Circulation

ORIGINAL RESEARCH ARTICLE

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

Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials

Gabriela Trifan, MD; Philip B. Gorelick, MD, MPH; Fernando D. Testai, MD, PhD

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 I^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 ($I^2 \leq 25\%$). 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

Stroke 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]

Correspondence to: Gabriela Trifan, MD, University of Illinois at Chicago, College of Medicine, 912 S Wood Street, M/C 796, 172C, Chicago, IL 60612. Email gtrifan@uic.edu

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For Sources of Funding and Disclosures, see page 2452.

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	acute coronary syndrome
CHANCE	Clopidogrel in High-Risk Patients With Acute Non-disabling Cerebrovascular Events
DAPT	dual antiplatelet therapy
MAPT	antiplatelet monotherapy
POINT	Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA
PRISMA	Preferred Reporting Items for Systematic 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
TIA	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 2012[8] and 2013[9] 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

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 software[11] was used to rate the quality of evidence for the outcomes of interest and to generate a summary of findings. The quality of the evidence was rated as moderate or low. Moderate 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 I^2 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 random-effects 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 ≤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.[8,9] Our search identified an additional 7 studies that met inclusion criteria.[4,6,26–30] The reasons for exclusion of other RCTs[31–47] are provided in Appendix III in the Data Supplement. Our final systematic review includes 17 studies with a combined total of 27 358 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–

