

VA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF ISCHEMIC HEART DISEASE MODULE B SUMMARY

DEFINITE/PROBABLE NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME (ACS) (UNSTABLE ANGINA/NON-ST-SEGMENT ELEVATION MI [NSTEMI])

KEY ELEMENTS

Patients with ACS (UA/NSTEMI) are at high risk for MI or death and are candidates for further aggressive diagnostic and therapeutic interventions that should include:

- Ensure emergency intervention
- Admission to an intensive- or intermediate-care unit
- Immediate cardiac rhythm monitoring
- Therapy directed at stabilizing ischemia (beta-blocker, NTG)
- Risk-stratification to determine prognosis and guide treatment. Assessment for risk of death or MI based on symptoms, level of biomarker (troponin, CK) and ECG
- Antithrombotic therapy tailored to individual risk that should include:
 - ASA
 - Heparin (UFH) or low molecular weight heparin (LMWH)
 - Clopidogrel if intervention is not planned

* UA/NSTEMI patients should *not* receive reperfusion fibrinolytic therapy

High-risk patients are candidates for further aggressive diagnostic and therapeutic interventions including

- Early (i.e., <48 hour) coronary angiography with subsequent revascularization if indicated.
- GP IIb/IIIa antagonist in addition to aspirin, heparin and clopidogrel in patients with continuing ischemia or with other high-risk features.
- GP IIb/IIIa antagonist may also be used in patients in whom an early invasive strategy is planned. GP IIb/IIIa can be administered just prior to PCI.

In patients not undergoing angiography:

Perform non-invasive evaluation (cardiac stress test and left ventricular [LV] function), and:

If LV function is compromised:

- Ensure pharmacologic therapy for ischemia, angina, and congestive heart failure
- Initiate ACE inhibitor therapy
- Consider referral to cardiology

All patients with suspected, but unproven, unstable angina should have further diagnostic testing to determine the accuracy of the diagnosis.

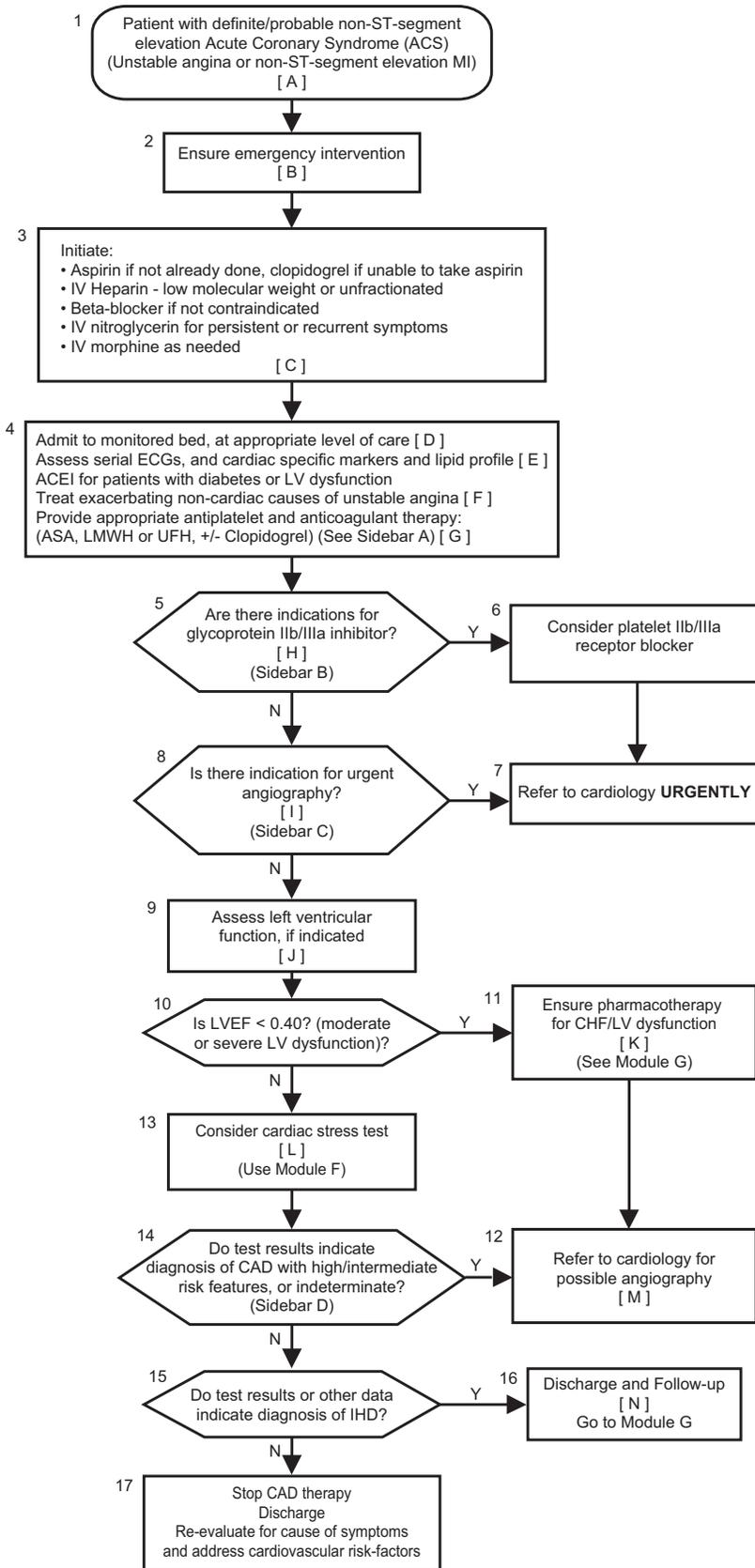
Discharge patient to home with appropriate follow-up.

