OBJECTIVES:

1) Describe the ACC/AHA guidelines for the treatment of high risk non-ST-segment elevation acute coronary syndromes.
2) Describe the clinical trial evidence and rationale for the use of aspirin, clopidogrel, and GP IIb/IIIa inhibitors in the treatment of high risk NSTE ACS.
3) Describe the clinical trial data supporting the use of a 600mg loading dose of clopidogrel in NSTE ACS.
4) Review the clinical trial data supporting the early use of GP IIb/IIIa inhibitors upstream, prior to coronary angiography, in high risk, troponin positive NSTE ACS patients.

INTRODUCTION

Although non-ST-segment elevation acute coronary syndromes (NSTE ACS) represent a well-recognized source of morbidity and mortality for patients with cardiovascular disease, evidence-based therapies shown to improve outcomes for NSTE ACS are frequently underutilized in appropriate patients, especially in the ED. The American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Management of Unstable Angina/Non-ST-Elevation Myocardial Infarction were promulgated in an effort to standardize and optimize the evaluation, diagnosis, and management of patients with NSTE ACS and to provide physicians with a framework for clinical decision-making. These guidelines are somewhat outdated, however, having last been published in 2002, and may not reflect recent clinical trial evidence. Specifically, new clinical trials data support the use of higher doses of glycoprotein IIB/IIIa inhibitor (GPI) therapy in the management of NSTE ACS. Whether or not these new developments will be included in the next rendition of the Guidelines, or into routine clinical care, remains to be seen. The intent of this NSTE ACS manuscript is to critically review some of these recent clinical trials involving the use of anti-platelet agents in NSTE ACS.

Anti-platelet Therapy 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 minimizing or reversing platelet and coagulation cascade activation are especially effective in NSTE ACS. Platelet inhibitors, including aspirin, clopidogrel, and GPI therapy have all been investigated in this group of patients with remarkable results. Specifically, new clinical trials data support the use of higher doses of clopidogrel and earlier administration of GP IIb/IIIa inhibitor therapy in the management of NSTE ACS.
recommend the early use of aspirin (160-325 mg po), clopidogrel (300 mg po), intravenous heparin or low molecular weight heparin (anti-thrombotic agents) and an intravenous GPI, initiated prior to an early percutaneous coronary intervention (PCI) approach [Figure 1]. High risk patients are typically defined as having old age, ongoing chest pain, hemodynamic or rhythm instability, elevated cardiac biomarkers, or new ischemic electrocardiographic (ECG) changes.

These data have led to the widespread use of a 600 mg loading dose of clopidogrel in the catheterization lab prior to PCI. Upstream use of the 600 mg loading dose in the emergency department (ED) or critical care unit (CCU) is not well defined, although pharmacokinetic and clinical data are very promising. Adaptation of the upstream dosing of clopidogrel in the ED appears to be limited more by the logistic complications of CABG-related bleeding than by issues of dose-response.

Figure 1. Class I recommended anti-platelet and anti-thrombin therapy in NSTE ACS, based on risk stratification to low, intermediate, and high risk for adverse outcomes. Reprinted with permission from Braunwald et al. J Am Coll Cardiol. 2000;36:970-1062.

Clopidogrel Dosing in High Risk NSTE ACS Patients

The ACC/AHA Guidelines recommend that high risk NSTE ACS patients receive clopidogrel 300 mg po load, and 75 mg per day, in addition to aspirin therapy, beginning at patient presentation and continuing for at least one month, and up to one year post discharge from the hospital. The 300 mg loading dose provides approximately 40-60% platelet inhibition after achievement of steady state levels. Recent pharmacokinetic data have suggested that a 600 mg loading dose of clopidogrel, and 75 mg po bid, is associated with as high as 80% initial platelet inhibition. In the recently completed ARMYDA-2 trial, a loading dose of 600 mg of clopidogrel prior to PCI was associated with a 67% reduction (p=0.041) in death, MI, and urgent revascularization compared to the standard 300 mg loading dose [Figure 2]. In ISAR-REACT-1, the loading dose of 600 mg of clopidogrel was found to be equivalent to clopidogrel plus a GPI in low risk elective PCI patients. These data have led to the widespread use of a 600 mg loading dose of clopidogrel in the catheterization lab prior to PCI. Upstream use of the 600 mg loading dose in the emergency department (ED) or critical care unit (CCU) is not well defined, although pharmacokinetic and clinical data are very promising. Adaptation of the upstream dosing of clopidogrel in the ED appears to be limited more by the logistic complications of CABG-related bleeding than by issues of dose-response.