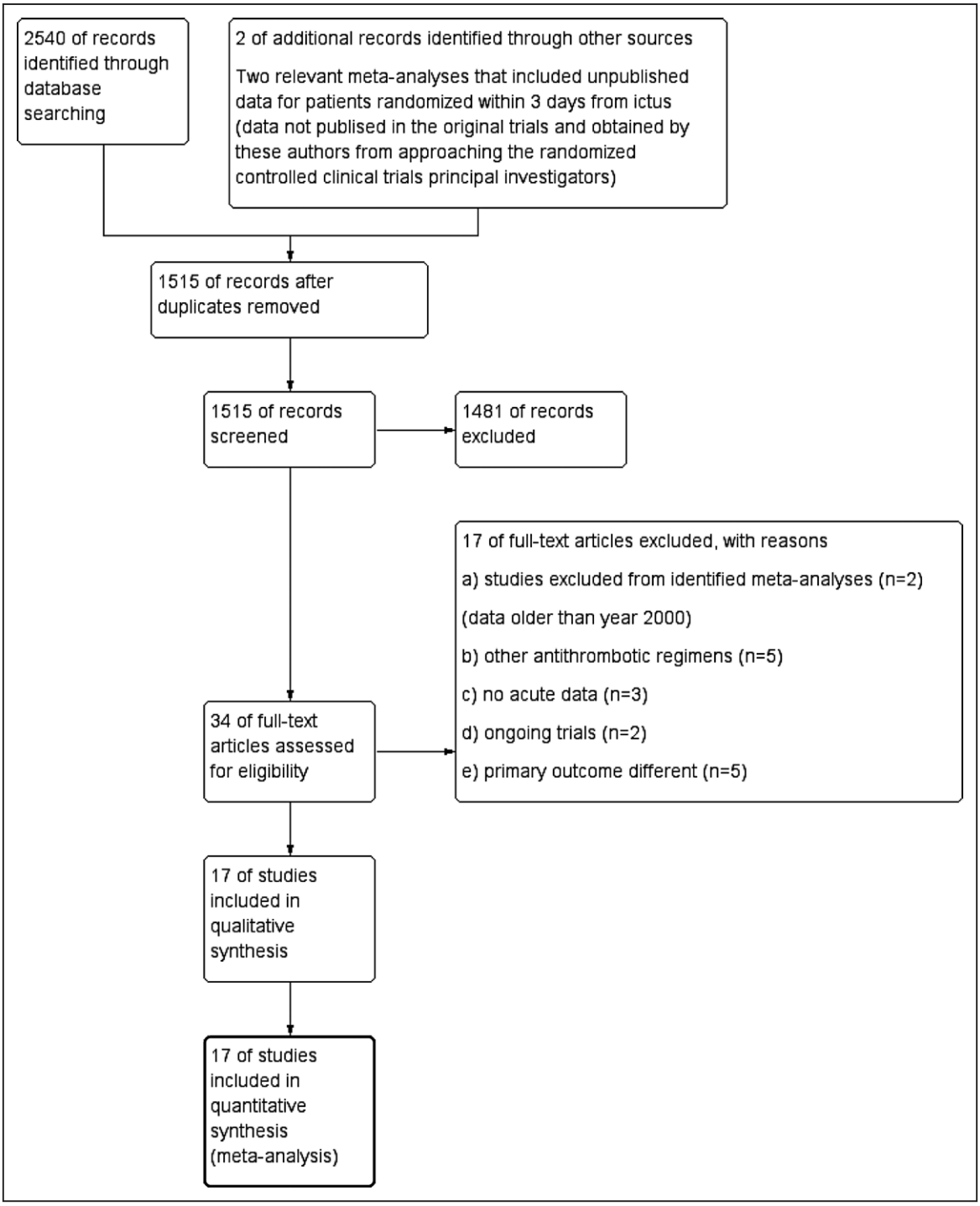

Figure 1. Flowchart for the included studies. PIs indicates principal investigators; and RCT, randomized controlled trial.

0.81], $P<0.00001$) for stroke recurrence (moderate certainty evidence), with mild heterogeneity ($I^2=21\%$; P for $\chi^2=0.2$). 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 ($I^2=0\%$; P for $\chi^2=0.86$). The absolute effect was 20 fewer events (95% CI, 10–30) per 1000 participants treated with DAPT (Table 2, Figure 2).

The most frequently used regimen for patients treated with DAPT for ≤30 days or >30 days was aspirin plus clopidogrel versus aspirin monotherapy. The use of aspirin plus clopidogrel for ≤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

Table 1. Baseline Characteristics

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
POINT[4]	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 (≤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, I^2=38%; P for χ^2=0.12) and composite outcome (RR, 0.71 [95% CI, 0.63–0.80], P<0.00001, I^2=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 (I^2=0%; P for χ^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, I^2=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 ≤30 days (RR, 1.52 [95% CI, 0.67–3.44], P=0.32, I^2=21%; P for χ^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, I^2=0%;

