Comparison of Ticagrelor vs Clopidogrel in Addition to Aspirin in Patients With Minor Ischemic Stroke and Transient Ischemic Attack
A Network Meta-analysis

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+ **Supplemental content**

IMPORTANCE Dual antiplatelet therapy (DAPT) with clopidogrel and aspirin is effective in preventing recurrent strokes after minor ischemic stroke or transient ischemic attack (TIA). However, there is emerging evidence for the use of ticagrelor and aspirin, and the 2 DAPT regimens have not been compared directly.

OBJECTIVE To compare ticagrelor and aspirin with clopidogrel and aspirin in patients with acute minor ischemic stroke or TIA in the prevention of recurrent strokes or death.

DATA SOURCES MEDLINE, Embase, and Cochrane from database inception until February 2021.

STUDY SELECTION Randomized clinical trials that enrolled adults with acute minor ischemic stroke or TIA and provided the mentioned interventions within 72 hours of symptom onset, with a minimum follow-up of 30 days.

DATA EXTRACTION AND SYNTHESIS PRISMA guidelines for network meta-analyses were followed. Two reviewers independently extracted data and appraised risk of bias. Fixed-effects models were fit using a bayesian approach to network meta-analysis. Between-group comparisons were estimated using hazard ratios (HRs) with 95% credible intervals (95% CrIs). Surface under the cumulative rank curve plots were produced.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of recurrent stroke or death up to 90 days. Secondary outcomes include major bleeding, mortality, adverse events, and functional disability. A sensitivity analysis was performed at 30 days for the primary outcome.

RESULTS A total of 4014 citations were screened; 5 randomized clinical trials were included. Data from 22 098 patients were analyzed, including 5517 in the clopidogrel and aspirin arm, 5859 in the ticagrelor and aspirin arm, and 10 722 in the aspirin arm. Both clopidogrel and aspirin (HR, 0.74; 95% CrI, 0.65-0.84) and ticagrelor and aspirin (HR, 0.79; 95% CrI, 0.68-0.91) were superior to aspirin in the prevention of recurrent stroke and death. There was no statistically significant difference between clopidogrel and aspirin compared with ticagrelor and aspirin (HR, 0.94; 95% CrI, 0.78-1.13). Both DAPT regimens had higher rates of major hemorrhage than aspirin alone. Clopidogrel and aspirin was associated with a decreased risk of functional disability compared with aspirin alone (HR, 0.82; 95% CrI, 0.74-0.91) and ticagrelor and aspirin (HR, 0.85; 95% CrI, 0.75-0.97).

CONCLUSIONS AND RELEVANCE DAPT combining aspirin with either ticagrelor or clopidogrel was superior to aspirin alone, but there was no statistically significant difference found between the 2 regimens for the primary outcome.

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P atients with minor ischemic stroke or transient ische-
mic attack (TIA) represent a population at high risk of
recurrent stroke.[1-4] In the subsequent 3 months, rates
of recurrent stroke range from 10% to 20%.[5] It is crucial to iden-
tify secondary prevention strategies in this high-risk popula-
tion to reduce morbidity and mortality.[6]

Multiple clinical trials established the superior efficacy of
short-term dual antiplatelet therapy (DAPT) with clopidogrel and
aspirin compared with antiplatelet monotherapy for secondary
stroke prevention following minor stroke or TIA.[7,8] This led to
revised guideline recommendations from multiple organiza-
tions, including the American Heart Association Guidelines
for the Prevention of Stroke in Patients With Stroke and TIA and
the Heart and Stroke Foundation of Canada Stroke Best Practice
Recommendations for Stroke Prevention.[9,10] Subsequently, the
recent publication of the Acute Stroke or Transient Ischaemic
Attack Treated with Ticagrelor and ASA [acetylsalicylic acid]
for Prevention of Stroke and Death (THALES) trial[11] in 2020 dem-
onstrated similar results using an alternative DAPT regimen;
the combination of ticagrelor and aspirin was also superior to
aspirin monotherapy in reducing the risk of stroke or death. This
prompted an expedited review from the European Stroke
Organization on the early use of DAPT in patients with minor
stroke or TIA, which established strong recommendations sup-
porting the use of clopidogrel and aspirin based on multiple trials
and weak recommendations supporting ticagrelor and aspirin
based on a single trial alone.[12]

