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

SUSPECTED ACUTE CORONARY SYNDROME UNSTABLE ANGINA OR NON-ST-SEGMENT ELEVATION MI

KEY ELEMENTS

- Ensure emergency intervention
- Assess the short-term risk of death or MI
- Admit to appropriate level of care
- Initiate antithrombotic and antiplatelet therapy as indicated
  - (ASA, heparin, enoxaparin, GP IIba/IIIa, clopidogrel)
- Refer to urgent angiography, if indicated
- Consider non-invasive evaluation (cardiac stress test and LV function) in patients not undergoing angiography
- Initiate ACE inhibitor therapy
- Ensure pharmacologic therapy for ischemia, angina, and CHF
- Discharge patient to home with appropriate follow-up.

The distinction between acute MI (STEMI or LBBB) and UA and NSTEMI is important!

- Immediate reperfusion, with either primary angioplasty or thrombolytic agents, has been shown to reduce mortality in patients with STEMI or LBBB MI
- **The use of thrombolytics may be potentially harmful in UA and NSTEM**

VA access to full guideline: http://www.oqp.med.va.gov/cpg/cpg.htm
DoD access to full guideline: http://www.QMO.amedd.army.mil

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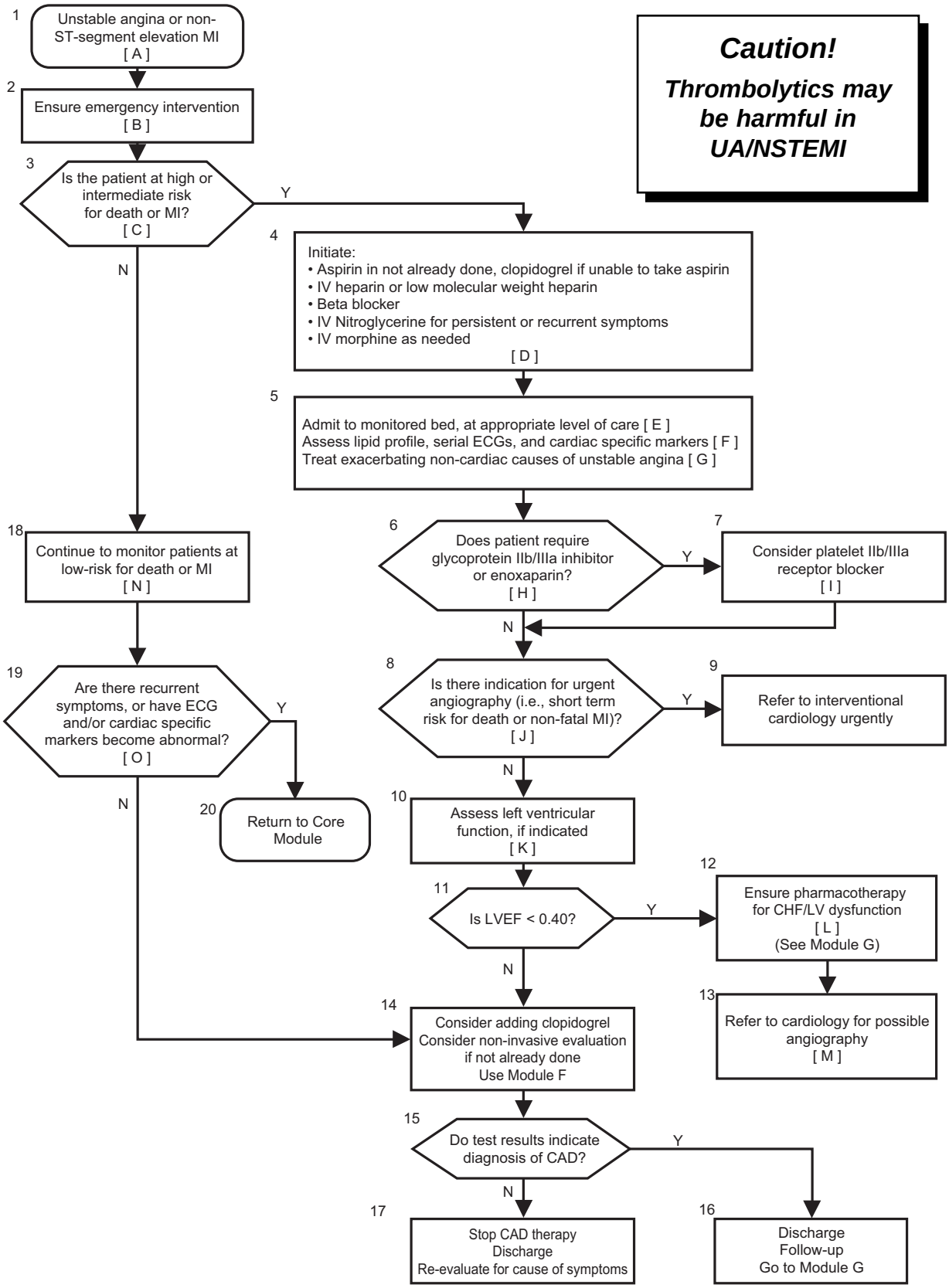
MANAGEMENT OF ISCHEMIC HEART DISEASE
Module B: Suspected Acute Coronary Syndrome
(Unstable Angina or Non-ST-Segment Elevation MI)

