The PCI guidelines published in 2005 and updated in 2007 provide excellent, albeit limited information for today’s practice.1 A bulk of new, relevant information has been published and has the potential to substantially affect the current practice of interventional cardiology. Newly proposed regimens using antithrombotics or antiplatelets for patients with both stable disease and non–ST-segment myocardial infarction (NSTEMI)/STEMI undergoing PCI have been published, and in some cases, the clinical outcomes have been improved. A few of these treatment options that merit discussion in the guidelines, including new uses of bivalirudin, shorter infusion of eptifibatide, high-dose tirofiban, clopidogrel loading dose, and platelet resistance, will be discussed in this article. Although new and exciting antiplatelet agents are currently being tested in large phase III clinical trials, this discussion will only focus on recently published data.

BIVALIRUDIN

Treatment with bivalirudin has been accepted by the PCI guidelines as an alternative for low-risk patients (class IIa recommendation).1 However, new research has been published that looks to expand its use for more complex scenarios, such as NSTEMI/STEMI. The ACUITY trial tested bivalirudin versus heparin (or low-molecular-weight heparin) plus glycoprotein [GP] IIb/IIIa inhibitors in moderate- to high-risk patients with NSTEMI using an early invasive approach.2 Both groups received a clopidogrel periprocedural loading dose of 300 mg (either before, but no longer than, 2 hours postprocedure); 13,819 patients were studied using a noninferiority design. The bivalirudin plus a GP IIb/IIIa inhibitor, as compared with heparin plus a GP IIb/IIIa inhibitor, was associated with noninferior 30-day rates of the composite ischemia endpoint (7.7% vs 7.3%), major bleeding (5.3% vs 5.7%), and the net clinical outcome endpoint (11.8% vs 11.7%). Bivalirudin alone, as compared with heparin plus a GP IIb/IIIa inhibitor, was associated with a noninferior rate of the composite ischemia endpoint (7.8% vs 7.3%, respectively; P=.32; risk ratio [RR], 1.08; 95% confidence interval [CI], 0.93–1.24), significantly reduced rates of major bleeding (3% vs 5.7%; P<.001; RR, 0.53; 95% CI, 0.43–0.65), and a net clinical outcome endpoint that included a composite of death, myocardial infarction (MI), unplanned revascularization for ischemia, and major bleeding at 30 days (10.1% vs 11.7%; P=.02; RR, 0.86; 95% CI, 0.77–0.97).2 These noninferior results continued after 1 year.3 An economic impact analysis of
the ACUITY trial showed that avoiding major bleeding may save up to $8,658 per event. A subrandomization of the ACUITY trial examined the influence of timing of administration of GP IIb/IIIa inhibitors on outcomes in patients with acute coronary syndrome undergoing an early invasive strategy. At 30 days, upstream treatment was associated with a 7.1% incidence of the ischemic composite endpoint, as compared with a 7.9% incidence in patients who received deferred treatment (RR, 1.12; 95% CI, 0.97–1.29); the study did not meet this noninferiority endpoint. The study also did not meet the noninferiority endpoint in patients undergoing PCI, in whom 9.5% of patients receiving deferred versus 8% receiving upstream GP IIb/IIIa inhibitors experienced a 19% increase in the rate of ischemic events (95% CI, 1–1.42).

A few design concerns question the broad applicability of these findings. The study was open-label, with almost 75% of patients receiving antiplatelet or anticoagulant therapies before randomization with crossover therapies. The trial definition of major bleeding was broad and included, among others, hematomas <5 cm. Drugs such as eptifibatide were not dosed based on creatinine clearance; thus, it is possible that overdosing occurred in patients with borderline renal function.

Based on the trial design, half of the patients randomly assigned to GP IIb/IIIa antagonists were to receive them deferred in the catheterization lab at the time of PCI. However, approximately half of the more than 40% of patients who were assigned to this group never received a GP IIb/IIIa antagonist, because they were treated medically or referred for coronary artery bypass grafting.

The HORIZONS AMI trial tested the hypothesis of treatment with bivalirudin versus heparin plus GP IIb/IIIa inhibitors in patients with STEMI; 3,602 patients were randomized. All patients received a loading dose of clopidogrel 300 to 600 mg before PCI. The two primary endpoints of the study were major bleeding and combined adverse clinical events (defined as a combination of major bleeding or major adverse cardiovascular events, including death, reinfarction, target vessel revascularization (TVR) for ischemia, and stroke at 30 days). Bivalirudin alone resulted in a reduced 30-day rate of adverse clinical events (9.2% vs 12.1%; RR, 0.76; 95% CI, 0.63–0.92; P=.005), mostly due to a lower rate of major bleeding (4.9% vs 8.3%; RR, 0.6; 95% CI, 0.46–0.77; P<.001). Interestingly, there was an increased risk of acute stent thrombosis within 24 hours in the bivalirudin group, but no significant increase was present by 30 days. Treatment with bivalirudin alone, as compared with heparin plus GP IIb/IIIa inhibitors, resulted in significantly lower 30-day rates of death from cardiac causes (1.8% vs 2.9%; RR, 0.62; 95% CI, 0.4–0.95; P=.03) and death from all causes (2.1% vs 3.1%; RR, 0.66; 95% CI, 0.44–1; P=.047). These results, however, were somewhat difficult to interpret because two-thirds of the patients assigned to treatment with bivalirudin received a bolus of unfractionated heparin before cardiac catheterization, posing a powerful confounder.

