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Efficacy and Safety of Using Dual Versus Monotherapy Antiplatelet Agents in Secondary Stroke Prevention

Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials

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BACKGROUND: Dual antiplatelet treatment (DAPT) with aspirin plus clopidogrel for a limited time is recommended after minor noncardioembolic stroke.

METHODS: We performed a meta-analysis of all major studies that compared the efficacy and safety of DAPT versus monotherapy for the secondary prevention of recurrent stroke or transient ischemic attack. The primary outcomes were stroke and the composite of stroke, transient ischemic attack, acute coronary syndrome, and death from any cause. The safety outcome was major hemorrhage. Relative risk (RR) and 95% CIs were calculated. Heterogeneity was assessed by P^2 and Cochrane Q statistics.

RESULTS: The analysis included 27 358 patients, the quality of evidence was moderate to low, and the heterogeneity for all the comparisons was low ($P \le 25\%$). Compared with monotherapy, DAPT reduced the risk of recurrent stroke (RR, 0.71 [95% CI, 0.63–0.81]) and composite outcome (RR, 0.76 [95% CI, 0.69–0.83]) but increased the risk of major bleeding (RR, 2.17 [95% CI, 1.45–3.25]). In the subgroup analysis, ≤ 30 days of DAPT increased the risk of hemorrhage relative to monotherapy (RR, 1.94 [95% CI, 1.08–3.52]). In the sensitivity analysis, the risk for hemorrhage with ≤ 30 days of DAPT after excluding the combination of aspirin plus ticagrelor was comparable to monotherapy (RR, 1.42 [95% CI, 0.77–2.60]). However, the risk for stroke recurrence and composite outcomes in the subgroup and sensitivity analyses remain decreased compared with monotherapy.

CONCLUSIONS: DAPT decreases the risk of recurrent stroke and composite events compared with monotherapy. DAPT increases the risk of major hemorrhage, except if the treatment is limited to 30 days and does not include the combination of aspirin plus ticagrelor.

Key Words: dual antiplatelet therapy
embolic stroke
ischemic attack, transient
safety
treatment outcome

S troke constitutes a leading cause of mortality and disability worldwide.¹ In patients with transient ischemic attack (TIA) or minor ischemic strokes, the stroke recurrence rate varies between 9.3% at day 7 and 16.1% at day 90.² Most noncardioembolic strokes are treated with antiplatelet monotherapy (MAPT). However, on the basis of the results of 2 independent large randomized controlled trials (RCTs), the CHANCE trial

(Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events)³ and the POINT trial (Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA),⁴ the American Heart Association/American Stroke Association acute ischemic stroke prevention guidelines consider the use of dual antiplatelet therapies (DAPTs) for a short period (21 days) after acute minor noncardioembolic stroke.⁵

For Sources of Funding and Disclosures, see page 2452.

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Clinical Perspective

What Is New?

- Compared with monotherapy, the use of dual antiplatelet treatment (DAPT) after stroke decreases the risk of recurrent stroke or transient ischemic attack (TIA), or the composite outcome of stroke, TIA, acute coronary syndrome, and death from any cause, but increases the risk of major hemorrhage.
- The risk of major hemorrhage is increased if DAPT is continued for >30 days or the regimen uses aspirin plus ticagrelor for ≤30 days.
- Except for aspirin plus ticagrelor, DAPT for ≤30 days decreases the risk of recurrent stroke/TIA and composite outcome but does not increase the risk of major hemorrhage compared with monotherapy.

What Are the Clinical Implications?

- The use of DAPT for ≤30 days after minor noncardioembolic ischemic stroke is superior to monotherapy for the prevention of recurrent stroke/TIA or the composite outcome of stroke, TIA, acute coronary syndrome, and death from any cause.
- Except for the combination of aspirin plus ticagrelor, the use of DAPT for ≤30 days does not increase the risk of major hemorrhage.

Nonstandard Abbreviations and Acronyms

ACS CHANCE	acute coronary syndrome Clopidogrel in High-Risk Patients With Acute Non-disabling Cerebrovascular Events
DAPT	dual antiplatelet therapy
MAPT	antiplatelet monotherapy
POINT	Clopidogrel and Aspirin in Acute Isch- emic Stroke and High-Risk TIA
PRISMA	Preferred Reporting Items for System- atic Reviews and Meta-Analyses
RCT	randomized controlled trial
ROBIS	Risk of Bias in Systematic Reviews
RoB2	Revised Cochrane Risk of Bias Tool for Randomized Trials
RR	risk ratio
THALES	Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA
ΤΙΑ	transient ischemic attack

More recently, the results of the THALES trial (Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA),⁶ the largest-to-date RCT comparing MAPT with DAPT, were reported. This study compared the efficacy and safety of 30-day treatment with aspirin monotherapy with the combination of aspirin and ticagrelor (a reversible direct adenosine diphosphate receptor antagonist) for the prevention of recurrent stroke after acute mild to moderate ischemic stroke (National Institutes of Health Stroke Scale score ≤5). This study showed that patients in the ticagrelor-aspirin group had a lower risk of the composite of stroke or death within 30 days, but an increased risk of severe bleeding compared with patients that received aspirin only.

The objective of this meta-analysis is to compare the efficacy and safety of DAPT with the efficacy and safety of MAPT in patients randomly assigned to either treatment within 3 days of experiencing ischemic stroke or TIA.

METHODS

Our study follows the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.⁷

The data that support the findings of this study are available from the corresponding author on reasonable request. The study was approved by the local institutional review committee. No informed consent was required from the human subjects given the nature of the analysis.

Eligibility Criteria

The study included RCTs that compared the efficacy and safety of DAPT and MAPT for adult patients with mild to moderate noncardioembolic acute ischemic stroke or TIA, who were randomly assigned to DAPT within 3 days from ictus. Observational studies, MAPT versus placebo, and noncontrolled studies were excluded.

Information Sources and Search Methods

PubMed, Embase, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and Medline were searched to find eligible studies. Key search words were "antiplatelet agent," "aspirin," "clopidogrel," "ticagrelor," "stroke," "cilostazol," "dipyridamole," "cerebral ischemia," "cerebral infarction," "ischemic stroke," "combined antiplatelet treatment," "randomized control trial," "transient ischemic attack," "dual versus monoantiplatelet" or "dual antiplatelet treatment" using the "AND" and "OR" advanced search functions. The search algorithm is presented in Appendix I in the Data Supplement.

Study Selection and Data Collection Process

The results of the search were screened for inclusion and exclusion criteria by 2 of the authors (F.D.T. and G.T.), and duplicate trials were removed. Disagreements were resolved using a third author (P.B.G.). To minimize heterogeneity, studies meeting the inclusion criteria were evaluated to ensure that the reported outcomes were similar. Search results identified 2 independent meta-analyses from 2012⁸ and 2013⁹ that compared the beneficial effect and safety of MAPT and DAPT after ischemic stroke. Some of the studies included in these meta-analyses had a randomization window that exceeded 3 days. Thus, the authors of these studies approached the principal investigators of the original RCT and obtained the data for the subgroup of

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patients who were randomly assigned within 3 days from ictus that were included in the analysis.

Using the ROBIS (Risk of Bias in Systematic Reviews) tool, we judged that these 2 meta-analyses resulted from a comprehensive literature search and had a low risk of bias on the basis of the domains checked (study eligibility criteria, identification and selection of results, data collection and study appraisal, synthesis, and findings). Therefore, we included these data in addition to results from RCTs that met our inclusion criteria and were published between 2012 and 2020. The PRISMA flow diagram summarizes the study selection process (Figure 1).

Statistical Analyses and Bias Assessment

Information on trial design, treatment arms, DAPT dosing, stroke severity, randomization time, DAPT treatment duration, length of study, study cohort characteristics, study design, and outcome measures (efficacy and safety) were collected.

