Options and outcomes with different antiplatelet strategies during primary percutaneous coronary intervention

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This editorial refers to ‘Influence of different antiplatelet treatment regimens for primary percutaneous coronary intervention on all-cause mortality†, by A. Witkowski et al., on page 1736

The antithrombotic armamentarium for the treatment of acute coronary syndromes has expanded so rapidly over the past decade that this evolution has challenged the pace at which large-scale clinical trials can be completed for new indications and cardiac society guidelines can be updated. For example, there are presently 60 different antiplatelet and anticoagulant combinations for drugs with Class I or II indications for the treatment of ST-segment elevation myocardial infarction (STEMI). Considering clopidogrel in particular, the current European Society of Cardiology (ESC) guidelines recommend an oral loading dose of at least 300 mg for patients undergoing primary percutaneous coronary intervention (PCI) (Class I, Level of Evidence C). In the acute phase of STEMI, a clopidogrel maintenance dose of 75 mg daily is recommended (I, A) and, while the optimal duration of clopidogrel has not been determined, therapy for 12 months in all STEMI patients is recommended (IIa, C). Similarly, the current American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend clopidogrel for patients with STEMI regardless of whether they undergo reperfusion with fibrinolytic therapy (I, A). These updates are based on the Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study (COMMIT/CCS-2) and the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-Thrombolysis in Myocardial Infarction (TIMI) 28 trials, which did not employ PCI as the primary reperfusion strategy. No prior large-scale trial or registry has demonstrated a mortality-lowering benefit from high-dose clopidogrel among primary PCI patients, though some relevant data are emerging.

Witkowski et al. report their findings among 7193 patients undergoing primary PCI during 2003 and included in a multicentre Polish STEMI registry. In particular, the authors retrospectively analysed data from 38 centres and separated patients according to the periprocedural use of a thienopyridine, a glycoprotein (GP) IIb/IIIa inhibitor, both, or neither, and compared survival among these groups using a national vital statistics database. All patients received aspirin, though baseline differences among the groups were numerous, and multiple statistical adjustments were needed. The authors observed the respective 1-year mortality rates to be 9.0, 10.4, 9.7, and 15.3%, and concluded that compared with aspirin treatment alone, groups receiving either or both antiplatelet adjuncts had a significantly lower mortality. Additionally, the authors compared survival among patients receiving dual antiplatelet therapy (aspirin and clopidogrel) with survival in those receiving triple antiplatelet therapy (aspirin, clopidogrel, and a GP IIb/IIIa inhibitor) and found no mortality benefit with the addition of a GP IIb/IIIa inhibitor.

These observations are interesting and provocative, and support multiple previous reports that aspirin therapy alone is inadequate for patients undergoing PCI in the setting of myocardial infarction. Yet for various clinical and non-clinical reasons, such patients have been undertreated with antiplatelet therapy—and they do poorly. For example, the 2003 ESC STEMI guidelines were published before patients in the present registry were enrolled, yet GP IIb/IIIa inhibitors were used in only roughly one-third of those for whom a Class I indication existed. There are different reasons why Class I guidelines are not applicable to all patients, and time is required for guidelines to become part of day-to-day practice, yet even randomized clinical trials have noted that protocol recommendations for antiplatelet therapy are not always followed. In PCI-CLARITY, where STEMI patients receiving aspirin, heparin, and fibrinolytic therapy were randomized to clopidogrel or placebo at admission, it was recommended that all patients undergoing PCI days after enrolment receive 300 mg open-label clopidogrel before the procedure since the study drug assignment was blinded. Despite this protocol recommendation, a rough quarter of patients were not loaded (or re-loaded)
with clopidogrel, and these patients had numerically more ischaemic events.9