EXECUTIVE SUMMARY

Unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI) are related clinical conditions that share a common pathophysiological basis. Both, acute myocardial infarction (AMI) with ST-segment elevation or bundle branch block (BBB) and UA and NSTEMI are referred to as acute coronary syndromes (ACS). The initial management of patients presenting with non-ST-segment elevation-ACS (NSTEMI-ACS) is identical to the approach for myocardial infarction (MI) with ST-segment elevation or left BBB. Patients with ACS are at high risk for MI or death and should be admitted to an intensive- or intermediate-care unit and receive immediate cardiac rhythm monitoring and medical therapy directed at stabilizing ischemia. However, UA/NSTEMI patients should not receive reperfusion fibrinolytic therapy. Patients whose clinical presentation suggests a high-risk for death and/or MI are candidates for further aggressive diagnostic and therapeutic interventions including glycoprotein IIb/IIIa receptor inhibitors and early (i.e., <48 hour) coronary angiography with subsequent revascularization if indicated. If left ventricular function (LV) is compromised, congestive heart failure/left ventricular dysfunction therapy should be initiated.

All patients with suspected UA/NSTEMI should be risk-stratified to determine their prognosis and guide their treatment. Patients, who do not have clinical findings that suggest either intermediate or high short-term risk of death or MI, should also be monitored. Monitoring of these patients can be performed either in an inpatient setting or in a specialized chest pain evaluation center, where they do not require initial medical treatment other than aspirin and sublingual nitroglycerin (NTG). All patients with suspected, but unproven, unstable angina should have further diagnostic testing to determine the accuracy of the diagnosis.

MANAGEMENT OF ISCHEMIC HEART DISEASE
Module B: Definite/Probable Acute Coronary Syndrome
(Unstable Angina or Non-ST-Segment Elevation MI)



B

Sidebar A (Box 4) - Antiplatelet and Anticoagulant Therapy

High Risk (Recurrent ischemia or other high risk features)	Moderate Risk (Likely/definite ACS)
Aspirin Clopidogrel* LMWH or UFH GP IIb/IIIa inhibitor	Aspirin Clopidogrel* LMWH or UFH

* Unless angiography is planned

Sidebar B (Box 5) - Indications for IIb/IIIa and Early Invasive Therapy in High Risk Patients

- a. Recurrent angina/ischemia despite therapy
- b. Elevated troponin (TnT or TnI)
- c. New or presumably new ST-segment depression

Sidebar C (Box 8) - Indications for Angiography in Intermediate Risk Patients

- d. New/recurrent angina/ischemia
- e. High risk findings on non-invasive testing
- f. Depressed left ventricular LV systolic function (e.g., ejection fraction (EF) <0.40)
- g. Hemodynamic instability (e.g., hypotension)
- h. Sustained ventricular tachycardia
- i. Previous PCI within 6 months
- j. Prior CABG

Consider Referral to Cardiology

- Prior myocardial infarction
- New T-wave inversion (>0.2 mV)
- Indeterminate troponin

Sidebar D (Box 14) - Cardiac Stress Test

High-Risk Findings

- Duke treadmill score less than or equal to -11 (estimated annual mortality >3%)
- Large stress-induced perfusion defect
- Stress-induced, multiple perfusion defects of moderate size
- Large fixed perfusion defect with LV dilation or increased lung uptake (thallium 201)
- Stress-induced, moderate perfusion defect with LV dilation or increased lung uptake (thallium-201)
- Echocardiographic wall motion abnormality involving >2 segments at ≤10 mg/kg/min dobutamine or HR <120/min

Intermediate-Risk Findings

- Duke treadmill score (greater than -11 and less than 5) (estimated annual mortality 1-3%)
- Moderate stress-induced perfusion defect without LV dilation or increased lung uptake
- Limited stress echocardiographic ischemia with wall motion abnormality involving ≤2 segments at higher doses of dobutamine (>10 mg/kg/min dobutamine)

MODULE B: DEFINITE/PROBABLE NON-ST ELEVATION ACUTE CORONARY SYNDROME (ACS) UNSTABLE ANGINA/NON-ST-SEGMENT ELEVATION MI

ANNOTATIONS

A. Patient with Definite/Probable Non-ST Elevation Acute Coronary Syndrome (Unstable Angina Or Non-ST-Segment Elevation MI)

Module B presents guidelines for the diagnosis and management of UA and the closely related condition, NSTEMI. UA/NSTEMI, together with ST-segment elevation myocardial infarction (STEMI), make up the acute coronary syndromes (ACS). Patients presenting with UA/NSTEMI are considered to have non-ST elevation ACS (NSTE-ACS)

UA is commonly considered to have three presentations: (1) rest angina; (2) new onset of severe angina, defined as at least Class III severity by the Canadian Cardiovascular Society (CCS) classification; and (3) increasing angina to at least CCS Class III severity. The hallmark of NSTEMI is an elevation of markers of myocardial injury in the blood stream (e.g., troponin I, troponin T, or CK-MB). Because the pathogenesis and responses to therapy of UA and NSTEMI are similar, they are considered together here, as well as in the American College of Cardiology and the American Heart Association (ACC/AHA) Guidelines for the Management of Patients with Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction (ACC/AHA UA - NSTEMI, 2002).

Patients presenting with ST-segment elevation myocardial infarction (STEMI) or MI with left bundle branch block (LBBB) should be managed using Module A of this guideline. The distinction between ST-segment

elevation myocardial infarction and non-ST elevation ACS is important, because immediate reperfusion, with either primary angioplasty or thrombolytic agents, has been shown to reduce mortality in patients with STEMI or LBBB MI, whereas the use of fibrinolytic agents may be potentially harmful in UA and NSTEMI.

Patients with Ischemic Heart Disease (IHD) who do not meet the criteria for ACS (as defined in the CORE Module) can be managed using Module C: Management of Stable Angina or Module G: Follow-up and Secondary Prevention.