To our knowledge, there are currently no large random-
ized clinical trials (RCTs) directly comparing these 2 DAPT regi-
mens. Hence, we performed a systematic review and net-
work meta-analysis (NMA) to synthesize available evidence
and compare the relative efficacy and safety of ticagrelor and
aspirin vs clopidogrel and aspirin in the acute minor ischemic
stroke and TIA populations.

Methods

The study protocol was registered with the Open Science
Framework and published in a peer-reviewed journal.[13] The
completed review has been prepared in consultation with
the Preferred Reporting Items for Systematic Reviews and
Meta-analyses (PRISMA) Extension Statement for Network
Meta-analysis.[14]

Inclusion Criteria

To be eligible, participants had to be adults presenting with
a National Institutes of Health Stroke Scale (NIHSS) score of
5 or less or an ABCD^2 score of 4 or higher for TIA and started
DAPT within 72 hours of presentation. The intervention and
comparator had to be among the following, in any dose or for-
mulation: ticagrelor and aspirin vs aspirin, clopidogrel and as-
pirin vs aspirin, or ticagrelor and aspirin vs clopidogrel and
aspirin. The outcomes required for inclusion were recurrent
stroke or death with a minimum follow-up period of 30 days.
Only RCTs were included. Studies that enrolled a pediatric
population, those with moderate or severe strokes, other stroke
subtypes (ie, cerebral venous sinus thrombosis), or those who

Key Points

Question In patients with minor ischemic stroke or transient
ischemic attack, how does ticagrelor and aspirin compare with
clopidogrel and aspirin in preventing recurrent ischemic strokes
and death?

Findings In this network meta-analysis including 22 098 patients
from 5 randomized clinical trials, dual antiplatelet therapy
combining aspirin with either ticagrelor or clopidogrel was superior
to aspirin alone, but there was no statistically significant difference
found between ticagrelor and clopidogrel in the prevention of
recurrent strokes or death.

Meaning Findings of this study suggest that short-term dual
antiplatelet therapy with aspirin and either ticagrelor or
clopidogrel is effective after minor ischemic stroke or transient
ischemic attack.

were administered thrombolysis or endovascular thrombec-
tomy were excluded.[13] Observational studies and studies not
written in French or English were also excluded.

Literature Search

We used the following databases: MEDLINE, Embase, and
Cochrane Registry of Clinical Trials and included articles from
database inception until February 2021. Additionally, we
searched the abstracts database from both the World Stroke
Congress and International Stroke Conference for potentially
relevant abstracts over the last 20 years. The search strategy
was developed with the assistance of a health science librar-
ian with expertise in systematic reviews and is detailed in
eTable 1 in the Supplement.

Article and Data Extraction

Two reviewers (S.D. and D.C.R.) independently completed level
1 (title and abstract) and level 2 (full-text) screening for ar-
ticles using Covidence Systematic Review Software. A pilot ex-
ercise was conducted initially for both levels of screening to
ensure consistency between reviewers. Discrepancies were
settled by discussion with a third reviewer (R.L.). Findings from
the screening process were summarized using a flow diagram
(Figure 1).[15]

A data extraction form was created a priori and piloted
independently by all reviewers. The data extracted included
journal article characteristics (journal name, publication
year, authors, and country of origin), study methodology
(article type), participant characteristics (age, presence of
risk factors, and intervention) and comparator details (medi-
cation name, dosage [loading dose and maintenance dose],
and duration), outcome data (death, number of strokes
[ischemic and hemorrhagic], functional dependence, bleed-
ing, and adverse events), and study results (odds ratios and
hazard ratios [HRs], if available).

