Meta-Analysis of the Efficacy and Safety of *Clopidogrel* Plus *Aspirin* as Compared to Antiplatelet Monotherapy for the Prevention of Vascular Events

Ashna D.K. Bowry, MBChB, M. Alan Brookhart, PhD, and Niteesh K. Choudhry, MD, PhD*

Antiplatelet agents are central to the treatment and prevention of cardiovascular disease. Although aspirin is the most widely used agent, randomized trials have assessed whether adding clopidogrel to aspirin ("dual-antiplatelet therapy") offers additional benefit with acceptable safety. Unfortunately, these trials have reached conflicting results, in part because of the heterogenous populations they studied. To clarify the role of dual-antiplatelet therapy for patients with vascular disease, a systematic review and meta-analysis of randomized controlled trials was performed. Medline and the Cochrane Collaboration and American College of Physicians Journal Club databases were searched for trials published from 1966 to August 2006 that compared aspirin and clopidogrel with antiplatelet monotherapy. Only trials that presented clinically relevant efficacy and safety outcomes were included. From each trial, demographic data and outcomes were recorded. Summary odds ratios and 95% confidence intervals (CIs) were calculated using a random-effects model. Eight trials comprising 91,744 patients were included. Mean follow-up ranged from 28 days to 18 months. Compared with aspirin alone, dual therapy with aspirin and clopidogrel reduced the odds ratio of the composite outcome of death, reinfarction, and stroke by 15% (95% CI 23% to 6%) in patients with acute coronary syndromes and by 34% (95% CI 44% to 22%) in patients who underwent percutaneous coronary intervention. Dual therapy also significantly reduced the odds of fatal and nonfatal reinfarction in these patient groups but did not significantly reduce the odds of all-cause mortality. Dual therapy was associated with significantly increased risk for major bleeding in studies >1 month in duration (odds ratio 1.80, 95% CI 1.40 to 2.30). In conclusion, combining aspirin and clopidogrel significantly reduces the odds of major cardiovascular events in patients with acute coronary syndromes or those who undergo percutaneous coronary intervention but at the expense of significant increases in the risk for bleeding. **(Am J Cardiol 2008;101:960–966)**

Over the past decade, clinical trials have assessed whether combining clopidogrel and aspirin ("dual-antiplatelet therapy") provides superior efficacy with an acceptable safety profile compared with antiplatelet monotherapy.[1–9] Unfortunately, these trials have had somewhat conflicting results, presumably because of substantial differences in the patient populations that have been studied. For example, the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial[1] enrolled patients with acute coronary syndromes (ACS), whereas the Management of Atherothrombosis With Clopidogrel in High-Risk Patients (MATCH) trial[7] investigated patients who have had a recent cerebrovascular event. As a consequence, there appears to be confusion about the appropriate use of clopidogrel in typical practice. To clarify the role of dual-antiplatelet therapy for patients with vascular disease, we performed a systematic review and meta-analysis of randomized controlled trials that compared combined clopidogrel and aspirin with antiplatelet monotherapy.

Methods

We performed an electronic search of Medline (1966 to August 2006); the Cochrane Collaboration's Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, and Cochrane Database of Systematic Reviews; and the American College of Physicians Journal Club database using medical subject headings and keywords related to aspirin and clopidogrel, cardiovascular disease (i.e., "unstable angina," "ACS," "myocardial infarction," "stroke," "percutaneous coronary intervention," and "cerebrovascular disease"), and study type (i.e., "randomized controlled trial"). We restricted our search to English-language studies conducted with human subjects. We retrieved potentially relevant reports and reviewed their reference lists to identify other studies that our search strategy may have missed.

We included trials if they (1) were randomized trials that compared clopidogrel and aspirin with aspirin or clopidogrel monotherapy; (2) measured clinically relevant efficacy outcomes, such as fatal or nonfatal reinfarction and all-cause mortality; and (3) reported safety outcomes, such as major bleeding.

Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. Manuscript received September 6, 2007; revised manuscript received and accepted November 21, 2007.

*Corresponding author: Tel: 617-278-0930; fax: 617-232-8602.