As with most registries and retrospective assessments, the current data provided by Witkowski et al. have important value mixed with caveats. As mentioned, there were many baseline characteristic differences among the treatment groups, and while extensive statistical adjustments and propensity scoring were utilized, there are probably unidentified or uncorrected factors that remain. These imbalances diminish to some degree the ability to compare mortality rates among the dual and triple antiplatelet therapy groups. So, too, despite the guidelines and practice patterns at the time of the registry, the authors have assessed and presented their data in a contemporary light—in other words asking, ‘Is there a mortality benefit to adding GP IIb/IIIa inhibitors to clopidogrel-treated patients?’ In 2003, the question among many investigators and clinicians was rather, ‘Would clopidogrel loading add benefit to patients receiving a GP IIb/IIIa inhibitor?’ This seemingly minor point is important since the registry did not collect specific data regarding timing and duration of clopidogrel administration. Many patients did not receive clopidogrel until after PCI, and it is uncertain how long following hospital discharge patients received the thienopyridine. Likewise, a substantial percentage of patients given a GP IIb/IIIa inhibitor received this as a bailout therapy, a situation known to be associated with poor outcome. Finally, information regarding the administration of other cardiovascular drugs (β-blockers, angiotensin-converting enzyme inhibitors, statins) known to affect 1-year mortality was not collected. There were also no quantitative measures of infarct size, residual left ventricular function, or placement of cardiodefibrillators.

In the setting of primary PCI, abciximab, a GP IIb/IIIa inhibitor, has been shown to provide an ~30% relative risk reduction in 1-year mortality; however, such patients were not treated routinely with a thienopyridine, and a meta-analysis was required to demonstrate this survival benefit. De Luca et al.10 performed a composite analysis with 11 placebo-controlled trials including 3912 patients with 1-year outcome and reported mortality rates to be lowered from 6.2 to 4.4% with abciximab. More recently than those trials, but in the setting of non-ST-segment elevation myocardial infarction, are the findings from the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 2 trial.11 In ISAR-REACT 2, an early and persistent ischaemic event reduction was provided by abciximab when added to aspirin and 600 mg of clopidogrel among 2022 high-risk patients. In contrast to the findings from the De Luca meta-analysis and ISAR-REACT 2, the Bavarian Reperfusion Alternatives Evaluation-3 (BRAVE-3) study6 may lend support to some of the observations made by Witkowski et al. In BRAVE-3, 800 STEMI patients receiving 600 mg of clopidogrel prior to coronary angiography were randomized to abciximab or placebo, and the overwhelming majority of patients then underwent PCI. The primary endpoint, scintigraphically assessed infarct size prior to hospital discharge, was not different between the two groups. Compared with placebo, there was also no 30-day mortality benefit provided by the addition of abciximab (2.5% vs. 3.2%, respectively), though the study was not designed or powered for this assessment. Similarly, Dangas et al.5 observed a notably low 30-day mortality rate (1.9%) among primary PCI patients receiving 600 mg of clopidogrel in a subanalysis of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, and found no overt ischaemic event reduction among high-dose clopidogrel-treated patients randomized to abciximab and heparin compared with those receiving bivalirudin, a direct thrombin inhibitor.

Despite these many clinical trial advances, there are residual uncertainties in the use of clopidogrel for primary PCI including the optimal loading dose, the required interval of treatment before PCI commences, and the presence and extent of residual benefit of adjunctive GP IIb/IIIa therapy—particularly among the sizable proportion of patients with a suboptimal clopidogrel effect secondary to certain concomitant medications, cytochrome genetic variants, such as CYP2C19*2, and other yet to be identified factors. What is certain is that the antithrombotic pharmacotherapeutic landscape will continue to evolve rapidly. Both the US Food and Drug Administration’s Cardiovascular and Renal Drugs Advisory Committee and the European Medicines Agency Committee for Medicinal Products for Human Use have recently recommended approval of the novel thienopyridine, prasugrel. Prasugrel is a more potent and rapidly acting thienopyridine, with less interindividual platelet inhibition variability compared with ticlopidine and clopidogrel. Indeed, in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 subgroup analysis of patients with STEMI undergoing primary PCI,12 prasugrel vs. clopidogrel provided a 32% relative risk reduction in the composite endpoint of cardiovascular death, myocardial infarction, and stroke at 30 days (6.5% vs. 9.5%), and this benefit persisted through 15 months (10.0% vs. 12.4%). By adding prasugrel to the permutations of recommended antiplatelet and anticoagulant agents in STEMI management, we will soon have 92 possible combinations, and the options are likely to increase steadily with new-generation platelet P2Y12 and protease-activated receptor (PAR-1) antagonists and novel anti-factor Xa agents.

Conflict of interest: DJM has received honoraria for serving as a consultant to Schering-Plough and Portola pharmaceuticals.

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