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Review

Optimal treatment of ACS patients: Issues and considerations for upstream antiplatelet therapy

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ABSTRACT

Acute coronary syndromes (ACS) caused by atherosclerotic plaque rupture are clinically manifested as an ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, or unstable angina. Regardless of the management strategy chosen, antithrombotic therapy is necessary to optimize patient outcomes. The American College of Cardiology/American Heart Association guidelines provide a degree of flexibility in the use of antithrombotic and antiplatelet therapies; although this is largely influenced by the clinical severity of the ACS presentation, it can still be difficult for clinicians to decide which antiplatelet therapy regimen should be used. In this article, current recommendations for the use of antiplatelet therapy in the management of ACS are reviewed, along with an overview of the timing of upstream treatment and the decision points involved in choosing the appropriate antiplatelet regimen.

1. Introduction

Acute coronary syndromes (ACS) commonly manifest as ST-elevation or non-ST-elevation myocardial infarction (STEMI or NSTEMI, respectively) or as chest pain or discomfort of increasing severity (unstable angina [UA]). Platelet activation and aggregation are central to the development of an occlusive thrombus and its attendant complications (Fig. 1). Accordingly, guidelines for the use of antiplatelet therapy in treating ACS have been established based upon a protective benefit in patients with STEMI or UA/NSTEMI [1,2].

Current guidelines dictate combination antiplatelet therapy. With the introduction of new antiplatelet options, incremental benefit must be weighed against bleeding risk. As new data emerge, the clinician is challenged to incorporate clinical findings and guideline-recommended antiplatelet therapies for ACS into everyday practice to optimize patient outcomes.

2. Clinical rationale for upstream antiplatelet therapy in ACS

Based on clinical research, antiplatelet therapy for ACS has evolved from the use of aspirin alone to combination antiplatelet therapy (Table 1). The addition of clopidogrel to aspirin in patients with STEMI reduces mortality and risk of major vascular events, regardless of whether patients also receive fibrinolytic therapy or undergo surgical intervention. In COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) and CLARITY–TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction), the addition of clopidogrel to aspirin and standard fibrinolytic therapy reduced the relative risk (RR) of the respective primary composite endpoints by 9% ($P=0.002$) and 36% ($P<0.001$), respectively, in patients with STEMI [3,4]. Similarly, in CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events), the addition of clopidogrel to aspirin within 48 h of UA/NSTEMI symptom onset significantly decreased the 30-day RR of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or stroke by 21% ($P=0.003$) [5,6]. The benefit of adding clopidogrel was apparent within 4 h of treatment initiation, significant by 24 h, and maintained through 12 months (20%; $P<0.001$) [5,6].

While the American College of Cardiology/American Heart Association (ACC/AHA) guidelines support early invasive management of NSTEMI [2], patients benefit from antiplatelet therapy whether they are managed medically or with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Although revascularization is associated with significant reductions in both morbidity and mortality [7], the procedure itself can stimulate thrombosis. Subsequently, in addition to antithrombotic therapy, evidence-based medicine supports the use of upstream dual antiplatelet therapy in patients undergoing PCI (Table 1). In PCI–CURE [8] and PCI–CLARITY [9], clopidogrel initiation before PCI reduced the RR of CV death and ischemic events by 25% (8% vs 6%; $P=0.047$) [8] and 41% (7.5% vs 12%; $P=0.001$) [9], respectively [8,9]. In CREDO (Clopidogrel for the Reduction of Events During Observation), while there was no significant reduction in the 28-day rate of death, MI, or stroke with clopidogrel in the total population (6.8% vs 8.3%; $P=0.23$), those receiving clopidogrel >6 h before PCI experienced a benefit of borderline significance (RR reduction, 38.6%; $P=0.051$) [10]. These studies clearly

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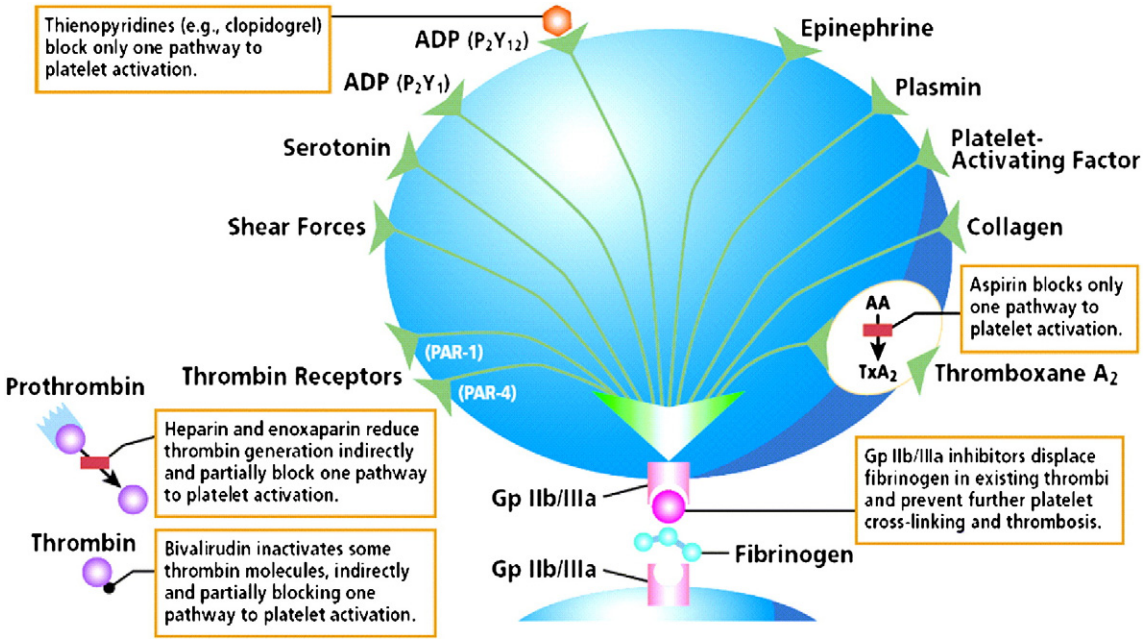

Fig. 1. Factors affecting platelet activation and aggregation, and points of intervention. ADP, adenosine diphosphate; GP, glycoprotein; PAR, protease-activated receptor. Reproduced with permission from Myers RI. BUMC Proc. 2005; 18: 331–336 [80].

support that, regardless of management strategy, clopidogrel pretreatment improves patient outcomes in the setting of either NSTEMI or STEMI.