B



SUSPECTED ACUTE CORONARY SYNDROME (UNSTABLE ANGINA/NON-ST-SEGMENT ELEVATION MI)

Module B presents guidelines for the diagnosis and management of unstable angina (UA) and the closely related condition, non-ST-elevation myocardial infarction (NSTEMI). Patients presenting with UA/NSTEMI are considered to be a subset of acute coronary syndrome (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 are similar in UA and NSTEMI, 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.

EMERGENCY INTERVENTION

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.

Oxygen (O_2): Supplemental oxygen should be administered on initial presentation, especially if congestive heart failure (CHF) or oxygen desaturation is present. For uncomplicated MIs, oxygen may be reassessed after six hours. CO_2 retention is not usually a concern with low flow nasal O_2, even in patients with severe chronic obstructive pulmonary disease (COPD).

Aspirin: 160 mg to 325 mg should be chewed immediately to accelerate absorption and should be given even if the patient is on chronic aspirin therapy.

Intravenous (IV): Intravenous access for the delivery of fluids and drugs should be obtained, with both antecubital veins used if possible for multiple infusions, especially if thrombolytic therapy is being considered. Unnecessary arterial and venous punctures should be avoided and experienced personnel should perform access. While the IV is being started, blood samples for cardiac enzymes/markers (i.e., troponin – preferred, CK, CK-MB acceptable), lipid profile, complete blood count (CBC), electrolytes, renal function, international normalized ratio (INR), and activated partial thromboplastin time (APTT) can be obtained, although immediate treatment of ACS should not be delayed by the results from these tests.

Sublingual nitroglycerin should be given, 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.

ECG: Obtain within 10 minutes of presentation and follow-up with a serial electrocardiogram (ECG). A right-sided ECG should be performed if a standard ECG suggests an inferior wall MI.

Adequate analgesia

Advanced cardiac life support (ACLS, 1999): algorithm should be applied, as indicated.

Chest X-ray: A portable chest radiograph should be performed, particularly to evaluate for mediastinal widening (aortic dissection), cardiac silhouette, and evidence of CHF.

Transportation: In many 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.

RISK STRATIFICATION

Patient at High or Intermediate Risk for Death or MI

The initial management of patients with 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 ECG findings.

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	• Accelerating tempo of ischemic symptoms in the preceding 48 hours	• Prior MI, peripheral or cerebrovascular disease, or coronary artery bypass graft (CABG) • Prior aspirin use	
Character of Pain	• Prolonged ongoing rest pain (>20 minutes)	• Prolonged rest angina (>20 minutes), now resolved, with moderate or high likelihood of coronary artery disease (CAD) • Rest angina (<20 minutes or relieved with rest or sublingual NTG)	• 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
Clinical Findings	• 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	• Age >70 years	
ECG Findings	• Transient ST-segment changes >0.05 mV in association with rest angina • BBB, new or presumed new • Sustained ventricular tachycardia	• T-wave inversions >0.2 mV • Pathological Q-waves	• Normal or unchanged ECG during an episode of chest discomfort
Cardiac Markers	• Elevated (e.g., TnT or TnI >0.1 μg/mL)	• Slightly elevated (e.g., TnT >0.01, but <0.1 μg/mL)	• Normal

Patients with ACS who have an intermediate- or high-risk of death and/or MI should be admitted to an inpatient unit with cardiac monitoring capabilities.