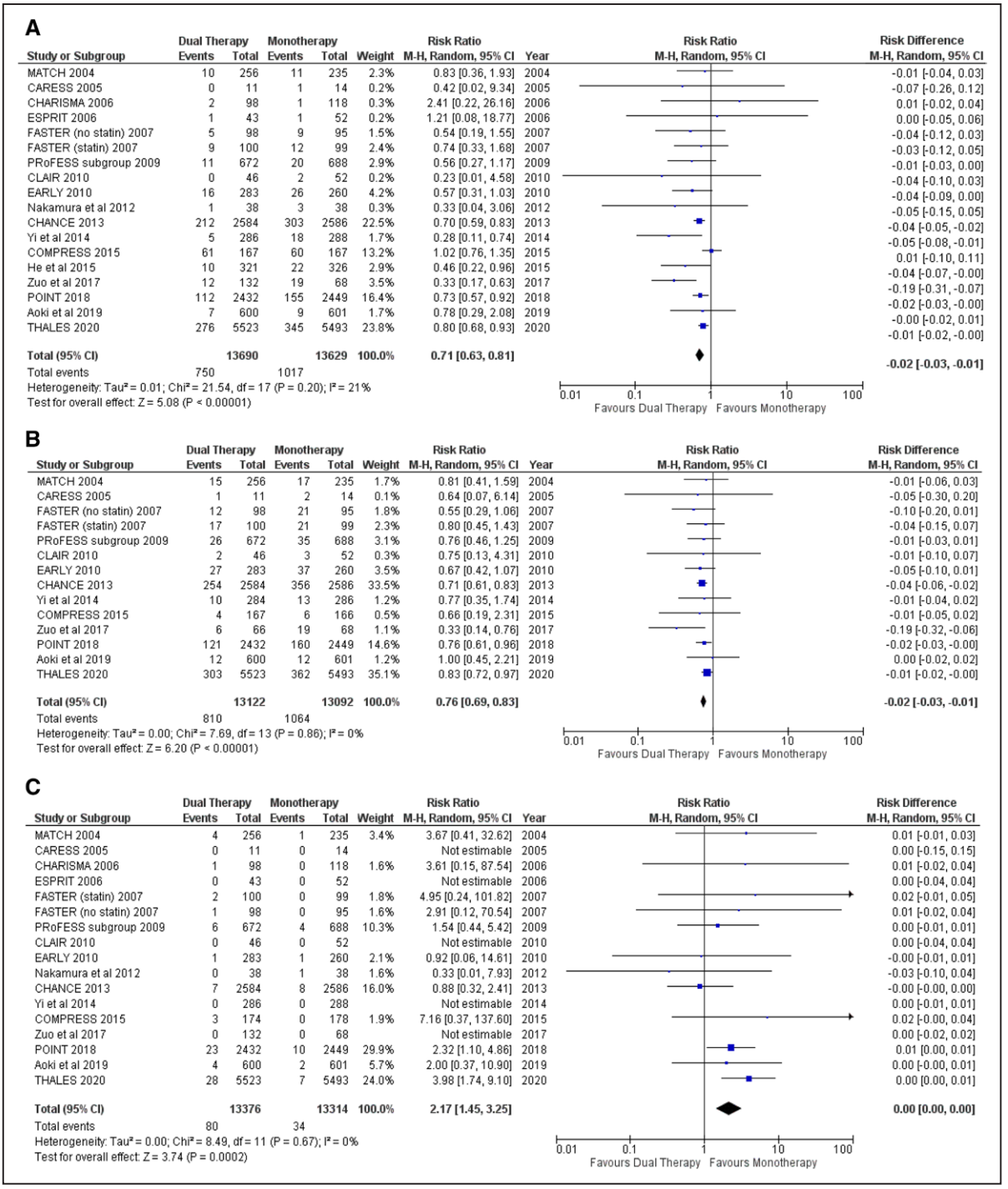

Figure 2. Efficacy and safety outcomes.
Risk ratio and absolute risk difference for stroke recurrence (**A**); composite outcome of stroke, transient ischemic attack, acute coronary syndrome, and death from any cause (**B**); and major hemorrhage (**C**) for patients receiving monotherapy or dual antiplatelet 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 ≤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, I^2=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

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

Outcomes	Illustrative comparative risks* (95% CI) in medium-risk population		Relative effect (95% CI)	Absolute effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)†
	Assumed risk	Corresponding risk				
	Mono-therapy	Dual therapy				
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)	27 319 (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)	19 684 (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)	26 214 (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)	23 837 (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)	26 690 (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)	24 583 (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)	13 567 (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)	11 016 (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§#

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).

†GRADE Working Group grades of evidence: ⊕⊕⊕⊖, "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 ⊕⊕⊖⊖, "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.

