Antiplatelet Polypharmacy in Primary Percutaneous Coronary Intervention

Trying to Understand When More Is Better

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Timely and sustained reperfusion in the ST-elevation myocardial infarction setting improves mortality, and primary percutaneous coronary intervention (PCI) is the guideline-favored revascularization strategy. Primary PCI requires pharmacological support with antiplatelet and antithrombin therapy, and many drugs and combinations are established for this purpose. Likewise, patients with ST-elevation myocardial infarction are at risk for subsequent ischemic events in the weeks to months after their index event, and long-term antiplatelet therapy is needed. Aspirin alone provides an inadequate effect on a substantial number of patients with atherosclerotic plaque rupture, whether the vascular disruption occurs as part of an acute coronary syndrome (ACS) or a PCI procedure. Indeed, patients with concomitant spontaneous plaque rupture (ie, troponin-positive ACS) and subsequent disruption from PCI have a particularly high rate of ischemic events with aspirin therapy alone and a notably large risk reduction with antiplatelet adjuncts, such as thienopyridines and glycoprotein IIb/IIIa inhibitors.

Platelet glycoprotein IIb/IIIa inhibitors have been studied in many placebo-controlled primary PCI trials. De Luca and colleagues performed a meta-analysis of such trials testing abciximab on 3949 patients. They reported an ≈30% reduction in mortality at 6 to 12 months. When these studies were performed, procedural thienopyridine use was infrequent, and appropriate loading doses had not been established. Of the 8 primary PCI trials in the meta-analysis, only 2 described administration of a thienopyridine loading dose, and maintenance therapy was continued for only several weeks. Since then, clopidogrel use has become commonplace, yet for a variety of reasons a placebo-controlled trial testing procedural clopidogrel in primary PCI was never performed. In the most recent scientific society guidelines, clopidogrel was given a class I recommendation for use in ST-elevation myocardial infarction1 and primary PCI. On the basis of the effectiveness of clopidogrel, a question intuitively emerged: Does aspirin in combination with a high loading dose of clopidogrel provide enough platelet inhibitory effect, or would the addition of more antiplatelet therapy be beneficial during and after PCI? Several studies addressing this question have been completed, yet among primary PCI cohorts the available information is not so clear.

The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) trials demonstrated that abciximab provided no reduction in a composite of ischemic events when added to aspirin and a 600-mg loading dose of clopidogrel among patients undergoing PCI for stable angina or troponin-negative ACS, meaning that dual antiplatelet therapy with aspirin and clopidogrel appeared adequate in these scenarios. In contrast, the subgroup of patients in ISAR-REACT-2 who were troponin positive did have an ≈30% relative risk reduction in the early occurrence of death, myocardial infarction, or urgent target vessel revascularization with abciximab. Carrying this idea further, these investigators then performed a mechanistic study similarly testing the addition of abciximab to aspirin and clopidogrel among primary PCI patients in the Bavarian Reperfusion Alternatives Evaluation-3 (BRAVE-3) study. Somewhat surprisingly, no reduction was observed in the infarct size scintigraphically assessed before hospital discharge or in mortality rates assessed at 30 days. This observation (along with a recent registry report from Witkowski et al7 among 7193 primary PCI patients) is not conclusive but casts a critical light on the use of polypharmacy antiplatelet therapy during primary PCI.

In this issue of Circulation, Chen et al8 consider their approach to triple antiplatelet therapy with the addition of cilostazol after primary PCI among patients pretreated with aspirin and clopidogrel. Cilostazol is a potent oral antiplatelet agent that increases intracellular cyclic AMP levels in platelets and endothelial cells by selective phosphodiesterase inhibition. It has been shown to block platelet aggregation to a variety of agonists and has been successfully used as an adjunctive or substitute antiplatelet agent in patients undergoing PCI, with no apparent increase in bleeding complications. Chen et al analyzed the Korean Acute Myocardial Infarction Registry (KAMIR) and retrospectively evaluated 4203 patients undergoing primary PCI who were treated with a drug-eluting stent and received either dual antiplatelet therapy (aspirin and clopidogrel; n = 2569) or triple antiplatelet therapy (aspirin, clopidogrel, and cilostazol; n = 1634). All patients received dual antiplatelet therapy for at least 6 months, and those receiving triple antiplatelet therapy were...
given cilostazol for at least 1 month. Major adverse cardiovascular events were fewer among those receiving triple antiplatelet therapy, including lower rates of in-hospital (3.4% versus 2.2%; \( P = 0.022 \)) and 8-month (4.9% versus 3.1%; \( P = 0.006 \)) all-cause mortality. Major bleeding complications were comparable between the dual- and triple-therapy groups.