Risk of Bias Assessment

Risk of bias of individual studies was assessed using the
Cochrane Risk of Bias tool for randomized trials version 2
(RoB2).[16] Raters independently implemented the tool, and any

disagreement in the rating was resolved by discussion. The effect of interest that was used for the RoB2 assessment was the effect of assignment to the intervention at baseline. The main outcome assessed for risk of bias was the results of the primary outcome: recurrent stroke or death. The domains of the RoB2 assessment tool were random sequence generation, effect of assignment, missing outcome data, measurement of the outcome, and selective outcome reporting. These domains were judged using high, some concerns, or low risk of bias judgments. Findings from these assessments have been summarized pictorially.

Statistical Analysis

Prior to performance of the NMAs, we appraised the clinical and methodologic characteristics of the included studies to judge the appropriateness of the transitivity assumption. We also conducted fixed-effects (FE) pairwise meta-analyses of the available data to inspect for statistical heterogeneity of treatment effects using I^2 values (eTable 2 in the Supplement).

We performed all NMAs using BUGSnet version 1.0.4 and JAGS packages in RStudio version 1.4.1106 (RStudio), evaluated under a bayesian framework with Markov Chain Monte Carlo simulation.[17-19] Because of the limited number of studies in all connections of the treatment network and given model fit was adequate, FE models were used for all primary analyses; analyses using random-effects (RE) models have also been provided (eTable 3 in the Supplement). All NMAs were performed using a model for binary outcomes using a cloglog link function to account for differences in follow-up time. We ran the estimation with a burn-in of 25 000 iterations and sampling of 50 000 iterations from 3 chains of initial values. Model fit was assessed by comparing the posterior total residual deviance with the number of unconstrained data points.[20] The selection between models was based on the deviance information criteria (DIC), with smaller values indicative of a greater fit and a difference greater than 5 points suggesting an important difference.[21,22] We evaluated consistency of direct and indirect evidence by fitting an unrelated means model and comparing DIC and residuals with those from the corresponding consistency model (eTable 4 in the Supplement).[21] Convergence was visually inspected using trace plots and Gelman-Rubin diagnostics.[20,23] HRs with 95% credible intervals (95% CrIs) were estimated using arm-based analyses based on aggregate data from intention-to-treat analyses presented in eligible articles. We also calculated secondary measures of treatment effect for each intervention in the form of surface under the cumulative rank curve (SUCRA) probabilities and treatment rankings.[19] P values were calculated using the χ^2 test of heterogeneity. Significance was set at $P < .05$, and all P values were 2-tailed.

The primary outcome was recurrent stroke or death at 90 days. Secondary outcomes included individual components of the composite outcome (ischemic stroke, hemorrhagic stroke, and mortality), functional disability, and safety outcomes (such as major bleeding and reports of adverse events). We defined functional disability as modified Rankin Scale scores of 2 to 6. A sensitivity analysis was done of the

Figure 1. PRISMA Flow Diagram
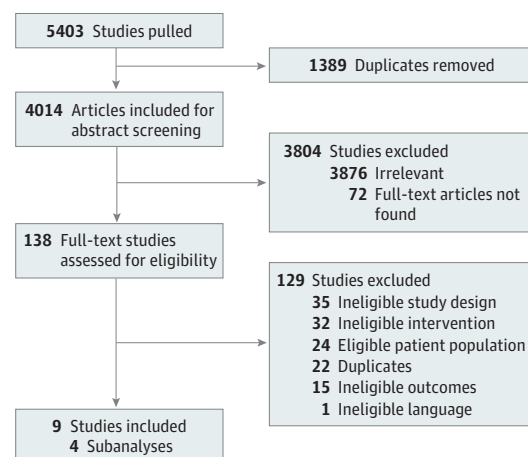
primary outcome at 30 days to account for varying lengths of treatment duration and follow-up time.

Results

The search identified 5403 studies, and after removing duplicates, we screened 4014 unique titles and abstracts. Subsequently, we assessed 138 articles in full-text review; reasons for exclusion are provided in Figure 1. Nine articles met eligibility for extraction, representing 5 RCTs and 4 subgroup analyses (Figure 1).[7,8,11,24-29] We found 3 RCTs comparing clopidogrel and aspirin with aspirin,[7,8,29] 1 comparing ticagrelor and aspirin with aspirin,[11] and 1 comparing the 2 DAPT regimens against each other.[28] In total, we analyzed data from 22 098 individuals: 10 722 received aspirin, 5517 received clopidogrel and aspirin, and 5859 received ticagrelor and aspirin; the corresponding network diagram is presented in **Figure 2**.