E-mail address: nchoudhry@partners.org (N.K. Choudhry).

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doi:10.1016/j.amjcard.2007.11.057

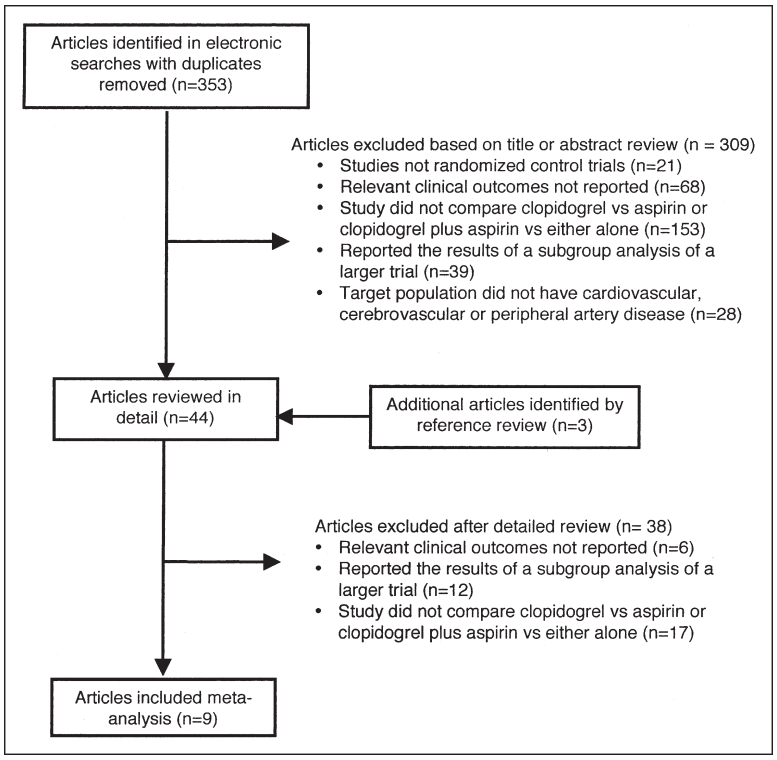

Figure 1. Published research review flow chart.

We excluded studies that did not present original data, compared antiplatelet monotherapy such as aspirin and clopidogrel without combination therapy arms, evaluated clopidogrel at different doses, and assessed surrogate outcomes, such as measures of platelet aggregation.

Two investigators independently extracted data on patient and study characteristics, outcomes, and study quality for each trial using a standardized protocol and reporting form. Disagreements were resolved by consensus. The quality of the included studies was evaluated using the Jadad score.[10]

The primary efficacy outcome for our analysis was the odds of major coronary events, which was defined as the composite outcome of death, stroke, or myocardial infarction (MI). Secondary efficacy outcomes included fatal or nonfatal MI, all-cause mortality, and ischemic stroke. Our primary safety outcome was major bleeding, typically defined as substantially disabling bleeding, causing a decrease in hemoglobin level of $\geq$5 g/dl or requiring the transfusion of $>$2 U of blood.

Studies were categorized into 3 subgroups on the basis of the subjects included: those with ACS, those who underwent percutaneous coronary intervention (PCI), and other subjects. We also subdivided trials with long ($>$30 days) compared with short follow-up times.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the outcomes (on the basis of intention-to-treat principles) in each study. We combined individual trial results using fixed- and random-effects models when $\geq$3 studies in a given study subgroup provided results. Conclusions were drawn on the basis of the results of the random-effects calculations, because these provide the most conservative estimates of effect size.

For each analysis, heterogeneity was explored in 2 ways. First, a plot of the OR was visually inspected. Second, a heterogeneity Q statistic was calculated and compared with a chi-square distribution with $k - 1$ degrees of freedom, where k is the number of trials in the analysis; heterogeneity was considered to be present when $Q > (k - 1)$.[11]

Results

Our search identified 370 reports, of which 8 reported on trials that met our inclusion criteria (Figure 1). Three studies each assessed patients with ACS and those who underwent PCI. The other 2 studies evaluated patients with recent ischemic strokes or transient ischemic attacks[7] and those with established vascular disease or multiple atherothrombotic risk factors.[8] All trials compared combined clopidogrel and aspirin with aspirin monotherapy, with the exception of the MATCH trial,[7] which compared dual therapy with clopidogrel monotherapy. All studies were of high methodologic quality. Details of the designs of the included trials are listed in Table 1.