The thienopyridine prasugrel, which has a more rapid onset of action and greater potency than clopidogrel [11,12], is another option for patients with ACS undergoing PCI. TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition)–TIMI 38 compared prasugrel plus aspirin with clopidogrel plus aspirin in 13,608 patients with ACS and known coronary anatomy scheduled to undergo PCI (Table 1) [13]. Prasugrel reduced the RR of CV death, nonfatal MI, or nonfatal stroke compared with clopidogrel by 19% (9.9% vs 12.1%; $P<0.001$), as well as the rate of definite or probable stent thrombosis (1.1% vs 2.4%; $P<0.001$) [13]. These benefits were accompanied by a significant increase in TIMI major bleeding (2.4% vs 1.8%; $P=0.03$), though no decrease in overall mortality (3.0% vs 3.2%; $P=0.64$) [13]. Among prasugrel recipients, *post-hoc* analyses showed decreased efficacy in patients with a history of ischemic stroke or transient ischemic attack and increased bleeding risk in those with a history of stroke or transient ischemic attack or in those who underwent CABG, weighed <60 kg, or were aged ≥75 years. These observations led to a US Food and Drug Administration (FDA)-mandated boxed warning, highlighting the prasugrel-associated bleeding risk. The efficacy and safety of prasugrel compared with clopidogrel in high-risk, medially managed patients with UA/NSTEMI are being investigated in TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage ACS); the prasugrel maintenance dose will be reduced in patients aged ≥75 years or those weighing <60 kg [14].

Ticagrelor, the first oral, direct, reversible inhibitor of the $P2Y_{12}$ receptor, has a faster onset and offset of action and inhibits platelet aggregation to a greater extent compared with clopidogrel [15]. In PLATO (Platelet Inhibition and Patient Outcome), which compared ticagrelor with clopidogrel in 18,624 patients with ACS given aspirin, ticagrelor significantly reduced the risk of CV death, MI, or stroke compared with clopidogrel (9.8% vs 11.7%; $P<0.001$) (Table 1) [16]. The risk of vascular mortality was also significantly reduced by ticagrelor (4.0% vs 5.1%; $P=0.001$) [16]. These benefits were observed regardless of presenting syndrome or management, all in the absence of a significant increase in trial-defined major bleeding (11.6% vs 11.2%; $P=0.43$). Despite the concern among some clinicians regarding the increased risk of fatal intracranial hemorrhage observed among ticagrelor recipients (0.1% vs 0.01%; $P=0.02$) [16], ticagrelor received positive recommendations for marketing approval in both the United States and Europe. The ongoing PEGASUS (Prevention With Ticagrelor of Secondary Thrombotic Events in High-risk Patients With Prior Acute Coronary Syndrome) trial (ClinicalTrials.gov identifier: NCT01225562) is assessing whether ticagrelor plus aspirin is better than aspirin alone at preventing CV death, MI, and stroke in patients ≥12 months post-MI. Despite negative results from earlier trials [17,18], additional studies of cangrelor, an intravenous, direct, reversible $P2Y_{12}$ receptor inhibitor, are also ongoing. The BRIDGE (Maintenance of Platelet Inhibition With Cangrelor After Discontinuation of Thienopyridines in Patients Undergoing Surgery; NCT00767507) trial is assessing the efficacy and safety of cangrelor as bridging antiplatelet therapy for patients undergoing CABG who have discontinued a thienopyridine. CHAMPION-PHOENIX (Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention;NCT01156571) is comparing cangrelor with standard-dose clopidogrel in patients undergoing PCI for stable angina or ACS.

The benefit of glycoprotein (GP) IIb/IIIa inhibitors, which block the final common pathway of platelet aggregation, in patients with ACS appears dependent on the management strategy and patient risk. In a meta-analysis of 11 trials that included 27,115 patients with STEMI treated with abciximab as an adjunct to reperfusion, GP IIb/IIIa inhibition reduced short- and long-term mortality in patients undergoing primary angioplasty (2.4% vs 3.4%, $P=0.047$ and 4.4% vs 6.2%, $P=0.01$, respectively), but not those treated by fibrinolysis (5.8% vs 5.8%, $P=0.95$ and 8.6% vs 8.3%, $P=0.41$) [19]. Similarly, patients who received fibrinolysis had an increased risk of bleeding complications when GP IIb/IIIa inhibitors were given (5.2% vs 3.1%; $P<0.001$), whereas those who underwent angioplasty did not (4.7% vs 4.1%; $P=0.36$). Meta-analysis of 31,402 patients with NSTEMI enrolled in 6 trials showed that the benefit of GP IIb/IIIa inhibition in preventing death or MI within 30 days was limited to men (odds ratio [OR], 0.81; 95% confidence interval [CI], 0.75–0.89 vs OR, 1.15; 95% CI, 1.01–1.30; $P_{interaction}<0.0001$) and those with elevated troponins (OR, 0.85; 95% CI, 0.71–1.03 vs OR, 1.17; 95% CI, 0.94–1.44;