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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

Running Title: *Trifan et al.; DAPT vs MAPT in Minor Noncardioembolic AIS or TIA*

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Abstract

Background: Dual antiplatelet treatment (DAPT) with aspirin plus clopidogrel for a limited time is recommended after minor non-cardioembolic stroke.
Methods: We performed a meta-analysis of all major studies that compared the efficacy and safety of DAPT versus monotherapy for secondary prevention of recurrent stroke or transient ischemic attack (TIA). The primary outcomes were stroke and the composite of stroke, TIA, acute coronary syndrome and death of all cause. The safety outcome was major hemorrhage. Relative risk (RR) and 95% confidence intervals (CI) were calculated. Heterogeneity was assessed by I^2 and Cochrane's Q statistics.
Results: The analysis included 27358 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 subgroup analysis, ≤30 days DAPT increased the risk of hemorrhage relative to monotherapy (RR=1.94, 95% CI=1.08-3.52). In 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 to 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; monotherapy; noncardioemblic stroke; TIA; efficacy

Non-standard Abbreviations and Acronyms
DAPT-dual antiplatelet therapy
TIA- transient ischemic attack
RCT- randomized controlled trial
CHANCE - Clopidogrel with aspirin in acute minor stroke or transient ischemic attack
POINT- Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA
THALES- Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA
P2Y12- adenosine diphosphate receptor
NIHSS- National Institutes of Health Stroke Scale
PRISMA- Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROBIS- Risk of Bias in Systematic Reviews
RoB2- Revised Cochrane risk of bias tool for randomized trials

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 of all causes 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 of all cause.
- Except for the combination of aspirin plus ticagrelor, the use of DAPT for ≤30 days does not increase the risk of major hemorrhage.

Introduction

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 non-cardioembolic strokes are treated with antiplatelet monotherapy (MAPT). However, based on the results of two independent large randomized controlled trials (RCTs), CHANCE (Clopidogrel with aspirin in acute minor stroke or transient ischemic attack) [3] and POINT (Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA) [4], the American Heart Association/American Stroke Association (AHA/ASA) acute ischemic stroke prevention guidelines give consideration to the use of dual antiplatelet agents (DAPT) for a short period of time (21 days) after acute minor non-cardioembolic stroke [5].

More recently, the results of THALES (Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA) [6], the largest-to-date RCT comparing MAPT to DAPT, were reported. This study compared the efficacy and safety of 30-day treatment with aspirin monotherapy to the combination of aspirin and ticagrelor (a reversible direct P2Y12 receptor antagonist) for the prevention of recurrent stroke after acute mild to moderate ischemic stroke (NIHSS 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.

Objective

The objective of this meta-analysis is to compare the efficacy and safety of DAPT to MAPT in patients randomized to either treatment within 3 days of experiencing IS 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 upon 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 non-cardioembolic acute ischemic stroke or TIA, who were randomized to DAPT within three days from ictus. Observational studies, MAPT versus placebo, and non-controlled studies were excluded.

Information Sources and Search Methods

PubMed, EMBASE, Cochrane Central registry of Controlled Trials, Clinical trial.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 “AND” and “OR” advanced search functions. The search algorithm is presented in **Appendix I.**

Study Selection and Data collection Process

The results of the search were screened for inclusion and exclusion criteria by two of the authors (FDT and GT) and duplicate trials were removed. Disagreements were resolved using a third author (PBG). To minimize heterogeneity, studies meeting the inclusion criteria were evaluated

to ensure that the reported outcomes were similar. Search results identified two 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 three 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 randomized within three days from ictus which were included in the analysis.

Using ROBIS tool, we judged that these two meta-analyses resulted from a comprehensive literature search and had a low risk of bias based on 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. 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's cohort characteristics, study design and outcome measures (efficacy and safety) were collected.

Two of the authors (GT and FDT) determined independently risk of bias for each eligible study using RoB2 tool [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 impact 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 Egger's test of the intercept [13].

Heterogeneity between studies was quantified using I^2 and Cochrane's Q (X^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% confidence intervals (CI) using random-effects models to investigate the distribution of true effects and how effects size varied across populations for each outcome. Primary outcomes are represented by the rate of stroke recurrence as defined in each trial (**Appendix II**). We used the composite of stroke/TIA, acute coronary syndrome (ACS) and death of any cause, an outcome reported in most of the studies, as a co-primary outcome. The primary safety outcome was the development of major hemorrhage as defined in each individual trial (**Appendix II)**. 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 based on 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 THALES study, which used a unique combination of antithrombotic agents and carried the largest weight in our meta-analysis. Since 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 outcomes were compared between MAPT and DAPT groups and between studies. Results are presented as RR and risk differences (RD) along with their corresponding 95% CI. The absolute number of events avoided per 1000 patients (absolute risk reduction) was calculated from RD. 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 randomized 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, though the RR in these cases could not be calculated.

Results

Study Selection and Characteristics

Search criteria yielded a total of 2540 studies, including ten [3, 17-25], which were included in the previous meta-analyses published in 2012 and 2013 [8, 9]. Our search identified additional seven studies that met inclusion criteria [4, 6, 26-30]. The reasons for exclusion of other RCTs [31-47] are provided in **Appendix III**. Our final systematic review includes 17 studies with a combined total of 27358 patients randomized 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% were male. **Supplemental Table I** 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 (**Supplemental Figure I)**. Some studies raised concerns regarding the randomization process due to unclear allocation concealment for participant and investigators [25], early termination due to slow enrollment [30], deviation from intended analysis [4], not use of intention-to-treat analysis [29] or unblinding prior to final analysis [28]. Visual inspection of the funnel plots revealed symmetry for all outcomes, and the 2-tailed *p*-values for Egger's intercept were <0.05 for all outcomes (**Supplemental Figure IV**).

Primary outcomes

Figure 2 depicts the analysis for stroke recurrence, composite outcome of stroke, TIA, ACS and death of all cause, and major hemorrhages for all the studies. There was a risk reduction of 29% (RR=0.71, 95% CI=0.63-0.81, p<0.00001) for stroke recurrence (moderate certainty evidence), with mild heterogeneity (I^2=21%; p for X^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 X^2=0.86). The absolute effect was 20 fewer events (95% CI=10-30) per 1000 participants treated with DAPT (**Table 2 and 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 death **(**moderate certainty evidence, **Figure 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, **Figure 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 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 X^2=0.12) and composite outcome (RR=0.71, 95% CI=0.63-0.80, p<0.00001, I^2=0%; p for X^2 >0.99, **Supplemental Figures II-III,** 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 X^2=0.67). The absolute effect was 3 additional major hemorrhages (95% CI=2 to 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 to 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 X^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 X^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%; p for X^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 X^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 non-cardioembolic ischemic strokes or TIA, DAPT reduces the risk of stroke recurrence and the composite of stroke, TIA, ACS and death of any cause, but increases the risk of severe hemorrhagic complications. These effects, however, are influenced by 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 when compared against the remaining DAPT regimens, but also showed a higher risk of major hemorrhage, while the remaining DAPT regimens did not. When DAPT regimens were continued for more than 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 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 non-inferior 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 patients receiving to 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].