Two of the authors (G.T. and F.D.T.) independently determined risk of bias for each eligible study using the RoB2 (Revised Cochrane risk of bias tool for randomized trials).¹⁰ GradePro software¹¹ was used to rate the quality of evidence for the outcomes of interest and to generate a summary of findings. The quality of evidence indicates that further research may change the estimates of efficacy and safety. Low quality of evidence indicates that further research may change the estimates of efficacy and safety. Low quality of evidence indicates that further research is very likely to have an important effect on our confidence in the estimate of effect for efficacy and safety.¹² Publication bias was investigated initially by visual inspection of funnel plots for asymmetry for each reported outcome, and statistically using the Egger test of the intercept.¹³

Heterogeneity between studies was quantified using P and Cochrane Q (χ^2) statistics. Heterogeneity was graded as low, moderate, and high as recommended by the American Heart Association.¹⁴ Subgroup and sensitivity analyses were done to explore heterogeneity.

We calculated risk ratios (RRs) and 95% CIs using randomeffects models to investigate the distribution of true effects and how effect size varied across populations for each outcome. Primary outcomes are represented by the rate of stroke recurrence as defined in each trial (Appendix II in the Data Supplement). We used the composite of stroke/TIA, acute coronary syndrome (ACS), and death from any cause, an outcome reported in most of the studies, as a coprimary outcome. The primary safety outcome was the development of major hemorrhage as defined in each individual trial (Appendix II in the Data Supplement). Primary analyses were done for efficacy and safety outcomes for all included trials to maximize the available data and minimize the bias that may result by excluding smaller trials. In secondary analyses, we investigated efficacy and safety outcomes on the basis of DAPT duration (≤30 days versus >30 days) and choice of DAPT (aspirin plus clopidogrel, aspirin plus ticagrelor, aspirin plus dipyridamole, and aspirin plus cilostazol). A sensitivity analysis was performed by excluding the results of the THALES study, which used a unique combination of antithrombotic agents and carried the largest weight in our meta-analysis. Because DAPT treatment duration in THALES was 1 month, the sensitivity analysis included studies that used DAPT for \leq 30 days.

Analyses were done using Cochrane Review Manager (v 5.4) and Comprehensive Meta-analysis software. 15

Descriptive characteristics of the studies were recorded. For studies that reported median and interquartile ranges, means were obtained using the method described by Hozo et al.¹⁶ Event rates for each efficacy and safety outcome were compared between MAPT and DAPT groups and between studies. Results are presented as RR and risk differences along with their corresponding 95% CI. The absolute number of events avoided per 1000 patients (absolute risk reduction) was calculated from risk differences. The absolute number of major hemorrhages caused by DAPT per 1000 participants (absolute risk increase) was generated by calculating the direct percentages from the number of events and number of randomly assigned patients. Studies with no events in the MAPT or DAPT groups were included in the figures if the outcome of interest was reported in the original study, although the RR in these cases could not be calculated.

RESULTS

Study Selection and Characteristics

Search criteria yielded a total of 2540 studies, including 10^{3,17-25} that were included in the previous meta-analyses published in 2012 and 2013.89 Our search identified an additional 7 studies that met inclusion criteria.4,6,26-30 The reasons for exclusion of other RCTs³¹⁻⁴⁷ are provided in Appendix III in the Data Supplement. Our final systematic review includes 17 studies with a combined total of 27358 patients randomly assigned to receive DAPT or MAPT within 3 days from stroke onset (Figure 1). Baseline characteristics of each cohort investigated are reported in Table 1. The most common MAPT was aspirin, and the most common DAPT regimen was aspirin plus clopidogrel. The mean age was 65 years, and 64% of the patients were male. Table I in the Data Supplement depicts the characteristics of the RCTs included in this meta-analysis.

Risk of Bias

The risk of bias across all studies and for each study included was low (Figure I in the Data Supplement). Some studies raised concerns regarding the randomization process because of unclear allocation concealment for participant and investigators,²⁵ early termination attributable to slow enrollment,³⁰ deviation from the intended analysis,⁴ not using intention-to-treat analysis,²⁹ or unblinding before the final analysis.²⁸ Visual inspection of the funnel plots revealed symmetry for all outcomes, and the 2-tailed *p* values for the Egger intercept were <0.05 for all outcomes (Figure IV in the Data Supplement).

Primary Outcomes

Figure 2 depicts the analysis for stroke recurrence, composite outcome of stroke, TIA, ACS, and death from any cause, and major hemorrhages for all the studies. There was a risk reduction of 29% (RR, 0.71 [95% CI, 0.63–

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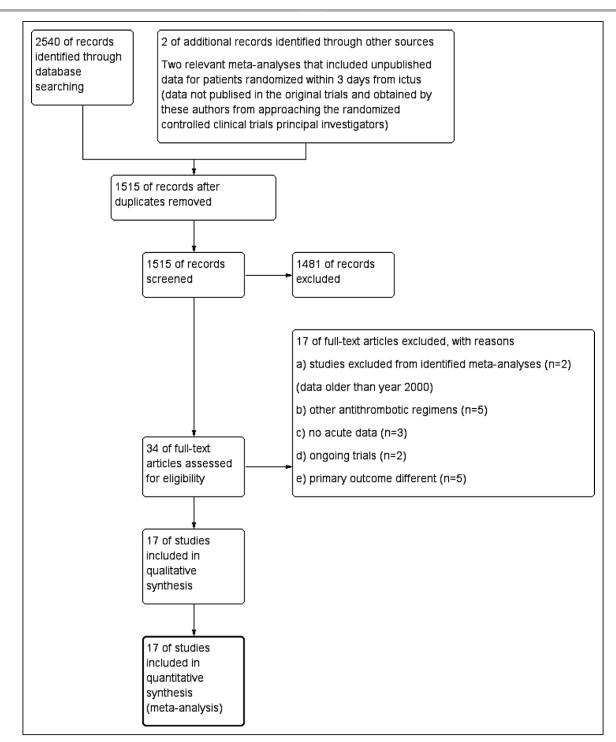


Figure 1. Flowchart for the included studies. PIs indicates principal investigators; and RCT, randomized controlled trial.

0.81], P<0.00001) for stroke recurrence (moderate certainty evidence), with mild heterogeneity (P=21%; P for χ^2 =0.2). The absolute effect was 20 fewer strokes (95% CI, 10-30) per 1000 participants treated with DAPT (Table 2, Figure 2). The risk reduction for the composite outcome was 24% (RR, 0.76 [95% CI, 0.69–0.83], P<0.00001; moderate certainty evidence) with no heterogeneity (P=0%; P for χ^2 =0.86). The absolute effect was 20 fewer events (95% Cl, 10-30) per 1000 participants treated with DAPT (Table 2, Figure 2).

The most frequently used regimen for patients treated with DAPT for \leq 30 days or >30 days was aspirin plus clopidogrel versus aspirin monotherapy. The use of aspirin plus clopidogrel for \leq 30 days resulted in a 33% risk reduction for stroke recurrence and a 29% risk reduction for the composite outcome of stroke, TIA, ACS, and all

Study	Treatment arms	Target population	Mean age, y	Male, %
MATCH ¹⁷	Clopidogrel vs aspirin plus clopidogrel	IS, TIA	66	63
CARESS ¹⁸	Aspirin vs aspirin plus clopidogrel	IS, TIA	65	69
ESPIRIT ²⁰	Aspirin vs aspirin plus dipyridamole	Minor IS, TIA	63	66
CHARISMA ¹⁹	Aspirin vs aspirin plus clopidogrel	IS, TIA	64	70
FASTER ²¹	Aspirin vs aspirin plus clopidogrel or clopidogrel plus simvastatin	Minor IS, TIA	68	53
PRoFESS ²³	Clopidogrel vs aspirin plus extended-release dipyridamole	IS	66	64
CLAIR ²⁴	Aspirin vs aspirin plus clopidogrel	Minor IS, TIA	58	78
EARLY ²²	Aspirin vs aspirin plus extended-release dipyridamole	IS, TIA	69	62
Nakamura et al ²⁵	Aspirin vs aspirin plus cilostazol	Minor IS	67	71
CHANCE ³	Aspirin vs clopidogrel plus aspirin	Minor IS, TIA	62	66
Yi et al ²⁶	Aspirin vs clopidogrel plus aspirin	Minor and moderate IS	69	55
He et al ²⁸	Aspirin vs aspirin plus clopidogrel	Minor IS, TIA	63	59
COMPRESS ²⁷	Aspirin vs clopidogrel plus aspirin	Minor IS	68	66
Zuo et al ²⁹	Aspirin vs clopidogrel plus aspirin	AIS, TIA	62	61
POINT⁴	Aspirin vs clopidogrel plus aspirin	Minor IS, TIA	65	55
Aoki et al ³⁰	Aspirin vs aspirin plus cilostazol	Minor IS	69	66
THALES ⁶	Aspirin vs ticagrelor plus aspirin	Minor IS, TIA	65	62

