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Risk–Benefit Profile of Long-Term Dual- Versus Single-Antiplatelet Therapy Among Patients With Ischemic Stroke

A Systematic Review and Meta-analysis

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Background: Dual-antiplatelet regimens for prevention of recurrent stroke promote antithrombotic effects but may increase the risk for hemorrhage.

Purpose: To qualitatively and quantitatively examine the risk for recurrent stroke and intracranial hemorrhage (ICH) linked to long-term dual- and single-antiplatelet therapy among patients with ischemic stroke and transient ischemic attack.

Data Sources: PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials through March 2013 without language restrictions.

Study Selection: The search identified 7 randomized, controlled trials that involved a total of 39 574 participants and reported recurrent stroke and ICH as outcome measures.

Data Extraction: All data from eligible studies were independently abstracted by 2 investigators according to a standard protocol.

Data Synthesis: Recurrent stroke risk did not differ between patients receiving dual-antiplatelet therapy and those receiving aspirin monotherapy (relative risk [RR], 0.89 [95% CI, 0.78 to 1.01]) or clopidogrel monotherapy (RR, 1.01 [CI, 0.93 to 1.08]). Risk for ICH did not differ between patients receiving dual-antiplatelet therapy and those receiving aspirin monotherapy (RR, 0.99 [CI, 0.70 to 1.42]) but was greater among patients receiving dual-antiplatelet therapy than among those receiving clopidogrel monotherapy (RR, 1.46 [CI, 1.17 to 1.82]).

Limitation: Agents used in dual- and single-antiplatelet therapies varied across trials, and the relatively modest number of trials limited subgroup analysis.

Conclusion: Compared with monotherapy, dual-antiplatelet therapy lasting more than 1 year after an index ischemic stroke or transient ischemic attack is not associated with a greater reduction in overall recurrent stroke risk. However, long-term dual-antiplatelet therapy is linked to higher risk for ICH than clopidogrel monotherapy in this patient population.

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Antiplatelet therapy is a standard treatment for patients with noncardioembolic ischemic stroke or transient ischemic attack (TIA) (1). Because the various available antiplatelet agents antagonize different steps in the process of platelet activation (1), it is reasonable to expect that combining 2 antiplatelet agents with differing actions may boost antithrombotic efficacy. However, although enhanced antithrombotic effects could provide patients with ischemic stroke and TIA with additional protection against future thrombotic events, they could also increase the risk for systemic or intracranial bleeding. Although a certain risk for bleeding may be acceptable in the context of even greater protection against ischemic events, it is important to quantify the magnitude of bleeding risk and how it varies with the nature of the index vascular event and the components and duration of antiplatelet treatment.

Among the various hemorrhagic complications of antiplatelet therapies, intracranial hemorrhage (ICH) has particularly devastating consequences because of its associated high rates of mortality and permanent disability. Compared with patients with symptomatic ischemic vascular disease in other organ beds, those with symptomatic cerebral ischemia might be especially prone to ICH with antithrombotic agents given their preexisting brain parenchymal injury and fragile cerebral vasculature. Moreover, the risk for ICH in these patients may increase with time. Although a recent meta-analysis suggested that dual-antiplatelet therapy decreases vascular risk after stroke without increasing ICH risk compared with single-antiplatelet therapy (2), only patients with an index stroke in the previous 3 days were included and about 31% of them received dual-antiplatelet therapy for 6 months or less (2). Because it is recommended that patients with ischemic stroke and TIA continue to receive antiplatelet treatment indefinitely after the index event (1), properly examining the ICH risk versus the overall recurrent stroke reduction benefit of long-term dual-antiplatelet therapy in these patients is important. To do this, we conducted a meta-analysis of randomized, controlled trials examining the effect of long-term antiplatelet treatment among patients with ischemic stroke and TIA.

Methods

This study was performed in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (3).

Data Sources and Searches

We searched PubMed (1966 to March 2013), EMBASE (1996 to March 2013), and the Cochrane Central Register of Controlled Trials with the terms "antiplatelet therapy" or "aspirin" or "dipyridamole" or "clopidogrel" or "ticlopidine" or "prasugrel" or "cilostazol" or "triflusal" or "glycoprotein IIb/IIIa receptor antagonists" or "thrombin receptor antagonist" or "atopaxar" or "vorapaxar" or "terutroban" AND "stroke" or "cerebrovascular disease" or