POINT [4] trial accounted for 18% of all participants in our meta-analysis and 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 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 to 0.81) but did not increase the risk of major hemorrhage compared with monotherapy.

These results support the hypothesis that, compared to MAPT, the use of aspirin plus clopidogrel for 30 days after stroke onset is beneficial and safe in patients with minor non-cardioembolic strokes. The combination of aspirin plus ticagrelor for 30 days or using other DAPT regimens for more than 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 of any cause. However, one should be cautious when analyzing these results as ischemic stroke and major hemorrhage may carry different weights on patient outcome. Valuable information will be obtained from CHANCE 2, an ongoing RCT that will investigate

the efficacy and safety of aspirin plus clopidogrel vs. aspirin plus ticagrelor in the prevention of recurrent stroke (CHANCE 2; NCT04078737).

Limitations

The current meta-analysis has limitations. First, the included studies had methodologic differences, such as the duration of treatment, type of agent, dosage, stroke severity, and etiology. However, all of them had similarities, such as the inclusion of mild to moderate strokes of non-cardioembolic origin and the use of similar safety outcomes. Second, we included the unpublished results from earlier trials that investigated DAPT regimens [8]. While we were unable to cross check the outcomes, the event rates were obtained directly from the principal investigators of the main studies and 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. Lastly, we reported the results as RRs and absolute effects. As 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 of all 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 more than 30 days after stroke, while effective to reduce the risk of stroke recurrence and composite events, is associated with a significant increase in the risk of major hemorrhage.

Conflict of Interest Disclosures

No conflict of interest or pertinent disclosures exist for any of the Authors.

Sources of Funding

None

Supplemental Materials

Appendix I-III

Supplemental Table I

Supplemental Figures I-IV

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Table 1. Baseline characteristics

Study	Treatment arms	Target population	Mean age (years)	Male (%)
MATCH [17]	clopidogrel versus aspirin plus clopidogrel	IS, TIA	66	63
CARESS [18]	aspirin versus aspirin plus clopidogrel	IS, TIA	65	69
ESPIRIT [20]	aspirin versus aspirin plus dipyridamole	Minor IS, TIA	63	66
CHARISMA [19]	versus aspirin plus clopidogrel	IS, TIA	64	70
FASTER [21]	aspirin versus aspirin plus clopidogrel or clopidogrel plus simvastatin	Minor IS, TIA	68	53
PRoFESS [23]	clopidogrel versus aspirin plus extended release dipyridamole	IS	66	64
CLAIR [24]	aspirin versus aspirin plus clopidogrel	Minor IS, TIA	58	78
EARLY [22]	aspirin versus aspirin plus extended-release dipyridamole	IS, TIA	69	62
Nakamura et al [25]	aspirin versus aspirin plus cilostazol	Minor IS	67	71
CHANCE [3]	aspirin versus clopidogrel plus aspirin	Minor IS, TIA	62	66
Yi et al [26]	aspirin versus clopidogrel plus aspirin	Minor and Moderate IS	69	55

He et al [28]	aspirin versus aspirin plus clopidogrel	Minor IS, TIA	63	59
COMPRESS [27]	aspirin versus clopidogrel plus aspirin	Minor IS	68	66
Zuo et al [29]	aspirin versus clopidogrel plus aspirin	AIS, TIA	62	61
POINT [4]	aspirin versus clopidogrel plus aspirin	Minor IS, TIA	65	55
Aoki et al [30]	Aspirin versus aspirin plus cilostazol	Minor IS	69	66
THALES [6]	aspirin versus ticagrelor plus aspirin	Minor IS, TIA	65	62

IS: ischemic stroke; TIA: transient ischemic attack.

Table 2. Summary of findings for efficacy and safety of monotherapy versus dual antiplatelet therapy in patients with acute ischemic stroke or transient ischemic attack

Outcomes	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	Absolute Effect (95% CI)	No of Participants (studies)	Quality of the Evidence (GRADE)
	Assumed Risk	Corresponding Risk				
	Monotherapy	Dual Therapy				
Stroke Recurrence all studies	Medium Risk Population		RR 0.71 (0.63 to 0.81)	20 fewer strokes per 1000 (10-30 fewer)	27319 (17 studies)	⊕⊕⊕⊖ **moderate**[1]
	75 per 1000	53 per 1000 (47 to 60)				
Stroke Recurrence with ≤30 days of DAPT	Medium Risk Population		RR 0.73 (0.62 to 0.87)	20 fewer strokes per 1000 (10 to 40 fewer)	19684 (9 studies)	⊕⊕⊕⊖ **moderate**[1]
	80 per 1000	59 per 1000 (50 to 70)				
Stroke recurrent with > 30 days of DAPT	Medium Risk Population		RR 0.67 (0.55 to 0.82)	10 fewer strokes per 1000 (None to 30 fewer)	7635 (8 studies)	⊕⊕⊖⊖ **low**[1,2]
	60 per 1000	40 per 1000 (33 to 49)				
Composite Outcome for all Studies	Medium Risk Population		RR 0.76 (0.69 to 0.83)	20 fewer strokes per 1000 (10 to 30 fewer)	26214 (17 studies)	⊕⊕⊕⊖ **moderate**[1]
	81 per 1000	62 per 1000 (56 to 67)				
Composite Outcome with ≤30 days of DAPT	Medium Risk Population		RR 0.76 (0.69 to 0.83)	20 fewer strokes per 1000 (10- 30 fewer)	23837 (9 studies)	⊕⊕⊕⊖ **moderate**[1]
	78 per 1000	59 per 1000 (54 to 65)				
Composite Outcome for >30 days of DAPT	Medium Risk Population		RR 0.72 (0.61 to 0.86)	20 fewer strokes per 1000 (None to 40 fewer)	7353 (6 studies)	⊕⊕⊖⊖ **low**[1,2]
	74 per 1000	53 per 1000 (45 to 64)				
Major Hemorrhage for all studies	Medium Risk Population		RR 2.17 (1.45 to 3.25)	3 more hemorrhage (2 to 5 more)	26690 (17 studies)	⊕⊕⊖⊖ **low**[2,3]
	3 per 1000	6 per 1000 (4 to 8)				
Major Hemorrhage with ≤30 days of DAPT	Medium Risk Population		RR 1.94 (1.08 to 3.52)	2 more hemorrhage (1 to 4 more)	24583 (11 studies)	⊕⊕⊕⊖ **moderate**[4,5]
	2 per 1000	4 per 1000 (2 to 7)				