Risk stratification of patients with NSTE-ACS

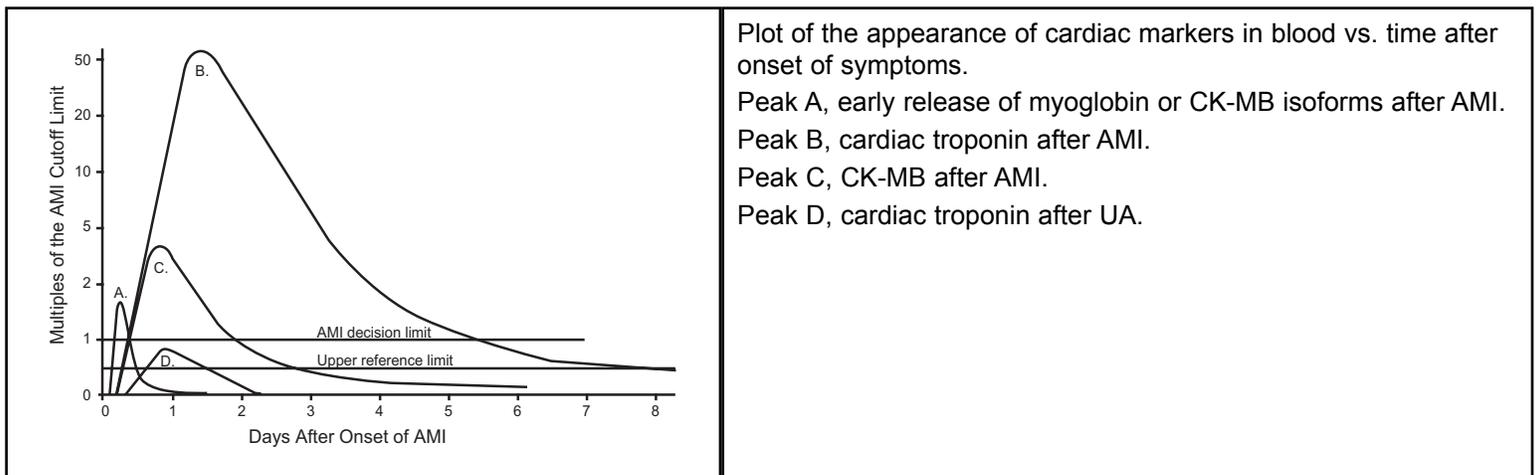
The initial management of patients with NSTE-ACS is determined by the predicted risk for adverse outcomes (e.g., death or MI). The degree of risk for a subsequent adverse cardiac event in patients with UA or NSTEMI can, in a large part, be assessed by determining presenting clinical features, including frequency and duration of symptoms, age, signs of hemodynamic instability or heart failure, elevated serum markers, and electrocardiogram (ECG) findings. Table 1 can be used to identify patients at high- or intermediate-risk for early adverse outcomes.

Table 1 is meant to offer general guidance and illustration, rather than rigid algorithm. Estimation of the short-term risks of death and nonfatal cardiac ischemic events in UA is a complex multivariable problem that cannot be fully specified in a table.

Short-Term Risk of Death or Nonfatal MI in Patients With UA (ACC/AHA UA - NSTEMI, 2000)

	High Risk	Intermediate Risk	Low Risk
Feature	At least 1 of the following features must be present.	No high-risk feature, but one of the following features must be present.	No high- or intermediate- risk feature, but any of the following features may be present.
History	<ul style="list-style-type: none"> Accelerating tempo of ischemic symptoms in the preceding 48 hours 	<ul style="list-style-type: none"> Prior MI, peripheral or cerebrovascular disease, or coronary artery bypass graft (CABG) Prior aspirin use 	
Character of Pain	<ul style="list-style-type: none"> Prolonged ongoing rest pain (>20 minutes) 	<ul style="list-style-type: none"> Prolonged rest angina (>20 minutes), now resolved, with moderate or high likelihood of coronary artery disease (CAD) (see Table 6, Core Module) Rest angina (<20 minutes or relieved with rest or sublingual NTG) 	<ul style="list-style-type: none"> New-onset CCS Class III or IV angina in the past 2 weeks without prolonged rest pain (>20 minutes), but with moderate or high likelihood of CAD (see Table 6, Core Module)
Clinical Findings	<ul style="list-style-type: none"> Pulmonary edema, most likely related to ischemia New or worsening mitral regurgitation (MR) murmur S3 or new/worsening rales Hypotension, bradycardia, or tachycardia Age >75 years 	<ul style="list-style-type: none"> Age >70 years 	
ECG Findings	<ul style="list-style-type: none"> Transient ST-segment changes >0.05 mV in association with rest angina BBB, new or presumed new Sustained ventricular tachycardia 	<ul style="list-style-type: none"> T-wave inversions >0.2 mV Pathological Q-waves 	<ul style="list-style-type: none"> Normal or unchanged ECG during an episode of chest discomfort
Cardiac Markers	<ul style="list-style-type: none"> Elevated (e.g., TnT or TnI >0.1 ng/mL) 	<ul style="list-style-type: none"> Slightly elevated (e.g., TnT >0.01, but <0.1 ng/mL) 	<ul style="list-style-type: none"> Normal

FIGURE 1: CARDIAC MARKERS IN BLOOD VS. TIME AFTER ONSET OF SYMPTOMS*



*Data are plotted on a relative scale, where 1.0 is set at the AMI cutoff concentration. (Adapted from ACC/AHA 2002)

The optimal management strategy for patients with ACS is the topic of very active ongoing investigation. The recommendations contained within this module closely correspond to the published guidelines of the American College of Cardiology and the American Heart Association (ACC/AHA UA - NSTEMI, 2002).

B. ENSURE EMERGENCY INTERVENTIONS

Institute specific interventions that are necessary early in the evaluation and treatment of AMI and UA.

1. Oxygen (O₂)

Supplemental oxygen should be administered to all patients with respiratory distress, those with cyanosis or those with documented desaturation. Oxygen should start on initial presentation and during the first 2 to 3 hours and continued if necessary to maintain oxygen saturations of at least 90%. Oxygen may be considered for all patients with suspected ACS. Because oxygen can actually cause systemic vasoconstriction, continued administration should be reassessed for uncomplicated patients. CO₂ retention is not usually a concern with low flow nasal O₂, even in patients with severe chronic obstructive pulmonary disease (COPD).