Table 1. **Characteristics of Included Trials**

Variable	Study, Year (Reference)		
	CHARISMA, 2011 (12)	ESPRIT, 2006 (13)	JASAP, 2011 (14)
Population	Ischemic stroke or TIA within 5 y	Minor ischemic stroke or TIA within 6 mo	Ischemic stroke within 1 wk to 6 mo
Dual-antiplatelet therapy and daily dose	Aspirin, 75 to 162 mg, plus clopidogrel, 75 mg	Aspirin, 30 to 325 mg (median, 75 mg), plus dipyridamole, 400 mg	Aspirin, 50 mg, plus dipyridamole, 400 mg
Single-antiplatelet therapy and daily dose	Aspirin, 75 to 162 mg	Aspirin, 30 to 325 mg (median, 75 mg)	Aspirin, 81 mg
Participants, *n*	4320	2739	1294
Men, %	63	66	72
Mean age, *y*	64.9	66	66.1
Treatment duration, *y*	2.1	3.5	1.3
Treatment discontinuation rate, %*	NA	34 vs. 13	29 vs. 25
Comorbid conditions, %*			
Hypertension	76 vs. 76	60 vs. 59	89 vs. 88
Diabetes mellitus	28 vs. 30	19 vs. 18	42 vs. 39
Previous stroke (before qualifying event)	NA	12 vs. 11	NA
Previous TIA (before qualifying event)	NA	NA	NA
Myocardial infarction	NA	7 vs. 7	NA
Peripheral artery disease	6 vs. 6	6 vs. 4	NA
Current smoking	19 vs. 20	36 vs. 37	19 vs. 19
Aspirin use at time of qualifying event	NA	23 vs. 22	NA
Statin use at any follow-up visit	NA	NA	NA

CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; ESPRIT = European/Australasian Stroke Prevention in Reversible Ischaemia Trial; JASAP = Japanese Aggrenox Stroke Prevention vs. Aspirin Programme; MATCH = Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischaemic Attack or Ischaemic Stroke; NA = not applicable; PRoFESS = Prevention Regimen for Effectively Avoiding Second Strokes; SPS3 = Secondary Prevention of Small Subcortical Strokes; TIA = transient ischemic attack; TOPALS = Tokai Panaldine Aspirin Long-Term Study.
* Dual therapy vs. monotherapy.
† Combination of stroke and TIA.
‡ Current or past smoking.

"cerebrovascular attack" or "ischemic stroke" or "brain infarct" or "intracranial hemorrhage" or "intracerebral hemorrhage" or "intraparenchymal hemorrhage" or "subdural hemorrhage" or "epidural hemorrhage" or "subarachnoid hemorrhage" or "brain hemorrhage" or "brain bleeding" or "hemorrhagic stroke". We restricted our search to humans and clinical trials. We also reviewed the introduction and discussion sections of retrieved trials and of a prior meta-analysis (2) to identify additional trials.

Study Selection

Studies were included if they were randomized, controlled trials; involved patients with a history of ischemic stroke or TIA; compared dual- and single-antiplatelet therapy; and had a treatment duration of at least 1 year. We excluded studies if daily aspirin doses outside current recommended doses (50 mg to 325 mg) for secondary stroke prevention from the American Heart Association and American Stroke Association were used (1), most (>50%) patients had atrial fibrillation (because anticoagulation therapy is now recommended in these patients) (1), or dual-antiplatelet therapy was used among a nonnegligible proportion of participants (>10%) in a comparator group.

Data Extraction and Quality Assessment

All data from eligible studies were independently abstracted by 2 investigators according to a standard protocol. Discrepancies were resolved by discussion with a third investigator and by referencing the original report. Recorded data variables were trial name, year of publication, country of origin, eligibility criteria, treatment regimens and daily dose for each group, mean age, proportion of men in the study, baseline characteristics, duration of follow-up, and number of participants and events for each group.

We assessed study quality using the Cochrane risk-of-bias algorithm (www.cochrane.org/training/cochrane-handbook) (4).

Data Synthesis and Analysis

The primary outcomes were the association of dual-antiplatelet therapy (compared with single-antiplatelet therapy) with risks for recurrent stroke and ICH. The analyses were conducted with stratification of the studies by comparators. We did not exclude traumatic brain hemorrhages. The secondary outcomes were risk for ischemic stroke, intracerebral hemorrhage, major vascular event, myocardial infarction, total death, vascular death, major bleeding, and major gastrointestinal bleeding.

We used relative risks (RRs) with 95% CIs to assess risks for recurrent stroke and ICH with dual- and single-antiplatelet therapies. We report absolute risks in terms of the difference in the number of events per 1000 patients and the respective 95% CI. All analyses were based on the intention-to-treat principle. Presentation and summarization of the results were stratified by comparator. We computed a random-effect estimate based on the Mantel–Haenszel method when 2 or more studies provided sufficient data for a given outcome. Statistical heterogene-