- Serial ECGs and enzymes will diagnose or exclude infarction, which have implications for the length of unit and hospital stay, and further add 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 and probably after any transfer, and subsequently at least daily.
- 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 is also acceptable. In patients with normal cardiac markers within 6 hours of symptom onset, another sample should be obtained in 6-12 hours. In patients with abnormal cardiac markers, repeat samples should be performed every 8 hours until peak.
- A lipid profile should be performed 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
Cardiac Troponins	• 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.	• 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.	• 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.
CK-MB	• Rapid, cost-efficient, accurate assays. • Detection of early reinfarction	• 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).	• Prior standard and still acceptable diagnostic test in most clinical circumstances. • Familiar to the majority of clinicians.
CK-MB Isoforms	• Early detection of MI.	• Specificity profile is similar to CK-MB. • Current assays require special expertise.	• 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. • Experience to date is predominantly in dedicated research centers.
Myoglobin	• High sensitivity. • Early detection of MI. • Detection of reperfusion • Most useful in ruling out MI.	• Very low specificity in the setting of skeletal muscle injury or disease. • Rapid return to normal range limits sensitivity, for later presentations.	• 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.

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.

Conditions and Medications Provoking or Exacerbating Ischemia	
Increased Oxygen Demand	**Decreased Oxygen Supply**
Noncardiac • Hyperthermia • Hyperthyroidism • Sympathomimetic toxicity (e.g., cocaine use) • Hypertension • Anxiety • Arteriovenous fistulae **Cardiac** • Hypertrophic cardiomyopathy • Aortic stenosis • Dilated cardiomyopathy • Tachycardia - Ventricular - Supraventricular **Medications** • Vasodilators • Excessive thyroid replacement • Vasoconstrictors	**Noncardiac** • Anemia • Hypoxemia - Pneumonia - Asthma - Chronic obstructive pulmonary disease - Pulmonary hypertension - Interstitial pulmonary fibrosis - Obstructive sleep apnea • Sickle cell disease • Sympathomimetic toxicity (e.g., cocaine use) • Hyperviscosity - Polycythemia - Leukemia - Thrombocytosis - Hypergammaglobulinemia **Cardiac** • Aortic stenosis • Hypertrophic cardiomyopathy **Medications**

TREATMENT

The goals of therapy include symptom relief and the prevention of subsequent death or MI. Fibrinolytic therapy should not be given unless ST-segment elevation/LBBB MI or a true posterior current of injury develops. 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 hospitalized patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance.

In hospitalized patients for whom an early noninterventional approach is planned, clopidogrel should be added to aspirin as soon as possible on admission and administered for at least 1 month and for up to 9 months

All patients with UA/NSTEMI should receive:

- Aspirin 160 mg to 325 mg, if not already given
- Clopidogrel 75 mg if hypersensitivity to aspirin or major GI intolerance
- IV unfractionated heparin (UFH) or subcutaneous low molecular weight heparin (LMWH)
- Beta-Blocker
- IV Nitroglycerine for persistent or recurrent symptoms
- IV Morphine – if needed

TREATMENT OF HIGH RISK PATIENTS

Glycoprotein IIb/IIIa Inhibitor or Enoxaparin

Simple clinical markers obtained at the initial presentation help identify patients, with intermediate to high probability of CAD as the etiology of the symptoms, who would benefit most from more aggressive intervention. The TIMI Risk Score is the sum of simple clinical markers derived from multivariate logistic regression of the TIMI IIB and ESSENCE trials that predicts risk of death, MI, or need for urgent revascularization in patients with intermediate to high probability of CAD. Patients with a score ≥3 should receive either enoxaparin or a glycoprotein IIb/IIIa receptor blocker, plus unfractionated heparin. Patients with a TIMI Risk Score ≤2 should receive either unfractionated heparin or enoxaparin.

