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OBJECTIVES:

1. Explain the mechanisms of action of the classes of anti-platelet drugs.
2. State the relative evidence weighting of the use of these drugs upstream of the cardiac catheterization laboratory, from the 2007 ACC/AHA Guidelines.
3. Discuss potential protocols that employ an evidence basis in the management of NSTEMI ACS patients in the ED.

INTRODUCTION

The American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly published practice guidelines for various aspects of cardiovascular disease since 1980. On August 6, 2007, the expert task force formed by these two organizations released an update¹ to their 2002 guidelines² on the evaluation and management of unstable angina (UA) and non-ST-segment elevation (NSTEMI) myocardial infarction (MI). Collectively, these entities are termed non ST-segment elevation acute coronary syndrome (NSTEMI ACS). These guidelines summarize recently published data, provide expert analysis of the clinical applicability of these data, and then include evidence-graded recommendations regarding how, if at all, these

data should be used in practice. They also provide an ideal framework from which a consistent, evidence-based approach to NSTEMI ACS care can be developed among emergency physicians, hospitalists, medical cardiologists, interventional cardiologists, and cardiothoracic surgeons at each institution.

The following is a review of the statements from this document regarding antiplatelet therapy, and its applicability to the “upstream” care environment. This is care provided prior to diagnostic angiography, which of course includes the emergency department (ED).

The 2007 Guidelines’ recommendations for antiplatelet therapy may be summarized as follows:

Evidence Rating	Recommendation
I-A	Aspirin should be administered to UA/NSTEMI patients as soon as possible.
I-A	Clopidogrel (300mg load, then 75mg/d) should be administered to UA/NSTEMI patients unable to take aspirin.
I-A	If early invasive strategy is selected, give clopidogrel (300mg load, then 75mg/d) or an IV GP IIb/IIIa inhibitor (GPI).
I-B	If a GPI is given upstream, eptifibatid or tirofiban is preferred over abciximab.
I-A	If a noninvasive strategy is chosen, initiate clopidogrel (300mg load, then 75mg/d) as soon as possible after admission and continue for at least 1 month.
I-B	...and continue ideally for up to 1 year
I-A	If an initial conservative therapy fails, add either clopidogrel or a GPI.
I-C	... upstream of angiography.
IIa-C	If an initial conservative therapy including clopidogrel fails, add a GPI upstream.
IIa-B	In early invasive strategy, it is reasonable to give both clopidogrel and a GPI.
IIa-B	In early invasive strategy, if bivalirudin is used as the anticoagulant, and at least 300mg clopidogrel was given. at least 6h before cath, then upstream GPI may be omitted.



ADVANCING THE STANDARD OF CARE: Cardiovascular, Neurovascular and Infectious Emergencies



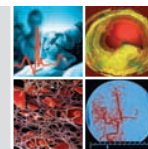
The use of aspirin (ASA) for patients with myocardial ischemia has been considered as standard of care for many years. The appropriate dose of ASA in the ACS patient is 162-324mg; doses higher than 325mg may improve cardiac outcomes, but only at the expense of increased bleeding complications, including stroke. Patients who report mild gastrointestinal upset from ASA should receive it regardless if ACS is suspected. Those patients truly allergic to ASA or who have major gastro-intestinal disturbance after its use should be given clopidogrel, 300mg as a loading dose, and then 75mg/day as an ASA substitute. This is the only FDA-labeled loading dose for clopidogrel in all indications pertinent to the ED, but many emergency physicians will collaborate with interventional cardiologists who load patients with NSTEMI ACS with 600mg prior to percutaneous coronary intervention (PCI). A small trial has shown favorable outcomes with this approach,³ but it has not been validated in large-studies. A major prospective trial, OASIS-7, is underway to compare the safety and efficacy of 300 vs 600mg loading doses of clopidogrel in NSTEMI ACS.

