Cardiovascular
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Dual Antiplatelet Option to Reduce Events in Atrial Fibrillation

In a multinational trial, the combination of clopidogrel and aspirin (ASA) was found to provide a significant reduction in the risk of major cardiovascular events, particularly stroke, in patients with atrial fibrillation (AF) who are not suitable for warfarin. It is estimated that up to 50% of AF patients are candidates for this alternative. Although the combination of clopidogrel/ASA was associated with an increased risk of bleeding events relative to ASA alone, the trial data suggest a net benefit for the substantial proportion of AF patients with a relative contraindication to warfarin, the prophylaxis of choice in this population.

ACTIVE A (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) enrolled 7554 AF patients in 580 participating centres in 33 countries. The principal investigator of this study, which is expected to alter guidelines, was Dr. Stuart Connolly, McMaster University, Hamilton, Ontario. Patients were eligible for the trial if they had a relative contraindication for warfarin, such as a high risk of bleeding, if physicians judged the patient unsuitable for warfarin for other reasons, such as a complicated clinical course, or if patients elected not to take warfarin. All patients received ASA 75 mg to 100 mg daily. They were randomized to clopidogrel 75 mg once daily or a matching placebo.

The hazard ratio (HR) for the primary composite outcome of stroke, myocardial infarction (MI), embolism outside of the central nervous system, and vascular death was 0.89 (95% CI, 0.81–0.98; *P*=0.014) in those taking dual antiplatelet therapy vs. those taking ASA alone. The greatest reduction resulting from the combination of clopidogrel/ASA was in the risk of stroke. A prespecified secondary outcome, stroke was reduced by 28% in those receiving clopidogrel/ASA vs. ASA alone (HR 0.72; 95% CI, 0.62-0.83; *P*<0.001). The 22% reduction in MI (HR 0.78; 95% CI, 0.59–1.03; *P*=0.077) approached statistical significance.

The rate per year of major bleeding, defined as overt blood loss requiring 2 or more units of blood, climbed from 1.3% among those receiving ASA alone to 2.0% among those taking clopidogrel/ASA. The rate per year of severe bleeds climbed from 1.0% to 1.5%. Both increases were statistically significant (*P*<0.001). The increase in the rate per year of fatal bleeds climbed from 0.2% to 0.3%, which was of borderline significance (*P*=0.07).

The increased risk of bleeding was judged acceptable on the basis of a net benefit. While a large proportion of major or severe bleeds, of which nearly 80% were extracranial, were controlled without sequelae, 65% of all strokes were disabling. In a calculation of relative benefit to risk, the combination of clopidogrel/ASA in 1000 AF patients treated for three years would be expected to produce 20 major bleeds of which three would be fatal. Over the same period, the combination would prevent 28 strokes of which 17 would be fatal or disabling.

Warfarin, which reduces risk of stroke by 38% in AF patients, also increases risk of major bleeds (Hart et al. *Ann Intern Med* 2007;146:857-67). Although warfarin should remain the first-line therapy in this population because of a potentially greater net benefit (Fuster et al. *Circulation* 2006;114:e257-e354), nearly half of AF patients fail to receive warfarin primarily due to contraindications (Tapson et al. *Arch Intern Med* 2005;165:1458-64). ACTIVE A identifies the combination of clopidogrel/ASA as an effective alternative in these individuals.

Relative risks should be carefully considered in selecting a strategy to prevent thrombus formation in AF patients. All current therapies obtain benefits with some increase in bleeding risk. Individualization of treatment to optimize the benefit-to-risk ratio is best conducted in consultation with patients well informed about treatment goals. In patients who are not candidates for warfarin, results of ACTIVE A identify an effective alternative strategy, addressing an unmet clinical need.

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Evaluating Interaction between Clopidogrel and PPIs: Results from Two Studies

The clinical significance of a drug interaction between proton pump inhibitors (PPIs) and clopidogrel, if any, does not appear to be a class effect. Two studies presented at the 2009 meeting of the American College of Cardiology explored the potential for PPIs to alter the antiplatelet activity and clinical outcomes of patients receiving clopidogrel. The studies were prompted by previously published evidence of a potential for clinically relevant impact of PPIs on clopidogrel metabolism.

In the larger of the two studies (Sibbing et al. Abstract 2515-736), the objective was to compare the effect of specific PPIs on the antiplatelet activity of clopidogrel. In this study, platelet aggregation was induced by adenosine diphosphate in whole blood samples from patients taking clopidogrel in advance of scheduled coronary angiography. The degree of platelet aggregation was measured with multiple platelet aggregometry (MEA) on a multiplate analyzer. Of the 1000 consecutive patients evaluated, 268 were on concomitant PPI therapy with one of three agents, pantoprazole, esomeprazole or omeprazole.

On MEA, platelet aggregation was slightly but not significantly lower on esomeprazole (209.0 AU*min) and pantoprazole (220.0 AU*min) when compared to those not taking a PPI (227.0 AU*min). In contrast, platelet aggregation was significantly greater among those taking omeprazole (295.5 AU*min; $P<0.001$ vs. no PPI). According to the authors of this study, these results are predicted by differences in the PPI pharmacology. While metabolism of omeprazole is dependent on the cytochrome P450 2C19 pathway, which is also important to clopidogrel bioactivation, neither esomeprazole nor pantoprazole has the same dependency.

The objective of the second study was to evaluate the impact of concomitant use of PPIs on cardiovascular (CV) outcomes among patients also taking clopidogrel (Ramirez et al. Abstract 2903-7). The single-centre study population was drawn from patients enrolled in a National Heart, Lung, and Blood Institute (NHLBI) registry. All had been discharged on clopidogrel after a percutaneous intervention (PCI). Adverse CV outcomes at one year were compared among those who were or were not taking a PPI.

Of the 535 patients in this analysis, 138 (25.8%) were on a concomitant PPI and 397 (74.2%) were not. In the group receiving a PPI, all commonly used agents in this drug class were represented. There were no baseline differences between these groups in regard to age, prevalence of diabetes, hypertension, renal dysfunction, smoking, or procedural success.

At the end of one year, there was a lower but not significantly different rate of many of the most significant adverse outcomes among those who were PPI users relative to nonusers. This included death (3.0% vs. 5.9%; $P=0.18$), myocardial infarction (3.7% vs. 4.2%; $P=0.83$), coronary artery bypass grafting (3.1% vs. 4.1%; $P=0.53$), and the combined end points of death and myocardial infarction (6.7% vs. 9.6%; $P=0.32$). Repeat PCI (13.4% vs. 10.1%; $P=0.23$) and repeat vascularization (15.8% vs. 14.2%; $P=0.65$) rates were slightly greater in the group receiving PPI relative to PPI nonusers, but, again, no difference was statistically significant.

Although the authors did not compare the relative influence of specific PPIs on risk of an adverse CV outcome in patients taking clopidogrel, no increased risk could be associated with PPIs as a class. On the basis of these data in a post-PCI population, the authors concluded that there is no evidence that concomitant use of PPIs and clopidogrel should be restricted.

Among patients who have appropriate indications for taking both clopidogrel and a PPI, the studies contribute to previous evidence that the risk of an interaction leading to clinically important change in the activity of clopidogrel is modest, even if the relative risk differs among specific PPIs. Until this relative risk can be clarified, it is reasonable to select a PPI that is not dependent on the P450 2C19 pathway. In weighing relative risks and benefits, particular attention should be paid to the potential for mortality reductions with clopidogrel that have been confirmed for several indications in large clinical trials.

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