We commend Mariscal et al on their thought-provoking investigation of the effects of preoperative clopidogrel and the need for blood transfusions. Although the evidence to support the effectiveness of thienopyridines such as clopidogrel to prevent ischemic complications is well known, the literature to support the safety of these agents around the time of surgery is conflicting. This study contributes to a growing body of literature seeking to outline the risk of surgical intervention in patients who have recently received clopidogrel. Their report helps to answer some questions, but raises additional questions regarding the complex problem of managing patients who require antiplatelet therapy and also need surgery.

Clopidogrel is a thienopyridine that binds to the P2Y12 adenosine diphosphate receptor, irreversibly resulting in platelet inhibition that lasts 5–10 days, the lifespan of the platelet. The degree of platelet inhibition is affected by many different genetic polymorphisms, as well as cellular and clinical factors. Therefore, some patients may be at higher risk for bleeding and others may be at an increased risk for ischemic complications. Three clinical practice guidelines (STS/SCA, ACC/AHA, ACCP) provide differing recommendations for discontinuing clopidogrel prior to surgery. The STS guidelines, published in March 2011, are the most aggressive and suggest P2Y12 inhibitors may be discontinued as early as 3 days prior to surgery. The 2011 ACC/AHA guidelines suggest holding clopidogrel at least 5 days prior to surgery if possible. At the other extreme, the 2008 ACCP guidelines suggest discontinuing clopidogrel 5 days, but preferably 10 days, prior to surgery. This controversy is partially related to the fact that the balance between bleeding and ischemia in patients on clopidogrel prior to surgery has yet to be determined and varies considerably from patient to patient. For example, a patient with a recent implementation of a drug-eluting stent in their proximal left anterior descending artery after an acute myocardial infarction has a different risk/benefit profile than a patient who received a bare metal stent 2 years ago. Furthermore, delaying surgery for a wash-out period has potentially significant implications for resource utilization, a concern that is always a factor when discussing management protocols that might effect a large patient population.

Another reason for the discrepancy in the guidelines is that several small retrospective studies have attempted to evaluate the affects clopidogrel on perioperative bleeding and need for transfusions, with conflicting results. These variable results could be related to interindividual variability of clopidogrel’s effect on platelets, variability in bleeding definitions and in surgical technique. Nijjer et al published a meta-analysis of 34 studies with 22,584 patients on the safety of clopidogrel continued until the time of coronary artery bypass graft surgery (CABG) in acute coronary syndrome patients. What is clear is that clopidogrel significantly increased the number of red blood cell, platelet, and fresh frozen plasma transfusions; however, the clinical significance of this is still being defined.

One of the reasons many retrospective studies and meta-analysis have been completed to evaluate the effect of clopidogrel on perioperative bleeding is because of there is not a standardized definition of bleeding. Two of the oldest definitions are the TIMI and GUSTO bleeding criteria. Many of the bleeding criteria used in these trials include some variation of these definitions, along with other surrogate markers of bleeding, including chest tube output and surgical reoperation. The end result is that is very difficult to determine the risks of bleeding complications with clopidogrel or, better yet, newer agents. To resolve this issue for future studies, the Bleeding Academic Research Consortium recently published recommended standardized bleeding definitions for percutaneous coronary intervention and CABG.

Cardiac operations consume up to 10–15% of the nation’s blood supply, which may be rising because of the increased complexity of cardiac surgical procedures. Traditionally, bleeding related to clopidogrel is treated with platelets and blood transfusions, which is a concern because recent literature indicates transfusions of packed red blood cells, fresh frozen plasma, and platelets have their own inherent risks, including infection, transfusion-related acute lung injury, ischemia, and increased mortality. In CABG patients, blood transfusions are associated with a unit-dependent, risk-adjusted increase in postoperative morbidity and mortality. Clearly, opportunities to reduce the need for blood transfusion, such as a transfusion protocol, are needed. The lack of triggers for transfusion may have led to variable outcomes in many of the studies. Many studies acknowledge a surgical bias in that patients recently treated with clopidogrel are frequently given platelets or blood products, despite laboratory studies demonstrating a lack of a coagulopathy, platelet dysfunction or overt evidence of bleeding, in the hope of reducing postoperative bleeding and related
Platelet function testing has been suggested for identifying patients who are at risk for bleeding because of platelet inhibition prior to surgery. Several platelet function tests exist, including light transmittance aggregometry, VerifyNow, and VASP. The optimal test to determine the relationship between platelet function activity and bleeding or need for transfusion is also yet to be identified. The understanding of these technologies, and just as importantly, the limitations, will be even more crucial as more potent platelet inhibitors are used, such as cangrelor, prasugrel, and ticagrelor. Without a doubt, clinicians need an effective tool for determining platelet function to assist in decision-making regarding the timing of surgery or the need to transfuse. Currently, the STS/SCA, ACC/AHA, and ACCP guidelines issue a weak level of evidence for the use of platelet function tests because of the lack of studies.

In addition, many of these agents are oral and their effects are long-acting, so there needs to be strategies in place to transition patients with short-acting medications who are awaiting surgery. Similar to patients who are treated with warfarin and are bridged with heparin, there needs to be an agent that can be safely and predictably used to transition patients on a P2Y12 receptor inhibitor to surgery. Nijjer et al suggest using glycoprotein IIb/IIIa inhibitors for this purpose. Although these agents are effective in preventing ischemic complications in patients with acute coronary syndrome, their major drawback is significant bleeding and bleeding-related complications. The maintenance of platelet inhibition with cangrelor after discontinuation of thienopyridines in patients undergoing surgery (BRIDGE) trial compared the safety and effectiveness of cangrelor, a short-acting (half-life 3–5 min), reversible, platelet inhibitor as a bridge to CABG to placebo in patients who recently received a thienopyridine. It is hoped that this study will shed some much-needed light on this very difficult and controversial clinical topic. Not only do we need protocols for transitioning patients, there needs to be studies and tools to assist the clinician in determining the individual patient risks of varying management algorithms, even if the “ideal” transitioning agent is discovered.

Although studies such as Mariscalco et al’s are important in providing answers to the consequences of treating patients with potentially active platelet inhibition related to clopidogrel, unfortunately this is only the tip of the iceberg. As new platelet inhibitors enter the market, a validated definition is essential to accurately translate bleeding markers into clinical outcomes and to avoid confounders in trial comparisons between agents. We also need reliable tools to measure the activity of these agents, with data and experience to guide how to respond to or counteract their effects. Until then, the best we will have are guidelines that, at best, leave us scratching our heads over the balance between the risks of ischemic and bleeding complications.

Disclosures
Conflict of Interest: Dr Firstenberg is a speaker for Sanofi-Aventis, the makers of Plavix/clopidogrel, and an Investigator for The Medicines Company, the makers of cangrelor. The other authors (Drs Blais and Burcham) have no other conflicts related to this manuscript. Dr Blais is on the advisory board for Eli Lilly, US distributor of prasugrel.

References