

tinuation therapy and increased systemic exposure to dexamethasone.³ We do not use antithrombin III for prophylaxis because data supporting its clinical usefulness are not conclusive.

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Clopidogrel plus Aspirin in Atrial Fibrillation

TO THE EDITOR: The investigators of ACTIVE (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) (May 14 issue)¹ address the pivotal clinical question, "Will the addition of clopidogrel to aspirin reduce the risk of vascular events in high-risk patients with atrial fibrillation for whom vitamin K antagonists are unsuitable?" The notion of the unsuitability of vitamin K antagonists warrants explanation, since the vast majority of patients in ACTIVE A (the part of the trial comparing clopidogrel plus aspirin with aspirin alone in patients with atrial fibrillation) did not have a risk factor for bleeding. Instead, "a physician's judgment that a vitamin K antagonist was inappropriate for the patient" (for 50% of the patients) and "the patient's preference not to take a vitamin K antagonist" (26%) dominated enrollment. Unfortunately, the authors do not provide a detailed explanation of the "physician's judgment" and "patient's preference" designations.² It is noteworthy that 8.5% of the patients were receiving vitamin K antagonists at inclusion, but this treatment was discontinued due to the unsuitability of these agents. Also, 10% of the patients switched to vitamin K antagonists during follow-up after discontinuing the study drug. Was this switch due to unreported stroke that occurred while the patient was receiving placebo or clopidogrel? In summary, the meaning of the unsuitability of vitamin K antagonists in ACTIVE A is unclear, and the article may cause physicians to avoid vitamin K antagonists inappropriately.

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TO THE EDITOR: The ACTIVE investigators report that the addition of clopidogrel to aspirin reduced the incidence of stroke, myocardial infarction, systemic embolism, and vascular death, as compared with aspirin therapy alone, in patients with atrial fibrillation. All patients received aspirin at a dose of 75 to 100 mg per day; doses of 75 to 325 mg per day are recommended for low-risk patients with atrial fibrillation. However, this recommended dose of aspirin was derived from a generalization of the results of trials of aspirin for all anti-thrombotic indications, and the recommended dose balanced the efficacy versus the safety of aspirin therapy.¹ Of all the randomized trials of aspirin in preventing thromboembolism in atrial fibrillation, only the Stroke Prevention in Atrial Fibrillation study, in which aspirin at a dose of 325 mg was given daily, showed a benefit.² Other randomized trials of lower doses of aspirin showed no benefit in atrial fibrillation.³ Thus, the ACTIVE study used an aspirin dose that has not been shown to provide any benefit in atrial fibrillation. Patients in the placebo group of ACTIVE potentially received no effective background anti-thrombotic therapy; thus, the outcome was biased in favor of the group assigned to clopidogrel.

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TO THE EDITOR: In ACTIVE A, the investigators explored the association between clopidogrel plus aspirin and the occurrence of a combined vascular clinical end point in patients who were considered to be ineligible for vitamin K-antagonist therapy. They report an absolute reduction of 0.8 percentage points in the yearly incidence of the composite end point; this benefit is balanced by an increase in the risk of major bleeding of 0.7 percentage points per patient per year. However, in observational studies,¹ the most frequent reason for not giving vitamin K antagonists was a specific risk of bleeding. In ACTIVE A, only 23% of the patients had such a risk. Among the 77% remaining patients, vitamin K antagonists were not administered because the patient declined treatment, the therapeutic international normalized ratio (INR) could not be maintained, or because of another unspecified reason based on the clinician's judgment. Thus, extending the results of ACTIVE A to a population with a high risk of hemorrhage would probably result in a much higher incidence of episodes of bleeding than the incidence reported in this trial.

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TO THE EDITOR: The ACTIVE investigators report that the addition of clopidogrel to aspirin in patients with atrial fibrillation for whom vitamin K-antagonist therapy was unsuitable reduced the risk of major vascular events but increased the risk of major hemorrhage. The overall effect of the combination of clopidogrel and aspirin, as compared with aspirin alone, was neutral. The rate of major vascular events decreased 0.8% per year, whereas the rate of major hemorrhage increased 0.7% per year (relative risk, 0.97; 95%

confidence interval, 0.89 to 1.06; $P=0.54$). Moreover, the rate of intracranial hemorrhage, which increased 87% with the combination therapy, was not considered a major vascular event. ACTIVE W,¹ the ACTIVE study that compared clopidogrel plus aspirin with a vitamin K agonist, previously showed that oral anticoagulation was superior to clopidogrel plus aspirin in patients with atrial fibrillation and was associated with similar risks of major bleeding (2.2% vs. 2.4% per year, $P=0.53$); these rates were similar to the 2.0% risk per year reported in ACTIVE A. ACTIVE A suggests that clopidogrel plus aspirin is not more or less effective than aspirin alone, and there is no evidence that the combination therapy carries a lower risk of bleeding than oral anticoagulants.

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TO THE EDITOR: The ACTIVE investigators found an absolute reduction of 0.9 percentage points in the risk of stroke per year among patients with atrial fibrillation with the addition of clopidogrel to aspirin, as compared with aspirin alone (2.4% vs. 3.3%). The number needed to treat with clopidogrel to avoid stroke in 1 patient was 111. Given the recent interest in health care costs, we were surprised to see no discussion of the potential costs of this treatment. Clopidogrel costs approximately \$152 (U.S. dollars) for a 30-day supply, according to one source.¹ Using a back-of-the-envelope decision analysis, we estimate it would cost \$202,464 to prevent a single stroke per year in this population (i.e., to treat 111 patients with clopidogrel for 1 year at a cost of \$1,824 per patient). Traditionally, \$50,000 per quality-adjusted life-year (QALY) is the cutoff point of cost-effectiveness. Admittedly, we do not factor in the cost of caring for patients with strokes, QALY reductions in patients with strokes, and other costs (e.g., the treatment of major bleeding), but this still seems too expensive a strategy to advocate.