The FDA decided that, based on the ACUITY trial, bivalirudin was nonapprovable for NSTEMI/STEMI indication because the noninferiority definitions were not observed during the trial (the trial only satisfied two of the 10 guidelines, five failed to be satisfied, and three were only partially satisfied). An expert consensus is needed to evaluate these results to update the PCI guidelines’ recommendations for the use of bivalirudin in the setting of high-risk NSTEMI and STEMI.

CLOPIDOGREL PRETREATMENT

Despite the excellent 2007 guideline updates (published in 2008), in which the recommendations for the clopidogrel loading dose were changed to encourage a loading dose of 600 mg and to continue 75 mg daily for at least 12 months after drug-eluting stent placement, there have been some interesting publications in this field that warrant some discussion in future guidelines.

The additional benefit of bivalirudin in patients with stable or unstable angina with negative markers who undergo PCI after a 600-mg loading dose of clopidogrel at least 2 hours before the PCI was tested in the ISAR-REACT 3 trial, in which 4,570 patients were randomly assigned in a double-blind manner to receive bivalirudin versus unfractionated heparin. The primary endpoint was the composite of death, MI, urgent TVR due to myocardial ischemia within 30 days after randomization, or major bleeding during the index hospitalization (with a net clinical benefit defined as a reduction in the incidence of the endpoint). The secondary endpoint was the composite of death, MI, or urgent TVR. The incidence of the primary endpoint was 8.3% in the bivalirudin group versus 8.7% in the unfractionated heparin group (RR, 0.94; 95% CI, 0.77–1.15; P=.57). The secondary endpoint occurred in 5.9% of the bivalirudin group and in 5% of the unfractionated heparin group (RR, 1.16; 95% CI, 0.91–1.49; P=.23). The incidence of major bleeding was 3.1% in the bivalirudin group versus 4.6% in the unfractionated heparin group (RR, 0.66; 95% CI, 0.49–0.9; P=.008). The investigators concluded that the ischemic events were not reduced by bivalirudin, but the bleeding risk was significantly reduced. These results may have clinical and economic relevance.
because pretreatment with clopidogrel and unfractionated heparin may suffice in low-risk PCI patients, providing that the bleeding risk is low. Moreover, the ISAR-SWEET trial tested the benefit of abciximab in 701 diabetic patients who received a loading dose of 600 mg of clopidogrel at least 2 hours before PCI. The primary endpoint of the trial was the composite incidence of death and MI at 1 year, which was 8.3% in the abciximab group versus 8.6% in the placebo group \((P=.91)\). These results, although tested in a relatively small group of patients in a trial that was underpowered, provide some insight in the elective use of GP IIb/IIIa inhibitors in patients who are appropriately preloaded with 600 mg of clopidogrel at least 2 hours preprocedure.

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**PLATELET FUNCTION TEST IN HIGH-RISK PATIENTS**

The 2005 guidelines give a class IIb recommendation to perform platelet aggregation studies with patients in whom subacute thrombosis may be catastrophic or lethal (unprotected left main, bifurcation left main, or last patent coronary vessel). Platelet aggregation studies may be considered and the dose of clopidogrel increased to 150 mg per day if less than 50% inhibition of platelet aggregation is demonstrated.\(^1\) This recommendation is based on level of evidence C, which reflects only consensus opinion of experts, case studies, or standard of care. The guidelines recommend using light transmission aggregometry as the preferred method to determine individual response to clopidogrel therapy in high-risk patients. However, the technical conditions are not specified. The guidelines do not specify what kind of agonist to use and at what concentration the platelet reactivity needs to be determined, nor the specific point in time when the test should be performed. It is not stated if the use of maximal aggregation is better than using the remaining aggregation at 6 minutes after adding the agonist. In addition, the guidelines do not clarify how to include the effect of differing anticoagulants in the test interpretation. It is not clear whether light transmission aggregometry is a better method to use over the point-of-care device VerifyNow (Accumetrics, San Diego, CA) or the flow cytometry assay that determines the levels of vasodilator-stimulated phosphoprotein. There appears to be a correlation between platelet function and clinical outcomes, but studies have limited power to correlate platelet function with clinical outcomes, and high noncompliance is a real problem in day-to-day practice. As more aggressive antiplatelet drugs become available, we will see greater platelet inhibition and less ischemic events, but we will also see more bleeding, higher drug discontinuation, and rebound platelet activation. A thorough discussion in the guidelines addressing all of these questions is desirable.