Table 1—Continued

Study, Year (Reference)			
MATCH, 2004 (15)	PRoFESS, 2008 (16)	SPS3, 2012 (17)	TOPALS, 2003 (18)
Ischemic stroke and TIA within 3 mo	Ischemic stroke within 90 d	Lacunar stroke within 180 d	Ischemic stroke within 1 to 6 mo or TIA within 3 mo
Aspirin, 75 mg, plus clopidogrel, 75 mg	Aspirin, 50 mg, plus dipyridamole, 400 mg	Aspirin, 325 mg, plus clopidogrel, 75 mg	Ticlopidine, 100 mg, plus aspirin, 81 mg
Clopidogrel, 75 mg	Clopidogrel, 75 mg	Aspirin, 325 mg	Ticlopidine, 200 mg
7599	20 332	3020	270
63	64	63	65
66.3	66.1	63	67.1
1.5	2.5	3.4	1.6
7 vs. 7	29 vs. 23	30 vs. 27	NA
78 vs. 78	74 vs. 74	76 vs. 74	50 vs. 45
68 vs. 68	29 vs. 28	35 vs. 38	24 vs. 21
27 vs. 26	18 vs. 18	15 vs. 15†	NA
19 vs. 19	9 vs. 9	NA	NA
5 vs. 5	7 vs. 7	NA	8 vs. 9
10 vs. 10	3 vs. 3	NA	NA
48 vs. 47‡	21 vs. 21	20 vs. 21	27 vs. 39‡
NA	NA	28 vs. 28	NA
NA	NA	84 vs. 85	NA

ity was assessed using the chi-square test and the I^2 statistic. We considered study-level estimates to be heterogeneous if the chi-square test was significant ($P < 0.10$) or the I^2 statistic was greater than 50%. Publication bias was assessed by visual examination of funnel plots when 10 or more studies were available. We used Stata, release 12.0 (metan command) (StataCorp, College Station, Texas), and Review Manager 5.1 (Nordic Cochrane Center, Copenhagen, Denmark) for the meta-analysis.

Role of the Funding Source

The funding sources had no role in the study design, data collection and analysis, or decision to submit the article for publication.

RESULTS

The literature review identified 14 full articles for detailed assessment. Of these, 2 were excluded because they did not report an end point of ICH (5, 6); 1 was excluded because 26% of the participants in a comparator group received dual-antiplatelet therapy (7); 2 were excluded because they used daily aspirin doses of 990 mg and 1300 mg (8, 9); 1 was excluded because all patients had atrial fibrillation (10); and 1 was excluded because it was derived from the same study population as another report (11) (**Appendix Figure**, available at www.annals.org). Our final analysis included 7 randomized, controlled trials (12–18) comprising 39 574 individuals, of whom 19 802 (50%) were randomly assigned to dual-antiplatelet therapy and 19 772 (50%) were randomly assigned to single-antiplatelet therapy. Three trials included patients with prior ischemic stroke (14, 16, 17), and another 4 trials included patients with prior ischemic stroke or TIA (12, 13, 15, 18). The characteristics and risk of bias of these trials are shown in **Tables 1** and **2**. The trials assessed the following antiplatelet therapies: aspirin plus clopidogrel versus aspirin monotherapy (2 trials) (12, 17), aspirin plus dipyridamole versus aspirin monotherapy (2 trials) (13, 14), aspirin plus clopidogrel versus clopidogrel monotherapy (1 trial) (15), aspirin plus dipyridamole versus clopidogrel monotherapy (1 trial) (16), and aspirin plus ticlopidine versus ticlopidine monotherapy (1 trial) (18). The treatment duration ranged from 1.3 to 3.5 years, and the sample sizes ranged from 270 to 20 332.

One study, TOPALS (Tokai Panaldine Aspirin Long-Term Study), was unique in that it used ticlopidine as a comparator. It was a small trial, and the quality of the evidence was low because of potential high risk of bias. The risk difference between aspirin plus ticlopidine versus ticlopidine monotherapy was inconclusive on recurrent stroke (risk difference, 0.2 [95% CI, −0.04 to 0.07]) and ICH (risk difference, 0.02 [CI, −0.01 to 0.04]) (18).

The risk of bias of most included trials was low, and the overall quality of evidence was moderate or high. The results from the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial had high risks of selection bias and reporting bias because the data were derived from a subgroup of patients with cerebrovascular disease (11, 12). ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia Trial) had high risks of performance bias and detection bias because it was an open, nonblinded study (13).

Primary Outcomes

The end point of recurrent stroke was reported in 4 studies with aspirin as a comparator and 2 studies with clopidogrel as a comparator. The risk for recurrent stroke