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The opinions expressed in this letter are solely those of the authors and do not reflect the official policies of William Beaumont Army Medical Center, the Department of Defense, the U.S. Army, or any federal agency.

1. Drugstore.com home page. (Accessed September 3, 2009, at <http://www.drugstore.com/>.)

TO THE EDITOR: The ACTIVE investigators report that there was no significant difference in the rate of myocardial infarction between the clopidogrel group and the placebo group, although the clopidogrel group had a significantly increased rate of gastrointestinal bleeding. There is growing interest in a possible interaction between clopidogrel and proton-pump inhibitors, since clopidogrel is converted to an active metabolite by the isoenzyme CYP2C19, which can be inhibited by proton-pump inhibitors.¹ Some reports on the concomitant use of clopidogrel with a proton-pump inhibitor showed an adverse cardiovascular outcome,² whereas others did not show any such effect.³ The concern regarding this interaction has also been raised by the Food and Drug Administration, which has issued an early communication and stressed the need for further studies.⁴

It would therefore be of interest to know how many patients in ACTIVE A received both clopidogrel and a proton-pump inhibitor, and the rate of cardiovascular events among these patients.

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THE AUTHORS REPLY: Pisters et al. raise the issue of how physicians decide whether warfarin is unsuitable for patients with atrial fibrillation. As we pointed out in our article, only about 50% of high-risk patients with atrial fibrillation receive warfarin. Many patients are unable or unwilling to make the considerable commitment required for safe warfarin therapy. Many patients cannot take adjusted-dose warfarin because of a lack of access to good anticoagulation monitoring, because of widely fluctuating or poorly controlled INRs, or because of other contraindications. International guidelines provide little specific guidance on how to assess the benefits and risks of warfarin treatment, and physicians must use their clinical judgment, weighing many factors.

Chua et al. suggest that the dosage of aspirin used in ACTIVE A was low. International guidelines^{1,2} recommend a wide range of aspirin dosages for use in atrial fibrillation because of the lack of convincing evidence that any one dosage is superior in atrial fibrillation.

Richard et al. discuss whether patients with a high risk of bleeding would benefit from the addition of clopidogrel to aspirin. The 23% of patients who were enrolled in ACTIVE A because of an increased relative risk of bleeding if given warfarin had a relative risk of major bleeding with clopidogrel that was similar to that of other patients in ACTIVE A.

Goldstein discusses the risk-benefit ratio of clopidogrel. Intracerebral bleeding in ACTIVE A was reported as part of the stroke outcome and also as intracranial hemorrhage. Subdural hematomas were not included as strokes but counted as intracranial bleeding. Considering all intracranial events (i.e., all strokes and subdural hematomas), the rate was 2.6% per year among 320 patients who received clopidogrel plus aspirin and 3.4% per year among 415 patients who received aspirin alone. Goldstein's statement that there is no evidence that the combination therapy carries a lower risk of bleeding than oral anticoagulants is not accurate. Among participants in ACTIVE W who were not receiving warfarin at entry, the risk of major bleeding was substantially lower with clopidogrel plus aspirin than with warfarin³; this

finding is in line with a recent systematic review.⁴ Available data indicate that clopidogrel plus aspirin carries a lower risk of major bleeding than warfarin unless the patient is safely taking warfarin already.

Lee and DeZee comment on the possible lack of cost-effectiveness of clopidogrel in atrial fibrillation, but they acknowledge that the long-term costs of caring for patients with stroke are very high, especially for the larger strokes seen in atrial fibrillation. Detailed economic analysis is required to understand the cost-effectiveness of clopidogrel in atrial fibrillation. With regard to the comments of Shalimar et al.: we did not collect data related to the use of proton-pump inhibitors in ACTIVE.

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Case 19-2009: Carcinoma of the Gastroesophageal Junction

TO THE EDITOR: In the Case Record of a 63-year-old woman with carcinoma of the gastroesophageal junction, Kwak et al. (June 18 issue)¹ provide an excellent overview of the available evidence-based perioperative treatment options, including adjuvant chemoradiation, neoadjuvant chemoradiation, and perioperative chemotherapy. These therapies have never been directly compared and therefore are all reasonable treatment options.²⁻⁴ The authors are to be complimented for reaching out in their effort to provide guidance in selecting the optimal treatment approach in particular subgroups of patients (personalized medicine). However, we do not understand why they eventually treated the described patient with both perioperative chemotherapy and additional postoperative chemoradiation. Since no clinical studies support this “double sequential” approach, we would ask the authors to elaborate on why they opted for this particular regimen and did not directly consider postoperative chemoradiation (an approach that is currently being evaluated in a Dutch multicenter trial) if they were so convinced about the disappointing effects of the administered preoperative chemotherapy on the basis of the pathological findings from the surgical specimens.

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THE DISCUSSANTS REPLY: Van der Vliet and colleagues challenge the “double sequential” approach in which a patient completes the entire preoperative and postoperative components of perioperative chemotherapy, on the basis of the results of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) study (Current Controlled Trials number, ISRCTN93793971),¹ followed by postoperative chemoradiation.²