These trials randomized 91,744 patients (45,868 to dual therapy with clopidogrel and aspirin and 45,874 to antiplatelet monotherapy). The mean follow-up period for the 8 trials ranged from 28 days to 18 months, the mean age of the enrolled patients ranged from 57.2 to 66.5 years, and the average proportion of men was 70%. There was a total of 5,033 deaths from all causes by the end of follow-up time (2,451 deaths in the combined aspirin and clopidogrel group and 2,582 in the antiplatelet monotherapy group).

Table 1
Characteristics of included trials

Characteristic	ACS			PCI			Other	
	CURE	COMMIT	CLARITY	PCI-CURE	CREDO	PCI-CLARITY	MATCH	CHARISMA
Publication year	2001	2005	2005	2001	2002	2005	2004	2006
Patients	Unstable angina/ NSTEMI	STEMI	STEMI	PCI substudy of CURE	CAD with symptoms of ischemia referred for PCI	PCI substudy of CLARITY	Recent ischemic stroke/TIA and cardiac risk factors	Established vascular disease or multiple risk factors
Intervention	Clopidogrel + aspirin vs aspirin alone	Clopidogrel + aspirin vs aspirin alone	Clopidogrel + aspirin vs aspirin alone	Clopidogrel + aspirin vs aspirin alone*	Clopidogrel + aspirin vs aspirin alone	Clopidogrel + aspirin vs aspirin alone and fibrinolytic†	Clopidogrel + aspirin vs clopidogrel alone	Clopidogrel + aspirin vs aspirin alone
No. of patients	12,562	45,852	2,658	1,863	2,116	19,185	7,599	15,603
Follow up, maximum (mean)	12 mo (9 mo)	28 days or discharge	30 days	12 mo (8 mo)	12 mo	30 days	18 mo	— (28 mo)‡
Patient characteristics								
Age (yrs)	64.2 ± 64.2	61.3 ± 61.4	57.7 ± 57.2	61.6 ± 61.4	61.5 ± 61.8	57.7 ± 56.9	66.5 ± 66.1	64.0 ± 64.0
Men	3,839/3,887	16,595/16,498	914/940	757/765	744/766	6,903/6,911	2,382/2,396	5,486/5,473
Previous MI	2,029/2,015	1,972/1,846	359/349	82/71	353/366	16/17	174/189	2,672/2,725
Hypertension	3,750/3,642	9,935/9,903	—	365/399	710/740	52/51	2,972/2,973	5,719/5,764
Previous TIA/stroke	274/232	—	—	—	67/74	19/19	1,727/1,696	1,942/1,895
Hypercholesterolemia	—	—	—	344/328	780/800	41/41	2,126/2,154	5,748/5,787
Diabetes mellitus	1,405/1,435	—	289/286	249/255	290/270	133/149	2,598/2,599	1,360/1,295
Smoker	3,790/3,841	—	887/865	406/396	339/313	480/469	1,825/1,772	284/271
Previous PCI	1,107/113§	—	84/85	176/185	902/916	54/48	—	398/434
Previous CABG	—	—	—	157/175	41/42	—	—	736/733
ST-segment depression	2,642/2,646	1,579/1,590	—	567/571	—	—	—	—
β-blocker use	664/696	—	—	—	—	1,554/1,559	1,457/1,533	3,678/3,690
Fibrinolysis	427/396	—	933/930	—	—	1,748/1,733	11,407/11,387	4,522/4,605

CABG = coronary artery bypass graft; CAD = coronary artery disease; NSTEMI = non-ST-segment elevation MI; STEMI = ST-segment elevation MI; TIA = transient ischemic attack.

* After PCI, patients received open-label clopidogrel or ticlopidine and aspirin for 2 to 4 weeks.