‖CI 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

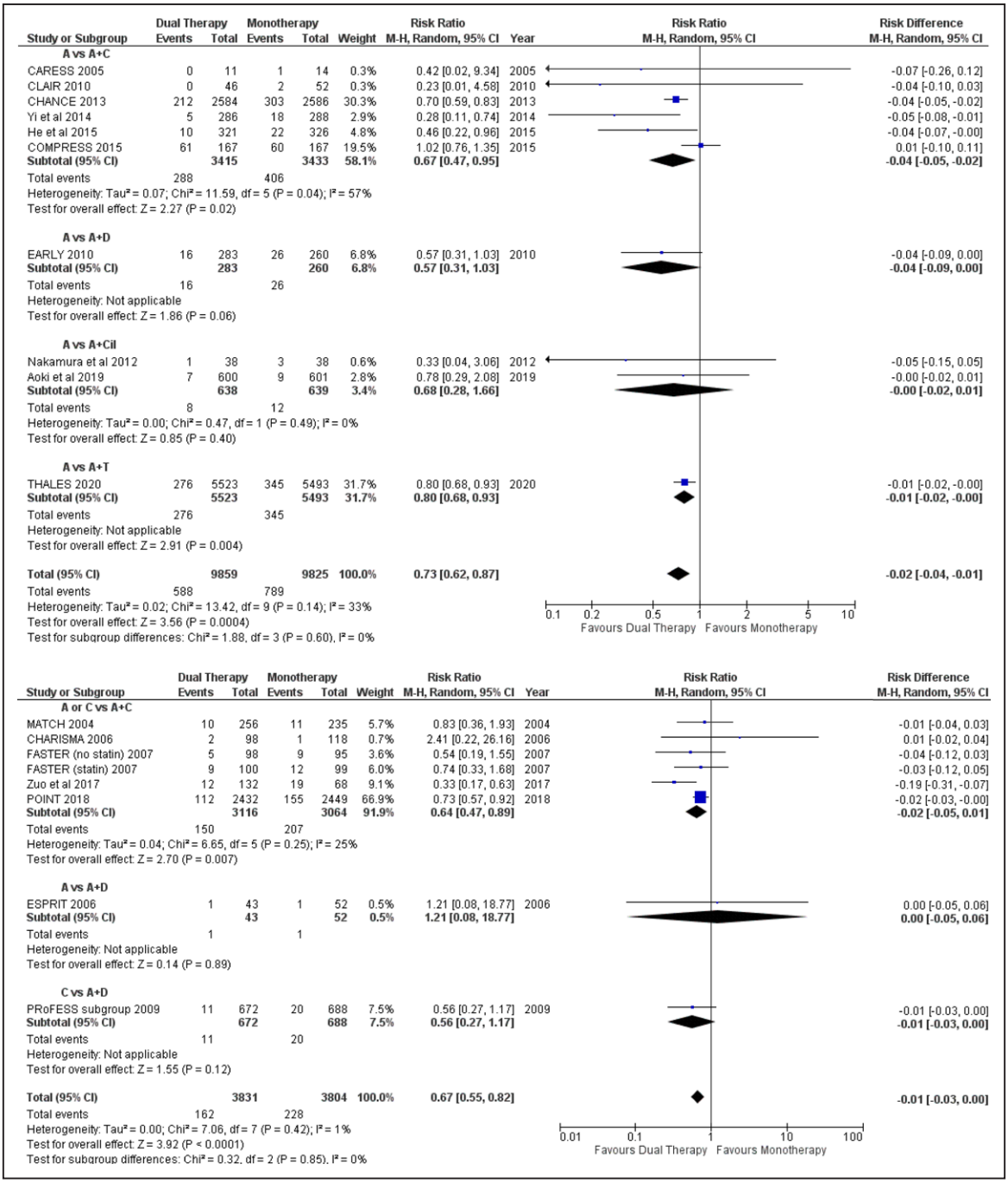

Figure 3. Risk of stroke recurrence on the basis of treatment duration.
Risk ratio and absolute risk difference for stroke recurrence associated with the use of dual therapy for ≤30 days (**Upper**) or >30 days (**Lower**). A indicates aspirin; A+C, aspirin plus clopidogrel; A+Cil, aspirin plus cilostazol; 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