2. Aspirin:

- All patients should chew non-coated aspirin, 160 mg to 325 mg, within 10 minutes of presentation to accelerate absorption.
- If a patient is unable to take aspirin by mouth because of nausea, vomiting, or other gastrointestinal disorders, 325 mg may be given as a suppository.
- Patients should be given aspirin, even if they are receiving anticoagulation (e.g., warfarin) or antiplatelet (e.g., aspirin or clopidogrel) at the time of presentation.
- Contraindications to aspirin include a documented allergy to salicylates, active bleeding, or active peptic ulcer disease.
- Subsequent aspirin dose of 81-325 mg per day should be given for chronic therapy. Chronic therapy with doses above 81 mg/day is associated with increased bleeding risk without incremental benefit.
- Patients who have an allergy to aspirin and no contraindication to antiplatelet therapy should be given clopidogrel 300 mg loading dose followed by 75 mg daily for at least a month.

3. 12-Lead ECG

A 12-lead ECG is an essential component of the evaluation of the patient with known or suspected ACS. For patients with ongoing symptoms, an urgent ECG should be obtained and interpreted within the first 10 minutes of the initial evaluation and followed up with 2 to 3 serial ECGs in the first 24 hours. A right-sided ECG should be performed if a standard ECG suggests an inferior wall MI.

4. Intravenous (IV) Access:

Intravenous access for the delivery of fluids and drugs should be obtained. While the IV is being started, blood samples for cardiac enzymes/markers (i.e., troponin, CK, and CK-MB), lipid profile, complete blood count (CBC), electrolytes, renal function, international normalized ratio (INR), and activated partial thromboplastin time (APTT) can be obtained. Immediate treatment of ACS should not be delayed by the results from these tests.

5. Sublingual nitroglycerin:

NTG should be given for ongoing chest pain or other ischemic symptoms, unless the patient is hypotensive or bradycardic, has taken sildenafil within the last 24 hours, or there is a strong suspicion of right ventricular infarction.

6. Cardiac monitor:

Patients with ACS, especially with suspected MI, should be placed on continuous cardiac monitoring as soon as possible. Potentially lethal ventricular arrhythmias can occur within seconds to hours from the onset of coronary ischemia, and monitoring will allow their immediate detection and treatment.

7. Adequate analgesia:

Adequate analgesia should be given promptly; morphine sulfate (IV) is effective, decreases the often excess sympathetic tone, and is a pulmonary vasodilator. Some patients may require a large dose. The patient should be monitored for hypotension and respiratory depression, but these are less likely in the anxious, hyperadrenergic patient who is kept supine.

8. Advanced cardiac life support (ACLS, 2000):

ACLS algorithm should be applied, as indicated.

9. Chest X-ray:

A chest x-ray should be obtained in the ED, particularly if there is concern about aortic dissection; however, treatment of hypotension, low cardiac output, arrhythmias, etc., usually has higher priority.

10. Transportation:

In some settings within the DoD or the VA systems, the patient will need to be urgently transported to a setting where an appropriate level of monitoring, evaluation, and treatment is available.

C. INITIATE:

- **Aspirin 162 mg to 325 mg, If Not Already Given (See Annotation B and Core Module)**
- **Clopidogrel 75 mg if hypersensitivity to aspirin or major GI intolerance**
- **IV Unfractionated Heparin (UFH) Or Subcutaneous Low Molecular Weight Heparin (LMWH)**
- **Beta-blocker if not contraindicated**
- **IV nitroglycerin for persistent or recurrent symptoms**
- **IV morphine as needed**

The goals of initial therapy include symptom relief and the prevention of subsequent MI or death. Antiplatelet therapy is a cornerstone in the management of UA/NSTEMI. Aspirin therapy should be initiated as soon as possible after presentation and continued indefinitely; Clopidogrel should be administered to patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance.

For patients with NSTEMI-ACS in whom an interventional approach has been precluded, clopidogrel should be added to aspirin as soon as possible and administered for at least 1 month and for up to 9 months.

Fibrinolytic therapy should not be given unless ST-segment elevation or LBBB MI are present. (See module A: Acute MI, ST-segment elevation MI).

Beta-blockers should be used in all patients with UA/NSTEMI unless contraindicated, with initial IV route, followed by oral dosing.

Aspirin (ASA)

Randomized trials have demonstrated that ASA reduces the risk of MI and vascular death in patients with unstable coronary disease

A dose as low as 75 mg has been shown to be effective in UA, and the ACC/AHA consensus suggests 75 mg to 325 mg daily after an initial dose of 162-325 mg. (Gibbons 2002).

Clopidogrel

There is strong evidence to support the addition of clopidogrel to ASA in the management of patients with UA and NSTEMI. Clopidogrel appears to be especially useful on admission in hospitals that do not have a routine policy of early invasive procedures and in patients who are not candidates or who do not wish to be considered for revascularization. In patients who undergo revascularization, clopidogrel should be started in conjunction with the procedure. Clopidogrel should be withheld in patients whom elective CABG is planned, for 5 to 7 days. The optimal duration of therapy with clopidogrel has not been determined. The major benefits were observed at 30 days, with small additional benefits observed over the subsequent treatment period out to one year.

IV Unfractionated Heparin

Several small randomized placebo controlled trials suggest that intravenous unfractionated heparin (UFH), in combination with aspirin, reduces the short-term likelihood (i.e., 2 to 7 days) of adverse clinical events in unstable coronary disease. The addition of UFH to ASA increases major bleeding from 0.4% (ASA alone) to 1.5% (ASA plus UFH). The optimal duration of therapy is unclear, but 2 to 5 days of treatment after stabilization is reasonable.

Enoxaparin

Enoxaparin is preferable to UFH as an anticoagulant in patients with UA/NSTEMI, in the absence of renal failure and unless CABG is planned within 24 hours.

