0%; risk difference [RD], 0.001 [95% CI, −0.001 to 0.003]; number needed

Table 1. Comparisons of 3 Included Clinical Trials

Trial	Subjects	Treatment onset	Sample size	Study type	Duration of treatment	Follow-up duration	Intervention with dosages
FASTER[12]	Acute minor stroke (NIHSS score ≤3)/TIA (WHO definition): Proportion not reported	<24 h; median: 8.2–9.1 h	396 (201/195)	Factorial design including a comparison between simvastatin and placebo	90 d	90 d	Loading dose 300 mg clopidogrel followed by 75 mg clopidogrel daily+81 mg aspirin daily for study duration. If patient naive to aspirin, loading dose 162 mg aspirin followed by 75 mg clopidogrel+81 mg aspirin daily for study duration
CHANCE[4]	Acute ischemic stroke with NIHSS score ≤3 or high-risk TIA (ABCD² ≥4)	<24 h; mean 13 h	5170 (2584/2586)	Randomized, double-blind, placebo-controlled	21 d	90 d	75–300 mg aspirin at discretion of physician, and loading dose 300 mg clopidogrel on day 1, followed by 75 mg clopidogrel+75 mg aspirin daily on days 2–21. Day 22–90, 75 mg clopidogrel alone
POINT[5]	Acute ischemic stroke with NIHSS score ≤3 or high-risk TIA (ABCD² ≥4)	<12 h; mean 7 h	4881 (2432/2449)	Randomized, double-blind, placebo-controlled	90 d	90 d	A loading dose of 600 mg clopidogrel on day 1, followed by 75 mg clopidogrel+50–325 mg aspirin daily from day 2 through 90. Recommended initial dose of 162 mg aspirin for 5 d, followed by 81 mg aspirin daily
THALES[10]	Acute ischemic stroke with NIHSS score ≤5 or high-risk TIA (ABCD² ≥6 or ipsilateral atherosclerotic stenosis ≥50%)	<24 h	11 016 (5523/5493)	Randomized, double-blind, placebo-controlled	30 d	30 d	A loading dose of 180 mg ticagrelor on day 1, followed by 180 mg ticagrelor+75–100 mg aspirin daily from day 2 through 60.

ABCD indicates age, blood pressure, clinical features, diabetes mellitus; CHANCE, Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Event; FASTER, Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence; NIHSS, National Institutes of Health Stroke Scale; POINT, Platelet-Oriented Inhibition in New TIA; THALES, The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death; and TIA, transient ischemic attack.

to treat, 1663 [95% CI, 258–1283]; Figure 3, Figure IV and Table II in the Data Supplement). Results from sensitivity analysis based on effect size of HR reported by individual study showed an identical result (Figure V in the Data Supplement).

Cardiovascular Death

Two studies including 10 051 patients reported cardiovascular death (CHANCE[4] reported cardiovascular death and POINT[5] reported ischemic vascular death). Pooled analysis showed no evidence indicating that DAPT was associated with an increased risk of cardiovascular death (RR, 1.34 [95% CI, 0.56–3.17], I^2=0%; Figure 3). Sensitivity analysis revealed a similar result (HR, 1.31 [95% CI, 0.55–3.12], I^2=0.09%; Figure V in the Data Supplement).

Severe or Moderate Bleeding

Four studies including 21 463 patients reported severe or moderate bleeding (FASTER[12] and CHANCE[4] reported severe and moderate bleeding, POINT[5] reported major hemorrhage), pooled results showed that DAPT was associated with increased risk of severe or moderate bleeding (RR, 2.17 [95% CI, 1.16–4.08], I^2=41%; RD, 0.003 [95% CI, <0.001–0.007]; Figure 3 and Figure IV in the Data Supplement). We further analyzed pooled data stratified by treatment regimen or duration and results showed that the association was mainly seen with ticagrelor (RR, 3.25 [95% CI, 1.66–6.39]) or treatment duration over 21 days (RR, 2.86 [95% CI, 1.75–4.67]; RD, 0.005 [95% CI, 0.003–0.007]; Figure 3 and Figure VI in the Data Supplement).