Major Hemorrhage with ≤30 days DAPT excluding THALES	Medium Risk Population		RR 1.42 (0.77 to 2.60)	1 more hemorrhage (1 fewer to 3 more)	13567 (10 studies)	⊕⊕⊕⊖ **moderate**[4,5]
	3 per 1000	4 per 1000 (2 to 7)				
Major Hemorrhage for THALES study	Medium Risk Population		RR 3.98 (1.74 to 9.10)	4 more hemorrhage (2 to 6 more)	11016 (1 study)	⊕⊕⊕⊖ **moderate**[5]
	1 per 1000	5 per 1000 (2 to 12)				
Major Hemorrhage with >30 days of DAPT	Medium Risk Population		RR 2.31 (1.29 to 4.12)	6 more hemorrhages (2 to 9 more)	7635 (8 studies)	⊕⊕⊖⊖ **low**[2,5]
	4 per 1000	9 per 1000 (5 to 16)				

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio.
**GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.Very low quality: We are very uncertain about the estimate. [1] Imprecision suspected as RRR greater than 25%. [2] 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; [3] CI includes both null effect and benefit; RR <0.75; [4] Interim analysis used for POINT study before trial discontinuation; [5] Total number of events is less than 300 and RR >1.25

Figure Legends

Figure 1. Flowchart for the included studies

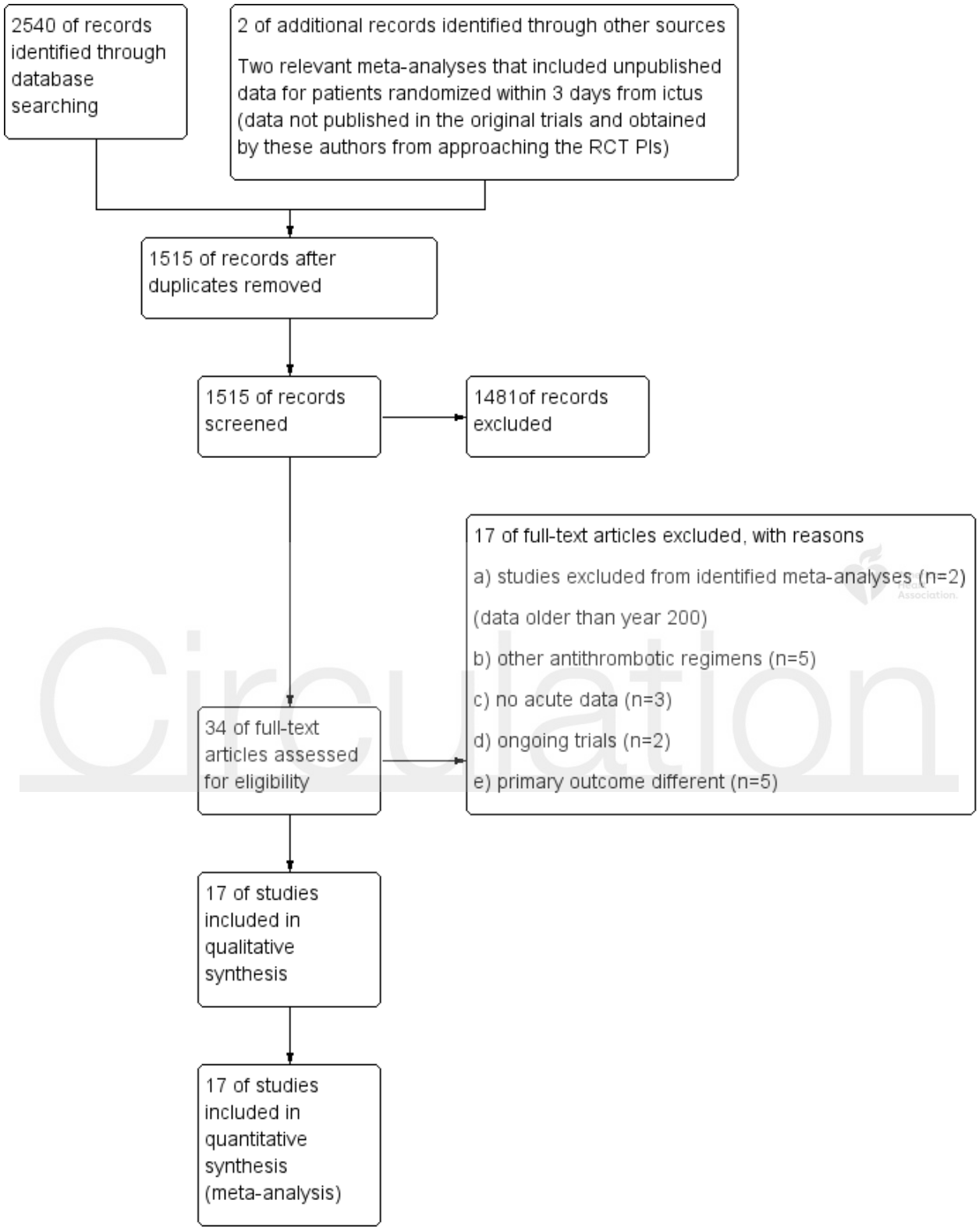
Figure 2. Efficacy and safety outcomes. Risk ratio and absolute risk difference for stroke recurrence (**A**), composite outcome of stroke, transient ischemic attack, acute coronary syndrome and death of any cause (**B**) and major hemorrhage (**C**) for patients receiving monotherapy or dual antiplatelet therapy. CI=confidence interval, M-H=Mantel-Haenszel method.

Figure 3. Risk of stroke recurrence based on treatment duration. Risk ratio and absolute risk difference for stroke recurrence associated with the use of dual therapy for ≤30 days (**upper panel**) or >30 days (**lower panel**). A=aspirin, A+C=aspirin plus clopidogrel, A+D=aspirin plus dipyridamole, A+Cil=aspirin plus cilostazol, A+T=aspirin plus ticagrelor, C=clopidogrel. CI=confidence interval, M-H=Mantel-Haenszel method.