Enoxaparin should not be used in patients with known creatinine clearance of less than approximately 30 cc/minute. Other low molecular weight heparin preparations have not yet demonstrated the degree of benefit observed with enoxaparin in the treatment of UA/NSTEMI.

Beta Blockers

Unless contraindicated, beta-blockers should be used in all patients with UA/NSTEMI, with initial IV route, followed by oral dosing, being preferable in patients with ongoing symptoms.

Beta-blockers should be continued indefinitely unless a contraindication arises. Contraindications to the use of beta-adrenergic blocking agents include: patients with second- or third- degree heart block (without a pacemaker), severe heart failure, severe reactive airway disease, hypotension (i.e., <90 mm Hg), and bradycardia (i.e., <50 bpm).

Reactive Airway Disease or COPD should not preclude the use of beta-blockers; however, when there is concern, an ultra short acting or short acting agent could be used.

Patients with diabetes, once considered a relative contraindication to beta-blockers, appear to derive as much, or more, mortality benefit from treatment with a beta-blocker following myocardial infarction as non-diabetics and without increased risk of hospitalization for diabetic complications.

Calcium Antagonists

In patients with ACS, for whom beta-blockers and nitrates are either unsuccessfully controlling ischemia or are contraindicated, calcium channel blockers may be considered in the absence of evidence of heart failure. The calcium antagonists verapamil and diltiazem have proven efficacy for symptomatic relief in patients with ACS and more limited evidence for a reduction in re-infarction. Cautions for the use of diltiazem and verapamil are similar to those listed for beta-blockers, with the exception that calcium antagonists may be safely used in patients with asthma.

ACE Inhibitors

ACE inhibitors should be given to all patients with LV systolic dysfunction, CHF or diabetes once the patient is hemodynamically stable and in the absence of recognized contraindications. ACE inhibitors may be considered in other patients with ACS especially if hypertension persists despite treatment with NTG and beta-blockers.

Nitroglycerin

Nitroglycerin (NTG) as a sublingual tablet or buccal spray should be given to the patient on presentation, as recommended in the Core Module, unless the patient has used sildenafil (Viagra) within the preceding 24 hours. If ischemic symptoms persist following three doses of NTG tablets or spray given five minutes apart and the initiation of an intravenous beta-adrenergic blocking agent, IV NTG should be initiated.

Morphine Sulphate

Intravenous morphine sulphate (1 mg to 5 mg) is commonly used for pain and anxiety relief in patients with ACS who do not achieve adequate symptomatic relief with antianginal medications. The rationale for its use is based on the perception that ongoing pain and/or anxiety provokes increases in blood pressure and heart rate, which in turn, increase myocardial oxygen demands in the setting of reduced supply. The principal precautions for its use in this setting are a known history of intolerance and hypotension.

Fibrinolytic therapy should *not* be given to patient with UA/NSTEMI unless ST-segment elevation/LBBB MI or a true posterior MI develops

D. ADMIT TO MONITORED BED, AT APPROPRIATE LEVEL OF CARE

Patients with intermediate- or high-risk of death and/or MI (see Table 1) should be admitted to an inpatient unit with cardiac monitoring capabilities to ensure for monitoring of the ECG and rapid availability of emergency medical care (e.g., ACLS) as well as, personnel trained in the recognition and management of cardiac arrhythmias..

E. ASSESS SERIAL ECGs, CARDIAC-SPECIFIC MARKERS AND LIPID PROFILE

- **Serial ECGs** are vital to diagnosis and prognosis of patient with ACS. This has implications for the length of unit and hospital stay, and further adds to risk assessment. Two to three serial ECGs should be performed within the first 24 hours. Serial ECGs should be performed for any clinical change, probably after any transfer and subsequently at least daily and especially on the day of discharge.

- **Cardiac biomarkers** should be performed in all patients with suspected ACS. A cardiac-specific troponin is preferred and should be measured in all patients. CK-MB by mass assay may have added value for early diagnosis. For patients with normal cardiac markers within 6 hours of symptom onset, another sample should be obtained over the subsequent 6-12 hours. In patients with elevated cardiac markers, repeat testing should be performed every 8 hours until they have peaked.
- **A lipid profile** should be performed as soon as possible after admission, within the first 24 hours.

Biochemical Cardiac-Markers for the Evaluation and Management of Patients Suspected of Having an ACS, but Without ST-Segment Elevation on 12-Lead ECG (ACC/AHA UA - NSTEMI, 2000)

Marker	Advantages	Disadvantages	Clinical Recommendations
CK-MB	<ul style="list-style-type: none"> • Rapid, cost-efficient, accurate assays • Detection of early reinfarction 	<ul style="list-style-type: none"> • Loss of specificity in the setting of skeletal muscle disease or injury, including surgery • Low sensitivity during very early MI (i.e., <6 hours after onset of symptoms) or later after onset of symptoms (i.e., >36 hours) and for minor myocardial damage (detectable by troponins) 	<ul style="list-style-type: none"> • Prior standard and still acceptable diagnostic test in most clinical circumstances
CK-MB Isoforms	<ul style="list-style-type: none"> • Early detection of MI 	<ul style="list-style-type: none"> • Specificity profile is similar to CK-MB • Current assays require special expertise 	<ul style="list-style-type: none"> • Useful for extremely early (i.e., 3 to 6 hours after onset of symptoms) detection of MI in centers with demonstrated familiarity with the assay technique
Myoglobin	<ul style="list-style-type: none"> • High sensitivity • Early detection of MI • Detection of reperfusion • Most useful in ruling out MI 	<ul style="list-style-type: none"> • Very low specificity in the setting of skeletal muscle injury or disease • Rapid return to normal range limits sensitivity, for later presentations 	<ul style="list-style-type: none"> • Should not be used as the only diagnostic marker, because of a lack of cardiac specificity • A more convenient early marker than CK-MB isoforms because of greater availability of assays for myoglobin. Rapid-release kinetics make myoglobin useful for the non-invasive monitoring of reperfusion in patients with established MI.
Cardiac Troponins	<ul style="list-style-type: none"> • Powerful tool for risk stratification • Greater sensitivity and specificity than CK-MB • Detection of recent MI up to 2 weeks after onset • Useful for the selection of therapy • Detection of reperfusion 	<ul style="list-style-type: none"> • Low sensitivity in very early phase of MI (i.e., <6 hours after onset of symptoms) and requires a repeat measurement at 8 to 12 hours, if negative • Limited ability to detect the late minor reinfarction 	<ul style="list-style-type: none"> • Useful as a single test to efficiently diagnose NSTEMI (including minor myocardial damage), with serial measurements; clinicians should familiarize themselves with diagnostic "cutoffs" used in their local hospital laboratory • Data on diagnostic performance and potential therapeutic implications are increasingly available from clinical trials

