A ntiplatelet therapy with aspirin has been unequivocally demonstrated to reduce the risk of ischemic complications across a broad spectrum of patients with vascular disease.1 This agent is also an important pharmacological adjunct to percutaneous and surgical coronary revascularization procedures. Administration of aspirin after coronary bypass graft operations had been the standard of care for many years, although early experience suggested that this agent would increase hemorrhagic complications if administered before surgery.2 However, subsequent evidence showed that preoperative aspirin improves survival without an appreciable increase in surgical bleeding.3 More recently, concerns regarding surgical bleeding risk have resurfaced with the introduction into clinical practice of a newer class of platelet inhibitors: the thienopyridines, ticlopidine and clopidogrel.

Thienopyridines interfere with platelet activation by selectively and irreversibly blocking a subunit of the adenosine diphosphate receptor. This provides an antiplatelet effect that is additive to the inhibition of the thromboxane A2 pathway by aspirin. The clinical benefit derived from the combination of aspirin and a thienopyridine first became apparent with trials demonstrating the efficacy of these agents in preventing subacute thrombosis after coronary stenting.4 Subsequently, large-scale clinical studies showed that long-term therapy (9 to 12 months) with aspirin and clopidogrel reduces ischemic complications compared with aspirin alone among patients with acute coronary syndromes5 or after percutaneous coronary revascularization.6 In the population of patients with acute coronary syndromes, dual antiplatelet therapy begins to reduce adverse outcomes as early as 2 hours after administration, and the magnitude of benefit expands over the following 9 months.7 Moreover, several lines of evidence suggest that the greatest suppression of ischemic events among patients undergoing percutaneous coronary revascularization is achieved if a 300- to 600-mg loading dose of clopidogrel is administered 2 to 6 hours before the interventional procedure is started.8–10 This pretreatment period likely reflects the time required for clopidogrel to achieve a nearly maximal antiplatelet effect. The weight of clinical trial evidence thus supports, and guidelines recommend, starting dual antiplatelet therapy early among patients presenting with acute coronary syndromes9 or upstream to anticipated percutaneous coronary intervention.10

The need for early administration of clopidogrel, however, creates a logistic difficulty. If this agent is administered early in the course of treatment for acute coronary syndrome or hours before percutaneous coronary revascularization (including elective and ad hoc procedures), many patients will have received clopidogrel before angiographic definition of their coronary anatomy. A subset of these patients will then be found to have coronary disease best treated by coronary artery bypass graft surgery. The antiplatelet effect of clopidogrel requires up to 5 days to dissipate after it is discontinued, and cardiac surgery performed before this time appears to carry an increased risk of bleeding complications.

Several reports have suggested an association between the preoperative use of clopidogrel and postoperative bleeding.11,12 These small series included fewer than 120 total patients who had received clopidogrel within 7 days of coronary artery bypass graft surgery and were found to require more frequent transfusion and surgical reexamination to control bleeding.11,12 Interestingly, there was a trend toward fewer deaths, myocardial infarctions, and strokes among patients who received preoperative clopidogrel in one study.12 In the largest series thus far reported, 415 patients who had received clopidogrel within 7 days of coronary surgery were compared with 1944 patients who had not received clopidogrel.13 Preoperative clopidogrel use in that study was associated with a 2- to 3-fold increase in red blood cell and platelet transfusion and a 5-fold increase in surgical reexamination to control bleeding. No study has demonstrated an influence of clopidogrel on operative mortality.

In this issue of Circulation, Kapetanakis and colleagues14 provide additional evidence of a relationship between clopidogrel use and surgical bleeding among 1572 patients who underwent exclusively off-pump coronary artery bypass graft surgery. This population is of interest because off-pump procedures are believed to decrease bleeding complications compared with coronary artery graft surgery using cardiopulmonary bypass.13 A total of 281 patients who had received clopidogrel within 7 days of surgery were compared with 1291 patients who had not received preoperative clopidogrel. After controlling for known predictors of increased surgical bleeding (advanced age, female gender, small body surface area, African American ancestry, renal insufficiency, and >4 grafted vessels), the investigators documented a 5-fold increase in reoperation to control bleeding, as well as an
increase in the need for transfusion of red blood cells and platelets. Operative mortality was the same in both groups. This study adds to the body of evidence documenting increased bleeding among patients who undergo either on-pump or off-pump surgical revascularization within 5 to 7 days of clopidogrel therapy. At the same time, the findings of this nonrandomized, unblinded retrospective analysis reinforce the controversy surrounding the optimal timing of clopidogrel administration, given the nonsignificant trends for only modest increases in bleeding observed in patients who continued clopidogrel within 5 days before surgery in prospective, double-blind, randomized trials (Clopidogrel in Unstable angina to prevent Recurrent Events [CURE] and Clopidogrel as Adjunctive Reperfusion Therapy [CLARITY]/Thrombolysis In Myocardial Infarction [TIMI] 28).15,16