Mild Bleeding

Three studies including 10 447 patients reported mild bleeding events (FASTER,[12] CHANCE,[4] and POINT[5]). There was no evidence indicating that DAPT was associated with higher risk of mild bleeding (RR, 1.25 [95% CI, 0.37–4.29], I^2=94%), neither with treatment duration over 21 days (RR, 1.31 [95% CI, 0.16–8.13], I^2=96%) nor within 21 days (RR, 1.58 [95% CI, 0.89–2.80]; Figure 3).

Other Outcomes

CHANCE[4] and POINT[5] reported myocardial infarction events, and pooled data showed that DAPT was not associated with an increased risk of myocardial infarction (RR, 1.45 [95% CI, 0.62–3.39], I^2=0%; Figure 4). A sensitivity analysis based on effect size reported by individual study showed a similar result (HR, 1.44 [95% CI, 0.62–3.36], I^2=0%; Figure VII in the Data Supplement). Three studies reported the composite outcome of stroke, myocardial infarction,

Table 2. Outcomes Reported in Eligible Studies

Outcomes	FASTER[12]	CHANCE[4]	POINT[5]	THALES[10]
Stroke	X	X	X	X
Ischemic stroke	X'	X	X	X
Hemorrhage stroke	X'	X	X	X
Intracranial hemorrhage	X	X	-	X
Extracranial hemorrhage	X	-	-	-
TIA	-	X	-	-
Myocardial infarction	-	X	X	-
CVD death	-	X	X'	-
All-cause death	-	X	X	X
Bleeding				
Severe or moderate	X'	X'	X'	X
Severe	X	X	-	X
Moderate	X	X	-	-
Mild	X	X	X	-
Any bleeding	-	X	-	-
Stroke/MI/CVD death	X	X	X'	-
Stroke/TIA/ACS/death	X	-	-	-
Stroke/death	-	-	-	X

- indicates not reported and can not be calculated; ACS, acute coronary syndrome; CHANCE, Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Event; CVD, cardiovascular disease; FASTER, Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence; MI, myocardial infarction; POINT, Platelet-Oriented Inhibition in New TIA; THALES, The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death; TIA, transient ischemic attack; X, directly reported; and X', similar results can be obtained or calculated.

or cardiovascular death. Pooled data showed that DAPT reduced the risk by 28% (RR, 0.72 [95% CI, 0.63–0.82], I^2=0%, RD, −0.025 [95% CI, −0.041 to −0.009]; Figure 4 and Figure VIII in the Data Supplement). Sensitivity analysis based on HR showed similar results (HR, 0.71 [95% CI, 0.62–0.81], I^2=0%; Figure VII in the Data Supplement).

DISCUSSION

In patients with noncardioembolic high-risk TIA or mild ischemic stroke, our meta-analysis revealed that DAPT with aspirin and either clopidogrel or ticagrelor significantly reduced the risk for subsequent stroke, without increased risk of hemorrhagic stroke, mild bleeding, all-cause mortality, or cardiovascular death when compared with aspirin alone. However, DAPT increased by 1.2× the risk for severe or moderate bleeding compared with aspirin alone.

Consistent with current international acute stroke guidelines, our meta-analysis also demonstrated that DAPT is more effective than aspirin for stroke prevention with a similar safety profile. The THALES[10] trial with the largest sample size contributed more than the CHANCE[4] and the POINT[5] trials to the meta-analysis. The THALES[10] trial followed-up for 30 days, lacking follow-up outcomes at 90 days, whereas the other 3 trials all had follow-up for 90 days. The heterogeneity of these trials is not significant except in the analysis for moderate or severe bleeding.