Table 2. **Risk-of-Bias Assessment of Included Trials**

Bias Type	Study, Year (Reference)		
	CHARISMA, 2011 (12)	ESPRIT, 2006 (13)	JASAP, 2011 (14)
Random sequence generation (selection bias)	High risk Comment: subgroup of patients with cerebrovascular disease in the CHARISMA trial (11)	Low risk Quote: "The randomisation codes and randomisation programme were generated" Comment: probably done	Unclear risk Quote: "randomized . . . in blocks of 8" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Low risk Quote: "study-drug assignment was performed centrally by an interactive voice-response system" Comment: probably done	Low risk Quote: "to the central trial office" Comment: probably done	Low risk Quote: "by an external enrollment center" Comment: probably done
Blinding of participants and personnel (performance bias)	Low risk Quote: "double-blind, placebo-controlled" Comment: probably done	High risk Quote: "open, non-blinded study" Comment: nonblinded	Unclear risk Quote: "double-blinded" Comment: insufficient information (matching placebo not mentioned)
Blinding of outcome assessment (detection bias)	Low risk Quote: "double blind" Comment: probably done	High risk Quote: "open, non-blinded study" Comment: nonblinded	Low risk Quote: "double blind" Comment: probably done
Incomplete outcome data (attrition bias)	Unclear risk Comment: insufficient reporting of attrition to permit judgment	Low risk Comment: 0.9% of patients excluded because of incomplete data	Unclear risk Comment: insufficient reporting of attrition to permit judgment
Selective reporting (reporting bias)	High risk Comment: post hoc analysis	Low risk Comment: study protocol is available (19, 20), and all of the study's prespecified outcomes of interest in the review have been reported in the prespecified way	Low risk Comment: study protocol is not available, but the published reports clearly include all expected outcomes, including those that were prespecified
Other potential bias	High risk Comment: post hoc analysis	Low risk Comment: study seems to be free of other sources of bias	Low risk Comment: study seems to be free of other sources of bias

CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; ESPRIT = European/Australasian Stroke Prevention in Reversible Ischaemia Trial; JASAP = Japanese Aggrenox Stroke Prevention vs. Aspirin Programme; MATCH = Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischaemic Attack or Ischaemic Stroke; PRoFESS = Prevention Regimen for Effectively Avoiding Second Strokes; SPS3 = Secondary Prevention of Small Subcortical Strokes; TOPALS = Tokai Panaldine Aspirin Long-Term Study.

did not differ between patients with stroke receiving dual-antiplatelet therapy and those receiving aspirin monotherapy (RR, 0.89 [CI, 0.78 to 1.01]) or clopidogrel monotherapy (RR, 1.01 [CI, 0.93 to 1.08]) (**Figure 1** and **Appendix Tables 1** and **2**, available at www.annals.org). The quality of the evidence was moderate among trials with aspirin as a comparator and high among trials with clopidogrel as a comparator. The end point of ICH was reported in 4 studies with aspirin as a comparator and 2 studies with clopidogrel as a comparator. The risk for ICH did not differ between patients with stroke receiving dual-antiplatelet therapy and those receiving aspirin monotherapy (RR, 0.99 [CI, 0.70 to 1.42]), but we found higher risk for ICH among patients with stroke receiving dual-antiplatelet therapy than among those receiving clopidogrel monotherapy (RR, 1.46 [CI, 1.17 to 1.82]; risk difference, 4 more events per 1000 patients [CI, 1 to 7 more events per 1000 patients]) (**Figure 2** and **Appendix Tables 1** and **2**). The quality of the evidence was moderate among trials with aspirin as a comparator and high among trials with clopidogrel as a comparator.

When 2 trials testing high-dose aspirin (daily doses of 990 mg and 1300 mg) were included for analysis, the overall results were similar (RR for recurrent stroke, 0.90 [CI, 0.77 to 1.04]; RR for ICH, 0.92 [CI, 0.62 to 1.36]).

Secondary Outcomes

Moderate-quality evidence indicated that there was no significant difference between dual-antiplatelet therapy and aspirin monotherapy in the risk for ischemic stroke, myocardial infarction, total death, vascular death, or intracerebral hemorrhage. We also found moderate-quality evidence that dual-antiplatelet therapy reduced risks for major vascular events compared with aspirin monotherapy (risk difference, 14 fewer events per 1000 patients [CI, 1 to 25 fewer events per 1000 patients]). Dual-antiplatelet therapy increased risk for major gastrointestinal bleeding compared with aspirin monotherapy (risk difference, 19 more events per 1000 patients [CI, 6 to 40 more events per 1000 patients]), but the quality of evidence was low (**Appendix Table 1**). There was no significant difference between dual-antiplatelet therapy and clopidogrel monotherapy in the risk for major vascular events, ischemic stroke, myocardial infarction, total death, or vascular death, and the quality of evidence was high. However, high-quality evidence indicated that dual-antiplatelet therapy increased major gastrointestinal bleeding compared with clopidogrel mono-