Overview of Study and Patient Characteristics

The mean and median ages were similar across all studies (**Table 1**). Inclusion criteria for stroke and TIA severity were comparable across studies with ranges of 0 to 5 and 4 to 7 for NIHSS and ABCD^2 scores, respectively; the Fast Assessment of Stroke and Transient Ischaemic Attack to Prevent Early Recurrence (FASTER) trial was an exception, as the ABCD^2 score had not been developed at the time of the trial (Table 1).[29,30] The timing from symptom onset to medication initiation was similar across studies—either within 12 or 24 hours for all trials (Table 1). The trials used similar loading and maintenance doses of clopidogrel and ticagrelor, while loading and maintenance doses for aspirin varied slightly between studies, although still within the known effective range (Table 1).[31] Overall treatment periods ranged from 21 days to 90 days. The definitions of stroke, bleeding events, and adverse events for each study are outlined in eTable 5 in the Supplement and were deemed homogeneous across studies. In terms of methodological homogeneity, all studies

Figure 2. Network Diagram of the Total Number of Patients Analyzed in Each Treatment Arm for All 90-Day Outcomes, Excluding Functional Disability
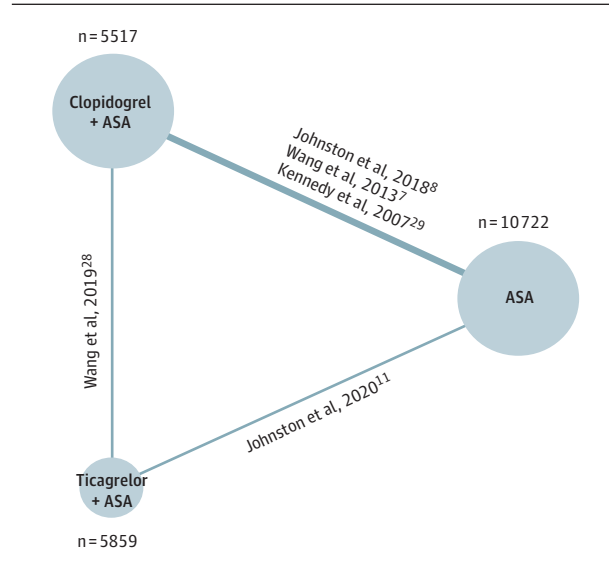
ASA indicates acetylsalicylic acid (aspirin).

had a low risk of bias across all RoB2 domains (eFigure 1 in the Supplement).

Figure 2 shows the networks of eligible treatment comparisons for the primary outcome—a composite of stroke or death up to 90 days. All other outcomes, except for functional disability and mortality, were reported in all 22 098 patients from a total of 5 trials evaluating 3 classes of interventions (Figure 2).[7,8,11,28,29] Functional disability and 30-day composite outcomes were both reported in 21 031 of 22 098 patients (95.2%) from a total of 3 trials (eFigure 2 in the Supplement),[7,8,11] and mortality up to 90 days was reported in 21 706 of 22 098 patients (98.2%) from a total of 4 trials (eFigure 3 in the Supplement).[7,8,11,28]

For all outcomes, comparisons of total posterior residual deviance with the number of unconstrained data points for all FE and RE NMAs suggested fit was adequate. Comparisons of DIC suggested no important differences in fit between FE and RE consistency models, and therefore results from FE models are presented for all analyses (eTable 4 in the Supplement). Comparisons of DIC and inspection of leverage plots provided no suggestions of violation of the consistency assumption. Details of model fit statistics and checks for inconsistency are provided in eTable 4 and eFigure 4 in the Supplement.

Primary Outcome: 90-Day Composite of Recurrent Stroke or Mortality
Clopidogrel and aspirin and ticagrelor and aspirin were both more efficacious in preventing stroke or death compared with aspirin alone (clopidogrel: HR, 0.74; 95% CrI, 0.65-0.84; ticagrelor: HR, 0.79; 95% CrI, 0.68-0.91; Table 2). There was no significant difference when comparing clopidogrel and aspirin with ticagrelor and aspirin (HR, 0.94; 95% CrI, 0.78-1.13). Clopidogrel and aspirin had the highest SUCRA value

for our primary outcome at 0.76, followed by ticagrelor and aspirin (SUCRA, 0.24), and aspirin alone (SUCRA, 0; Table 2).

Ischemic Stroke
Ischemic strokes contributed most to the primary composite outcome. Compared with aspirin, clopidogrel and aspirin (HR, 0.71; 95% CrI, 0.62-0.82) and ticagrelor and aspirin (odds ratio, 0.74; 95% CrI, 0.64-0.86) resulted in significant reductions in recurrent ischemic stroke (Table 2). SUCRA values suggest that clopidogrel and aspirin may be associated with the lowest risk of recurrent ischemic stroke at 90 days (SUCRA, 0.66), while aspirin appeared to have the highest risk (SUCRA, 0; Table 2).

Hemorrhagic Stroke
Neither DAPT regimen resulted in a significant increase of hemorrhagic stroke compared with aspirin (Table 2). There was also no significant difference in the number of hemorrhagic strokes between the 2 DAPT regimens (HR, 0.67; 95% CrI, 0.26-1.70; Table 2). Based on SUCRA values, ticagrelor and aspirin was associated with the highest risk of hemorrhagic stroke (SUCRA, 0.12; Table 2).

Major Hemorrhage
Clopidogrel and aspirin and ticagrelor and aspirin both resulted in a significant increase in major hemorrhage compared with aspirin alone (clopidogrel: HR, 1.78; 95% CrI, 1.09-2.92; ticagrelor: HR, 2.63; 95% CrI, 1.51-4.82; Table 2). SUCRA values further suggest that aspirin is associated with the lowest risk of major hemorrhage (SUCRA, 0.99), followed by clopidogrel and aspirin (SUCRA, 0.01) and ticagrelor and aspirin (SUCRA, 0; Table 2).

Functional Disability
Clopidogrel and aspirin was associated with a lower risk of 90-day functional disability compared with aspirin alone and compared with ticagrelor and aspirin (clopidogrel: HR, 0.82; 95% CrI, 0.74-0.91; ticagrelor: HR, 0.85; 95% CrI, 0.75-0.97). SUCRA values confirmed clopidogrel and aspirin to be the best treatment, with a SUCRA value of 0.99, compared with 0.01 for ticagrelor and aspirin and 0 for aspirin monotherapy (Table 2).

Mortality and Serious Adverse Events
There was no difference in the risk of 90-day mortality or adverse events between any of the treatment regimens (Table 2). However, SUCRA values can provide some indication of possible ordering of treatments based on probabilities of being the best treatment: ticagrelor and aspirin was associated with the highest SUCRA value (0.78) for mortality, while aspirin alone was associated with the lowest SUCRA value (0.09). The complete definitions for individual outcomes in each included trial are included in eTable 5 in the Supplement; while the FASTER and Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events (CHANCE) trials included study outcomes (ie, hemorrhagic strokes) in their definitions for adverse events,[7,29] the Platelet-Oriented Inhibition in New TIA and Minor

Table 1. Study and Patient Characteristics of Included Studies for Analysis

Parameter	CHANCE[7]	FASTER[29]	POINT[8]	PRINCE[28]	THALES[11]
Study design	Parallel, double-blind, placebo-controlled RCT	Factorial, double-blind RCT	Parallel, double-blind, placebo-controlled RCT	Parallel, open-label RCT	Parallel, double-blind placebo-controlled RCT
Sample size of active/control arms	Clopidogrel and ASA: 2584; ASA: 2586	Clopidogrel and ASA: 198; ASA: 194	Clopidogrel and ASA: 2432; ASA: 2449	Ticagrelor and ASA: 336; Clopidogrel and ASA: 339	Ticagrelor and ASA: 5523; ASA: 5493
Treatment window from symptom onset, h	24	24	12	24	24
NIHSS score, range	0-3	0-3	0-3	0-3	0-5
ABCD^2 score, range	4-7	NA	4-7	4-7	6-7
DAPT treatment duration, d	21	90	90	21	30
Country of publication	China	Canada	US	China	US
Countries that attended the trial	China	Canada, US	Australia, Canada, Finland, France, Germany, Mexico, New Zealand, Spain, United Kingdom, US	China	Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, China, Czechia, France, Germany, Hong Kong, Hungary, India, Italy, Mexico, Peru, Poland, Romania, Russia, Saudi Arabia, Slovakia, South Korea, Spain, Sweden, Taiwan, Thailand, Ukraine, Vietnam
Clopidogrel					
Loading dose, mg	300	300	600	300	NA
Maintenance dose, mg	75	75	75	75	NA
Maintenance duration, d	2-90	2-90	2-90	2-90	NA
Ticagrelor					
Loading dose, mg	NA	NA	NA	180	180
Maintenance dose, mg	NA	NA	NA	90	90
Maintenance duration, d	NA	NA	NA	2-90	2-30
ASA					
Loading dose, mg	75-300	162	50-325	100-300	300-325
Maintenance dose, mg	75	81	50-325	100	75-100
Maintenance duration, d	Clopidogrel and ASA: 2-21; ASA: 2-90	Clopidogrel and ASA: 2-90; ASA: 2-90	Clopidogrel and ASA: 2-90; ASA: 2-90	Ticagrelor and ASA: 2-21; Clopidogrel and ASA: 2-21	Ticagrelor and ASA: 2-30; ASA: 2-30
Follow-up period, d	90	90	90 (76-104)	7-90	30-60
Median age, y	Clopidogrel and ASA: 63; ASA: 62	Clopidogrel and ASA mean age: with simvastatin, 67.1; without simvastatin, 68.9; ASA mean age: with simvastatin, 66.6; without simvastatin, 69.8	Clopidogrel and ASA: 65 ASA: 65	Ticagrelor and ASA: 62; clopidogrel and ASA: 61	Ticagrelor and ASA mean age: 65.2; ASA mean age: 65.1
Male, %	66.2	52.8	55.1	73.2	61.7
White, %	NA	91.8	75.1	NA	53.8

Abbreviations: ASA, acetylsalicylic acid (aspirin); DAPT, dual antiplatelet therapy; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; RCT, randomized clinical trial.

Table 2. Fixed-Effects Model Measures for Efficacy and Safety Up to 90 Days and 30 Days for Studies With Available Data[a]

Outcome measure	Estimates from NMA			SUCRA[b]		
	HR (95% CrI)					
	Clopidogrel and ASA vs ASA	Ticagrelor and ASA vs ASA	Clopidogrel and ASA vs ticagrelor and ASA	Clopidogrel and ASA	Ticagrelor and ASA	ASA
Outcomes up to 90 d						
Primary composite outcome of stroke and death	0.74 (0.65-0.84)[c]	0.79 (0.68-0.91)[c]	0.94 (0.78-1.13)	0.76	0.24	0
Ischemic stroke only	0.71 (0.62-0.82)[c]	0.74 (0.64-0.86)[c]	0.96 (0.79-1.17)	0.66	0.34	0
Hemorrhagic stroke only	0.99 (0.54-1.83)	1.48 (0.63-3.61)	0.67 (0.26-1.70)	0.46	0.12	0.42
Mortality	0.64 (0.45-0.91)[c]	0.53 (0.36-0.77)[c]	1.20 (0.76-1.90)	0.22	0.78	0
Major hemorrhage	1.78 (1.09-2.92)[c]	2.63 (1.51-4.82)[c]	0.68 (0.33-1.33)	0.01	0	0.99
Adverse events	1.03 (0.89-1.18)	0.86 (0.75-1.00)	1.19 (0.98-1.44)	0.04	0.94	0.02
Functional disability	0.82 (0.74-0.91)[c]	0.96 (0.89-1.04)	0.85 (0.75-0.97)[c]	0.99	0.01	0
Outcomes up to 30 d						
Composite outcome of stroke and death	0.68 (0.59-0.79)[c]	0.82 (0.71-0.95)[c]	0.83 (0.68-1.02)	0.96	0.04	0

Abbreviations: ASA, acetylsalicylic acid (aspirin); CrI, credible interval; NMA, network meta-analysis; HR, hazard ratio; SUCRA, surface under the cumulative rank curve.