Figure 4. Risk of stroke, transient ischemic attack, acute coronary syndrome, or death of any cause based on treatment duration. Risk ratio and absolute risk difference for the composite outcome of stroke, transient ischemic attack, acute coronary syndrome, or death of any cause associated with the use of dual therapy for ≤30 days (**upper panel**) or >30 days (**lower panel**). A=aspirin, A+C=aspirin plus clopidogrel, A+D=aspirin plus dipyridamole, A+Cil=aspirin plus cilostazol, A+T=aspirin plus ticagrelor, C=clopidogrel. CI=confidence interval, M-H=Mantel-Haenszel method.

Figure 5. Risk of major hemorrhage based on treatment duration. Risk ratio and absolute risk difference for major hemorrhage associated with the use of dual therapy for ≤ 30 days (**upper panel**) or >30 days (**lower panel**). A=aspirin, A+C=aspirin plus clopidogrel, A+D=aspirin plus dipyridamole, A+Cil=aspirin plus cilostazol, A+T=aspirin plus ticagrelor, C=clopidogrel. CI=confidence interval, M-H=Mantel-Haenszel method.

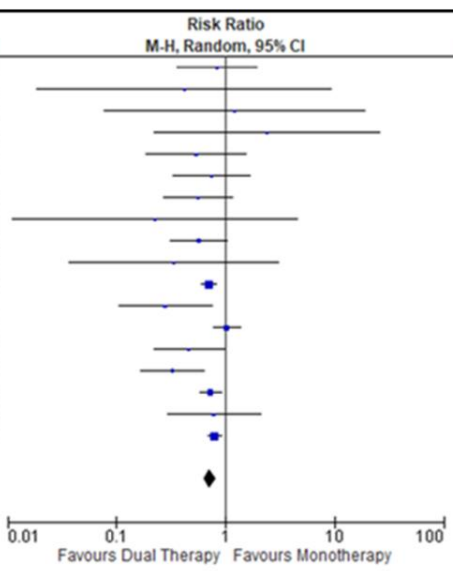
Figure 6. Risk of major hemorrhage based on antithrombotic regimen. Risk ratio and absolute risk difference for major hemorrhage associated with the use of monotherapy or dual therapy for ≤30 days stratified by use of aspirin plus ticagrelor (**upper panel**) or other combinations (**lower panel**). A=aspirin, A+C=aspirin plus clopidogrel, A+D=aspirin plus dipyridamole, A+Cil=aspirin plus cilostazol, A+T=aspirin plus ticagrelor, C=clopidogrel. CI=confidence interval, M-H=Mantel-Haenszel method.


2540 of records identified through database searching
2 of additional records identified through other sources
Two relevant meta-analyses that included unpublished data for patients randomized within 3 days from ictus (data not published in the original trials and obtained by these authors from approaching the RCT PIs)
1515 of records after duplicates removed
1515 of records screened
1481of records excluded
17 of full-text articles excluded, with reasons
a) studies excluded from identified meta-analyses (n=2)
(data older than year 200)
b) other antithrombotic regimens (n=5)
c) no acute data (n=3)
d) ongoing trials (n=2)
e) primary outcome different (n=5)
34 of full-text articles assessed for eligibility
17 of studies included in qualitative synthesis
17 of studies included in quantitative synthesis (meta-analysis)

A

Study or Subgroup	Dual Therapy Events	Dual Therapy Total	Monotherapy Events	Monotherapy Total	Weight	Risk Ratio M-H, Random, 95% CI	Year	Risk Difference M-H, Random, 95% CI
MATCH 2004	10	256	11	235	2.3%	0.83 [0.36, 1.93]	2004	-0.01 [-0.04, 0.03]
CARESS 2005	0	11	1	14	0.2%	0.42 [0.02, 9.34]	2005	-0.07 [-0.26, 0.12]
ESPRIT 2006	1	43	1	52	0.2%	1.21 [0.08, 18.77]	2006	0.00 [-0.05, 0.06]
CHARISMA 2006	2	98	1	118	0.3%	2.41 [0.22, 26.16]	2006	0.01 [-0.02, 0.04]
FASTER (no statin) 2007	5	98	9	95	1.5%	0.54 [0.19, 1.55]	2007	-0.04 [-0.12, 0.03]
FASTER (statin) 2007	9	100	12	99	2.4%	0.74 [0.33, 1.68]	2007	-0.03 [-0.12, 0.05]
PRoFESS 2009	11	672	20	688	2.9%	0.56 [0.27, 1.17]	2009	-0.01 [-0.03, 0.00]
CLAIR 2010	0	46	2	52	0.2%	0.23 [0.01, 4.58]	2010	-0.04 [-0.10, 0.03]
EARLY 2010	16	283	26	260	4.2%	0.57 [0.31, 1.03]	2010	-0.04 [-0.09, 0.00]
Nakamura et al 2012	1	38	3	38	0.3%	0.33 [0.04, 3.06]	2012	-0.05 [-0.15, 0.05]
CHANCE 2013	212	2584	303	2586	22.5%	0.70 [0.59, 0.83]	2013	-0.04 [-0.05, -0.02]
Yi et al 2014	5	286	18	288	1.7%	0.28 [0.11, 0.74]	2014	-0.05 [-0.08, -0.01]
COMPRESS 2015	61	167	60	167	13.2%	1.02 [0.76, 1.35]	2015	0.01 [-0.10, 0.11]
He et al 2015	10	321	22	326	2.9%	0.46 [0.22, 0.96]	2015	-0.04 [-0.07, -0.00]
Zuo et al 2017	12	132	19	68	3.5%	0.33 [0.17, 0.63]	2017	-0.19 [-0.31, -0.07]
POINT 2018	112	2432	155	2449	16.4%	0.73 [0.57, 0.92]	2018	-0.02 [-0.03, -0.00]
Aoki et al 2019	7	600	9	601	1.7%	0.78 [0.29, 2.08]	2019	-0.00 [-0.02, 0.01]
THALES 2020	276	5523	345	5493	23.8%	0.80 [0.68, 0.93]	2020	-0.01 [-0.02, -0.00]
Total (95% CI)		**13690**		**13629**	**100.0%**	**0.71 [0.63, 0.81]**		**-0.02 [-0.03, -0.01]**
Total events	750		1017					