F. TREAT EXACERBATING NON-CARDIAC CAUSES OF UNSTABLE ANGINA

Several conditions may provoke or exacerbate angina and ischemia even though the existing coronary disease is not otherwise significant. In particular, conditions that increase oxygen demand or decrease oxygen supply may provoke ischemic symptoms in patients who otherwise would not have symptoms, if based exclusively on atherosclerotic lesions.

**Table 3. Conditions and Medications Provoking or Exacerbating Ischemia
(adapted from the ACC/AHA Stable Angina guidelines, 2003)**

INCREASED OXYGEN DEMAND	DECREASED OXYGEN SUPPLY
<p>Noncardiac</p> <ul style="list-style-type: none"> • Hyperthermia • Hyperthyroidism • Sympathomimetic toxicity (e.g., cocaine use) • Hypertension • Anxiety • Arteriovenous fistulae <p>Cardiac</p> <ul style="list-style-type: none"> • Hypertrophic cardiomyopathy • Aortic stenosis • Dilated cardiomyopathy • Tachycardia <ul style="list-style-type: none"> - Ventricular - Supraventricular <p>Medications</p> <ul style="list-style-type: none"> • Vasodilators • Excessive thyroid replacement 	<p>Noncardiac</p> <ul style="list-style-type: none"> • Anemia • Hypoxemia <ul style="list-style-type: none"> - Pneumonia - Asthma - Chronic obstructive pulmonary disease - Pulmonary hypertension - Interstitial pulmonary fibrosis - Obstructive sleep apnea • Sickle cell disease • Sympathomimetic toxicity (e.g., cocaine use) • Hyperviscosity <ul style="list-style-type: none"> - Polycythemia - Leukemia - Thrombocytosis - Hypergammaglobulinemia <p>Cardiac</p> <ul style="list-style-type: none"> • Aortic stenosis • Hypertrophic cardiomyopathy <p>Medications</p> <ul style="list-style-type: none"> • Vasoconstrictors

G. PROVIDE APPROPRIATE ANTIPLATELET AND ANTICOAGULANT THERAPY

Provide antithrombotic therapy to modify the disease process and its progression to death, MI, or recurrent MI

Patients with NSTEMI-ACS who are at short-term intermediate- or high-risk of death or MI should be given appropriate antiplatelet therapy. The specific antiplatelet therapy recommended depends on whether the patient is to undergo prompt revascularization and whether the revascularization is via percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG).

A combination of ASA, heparin, and a platelet GP IIb/IIIa receptor antagonist represents the most comprehensive therapy. The intensity of treatment should be tailored to individual risk. Triple antithrombotic treatment (a GP IIb/IIIa inhibitor, in addition to aspirin and heparin or low molecular weight heparin) should be used in patients with continuing ischemia or with other high-risk features and in patients in whom an early invasive strategy is planned. (see Table 4) The GP IIb/IIIa antagonist may also be administered just prior to PCI. If intervention is not planned, clopidogrel should be added to aspirin, heparin and GP IIb/IIIa.

Table 4: Antiplatelet and Anticoagulant Therapy

HIGH RISK ACS Continuing Ischemia or Other High-Risk Features			MODERATE RISK Likely/definite ACS	LOW RISK Possible ACS
No Planned Intervention	Planned Intervention			
		PCI□	CABG□	
Aspirin	Aspirin	Aspirin	Aspirin	Aspirin
Clopidogrel	—	—	Clopidogrel	Clopidogrel
LMWH or UFH	LMWH or UFH	UFH	LMWH or UFH	—
Platelet GP IIb/IIIa antagonist: Eptifibatide Tirofiban	Platelet GP IIb/IIIa antagonist: Abciximab Eptifibatide	Platelet GP IIb/IIIa antagonist: Eptifibatide Tirofiban	—	—

If LMWH is used during the period of initial stabilization, the dose can be withheld on the morning of the procedure; and if an intervention is required and more than 8 hours has elapsed since the last dose of LMWH, UFH can be used for PCI according to usual practice patterns. Because the anticoagulant effect of UFH can be more readily reversed than that of LMWH, UFH is preferred in patients likely to undergo CABG within 24 h. **Table 5** shows the recommended doses of the various agents.

Table 5: Antiplatelet and Anticoagulant Agents

Aspirin	160 mg to 325 mg. No trial has directly compared the efficacy of different doses of ASA in patients who present with UA/NSTEMI. However, trials in secondary prevention of stroke, MI, death, and graft occlusion have not shown an added benefit for ASA doses of greater than 80 and 160 mg per day but have shown a higher risk of bleeding.
Clopidogrel	Loading dose of 300 mg followed by 75 mg daily. In patients in whom an early noninterventional approach is planned, clopidogrel should be added to ASA as soon as possible on admission and administered for at least 1 month and for up to 9 months
Enoxaparin	Enoxaparin is given as 1 mg/kg sq bid. A bolus of enoxaparin 30 mg IV may be given initially. Enoxaparin is preferable to UFH as an anticoagulant in patients with UA/NSTEMI, in the absence of renal failure and unless CABG is planned within 24 hours.
UFH	Because the anticoagulant effect of UFH can be more readily reversed than that of LMWH, UFH is preferred in patients likely to undergo CABG within 24 h. UFH is also preferred in patients with renal failure.
Abciximab	Abciximab is bolused at 0.25 mg/kg, then infused at 0.125 mcg/kg/min (maximum of 10 mcg/min) for 18 to 24 hours, or 12 hours post-PCI.
Eptifibatide	Eptifibatide is bolused at 180 mcg/kg (maximum 22.6 mg) and then infused at 2 mcg/kg/min (maximum of 15mg/hr) for up to 72 hours. If a PCI is performed, the infusion is decreased to 0.5 mcg/kg/min and continued for 20 to 24 hours post-procedure. If serum creatinine is ≥ 2.0 , but < 4.0 mg/dL, the bolus should be reduced to 135 mcg/kg and the infusion to 0.5 mcg/kg/min. If the serum creatinine is ≥ 4.0 , this agent should not be used.
Tirofiban	Tirofiban is given at 0.4 mcg/kg/min for 30 minutes, then 0.1 mcg/kg/min for 48 to 96 hours, or 12 to 24 hours post-PCI.

