Clopidogrel as Antithrombotic Therapy in Atrial Fibrillation

To the Editor:

Clopidogrel is a new antiplatelet drug that has been largely used in several settings of coronary artery disease. Its role in the prevention of thromboembolic events in patients with atrial fibrillation was not definitely stated, but some preliminary randomized trials have been recently published. However, these initial experiences were not mentioned in the excellent article of Singer et al regarding antithrombotic therapy in atrial fibrillation from the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy.

Initially, Muller et al evaluated the effect of the association of aspirin (300 mg/d) plus clopidogrel (75 mg/d) vs oral anticoagulation (international normalized ratio, 2 to 3) on coagulation in 20 patients with nonvalvular atrial fibrillation. Aspirin plus clopidogrel significantly inhibited platelet aggregation, fibrinogen receptor activation and release of P-selectin, and prolonged in vitro bleeding time. Coagulation parameters (platelet-dependent thrombin generation, antithrombin III, thrombin-antithrombin III complex, prothrombin fragment 1 + 2) were not significantly affected. Thus, the authors concluded that combined antiplatelet therapy is superior to aspirin monotherapy in inhibiting platelet function but does not seem to substantially modulate coagulation cascade in patients with nonvalvular atrial fibrillation.

In the same year, Kamath et al randomized 70 patients with nonvalvular atrial fibrillation to either dose-adjusted warfarin (international normalized ratio, 2 to 3) or combination therapy with aspirin (75 mg/d) and clopidogrel (75 mg/d). Pretreatment levels of fibrin d-dimer, β-thromboglobulin, and soluble P-selectin were raised in patients with atrial fibrillation, whereas plasma prothrombin fragment 1 + 2 levels and platelet aggregation were not different from control subjects. Dose-adjusted warfarin reduced plasma levels of fibrin d-dimer, prothrombin fragment 1 + 2 and β-thromboglobulin levels, enhanced plasma levels of soluble P-selectin, and had no significant effect on platelet aggregation. Aspirin plus clopidogrel therapy made no difference to the plasma markers of thrombogenesis or platelet activation, but the platelet aggregation responses to adenosine diphosphate and epinephrine were decreased. Thus, the authors concluded that association of aspirin plus clopidogrel failed to reduce plasma indexes of thrombogenesis and platelet activation in atrial fibrillation, although some aspects of ex vivo platelet aggregation were altered. They considered that anticoagulation with warfarin may be superior to combination of aspirin plus clopidogrel as thromboprophylaxis in atrial fibrillation.

Finally, Lorenzoni et al evaluated the short-term safety and efficacy of aspirin plus clopidogrel as antithrombotic therapy in nonvalvular atrial fibrillation. Thirty patients with non–high-risk permanent or persistent atrial fibrillation awaiting cardioversion underwent transesophageal echocardiography to exclude left-heart thrombi and were randomized to receive warfarin (international normalized ratio, 2 to 3) or aspirin (100 mg/d) plus clopidogrel (75 mg/d). Bleeding time, not affected by warfarin, was prolonged by aspirin and further by adding clopidogrel. Thromboxane B2, not affected by warfarin, was reduced by aspirin but not further by clopidogrel. No thrombi or dense spontaneous echocontrast were found at the 3-week transesophageal echocardiography. Patients underwent electrical cardioversion to achieve sinus rhythm, and no thromboembolic or hemorrhagic events occurred in both study arms throughout the 3-week treatment and a further 3-month follow-up. Thus, the authors concluded that the combination of aspirin plus clopidogrel and warfarin were equally safe and effective in preventing thromboembolism in this small group of patients with non–high-risk atrial fibrillation.

These preliminary studies suggest that the association of clopidogrel to aspirin is superior to aspirin alone in the prevention of thromboembolic events in patients with atrial fibrillation. Compared with dose-adjusted oral anticoagulation, their data did not allow definite conclusions. Further randomized trials should be performed to define the role of the combination of clopidogrel plus aspirin in comparison with dose-adjusted warfarin in patients with atrial fibrillation.

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REFERENCES

To the Editor:

We appreciate the thoughtful summary by Drs. Veloso and de Paula of early-stage studies on the antiplatelet and anticoagulant effects of combination therapy with aspirin and clopidogrel in patients with atrial fibrillation. Large randomized trials with clinical end points would be needed before we could formulate recommendations on the use of therapy with clopidogrel plus aspirin in patients with atrial fibrillation. We look forward to the results of the ACTIVE II set of trials, and we anticipate including these results in the atrial fibrillation chapter in the next American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy.

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REFERENCES