# No Clear Advantage of Dual Antiplatelet Therapy Over Aspirin Alone in Stable Patients with High Cardiovascular Risk

*Bhatt DL, Fox KAA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354:1706–17.*

## Study Overview

Objective. To compare the effect of aspirin plus clopidogrel versus aspirin alone on atherothrombotic events in a broad population of high-risk patients.

Design. Multicenter, randomized, double-blind, placebo-controlled study.

Setting and participants. 15,603 patients aged ≥ 45 years with either documented clinically overt coronary artery, peripheral arterial, or cerebrovascular disease ("symptomatic"), or with multiple major atherothrombotic risk factors ("asymptomatic"). Patients were excluded if they were on long-term oral antithrombotic or nonsteroidal anti-inflammatory medications or if they had established indications for clopidogrel therapy.

Intervention. Participants were randomly assigned to receive clopidogrel (75 mg/day) or placebo. In addition, all patients received aspirin (75–162 mg/day). Investigators were encouraged to use appropriate standard therapies (eg, β blockers, statins) when indicated. Multiple prespecified subgroup analyses were performed, including those for patients with symptomatic and asymptomatic atherosclerosis; patients with and without diabetes, hypertension, hypercholesterolemia, peripheral arterial disease, prior cardiac or vascular surgery, prior myocardial infarction (MI), prior stroke, and prior transient ischemic attack; and patients who used and did not use several cardiovascular or cholesterol-lowering drugs. The study had 90% power to detect a 20% relative risk (RR) reduction in the primary efficacy endpoint. Patients were followed for a median of 28 months.

Main outcome measures. The primary efficacy endpoint was the first occurrence of MI, stroke, or cardiovascular death. The principal secondary efficacy endpoint was the first occurrence of any of the aforementioned events plus hospitalization for unstable angina, a transient ischemic event, or arterial revascularization. Safety endpoints included severe bleeding (fatal bleeding, intracranial hemorrhage, or bleeding that caused hemodynamic compromise requiring specific interventions) and moderate bleeding (bleeding leading to transfusion but not meeting the requirement for severe bleeding).

Main results. The primary efficacy endpoint occurred in 6.8% of the dual therapy group and in 7.3% of the aspirin alone group (RR, 0.93 [95% confidence interval {CI}, 0.83–1.05); this difference was not significant. The secondary efficacy endpoint occurred in 16.7% of dual therapy patients and 17.9% of aspirin alone patients (RR, 0.92 [95% CI, 0.86–0.995]; $P = 0.04$). There was a trend toward more severe bleeding in the dual therapy group (1.7% versus 1.3%; RR, 1.25 [95% CI, 0.97–1.61]), and moderate bleeding was more common in

the dual treatment group (2.1% versus 1.3%; RR, 1.62 [95% CI, 1.27–2.10]) as compared with aspirin alone. In subgroup analysis of asymptomatic patients, the rate of the primary efficacy endpoint was 6.6% in the dual therapy group versus 5.5% in the aspirin alone group (RR, 1.2 [95% CI, 0.91–1.59]; $P = 0.20$), and the rate of death from cardiovascular causes was 3.9% versus 2.2% ($P = 0.01$). In the group with clinically overt atherosclerosis, the rate of the primary efficacy endpoint was 6.9% in the dual therapy group and 7.9% in the aspirin alone group (RR, 0.88 [95% CI, 0.77–0.998]; $P = 0.046$).

Conclusions. Overall, clopidogrel plus aspirin was no more effective than aspirin alone in reducing the rate of MI, stroke, or cardiovascular death, and moderate bleeding was increased. Subgroup analysis demonstrated a potential benefit of dual therapy in patients with symptomatic disease but demonstrated potential harm in patients with asymptomatic disease and multiple risk factors.

## Commentary

In this large population of adults at high risk for atherothrombotic events, dual antiplatelet therapy with clopidogrel plus aspirin did not significantly alter the primary efficacy endpoint. When hospitalizations and revascularizations were included (the secondary endpoint), there was a marginally significant reduction from 17.9% to 16.7%, an absolute reduction in events of 1.2% over 28 months with a nonsignificant increase in severe bleeding of 0.4%, and a significant increase in moderate bleeding of 0.8%. This trial by Bhatt et al provides good evidence that dual antiplatelet therapy in a more stable patient population does not yield the substantial risk reduction observed in patients with acute coronary syndromes or undergoing percutaneous coronary revascularization [1–5].

The findings in the subgroup analysis are intriguing but must be interpreted with extreme caution given the number of comparisons performed and marginal statistical significance of the findings. Is it possible that dual antiplatelet therapy prevents atherothrombotic events in patients who have experienced an occlusive vascular event but raises the risk for patients who have not? An as yet undiscovered difference in platelet function or vascular biology between these groups could explain the unexpected subgroup findings, but additional research is needed to answer this question.

The results from this study are similar to those reported by Diener et al [6], in which clopidogrel alone was compared with clopidogrel plus aspirin in patients with recent ischemic stroke or transient cerebral ischemia. In that study, dual therapy yielded a nonsignificant RR reduction of 6.4% in the primary endpoint and an increased risk of bleeding compared with clopidogrel alone. However, a notable difference in the Diener et al trial was an excess of intracranial hemorrhage in those on dual therapy versus clopidogrel alone (1.1% versus 0.7%; difference, 0.4% [95% CI, –0.01% to 0.82%]). The studies by Bhatt et al and Diener et al suggest that dual antiplatelet therapy should not be used routinely in patients at high risk for atherothrombotic events.

## Applications for Clinical Practice

The benefits previously seen with the use of dual antiplatelet therapy in patients with acute coronary syndromes or undergoing percutaneous revascularization were not evident in this clinically stable population. At present, evidence to support prescribing dual antiplatelet therapy to clinically stable patients at high risk for atherothrombotic events is lacking. Further research is needed to explore the questions raised by the subgroup analysis of this study.

*—Review by Stephen D. Persell, MD, MPH*

## References


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