



CHARISMA trial results released early

Dual antiplatelet therapy should be avoided in those with stable disease

IS CLOPIDOGREL PLUS LOW-DOSE ASA SUPERIOR TO ASA alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular (CV) causes in patients at risk for a CV event? In an attempt to answer this question, the *New England Journal of Medicine* released the international, double-blind, placebo-controlled CHARISMA trial early (to coincide with the American College of Cardiology meeting).

For a median of 28 months, CHARISMA followed 15,603 patients aged 45 years or older, with multiple risk factors for or documented cardiac, cerebrovascular, or peripheral arterial disease. Approximately 80% of patients had history of disease, with 20% enrolled based on risk factors. Major risk factors included diabetes and diabetic nephropathy; minor risk factors included hypertension, hypercholesterolemia, and smoking.

Patients were randomized to low-dose ASA 75 to 162 mg daily or low-dose ASA 75 to 162 mg plus clopidogrel 75 mg daily. The primary efficacy endpoint was a composite of myocardial infarction (MI), stroke, or death from CV causes (including hemorrhage). The safety endpoint was severe bleeding, defined as fatal bleeding, primary or post-traumatic intracranial hemorrhage, or bleeding resulting in hemodynamic compromise requiring intervention. The trial was powered so that patients were followed until a common study end date based on the pre-specified target of 1040 primary efficacy points was reached.

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Clopidogrel plus low-dose ASA provided no benefit over ASA alone (6.8% vs 7.3%, RR = 0.93, 95% CI, 0.83 to 1.05, $p = 0.22$). The difference in severe bleeding was not significant ($p = 0.09$). Combination therapy was associated with an increase in moderate bleeding, defined as requiring a transfusion ($p < 0.001$).

The secondary endpoint — first occurrence of MI, stroke, death from CV causes, or hospitalization for unstable angina, transient ischemic attack, or a revascularization — was 16.7% for combination therapy vs 17.9% for ASA alone (RR = 0.92, 95% CI, 0.86 to 0.995, $p = 0.04$).

The primary endpoint among patients with multiple risk factors ($p = 0.20$) and death from CV causes ($p = 0.01$) was higher with combination therapy. In patients with established disease taking clopidogrel plus ASA there was a decrease in the primary outcome by 12.5% ($p = 0.046$).

In summary, clopidogrel plus ASA is not superior to ASA alone in MI, stroke, or death from CV causes in patients at risk for an

event. The evidence suggests clopidogrel may be of benefit in patients with documented disease and cause harm in those with risk factors for future disease. For now, dual antiplatelet therapy should be avoided in patients with stable disease until the results of CHARISMA can be fully explained. ■

Reference

1. 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;16:1706-17.



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