

**CLOPIDOGREL COMBINED WITH  
ACETYLSALICYLIC ACID IS NOT MORE  
EFFICIENT THAN USING  
ACETYLSALICYLIC ACID ALONE IN THE  
PREVENTION OF CARDIOVASCULAR  
EVENTS IN HIGH RISK  
CARDIOVASCULAR PATIENTS  
WITH STABLE DISEASE**

Comment to the POEM "Clopidogrel + ASA no better than ASA alone for high risk patients. Available at URL: <http://www.infoPOEMS.com> and at [www.aafp.org/aafp/20061001/tips/7.html](http://www.aafp.org/aafp/20061001/tips/7.html) [accessed on 07/10/2006].

Reference: Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006 April 20; 354 (16):1706-17.

**Clinical question:**

**Is treatment with Acetylsalicylic Acid (ASA) combined with Clopidogrel efficient in the prevention of cardiovascular events in high risk cardiovascular patients with stable disease?**

The CHARISMA Study (*Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance*) was a prospective, randomised, double-blinded study, controlled against placebo that included 15,603 patients aged 45 or over, with symptoms of stable cardiovascular disease (symptomatic coronary, cerebrovascular or arterial disease) or with multiple risk factors (Table I – for inclusion the patient should have two *major* risk factors or three *minor* or one *major* and two *minor*). Patients with recent myocardial infarction (MI) or acute coronary syndrome were excluded. Patients were divided in two groups. One group was treated with ASA (75 to 162 mg/day) and clopidogrel (75 mg/day) and the other treated with ASA (75 to 162 mg/day) and placebo.

The mean follow-up time was 28 months. The primary endpoint was

a combination of events that included the number of acute MIs, strokes or number of cardiovascular deaths. The secondary endpoints included events like hospital admission for ischemic events, coronary revascularisation, transient ischemic accident and mortality for all causes, among others. The mean age of patients was 64 years, 80% were Caucasian, 70% were males. Approximately 75 % of patients were excluded for having symptoms of stable cardiovascular disease and the remainder because they had multiple risk factors.

Regarding the primary endpoint, the occurrence was 6.8% in the ASA + clopidogrel group and 7.3% in the ASA + placebo group (RR (relative risk) – 0.93; CI 95% 0.83 to 1.05; p=0.22).

Regarding the main secondary endpoint that included hospital admissions for ischemic events, the incidence was 16.7% and 17.9% respectively (RR – 0.92; CI 95% 0.86 to 0.995; p=0.04).

The occurrence of severe hemorrhagic events was 1.7% and 1.3% for the experimental and control groups respectively (RR – 1.25; CI 95% 0.97 to 1.61; p=0.09). The occurrence of death for cardiovascular causes was higher in the ASA + clopidogrel group, 3.9% vs 2.2%, p=0.01.

The occurrence of death for all causes was also higher in the ASA + clopidogrel group, 5.4% vs 3.8%, p=0.04.

The authors concluded that, over all, clopidogrel combined with ASA was not significantly more efficient in the prevention of MI, stroke or in the prevention of deaths from cardiovascular causes when compared with ASA alone in patients with stable cardiovascular disease or with multiple risk factors. **(LOE=1b)**

**Comment**

Evidence already exists that ASA is efficient in the prevention of cardiovascular events in patients with a high risk of cardiovascular disease and that clopidogrel increases the preventive efficacy when combined with ASA in patients with acute MI, unstable angina or after stent placement. Nevertheless it was not known if clopidogrel also had increased preventive efficacy when combined with ASA in stable patients with high risk of cardiovascular disease. This study by Bhatt *et al* answers that question and hence its relevance.

According to these results, double treatment with platelet anti-aggregates should be avoided, because its risks seem to outweigh possible benefits. An additional point for consideration by Portuguese family physicians, even though the article did not address financial issues is that clopidogrel is one of the medicines that weighs heavily in the drug budget of the Portuguese National Health Service.

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**TABLE I**

**ATHEROTHROMBOTIC RISK FACTORS CONSIDERED IN CHARISMA**

**Major risk factors**

- Type I or II Diabetes mellitus
- Diabetic nephropathy
- Ankle brachial index < 0.9
- Asymptomatic carotid stenosis
- One or more carotid plaques

**Minor risk factors**

- Systolic blood pressure ≥ 150 mm Hg, after three months under treatment
- Primary hypercholesterolemia