The TIMI Risk Score

	Predictor Variables
1	Age ≥ 65 years
2	At least 3 risk factors for CAD • Family history of CAD; hypertension, hyperlipidemia, or diabetes; or current smoker
3	Significant CAD • Prior coronary stenosis ≥ 50%
4	ST-deviation • ST depression ≥ 0.05 mV
5	Two or more anginal events in the last 24 hours
6	Elevated serum cardiac markers
7	Use of aspirin in the preceding 7 days

Consider Platelet IIb/IIIa Receptor Blocker

In patients for whom an interventional approach is planned (catheterization or PCI), a GP IIb/IIIa inhibitor (in addition to aspirin and heparin or low molecular weight heparin) is recommended. The GP IIb/IIIa antagonist may also be administered just prior to PCI. In patients for whom a PCI is planned and who are not at high risk for bleeding, clopidogrel should be started and continued for at least 1 month and for up to 9 months. Clopidogrel (in addition to aspirin and heparin or low molecular weight heparin) is recommended for patients with UA/NSTEMI for whom a noninterventional approach is planned.

No head-to-head comparison of clopidogrel, a GP IIb/IIIa inhibitor, and their combination has been reported. The addition of a GP IIb/IIIa inhibitor to a subset of patients in the CURE trial who were receiving aspirin, clopidogrel, and heparin appeared to be well tolerated, and current practice frequently involves the use of this combination of drugs. However, until further information on the safety and efficacy of such quadruple therapy becomes available, the ACC/AHA (UA/NSTEMI 2002) recommend to consider the addition of a GP IIb/IIIa inhibitor for patients with UA/NSTEMI who are receiving aspirin, clopidogrel, and unfractionated or low molecular weight heparin and who are referred for an invasive strategy. A Class I recommendation is made for a GP IIb/IIIa inhibitor at the time of PCI in patients receiving heparin and aspirin.

Glycoprotein IIb/IIIa inhibitor drugs available for intravenous use include abciximab, eptifibatide, and tirofiban hydrochloride. All have shown efficacy in clinical trials, but the efficacy of abciximab has been primarily demonstrated in trials where patients also received a percutaneous coronary intervention (PCI). In the four trials in which glycoprotein IIb/IIIa inhibitors were used as part of the primary medical management of ACSs, either eptifibatide or tirofiban was given. Combined, these four trials enrolled over 18,000 patients and overall showed an approximate 10 percent decrease in the relative rate of death or non-fatal MI, at 30 days. There have been no direct comparison trials between eptifibatide and tirofiban.

These trials have also demonstrated an acceptable safety profile for these drugs, even when used with concomitant aspirin and heparin. Bleeding is the principal adverse effect, but can be minimized by the use of low-dose, weight-adjusted heparin. Early pilot studies suggest that these drugs may also be used safely with LMWH. An increased risk of intracranial hemorrhage has not been shown. Significant thrombocytopenia is uncommon, occurring in less than 1 percent of patients. Active bleeding is an absolute contraindications to the use of glycoprotein IIb/IIIa inhibitors.

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 $\geq$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 $\geq$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.

Abciximab-should be used only for patients receiving PCI

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. *Abciximab should be avoided in patients for whom PCI is not planned.* All these agents should be stopped prior to CABG, and should be used carefully with UFH at reduced doses with frequent APTTs. The use of these agents with LMWH is being studied, but is potentially problematic because the APTT level does not reflect the full anticoagulant effect of LMWH.

Enoxaparin

Patients with a TIMI Risk Score of 3 or greater should be considered for either enoxaparin or glycoprotein IIb/IIIa receptor blocker, plus unfractionated heparin, as well as the usual therapy of aspirin and beta-blocker. If the patient is a candidate for cardiac catheterization that can be performed within 48 hours of presentation, glycoprotein IIb/IIIa inhibitor plus unfractionated heparin is preferred over enoxaparin. If enoxaparin is given, it should be given as 1 mg/kg sq bid. A bolus of enoxaparin 30 mg IV may be given initially.

Indications For Urgent Angiography (i.e., Short-Term Risk for Death or Non-Fatal MI)

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

- Patients with recurrent angina/ischemia at rest or with low-level activities, despite intensive anti-ischemic therapy
- 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 left ventricular (LV) systolic function (e.g., ejection fraction (EF) <0.40 on an 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 (ACC/AHA Class IIa recommendation and an evidence level C):

- Patients with repeated presentations with UA/NSTEMI despite therapy and without evidence of ongoing ischemia or high risk
- Patients >65 years old
- Patients who present with ST-segment depression or elevated cardiac markers and no contraindications to revascularization

If ischemic symptoms or signs (including hypotension or pulmonary congestion) continue for one hour, despite all efforts, the patient should be considered for coronary arteriography and subsequent emergency revascularization, either percutaneously or surgically, as appropriate.

