Clopidogrel Versus Aspirin After Cardiac Surgery
To the Editor:

The subgroup analysis from the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial by Bhatt et al. suggests a superiority of clopidogrel versus aspirin in patients who have had cardiac surgery. However, this post-hoc analysis of a non-prespecified subgroup does not properly address the qualifying event by which patients were randomized into the larger CAPRIE trial, except for the last sentence of Study Limitations. Only patients who had had previous cardiac surgery and a qualifying event (such as a recent [within <30 days] myocardial infarction or ischemic stroke, or objective evidence of lower-extremity ischemia) were eligible for the trial and thus for the analysis by Bhatt.1

Almost all patients with previous cardiac surgery will have been on aspirin therapy. When such a group of patients develops a new ischemic event like those described above, they do so under aspirin protection and therefore may benefit from an alternative antiplatelet strategy like clopidogrel therapy. Furthermore, they have a significantly higher (57%), not somewhat higher, risk than the general CAPRIE population (ie, follow-up vascular death, myocardial infarction, and stroke rate of 9.1% on aspirin versus 5.8% in the main trial, \( P < 0.001 \))

The readers of Bhatt’s analysis could easily conclude that clopidogrel is superior in patients recovering from cardiac surgery, but this cannot be the conclusion of the analysis as described above. Therefore, the Conclusion of Bhatt’s abstract would more properly read, “Compared with aspirin, clopidogrel therapy results in a striking reduction in the significantly elevated risk for recurrent ischemic events seen in patients with a history of prior cardiac surgery and a subsequent ischemic event like myocardial infarction, stroke, or limb ischemia.”

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Response
In our analysis of the patients with previous coronary artery bypass grafting (CABG) from the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study, we demonstrated a clinically significant reduction in recurrent ischemic events in patients randomized to clopidogrel instead of aspirin use.2 After multivariate modeling incorporating all available baseline variables, this result remained highly statistically significant. As we pointed out in our article under Study Limitations, this was not a prespecified analysis. Nevertheless, given the previous positive experience of the adenosine diphosphate antagonist ticlopidine in preserving bypass graft patency, it was logical to examine the efficacy of clopidogrel in CABG.2,3 As we clearly stated in our Study Limitations, all patients in CAPRIE had had a qualifying ischemic event. Presumably, a significant percentage of patients undergoing CABG do so because of ischemia. Whether patients with stable angina, a positive stress test, and no overt prior ischemic event who undergo elective CABG would derive as much benefit cannot be directly answered by our analysis.

Recently, prior revascularization was found to demarcate benefit from the addition of clopidogrel to aspirin alone in the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) study.4 Those patients with prior revascularization derived a much larger risk reduction (45% relative risk reduction compared with 20% in the overall trial) than did patients without such a history. Furthermore, the interaction term between revascularization and benefit from clopidogrel plus aspirin in CURE was significant (\( P = 0.0014 \)), meaning that there was a particular benefit from more potent antiplatelet therapy in this subgroup. In our own analysis of CAPRIE, the interaction term for benefit of clopidogrel over aspirin in patients with previous CABG was also significant (coincidentally, \( P = 0.0014 \)).

Nevertheless, as stated in our discussion, we agree that further study is necessary to define the optimal antiplatelet regimen for secondary prevention in patients who have undergone CABG. The CURE study has demonstrated the value of dual-antiplatelet therapy with clopidogrel plus aspirin in patients presenting with acute coronary syndromes. However, questions remain about the exact role of clopidogrel in the subset of patients who underwent CABG, such as the appropriate timing for initiation of clopidogrel treatment in relation to the surgery. The recently completed Clopidogrel for the Reduction of Events During Observation (CREDO) trial will allow an evaluation of prolonged dual-antiplatelet therapy after coronary stenting in both the elective and urgent settings. Therefore, we reiterate that a dedicated randomized clinical trial of clopidogrel plus aspirin versus aspirin alone (or clopidogrel alone) after CABG performed for a range of elective and urgent indications is warranted.

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