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OBJECTIVES:

1. Participants should be able to understand the pathophysiology of unstable angina/non ST-segment elevation MI (NSTEMI) as it relates to the use of antithrombin agents and platelet inhibitors.
2. Participants should understand the appropriate matching of cardiovascular risk with the invasive versus conservative treatment strategies in NSTEMI.
3. Participants should understand the appropriate application of cardiovascular medications, including antithrombins and platelet inhibitors, in the treatment of NSTEMI, as indicated by the new ACC/AHA guidelines.


INTRODUCTION

The 2002 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Management of Unstable Angina/Non-ST-Segment Elevation Myocardial Infarction (NSTEMI) have finally been revised, updated, and released to the public as of August, 2007.^{1,2} The new ACC/AHA Guidelines incorporate recent clinical trials data and include updated recommendations on treatment strategies and interventions for NSTEMI ACS. Each treatment strategy or pharmacologic intervention is recommended based on its efficacy (Class I effective, IIa and IIb less effective or controversial, and III harmful) and the level of evidence supporting that recommendation (Level A with thousands of patients enrolled in randomized controlled trials, B with less clinical trial evidence, and C based on consensus). The resulting recommendations are a bit more complex than the 2002 version, and include many more options for therapy. They

are also much more “cardiology friendly” with an obvious inclination toward an invasive pathway of treatment.³ The new guidelines force an early decision as to whether an invasive versus conservative treatment pathway is chosen, and provide recommendations for antiplatelet and antithrombin treatments for each of those pathways. This section will focus on the upstream ED-based treatment of NSTEMI ACS, with particular attention to antiplatelet and antithrombin therapies which should be initiated in the ED.

Risk Stratification and Conservative versus Invasive Pathways

The guidelines recommend the early use of risk stratification for all patients with chest pain or other anginal equivalents and presumed NSTEMI ACS (Figure 1). These diagnostic guidelines don't differ significantly from the 2002 version. Similarly, treatment with aspirin 325 mg orally on arrival in addition to anti-ischemic therapy including nitrates, beta blockers, ACE inhibitors has not changed significantly (Figure 2). The results of risk stratification should be used to



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Early Risk Stratification of NSTEMI-ACS				
I	IIa	IIb	III	
B				12-lead ECG (within 10 minutes)
B				Troponin or CK-MB assay • Immediate • Repeated within 8-12 hours of symptoms, if negative
B				Repeat ECG if negative and clinical suspicion is high for ACS
	B			TIMI or PURSUIT risk scoring
		B		BNP for risk assessment
B				Search for non-coronary causes of symptoms

Figure 1: Risk Stratification Tools Recommended by the 2007 ACC/AHA Guidelines for NSTEMI ACS. TIMI = Thrombolysis in Myocardial Infarction; BNP = brain natriuretic peptide.

Hospital Care: Invasive or Conservative				
Anti-Ischemic Therapy				
I	IIa	IIb	III	
C				Continuous O ₂
C				NTG sublingual in ED
B				Nitrates intravenous for pain relief, BP control
B				β-blocker orally <24 hours if not contraindicated
A				ACE inhibitor po <24 hours for patients with LVEF <40 or DM

Figure 2: Early Hospital Care for presumed NSTEMI ACS: Anti-Ischemic Therapy. NTG = nitroglycerin; LVEF = left ventricular ejection fraction; DM = diabetes mellitus.

determine downstream management strategies. Patients at higher risk should undergo an invasive pathway (Figure 3), with upstream antiplatelet and antithrombin therapy prior to planned cardiac catheterization. Lower risk patients should pursue a conservative strategy, with a less aggressive set of antithrombin and antiplatelet recommendations. It's clear from the new guidelines, however, that the treatment of NSTEMI ACS with aggressive antiplatelet and antithrombin agents is strongly encouraged, but flexibility is given for alternative approaches based on physician or patient preference. This recommendation is based on solid data, from many

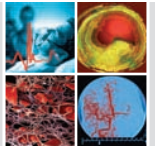
Invasive Strategy Clinical Criteria (Class IA)

- Recurrent chest pain
- Elevated troponin
- ST depression
- Signs of CHF
- Sustained VT
- Hemodynamic instability
- PCI in last month
- High-risk noninvasive testing results
- Prior CABG
- TIMI >3
- LVEF <40%
- Diabetes

Figure 3: Clinical criteria for patients recommended to the invasive pathway for treatment of NSTEMI ACS. TIMI = Thrombolysis in Myocardial Infarction; CHF = congestive heart failure; VT = ventricular tachycardia; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; LVEF = left ventricular ejection fraction.

randomized controlled trials including TACTICS, FRISC II, TRUCS, RITA 3, and VINO, all of which favor an invasive treatment pathway for high risk patients.³⁻⁶ In contrast to these trials, the recent ICTUS trial showed no benefit to an invasive strategy in patients with aggressive medical management for NSTEMI ACS.⁷ It should be noted, however, that even in the ICTUS trial, almost half of the “conservatively” treated patients received revascularization.