Table 2—**Continued**

Study, Year (Reference)			
MATCH, 2004 (15)	**PRoFESS, 2008 (16)**	**SPS3, 2012 (17)**	**TOPALS, 2003 (18)**
Low risk Quote: "randomly allocated . . . based on a computer-generated list of treatment numbers" Comment: probably done	Unclear risk Quote: "randomly assigned" Comment: insufficient information about the sequence generation process	Low risk Quote: "generated using a permuted-block design" Comment: probably done	Unclear risk Quote: "randomly allocated" Comment: insufficient information about the sequence generation process
Low risk Quote: "with an interactive voice-response system (by phone)" Comment: probably done	Low risk Quote: "through a central telephone randomization system" Comment: probably done	Low risk Quote: "protected from previewing" Comment: probably done	Unclear risk Comment: insufficient information
Low risk Quote: "double blind, allocated either aspirin 75 mg once daily or matching placebo" Comment: probably done	Low risk Quote: "double-blind, either active or matching placebo" Comment: probably done	Low risk Quote: "double blind to take clopidogrel 75 mg daily or the matching placebo" Comment: probably done	Unclear risk Comment: insufficient information
Low risk Quote: "double blind" Comment: probably done	Low risk Quote: "double blind" Comment: probably done	Low risk Quote: "double blind" Comment: probably done	Unclear risk Comment: insufficient information
Low risk Comment: 0.1% of patients lost to follow-up	Low risk Comment: 0.6% of patients lost to follow-up	Low risk Comment: 1.8% of patients lost to follow-up	Unclear risk Comment: insufficient reporting of attrition to permit judgment
Low risk Comment: study protocol is available (21), and all of the study's prespecified outcomes of interest in the review have been reported in the prespecified way	Low risk Comment: study protocol is available (22), and all of the study's prespecified outcomes of interest in the review have been reported in the prespecified way	Low risk Comment: study protocol is available (23), and all of the study's prespecified outcomes of interest in the review have been reported in the prespecified way	Low risk Comment: study protocol is not available, but the published reports clearly include all expected outcomes, including those that were prespecified
Low risk Comment: study seems to be free of other sources of bias	Low risk Comment: study seems to be free of other sources of bias	Low risk Comment: study seems to be free of other sources of bias	Low risk Comment: study seems to be free of other sources of bias

therapy (risk difference, 3 more events per 1000 patients [CI, 1 to 10 more events per 1000 patients]). Dual-antiplatelet therapy increased intracerebral hemorrhage compared with clopidogrel monotherapy (risk difference, 3 more events per 1000 patients [CI, 1 to 6 more events per 1000 patients]), but the quality of evidence was moderate (**Appendix Table 2**).

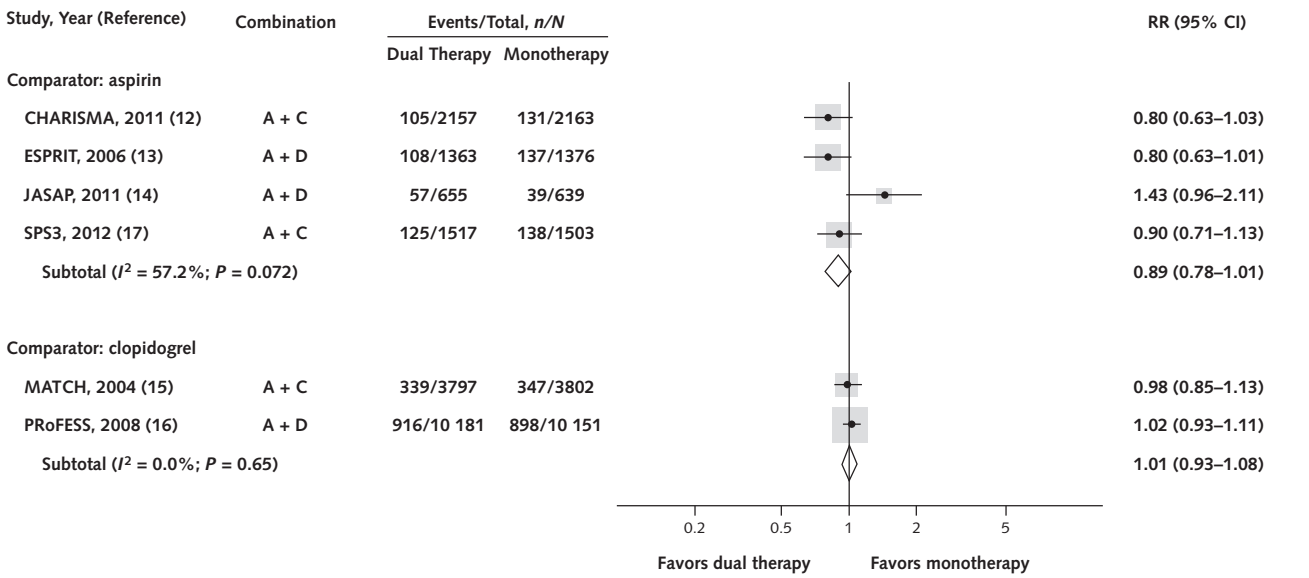
DISCUSSION

In 4 randomized, controlled trials with aspirin as a comparator, the risks for recurrent stroke and ICH did not differ between dual- and single-antiplatelet therapy among patients with ischemic stroke or TIA. However, in 2 randomized, controlled trials with clopidogrel as a comparator, the risk for recurrent stroke did not differ between dual- and single-antiplatelet therapy but there was a 46% greater risk for ICH among patients with ischemic stroke or TIA who received dual-antiplatelet therapy. Both trials with clopidogrel as a comparator had low overall risk of bias. Among 1000 patients with ischemic stroke, dual-antiplatelet therapy was associated with 1 to 7 more ICH events than clopidogrel monotherapy and seemed to provide no significant additional benefit in reducing ischemic stroke events.