CARESS indicates Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis; CHANCE, Clopidogrel With Aspirin in Acute Minor Stroke or Transient Ischemic Attack; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance; CLAIR, Clopidogrel Plus Aspirin Versus Aspirin Alone for Reducing Embolisation in Patients With Acute Symptomatic Cerebral or Carotid Artery Stenosis; COMPRESS, Combination of Clopidogrel and Aspirin for Prevention of Early Recurrence in Acute Atherothrombotic Stroke; EARLY, EARLY 3-Months Aggrenox Treatment Started Within 24 hrs of Ischemic Stroke Onset vs. After One Week 100 mg ASA; ESPRIT, European/Australasian Stroke Prevention in Reversible Ischaemia Trial; FASTER, Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence; IS, ischemic stroke; MATCH, Management of Atherothrombosis With Clopidogrel in High-Risk Patients With Recent Transient Ischaemic Attack or Ischaemic Stroke; POINT, Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA; PRoFESS, Prevention Regimen For Effectively Avoiding Second Strokes; THALES, Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA; and TIA, transient ischemic attack.

death (moderate certainty evidence; Figures 3 and 4). When used for >30 days, aspirin plus clopidogrel was associated with a 36% risk reduction for stroke recurrence and a 29% risk reduction for the composite outcome (low certainty evidence; Figures 3 and 4).

The combinations of aspirin versus aspirin plus dipyridamole or aspirin plus cilostazol were not superior to MAPT for any of the primary outcomes at either time duration (\leq 30 days or >30 days of DAPT; Figures 3 and 4).

By design, the length of treatment in THALES was 30 days. When analyzed by the agent used, the combination of aspirin and ticagrelor showed a significant reduction in the risk of stroke recurrence (RR, 0.80 [95% CI, 0.68-0.93], P=0.004) and composite outcome (RR, 0.83 [95% CI, 0.72-0.97], P=0.02) relative to aspirin with moderate certainty evidence. Similarly, the rest of the regimens that also used DAPT for ≤30 days showed a significant reduction in the risk of stroke recurrence (RR, 0.68 [95% CI, 0.52–0.88], P=0.003, P=38%; P for χ^2 =0.12) and composite outcome (RR, 0.71 [95% CI, 0.63–0.80], *P*<0.00001, *P*=0%; *P* for χ^2 >0.99; Figures II and III in the Data Supplement, moderate certainty evidence for both outcomes) relative to monotherapy.

Safety Outcomes

We observed a 2-fold increased risk of severe hemorrhage associated with DAPT compared with monotherapy (RR, 2.17 [95% CI, 1.45-3.25], P=0.0002, low certainty evidence) with no heterogeneity (P=0%; P for $\chi^2=0.67$). The absolute effect was 3 additional major hemorrhages (95% CI, 2–5) per 1000 participants treated with DAPT (Table 2, Figure 2).

The risk of major hemorrhage was also increased in patients treated with aspirin plus ticagrelor for ≤30 days (RR, 3.98 [95% CI, 1.74–9.10], P=0.001, moderate certainty evidence) with 4 additional hemorrhages per 1000 participants (95% CI, 2-6). An excess in major hemorrhage was also observed in patients receiving DAPT for >30 days irrespective of the combination used (RR, 2.31 [95% CI, 1.29–4.12], *P*=0.005, *P*=0%; *P* for χ^2 =0.92, low certainty evidence; Table 2, Figure 5).

In secondary analysis, the risk for major hemorrhage for aspirin plus clopidogrel was comparable to monotherapy when used for \leq 30 days (RR, 1.52 [95% CI, 0.67-3.44], P=0.32, P=21%; P for $\chi^2=0.28$, moderate certainty evidence), but it was significantly elevated if the treatment was extended for a longer period of time (RR, 2.57 [95% CI, 1.34-4.95], P=0.005, P=0%;

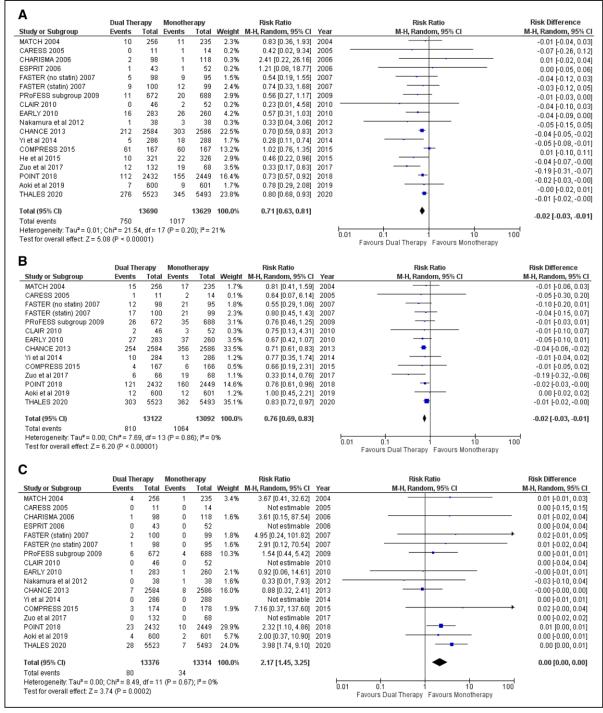


Figure 2. Efficacy and safety outcomes.

Risk ratio and absolute risk difference for stroke recurrence (**A**); composite outcome of stroke, transient ischemic attack, acute coronary syndrome, and death from any cause (**B**); and major hemorrhage (**C**) for patients receiving monotherapy or dual antiplatelet therapy. M-H indicates Mantel-Haenszel method.

P for χ^2 =0.41, low certainty evidence; Figure 5). In sensitivity analysis, the risk of hemorrhage in patients treated for \leq 30 days with DAPT combinations that did not include ticagrelor was comparable to that in the MAPT group (RR, 1.42 [95% CI, 0.77-2.60], *P*=0.26, *P*=0; *P* for χ^2 =0.61, moderate certainty evidence; Table 2, Figure 6).

