

Novel Anti-platelet and Anti-thrombin Therapy for Acute Coronary Syndromes: STEMI and NSTEMI Optimal Anti-platelet and Anti-thrombotic Therapy in the Emergency Department

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Objectives:

1. Discuss the pathophysiology of acute coronary syndrome, STEMI and NSTEMI, to provide a basis for understanding therapies for these two disease processes.
2. Provide a basis for the thrombosis and platelet aggregation pathways which allow the clinician to understand agents which antagonize these processes.
3. Discuss specific anti-platelet treatments such as aspirin, thienopyridine ADP receptor inhibitors, and thrombin receptor antagonist.
4. Provide a fundamental knowledge base for emergency physicians to interact with other health care providers including cardiologists, hospitalists, pharmacists, and hospital administrators to provide optimal care for patients with STEMI and NSTEMI.

Introduction

Therapeutic advances in medicine are a significant challenge to the practicing clinician. Remaining current, particularly in a field as complex as acute coronary syndrome (ACS) therapy, requires almost continual effort. For emergency physicians and hospitalists alike, the last 15 years of research has provided clinicians with enormous information regarding ACS including insights

on pathophysiology, complications of the disease, and new anti-thrombin and anti-platelets therapies. In particular, the platelet in ACS has become a primary target for treatment advances. In this review of novel anti-platelet therapies for ACS, the evolution of these agents over the last 3 years will be described.

Pathophysiology and Platelet Biology in ACS

In patients with ACS, rupture of an atherosclerotic plaque in an epicardial coronary artery initiates a cascade of biochemical events ultimately causing myocardial ischemia and infarction. The ruptured plaque exposes circulating blood to von Willebrand factor and collagen which cause aggregation of platelets on the denuded endothelial surface. The stimulation of the coagulation pathway by the aggregating platelets releases thrombin, the most potent of platelet agonists. In addition, the extracellular release of thromboxane A₂ and ADP, secondary agonists which activate platelets, enhances platelet aggregation. The activated platelet also expresses glycoprotein IIb/IIIa surface receptors which bridge platelets together through fibrinogen. The aggregation of platelets, associated with insoluble fibrin generated through the thrombin-mediated change of fibrinogen, causes the development of the clot which occludes the coronary artery lumen adjacent to the ruptured plaque (Figures 1 and 2).¹

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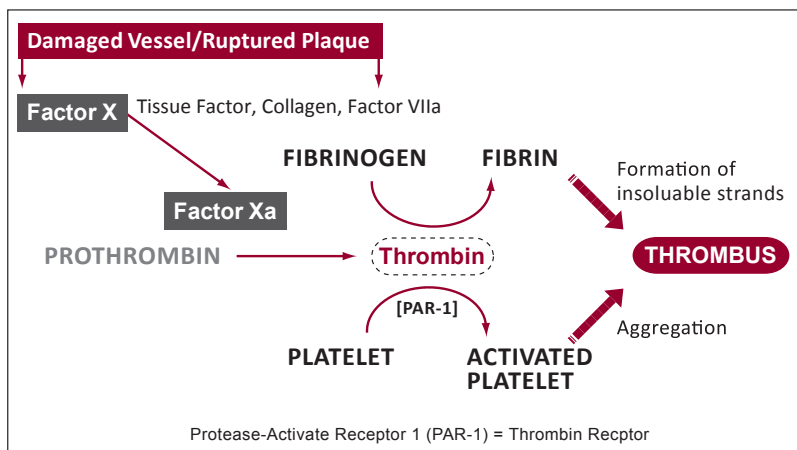


Figure 1: Formation of a thrombus in ACS.

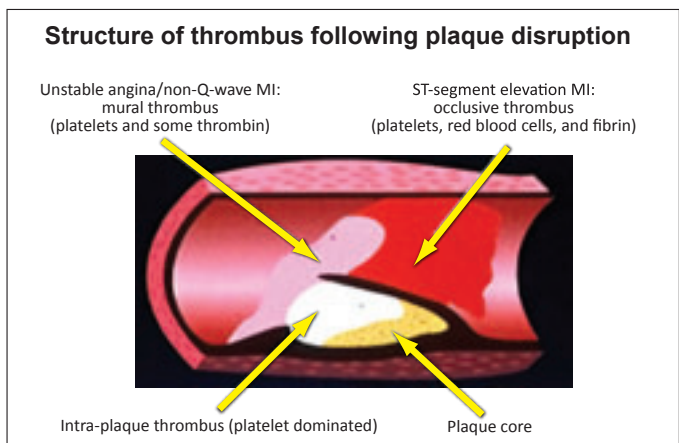


Figure 2: Structure of thrombus following plaque disruption. Adapted and reprinted with permission from Davies MJ. *Circulation* 1990; 82(supp II):II-38-II-46.