These results support the notion that the judicious use of even more antiplatelet therapy, at least in the early phase after ST-elevation myocardial infarction, may be protective. The study has the usual limitations inherent to registry-based data, including selection and allocation biases. However, it is probable that many, but not all, differences between the treatment groups were statistically taken into account. On the basis of this and earlier studies, one is left trying to understand when more antiplatelet therapy is better in primary PCI. Is more therapy better before, during, or after the procedure, and for how long? Because clopidogrel is a pro-drug, it requires hours to be metabolized, and a 600-mg loading dose given at least 2 hours before the procedure has become the standard of care target. In the KAMIR registry, some patients received 300 mg of clopidogrel whereas others received 600 mg, and this difference plausibly affected the results. So, too, twice as many patients in the triple-therapy group were treated during the procedure with a glycoprotein IIb/IIIa inhibitor, making them more akin to a quadruple antiplatelet therapy group. Finally, considering the postprocedure course, the 30-day minimum treatment with cilostazol that Chen et al used is empirical, although guidelines and other trials have called for more intensive antiplatelet therapy in the first month after ACS.\(^1\) Whether these observations from the KAMIR registry are applicable to daily practice is debatable. Although the findings are supported by another randomized trial,\(^12\) the growing armamentarium of quicker, more reliable, and reversible antiplatelet agents leaves the need for cilostazol uncertain.

The results from the Trial to Assess Improvement in Therapeutic Outcomes By Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 study also provide some insights for considering the questions about the “when” relative to platelet inhibition. The TRITON-TIMI 38 trial showed that prasugrel, a more potent and fast-acting thienopyridine than clopidogrel, provides more protection against ischemic events than clopidogrel among patients with ACS. Montalescot et al reported on the subgroup of these patients who were undergoing primary PCI\(^13\) and showed that prasugrel provided a 20% relative risk reduction in the composite end point of 30-day cardiovascular death, myocardial infarction, and stroke (6.6% versus 8.2%) with no increase in TIMI major bleeding. This early benefit was compared with a 300-mg loading dose of clopidogrel, again suggesting that more antiplatelet effect than this is needed during and immediately after the procedure. Another potentially relevant observation between TRITON-TIMI 38 and the current report by Chen et al is the possibility of an accumulation of bleeding risk with more potent or polypharmacy antiplatelet therapy over time. Between 1- and 15-month follow-up in TRITON-TIMI 38, bleeding events occurred more frequently with prasugrel such that, at late follow-up in the primary PCI cohort, major bleeding increased from 1.2% to 3.1% with prasugrel and from 1.5% to 1.9% with clopidogrel. Therefore, it may have been appropriate to only give cilostazol for the first month after PCI, although this notion is speculative.

Cardiovascular medicine continues to witness an evolving paradigm, whereby a combination of drugs is used to address the complex biology of platelet function in the setting of atherosclerosis and inflammation. It is unlikely that a single therapy or perhaps even dual antiplatelet therapy will ever be perfectly effective in the acute setting because doses potent enough to cover the spectrum of platelet reactivity, overcome genetic differences,\(^14\) and mitigate interference from concomitant drugs\(^15\) will result in unacceptable rates of bleeding, particularly over time. This prediction is more than heady speculation because ACS will remain the leading cause of death among industrialized countries for the foreseeable future, and many new antiplatelet agents are in development, including rapid-effecting and rapid-reversing P2Y\(_{12}\) and protease-activated receptor-1 antagonists.\(^16\) Until individuals can have antiplatelet therapies quickly and conveniently measured and adjusted, polypharmacy will be a needed concept in the arsenal.

**Disclosures**

Dr Moliterno has received past honoraria for serving as a consultant to Schering-Plough and Portola Pharmaceuticals.

**References**


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