† Patients who underwent stenting received open-label clopidogrel after diagnostic angiography.

‡ Median follow-up time.

§ This includes prior PCI or CABG.

Table 2
Summary of treatment effects from combined clopidogrel and aspirin versus aspirin alone for trials of acute coronary syndromes

	OR (95% CI)*				
Trial	Major Coronary Events	All-Cause Mortality	Fatal or Nonfatal MI	Ischemic Stroke	Major Bleeding
CURE	0.80 (0.71–0.89)	0.92 (0.60–1.40)	0.77 (0.66–0.89)	0.87 (0.64–1.18)	1.76 (1.52–2.03)
COMMIT	0.91 (0.85–0.96)	0.93 (0.87–0.99)	0.86 (0.76–0.97)	0.86 (0.72–1.04)	1.07 (0.84–1.37)
CLARITY	0.81 (0.65–1.02)	0.68 (0.50–0.93)	0.70 (0.47–1.03)	0.53 (0.29–0.97)	1.09 (0.66–1.80)
Combined effect	0.85 (0.77–0.94)	0.86 (0.71–1.04)	0.81 (0.74–0.89)	0.84 (0.72–0.98)	1.31 (0.88–1.94)
p value for heterogeneity	0.12	0.16	0.37	0.30	0.001

* Data are presented as the ratio of the odds of the outcome in the dual-antiplatelet therapy group compared with the single-antiplatelet therapy group.

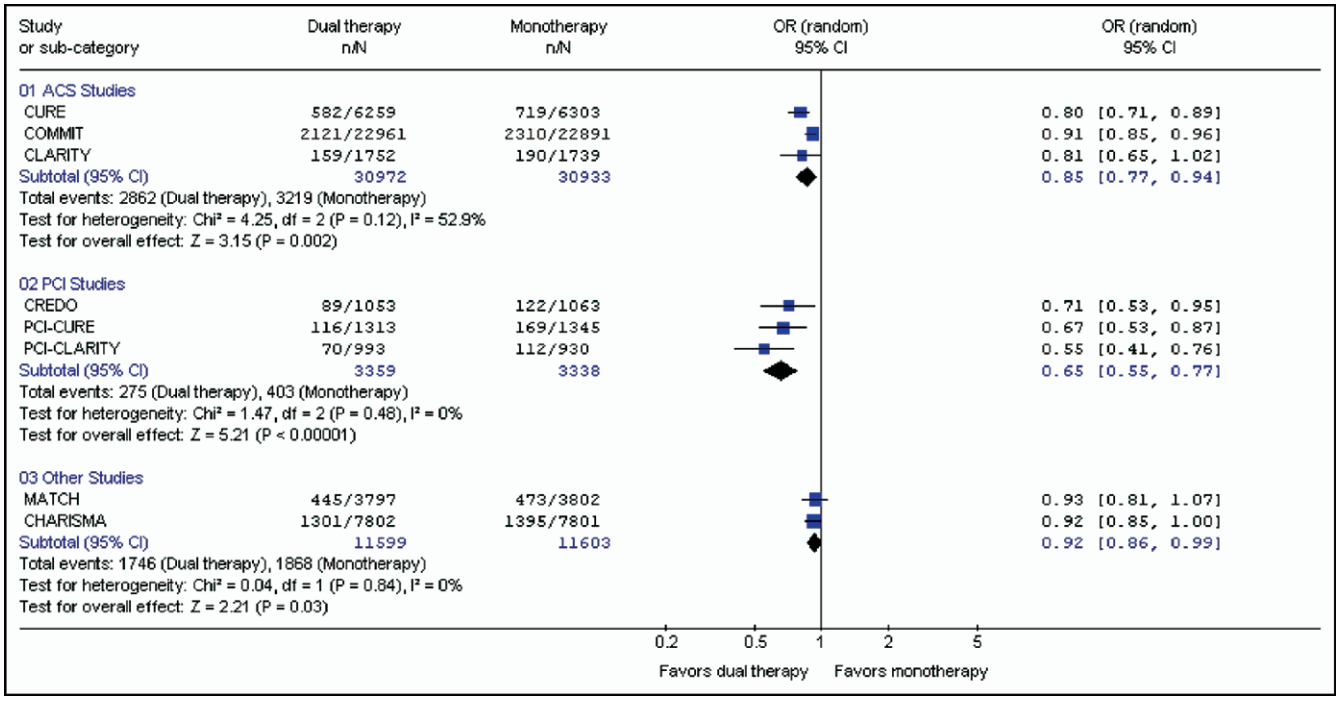

Figure 2. Plotted ORs and 95% CIs for major coronary events.