The multiple platelet receptors for these agonists which activate and aggregate platelets all serve as potential therapeutic targets. Thromboxane A₂, ADP through the P₂Y₁₂ receptor, and glycoprotein IIb/IIIa receptor all have been identified and successfully inhibited by agents which are currently available to the practicing acute care physician. It is important for the clinician to be aware of these pharmacologic therapies and ideally to understand the basis for their use in the patient with ACS (Figure 3).

Currently Available Therapy

Perhaps the best known treatment for ACS, aspirin, acts through inhibition of thromboxane A₂ production and cyclo-oxygenase. This mainstay of treatment should be given to all patients with ACS, unless there is a known allergy to aspirin. This is considered a Class I, level of evidence A, recommendation from the 2007 ACC/AHA Guidelines for the treatment of unstable angina/non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI).^{2,3}

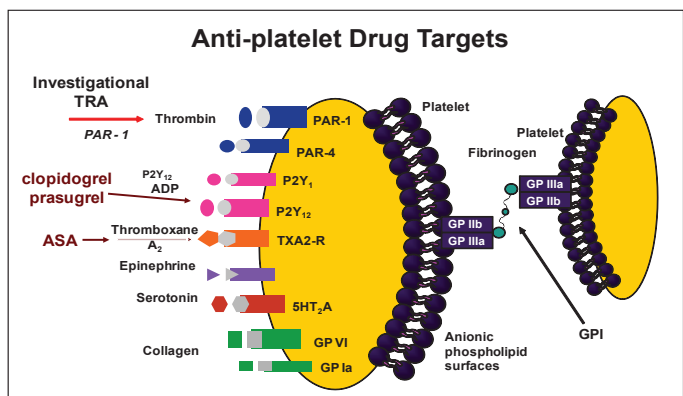


Figure 3: Anti-platelet drug target receptors in acute coronary syndrome.

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Similarly, the thienopyridine clopidogrel, an irreversible antagonist of the P₂Y₁₂ receptor on the platelet, is a Class I A recommendation for NSTEMI and STEMI ACS as a 300 mg bolus followed by a 75 mg daily dose.⁴ Recently, presentation of the CURRENT trial at the European Society of Cardiology Meeting in Barcelona, identified an increased loading dose of 600 mg clopidogrel prior to percutaneous coronary intervention improved outcomes with minimal increase in TIMI major bleeding rates.⁵ Finally, multiple glycoprotein IIb/IIIa receptor antagonists including integrilin, abciximab, and tirofiban have support as major anti-platelet therapies for ACS by the guidelines.

Novel Anti-platelet Agents

Over the last 3 years, multiple new anti-platelet agents have been investigated. Prasugrel, ticagrelor, cangrelor, and thrombin receptor antagonist have now been studied in Phase III trials and will be discussed in this review. Only prasugrel has been approved by the FDA for use in the clinical setting.

Prasugrel

In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON-TIMI 38), prasugrel 60 mg loading dose followed by a 10 mg per day regimen was compared to the standard 300 mg loading dose plus a 75 mg daily dose of clopidogrel for up to 15 months in 13,608 moderate to high risk ACS patients undergoing PCI.⁶

For the primary endpoint of cardiovascular death, nonfatal MI, or stroke, there was a 19% relative risk reduction in the prasugrel treated group (642 patients, 9.9%) versus the clopidogrel treated group (781 patients, 12.1%) – (hazard ratio 0.81; 95% confidence interval 0.73 - 0.90; p = 0.0004). Reduction in MI drove the difference in primary outcome between the two groups (Figure 4).

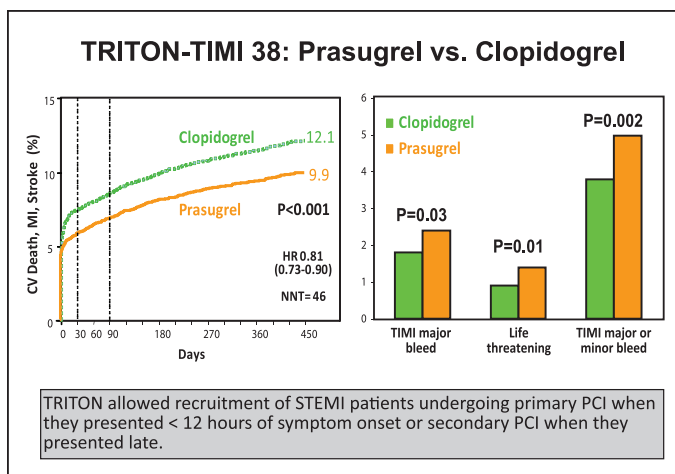


Figure 4: TRITON-TIMI 38 – prasugrel versus clopidogrel therapy. Adapted and reprinted with permission from Wiviott SD, et al. *N Engl J Med* 2007;357:2001-2015.