H. ARE THERE INDICATIONS FOR GLYCOPROTEIN IIb/IIIa RECEPTOR ANTAGONISTS ?

GP IIb/IIIa receptor antagonists are indicated in all patients in whom an invasive management strategy is followed as well as patients being managed non-invasively with one or more high-risk features. ACS patients with one or more of the following high-risk features may benefit from the addition of a Glycoprotein IIb/IIIa receptor antagonist:

- 1) Patients with elevated serum troponin
- 2) New or presumably new ST-segment depression ≥ 1.0 mm in two or more contiguous leads.
- 3) Patients with recurrent angina or other ischemic symptoms despite initial medical therapy
- 4) Other high risk features (see table 1).

I. IS THERE INDICATION FOR URGENT ANGIOGRAPHY?

An early invasive strategy is recommended in patients with UA/NSTEMI who present with any of the following high-risk indicators:

- Patients with recurrent angina/ischemia at rest or with low-level activities, despite intensive anti-ischemic therapy
- Patient with elevated cardiac markers (TnI or TnT) and no contraindications to revascularization
- Patients who present with new or presumably new ST-segment depression
- Recurrent angina/ischemia with CHF symptoms, an S3 gallop, pulmonary edema, worsening rales, or new or worsening MR
- High risk findings on non-invasive stress testing
- Depressed LV systolic function (e.g., EF <0.40 on a non-invasive study)
- Hemodynamic instability
- Sustained ventricular tachycardia
- Previous PCI within 6 months
- Prior CABG

Many cardiologists also recommend an early invasive strategy for the following subgroups of patients

- Patients having repeated presentations with UA/NSTEMI despite therapy even in the absence of evidence of ongoing ischemia or high risk
- Patients with prior MI
- Patient with indeterminate biomarkers elevation
- New or presumed new ischemic T wave inversion (>0.2 mV)
- Ongoing ischemic symptoms or signs refractory to appropriate medical therapy.

Invasive strategy should be *avoided* if:

- Risks of the procedure are not likely to outweigh the benefits (life expectancy)
- Patients would not consent to revascularization regardless of the findings
- Precluded by other comorbidity (e.g., active GI bleeding)

In the absence of above findings, most cardiologists prefer an invasive strategy. RCT data suggest that medical therapy be continued until invasive therapy is available. It appears that a modern invasive strategy, preceded by modern antiischemic and antithrombotic medication, in high-risk patients with unstable coronary artery disease reduces death, myocardial infarction, symptoms, and readmissions compared to a conservative strategy.

In the early conservative strategy, coronary angiography is reserved for patients with evidence of recurrent ischemia (angina at rest or with minimal activity or dynamic ST-segment changes) or a strongly positive stress test despite vigorous medical therapy. In the *early invasive strategy*, patients without clinically obvious contraindications to coronary revascularization are routinely recommended for coronary angiography and angiographically directed revascularization, if possible

Coronary arteriography *should not* be performed in patients with extensive comorbidities (e.g., liver or pulmonary failure or cancer) that are likely to make the risks of revascularization outweigh the benefits (unless clarification of the correct diagnosis by cardiac catheterization is believed to be necessary). Similarly, coronary arteriography *should not* be performed in patients who will not consent to revascularization, regardless of the findings.

If patients are stable, risk stratification can continue electively with assessment of systolic function. If, at any time, previously stabilized patients in this module become unstable again, they will return to this box in the algorithm.

J. ASSESS LEFT VENTRICULAR FUNCTION, IF INDICATED

LV systolic function may be assessed by contrast angiography at cardiac catheterization, two-dimensional cardiac ultrasound or radionuclide ventriculography. The relative advantages and disadvantages of cardiac ultrasound versus radionuclide ventriculography are presented in Table 6.

Test	Advantages	Disadvantages
Echocardiogram	<ul style="list-style-type: none">• Permits concomitant assessment of valvular disease, ventricular hypertrophy and left atrial size• Can detect pericardial effusion and LV thrombus• Usually less expensive and more widely available than radionuclide studies	<ul style="list-style-type: none">• Provides only semi-quantitative estimate of EF• Technically inadequate study in as many as 18% of patients and particularly difficult in patients with emphysema
Radionuclide ventriculography	<ul style="list-style-type: none">• More precise, reliable, and quantitative measurement of ejection fraction, compared to echocardiography• Better assessment of right ventricular function	<ul style="list-style-type: none">• Limited assessment of valvular function and ventricular hypertrophy• Requires venipuncture and radiation exposure• Should generally not be used with patients with irregular heart rhythm

Adapted from AHCPR Heart Failure Clinical Practice Guideline, 1995

If the patient, otherwise, does not have an indication for prompt left heart catheterization and LVEF assessment is not available in the hospital, this test can also be performed as an outpatient. Of note, Silver et al., (1994) developed a clinical rule to predict LVEF ≥ 0.40 , with a positive predictive value of 98% in those patients who have ALL of the following characteristics:

- Interpretive ECG (without LBBB, ventricular pacing, or LV with strain pattern)
- No prior Q-wave MI
- No history of CHF
- Index MI which is not a Q-wave anterior infarction

K. ENSURE PHARMACOTHERAPY FOR CONGESTIVE HEART FAILURE (CHF)/LV DYSFUNCTION

Beta-Blockers

In patients with moderate to severe CHF symptoms, beta-blockers have been shown to improve symptoms, New York Heart Association (NYHA) class and overall morbidity and mortality. Thus far, studies support use of carvedilol, metoprolol, and bisoprolol for this indication. Before using beta-blockers, all patients should be on optimal doses of an ACE-inhibitor, as in the clinical trials. Beta-blockers should not be used in uncompensated CHF and should be used with great caution in patients with Class IV CHF. Early termination of the COPERNICUS trial, which studied carvedilol in the setting of severe CHF, may alter this practice in the near future.