**GP IIb/IIIa INHIBITORS**

There have been several recent publications regarding shorter infusions of GP IIb/IIIa inhibitors. The rationale is that once the loading dose of clopidogrel is absorbed (2 to 6 hours, depending on the dose), the infusion may be unnecessary in uncomplicated PCI patients and may even increase bleeding. In the BRIEF-PCI study, 624 patients were randomized to either a standard 18-hour eptifibatide infusion or an abbreviated infusion of <2 hours. This included patients with stable angina, acute coronary syndrome, or recent STEMI who underwent successful nonemergent coronary stenting. The primary endpoint was the incidence of periprocedural ischemic myocardial injury, defined as a postprocedure troponin-I elevation of >0.26 µg/L measured in a core laboratory. The abbreviated regimen was compared with the 18-hour regimen using a prespecified noninferiority analysis. Secondary endpoints included death, MI, urgent TVR at 30 days, and in-hospital major bleeding. The incidence of periprocedural ischemic myocardial injury was 30.1% in the brief group versus 28.3% in the standard group \((mean \ difference, 1.8\%; P=.012 \text{ for noninferiority})\). The 30-day incidence of MI was 4.8% in the brief group versus 4.5% in the standard group \((P=NS)\), and no deaths occurred. Urgent TVR was 0.6% in either group \((P=NS)\). Most importantly, major bleeding postprocedure defined as REPLACE 2 was less frequent in the brief group (1% vs 4.2%; \(P=.02\)) (major bleeding was defined as intracranial, intracocular, or retroperitoneal hemorrhage, clinically overt blood loss resulting in a decrease in hemoglobin of more than 3 g/dL, any decrease in hemoglobin of more than 4 g/dL, or transfusion of two or more units of packed red blood cells or whole blood. Minor bleeding was defined as clinically overt bleeding that did not meet criteria for major bleeding). The investigators concluded that an abbreviated infusion is safe and decreases postprocedural bleeding. A subanalysis of the same study assessed patients with aspirin or
clopidogrel resistance by laboratory analysis and found that there was no difference in myonecrosis prevalence in patients with aspirin or clopidogrel resistance if a concomitant infusion of eptifibatide was used. The possible impact of these publications resides in the economic benefit of shortening the eptifibatide infusion and decreasing the risk of bleeding in patients undergoing PCI.

European data recently published about high-dose tirofiban suggest the noninferiority of this approach in treating patients with STEMI undergoing primary PCI when compared to abciximab. The MULTISTRATEGY trial randomized patients with STEMI or new left bundle branch block to abciximab with an uncoated stent versus tirofiban with a sirolimus-coated stent. In patients with STEMI being managed with primary PCI, heparin plus tirofiban double bolus was shown to be noninferior to abciximab in its effect on ST-segment resolution 90 minutes postprocedure. At 30 days, and again at 8 months, rates of MACE were similar between the HDB tirofiban and abciximab groups, independent of the use of sirolimus-eluting stents or bare-metal stents.

The On-TIME 2 trial was designed to test the safety of HDB tirofiban in the prehospital setting. In a double-blind, randomized, placebo-controlled trial in 24 centers in Europe, 984 patients with STEMI who were candidates for in-hospital PCI were randomly assigned to either HDB tirofiban or placebo, in addition to aspirin, heparin, and clopidogrel (600 mg). Prehospital administration of HDB tirofiban, in conjunction with adjunctive antithrombotic therapy, was shown to be safe and effective management strategy for patients with STEMI undergoing primary PCI. This resulted in a significantly greater percentage of patients with ST-segment resolution at 60 minutes. The addition of prehospital administration of HDB tirofiban also resulted in a significantly lower incidence of abrupt closure as measured by TIMI flow after PCI.

CONCLUSION

The ever-changing horizon of interventional cardiology makes guidelines almost impossible to keep up-to-date; even as they are being published, they are becoming obsolete. The complex and robust body of data that is constantly being upgraded makes it challenging for the guideline committees to summarize and standardize the treatments for cardiologists. The current financial constraints and the need to explore less costly and more effective treatments pose a new challenge that also needs to be addressed by the guidelines. Some of the articles reviewed here may impact costs significantly, hence they need to be discussed and embraced if deemed appropriate for the current interventional practice.

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