Determination of downstream management strategy at the time of initial presentation may be difficult for emergency physicians as well as for their cardiology colleagues. Serial troponins, serial ECGs, observation, and even stress testing may be needed prior to determination of invasive versus conservative strategies. This presents a significant impediment in translating the new ACC/AHA guidelines into clinical practice. The treatment pathways for patients who are “undetermined” with regard to conservative or invasive pathways are not defined, causing confusion and perhaps undertreatment of patients with NSTEMI ACS.



The Invasive Management Pathway:

High risk NSTEMI ACS patients, including those with ECG changes, elevated troponin levels, or elevated TIMI scores are recommended to undergo cardiac angiography within 48 hours (Class IA). Upstream, prior to angiography, Class IA recommended therapies include aspirin (160-325 mg po), an antithrombin agent such as unfractionated heparin (UFH) or enoxaparin (ENOX), and either clopidogrel (300 mg. po) *or* an intravenous glycoprotein IIb/IIIa inhibitor (GPI) (Figure 4).^{8,9} Aspirin and clopidogrel continue to receive their Class IA recommendations carried over from the 2002 guidelines.^{10,11} Clopidogrel's loading dose recommendation remains at 300 mg for medical management pre-cardiac catheterization. Loading doses of 600 mg have been extensively evaluated in cardiac catheterization laboratory trials like ARMYDA 2 and ISAR REACT, but medical management trials of clopidogrel have only utilized the 300 mg loading dose.¹²⁻¹⁴ Similarly, UFH and enoxaparin's upstream recommendation remains Class IA based on many years of experience, and the supporting evidence of the SYNERGY trial, where both UFH and enoxaparin were found to be effective in NSTEMI ACS patients treated with an invasive strategy.¹⁵

Alternatives to UFH/enoxaparin include bivalirudin and fondaparinux (Class IB). Bivalirudin was studied in the ACUITY trial, where moderate to high risk NSTEMI ACS patients were randomized to receive either bivalirudin or UFH/ENOX + GPI upstream prior to catheterization.¹⁶ Bivalirudin was found to be superior in terms of net clinical benefit defined as bleeding plus ischemia, to UFH/ENOX + GPI. Bivalirudin's most notable advantage in this patient population is its reduction in bleeding, especially in the catheterization laboratory, and it should be considered an alternative to UFH/ENOX in patients with high bleeding risk. Fondaparinux, a direct Xa inhibitor, was compared to enoxaparin in the OASIS 5 trial.¹⁷ Fondaparinux was found to be equivalent to ENOX in terms of death, MI, and urgent intervention, but was associated with significantly less bleeding. It's long half-life, contraindication in chronic renal failure, and tendency toward complications in the cardiac catheterization laboratory make it a difficult drug to use in the invasive strategy, therefore utilization in NSTEMI ACS in the United States has been limited.

Glycoprotein inhibitors are considered an alternative to clopidogrel in the upstream invasive strategy.¹⁸⁻²² Given the logistic concerns of upstream clopidogrel for patients who might undergo coronary artery bypass grafting, many practitioners choose not to use clopidogrel prior to cardiac catheterization and subsequent definition of coronary anatomy. The new guidelines allow GPIs to be substituted for clopidogrel as an "or" recommendation in the invasive strategy. It's clear from the guidelines that in the

Initial Invasive Strategy:				
Antiplatelet and Anticoagulant Therapy				
I	IIa	IIb	III	
A				ASA on arrival, clopidogrel if ASA allergic
A				Antithrombin on arrival
A				• UFH or Enoxaparin
B				• Bivalirudin or fondaparinux
A				Prior to angiography, initiate clopidogrel or intravenous GP IIb/IIIa inhibitor
	B			Prior to angiography, both clopidogrel <u>and</u> intravenous GP IIb/IIIa inhibitor with high-risk features, early recurrent ischemic symptoms, elevated troponin

Figure 4: Recommended upstream antiplatelet and antithrombin therapies for patients prior to coronary angiography in the invasive pathway for NSTEMI ACS.