On balance, the weight of published data convincingly argues that preoperative clopidogrel therapy increases the risk of perioperative bleeding. On the basis of these cumulative findings, Kapetanakis and associates14 have suggested a restrictive use of clopidogrel, wherein administration of this drug is withheld until coronary anatomy is defined and the need for surgical revascularization is clarified. Such an approach, however, would delay thienopyridine therapy to the majority of patients who are best treated medically or with percutaneous revascularization and therefore do not require surgery. On the basis of clinical trial data, delaying the use of clopidogrel for 24 hours would be expected to result in 1 extra composite event (death, myocardial infarction, stroke, or severe ischemia) for every 142 patients with an acute coronary syndrome.5 Although referral patterns vary, a large contemporary trial recently documented that only 19% of patients with an acute coronary syndrome underwent surgical revascularization within 30 days.17 Therefore, withholding clopidogrel therapy until coronary anatomy is defined would increase the risk of irreversible ischemic events in the majority of patients to prevent manageable bleeding complications in a minority.

The tradeoff of increased ischemic events in exchange for less perioperative bleeding treatment seems particularly unfavorable given that the risk of bleeding related to preoperative use of clopidogrel may be attenuated or eliminated by delaying surgery for a period after discontinuation of clopidogrel therapy. Although clinical trial data suggest that excess bleeding is reduced to baseline when clopidogrel is held for at least 5 days before surgical revascularization,5 a shorter delay may also be sufficient as long as clopidogrel is not given the day of surgery.16 Unfortunately, Kapetanakis and colleagues14 did not provide information in their series on when the last dose of clopidogrel was given before surgery. Such data could have been used to more precisely define how much delay between clopidogrel therapy and surgery is required to abrogate excess bleeding. Delaying coronary artery bypass graft surgery is not an unreasonable option for most patients because few will require immediate surgery because of refractory ischemia in the current era of aggressive pharmacological therapy (aspirin, heparin, glycoprotein IIb/IIIa inhibitors, β-blockers, and nitrates) and mechanical support (intra-aortic balloon counterpulsation). Similarly, only a very small proportion of patients will require emergent surgical revascularization as a result of failed percutaneous coronary intervention; currently, the rate of referral for immediate surgery in this setting is only 0.3%.18 In those rare instances in which surgical revascularization is required before the antiplatelet effect of clopidogrel has diminished, further perioperative measures to ameliorate an excess risk of bleeding may be indicated. For all patients undergoing surgical revascularization, simply using low-dose aspirin (≤100 mg daily) can reduce excess bleeding compared with high-dose aspirin (≥200 mg daily) without reducing clinical efficacy.19

Although the balance of risk versus benefit favors empiric administration of clopidogrel to most patients with an acute coronary syndrome or in anticipation of percutaneous revascularization, it is reasonable to withhold clopidogrel until after coronary angiography in situations in which there is a high likelihood that surgery will ultimately be required. For example, patients with significant concomitant valvular disease, hemodynamic instability that signals a mechanical complication, diabetes with impaired ventricular function, or stress testing consistent with extensive multivessel disease might be expected to be more suitable for cardiac surgery than for percutaneous revascularization. Algorithms have also been devised to more reliably predict which acute coronary syndrome patients will require surgical revascularization during their index hospitalization.20 If thienopyridines are withheld, however, other enhanced and short-acting antiplatelet or antithrombotic therapies beyond aspirin and heparin should be used. Clinical trial data suggest that substantial benefit would be achieved with glycoprotein IIb/IIIa inhibitors in the setting of an acute coronary syndrome or during percutaneous coronary intervention or with bivalirudin during percutaneous revascularization.21

In summary, clopidogrel is a powerful cardiovascular medication that produces early and long-term benefits. For most patients with an acute coronary syndrome, the evidence supports starting aspirin and clopidogrel as soon as possible during their hospital course and defining coronary anatomy expeditiously. Patients treated medically or by percutaneous revascularization should be maintained on long-term aspirin and clopidogrel therapy. For patients who undergo coronary artery bypass grafting, clopidogrel should be discontinued, surgery delayed for up to 5 days, and low-dose aspirin used perioperatively. This management strategy will allow clopidogrel to provide a “single-edged sword” of benefit to the majority of patients for whom this therapy is indicated, without an important burden of increased bleeding.

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