With regards to the severe or moderate bleeding, the increased risk in DAPT was mainly driven by the THALES[10] trial using aspirin plus ticagrelor. In addition, long treatment duration of DAPT in POINT[5] and THALES[10] trials (90 and 30 days, respectively) may account for the high risk of severe or moderate bleeding. The loading dose of clopidogrel in the POINT[5] was 600 mg, which is higher than that of the CHANCE[4] trial

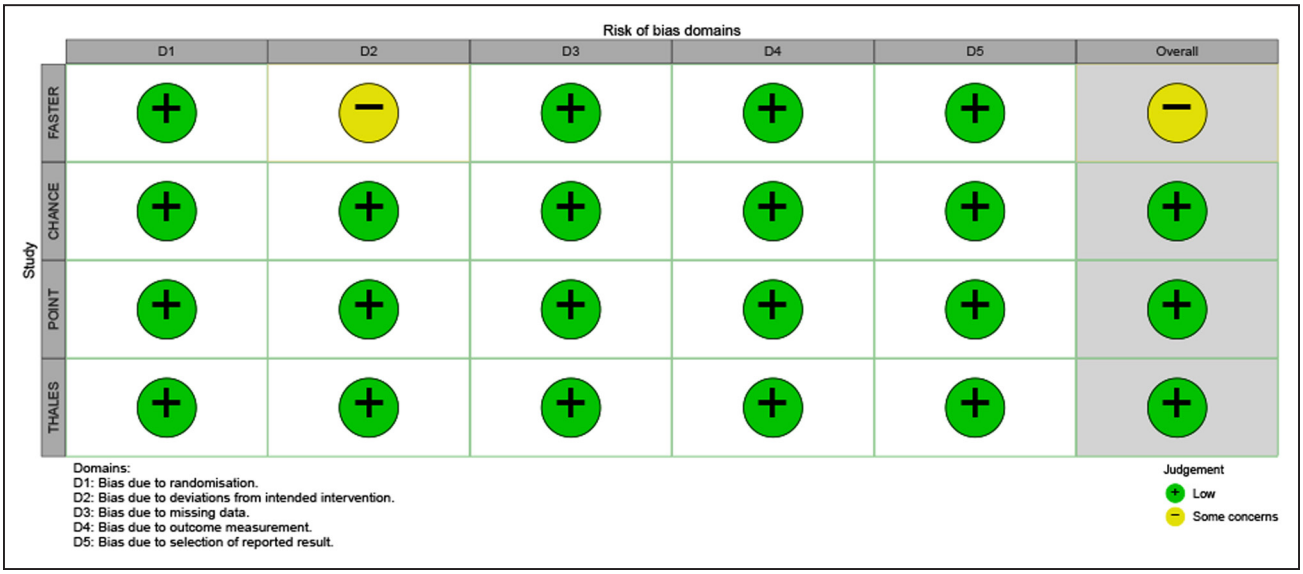

Figure 1. Risk of bias assessment for stroke outcome, severe or moderate bleeding.
CHANCE indicates Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Event; FASTER, Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence; POINT, Platelet-Oriented Inhibition in New TIA; and THALES, The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death.

