INTRODUCTION

Patients presenting to the emergency department (ED) with chest pain and non-ST-segment elevation acute coronary syndromes (NSTE ACS) are at significant risk for short-term and long-term morbidity and mortality. Randomized clinical trials have demonstrated 30-day combined incidences of death, MI, and urgent revascularization of over 15% in these patients1-6, and current ACC/AHA guidelines recommend early aggressive medical therapy followed by definition of coronary anatomy and subsequent revascularization in high risk NSTE ACS patients.7,8 Upon patient identification in the ED, medical therapies including platelet and thrombin inhibitors should be initiated early and continued through angiography. The emergency physician must be knowledgeable in the utilization of pharmacological agents used to treat NSTE ACS. Platelet inhibitors are an important piece of this pharmacological armamentarium.

Platelet Inhibitors in NSTE ACS:
The pathophysiology of NSTE ACS is initiated by the endothelial rupture of an atherosclerotic coronary artery plaque. Plaque rupture leads to platelet aggregation, platelet activation, fibrin deposition, and downstream myocardial ischemia and necrosis. Therapies aimed at reversing platelet activation, platelet aggregation, and coagulation cascade activation are especially effective in NSTE ACS. Platelet inhibitors, including aspirin, clopidogrel, and glycoprotein IIb/IIIa (GP) receptor blockers have all been investigated in this group of patients with remarkable results.

Oral Antiplatelet Agents:
The two oral antiplatelet agents indicated for the treatment of NSTE ACS are aspirin and clopidogrel.7,8 The Class IA recommendation for aspirin in the acute treatment of NSTE ACS is based mostly on substantial evidence from STEMI trials, where aspirin was shown to significantly reduce the incidence of death, MI, and stroke compared to placebo.9 The evidence for it’s effectiveness in NSTE ACS is less compelling, but still substantial. The Antiplatelet Trialists Collaboration, in a compilation of NSTE ACS trials, demonstrated significant benefit to early aspirin, in addition to antithrombin therapy, in NSTE ACS.10 The initial dose of aspirin remains controversial, although most authors recommend 325 mg. chewed, either initiated on arrival in the ED or in the pre-hospital arena. The maintenance dose is recommended at 75-150 mg daily, with most patients choosing the 81 mg baby aspirin for daily prophylaxis, especially when combined with clopidogrel.11

OBJECTIVES:
1. To describe the pathophysiology of non-ST-segment elevation acute coronary syndrome (NSTE ACS) as it relates to the use of platelet inhibitors
2. To describe the major clinical trials data supporting oral and IV platelet inhibitors in NSTE ACS
3. To describe the concept and clinical advantages of pretreatment with oral and IV platelet inhibitors prior to angiography and PCI in patients with NSTE ACS
4. To describe the impact of incorporating antiplatelet therapy with other cardiovascular medications, including percutaneous intervention, in the treatment of NSTE ACS as indicated by the ACC/AHA guidelines
Clopidogrel is recommended by the ACC/AHA Guidelines as a Class IA therapy for NSTE ACS based mostly on the results of the CURE trial.\textsuperscript{12} The CURE trial randomized over 12,500 patients with NSTE ACS to aspirin plus placebo versus aspirin plus clopidogrel, administered during initial hospitalization and continued for one year after discharge. Clopidogrel utilization was associated with a statistically significant reduction in death, MI, and stroke at one year. An even more substantial beneficial effect was noted in patients who underwent PCI during their hospitalization, with an absolute reduction in death and MI of 4% at one year (Figure 1). The clinical benefits of clopidogrel in NSTE ACS have been substantiated in PCI trials like EPISTENT\textsuperscript{14} and ESPRIT\textsuperscript{15}, as well as the recently completed CREDO trial.\textsuperscript{16} In the CREDO trial, the administration of clopidogrel between 6-24 hours prior to PCI was associated with improved outcomes versus placebo in patients treated with PCI. Clopidogrel’s benefits were noted to be additive to GP IIb/IIIa inhibitors in PCI as well.

The ACC/AHA guidelines recommend early administration of clopidogrel 300mg orally at the time of patient identification as high risk.\textsuperscript{7,8} The early utilization of clopidogrel in the ED remains somewhat controversial, however, due to downstream bleeding concerns. In the CURE trial, patients who underwent CABG while taking clopidogrel had a higher incidence of surgical bleeding complications.\textsuperscript{12} As such, the guidelines recommend holding clopidogrel for 5 days prior to CABG. This often leads to the withholding clopidogrel in the ED and prior to catheterization, until the coronary anatomy is defined, and the determination is made that patient is not destined for CABG.

A second controversial issue with clopidogrel revolves around the appropriate loading dose. Pharmacokinetic studies have shown that a 600mg. loading dose confers earlier, more therapeutic antiplatelet function than the recommended 300 mg dose.\textsuperscript{17,18} In the ISAR REACT trial, clopidogrel 600 mg. loading was found to be equivalent to IV IIb/IIIa agents in elective PCI, albeit in extremely low risk patients.\textsuperscript{19} These studies have led many practitioners to alter their loading dose of clopidogrel to 600 mg. at the time of patient identification.