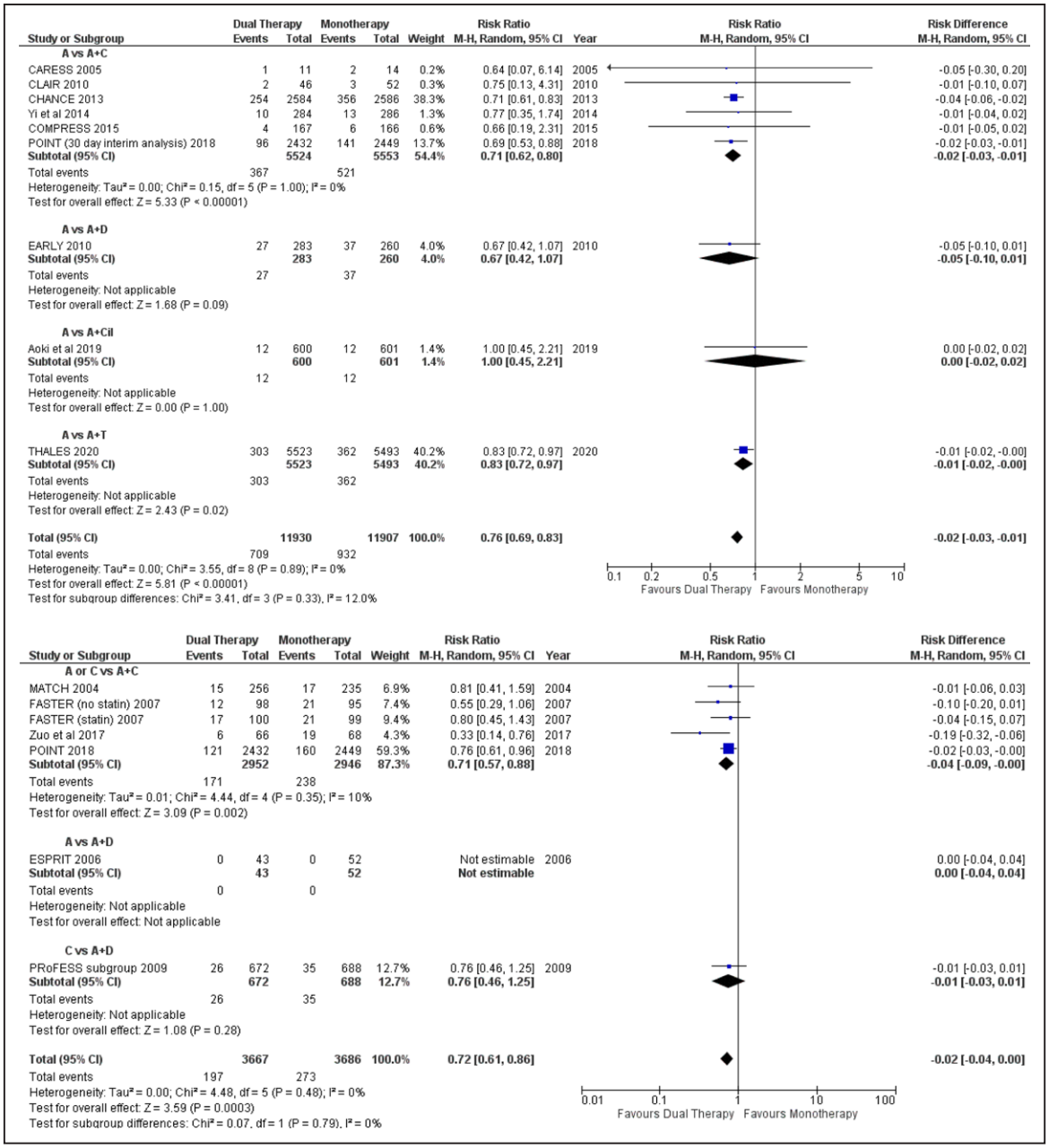

Figure 4. Risk of stroke, transient ischemic attack, acute coronary syndrome, or death from any cause on the basis of treatment duration.

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 ≤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 meta-analysis 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). THALES[6] 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 POINT[4] and CHANCE.[3]

The POINT[4] 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 POINT[4] done at 30 days of treatment, however, the risk of major hemorrhage was not significantly increased in