ASA = aspirin; UFH = unfractionated heparin; GP = glycoprotein

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invasive strategy, aspirin alone is not an effective or recommended antiplatelet strategy. Both clopidogrel and small molecule GPIs have been shown to be effective in reducing ischemic events during medical management pre-catheterization. An alternative to upstream GPIs is the combination of bivalirudin/clopidogrel (Class IIaB), based on the ACUTY trial.¹⁶ For patients at highest risk, especially those with elevated troponin levels, recurrent ischemia, or delay to coronary intervention, the guidelines give a Class IIaB recommendation to therapy with both clopidogrel *and* GPIs upstream, prior to coronary angiography. This recommendation is based on studies such as ISAR REACT 2, which demonstrated that in high risk patients, especially those who are troponin positive, a GPI is needed in addition to clopidogrel to assure maximum antiplatelet activity and reduce ischemic endpoints.¹⁴

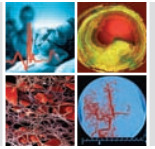
The invasive management pathway recommendations can be a bit confusing, due mostly to the myriad of pharmacotherapeutic options available for upstream treatment pre-cardiac catheterization. Each patient should be viewed individually, and their antiplatelet/antithrombin treatments should be tailored to maximize their individual risk and benefit profiles. For instance, patients in whom ischemic risk is a maximum concern should probably be treated upstream with the antithrombin/clopidogrel/GPI combination, especially if significant delays to cardiac catheterization are anticipated, such as over a weekend. Patients who are at less ischemic risk, but have more bleeding risk should be considered for clopidogrel plus fondaparinux or bivalirudin therapy, with GPIs withheld until the coronary anatomy is defined. Factors to be considered in these decisions include troponin levels, ECG changes, age, gender, diabetes mellitus, creatinine clearance, and anticipated delays to catheterization. It's clear that the new clinical trial results have left the clinician with more options and more opportunity to tailor therapy and maximize outcomes.

The Conservative Management Pathway:

Patients with lower risk for adverse outcomes, negative serum markers, nondiagnostic ECGs, and TIMI scores ≤ 3 are recommended for a conservative treatment pathway, where coronary angiography is not mandated. Patients in this conservative treatment pathway should receive aspirin, clopidogrel, and an antithrombin agent during their hospitalization, all Class IA recommendations (Figure 5). Antithrombin choices include UFH and ENOX (Class IA), and fondaparinux (Class IB, especially in patients with high bleeding risk). Enoxaparin and fondaparinux are preferred over UFH unless CABG is planned in the next 24 hours (Class IIaB). These treatment recommendations for upstream clopidogrel and antithrombins use are stronger (Class IA) than the 2002 guideline recommendations for this group of "intermediate risk" patients. If a conservatively managed patient develops recurrent ischemia, new ECG changes, or other high risk features during their hospitalization, coronary angiography becomes a Class IA recommendation. These patients would then be switched by the clinician to an upstream invasive antithrombin/antiplatelet regimen as outlined above.

Conservative Therapy:				
Initial Anti-thrombotic Therapy				
I	IIa	IIb	III	
A				ASA, clopidogrel on arrival
A				Enoxaparin or UFH
B				Fondaparinux, especially in patients with bleeding risk
	B			Enoxaparin or fondaparinux preferred over UFH unless CABG planned <24 hours

Figure 5: Recommended initial antiplatelet and antithrombin therapies for patients relegated to the conservative treatment pathway for NSTEMI ACS. ASA = aspirin; UFH = unfractionated heparin; CABG = coronary artery bypass grafting.

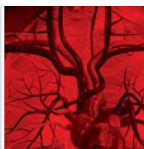


SUMMARY

The ramifications of these new guidelines remain unclear. The guidelines are definitely more “invasive friendly” than the 2002 guidelines, recommending an invasive pathway for a large portion of patients with possible NSTEMI ACS. They link antiplatelet and antithrombin treatments to invasive versus conservative pathways rather than patient-specific risk factors, which may seem confusing and counter-intuitive to emergency physicians. They also recommend a much wider range of treatment options than the prior guidelines. Emergency physicians must be fluent in the language of these guidelines and familiar with their recommendations to assure the best care for their patients with NSTEMI ACS. The new guidelines publication should provide the impetus locally for emergency physicians to meet with their cardiology and internal medicine colleagues to review or revise their NSTEMI ACS pathways. With the many options available, and the need for a tailored approach to each patient, communication between these specialties is imperative to assure the best outcomes for patients.

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