Assessment of Left Ventricular Function

LV systolic function may be assessed by contrast angiography at cardiac catheterization, two-dimensional cardiac ultrasound, and radionuclide ventriculography. 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 $\geq$0.40, with a positive predictive value of 98 percent 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

THERAPY FOR CHF/LV-DYSFUNCTION

ACE Inhibitors

ACE inhibitors should be given to all patients, in the absence of recognized contraindications, with CHF evidence for 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.

Multiple trials have convincingly demonstrated the benefit of ACE inhibitor therapy in patients with CHF, due to LV systolic dysfunction (both ischemic and non-ischemic dysfunction). Clinical benefits include less dyspnea, improved exercise tolerance, reduced need for emergency care for heart failure, and improved survival. In both the SOLVD trial (1991) and the Veterans Heart Failure Trial (V-HeFT-II), patients with reduced LVEF and symptoms of heart failure had improved survival with enalapril. In another trial in asymptomatic patients after MI with documented LV dysfunction, captopril reduced mortality and ischemic events compared with a placebo. A meta-analysis of 32 randomized placebo controlled trials (RCTs) of ACE inhibitors for symptomatic heart failure found an overall decrease in mortality of 28 percent (absolute risk reduction, 6.1 percent, NNT=16). The greatest benefit was found for NYHA class IV failure, LVEF <25 percent, and CHF due to IHD.

Moderate to high doses of ACE inhibitors were used in all the trials. In the ATLAS study (1999), patients with moderate to severe heart failure were randomized to either a low dose (2.5 mg to 5 mg/day) or high dose (32.5 to 35 mg/day) of lisinopril. Those patients randomized to the higher dose regimen had a 12 percent lower risk of death or hospitalization at 3 to 5 years of follow-up. In a more recent study, patients with moderate CHF were randomized between moderate- (20 mg/day) and high-dose (60 mg/day) enalapril. Following 12 months of therapy, there were no differences in survival or other clinical variables. In patients intolerant of ACE inhibitors, an angiotensin II receptor blocker (ARB) should be prescribed.

Results from a recent large-scale, randomized, placebo controlled clinical trial suggest that all patients with IHD, irrespective of EF, may benefit from routine treatment with an ACE inhibitor (ramipril). If these results are confirmed by other ongoing trials, involving other ACE inhibitors, and in patients under the age of 55, treatment with an ACE inhibitor will likely become the standard of care for all patients with IHD, irrespective of LV function. Pending the outcome of these trials, no firm recommendations can be made at this time for the routine use of ACE inhibitors in all patients with IHD.

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.

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 should be considered for referral to cardiology for possible coronary anginography 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.

TREATMENT OF PATIENTS WITH LOW RISK

Continue to Monitor Patients at Low-Risk for Death or MI

For patients with suspected ACS who, at initial presentation, do not have clinical features suggesting intermediate- or high-risk for death or MI, the following are recommended:

- Initial treatment with 160 mg to 325 mg of chewable aspirin
- Initial treatment with sublingual NTG for angina or suspected anginal equivalents
- Continuous ECG monitoring and continued surveillance of vital signs and for recurrent symptoms, for at least 6 to 12 hours, in an appropriate facility-specific unit
- A 12-lead ECG at the time of admission and at least 6 hours from the onset of symptoms
- Assessment of serum cardiac markers of myocardial injury (e.g., CPK-MB or troponin) at the time of presentation and at least 6 hours from the onset of symptoms
- Early stress testing for patients who do not develop clinical indicators of intermediate- or high-risk by the end of the monitoring period
- Hospital admission and intensification of medical therapy for patients who develop clinical indicators of intermediate- or high-risk by the end of the monitoring period

Low Risk Patients Can Become High Risk

Patients with recurrent symptoms, positive cardiac specific markers, or evolutionary or dynamic ECG changes are considered high risk. These patients should be put on emergency interventions for Acute Coronary Syndrome and assessed for aggressive therapy. Patients, who remain at low risk, even after an observation period of at least 6 to 12 hours, can be safely discharged for an expeditious outpatient diagnostic evaluation.