Although 1 to 7 more ICH events per 1000 patients may seem modest, even with no apparent ischemic stroke preventative benefit, ICH is generally associated with a higher risk for death and incurs greater loss of health over a lifetime than ischemic stroke (24–26). On the basis of the findings of NEMESIS (North East Melbourne Stroke Incidence Study), where the average quality-adjusted life-years was 6.17 for intracerebral hemorrhage (25), dual-antiplatelet therapy versus clopidogrel monotherapy would incur loss of an additional 24.68 quality-adjusted life-years for 1000 patients in addition to increased costs and potentially higher risk for other systemic hemorrhages. Nearly 7 million individuals in the United States have had a stroke (27), which were noncardioembolic ischemic strokes that require indefinite use of antiplatelet therapy. Long-term dual-antiplatelet therapy, as opposed to clopidogrel monotherapy, may predispose a considerable number of these persons to risk for ICH. Furthermore, we found that, compared with clopidogrel monotherapy, long-term dual-antiplatelet therapy does not seem to further reduce recurrent stroke, major vascular events, myocardial infarction, or death in patients with ischemic stroke or TIA. Therefore, the overall clinical risk–benefit profile of long-term dual-antiplatelet therapy compared with clopidogrel monotherapy is not necessarily favorable for future vascular risk reduction in this patient population.

In addition to higher risk for ICH, dual-antiplatelet therapy was associated with a higher rate of major gastro-

Figure 1. **Separate and pooled RR and 95% CI estimates for recurrent stroke (dual therapy vs. monotherapy), stratified by comparator.**



A = aspirin; C = clopidogrel; CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; D = dipyridamole; ESPRIT = European/Australasian Stroke Prevention in Reversible Ischaemia Trial; JASAP = Japanese Aggrenox Stroke Prevention vs. Aspirin Programme; MATCH = Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischaemic Attack or Ischaemic Stroke; PRoFESS = Prevention Regimen for Effectively Avoiding Second Strokes; RR = relative risk; SPS3 = Secondary Prevention of Small Subcortical Strokes.

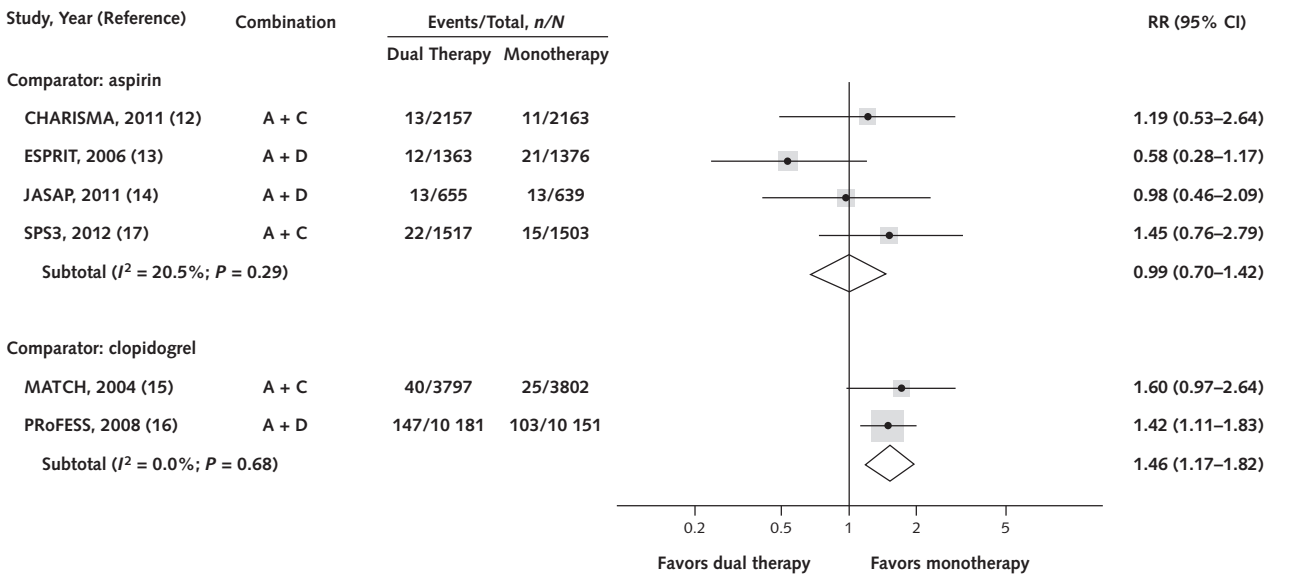
intestinal bleeding events than clopidogrel monotherapy. However, clopidogrel monotherapy has a lower risk for gastrointestinal bleeding than aspirin monotherapy (28). Because dual-antiplatelet therapy regimens typically include aspirin, it would seem logical that dual-antiplatelet therapy would have a higher risk for gastrointestinal bleeding than clopidogrel monotherapy.