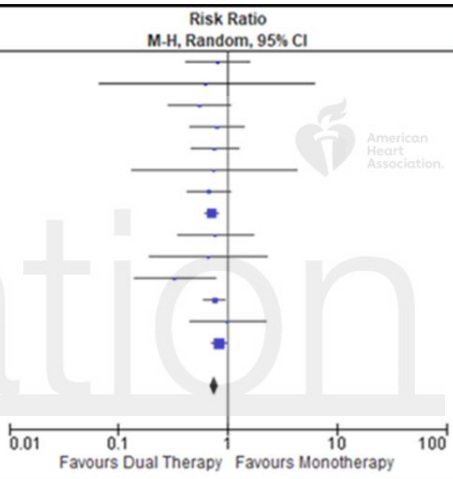
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 21.54$, df = 17 (P = 0.20); $I^2 = 21\%$
Test for overall effect: Z = 5.08 (P < 0.00001)



B

Study or Subgroup	Dual Therapy Events	Dual Therapy Total	Monotherapy Events	Monotherapy Total	Weight	Risk Ratio M-H, Random, 95% CI	Year	Risk Difference M-H, Random, 95% CI
MATCH 2004	15	256	17	235	1.7%	0.81 [0.41, 1.59]	2004	-0.01 [-0.06, 0.03]
CARESS 2005	1	11	2	14	0.1%	0.64 [0.07, 6.14]	2005	-0.05 [-0.30, 0.20]
FASTER (no statin) 2007	12	98	21	95	1.8%	0.55 [0.29, 1.06]	2007	-0.10 [-0.20, 0.01]
FASTER (statin) 2007	17	100	21	99	2.3%	0.80 [0.45, 1.43]	2007	-0.04 [-0.15, 0.07]
PRoFESS 2009	26	672	35	688	3.1%	0.76 [0.46, 1.25]	2009	-0.01 [-0.03, 0.01]
CLAIR 2010	2	46	3	52	0.3%	0.75 [0.13, 4.31]	2010	-0.01 [-0.10, 0.07]
EARLY 2010	27	283	37	260	3.5%	0.67 [0.42, 1.07]	2010	-0.05 [-0.10, 0.01]
CHANCE 2013	254	2584	356	2586	33.5%	0.71 [0.61, 0.83]	2013	-0.04 [-0.06, -0.02]
Yi et al 2014	10	284	13	286	1.2%	0.77 [0.35, 1.74]	2014	-0.01 [-0.04, 0.02]
COMPRESS 2015	4	167	6	166	0.5%	0.66 [0.19, 2.31]	2015	-0.01 [-0.05, 0.02]
Zuo et al 2017	6	66	19	68	1.1%	0.33 [0.14, 0.76]	2017	-0.19 [-0.32, -0.06]
POINT 2018	121	2432	160	2449	14.6%	0.76 [0.61, 0.96]	2018	-0.02 [-0.03, -0.00]
Aoki et al 2019	12	600	12	601	1.2%	1.00 [0.45, 2.21]	2019	0.00 [-0.02, 0.02]
THALES 2020	303	5523	362	5493	35.1%	0.83 [0.72, 0.97]	2020	-0.01 [-0.02, -0.00]
Total (95% CI)		**13122**		**13092**	**100.0%**	**0.76 [0.69, 0.83]**		**-0.02 [-0.03, -0.01]**
Total events	810		1064					

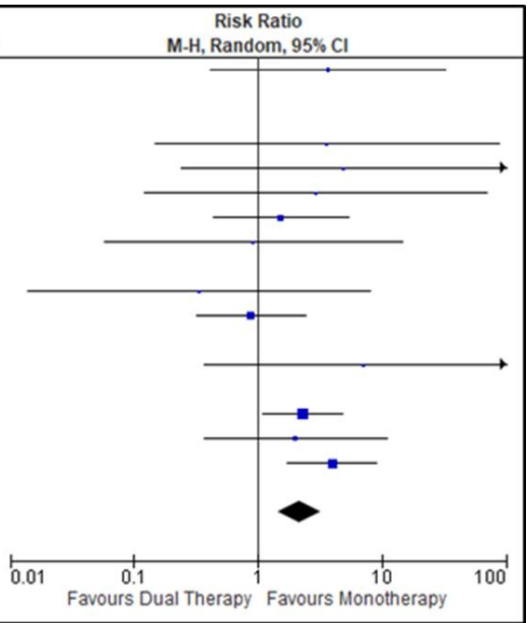
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.69$, df = 13 (P = 0.86); $I^2 = 0\%$
Test for overall effect: Z = 6.20 (P < 0.00001)

