

Safety of Aspirin, Clopidogrel, and Acenocoumarol Combination in Patients Requiring Anticoagulation

To the Editor,

In daily clinical practice, we often see patients with an indication for aspirin and clopidogrel, mainly after a percutaneous coronary intervention, who are also under treatment with oral anticoagulants (OAC). Although the risk of bleeding complications associated with the three drugs may appear excessive, in reality, there is a paucity of data in the literature regarding the safety of this combination in clinical practice.¹⁻³

In order to determine the safety of acenocoumarol combined with aspirin and clopidogrel, we assessed the cumulative incidence of major bleeding (MB) events presented by patients under triple therapy.

We describe an observational study of 43 consecutive patients (mean age, 66.6 [10] years; 81% men), 26% of them with chronic renal failure, and 5% with a history of gastrointestinal bleeding. The indication for OAC was atrial fibrillation in 60.5%, artificial valve in 11.6%, intraventricular thrombus in 23.3%, history of pulmonary thromboembolism in 2.3%, and intra-aortic thrombus in 2.3%. Aspirin and clopidogrel were indicated in 36 patients after PCI, and in 7 for unstable angina. The aspirin dose was 150 mg/day in 1 patient, 200 mg/day in 4 patients, and 100 mg/day in the rest.

After a follow-up of 135 days (range, 12-765), 4 patients (9.3%; 95% confidence interval [CI], 2.59-22.13) presented MB. The first was a 73-year-old man who was prescribed 150 mg of aspirin and was admitted 15 days later for lower gastrointestinal bleeding (colon diverticula). The second, a 64-year-old, was receiving 200 mg of aspirin and received a definitive pacemaker during the same hospitalization. Twelve days later he was readmitted with a large hematoma in the area of the pacemaker implant. The third patient, a 57-year-old man, was admitted for cerebral ischemic event plus acute myocardial infarction. Intra-aortic mural thrombi were identified, and aspirin was prescribed at a dose of 100 mg. After 128 days he was hospitalized for upper gastrointestinal bleeding (erosive duodenitis) and transfusion of 2 units of packed red blood cells. The fourth, an 81-year-old woman under aspirin therapy (100

mg), had a history of upper gastrointestinal bleeding. She was admitted at 90 days for lower gastrointestinal bleeding and required 5 units of packed red blood cells. All of these patients had an international normalized ratio (INR) within normal range at the time of admission.

Our results, which are similar to those published in the scientific literature¹⁻³ (Table), indicate that the risk of MB in patients receiving dual antiplatelet therapy plus OAC may be higher than that of patients on dual antiplatelet therapy alone.⁴ Two of the patients with a bleeding event received high doses of aspirin, and the fourth, who had a high previous risk of bleeding, was kept on long-term triple therapy.

The absence of published recommendations means that treatment among these patients varies considerably.⁵ Until larger studies are published, triple therapy should be reserved for patients with high thromboembolic risk with the use of low doses of aspirin, an international normalized ratio (INR) <2.5, and with therapy as short as possible. In addition, a careful risk-benefit study should be performed when deciding on implantation of a drug-eluting stent, since these stents require dual antiplatelet therapy for a longer period of time.

Jorge Sánchez-Torrijos,
Margarita Gudín-Uriel,
and Francisco Ridocci-Soriano

Servicio de Cardiología, Consorcio Hospital General Universitario, Valencia, Spain

REFERENCES

- Orford JL, Fasseas P, Melby S, Burger K, Steinhubl SR, Holmes DR, et al. Safety and efficacy of aspirin, clopidogrel and warfarin after coronary stent placement in patients with an indication for anticoagulation. *Am Heart J*. 2004;147:463-7.
- Buresly K, Eisengerg MJ, Zhang X, Pilote L. Bleeding complications associated with combinations of aspirin, thienopyridine derivatives, and warfarin in elderly patients following acute myocardial infarction. *Arch Intern Med*. 2005;165:784-9.
- Rubboli A, Colleta M, Sangiorgio P, Di Pasquale G. Antithrombotic strategies in patients with an indication for long-term anticoagulation undergoing coronary artery stenting: safety and efficacy data from a single center. *Ital Heart J*. 2004;5:919-25.
- Andreotti F, Testa L, Biondi-Zoccai G, Crea F. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an

Studies on the Safety of Combined Oral Anticoagulation and Dual Antiplatelet Therapy

Author, Year, and Literature Reference	Patients, No.	Time at Risk, Days	Major Bleeding, No. (%)	Minor Bleeding, No. (%)
Orford et al, 2004 ¹	65	—*	2 (3)	4 (6)
Buresly et al, 2005 ²	143	—†	1 (0.7)	—
Rubboli et al, 2004 ³	16	32.3 (5.4)	2 (12.5)	2 (12.5)
In-house series	43	135 (range, 12-765)	4 (9.3)	—

*The actual time under therapy is not reported; patients were contacted at six months and one year.

†The time under therapy of all groups as a whole is reported, 654 days (range, 5-1551), but not of the specific group that received triple therapy.

- updated and comprehensive meta-analysis of 25307 patients. *Eur Heart J.* 2006;27:519-26.
5. Rubboli A, Colleta M, Sangiorgio P, Di Pascuale G. Antithrombotic treatment after coronary artery stenting in patients on chronic oral anticoagulation: an international survey of current clinical practice. *Ital Heart J.* 2004;5:851-6.