Three studies compared aspirin combined with clopidogrel with aspirin monotherapy in patients with ACS. Two of these trials evaluated patients with ST-segment elevation MI,[2,3] and the other enrolled patients with non-ST-segment elevation MI and unstable angina.[1] Study-specific and pooled results for the 3 studies are listed in Table 2. Dual-antiplatelet therapy produced a 15% reduction in the odds of major coronary events (OR 0.85, 95% CI 0.77 to 0.94; Figure 2) and a 19% reduction in the odds of fatal or nonfatal MI (OR 0.81, 95% CI 0.74 to 0.89; Table 2) but was not associated with a significant reduction in all-cause mortality (OR 0.86, 95% CI 0.71 to 1.04; Figure 3) or an increase in the odds of major bleeding (OR 1.31, 95% CI 0.88 to 1.94). No significant heterogeneity was present in the trial outcomes for these studies, with the exception of major bleeding.

Three studies compared aspirin combined with clopidogrel with aspirin monotherapy in patients who underwent PCI. Two of these trials were substudies of ACS trials,[4,6] and the other enrolled patients with symptomatic ischemia who were referred for PCI.[5] Study-specific and pooled results for the 3 studies are listed in Table 3. Dual-antiplatelet therapy produced a 34% reduction in the odds of major coronary events (OR 0.66, 95% CI 0.56 to 0.78; Figure 2) but, as with the ACS trials, was not associated with a significant reduction in all-cause mortality (OR 0.79, 95% CI 0.54 to 1.17; Figure 3) or an increase in the odds of major bleeding (OR 1.24, 95% CI 0.97 to 1.59). No significant heterogeneity was present in the trial outcomes for these studies.

Two additional studies compared combined aspirin and clopidogrel with antiplatelet monotherapy (see Table 4). The MATCH trial[7] evaluated patients with recent ischemic stroke or transient ischemic attack, and the Clopidogrel for High Atherothrombotic Risk, Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial[8] assessed patients with established vascular disease or multiple atherothrombotic risk factors. Although dual therapy did not significantly affect any of the major cardiovascular or mortality outcomes measured, the risk for major bleeding was significantly increased.

Four trials—CURE, Clopidogrel for Reduction of Events During Observation (CREDO), MATCH and CHARISMA—evaluated efficacy and safety outcomes over mean follow-up

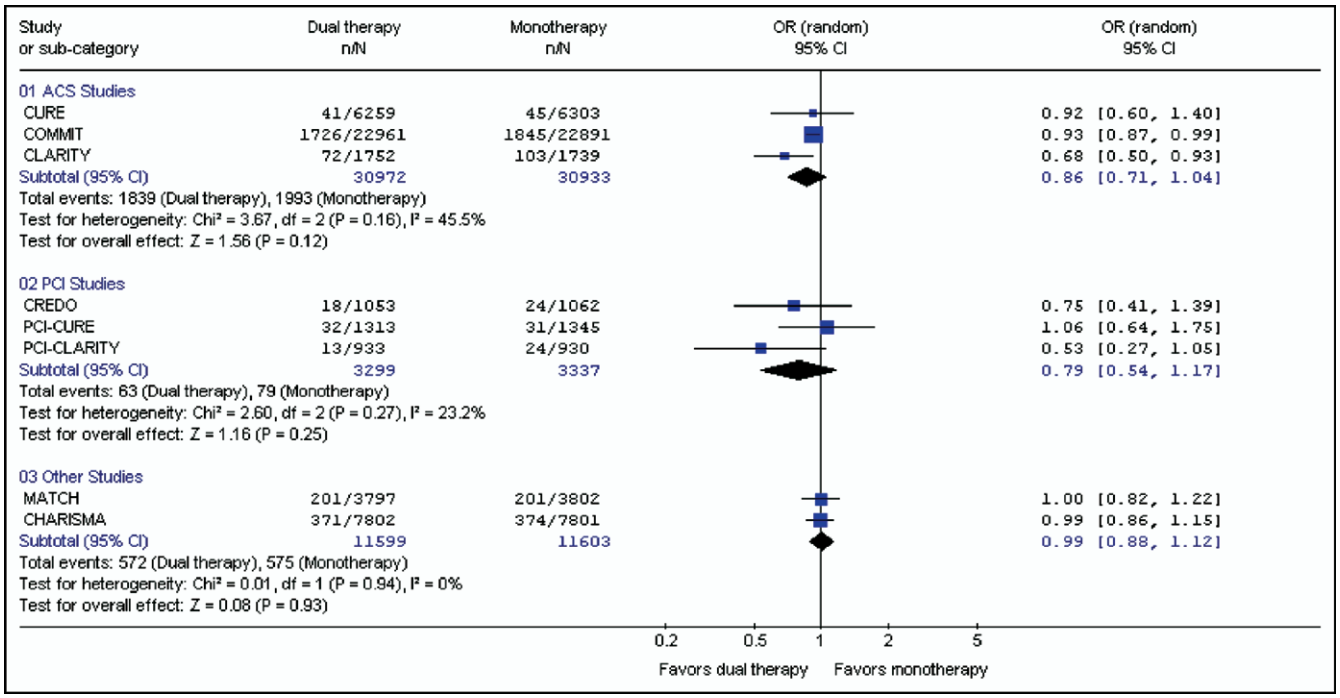

Figure 3. Plotted ORs and 95% CIs for all-cause mortality.

Table 3
Summary of treatment effects of combined clopidogrel and aspirin versus aspirin alone for percutaneous coronary intervention trials

	OR (95% CI)*				
Trial	Major Coronary Events	All-Cause Mortality	Fatal or Nonfatal MI	Ischemic Stroke	Major Bleeding
PCI-CURE	0.67 (0.53–0.87)	1.06 (0.64–1.75)	0.70 (0.50–0.98)	—	1.12 (0.69–1.81)
CREDO	0.71 (0.53–0.95)	0.75 (0.41–1.40)	0.77 (0.56–1.07)	0.76 (0.32–1.80)	1.35 (0.98–1.87)
PCI-CLARITY	0.59 (0.43–0.81)	0.53 (0.27–1.05)	0.64 (0.45–0.91)	0.33 (0.11–1.03)	1.06 (0.54–2.06)
Combined effect	0.66 (0.56–0.78)	0.79 (0.54–1.17)	0.70 (0.58–0.86)	—†	1.24 (0.97–1.59)
p value for heterogeneity	0.687	0.272	0.748	0.255	0.713

* Data are presented as the ratio of the odds of the outcome in the dual-antiplatelet therapy group compared with the single-antiplatelet therapy group.
† Data were not combined, because only 2 trials presented data for this outcome.

Table 4
Summary of treatment effects of combined clopidogrel and aspirin versus aspirin alone for trials of other conditions

	OR (95% CI)*				
Trial	Major Coronary Events	All-Cause Mortality	Fatal or Nonfatal MI	Ischemic Stroke	Major Bleeding
MATCH	0.93 (0.81–1.07)	1.00 (0.82–1.22)	1.08 (0.77–1.50)	0.92 (0.79–1.08)	3.37 (2.09–5.44)
CHARISMA	0.92 (0.85–1.00)	0.99 (0.86–1.15)	0.92 (0.74–1.16)	0.80 (0.64–1.03)	1.64 (1.27–2.10)

* Data are presented as the ratio of the odds of the outcome in the dual-antiplatelet therapy group compared with the single-antiplatelet therapy group.

periods ranging from 8 to 28 months (see Table 5). The odds of major coronary events were significantly reduced in these trials (OR 0.67, 95% CI 0.55 to 0.82), as were the odds of fatal or nonfatal MI (OR 0.70, 95% CI 0.58 to 0.86). As with the other studies, all-cause mortality did not differ between patients receiving dual- and single-antiplatelet therapy (OR 0.80, 95% CI 0.54 to 1.17). The odds of major bleeding were increased by 80% with dual-antiplatelet therapy in these long-term studies (OR 1.80, 95% CI 1.40 to 2.30; Figure 4). In contrast, major bleeding was not increased substantially in the short-term Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) and Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) trial.

Table 5
Efficacy and bleeding outcomes with dual therapy versus monotherapy in long-term and short-term trials

Duration	Trial	OR for Major Bleeding (95% CI)*
Long-term trials	CURE	1.76 (1.52–2.03)
	CREDO	1.35 (0.98–1.87)
	MATCH	3.37 (2.09–5.44)
	CHARISMA	1.64 (1.27–2.10)
	Combined effect	1.80 (1.41–2.30)
Short-term trials	COMMIT	1.07 (0.84–1.37)
	CLARITY	1.09 (0.66–1.80)

* Data are presented as the ratio of the odds of the outcome in the dual-antiplatelet therapy group compared with the single-antiplatelet therapy group.

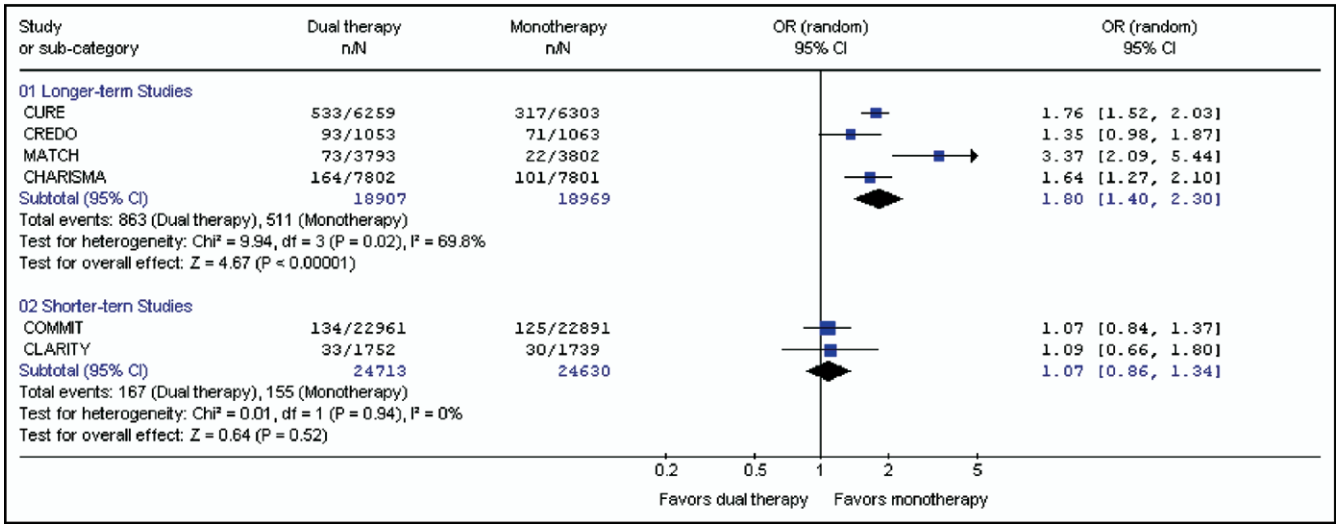

Figure 4. Plotted ORs and 95% CIs for major bleeding.

Table 6
Net clinical benefit from combined clopidogrel and aspirin therapy compared with aspirin monotherapy

Patient Subgroup	No. Needed to Treat (to Prevent 1 Major Coronary Event)*	No. Needed to Harm (to Cause 1 Major Bleeding Event)†	Net Clinical Benefit‡
ACS	67§	293	−227
PCI	9‖	114	−105

* A smaller number needed to treat suggests that few patients need to be treated to prevent 1 major coronary event (i.e., lower numbers are better).