Since the publication of the 2002 ACC/AHA guidelines, there are only scant new data on clopidogrel, but a combination of broad clinical experience,⁴ its ease of administration, the broader use of drug-eluting stents by interventional cardiologists, and its linkage to potential new antithrombotic regimens, particularly bivalirudin, has resulted in wider recommendations for its use. Clopidogrel is usually used in coronary artery disease/acute coronary syndrome management in conjunction with ASA, not instead of ASA, as is discussed above in the narrow context of ASA allergy. The entire issue of clopidogrel loading is problematic for the emergency physician, who must be concerned that the ACS patient may require coronary artery bypass grafting (CABG) after diagnostic catheterization, and a recent load of clopidogrel will delay or complicate surgery. Even though there is no validated clinical or mathematical model which enables accurate prediction of the need for CABG prior to diagnostic angiography in the ED, the 2007 Guidelines retain the caveat issued in 2002 that clopidogrel should be withheld if CABG is anticipated within 5-7 days.

Clearly there is a need for collaboration among an institution's emergency physicians, cardiologists, and cardiothoracic surgeons, to determine an optimal approach to upstream antiplatelet management. In contemporary practice, the rate of CABG during the index hospitalization among NSTEMI ACS patients with elevated biomarkers or clearly ischemic ST-segment/T-wave changes is approximately 12%.⁵ In patients without high-risk features, the likelihood of CABG is much lower, with the rate of truly emergent CABG procedures at only about 1%.⁶ It is important that stakeholders in each facility be aware of their own incidence of CABG in ACS patients, as a low frequency rate may support broader upstream use of clopidogrel, accepting the increased risk of bleeding if CABG ensues, in order to improve protection from ischemic events for the majority of patients not receiving surgery. Analysis of the CURE data which are typically used to show a long-term benefit to clopidogrel plus ASA compared to ASA monotherapy, actually show the efficacy curves diverge significantly as early as 24 hours after oral loading.⁷ If diagnostic angiography and therefore the opportunity even to consider CABG is delayed longer than 24 hours, upstream use may become more appealing.

An important change between the 2002 and 2007 Guidelines is a new "either/or" approach to clopidogrel and glycoprotein IIb/IIIa inhibitors (GPI) in upstream management of NSTEMI ACS.¹ For patients undergoing early intervention, there is a new Class I-A recommendation that patients receive a loading dose of clopidogrel *or* a small-molecule GPI, and a new Class IIa-B recommendation that patients managed with an early invasive strategy should receive *both* clopidogrel *and* a GPI.¹ The latter approach is actually more intuitive, because the two antiplatelet agents have different mechanisms as clopidogrel inhibits platelet activation, while GPIs inhibit aggregation of platelets already activated, and sites (P2Y₁₂ vs GP IIb/IIIa receptors) of action. It must be understood, however, that "triple" antiplatelet therapy - ASA + clopidogrel + GPI increases bleeding risk compared to dual therapy - ASA + clopidogrel *or* ASA+GPI, especially if the patient ultimately is found to require surgery. If either bleeding

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risk, qualitatively assessed in the ED with the knowledge that general high-risk factors are advanced age, female gender, renal insufficiency, and pre-existing anemia, or likelihood of CABG is considered elevated, the safer approach is to use a small-molecule GPI because its effects are short-lived and can be discontinued if CABG is required. Clopidogrel's action on platelets is irreversible. The clopidogrel-or-GPI approach is difficult to support when making upstream treatment decisions, as patients with symptoms of ACS in the ED can be assumed already to have activated platelets, and GPIs are the only class of drugs which inhibit platelet aggregation. Furthermore, clopidogrel and GPIs have never been compared directly in a prospective study.

A recent clinical trial, Intracoronary Stenting with Antithrombotic Regimen (ISAR)-REACT-2,⁸ illustrates the concept of clopidogrel plus GPI therapy. In this study, 2,022 patients with NSTEMI ACS undergoing PCI received ASA, unfractionated heparin (UFH), 600mg clopidogrel, and either abciximab as a 12 hour infusion or placebo. Overall, the patients receiving abciximab experienced a lower rate of death or MI (8.9 vs 11.9%), but the benefit was entirely confined to those patients who had elevated troponin levels. Further, there was no difference between the two groups in bleeding complications.⁸ This study supports the addition of a GPI to even high-dose clopidogrel in NSTEMI ACS patients who have elevated biomarkers. Risk-based treatment decisions of this nature are particularly useful in the ED.