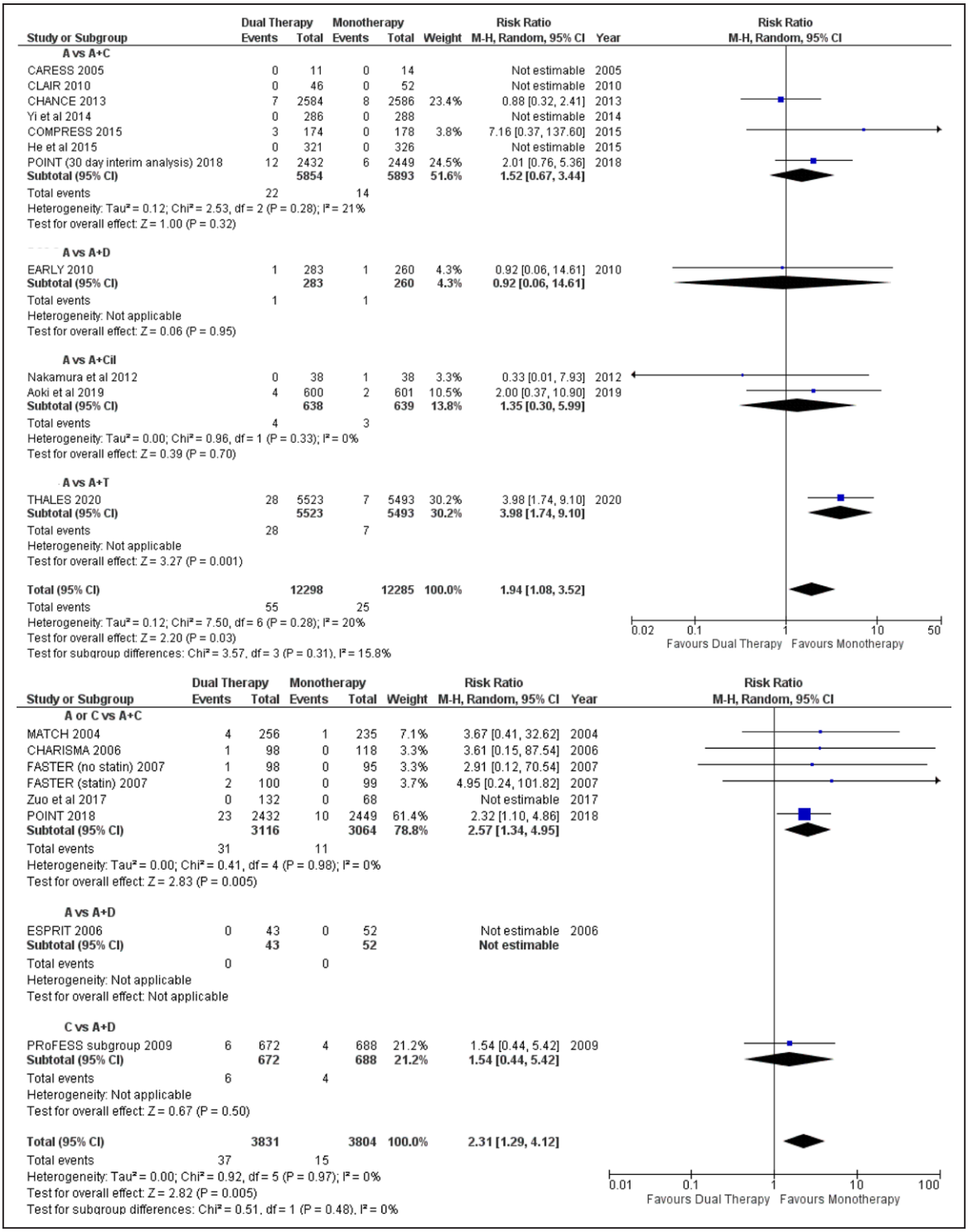

Figure 5. Risk of major hemorrhage on the basis of treatment duration.
Risk ratio and absolute risk difference for major hemorrhage associated with the use of dual therapy for ≤30 days (**Upper**) or >30 days (**Lower**). A indicates aspirin; A+C, aspirin plus clopidogrel; A+Cil, aspirin plus cilostazol; 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 treatment 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