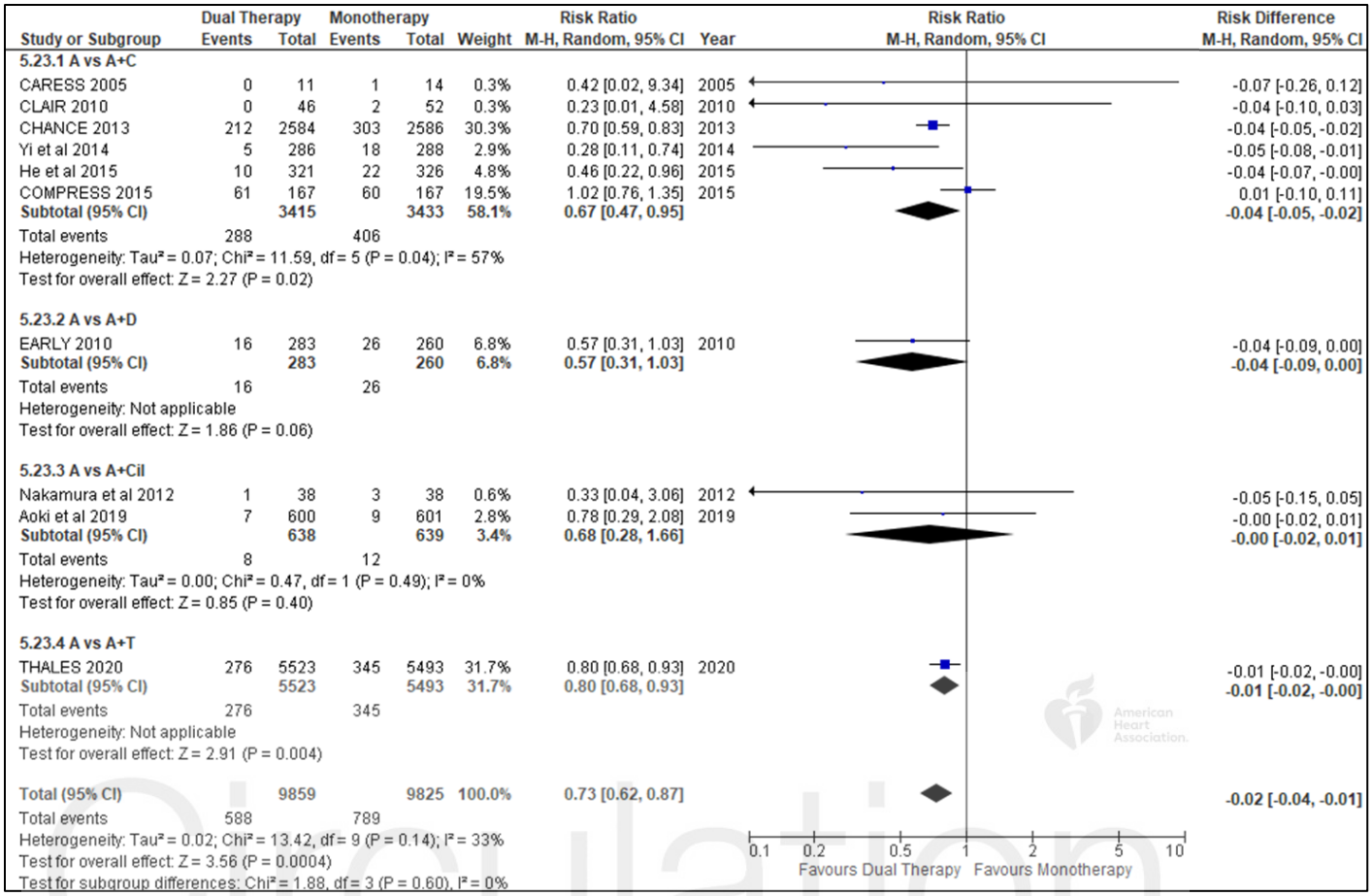


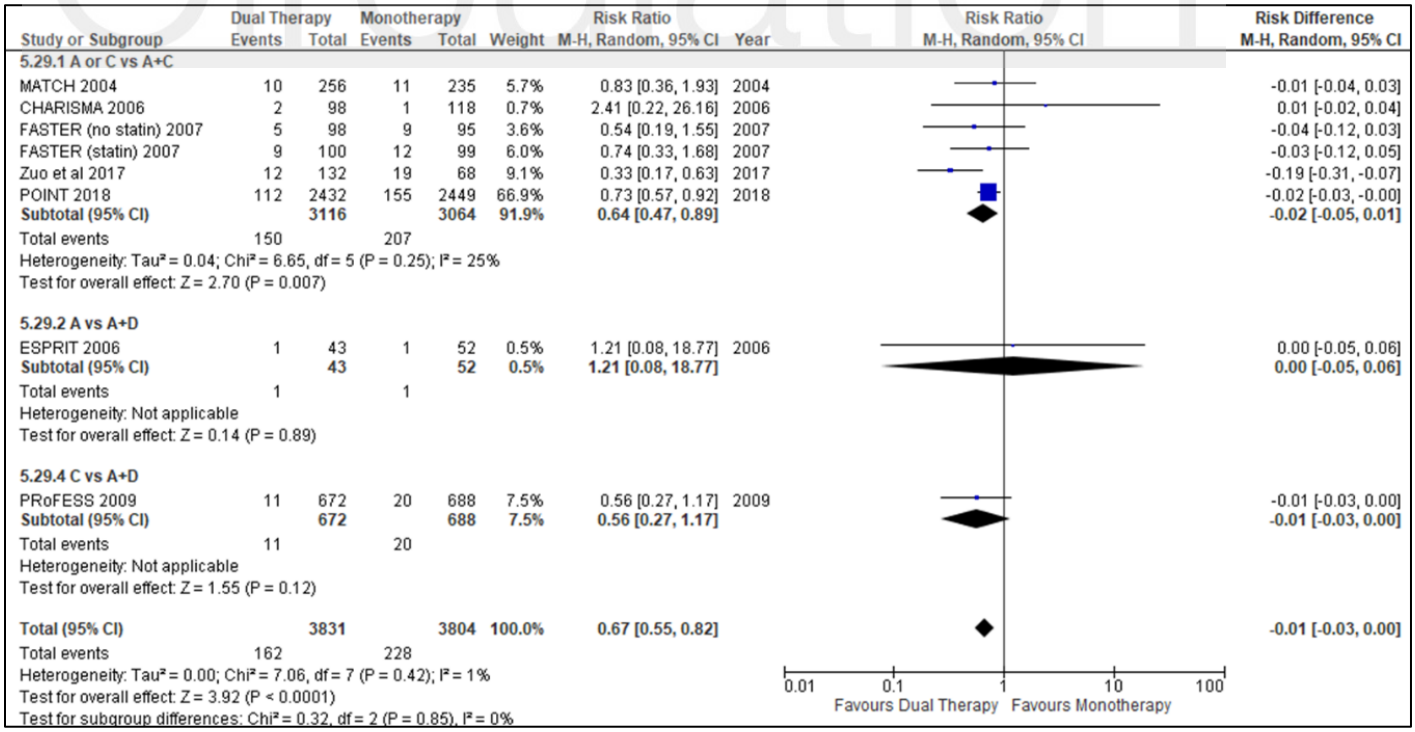
C

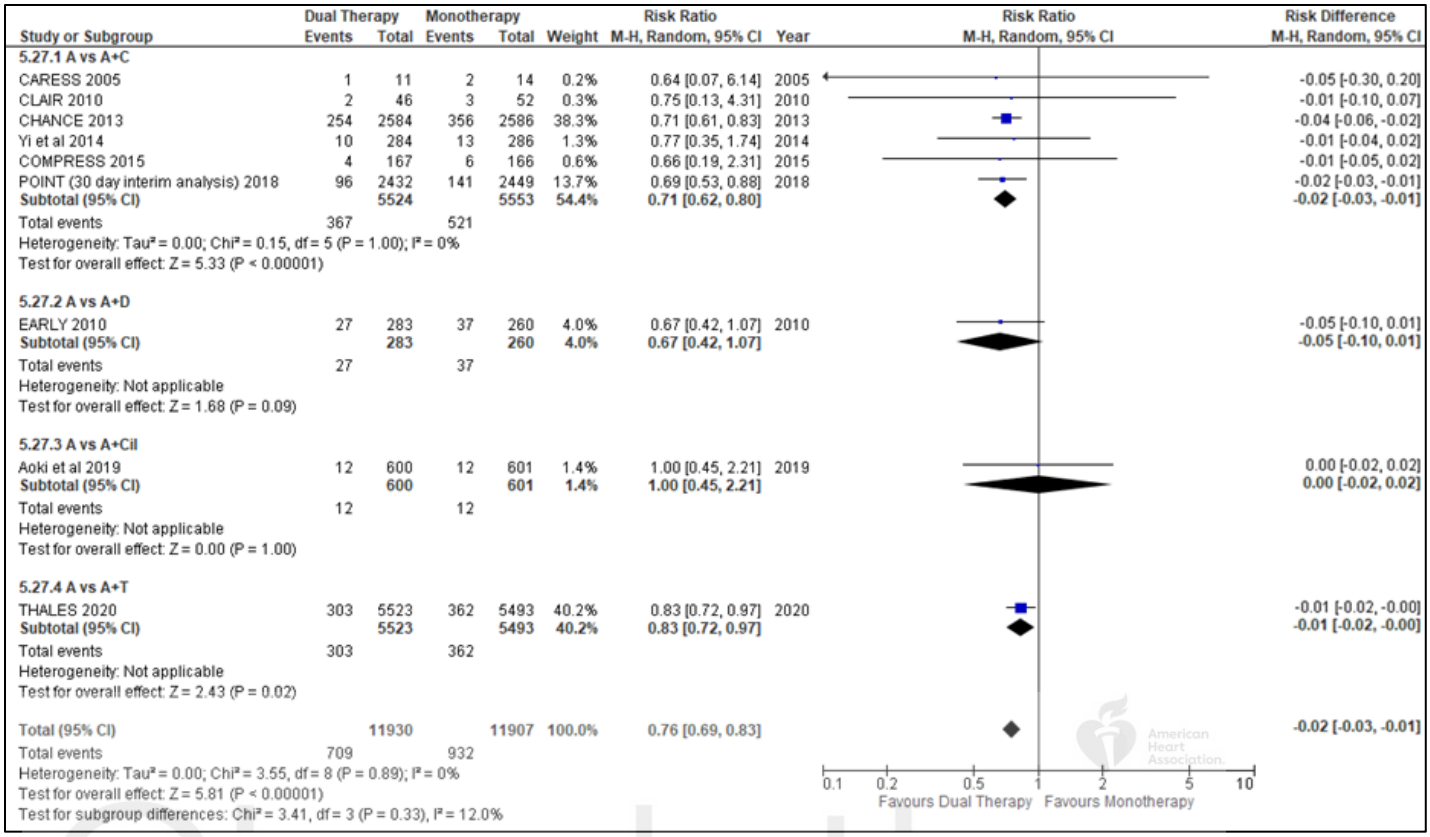
Study or Subgroup	Dual Therapy Events	Dual Therapy Total	Monotherapy Events	Monotherapy Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
MATCH 2004	4	256	1	235	3.4%	3.67 [0.41, 32.62]	2004
CARESS 2005	0	11	0	14		Not estimable	2005
ESPRIT 2006	0	43	0	52		Not estimable	2006
CHARISMA 2006	1	98	0	118	1.6%	3.61 [0.15, 87.54]	2006
FASTER (statin) 2007	2	100	0	99	1.8%	4.95 [0.24, 101.82]	2007
FASTER (no statin) 2007	1	98	0	95	1.6%	2.91 [0.12, 70.54]	2007
PRoFESS 2009	6	672	4	688	10.3%	1.54 [0.44, 5.42]	2009
EARLY 2010	1	283	1	260	2.1%	0.92 [0.06, 14.61]	2010
CLAIR 2010	0	46	0	52		Not estimable	2010