**Figure 1.**

Upstream clopidogrel before PCI*: Reduction in Death/MI in Patients Receiving Clopidogrel following PCI in the PCI-CURE Substudy.\textsuperscript{13}
Intravenous Antiplatelet Agents

A large body of evidence now supports the substantial clinical benefit of adjunctive platelet GP IIb/IIIa utilization with percutaneous intervention in the setting of unstable angina and non ST elevation myocardial infarction. ACC/AHA guidelines recommend GP IIb/IIIa therapy in NSTE ACS patients in whom PCI is anticipated, and those patients deemed at high risk of short term adverse outcome. Patients with elevated troponin levels, ST deviation (ST depression or transient elevation) on their ECG, or other high risk features (ongoing pain, rest pain, CHF, atrial fibrillation, hypotension, or advanced age) should be considered for both GP IIb/IIIa therapy followed by PCI within 48 hours. All three GP IIb/IIIa inhibitors have been shown to be effective in association with PCI in this patient population and are utilized to a widespread extent in the catheterization laboratory.

A smaller but significant benefit with GP IIb/IIIa inhibitors is also discerned in the time period following initiation of treatment but prior to percutaneous intervention. Consequently, ACC/AHA guidelines advocate the utilization of GP IIb/IIIa inhibitors in NSTE ACS patients destined for early angiography and subsequent intervention before the time of percutaneous intervention. Despite these recommendations, utilization of GP IIb/IIIa inhibitors in the ED and in the pre-intervention period remains relatively low.

Antiplatelet Utilization in the CRUSADE Initiative

The CRUSADE registry is an ongoing voluntary observational quality improvement and research initiative for hospitalized patients presenting with NSTE ACS. At the time of this publication, the CRUSADE registry population consisted of well over 100,000 patients admitted with a NSTE ACS to participating hospitals. CRUSADE patients are included in the registry if they present with chest pain of less than 24 hours and suspected NSTE ACS with either ST deviation (ST depression or transient (<30 minutes) on the resting EKG), a positive troponin assay based on the local site cut-off or both.

Data from the CRUSADE initiative illustrate the relatively low utilization of appropriate antiplatelet therapy in the ED and in the first 24 hours after hospital admission. Utilization of early aspirin in the CRUSADE initiative averages over 97%, while the utilization of other antiplatelet agents remains suboptimal (Figure 3). In patients with high risk NSTE ACS, such as those with elevated troponin

Figure 2.
Benefits of GP IIb/IIIa Therapy Before and After PCI: Meta Analysis of Randomized Controlled Trials of GpIIb/IIIa Inhibitors in NSTE ACS (CAPTURE, PURSUIT, PRISM-PLUS)
levels or ST deviation, it is imperative to provide optimum antiplatelet protection in the time period after patient identification in the ED and prior to subsequent PCI. Yet, according to CRUSADE data, 34% of these patients receive aspirin as their sole antiplatelet therapy. This represents a prime target for quality assurance programs and NSTE ACS program initiatives.

In another recent analysis of the CRUSADE database, patients who received early treatment with a GP IIb/IIIa inhibitor were compared with those who were untreated or treated > 24 hours after index hospital presentation. Patient baseline demographics, clinical characteristics, care patterns, and in-hospital outcomes, as well as the features of hospitals to which they were admitted were compared between groups. Patients receiving early GP IIb/IIIa therapy were significantly different from their counterparts who did not receive early GP IIb/IIIa therapy, and medical treatment varied significantly between the two groups. Patients who received early GP IIb/IIIa therapy were more likely to be treated with antithrombin or oral antiplatelet agents, and were more likely to receive early angiography and PCI. They also had a significantly lower length of stay in the hospital.

In this analysis, early GP IIb/IIIa treatment was associated with a significant reduction in unadjusted mortality. After using logistic regression analysis adjusting for patient risk, treatment propensity, and hospital characteristics, early GP IIb/IIIa inhibition was associated with a strong statistical trend towards reduction in in-hospital mortality (OR 0.90, 95% CI, 0.81-1.03) [Figure 4]. These CRUSADE results are consistent with other analyses of GP IIb/IIIa effectiveness in NSTE ACS [Figure 4]. In a meta-analysis of GP IIb/IIIa randomized clinical trials, Boersma, et showed a trend toward decreased mortality with GP IIb/IIIa inhibition utilization. A similar mortality benefit was reported by Peterson and colleagues using the NRMI-4 registry database. Results from the CRUSADE registry now appear to further corroborate these observations. In the highest risk patients with troponin positivity, early GP IIb/IIIa use is associated with a statistically significant reduction in mortality.

These observational registry data will be investigated further in the EARLY-ACS trial. In this ongoing 10,500 patient prospective randomized clinical trial, patients with NSTE ACS will be randomized to...
either ED-initiated versus cath-lab initiated GP IIb/IIIa therapy. Primary outcomes include death, MI, and urgent revascularization in the first 96 hours after admission. This trial should clarify the role of ED initiated GP IIb/IIIa inhibitors in NSTE ACS.

**Implications for ED Clinical Practice**

Emergency physicians are often faced with critical decisions in the care of NSTE ACS patients. One of the more controversial of these decisions revolves around the question of initiation of either clopidogrel or a GP IIb/IIIa inhibitor in the ED versus the later in the catheterization lab. Evidence from randomized clinical trials has supported early use of clopidogrel and GP IIb/IIIa inhibitors in the time period prior to PCI, but both antiplatelet agents are still underutilized in this setting as evidenced by the CRUSADE registry. Patients with chest pain and presumed NSTE ACS are at highest risk for recurrent ischemia, recurrent MI, and death in the 24-48 hours after admission and prior to cardiac catheterization. It is imperative that emergency physicians treat these patients aggressively and expectantly during this vulnerable period. Platelet inhibitors play a crucial role in that aggressive treatment.

**Figure 4.**

Adjusted Mortality by Early GP IIb/IIIa Inhibitor Use: Randomized Clinical Trials and Observational Registries

In the highest risk patients with troponin positivity, early GP IIb/IIIa use is associated with a statistically significant reduction in mortality.
REFERENCES:


