

# Addition of clopidogrel to aspirin may have increased risk for cardiovascular death in a primary prevention population

Wang TH, Bhatt DL, Fox KA, et al. An analysis of mortality rates with dual-antiplatelet therapy in the primary prevention population of the CHARISMA trial. *Eur Heart J*. 2007;28:2200-7.

**Clinical impact ratings:** GIM/FP/GP ★★★★★★ Cardiology ★★★★★☆☆

## QUESTION

In patients with risk factors but no history of cardiovascular disease (CVD), does the addition of clopidogrel to aspirin for primary prevention of CVD events increase risk for CV death?

## METHODS

**Design:** Post hoc subgroup analysis of a randomized placebo-controlled trial.

**Allocation:** {Concealed}†.\*

**Blinding:** {Blinded (clinicians, patients, data collectors, outcome assessors, data analysts, and data safety and monitoring committee)}†.\*

**Follow-up period:** {Median 28 months}†.

**Setting:** {768 sites in 32 countries}†.

**Patients:** 2289 patients (≥ 45 years of age)† (mean age 64 y, 57% men) who had multiple risk factors for CVD but no reported history of CVD (except for untreated peripheral arterial disease). This post hoc subgroup, called the “primary prevention” subgroup, represents 70% of the prespecified “asymptomatic” subgroup (which included patients with a self-reported but undocumented history of CVD) and 15% of the total trial enrollment.

**Intervention:** Clopidogrel {75 mg/d}† plus aspirin {75 to 162 mg/d}† ( $n = 1148$ ) or placebo plus aspirin ( $n = 1141$ ).

**Outcomes:** CV death, overall death, myocardial infarction (MI), stroke, composite endpoint (CV death, MI, or stroke), and bleeding.

**Patient follow-up:** 100% (intention-to-treat analysis).

## MAIN RESULTS

Groups did not differ for any outcome (Table). The increase in CV mortality with clopidogrel previously observed in the asymptomatic subgroup (3.9% vs 2.2%,  $P = 0.01$ ) was also seen in the primary prevention subgroup but did not reach statistical significance (3.0% vs 1.8%,  $P = 0.07$ ). Controlling for other risk factors (age, race, history of heart failure, systolic blood pressure, and atrial fib-

illation), the hazard ratio for CV mortality with clopidogrel use in addition to aspirin in the primary prevention subgroup was 1.72 (95% CI 0.99 to 2.97).

## CONCLUSION

In a primary prevention population, the addition of clopidogrel to aspirin did not reduce risk for cardiovascular disease and may have increased risk for cardiovascular death.

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\*See Glossary.

†ACP J Club. 2006;145:33.

## Clopidogrel plus aspirin vs aspirin alone for prevention of cardiovascular (CV) disease in patients with risk factors but no history of CV disease†

Outcomes at median 28 mo	Clopidogrel + aspirin	Aspirin alone	RRI (95% CI)
CV death	3.0%	1.8%	61% (–5 to 174)
Overall death	4.4%	3.2%	37% (–9 to 107)
MI	1.7%	1.5%	17% (–38 to 120)
Stroke	2.4%	1.9%	26% (–27 to 118)
CV death, MI, or stroke	5.7%	4.7%	20% (–16 to 70)
Severe bleeding	2.0%	1.4%	43% (–23 to 166)
Moderate or severe bleeding	3.9%	3.0%	32% (–15 to 103)

†MI = myocardial infarction; other abbreviations defined in Glossary. RRI and CI calculated from data in article; all results were statistically nonsignificant.

## COMMENTARY

The efficacy of the combination of aspirin and clopidogrel in preventing recurrent CV events in acute coronary syndromes is well-established. Many clinicians are extrapolating this finding to high-risk primary prevention populations, despite a lack of supporting data. Now, Wang and colleagues have supplied such data from the CHARISMA trial, and the findings provide evidence against this application.

This post hoc analysis of patients in the asymptomatic subgroup without previous CVD (the “primary prevention cohort”) showed that adding clopidogrel to aspirin provided no benefit in reducing CV events. The CHARISMA trial as a whole (which included mainly patients with established atherothrombotic disease) also did not show any benefit of dual antiplatelet therapy. Similar to results in the asymptomatic subgroup of the original CHARISMA trial, Wang and colleagues found increased risk (although only approaching statistical significance) for CV mortality associated with dual antiplatelet therapy. The analysis excluded 995 patients who had reported a history of CVD; this decrease in sample size reduced the power to detect a difference in CV mortality in the primary prevention cohort.

Oddly, the increased risk for death could not be attributed only to an excessive incidence of hemorrhage. Other questions remain regarding this effect, including concerns about the validity of the study. Potential expla-

nations for the increase in mortality and lack of beneficial effect include factors attributable to possible inadequacy of randomization, such as differential rates of adherence that could cause rebound platelet activation in the dual antiplatelet–therapy group, a higher proportion of patients with diabetes in the dual antiplatelet–therapy group, and other unknown factors unequally distributed between groups that may have predisposed the patients receiving dual antiplatelet therapy to worse outcomes. Finally, all subgroup analyses, even if prespecified, should be interpreted with caution and corroborated with primary–outcome trials before definitive conclusions are drawn about benefit or harm.

Regardless of whether the results are themselves conclusive, the study by Wang and colleagues reinforces the finding that dual antiplatelet therapy (with aspirin and clopidogrel) does not prevent CV events more than aspirin alone in patients without CVD. Until there is evidence of benefit of combination antiplatelet therapy, perhaps involving other glycoprotein IIb/IIIa inhibitors, this treatment should be avoided in primary prevention populations, especially now that evidence exists that it may be harmful.

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