Managing Thienopyridine Therapy in Acute Coronary Syndromes: Novel Antiplatelet Agents Prasugrel and Ticagrelor

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Objectives:
1. Describe the appropriate application of oral antiplatelet agents in NSTE ACS and STEMI, according to the new ACC/AHA 2009 PCI/STEMI guideline recommendations
2. Describe the mechanism of action of prasugrel and the trial design and results of TRITON TIMI 38
3. Describe the mechanism of action of ticagrelor, and the trial design and results of the PLATO trial
4. Describe the potential applications of prasugrel and ticagrelor in patients with STEMI and NSTE ACS

Introduction

The 2009 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for Percutaneous Coronary Intervention (PCI) and Management of ST segment elevation Myocardial Infarction (STEMI) were revised, updated, and released to the public in December of 2009.1,2 The new ACC/AHA Guidelines incorporate recent clinical trials data and include updated recommendations on treatment strategies for STEMI and Non-ST-segment elevation acute coronary syndromes (NSTE ACS) treated with PCI. The new guidelines assign a I-B recommendation for the use of prasugrel 60 mg orally as a loading dose at the time of primary PCI for STEMI. They also assign a I-B recommendation for prasugrel 60 mg orally as a loading dose at the time of PCI for NSTE ACS, except in patients already on clopidogrel. The guidelines also include a class III recommendation (harmful) for the use of prasugrel in patients with age >75 years old, weight <60 kg, or a prior history of transient ischemic attack (TIA) or stroke. Emergency physicians should be aware of prasugrel's mechanism of action, pharmacology, and clinical application in the treatment of these patients.

Novel Antiplatelet Therapy

As an alternative to clopidogrel in NSTE ACS, the novel platelet P2Y12 inhibitor prasugrel was recently evaluated in the TIMI 38 trial.3 Prasugrel is a more potent oral platelet inhibitor than clopidogrel, with a higher and more predictable range of platelet inhibition after administration, overcoming the issues of clopidogrel nonresponders.4 It is not a pro-drug, and is therefore more quickly biologically active after oral administration. It is metabolized by a different pathway than clopidogrel, eliminating the issue of genetically related slow metabolism or competitive slow metabolism with concomitant proton pump inhibitor (PPI) administration. It has a longer half life than clopidogrel, however, making reversibility more difficult in patients proceeding to coronary artery bypass grafting.

In the TIMI 38 trial, 13,608 patients with either STEMI or moderate to high risk NSTE ACS and planned intervention for a known intracoronary lesion were randomized in a double blind fashion to receive either a 300 mg load of clopidogrel and 75 mg per day, or a 60 mg load of prasugrel and 10 mg a day, beginning at the time of cardiac catheterization and continuing for a year.3 It should be noted that this randomization occurred after the initial angiogram. Prasugrel was not evaluated upstream in the emergency department (ED) in NSTE ACS, but only in the catheterization lab after the coronary anatomy was defined. The primary outcome of the trial was death, MI, or stroke at one year. Safety outcomes were also analyzed to determine net clinical benefit. At one year, prasugrel was associated with a 19% reduction in death, MI, and stroke (HR 0.81, 95% CI 0.73-0.90) compared to clopidogrel (Figure 1). Bleeding was increased in the prasugrel group, however, with an overall 0.6% increase in major bleeding (2.4% versus 1.8%, HR 1.32, 95% CI 1.03-1.68). Fatal bleeding, transfusions, and coronary artery bypass grafting (CABG) bleeding were all significantly higher in the prasugrel group, and bleeding was especially higher in the elderly (>75 yo), patients with low body weight, and in patients with prior TIA or Stroke (Figure 2). There was a definite trade-off noted between increased efficacy and increased bleeding, prompting the authors of the study to caution against the use of prasugrel in these high risk groups. The lack of any pre-catheterization medical management in the TIMI 38 trial, and the high rate of CABG-related bleeding, makes this drug less applicable to the ED setting in NSTE ACS.