DISCUSSION

Summary of Evidence

Our results show that, in patients with minor and moderate acute noncardioembolic ischemic strokes or TIA, DAPT reduces the risk of stroke recurrence and the composite of stroke, TIA, ACS, and death from any cause, but

		comparative 6 Cl) in medium- ation				
	Assumed risk	Corresponding risk			No. of	
Outcomes	Mono- therapy	Dual therapy	Relative effect (95% Cl)	Absolute effect (95% CI)	participants (studies)	Quality of the evidence (GRADE)†
Stroke recurrence all studies	75/1000	53/1000 (47–60)	RR, 0.71 (0.63–0.81)	20 fewer strokes per 1000 (10–30 fewer)	27319 (17)	⊕⊕⊕⊝ Moderate‡
Stroke recurrence with ≤30 days of DAPT	80/1000	59/1000 (50–70)	RR, 0.73 (0.62–0.87)	20 fewer strokes per 1000 (10–40 fewer)	19684 (9)	⊕⊕⊕⊝ Moderate‡
Stroke recurrence with >30 days of DAPT	60/1000	40/1000 (33–49)	RR, 0.67 (0.55–0.82)	10 fewer strokes per 1000 (none to 30 fewer)	7635 (8)	⊕⊕⊝⊝ Low≠,§
Composite outcome for all studies	81/1000	62/1000 (56–67)	RR, 0.76 (0.69–0.83)	20 fewer strokes per 1000 (10–30 fewer)	26214 (17)	⊕⊕⊕⊝ Moderate≠
Composite outcome with ≤30 days of DAPT	78/1000	59/1000 (54–65)	RR, 0.76 (0.69–0.83)	20 fewer strokes per 1000 (10–30 fewer)	23837 (9)	⊕⊕⊕⊝ Moderate≠
Composite outcome for >30 days of DAPT	74/1000	53/1000 (45–64)	RR, 0.72 (0.61–0.86)	20 fewer strokes per 1000 (none to 40 fewer)	7353 (6)	⊕⊕⊝⊝ Low≠,§
Major hemorrhage for all studies	3/1000	6/1000 (4–8)	RR, 2.17 (1.45–3.25)	3 more hemorrhages (2–5 more)	26690 (17)	⊕⊕⊝⊝ Low§,∥
Major hemorrhage with ≤30 days of DAPT	2/1000	4/1000 (2-7)	RR, 1.94 (1.08–3.52)	2 more hemorrhages (1–4 more)	24583 (11)	⊕⊕⊕⊝ Moderate¶,#
Major hemorrhage with ≤30 days DAPT excluding THALES	3/1000	4/1000 (2-7)	RR, 1.42 (0.77–2.60)	1 more hemorrhage (1 fewer to 3 more)	13567 (10)	⊕⊕⊕⊝ Moderate¶,#
Major hemorrhage for THALES study	1/1000	5/1000 (2-12)	RR, 3.98 (1.74–9.10)	4 more hemorrhages (2–6 more)	11016 (1)	⊕⊕⊕⊝ Moderate#
Major hemorrhage with >30 days of DAPT	4/1000	9/1000 (5–16)	RR, 2.31 (1.29–4.12)	6 more hemorrhages (2–9 more)	7635 (8)	⊕⊕⊝⊝ Low§#

Table 2.	Summary of Findings for Efficacy and Safety of Monotherapy Versus DAPT in Patients With Acute Ischemic
Stroke o	r TIA

DAPT indicates dual antiplatelet therapy; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; POINT, Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA; RR, risk ratio; THALES, Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA; TIA, transient ischemic attack.

*The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

 \pm GRADE Working Group grades of evidence: $\oplus \oplus \oplus \odot$, "moderate" indicates that further research is likely to have an important effect on our confidence in the estimate of effect and may change the estimate; and $\oplus \oplus \odot \odot$, "low" indicates that further research is very likely to have an important effect on our confidence in the estimate of effect and is likely to change the estimate.

+Imprecision suspected as RR reduction >25%.

§Risk of bias suspected as POINT trial was discontinued early; discontinuation of a trial medication also occurred in 29.6% of the patients in the group receiving clopidogrel plus aspirin and in 27.5% of those receiving aspirin alone.

||Cl includes both null effect and benefit; RR <0.75.

¶Interim analysis used for POINT study before trial discontinuation.

#The total number of events is <300 and RR >1.25.

increases the risk of severe hemorrhagic complications. These effects, however, are influenced by the length of treatment and the type of agent used.

Among different DAPT regimens, the beneficial effect favors the use of aspirin plus clopidogrel, aspirin plus dipyridamole, and aspirin plus ticagrelor. The risk of major hemorrhage was increased with the combinations of aspirin plus clopidogrel or aspirin plus ticagrelor. However, it should be noted that studies that used aspirin and clopidogrel or aspirin and ticagrelor accounted for almost 90% of the total patients included in this meta-analysis, which raises the question of statistical power for the remaining comparisons. Among patients treated for ≤30 days, aspirin plus ticagrelor showed similar efficacy for reducing the risk of stroke recurrence and composite outcome in comparison with the remaining DAPT regimens, but also showed a higher risk of major hemorrhage, whereas the remaining DAPT regimens did not. When DAPT regimens were continued for >30 days, the risk of major bleeding was similar to that of aspirin plus ticagrelor.

Properly powered studies comparing the efficacy and safety of ticagrelor to clopidogrel monotherapy or in combination with other antithrombotic agents for the