† A smaller number needed to harm suggests that few patients need to be treated to cause 1 major bleeding event (i.e., higher numbers are better).

‡ Number needed to treat minus number needed to harm. Negative numbers imply that the benefits outweigh the harms.

§ Calculated assuming a baseline risk of major cardiovascular events of 10% in patients after ACS (as observed in patients treated with aspirin alone in the 3 ACS trials) over a 4.6-month period.

‖ Calculated assuming a baseline risk of major cardiovascular events of 34% in patients after PCI (as observed in patients treated with aspirin alone in the 3 PCI trials) over an 8.3-month period.

Discussion

This meta-analysis of randomized controlled trials demonstrates that the use of clopidogrel in combination with aspirin for patients with ACS or those who undergo PCI significantly reduces the odds of major coronary events and fatal or nonfatal MI, compared with aspirin alone. In contrast, dual-antiplatelet therapy does not reduce the odds of all-cause mortality in these patients, is not superior to antiplatelet monotherapy for patients with subacute vascular disease or recent stroke, and when administered for ≥1 year substantially increases the risk for major bleeding. On balance, the benefits of dual therapy outweigh the harms for patients with ACS or those who undergo PCI but not for other patient subgroups (see Table 6).

The favorable risk-benefit trade-off we observed clearly supports existing guidelines for patients with ACS and those who undergo PCI.[12,13] The American Heart Association and American College of Cardiology guidelines for non-ST-segment elevation MI recommend the use of dual-antiplatelet therapy for up to 9 months in patients with low risk for bleeding.[12] Similarly, the current American Heart Association and American College of Cardiology and European Society of Cardiology guidelines for PCI recommend dual-antiplatelet therapy for up to 1 year after stent insertion.[12,14] Cost-effectiveness analyses are in keeping with these recommendations and have found that the use of clopidogrel plus aspirin compared with aspirin alone has an incremental cost-effectiveness ratio well below accepted thresholds for commonly used therapies.[15–17]

However, our results also highlight the narrow therapeutic trade-off between the benefits and risks of dual-antiplatelet therapy. Furthermore, when dual antiplatelet therapy is continued beyond the immediate post–acute care period, the risk for bleeding increases substantially. For example, assuming a baseline risk for major bleeding of 1.9% over a 13-month period (on the basis of the mean event rate in patients treated with aspirin alone in the 4 longer term trials), an 80% increase in the odds of major bleeding is equivalent to an absolute risk increase of 1.5%. Therefore, only 66 patients would need to be treated for 13 months to cause 1 additional major hemorrhage. Similarly, for patients with symptomatic vascular disease enrolled in the CHARISMA trial, who, in contrast to other participants in this trial, may particularly benefit from dual-antiplatelet therapy,[18] the relative balance between benefits and risks may not be entirely clear because of the progressive increase in bleeding risk over time.

This balance may also be important when considering the duration of therapy for patients after PCI. Recent reports have highlighted the increased risk for late thrombosis in patients with drug-eluting stents (DES). Rates of death and MI 6 months after DES insertion were 3.3% higher than in patients with bare-metal stents.[19] As a result, patients who continue clopidogrel and aspirin for longer after DES insertion have better cardiac outcomes than patients who use these therapies for shorter periods of time.[19] However, our results suggest that these patients are also likely to experience higher rates of bleeding, and therefore calls for clinical

trials clarifying the appropriate use of DES and long-term dual-antiplatelet therapy for patients with stable and unstable coronary disease are particularly important.

Our findings are in keeping with those of previous analyses. A recent systematic review concluded that the use of dual therapy in patients with ACS, especially in the acute phase, has a favorable risk/benefit ratio, whereas in stable patients with cardiovascular disease, it is associated with an increased risk for bleeding.[20] Another clinical review analyzed the role of antiplatelet therapy in subgroups of patients with cerebrovascular disease, coronary artery disease, and peripheral arterial disease, also confirming the benefits of treatment with dual therapy in patients with established ACS and peripheral arterial disease.[21] Our study extends these analyses by reinforcing these conclusions and more specifically addressing the bleeding safety outcomes in trials with long-term follow-up.

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