In trials with aspirin as a comparator, we found a 13% lower risk for major vascular events among patients with ischemic stroke or TIA who received long-term dual-antiplatelet therapy. Among 1000 patients with ischemic stroke, dual-antiplatelet therapy was associated with 1 to 25 fewer major vascular events than aspirin monotherapy. Of 4 trials with aspirin as a comparator, 2 reported rates of aspirin use at the time of the qualifying event as 23% and 28% (13, 17). Although neither direct nor robust evidence is available, it might be reasonable to speculate that patients in this situation—the "aspirin treatment failures"—may have a higher baseline risk for future ischemic events when they continue to take aspirin (29).

The current meta-analysis does not exclude the potential benefit of short-term dual-antiplatelet therapy in the acute stage of ischemic stroke or TIA. Given the high early risk for stroke after TIA and ischemic stroke, a short course of dual-antiplatelet therapy, such as aspirin plus clopidogrel, might be beneficial (30–32). The optimum duration of dual therapy to prevent early recurrence without excessive increased risk for ICH is unknown. One study by Geraghty and colleagues (31) found that a 30-day course of clopidogrel plus aspirin was associated with a low rate of early recurrent stroke, and there was no obvious rebound effect after clopidogrel was withdrawn. A trial that enrolled 5170 Chinese patients with TIA or minor ischemic stroke in the previous 24 hours showed that a 21-day course of dual-antiplatelet therapy (clopidogrel plus aspirin) had lower risks for recurrent stroke and major cardiovascular events (stroke, myocardial infarction, and vascular death) than aspirin monotherapy without increasing hemorrhagic stroke or severe bleeding events (33). Another large North American trial is ongoing and may provide more evidence about whether short-term dual-antiplatelet therapy reduces recurrent ischemic events without increasing the risk for ICH (34).

We note several limitations of our study. First, a meta-analysis is a retrospective approach that can be constrained by the comprehensiveness of searches, methodological rigor of the included studies, and publication bias. We tried to maximize study identification and minimize bias by developing the study protocol a priori and using explicit criteria for study selection, data collection, and data analysis. Second, because this is a study-level meta-analysis, limitations of the original trials probably affected the overall results. An individual-patient data meta-analysis would have helped to mitigate this concern. Third, although we pooled

Figure 2. **Separate and pooled RR and 95% CI estimates for intracranial hemorrhage (dual therapy vs. monotherapy), stratified by comparator.**



A = aspirin; C = clopidogrel; CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; D = dipyridamole; ESPRIT = European/Australasian Stroke Prevention in Reversible Ischaemia Trial; JASAP = Japanese Aggrenox Stroke Prevention vs. Aspirin Programme; MATCH = Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischaemic Attack or Ischaemic Stroke; PRoFESS = Prevention Regimen for Effectively Avoiding Second Strokes; RR = relative risk; SPS3 = Secondary Prevention of Small Subcortical Strokes.

data with stratification of the studies by comparators to reduce heterogeneity, the antiplatelet agents used in dual therapy varied across trials. Still, this meta-analysis is, to our knowledge, the most robust evidence to date for a strategy of long-term dual-antiplatelet therapy as opposed to single-antiplatelet therapy for secondary stroke prevention.

In summary, this meta-analysis of completed clinical trials indicates that dual-antiplatelet therapy had a neutral effect on the prevention of recurrent stroke and ICH events compared with aspirin monotherapy. However, compared with clopidogrel monotherapy, long-term dual-antiplatelet therapy seemed to increase the risk for ICH in persons with a prior ischemic stroke or TIA and does not further prevent recurrent ischemic events. As such, long-term clopidogrel monotherapy may be a better choice than long-term dual-antiplatelet therapy for secondary stroke prevention among patients with ischemic stroke or TIA.

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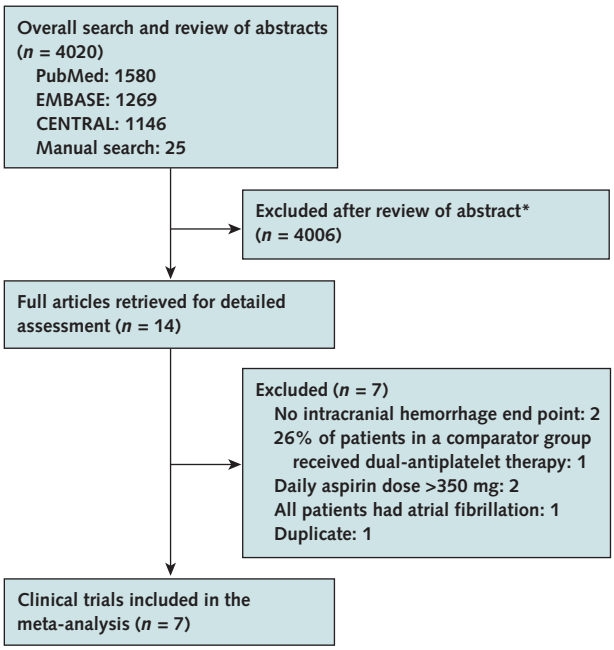
Appendix Figure. **Summary of evidence search and selection.**



CENTRAL = Cochrane Central Register of Controlled Trials.
* Articles were excluded if the studies were reviews or duplicates, had treatment duration <1 y, compared 2 types of monotherapy or 2 types of dual therapy, or did not involve patients with stroke or transient ischemic attack.