	Dual The			otherap			Risk Ratio		Risk Ratio	Risk Difference
Study or Subgroup A vs A+C	Events	Total	Even	ts To	otal W	eight M	-H, Random, 95% Cl	Year	M-H, Random, 95% Cl	M-H, Random, 95% Cl
CARESS 2005		4.4		4	4.4	0.3%	0.42 [0.02, 9.34]	2005		0.0710.00.0401
CLAIR 2010	0	11 46		1		0.3%	0.23 [0.01, 4.58]			-0.07 [-0.26, 0.12] -0.04 [-0.10, 0.03]
CHANCE 2013	212	2584				0.3%	0.70 [0.59, 0.83]			-0.04 [-0.05, -0.02]
Yi et al 2014	5	286				2.9%	0.28 [0.11, 0.74]			-0.05 [-0.08, -0.01]
He et al 2015	10	321				4.8%	0.46 [0.22, 0.96]	2015		-0.04 [-0.07, -0.00]
COMPRESS 2015	61	167				9.5%	1.02 [0.76, 1.35]	2015	_ _	0.01 [-0.10, 0.11]
Subtotal (95% CI)		3415				58.1%	0.67 [0.47, 0.95]			-0.04 [-0.05, -0.02]
Total events	288		40	06						
Heterogeneity: Tau² = 0 Test for overall effect: Z			df = 5	(P = 0.0	4); ²=	57%				
A vs A+D										
EARLY 2010	16	283	1			6.8%	0.57 [0.31, 1.03]	2010		-0.04 [-0.09, 0.00]
Subtotal (95% CI)		283			260	6.8%	0.57 [0.31, 1.03]			-0.04 [-0.09, 0.00]
Total events	16		2	26						
Heterogeneity: Not app										
Test for overall effect: Z	= 1.86 (P =	0.06)								
A										
A vs A+Cil				2	20	0.60	0.00.004.0.007	204.0		0.051045.005
Nakamura et al 2012 Roki et al 2010	1	38		3		0.6%	0.33 [0.04, 3.06]			-0.05 [-0.15, 0.05]
Aoki et al 2019 Subtotal (95% Cl)	7	600 638				2.8% 3.4%	0.78 [0.29, 2.08] 0.68 [0.28, 1.66]	2019		-0.00 [-0.02, 0.01] - 0.00 [-0.02, 0.01]
	8	038			555	J.470	0.00 [0.20, 1.00]			-0.00 [-0.02, 0.01]
Total events Heterogeneity: Tau ² = 0	-	0.47.46		12	N 1 2 - 0	ov.				
Test for overall effect: Z				- 0.43), I = 0					
A vs A+T										
THALES 2020	276	5523	34			1.7%	0.80 [0.68, 0.93]	2020	*	-0.01 [-0.02, -0.00]
Subtotal (95% CI)		5523	-		193 3	81.7%	0.80 [0.68, 0.93]		•	-0.01 [-0.02, -0.00]
Total events	276		34	45						
Heterogeneity: Not app										
Test for overall effect: Z	= 2.91 (P =	0.004)								
Total (95% CI)		9859		99	325 10	0.0%	0.73 [0.62, 0.87]		•	-0.02 [-0.04, -0.01]
Total events	588	3033	70	89	25 1	0.070	0.75 [0.02, 0.07]		•	-0.02 [-0.04, -0.04]
Heterogeneity: Tau ² = 0		1342 0			4): 1 ² =	33%				
Test for overall effect: Z				(1 - 0.1	-7,1 -	00,0			0.1 0.2 0.5 1 2 5 10	
Test for subaroup differ				3 (P = 0	.60). I ^z	= 0%			Favours Dual Therapy Favours Monotherapy	
		Therapy		lonothe			Risk Ratio		Risk Ratio	Risk Difference
Study or Subgroup	Event	s To	ital E	vents	Total	Weight	M-H, Random, 95%	CI Ye	M-H, Random, 95% Cl	M-H, Random, 95% CI
A or C vs A+C										
MATCH 2004			256 98	11	235					-0.01 [-0.04, 0.03]
CHARISMA 2006 FASTER (no statin) 200			98 98	1 9	118 95					0.01 [-0.02, 0.04]
FASTER (statin) 2007			00	12	99		0.54 [0.19, 1.5 0.74 [0.33, 1.6			-0.04 [-0.12, 0.03] -0.03 [-0.12, 0.05]
Zuo et al 2017			32	19	68		0.33 [0.17, 0.6			-0.19 [-0.31, -0.07]
POINT 2018	11		32	155	2449		0.73 [0.57, 0.9			-0.02 [-0.03, -0.00]
Subtotal (95% CI)			16		3064		0.64 [0.47, 0.8		▲	-0.02 [-0.05, 0.01]
Total events	15	0		207					-	
Heterogeneity: Tau ² = 0.	04; Chi ² = 6	.65, df=	= 5 (P	= 0.25);	I ² = 25	%				
Test for overall effect: Z	= 2.70 (P =	0.007)								
A vs A+D										
ESPRIT 2006			43	1	52					0.00 [-0.05, 0.06]
			43		52	0.5%	1.21 [0.08, 18.7	4		0.00 [-0.05, 0.06]
Subtotal (95% CI)										
Subtotal (95% CI) Total events		1		1						
Subtotal (95% CI)	icable	1		1						
Subtotal (95% CI) Total events Heterogeneity: Not appl	icable	1		1						
Subtotal (95% CI) Total events Heterogeneity: Not appl Test for overall effect: Z: C vs A+D PRoFESS subgroup 20	icable = 0.14 (P =	1 0.89) 1 6	572	20	688					-0.01 (-0.03. 0.001
Subtotal (95% CI) Total events Heterogeneity: Not appl Test for overall effect: Z: C vs A+D PROFESS subgroup 20 Subtotal (95% CI)	icable = 0.14 (P =	1 0.89) 1 6	072 072		688 688					-0.01 [-0.03, 0.00] - 0.01 [-0.03, 0.00]
Subtotal (95% CI) Total events Heterogeneity: Not appl Test for overall effect: Z: C vs A+D PROFESS subgroup 20 Subtotal (95% CI) Total events	icable = 0.14 (P = 09 1 1	1 0.89) 1 6								
Subtotal (95% CI) Total events Heterogeneity: Not appl Test for overall effect: Z: C vs A+D PROFESS subgroup 20 Subtotal (95% CI)	icable = 0.14 (P = 09 1 1	1 0.89) 1 6 6		20					•	
Subtotal (95% CI) Total events Heterogeneity: Not appl Test for overall effect: Z: C vs A+D PROFESS subgroup 20 Subtotal (95% CI) Total events	icable = 0.14 (P = 09 1 icable	1 0.89) 1 6 1		20						
Subtotal (95% CI) Total events Heterogeneity: Not appl Test for overall effect. Z: C vs A+D PROFESS subgroup 20 Subtotal (95% CI) Total events Heterogeneity: Not appl Test for overall effect. Z:	icable = 0.14 (P = 09 1 icable	1 0.89) 1 6 1 0.12)	572	20	688	7.5%	0.56 [0.27, 1.1	7]		-0.01 [⁻ 0.03, 0.00]
Subtotal (95% CI) Total events Heterogeneity. Not appi Test for overall effect. Z: C vs A+D PROFESS subgroup 20 Subtotal (95% CI) Total events Heterogeneity. Not appi Test for overall effect. Z: Total (95% CI)	icable = 0.14 (P = 09 1 icable = 1.55 (P =	1 0.89) 1 6 1 0.12) 38		20 20	688		0.56 [0.27, 1.1	7]	•	
Subtotal (95% CI) Total events Heterogeneily: Not appi Test for overall effect. Z: C vs A+D PROFESS subgroup 20 Subtotal (95% CI) Total events Heterogeneily: Not appi Test for overall effect. Z: Total (95% CI) Total events	icable = 0.14 (P = 09 1 icable = 1.55 (P = 16	1 0.89) 1 6 1 0.12) 38 2	31	20 20 228	688 3804	7.5%	0.56 [0.27, 1.1	7]	•	-0.01 [-0.03, 0.00]
Subtotal (95% CI) Total events Heterogeneity: Not appl Test for overall effect. Z: C vs A+D PROFESS subgroup 20 Subtotal (95% CI) Total events Heterogeneity: Not appl Test for overall effect. Z: Total (95% CI) Total events Heterogeneity: Tau ² = 0.	icable = 0.14 (P = 09 1 icable = 1.55 (P = 16 00; Chi ² = 7	1 0.89) 1 6 1 0.12) 38 2 2.06, df=	31 = 7 (P	20 20 228	688 3804	7.5%	0.56 [0.27, 1.1	7]		-0.01 [-0.03, 0.00]
Subtotal (95% CI) Total events Heterogeneity, Not appi Test for overall effect. Z: C vs A+D PROFESS subgroup 20 Subtotal (95% CI) Total events Heterogeneity; Not appi Test for overall effect. Z: Total (95% CI) Total events Heterogeneity; Tau [*] = 0. Test for overall effect. Z:	icable = 0.14 (P = 09 1 icable = 1.55 (P = 16 00; Chi ^P = 7 = 3.92 (P <	1 0.89) 1 6 1 0.12) 38 2 0.06, df= 0.0001)	572 131 = 7 (P	20 20 228 = 0.42);	688 3804 ; I² = 1 %	7.5%	0.56 [0.27, 1.1	7]	•	-0.01 [-0.03, 0.00]
Subtotal (95% CI) Total events Heterogeneity: Not appl Test for overall effect. Z: C vs A+D PROFESS subgroup 20 Subtotal (95% CI) Total events Heterogeneity: Not appl Test for overall effect. Z: Total (95% CI) Total events Heterogeneity: Tau"= 0.	icable = 0.14 (P = 09 1 icable = 1.55 (P = 16 00; Chi ^P = 7 = 3.92 (P <	1 0.89) 1 6 1 0.12) 38 2 0.06, df= 0.0001)	572 131 = 7 (P	20 20 228 = 0.42);	688 3804 ; I² = 1 %	7.5%	0.56 [0.27, 1.1	7]	+ b.01 0.1 1 10 100	-0.01 [-0.03, 0.00]

Figure 3. Risk of stroke recurrence on the basis of treatment duration.

Risk ratio and absolute risk difference for stroke recurrence associated with the use of dual therapy for \leq 30 days (**Upper**) or >30 days (**Lower**). A indicates aspirin; A+C, aspirin plus clopidogrel; A+Cil, aspirin plus cilostazol; A+D, aspirin plus dipyridamole; A+T, aspirin plus ticagrelor, C, clopidogrel; and M-H, Mantel-Haenszel method.

prevention of recurrent stroke are lacking. However, the results of an open label study including patients with minor stroke/TIA and large artery intracranial disease demonstrated that ticagrelor plus aspirin is superior to clopidogrel plus aspirin for the reduction of platelet reactivity. This study was not powered to assess clinical efficacy. However, a higher frequency of bleeding of any type was observed in the group of patients receiving ticagrelor plus aspirin. In addition, studies done in patients with cardiac disease found, similarly to our results, that dual therapy with ticagrelor and aspirin yielded higher bleeding complications than aspirin plus clopidogrel, and that ticagrelor monotherapy was noninferior in preventing composite outcome of death from any cause, ACS, or stroke.^{48–50} Thus, it is possible that the excess in the number of major hemorrhages noted in our study among