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In TRITON-TIMI 38, there was a significant difference in major bleeding, occurring in 2.4% of prasugrel patients versus 1.8% of clopidogrel treated patients (hazard ratio 1.32; 95% CI 1.03 – 1.68; p = 0.03). In particular, patients with a history of transient ischemic attack (TIA) or stroke, patients 75 years of age or older, and patients with a body weight <60 kg were at greater risk for bleeding. The drug should be avoided in patients with cerebrovascular disease as they are at increased risk for intracranial hemorrhage.

In a pre-designed substudy from TRITON-TIMI 38 of prasugrel versus clopidogrel in patients with STEMI undergoing PCI, a reduction in the primary endpoint was seen similar to the overall study without a significant difference in major bleeding between the two groups.⁷ This was likely due to the decreased age and increased weight of STEMI patients in the TRITON-TIMI 38 trial, and the lower incidence of cerebrovascular disease in this cohort. In receiving approval by the FDA in 2009, a boxed warning was given to avoid using prasugrel in

patients with active pathological bleeding or a history of TIA or stroke. Caution was advised in using prasugrel for patients aged 75 years of age or older, except in high risk patients with diabetes or prior myocardial infarction. Low weight patients, particularly individuals 60 kg or less, should be treated with caution.

The increase in efficacy of the thienopyridine prasugrel is thought to be due to more efficient metabolism by the cytochrome P450 system. This two step metabolism occurs in the gut and in the liver which synthesizes a pharmacologically active metabolite. Hence, prasugrel is absorbed by the gut and rapidly metabolized providing maximal inhibition of platelets in approximately one hour. In contrast, clopidogrel is metabolized in a 2 step process primarily by cytochrome P3A₄ in the liver. This cytochrome is variably present in patients or can be inhibited by commonly used drugs metabolized by this enzyme system. Approximately 85% of the dose of clopidogrel is metabolized to inactive metabolites (Figure 5). Typically, the maximum platelet inhibitory effect of clopidogrel is seen 4-6 hours after the oral loading dose is given. It is for these reasons the double bolus loading dose of 600 mg was chosen for evaluation in the CURRENT trial.⁵

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Cangrelor

Binding of both clopidogrel and prasugrel to the P₂Y₁₂ receptor of the platelet is covalent and therefore irreversible. In contrast, an intravenous agent cangrelor, which inhibits the same receptor in a rapid onset, rapid offset, and reversible fashion, has recently been evaluated. Despite several successful Phase II studies, the recent Phase III trials CHAMPION-PCI and CHAMPION-PLATFORM were prematurely stopped when cangrelor was not found to be superior to clopidogrel 600 mg as a bolus dose.

Ticagrelor

An oral, reversible inhibitor of the P₂Y₁₂ ADP receptor of platelets has been evaluated in a number of Phase II trials and the recently completed and published PLATO Phase III trial. In the PLATO study, high risk ACS patients presenting to the hospital within 24 hours of symptom onset were eligible for enrollment. In this multinational study of 18,624 patients