Appendix Table 1. **Summary of Quality Assessments and Findings for Primary and Secondary Outcomes: Aspirin as Comparator**

Outcome	Studies, *n**	Limitation	Inconsistency	Indirectness	Imprecision	Publication Bias	Events/Total, *n/N*		RR (95% CI)	Control Risk, *events per 1000 patients*†	Risk Difference (95% CI)	Quality
							Monotherapy	Dual Therapy				
All recurrent stroke	4	No serious limitations	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	445/5681	395/5692	0.89 (0.78–1.01)	76	Not significant	Moderate
Intracranial hemorrhage	4	No serious limitations	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	60/5681	60/5692	0.99 (0.70–1.42)	12	Not significant	Moderate
Major vascular events	4	No serious limitations	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	628/5681	542/5692	0.87 (0.76–0.99)	106	14 fewer events (1–25 fewer) per 1000 patients	Moderate
Ischemic stroke	4	No serious limitations	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	332/5692	386/5681	0.87 (0.72–1.05)	66	Not significant	Moderate
Myocardial infarction	4	No serious limitations	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	146/5681	126/5692	0.85 (0.60–1.20)	25	Not significant	Moderate
Total death	3	No serious limitations	Serious inconsistency	No serious indirectness	No serious imprecision	Undetected	194/3518	210/3535	0.97 (0.58–1.62)	51	Not significant	Moderate
Vascular death	3	No serious limitations	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	151/5042	127/5037	0.87 (0.63–1.21)	33	Not significant	Moderate
Major bleeding	4	No serious limitations	Serious inconsistency	Serious indirectness	Serious imprecision	Undetected	170/5692	207/5681	1.11 (0.69–1.79)	37	Not significant	Low
Intracerebral hemorrhage	3	No serious limitations	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	26/4305	40/4329	1.52 (0.93–2.49)	5	Not significant	Moderate
Major gastrointestinal bleeding	1	NA‡	NA‡	NA‡	NA‡	Serious publication bias	28/1503	58/1517	2.05 (1.31–3.20)	18	19 more events (6–40 more) per 1000 patients	Low

NA = not applicable; RR = relative risk.
* All studies were randomized, controlled trials.
† Based on the median control group risk across studies.
‡ One trial reported this outcome.

Appendix Table 2. **Summary of Quality Assessments and Findings for Primary and Secondary Outcomes: Clopidogrel as Comparator**

Outcome	Studies, *n**	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Events/Total, *n/N*		RR (95% CI)	Control Risk, *events per 1000 patients*†	Risk Difference (95% CI)	Quality
							Monotherapy	Dual Therapy				
All recurrent stroke	2	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Unknown‡	1245/13 953	1255/13 978	1.01 (0.93–1.08)	89	Not significant	High
Intracranial hemorrhage	2	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Unknown‡	128/13 953	187/13 978	1.46 (1.17–1.82)	8	4 more events (1–7 more) per 1000 patients	High
Major vascular events	2	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Unknown‡	1806/13 953	1778/13 978	0.98 (0.92–1.04)	128	Not significant	High
Ischemic stroke	2	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Unknown‡	1140/13 953	1098/13 978	0.96 (0.89–1.04)	84	Not significant	High
Myocardial infarction	2	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Unknown‡	265/13 953	251/13 978	0.95 (0.80–1.12)	19	Not significant	High
Total death	2	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Unknown‡	957/13 953	940/13 978	0.98 (0.90–1.07)	64	Not significant	High
Vascular death	2	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Unknown‡	580/13 953	559/13 978	0.96 (0.86–1.08)	39	Not significant	High
Major bleeding	2	No serious limitations	Serious inconsistency	No serious indirectness	Serious imprecision	Unknown‡	387/13 953	492/13 978	1.90 (0.67–5.41)	21	Not significant	Moderate
Intracerebral hemorrhage	1	NA§	NA§	NA§	NA§	Unknown§	55/10 151	90/10 181	1.63 (1.17–2.28)	5	3 more events (1–6 more) per 1000 patients	Moderate
Major gastrointestinal bleeding	2	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision	Unknown‡	18/13 953	53/13 978	2.62 (1.10–6.22)	2	3 more events (1–10 more) per 1000 patients	High

NA = not applicable; RR = relative risk.
* All studies were randomized, controlled trials.
† Based on the median control group risk across studies.
‡ Two trials reported this outcome.
§ One trial reported this outcome.