The TRITON-TIMI 38 trial also enrolled 3534 patients with STEMI treated with either primary or secondary PCI.5 In these patients, prasugrel 60 mg resulted in a 19% relative risk reduction in death, MI, and stroke at 15 months (HR 0.81, 95% CI 0.66-0.99) compared to clopidogrel 300 mg. Bleeding still trended worse in the prasugrel arm, but there were no
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Figure 1. Primary Outcome Results of the TIMI 38 Trial: Cardiovascular death, MI, Stroke

![Graph showing primary outcome results of TIMI 38 trial.](image)


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Another novel antiplatelet, which is presently under review by the FDA for approval in ACS, is ticagrelor. Like prasugrel, ticagrelor is a novel adenosine diphosphate (ADP) P2Y12 inhibitor. Unlike prasugrel, however, it is not a thienopyridine. It blocks the conversion of cyclic AMP to ADP at the P2Y12 site, but does not directly bind the P2Y12 site. Oral intake of ticagrelor results in rapid onset of potent antiplatelet activity, higher than levels seen with clopidogrel. Ticagrelor has a shorter half life than clopidogrel, however, necessitating twice daily dosing, and theoretically leading to earlier reversal of antiplatelet activity after ceasing therapy.

Ticagrelor was recently evaluated in the PLATO trial, which enrolled 18,624 patients with either STEMI or NSTE ACS destined for the catheterization laboratory. Unlike in TRITON, patients in PLATO were enrolled and randomized prior to their coronary angiograms. Also, unlike in TRITON, the loading dose of clopidogrel was not specified, allowing a significant percentage of patients in the clopidogrel arm to receive a 600 mg loading dose prior to PCI. Approximately 70% of the patients in the PLATO trial underwent PCI, and 30% were treated with CABG, medical therapy, or no therapy. The primary outcome of the trial was death, MI, and stroke at one year.

Ticagrelor resulted in a 16% reduction in death, MI, and stroke in ACS patients at one year (HR 0.84, 95% CI 0.75-0.94) compared to clopidogrel (Figure 3). In addition, cardiac mortality was reduced in the ticagrelor group at one year from 5.1% to 4.0% (HR 0.79, 95% CI 0.69-0.91). Total major bleeding, transfusions, and life-threatening bleeding were not significantly different between groups, but when non-CABG statistically significant differences in bleeding, including life threatening bleeding. Unlike the NSTE ACS population in TRITON, the STEMI patients were often randomized to prasugrel upstream, prior to angiography. As such, these results support the use of prasugrel in the ED for STEMI patients.
bleeding alone is analyzed, there was a significant increase in non-CABG bleeding with ticagrelor (4.5% versus 3.8%, \( p = 0.026 \)). This was offset by a nonsignificant decrease in CABG bleeding with ticagrelor (7.4% versus 7.9%, \( p = \text{NS} \)). Despite theoretical advantages of a short half-life antiplatelet agent in patients proceeding to CABG after angiogram, there were no significant reductions in bleeding in the CABG cohort in PLATO.9

The PLATO trial enrolled 8,430 patients with STEMI, randomized to ticagrelor versus clopidogrel.9 In these patients, ticagrelor resulted in a 15% relative risk reduction in death, MI, and stroke at one year compared to clopidogrel (HR 0.85, 95% CI 0.74-0.97). Bleeding rates in the STEMI patients were similar between ticagrelor and clopidogrel, making ticagrelor a viable option in ED treatment of STEMI prior to primary PCI.

Both prasugrel and ticagrelor are oral agents which provide significantly higher antiplatelet activity than clopidogrel. Both have been investigated in STEMI and NSTE ACS patients treated by an invasive pathway, and both provide significant reductions in ischemic endpoints compared to clopidogrel. In the case of prasugrel, this advantage is mitigated by an increase in life-threatening bleeding. Prasugrel also cannot be used upstream in NSTE ACS patients prior to catheterization. It also should be avoided in patients with age >75, weight <60 kg, and a prior history of CVA and stroke. It remains, however, a viable option for STEMI therapy upstream prior to primary PCI. Ticagrelor does not have prasugrel’s bleeding issues, and can be used upstream in NSTE ACS as well as STEMI. It also provides a death benefit at one year in ACS patients. It is not yet, however, FDA approved. It may prove to be a viable oral antiplatelet in high risk NSTE ACS and STEMI.
References