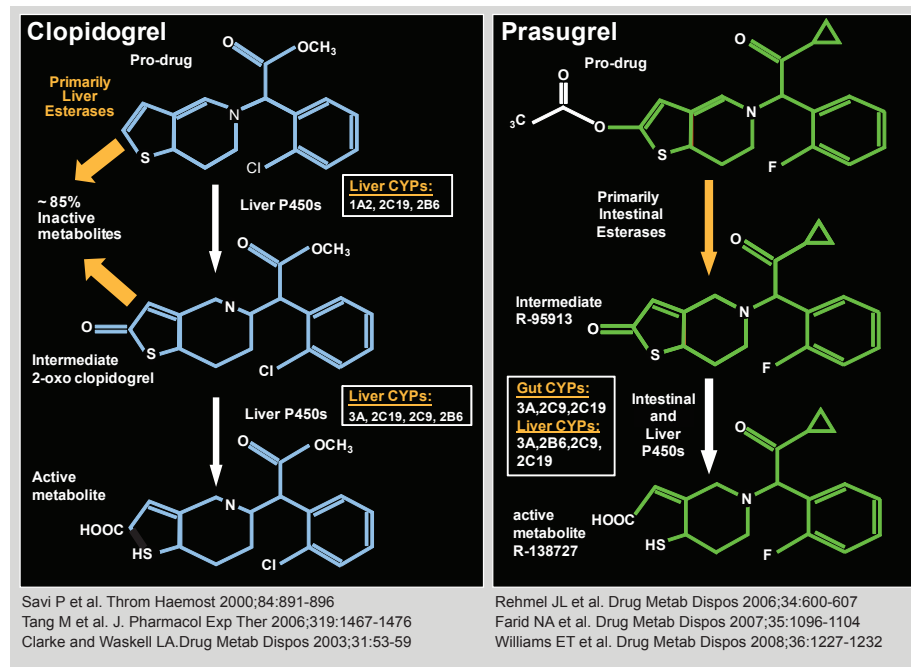


Figure 5: Generation of active metabolites of clopidogrel and prasugrel. Adapted and reprinted with permission Rehmel JL et al. Drug Metab Dispos 2006;34:600-607, Farid NA et al. Drug Metab Dispos 2007;35:1096-1104, Williams ET et al. Drug Metab Dispos 2008;36:1227-1232, Savi P et al. Throm Haemost 2000;84:891-896, Tang M et al. J. Pharmacol Exp Ther 2006;319:1467-1476, Clarke and Waskell LA. Drug Metab Dispos 2003;31:53-59.

with ACS, ticagrelor 180 mg loading dose and 90 mg twice daily maintenance dose was compared to clopidogrel (300-600 mg loading dose followed by a 75 mg daily maintenance dose) in a randomized double blind fashion.

For the primary endpoint, defined as a composite of death from any vascular cause, myocardial infarction, or stroke, ticagrelor was found to have a 9.8% occurrence of the primary endpoint versus 11.7% in those patients treated with clopidogrel (hazard ratio 0.84; 95% CI 0.77 – 0.92; p < 0.0001).

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versus 6.9% in the clopidogrel group, p = 0.005) and death from vascular causes (4.0% versus 5.1%, p = 0.001) was also observed in the experimental group. No difference in major bleeding was observed in the ticagrelor versus clopidogrel group (11.6% versus 11.2%, p = 0.43), however, bleeding not related to coronary artery bypass grafting (4.5% versus 3.8%, p = 0.03), including more instances of fatal intracranial bleeding, was greater in the ticagrelor treated group (Figure 6).⁹

Thrombin Receptor Antagonist

An inhibitor of the thrombin receptor on the platelet, the thrombin receptor antagonist SCH 530348, represents a new class of drug effective at decreasing platelet aggregation in ACS. This agent has minimal effect on bleeding time, suggesting it may have additive benefit to the other agents previously detailed in this review. Binding to the

protease-activated receptor (PAR)-1, the signaling of intra-platelet calcium ion elevation is decreased by TRA blunting of the response to thrombin and collagen stimulation.¹⁰

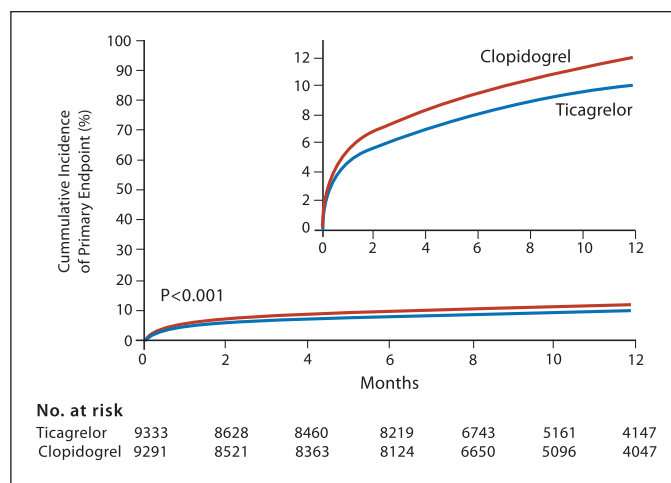


Figure 6: Cumulative Kaplan–Meier Estimates of the Time to the First Adjudicated Occurrence of the Primary Efficacy End Point. The primary end point — a composite of death from vascular causes, myocardial infarction, or stroke — occurred significantly less often in the ticagrelor group than in the clopidogrel group (9.8% vs. 11.7% at 12 months; hazard ratio, 0.84; 95% confidence interval, 0.77 to 0.92; P<0.001). Reprinted with permission from Wallentin L, et al., N Engl J Med 2009;361:1045-57.