Nakamura et al 2012	0	38	1	38	1.6%	0.33 [0.01, 7.93]	2012
CHANCE 2013	7	2584	8	2586	16.0%	0.88 [0.32, 2.41]	2013
Yi et al 2014	0	286	0	288		Not estimable	2014
COMPRESS 2015	3	174	0	178	1.9%	7.16 [0.37, 137.60]	2015
Zuo et al 2017	0	132	0	68		Not estimable	2017
POINT 2018	23	2432	10	2449	29.9%	2.32 [1.10, 4.86]	2018
Aoki et al 2019	4	600	2	601	5.7%	2.00 [0.37, 10.90]	2019
THALES 2020	28	5523	7	5493	24.0%	3.98 [1.74, 9.10]	2020
Total (95% CI)		**13376**		**13314**	**100.0%**	**2.17 [1.45, 3.25]**	
Total events	80		34				

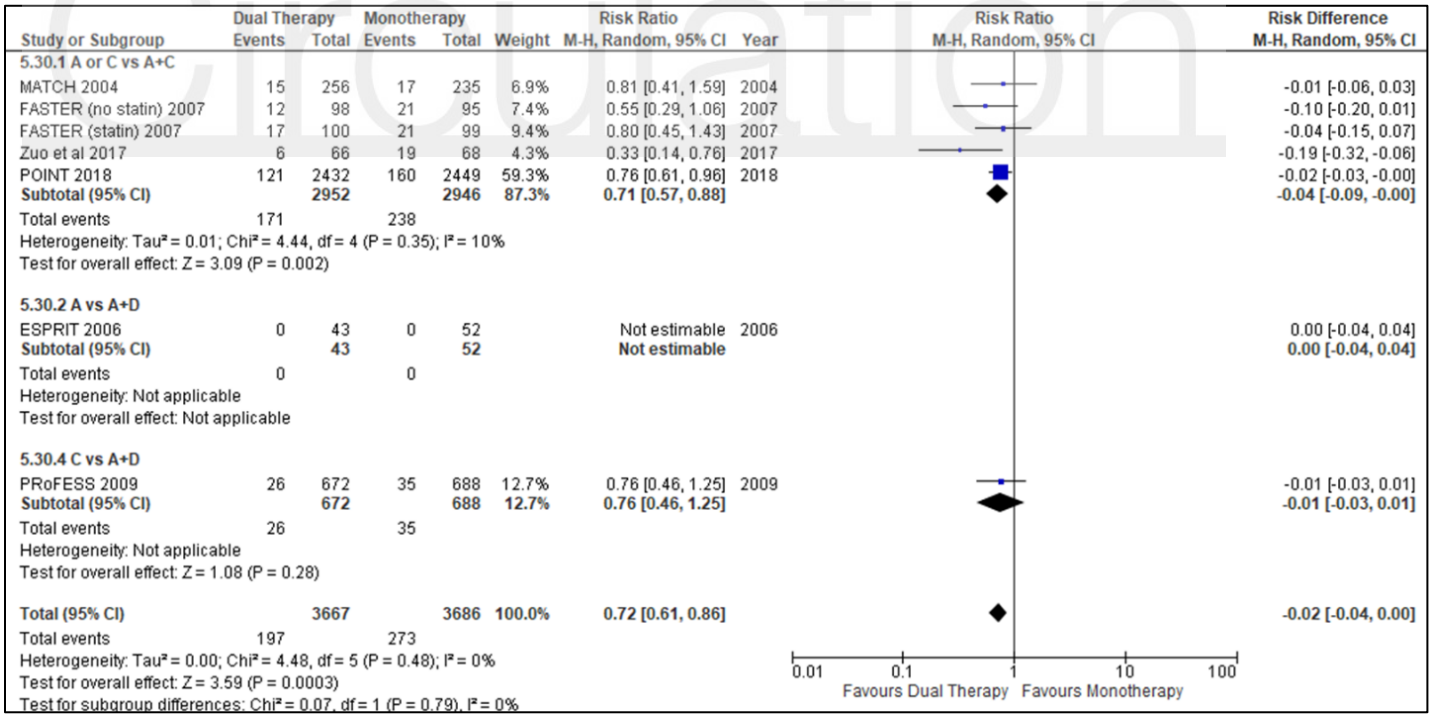
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.49$, df = 11 (P = 0.67); $I^2 = 0\%$
Test for overall effect: Z = 3.74 (P = 0.0002)