Dual Therapy Montherapy Ratio Risk Ratio Risk Ratio Risk Ratio Risk Ratio Risk Ratio Mith Random, 95% CI Study of Marka Total Vents Total Weight M.H. Random, 95% CI M.H. Random, 95% CI 0.01 [-0.01	
Avs A+C	5576 61
CLAR 2010 2 46 3 52 0.3% 0.75 [0.13, 4, 31] 2010 -0.01 [0.11 CHANCE 2013 254 258 38.3% 0.71 [0.61, 0.83] 2013 -0.04 [0.06 Y1 et al 2014 10 284 13 266 1.3% 0.77 [0.35, 1.74] 2014 -0.01 [0.01 COMPRESS 2015 4 167 6 166 0.6% 0.66 [0.19, 2.31] 2015 -0.01 [0.01 -0.	
CHANCE 2013 254 2584 356 2586 38.3% 0.77 [0.61, 0.83] 2013 -0.04 [0.06] Yi et al 2014 10 284 13 286 1.3% 0.77 [0.51, 0.83] 2013 -0.01 [0.00] COMPRESS 2015 4 167 6 166 0.68 0.68 [0.19, 2.31] 2014 -0.01 [0.00] POINT (30 day interim analysis) 2018 96 2.432 141 2449 13.7% 0.68 [0.59, 2.31] 2015 -0.02 [0.03] Total events 367 5524 5553 54.4% 0.71 [0.62, 0.80] -0.02 [0.03] -0.02 [0.03] Total events 367 521 553 54.4% 0.71 [0.62, 0.80] -0.05 [0.11] -0.05 [0.00] Test for overall effect Z = 5.33 (P < 0.00001)	0, 0.20]
Yi et al 2014 10 284 13 296 1.3% 0.77 [0.35, 1.74] 2014 -0.01 [-0.0 COMPRESS 2015 4 167 6 166 0.6% 0.66 [0.19, 2.31] 2015 -0.01 [-0.0 -0.01 [-0.0 Stubtoral (95% CI) 96 2432 141 2449 13.7% 0.77 [0.35, 1.74] 2014 -0.01 [-0.0 -0.05 [-0.10 -0.05 [-0.10 -0.05 [-0.10 -0.05 [-0.10 -0.05 [-0.10 -0.05 [-0.10 -0.05 [-0.10 -0.05 [-0.10 -0.05 [-0.10 -0.05 [-0.10 -0.05 [-0.10 -0.05 [-0.10 <t< td=""><td></td></t<>	
COMPRESS 2015 4 167 6 166 0.68% 0.66 [0.19, 2.31] 2015 -0.01 [-0.01 POINT (30 day interim analysis) 2018 96 2432 141 2449 13.7% 0.69 [0.53, 0.68] 2018 -0.02 [-0.03 Subtotal (95% CI) 555 554.4% 0.71 [0.62, 0.80] -0.01 [-0.01 -0.02 [-0.03 Total events 367 521 -0.01 [-0.01 -0.02 [-0.03 -0.02 [-0.03 Test for overall effect Z = 5.33 (P < 0.0001)	
POINT (30 day interim analysis) 2018 96 2432 141 2449 13.7% 0.69 [0.53, 0.69] 2018 -0.02 [-0.03 Subtotal (95% CI) 5524 5553 54.4% 0.71 [0.62, 0.80] -0.02 [-0.03 -0.02 [-0.03 Total events 367 521 5553 54.4% 0.71 [0.62, 0.80] -0.02 [-0.03 Testfor overall effect: Z = 5.33 (P < 0.00001)	
Subtotal (95% CI) 5524 5553 54.4% 0.71 [0.62, 0.80] ● -0.02 [-0.03] Total events 367 521 51 -0.02 [-0.03] ● -0.02 [-0.03] ● -0.02 [-0.03] ● -0.02 [-0.03] ● -0.02 [-0.03] ● -0.02 [-0.03] ● -0.02 [-0.03] ● -0.02 [-0.03] ● -0.02 [-0.03] ● -0.02 [-0.03] ● -0.02 [-0.03] ● -0.02 [-0.03] ● -0.02 [-0.03] ● -0.02 [-0.03] ● -0.05 [-0.11] ● -0.05 [-0.11] ● -0.05 [-0.11] ● -0.05 [-0.11] ● -0.05 [-0.11] ● -0.05 [-0.11] ● -0.05 [-0.11] ● -0.05 [-0.11] ● -0.05 [-0.11] ● 0.05 [-0.11] ● 0.05 [-0.11] ● 0.05 [-0.11] ●	
Total events 367 521 Heterogeneity: Tau* = 0.00; Chi* = 0.15, dr = 5 (P = 1.00); P* = 0% Test for overall effect: Z = 5.33 (P < 0.00001)	0.01]
Heterogeneity: Tau ² = 0.00; Chi ^a = 0.15, off = 5 (P = 1.00); P = 0% Test for overall effect: Z = 5.33 (P < 0.00001)	,,
EARLY 2010 27 283 37 260 4.0% 0.67 [0.42, 1.07] 2010 -0.05 [-0.11 Subtotal (95% CI) 283 260 4.0% 0.67 [0.42, 1.07] 2010 -0.05 [-0.11 Total events 27 37 -0.05 [-0.11 -0.05 [-0.11 -0.05 [-0.11 Total events 27 37 -0.05 [-0.11 -0.05 [-0.11 -0.05 [-0.11 Avs A+CII Avs A+CII -0.05 [-0.11 -0.05 [-0.11 -0.05 [-0.11 -0.05 [-0.11 Aki et al 2019 -0.05 [-0.11 -0.05 [-0.11 -0.05 [-0.11 -0.05 [-0.11 -0.05 [-0.11 Subtotal (95% CI) 600 11 1.4% 1.00 [0.45, 2.21] 2019 -0.00 [-0.02 Total events 12 12 12 -0.01 -0.05 [-0.10 -0.00 [-0.02 Heterogeneity: Not applicable 12 12 12 -0.00 [-0.02 -0.00 [-0.02 -0.00 [-0.02	
EARLY 2010 27 283 37 260 4.0% 0.67 [0.42, 1.07] 2010 -0.05 [-0.11 Subtotal (95% CI) 283 260 4.0% 0.67 [0.42, 1.07] 2010 -0.05 [-0.11 Total events 27 37 -0.05 [-0.11 -0.05 [-0.11 -0.05 [-0.11 Total events 27 37 -0.05 [-0.11 -0.05 [-0.11 -0.05 [-0.11 Avs A+CII Avs A+CII -0.05 [-0.11 -0.05 [-0.11 -0.05 [-0.11 -0.05 [-0.11 Aki et al 2019 -0.05 [-0.11 -0.05 [-0.11 -0.05 [-0.11 -0.05 [-0.11 -0.05 [-0.11 Subtotal (95% CI) 600 11 1.4% 1.00 [0.45, 2.21] 2019 -0.00 [-0.02 Total events 12 12 12 -0.01 -0.05 [-0.10 -0.00 [-0.02 Heterogeneity: Not applicable 12 12 12 -0.00 [-0.02 -0.00 [-0.02 -0.00 [-0.02	
Subtotal (95% CI) 283 260 4.0% 0.67 [0.42, 1.07] -0.05 [-0.10 Total events 27 37 - - - - - - 0.05 [-0.10 Total events 27 37 - - - - - - 0.05 [-0.10 Heterogeneity: Not applicable - <th< td=""><td>0 0 011</td></th<>	0 0 011
Total events 27 37 Heterogeneity: Not applicable Total events 27 37 Heterogeneity: Not applicable Avs A+Cil Aoki et al 2019 1.2 600 601 1.4% 1.00 [0.45, 2.21] 2019 0.00 [-0.02 Stubtoal (95% CI) 600 601 1.4% 1.00 [0.45, 2.21] 0.00 [-0.02 0.00 [-0.02 Total events 12 12 12 1.00 [0.45, 2.21] 0.00 [-0.02	
Heterogeneity: Not applicable Test for overall effect: Z = 1.68 (P = 0.09) Avs A+Cli Aoki et al 2019 12 600 12 601 1.4% 1.00 [0.45, 2.21] 2019 0.00 [-0.02 Stubtoal (95% Cl) 600 601 1.4% 1.00 [0.45, 2.21] 0.00 [-0.02 Total events 12 12 Heterogeneity: Not applicable	
A vs A+Cil Aoki et al 2019 12 600 1.4% 1.00 [0.45, 2.21] 2019 0.00 [-0.02 Stubtotal (95% Ci) 600 601 1.4% 1.00 [0.45, 2.21] 0.00 [-0.02 Total events 12 12 12 1.00 [0.45, 2.21] 0.00 [-0.02 Heterogeneity: Not applicable 12 13 13 13 13 13 13 13 14	
Aoki et al 2019 12 600 12 601 1.4% 1.00 [0.45, 2.21] 2019 0.00 [-0.02 Subtotal (95% CI) 600 601 1.4% 1.00 [0.45, 2.21] 0.00 [-0.02 0.00 [-0.02 Total events 12 12 12 12 0.00 [-0.0	
Stubiotal (95% CI) 600 601 1.4% 1.00 [0.45, 2.21] 0.00 [-0.02 Total events 12	
Total events 12 12 Heterogeneity: Not applicable	2, 0.02] 2, 0.021
Heterogeneity: Not applicable	., 0.02]
A vs A+T	
THALES 2020 303 5523 362 5493 40.2% 0.83 [0.72, 0.97] 2020 -0.01 [-0.02	2, -0.00]
Subtotal (95% CI) 5523 5493 40.2% 0.83 [0.72, 0.97] \blacklozenge -0.01 [-0.02	, -0.00]
Total events 303 362	
Heterogeneity: Not applicable Test for overall effect: Z = 2.43 (P = 0.02)	
Total (95% Cl) 11930 11907 100.0% 0.76 [0.69, 0.83] 🔶 -0.02 [-0.03	, -0.01]
Total events 709 932	
Heterogeneity, Tau ² = 0.00; Chi ² = 3.55, df = 8 (P = 0.89); P = 0% $\frac{1}{2} + \frac{1}{2} + \frac$	
Test for overall effect: Z = 5.81 (P < 0.00001) Test for subgroup differences: Chi ^p = 3.41, df = 3 (P = 0.33), I ^p = 12.0% Favours Dual Therapy	
$15511015404(104) 4006161065, 000 - 0.41, 41 - 5 (r - 0.33), 1 - 12.0 \infty$	
Dual Therapy Monotherapy Risk Ratio Risk Ratio Risk Ratio Risk Differen	
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% Cl Year M-H, Random, 95% Cl M-H, 85% C	99% CI
MATCH 2004 15 256 17 235 6.9% 0.81 [0.41, 1.59] 2004 -0.01 [-0.06 FASTER (no statin) 2007 12 98 21 95 7.4% 0.55 [0.29, 1.06] 2007 -0.10 [-0.20	
PASTER (risitatin) 2007 17 100 21 99 9.4% 0.080 [0.45, 1.43] 2007	
Zuo eta 10/2017 6 66 19 68 4.3% 0.33 [0.14, 0.76] 2017	
POINT 2018 121 2432 160 2449 59.3% 0.76 [0.61, 0.96] 2018 - 0.02 (-0.03)	
Subtotal (95% CI) 2952 2946 87.3% 0.71 [0.57, 0.88]	
Total events 171 238	
Heterogeneity: Tau ² = 0.01; Chi ² = 4.44, df = 4 (P = 0.35); i ² = 10% Test for overall effect: Z = 3.09 (P = 0.002)	
A vs A+D	
ESPRIT 2006 0 43 0 52 Not estimable 2006 0.00 [-0.04	
Subtotal (95% CI) 43 52 Not estimable 0.00 [-0.04	, 0.04]
Total events 0 0	
Heterogeneity: Not applicable	
Test for overall effect: Not applicable	
C vs A+D PRoFESS subgroup 2009 26 672 35 688 12.7% 0.76 (0.46 1.25) 2009 -0.01 F0.03	3 0 0 1 1
Subtotal (95% CI) 672 688 12.7% 0.76 [0.46, 1.25]	
Total events 26 35	
Heterogeneity. Not applicable Test for overall effect: Z = 1.08 (P = 0.28)	
	0.001
Tatal (05% Ch) 3667 3606 100 0% 0.73 (0.64 0.96)	, 0.00]
Total (95% Cl) 3667 3686 100.0% 0.72 [0.61, 0.86] ♦ -0.02 [-0.04	
Total events 197 273	
Total events 197 273 Heterogeneity: Tau ² = 0.00; Chi ² = 4.48, df = 5 (P = 0.48); l ² = 0%	
Total events 197 273	