Figure 2. Results of the ARMYDA 2 Trial: Reduction in death, MI and target vessel revascularization with 600 mg clopidogrel loading dose versus the standard 300 mg dose. Reprinted with permission from Patti G, et al. Circulation. 2005;111:2099-2106.

Utilization of GPIs in Addition to Clopidogrel in High Risk NSTE ACS

The rather compelling data supporting the effectiveness of 600 mg loading doses of clopidogrel in PCI evaluate the utility of GPIs in addition to clopidogrel in high-risk NSTE ACS. The recently completed ISAR REACT-2 trial investigated whether a 600 mg loading dose of clopidogrel was as effective as 600 mg of clopidogrel plus the GPI abciximab in high risk patients undergoing PCI. The 2,022 high risk NSTE ACS patients in ISAR REACT-2 had either elevated troponin levels or ischemic ECG changes evident prior to PCI. Glycoprotein IIb/IIIa receptor blockers utilization in addition to clopidogrel administration resulted in a statistically significant reduction in death, MI, and urgent revascularization in
high risk patients (p=0.03) when compared to clopidogrel alone. This benefit was most notable in troponin positive patients (p=0.02) (Figure 3) and absent in troponin negative patients (p=0.98). The results of this trial underscore the need for GPIs, as an adjunct to PCI, in NSTE ACS patients who are high risk, and especially those who are troponin positive. Its applicability to ED or CCU GPI therapy upstream is limited, however, by the catheterization laboratory administration of these drugs in the original trial design.

Figure 3. Results of the ISAR REACT-2 trial: Reduction in ischemic outcomes in troponin-positive patients treated with clopidogrel plus GPI versus clopidogrel alone. Reprinted with permission from results presented at the ACC 2006, Kastrati A. et al. (Ref 13).

Early GPI Use in High Risk NSTE ACS: The ACUITY Timing Trial:
A large body of evidence now supports the substantial clinical benefit of adjunctive platelet GPI utilization with PCI in the setting of NSTE ACS. 3.5 A smaller but significant benefit with GP IIb/IIIa inhibitors is also discerned in the time period following initiation of treatment but prior to PCI (Figure 4),14,15 yet controversy still exists as to the benefits of upstream pre-catheterization GPI therapy. The recently completed ACUITY Timing trial attempted to address the effectiveness of early (in the ED or CCU) versus late (catheterization laboratory) initiation of GPI therapy in moderate and high risk NSTE ACS patients.16 Of the 9,207 patients in the ACUITY timing trial, 4,605 patients were treated with ED or CCU GPI versus 4,602 in the cardiac catheterization laboratory. Whereas the quadruple endpoint of death, MI, unplanned intervention, and bleeding was not different between groups, the upstream GPI group tended to have less ischemic events, and in those patients who underwent PCI, this difference was statistically significant (p=0.05) (Figure 5). The results of this trial favored an early GPI treatment strategy, Figure 5. Results from the ACUITY timing trial: Net clinical outcome, ischemia and bleeding endpoints stratified by patient management strategy. Reprinted with permission form results presented at the ACC 2006, Stone GW et al. (Ref 16).
but there were limitations to the trial which temper its conclusions. First, the patients involved in the ACUITY Timing trial were not truly high risk, with only 57% having troponin biomarker positivity, and therefore many may not have even been eligible to receive upstream GPI as indicated in the ACC/AHA guidelines. Second, the time from admission to cardiac catheterization was a median 19.7 hours, while the median early GPI treatment time was only 6.2 hours, limiting the applicability of these results to the ED. Finally, the ischemia benefit of ED or CCU GPI use was offset by an increase in bleeding in the cardiac catheterization laboratory, resulting in no net clinical benefit. Whereas the results of the ACUITY Timing Trial are intriguing, questions remain regarding the effectiveness of upstream GPI utilization. The much anticipated EARLY-ACS trial, which randomizes high risk NSTE ACS patients to ED versus cardiac catheterization laboratory eptifibatide, should provide a definitive answer to this important question.

SUMMARY

The ISAR REACT-2 trial and the ACUITY Timing trial are only two examples of the many recent clinical trials involving the care of patients with NSTE ACS using anti-platelet agents. Like many past studies, these recent trials answer some clinical questions, but raise others at the same time. Their results must be interpreted in regards to current practice, with emphasis on their applicability in the emergency setting. Lessons from these trials may change practice, or provide an improved evidence basis for current ED therapy for NSTE ACS. Emergency physicians should become aware of these trial results and other studies to provide optimal care for high-risk NSTE ACS patients.

REFERENCES