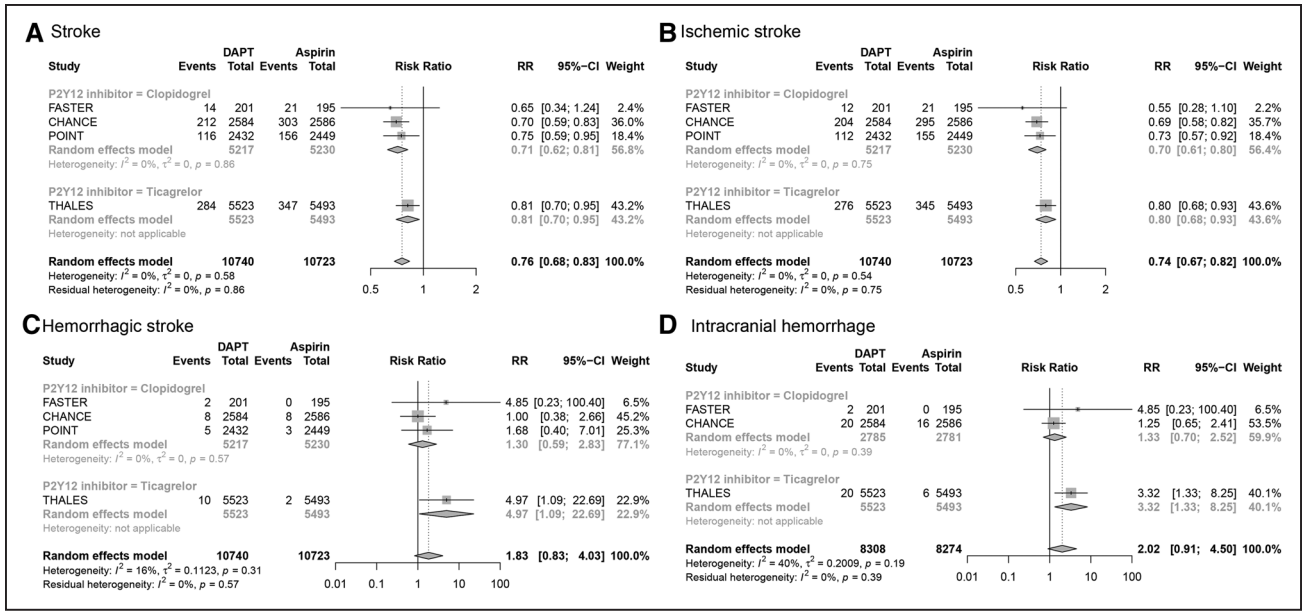

Figure 2. Forest plot for stroke outcomes.
A, Stroke; (**B**) ischemic stroke; (**C**) hemorrhagic stroke; (**D**) intracranial hemorrhage. CHANCE indicates Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Event; DAPT, dual antiplatelet; FASTER, Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence; POINT, Platelet-Oriented Inhibition in New TIA; RR, risk ratio; and THALES, The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death.

300 mg. The current meta-analysis suggests that the net benefit of DAPT appears to be optimal with 21 days of treatment, as suggested by prior time-course analyses of these trials.[14,15] However, the 21 days of treatment protocol was only performed in one trial, a further pooled analysis of individual data from CHANCE,[4] POINT,[5] and THALES[10] may provide more evidence of the optimal treatment duration.

In addition, serious bleeding can usually be prevented by effective medical therapy. Effective blood pressure control virtually eliminates intracerebral hemorrhage,[16–18] as was observed in the NASCET trial (North American Symptomatic Carotid Endarterectomy Trial),[17] intracerebral hemorrhage or subarachnoid hemorrhage was 0.5% in the medical arm with effective blood pressure control. Additionally, detection and treatment of

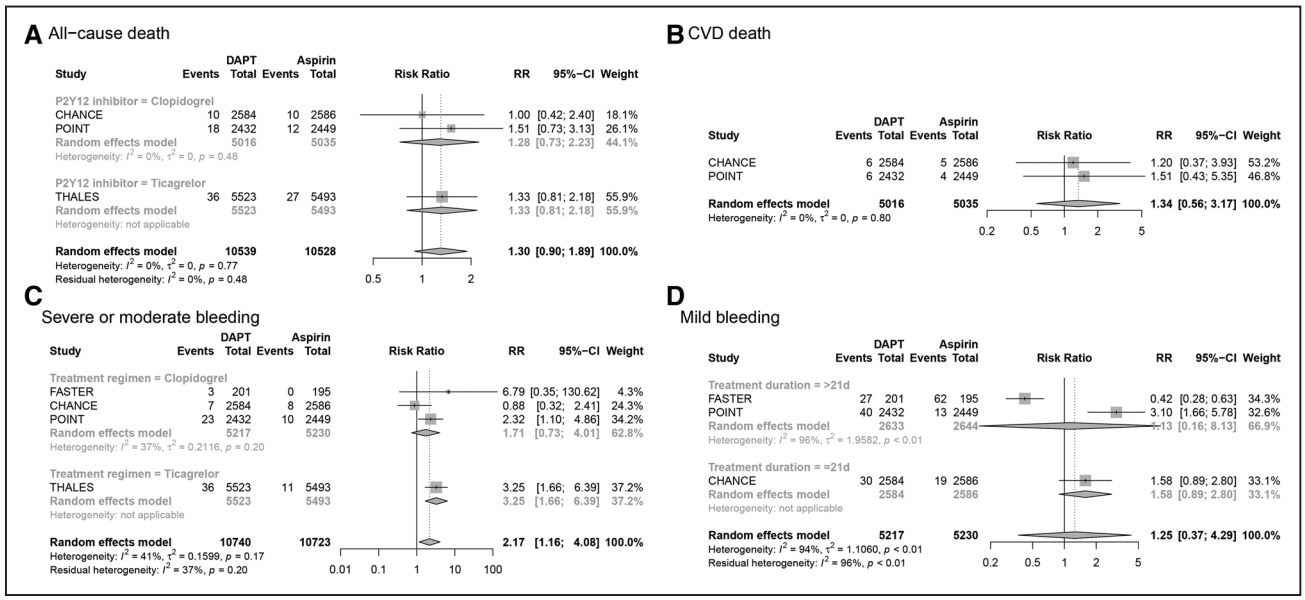

Figure 3. Forest plot for death and bleeding outcomes.
A, All-cause death; (**B**) cardiovascular disease death; (**C**) severe or moderate bleeding; (**D**) mild bleeding. CHANCE indicates Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Event; DAPT, dual antiplatelet; FASTER, Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence; POINT, Platelet-Oriented Inhibition in New TIA; RR, risk ratio; and THALES, The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death.

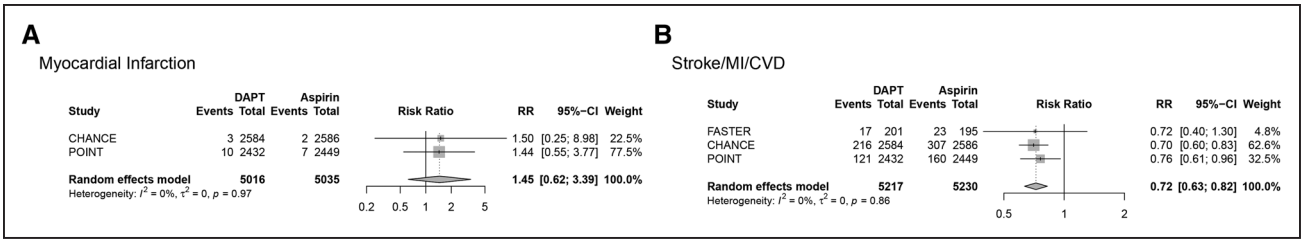

Figure 4. Forest plot for myocardial infarction (MI) and the composite outcome of stroke, MI, or cardiovascular disease (CVD) death.

A, Myocardial infarction; (**B**) stroke/myocardial infarction/cardiovascular disease death. CHANCE indicates Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Event; DAPT, dual antiplatelet; FASTER, Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence; POINT, Platelet-Oriented Inhibition in New TIA; RR, risk ratio; and THALES, The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death.

helicobacter pylori could prevent many major gastrointestinal hemorrhages.[19]

Our meta-analysis searched for trials on ticagrelor and included the recent THALES[10] trial, which extended the evidence of DAPT use beyond aspirin + clopidogrel to aspirin + clopidogrel/ticagrelor. The DAPT use of aspirin+ticagrelor has not been addressed in previous meta-analyses.[20–24] A recent meta-analysis by Hao et al[21] that compared clopidogrel plus aspirin versus aspirin alone, when DAPT was started within 24 hours of symptom onset that demonstrated a reduced risk of nonfatal recurrent stroke, without an apparent impact on all-cause mortality but with a likely increase in moderate or severe extracranial bleeding. Our meta-analysis also included recently published data from the THALES trial, and we performed more sensitivity analyses (stratified by treatment regimen or duration, used effect size of HR, RD, and number needed to treat) to draw more robust conclusions about DAPT.

The study was limited by lack of individual patient data of the included trials, which will provide more detailed results. However, we retrieved the main results from the included trials, and the consistency of the findings offers very convincing conclusions. Another limitation is that data extraction and analyses were not blinded to the authors, journals, or institutions of the publications, raising the possibility of assessor bias. However, 2 investigators performed the literature screening and data extraction independently, and the third investigator resolved discrepancies. Finally, 4 eligible trials were included, which prevented us from assessing publication bias. However, given the size and cost of trials in the field and no record of prior and unpublished major trials, publication bias is unlikely to have influenced the findings.

CONCLUSIONS

In patients with noncardioembolic high-risk TIA or mild ischemic stroke, DAPT with aspirin and either clopidogrel or ticagrelor is more effective than aspirin alone for stroke prevention with a small absolute increase in risk of severe or moderate bleeding.

ARTICLE INFORMATION

Received October 12, 2020; final revision received December 18, 2020; accepted March 22, 2021.
The podcast and transcript are available at https://www.ahajournals.org/str/podcast.

Affiliations

China National Clinical Research Center for Neurological Diseases (Z.-X.L., Y. Xiong, H.-Q.G., Y.-J.W.) and Vascular Neurology, Department of Neurology (Z.-X.L., Y. Xiong, Y.-J.W.), Beijing Tiantan Hospital, Capital Medical University, China. Chinese Institute for Brain Research, Beijing, China (Z.-X.L., Y. Xiong). Stroke Division, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA (M.F.). Department of Neurology, Duke University Medical Center, Durham, NC (Y. Xian). Duke Clinical Research Institute, Duke University, Durham, NC (Y. Xian). Dell Medical School, University of Texas, Austin (S.C.J.). Beijing Key Laboratory of Translational Medicine for Cerebrovascular Disease, China (Y.-J.W.).

Sources of Funding

This work was supported by grants from the Beijing Talents Project (2018A13), Beijing Municipal Science and Technology Commission (D171100003017002), and National Natural Science Foundation of China (81671172).

Disclosures

Dr Johnston reports grants from AstraZeneca and other from Sanofi during the conduct of the study. The other authors report no conflicts.

Supplemental Materials

Online Tables I–II
Online Figures I–VIII

REFERENCES

1. von Weitzel-Mudersbach P, Andersen G, Hundborg HH, Johnsen SP. Transient ischemic attack and minor stroke are the most common manifestations of acute cerebrovascular disease: a prospective, population-based study–the Aarhus TIA study. *Neuroepidemiology*. 2013;40:50–55. doi: 10.1159/000341696
2. 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;328:326. doi: 10.1136/bmj.37991.635266.44
3. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA*. 2000;284:2901–2906. doi: 10.1001/jama.284.22.2901
4. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, Wang C, Li H, Meng X, Cui L, et al; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med*. 2013;369:11–19. doi: 10.1056/NEJMoa1215340

5. Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, Kim AS, Lindblad AS, Palesch YY; Clinical Research Collaboration, Neurological Emergencies Treatment Trials Network, and the POINT Investigators. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med*. 2018;379:215–225. doi: 10.1056/NEJMoa1800410
6. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50:e344–e418. doi: 10.1161/STR.0000000000000211
7. Wang Y, Zhao X, Lin J, Li H, Johnston SC, Lin Y, Pan Y, Liu L, Wang D, Wang C, et al; CHANCE investigators. Association between CYP2C19 loss-of-function Allele status and efficacy of clopidogrel for risk reduction among patients with minor stroke or transient ischemic attack. *JAMA*. 2016;316:70–78. doi: 10.1001/jama.2016.8662
8. Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. *Eur Heart J*. 2006;27:1038–1047. doi: 10.1093/eurheartj/ehi754
9. Storey RF, Husted S, Harrington RA, Heptinstall S, Wilcox RG, Peters G, Wickens M, Emanuelsson H, Gurbel P, Grande P, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2007;50:1852–1856. doi: 10.1016/j.jacc.2007.07.058
10. Johnston SC, Amarenco P, Denison H, Evans SR, Himmelmann A, James S, Knutsson M, Ladenvall P, Molina CA, Wang Y; THALES Investigators. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. *N Engl J Med*. 2020;383:207–217. doi: 10.1056/NEJMoa1916870
11. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi: 10.1136/bmj.l4898
12. Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM; FASTER Investigators. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. *Lancet Neurol*. 2007;6:961–969. doi: 10.1016/S1474-4422(07)70250-8
13. Johnston SC, Easton JD, Farrant M, Barsan W, Battenhouse H, Conwit R, Dillon C, Elm J, Lindblad A, Morgenstern L, et al. Platelet-oriented inhibition in new TIA and minor ischemic stroke (POINT) trial: rationale and design. *Int J Stroke*. 2013;8:479–483. doi: 10.1111/ijs.12129
14. Pan Y, Elm JJ, Li H, Easton JD, Wang Y, Farrant M, Meng X, Kim AS, Zhao X, Meurer WJ, et al. Outcomes associated with clopidogrel-aspirin use in minor stroke or transient ischemic attack: a pooled analysis of clopidogrel in high-risk patients with acute non-disabling cerebrovascular events (CHANCE) and platelet-oriented inhibition in new TIA and minor ischemic stroke (POINT) Trials. *JAMA Neurol*. 2019;76:1466–1473. doi: 10.1001/jamaneurol.2019.2531
15. Johnston SC, Elm JJ, Easton JD, Farrant M, Barsan WG, Kim AS, Lindblad AS, Palesch YY, Zurita KG, Albers GW, et al; POINT and Neurological Emergencies Treatment Trials Network Investigators. Time course for benefit and risk of clopidogrel and aspirin after acute transient ischemic attack and minor ischemic stroke. *Circulation*. 2019;140:658–664. doi: 10.1161/CIRCULATIONAHA.119.040713
16. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med*. 1988;318:1728–1733. doi: 10.1056/NEJM198806303182605
17. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, Rankin RN, Clagett GP, Hachinski VC, Sackett DL, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*. 1998;339:1415–1425. doi: 10.1056/NEJM199811123392002
18. Spence JD. Antihypertensive drugs and prevention of atherosclerotic stroke. *Stroke*. 1986;17:808–810. doi: 10.1161/01.str.17.5.808
19. Chan FK, Ching JY, Hung LC, Wong VW, Leung VK, Kung NN, Hui AJ, Wu JC, Leung WK, Lee VW, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N Engl J Med*. 2005;352:238–244. doi: 10.1056/NEJMoa042087
20. Ding L, Peng B. Efficacy and safety of dual antiplatelet therapy in the elderly for stroke prevention: a systematic review and meta-analysis. *Eur J Neurol*. 2018;25:1276–1284. doi: 10.1111/ene.13695
21. Hao Q, Tampi M, O'Donnell M, Foroutan F, Siemieniuk RA, Guyatt G. Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack: systematic review and meta-analysis. *BMJ*. 2018;363:k5108. doi: 10.1136/bmj.k5108
22. Huang Y, Li M, Li JY, Li M, Xia YP, Mao L, Hu B. The efficacy and adverse reaction of bleeding of clopidogrel plus aspirin as compared to aspirin alone after stroke or TIA: a systematic review. *PLoS One*. 2013;8:e65754. doi: 10.1371/journal.pone.0065754
23. Liu Y, Fei Z, Wang W, Fang J, Zou M, Cheng G. Efficacy and safety of short-term dual- versus mono-antiplatelet therapy in patients with ischemic stroke or TIA: a meta-analysis of 10 randomized controlled trials. *J Neurol*. 2016;263:2247–2259. doi: 10.1007/s00415-016-8260-7
24. Palacio S, Hart RG, Pearce LA, Anderson DC, Sharma M, Birnbaum LA, Benavente OR. Effect of addition of clopidogrel to aspirin on stroke incidence: meta-analysis of randomized trials. *Int J Stroke*. 2015;10:686–691. doi: 10.1111/ijs.12050