Dual Therapy
Monotherapy
Risk Ratio
Risk Ratio
Risk Difference
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
M-H, Random, 95% CI
5.27.1 A vs A+C
CARESS 2005 1 11 2 14 0.2% 0.64 [0.07, 6.14] 2005 -0.05 [-0.30, 0.20]
CLAIR 2010 2 46 3 52 0.3% 0.75 [0.13, 4.31] 2010 -0.01 [-0.10, 0.07]
CHANCE 2013 254 2584 356 2586 38.3% 0.71 [0.61, 0.83] 2013 -0.04 [-0.06, -0.02]
Yi et al 2014 10 284 13 286 1.3% 0.77 [0.35, 1.74] 2014 -0.01 [-0.04, 0.02]
COMPRESS 2015 4 167 6 166 0.6% 0.66 [0.19, 2.31] 2015 -0.01 [-0.05, 0.02]
POINT (30 day interim analysis) 2018 96 2432 141 2449 13.7% 0.69 [0.53, 0.88] 2018 -0.02 [-0.03, -0.01]
Subtotal (95% CI) 5524 5553 54.4% 0.71 [0.62, 0.80] -0.02 [-0.03, -0.01]
Total events 367 521
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 5 (P = 1.00); I² = 0%
Test for overall effect: Z = 5.33 (P < 0.00001)
5.27.2 A vs A+D
EARLY 2010 27 283 37 260 4.0% 0.67 [0.42, 1.07] 2010 -0.05 [-0.10, 0.01]
Subtotal (95% CI) 283 260 4.0% 0.67 [0.42, 1.07] -0.05 [-0.10, 0.01]
Total events 27 37
Heterogeneity: Not applicable
Test for overall effect: Z = 1.68 (P = 0.09)
5.27.3 A vs A+CiI
Aoki et al 2019 12 600 12 601 1.4% 1.00 [0.45, 2.21] 2019 0.00 [-0.02, 0.02]
Subtotal (95% CI) 600 601 1.4% 1.00 [0.45, 2.21] 0.00 [-0.02, 0.02]
Total events 12 12
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
5.27.4 A vs A+T
THALES 2020 303 5523 362 5493 40.2% 0.83 [0.72, 0.97] 2020 -0.01 [-0.02, -0.00]
Subtotal (95% CI) 5523 5493 40.2% 0.83 [0.72, 0.97] -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% CI) 11930 11907 100.0% 0.76 [0.69, 0.83] -0.02 [-0.03, -0.01]
Total events 709 932
Heterogeneity: Tau² = 0.00; Chi² = 3.55, df = 8 (P = 0.89); I² = 0%
Test for overall effect: Z = 5.81 (P < 0.00001)
Test for subgroup differences: Chi² = 3.41, df = 3 (P = 0.33), I² = 12.0%
0.1 0.2 0.5 1 2 5 10
Favours Dual Therapy Favours Monotherapy
American Heart Association


Dual Therapy
Monotherapy
Risk Ratio
Risk Ratio
Risk Difference
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
M-H, Random, 95% CI
5.30.1 A or C vs A+C
MATCH 2004 15 256 17 235 6.9% 0.81 [0.41, 1.59] 2004 -0.01 [-0.06, 0.03]
FASTER (no statin) 2007 12 98 21 95 7.4% 0.55 [0.29, 1.06] 2007 -0.10 [-0.20, 0.01]
FASTER (statin) 2007 17 100 21 99 9.4% 0.80 [0.45, 1.43] 2007 -0.04 [-0.15, 0.07]
Zuo et al 2017 6 66 19 68 4.3% 0.33 [0.14, 0.76] 2017 -0.19 [-0.32, -0.06]
POINT 2018 121 2432 160 2449 59.3% 0.76 [0.61, 0.96] 2018 -0.02 [-0.03, -0.00]
Subtotal (95% CI) 2952 2946 87.3% 0.71 [0.57, 0.88] -0.04 [-0.09, -0.00]
Total events 171 238
Heterogeneity: Tau² = 0.01; Chi² = 4.44, df = 4 (P = 0.35); I² = 10%
Test for overall effect: Z = 3.09 (P = 0.002)
5.30.2 A vs A+D
ESPRIT 2006 0 43 0 52 Not estimable 2006 0.00 [-0.04, 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
5.30.4 C vs A+D
PRoFESS 2009 26 672 35 688 12.7% 0.76 [0.46, 1.25] 2009 -0.01 [-0.03, 0.01]
Subtotal (95% CI) 672 688 12.7% 0.76 [0.46, 1.25] -0.01 [-0.03, 0.01]
Total events 26 35
Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)
Total (95% CI) 3667 3686 100.0% 0.72 [0.61, 0.86] -0.02 [-0.04, 0.00]
Total events 197 273
Heterogeneity: Tau² = 0.00; Chi² = 4.48, df = 5 (P = 0.48); I² = 0%
Test for overall effect: Z = 3.59 (P = 0.0003)
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%
0.01 0.1 1 10 100
Favours Dual Therapy Favours Monotherapy