Figure 4. Risk of stroke, transient ischemic attack, acute coronary syndrome, or death from any cause on the basis of treatment duration.

Risk ratio and absolute risk difference for the composite outcome of stroke, transient ischemic attack, acute coronary syndrome, or death from any cause associated with the use of dual therapy for \leq 30 days (**Upper**) or >30 days (**Lower**). A indicates aspirin; A+C, aspirin plus clopidogrel; A+Cil, aspirin plus cilostazol; A+D, aspirin plus dipyridamole; A+T, aspirin plus ticagrelor; C, clopidogrel; and M-H, Mantel-Haenszel method.

patients receiving aspirin plus ticagrelor may reflect an intrinsic risk associated with ticagrelor.³⁹

Our findings on DAPT efficacy are similar to prior published studies that did not include the comparison of aspirin versus aspirin plus ticagrelor.^{8,9} Our metaanalysis is the first one to show that, when the results from THALES are combined with previous studies that investigated the use of different DAPT regimens, there is a significant increase in the risk of major bleeding (Table 2). THALES⁶ was the largest study included in our analysis and accounted for 41% of all the participants. Other large independent trials included in our study were POINT⁴ and CHANCE.³

The POINT⁴ trial accounted for 18% of all participants in our meta-analysis, and the authors used the combination of aspirin plus clopidogrel for 90 days. The results of this trial showed that, at 90 days, the bleeding risk was increased 2 times in the aspirin plus clopidogrel group, compared with aspirin treatment alone, similar to the results from THALES.⁶ In an interim analysis of POINT⁴ done at 30 days of treatment, however, the risk of major hemorrhage was not significantly increased in

