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.†‡

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.

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REFERENCES

4. Andreotti F, Testa L, Biondi-Zoccai G, Crea F. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an

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

<table>
<thead>
<tr>
<th>Author, Year, and Literature Reference</th>
<th>Patients, No.</th>
<th>Time at Risk, Days</th>
<th>Major Bleeding, No. (%)</th>
<th>Minor Bleeding, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orford et al, 2004†</td>
<td>65</td>
<td>~</td>
<td>2 (3)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Buresly et al, 2005‡</td>
<td>143</td>
<td>~</td>
<td>1 (0.7)</td>
<td>–</td>
</tr>
<tr>
<td>Rubboli et al, 2004³</td>
<td>16</td>
<td>32.3 (5.4)</td>
<td>2 (12.5)</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>In-house series</td>
<td>43</td>
<td>135 (range, 12-765)</td>
<td>4 (9.3)</td>
<td>–</td>
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</tbody>
</table>

†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.

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To the Editor,

We describe the case of a 77-year-old woman, ex-smoker, with mild emphysema, and bronchial hyperreactivity, admitted 2 years earlier at another hospital for bronchospasm with severe concomitant heart failure, who required treatment with vasoactive amines and ventilation support. The clinical condition was associated with generalized T-wave negativity, inversion mild enzyme elevation and alterations in cardiac contractility assessed as “consistent with myopericarditis”; the symptoms had all resolved at the time of discharge.

The patient was asymptomatic when she suddenly experienced sudden severe exertional dyspnea followed shortly afterwards by cardiorespiratory arrest. Basic cardiopulmonary resuscitation maneuvers were started immediately, followed by advanced maneuvers at 3 min. After monitoring the patient, sustained monomorphic ventricular tachycardia at 150 bpm was observed (Figure 1A); electrical cardioversion was applied and sinus rhythm recovered (Figure 1B). The patient was hemodynamically stable upon arrival to the emergency room. Echocardiography showed akinesia of the apical and middle segments with a left ventricular ejection fraction of 25%. Creatine kinase and troponin I concentrations were initially normal, but increased at 12 h to 374 U/L and 3.6 µg/L, respectively. NT-pro-BNP, a marker of acute heart failure, was raised to 15 944 pg/mL.

Clinical progress was favorable with diuretic and inotropic treatment. An electrocardiogram performed at 48 h shown deep, generalized T-wave inversion with QT interval prolongation (Figure 1C). The patient underwent catheterization, with no significant coronary lesions observed. Left ventriculography showed severe systolic dysfunction in the apical and middle segments (Figure 2). The endomyocardial biopsy was nonspecific.

On day 6 post-admission, the patient underwent an electrophysiological study. Sustained ventricular tachycardia