[a] Thirty-day outcomes and functional disability only include data from the THALES, POINT, and CHANCE trials; mortality only included data from the

THALES, POINT, CHANCE, and PRINCE trials.

[b] Values nearest 1 denote preferred treatment.

[c] P < .05.

Ischemic Stroke (POINT) and THALES trials excluded components of the primary efficacy outcome measures, including strokes.[8,11]

Sensitivity Analysis for 30-Day Recurrent Stroke and Mortality

Compared with aspirin, both clopidogrel and aspirin as well as ticagrelor and aspirin resulted in a significant reduction of recurrent stroke or mortality at 30 days (clopidogrel: HR, 0.68; 95% CrI, 0.59-0.79; ticagrelor: HR, 0.82; 95% CrI, 0.71-0.95; Table 2). There was no significant difference when comparing clopidogrel and aspirin with ticagrelor and aspirin (HR, 0.83; 95% CrI, 0.68-1.02; Table 2). Based on SUCRA values, clopidogrel and aspirin was associated with the lowest risk of recurrent stroke or death up to 30 days (SUCRA, 0.96), followed by ticagrelor and clopidogrel (SUCRA, 0.04) and aspirin (SUCRA, 0).

Discussion

In this systematic review and NMA, we found no statistically significant difference in efficacy between clopidogrel and aspirin as well as ticagrelor and aspirin in the prevention of recurrent strokes or death up to 90 days. Moreover, we have confirmed that either regimen of DAPT was superior to aspirin alone. Ischemic strokes made up most of the events in the composite primary outcome, and there was no difference noted between the 2 DAPT regimens in preventing their recurrence. While both DAPT regimens were associated with higher rates of major bleeding compared with aspirin alone, no difference was noted between ticagrelor and aspirin and clopidogrel and aspirin. Lastly, clopidogrel and aspirin was associated with a lower risk of functional disability compared with aspirin alone and ticagrelor and aspirin.

Calculated probabilities using SUCRA plots revealed that ranking of the regimens assessed in the prevention of the primary outcome is as follows: clopidogrel and aspirin had the highest SUCRA value (ie, suggesting it is likely the best treatment), followed by ticagrelor and aspirin and aspirin monotherapy. Rankings based on SUCRA values should be interpreted with caution, particularly since comparisons of HRs across treatments were not significant for most secondary outcomes.

Our results are in line with the latest rapid review from the European Stroke Organization stating stronger evidence for the acute, short-term use of clopidogrel and aspirin compared with ticagrelor and aspirin in the minor ischemic stroke and TIA population.[12] This is largely because of a greater number of trials evaluating the use of clopidogrel and aspirin in our study cohort.[7,8,29] Conversely, the THALES trial was the only RCT evaluating the use of ticagrelor and aspirin compared with aspirin,[11] resulting in a lower level of evidence recommendation. We provide further evidence to support this recommendation, as our rankings suggest clopidogrel and aspirin was the best treatment in preventing recurrent strokes and death, both at 30 days and 90 days. Furthermore, there was a trend toward favoring clopidogrel and aspirin compared with ticagrelor and aspirin for prevention of functional disability and bleeding-related complications. This is similar to previous meta-studies in the cardiology literature, reporting higher events of bleeding with ticagrelor DAPT compared with clopidogrel DAPT following myocardial infarction and percutaneous coronary intervention.[32,33]