The 2007 Guidelines' new Class IIa-B recommendation to consider omitting upstream GPI in patients receiving bivalirudin if at least 300mg of clopidogrel can be given 6 hours or more prior to catheterization and PCI¹ (based on data from ACUITY⁹) may also be problematic in the upstream setting. Bivalirudin is not as yet labeled for use outside the cardiac catheterization laboratory, and emergency physicians can't always anticipate the length of the pre-catheterization interval. Furthermore, the CLEAR PLATELETS and CREDO studies demonstrate the liabilities of relying upon a clinical benefit to be

achieved from 300mg of clopidogrel in as little as six hours. In CLEAR PLATELETS, PCI patients given 300 or 600mg of clopidogrel achieved only 20% and 50% platelet inhibition, respectively, at *eight* hours (using 5µmol/L ADP); patients given clopidogrel plus standard-dose eptifibatid were at 100% inhibition by *three* hours. Additionally, higher levels of platelet inhibition resulted in less cardiac biomarker leak after PCI.¹⁰ In CREDO, clinical benefit after a 300mg load of clopidogrel was not reliably achieved until *fifteen* hours after dosing. At times to procedure less than six hours after load, the benefit was the same as for placebo.¹¹ In ACUITY, bivalirudin given with GPI lost some of its safety advantage, but ischemic efficacy trended toward improvement.⁹ Even with the combination of bivalirudin and clopidogrel, additional antiplatelet therapy may be appropriate.

Contemporary registry data from the CRUSADE initiative confirm the utility of GPI therapy in high-risk NSTEMI ACS therapy.⁵ These data also demonstrate the potential for bleeding, an adverse effect of GPI therapy often associated with inappropriately high doses.¹² The small molecule GPIs are excreted through the kidneys, and doses should be adjusted both for creatinine clearance and actual body weight.^{13,14} When this is done, the likelihood of major bleeding with appropriate dosing in contemporary practice significantly diminishes.⁵ One of the primary success stories of the CRUSADE registry is once the problem with excessive dosing of GPIs and anticoagulants was highlighted in institutional reports peer-reviewed presentations, and articles, the incidence of such treatment errors in CRUSADE hospitals precipitously dropped. Appropriate dosing of GPIs may require an accurate body weight and adjustment by estimated creatinine clearance. This estimate, which is also important in dosing anticoagulants, is straightforward and can be made in the ED according to the formula:

$$\frac{(140 - \text{age in years})(\text{weight in kg})}{(72)(\text{serum creatinine in mg/dL})}$$

* The result should be multiplied by 0.85 for female patients.

SUMMARY

Emergency physicians and cardiologists must collaborate in addressing proper patient selection, timing of initiation, dose adjustments for kidney function, and expected management strategy in reaching a sound, consistent, risk-appropriate protocol for antiplatelet therapy in NSTEMI/ACS. Aspirin should be given as soon as possible after ACS is suspected or recognized. Oral antiplatelet therapy with clopidogrel is simple and clearly offers ischemic benefit, but is associated with substantially increased bleeding risk if the patient requires near-term CABG which can't be delayed five days. Small molecule GPIIb/IIIa therapy is reversible and offers ischemic protection when platelets are already activated, but are also associated with bleeding risk. This complication can be minimized with proper dosing based on weight and estimated creatinine clearance. Patients without bleeding risk and who are unlikely to require CABG, though not easily quantified, may benefit from "triple" antiplatelet therapy with ASA, clopidogrel, and GPIIb/IIIa. The use of clopidogrel and bivalirudin together without GPIIb/IIIa has implications both for ischemic outcomes and bleeding concerns if unanticipated CABG is required. This approach may be appropriate in selected patients, particularly those at lower ischemic risk, such as those who do not have elevated cardiac biomarkers.

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