ACE-Inhibitors

ACE-inhibitors should be given to all patients, in the absence of recognized contraindications, with LV systolic dysfunction (EF <0.40), and all attempts should be made to have patients on at least 20 mg of enalapril, or its equivalent, a day. ACE Inhibitors should be strongly considered for all patients with diabetes and/or hypertension, and can be considered for all IHD patients based on the HOPE study.

L. CONSIDER CARDIAC STRESS TEST

All patients with suspected UA/NSTEMI should be risk-stratified to determine their prognosis and guide their treatment. Patients, who do not have clinical findings that suggest either intermediate or high short-term risk of death or MI (i.e. troponin elevations, ECG changes), should receive a stress imaging study prior to discharge as final confirmation of the absence of high risk. All patients with suspected, but unproven, unstable angina should have further diagnostic testing to determine the accuracy of the diagnosis.

Indications for Non-Invasive Evaluation:

- Establish or confirm a diagnosis of ischemic heart disease
- Estimate prognosis in patients with known or suspected ischemic heart disease (IHD)
- Assess the effects of therapy.

Patients with contraindications to exercise testing should undergo pharmacologic stress testing with an imaging modality.

Establishing diagnoses:

- Is most useful if the pre-test probability of coronary artery disease (CAD) is Intermediate (10% to 90%)
- Should generally not be done in patients with very high or very low probabilities of CAD.

Variables useful in estimating prognosis include:

- Maximum workload achieved
- Heart rate and blood pressure responses to exercise
- Occurrence and degree of ST-segment deviation
- Occurrence and duration of ischemic symptoms
- Size and number of stress-induced myocardial perfusion or wall motion abnormalities.

For detailed discussion of Non-Invasive evaluation see Module F – Non Invasive Evaluation

M. REFER TO CARDIOLOGY FOR POSSIBLE ANGIOGRAPHY

The survival benefits of myocardial revascularization are most pronounced among patients with LV dysfunction. Therefore, all patients with NSTEMI/UA who are found to have a reduced EF (<0.40) on non-invasive testing or found to have high- or intermediate-risk for death or MI on a stress test should be considered for referral to cardiology for possible coronary angiography and subsequent revascularization. This recommendation applies even to patients who do not have clinical signs and symptoms of heart failure and to those whose ischemic symptoms have been stabilized.

Patients with UA/NSTEMI who have been stabilized on medical therapy, but who are found to have LV dysfunction, may benefit from further risk stratification using coronary angiography to determine their likelihood of benefit from revascularization. This decision most properly resides with a specialist in cardiovascular diseases, since this specialist is in the best position to discuss the relative risks and benefits of bypass surgery versus medical therapy or percutaneous revascularization.

Patients with the following coronary anatomic findings should be considered for bypass surgery:

- Significant left main coronary artery stenosis
- Left main equivalent: significant stenosis (70%) of proximal LAD and proximal left circumflex artery
- Three-vessel disease (survival benefit is greater in patients with abnormal LV function; e.g., with an EF <0.50.)
- Proximal LAD stenosis where PCI is technically difficult

The following list includes examples of non-invasive test results that indicate intermediate- or high-risk, for which cardiology referral for coronary angiography should be considered.

High-Risk (greater than 3% annual mortality rate):

- Severe resting LV dysfunction (LVEF<0.35)
- High-risk Duke treadmill score (score \leq -11)
- Severe exercise LV dysfunction (exercise LVEF<0.35)
- Stress-induced large perfusion defect (particularly if anterior)
- Stress-induced moderate-size multiple perfusion defects
- Large, fixed perfusion defect with LV dilatation or increased lung uptake (thallium-201)
- Stress-induced moderate-size perfusion defect with LV dilatation or increased lung uptake (thallium-201)
- Echocardiographic wall motion abnormality (involving >2 segments) developing at low dose of dobutamine (\leq 10 mg/ kg/min) or at a low heart rate (<120 bpm)
- Stress echocardiographic evidence of extensive ischemia

Intermediate-Risk (1%-3% annual mortality rate):

- Mild/moderate resting left ventricular dysfunction (LVEF = 0.35 to 0.49)
- Intermediate-risk Duke treadmill score (greater than -11 and less than 5)
- Stress-induced moderate perfusion defect without LV dilation or increased lung intake (thallium-201)
- Limited stress echocardiographic ischemia with a wall motion abnormality only at higher doses of dobutamine involving less than or equal to two segments

N. DISCHARGE

The acute phase of UA/NSTEMI is usually over within 2 months. The risk of progression to MI or the development of recurrent MI or death is highest during that period. At 1 to 3 months after the acute phase, most patients resume a clinical course similar to that in patients with chronic stable coronary

Disease

Many patients with UA/NSTEMI have chronic stable angina at hospital discharge. The management of the patient with stable CAD is detailed in Module C of this guideline.

The selection of a medical regimen is individualized to the specific needs of each patient based on the in-hospital findings and events, the risk factors for CAD, drug tolerability, or the type of recent procedure. The mnemonic ABCDE (Aspirin and antianginals; Beta-blockers and blood pressure; Cholesterol and cigarettes; Diet and diabetes; Education and exercise) has been found to be useful in guiding treatment.

For follow-up and secondary prevention see Module G of this guideline