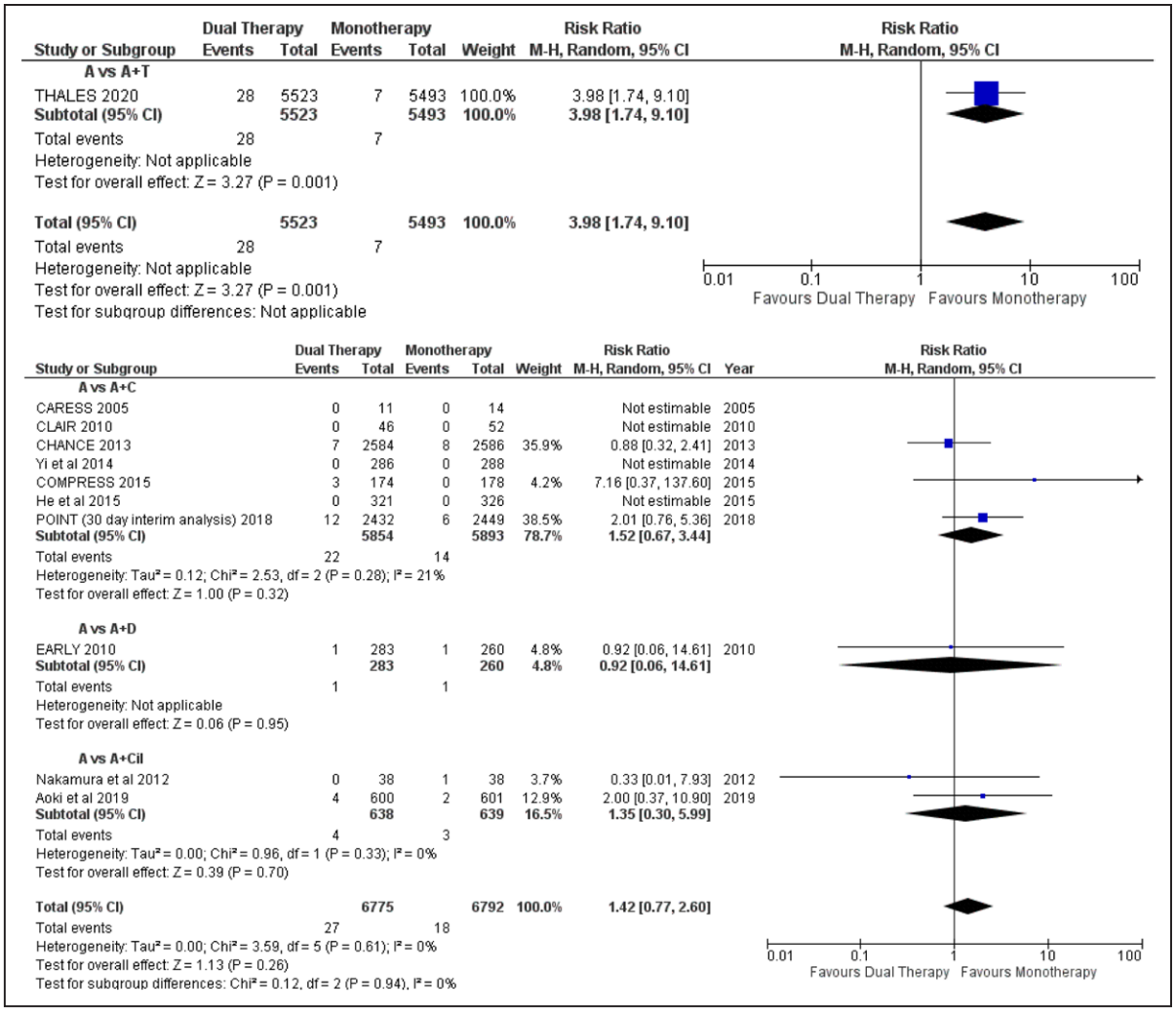

Figure 6. Risk of major hemorrhage on the basis of antithrombotic regimen.
Risk ratio and absolute risk difference for major hemorrhage associated with the use of monotherapy or dual therapy for ≤30 days stratified by use of aspirin plus ticagrelor (**Upper**) or other combinations (**Lower**). A indicates 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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Affiliation

Department of Neurology and Rehabilitation, University of Illinois at Chicago, College of Medicine.

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Supplemental Materials

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

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