Despite strong existing evidence to support the use of clopidogrel and aspirin in acute minor ischemic stroke and TIA,[1,9,10] clopidogrel may not be a universal therapy, as genetic variations may render the drug ineffective. Clopidogrel is a prodrug that requires enzyme activation by *CYP2C19* to be converted to its active metabolite form.[34] Individuals who carry

nonfunctional copies of *CYP2C19* are considered nonmetabolizers and may clinically present with recurrent ischemic events despite medication compliance.[35,36] The prevalence of clopidogrel resistance in the general population is highly variable in the literature, largely depending on the race and ethnicity of the population under study and definitions used.[37] It is estimated that approximately 30% of the US population carries a loss-of-function allele for the *CYP2C19* gene, and in Chinese populations, it may be as high as 60%.[36,38] Despite this, clopidogrel and aspirin seems to be an effective therapy for stroke prevention even when tested in a predominantly Chinese population (eg, CHANCE trial[7]), and therefore, the clinical significance of clopidogrel resistance remains unknown. Recently, the introduction of genetic testing in medicine has opened the door to new possibilities for personalized medicine: the genetic substudy of the CHANCE trial showed that clopidogrel and aspirin reduced the risk of stroke recurrence only in noncarriers of the *CYP2C19* loss-of-function allele and not in carriers.[39] However, routine genetic testing for clopidogrel resistance is not currently recommended for any indication. If a patient clinically presents with clopidogrel failure, an effective and safe alternative medication may be needed.[38,39] Our results support the use of ticagrelor and aspirin as an effective alternative therapy for these patients, given its comparable efficacy in prevention of recurrent strokes and death. The ongoing CHANCE-2 clinical trial in China will provide further insight after completion,[40] as it randomizes patients with minor stroke or TIA with *CYP2C19* loss-of-function allele to either ticagrelor and aspirin or clopidogrel and aspirin.[41] In the future, the choice of DAPT may be more precise and individualized based on genotype testing of *CYP2C19*. Until then, our results provide a direct comparison between the efficacy and safety of clopidogrel and aspirin vs ticagrelor and aspirin in the minor stroke and TIA populations.

Strengths and Limitations

The strengths of our study include the publication of an a priori protocol and comprehensive search strategy encompassing 3 databases.[13] Furthermore, the NMA is unique in its ability to produce rankings of treatments based on calculated probabilities, which is novel for this topic.[12,42] Nonetheless, there are a number of limitations that must be considered. First, by focusing on RCTs, we may have overlooked potential data from nonrandomized and gray literature. However, we believe this is also a strength, as it focuses only on article types with the highest hierarchy of evidence. Second, treatment durations differed between studies: patients enrolled in the CHANCE and Platelet Reactivity in Acute Stroke or Transient Ischaemic Attack (PRINCE) trials received DAPT for 21 days,[7,28] those in the THALES trial received DAPT for 30 days,[11] and patients in the POINT and FASTER trials were on DAPT for 90 days.[8,29] Furthermore, the THALES trial only reported outcomes up to 30 days. While our statistical analysis strategy using HRs accounts for varying follow-up times, this does not replace RCT-level data that actually follows patients for the entire 90-day period. To account for differences in treatment durations, we performed a post hoc analysis looking at the primary composite outcome at 30 days, which revealed similar findings. Owing to incomplete reporting of specific outcomes across trials, we were unable to report our prespecified primary outcome (ie, ischemic stroke alone at 30 days). However, we believe that the composite outcome of recurrent strokes or death is more clinically impactful than recurrent ischemic strokes and is in line with the primary outcomes reported across individual trials. Next, assessment of publication bias is difficult in an NMA owing to limited numbers of studies for each pairwise comparison.[14] Additionally, given the slight differences in inclusion and exclusion criteria between studies, there may be residual clinical and statistical heterogeneity between trials, although this is felt to be minimal.

Conclusions

In this NMA, DAPT was superior to aspirin in the prevention of recurrent strokes or death, but no statistically significant difference was found between clopidogrel and aspirin and ticagrelor and aspirin. The use of clopidogrel and aspirin was associated with a decreased risk for functional disability compared with ticagrelor and aspirin. Our study suggests aspirin and ticagrelor is a reasonable alternative to aspirin and clopidogrel where there is clopidogrel failure or intolerance.

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