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In the TRA-PCI study, SCH 530348 was used in addition to conventional treatment in addition to aspirin plus clopidogrel 300 or 600 mg as a loading dose with a maintenance dose of 75 mg for 1,030 patients scheduled for angiography and possible stenting. The SCH 430348 regimen was added in a 3:1 randomization scheme at 10, 20 or 40 mg loading doses, followed by a 0.5, 1.0, or 2.5 mg maintenance dose. The primary endpoint was TIMI major or minor bleeding in the PCI cohort at 60 days with a secondary endpoint of death or major cardiovascular events (Figures 7 and 8). On the basis of the success of the TRA-PCI study, the 40 mg loading dose and 2.5 mg maintenance were chosen for 2 large Phase III clinical trials which are now ongoing. In the TRA-CER trial, SCH 530348 will be evaluated in approximately 10,000 patients with ACS for at least 1 year. In the other trial, TRA 2P-TIMI 50 study, approximately 19,500 patients with a history of MI, ischemic stroke, or peripheral arterial disease will receive a 2.5 mg maintenance dose of the thrombin receptor antagonist versus placebo for secondary prevention.

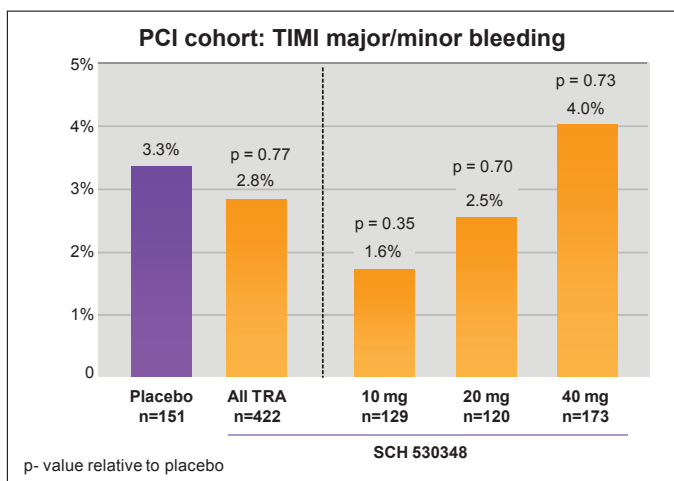


Figure 7: Bleeding in the PCI cohort in TRA-PCI. Adapted and reprinted with permission for Becker R. et al. Lancet 2009;373:919-928.

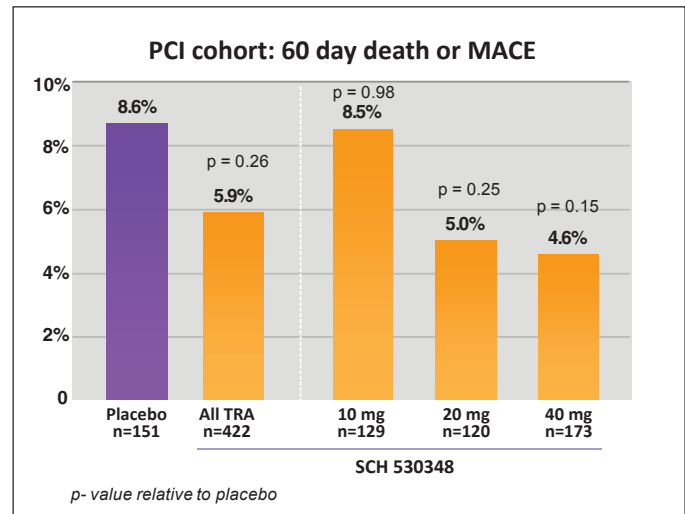


Figure 8: Sixty day death or major adverse clinical events (MACE) in TRA-PCI PCI cohort. Adapted and reprinted with permission for Becker R. et al. Lancet 2009;373:919-928.

Conclusion

Anti-platelet agents such as aspirin, clopidogrel, and the glycoprotein IIb/IIIa inhibitors have been the mainstay for treatment of NSTEMI and STEMI for the last decade. Novel anti-platelet drugs have been investigated which have the potential to improve care for patients with ACS. It is important for acute care physicians such as emergency physicians and hospitalists to understand the basic mechanism of action for these new drugs to optimally treat their future patients. In addition, having a working knowledge of the pharmacology of anti-platelet agents will improve communication and collaboration with cardiology colleagues caring for patients with ACS.

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