		ual The	rapy	Monothe	rapy		Risk Ratio		Risk Ratio
tudy or Subgroup	E	vents	Total	Events	Total	Weight	M-H, Random, 95% C	Year	M-H, Random, 95% Cl
A vs A+C									
ARESS 2005		0	11	0	14		Not estimable	2005	
LAIR 2010		0	46	0	52		Not estimable	2010	
HANCE 2013		7	2584	8	2586	23.4%	0.88 [0.32, 2.41]	2013	_
i et al 2014		0	286	0	288		Not estimable		
OMPRESS 2015		3	174	Ō	178	3.8%	7.16 [0.37, 137.60		
le et al 2015		Ő	321	0	326	0.070	Not estimable		
	> 2010	12	2432	6	2449	24.5%			
'OINT (30 day interim analysi: Subtotal (95% CI)	5) 2010	12	5854	0	5893	51.6%	2.01 [0.76, 5.36] 1.52 [0.67, 3.44]		
		~~	3034		3033	51.070	1.52 [0.07, 5.44]		
'otal events leterogeneity: Tauª = 0.12; Ch 'est for overall effect: Z = 1.00		22 = 2 (P =	0.28); lª	14 = 21%					
A vs A+D									
ARLY 2010		1	283	1	260	4.3%	0.92 [0.06, 14.61]	2010	
Subtotal (95% CI)			283		260	4.3%	0.92 [0.06, 14.61]		
otal events		1		1					
leterogeneity: Not applicable fest for overall effect: Z = 0.06	(P = 0.95)								
A vs A+Cil			20	4	20	2.2%	0.0010.04.7.00	2040	•
lakamura et al 2012 aki et al 2019		0	38	1	38	3.3%	0.33 [0.01, 7.93]		,
oki et al 2019 ubtotol (05% CI)		4	600	2	601	10.5%	2.00 [0.37, 10.90]		
ubtotal (95% CI)		_	638	_	639	13.8%	1.35 [0.30, 5.99]		
otal events		4		3					
leterogeneity: Tau ² = 0.00; Ch est for overall effect: Z = 0.39		= 1 (P =	0.33); I ^a	ⁱ = 0%					
A vs A+T									
HALES 2020		28	5523	7	5493	30.2%	3.98 [1.74, 9.10]	2020	
ubtotal (95% CI)			5523	•	5493	30.2%	3.98 [1.74, 9.10]		
otal events		28		7			• • •		
leterogeneity: Not applicable		20							
	(P = 0.001)								
est for overall effect: Z = 3.27	(P = 0.001)		40000		10005	100 00	1011100 5		
est for overall effect: Z = 3.27 otal (95% CI)	(P = 0.001)		12298		12285	100.0%	1.94 [1.08, 3.52]		•
est for overall effect: Z = 3.27 otal (95% CI) iotal events		55		25	12285	100.0%	1.94 [1.08, 3.52]		•
est for overall effect: Z = 3.27 otal (95% CI)					12285	100.0%	1.94 [1.08, 3.52]		
est for overall effect: Z = 3.27 otal (95% CI) iotal events	hi² = 7.50, df:				12285	100.0%	1.94 [1.08, 3.52]		
est for overall effect: Z = 3.27 otal (95% CI) iotal events leterogeneity: Tau ² = 0.12; Ch	hi² = 7.50, df: (P = 0.03)	= 6 (P =	0.28); Iª	= 20%		100.0%	1.94 [1.08, 3.52]		0.02 0.1 1 10 5 Favours Dual Therapy Favours Monotherapy
est for overall effect: Z = 3.27 otal (95% CI) otal events leterogeneity: Tau ² = 0.12; CP est for overall effect: Z = 2.20	hi² = 7.50, df: (P = 0.03) : Chi² = 3.57,	= 6 (P = . df = 3 (0.28); Iª P = 0.31	²= 20%), I²= 15.8					Favours Dual Therapy Favours Monotherapy
est for overall effect: Z = 3.27 otal (95% CI) otal events leterogeneity: Tau ² = 0.12; CP est for overall effect: Z = 2.20	hi² = 7.50, df: (P = 0.03)	= 6 (P = . df = 3 (apy	0.28); Iª	*= 20%), I*= 15.8 herapy	1%		1.94 [1.08, 3.52] Risk Ratio Random, 95% Cl Ye		
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Figure 5. Risk of major hemorrhage on the basis of treatment duration.

Risk ratio and absolute risk difference for major hemorrhage associated with the use of dual therapy for \leq 30 days (**Upper**) or >30 days (**Lower**). A indicates aspirin; A+C, aspirin plus clopidogrel; A+Cil, aspirin plus cilostazol; A+D, aspirin plus dipyridamole; A+T, aspirin plus ticagrelor; C, clopidogrel; and M-H, Mantel-Haenszel method.

the aspirin plus clopidogrel group compared with aspirin monotherapy (RR, 0.50 [95% CI, 0.19–1.32], P=0.16). Another large study, CHANCE,³ accounted for 19% of our study's participants. This study used the combination of aspirin plus clopidogrel for 21 days, and dual treat-

ment reduced the risk of stroke (hazard ratio, 0.68 [95% CI, 0.57–0.81]) but did not increase the risk of major hemorrhage compared with monotherapy.

These results support the hypothesis that, compared with MAPT, the use of aspirin plus clopidogrel for 30

<u>Original research</u>

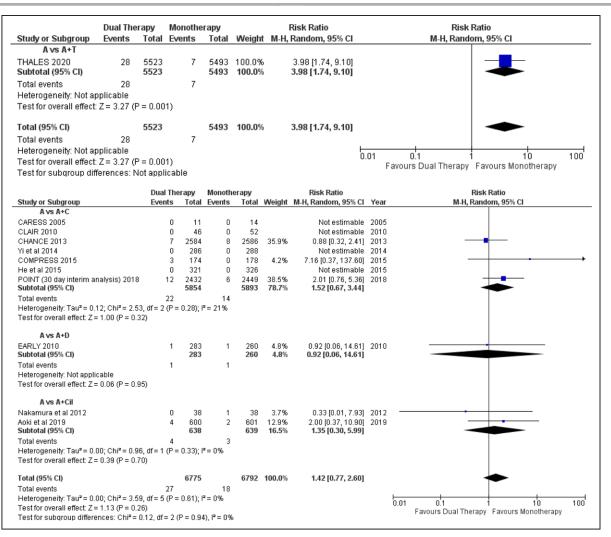


Figure 6. Risk of major hemorrhage on the basis of antithrombotic regimen.

Risk ratio and absolute risk difference for major hemorrhage associated with the use of monotherapy or dual therapy for \leq 30 days stratified by use of aspirin plus ticagrelor (**Upper**) or other combinations (**Lower**). A indicates aspirin; A+C, aspirin plus clopidogrel; A+Cil, aspirin plus cilostazol; A+D, aspirin plus dipyridamole; A+T, aspirin plus ticagrelor; C, clopidogrel; and M-H, Mantel-Haenszel method.

days after stroke onset is beneficial and safe in patients with minor noncardioembolic strokes. The combination of aspirin plus ticagrelor for 30 days or using other DAPT regimens for >30 days, although effective for reducing the risk for stroke recurrence and composite efficacy outcomes, is associated with a higher risk of bleeding. Therefore, our results suggest that dual treatment with aspirin plus clopidogrel may be preferable to aspirin plus ticagrelor, particularly when used for no more than a month. In addition, the beneficial effect of dual treatment seems to extend to the prevention of the composite of stroke, TIA, AMI, and death from any cause. However, one should be cautious when analyzing these results because ischemic stroke and major hemorrhage may carry different weights on patient outcome. Valuable information will be obtained from CHANCE 2 (Clopidogrel With Aspirin in High-risk Patients With Acute Nondisabling Cerebrovascular Events II; URL: http://www. clinicaltrials.gov. Unique identifier: NCT04078737), an ongoing RCT that will investigate the efficacy and safety of aspirin plus clopidogrel versus aspirin plus ticagrelor in the prevention of recurrent stroke.

Limitations

The current meta-analysis has limitations. First, the included studies had methodologic differences, such as the duration of treatment, type of agent, dosage, and stroke severity. However, all of them had similarities, such as the inclusion of mild to moderate strokes of noncardioembolic origin and the use of similar safety outcomes. Second, we included the unpublished results from earlier trials that investigated DAPT regimens.⁸ Although we were unable to cross-check the outcomes, the event rates were obtained directly from the principal investigators of the main studies; hence, we expect them to be accurate. Third, the THALES study alone accounted for 41% of all the participants in our study and drove the main safety outcome. However, the large sample size of our study permitted us to compare the results from THALES against all other studies, which allowed us to identify the optimal DAPT combination and duration of treatment. Last, we reported the results as RRs and absolute effects. Because the absolute risk for control varies between trials, these absolute results should be interpreted with caution.

Conclusions

Short-term (≤30 days) treatment with aspirin plus clopidogrel started within 3 days from acute minor to moderate ischemic stroke or TIA decreases the risk of stroke recurrence and composite events of all strokes, TIAs, ACS, and death from any cause relative to MAPT without a significant increase in the risk of major hemorrhage. Use of aspirin plus ticagrelor for 30 days or other DAPTs for >30 days after stroke, although effective to reduce the risk of stroke recurrence and composite events, is associated with a significant increase in the risk of major hemorrhage.

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Supplemental Materials

Appendixes I–III Data Supplement Table I Data Supplement Figures I–-IV

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