

UCLA Chest Pain and Acute Coronary Syndrome Patient Management Guideline

I. Introduction

Acute coronary syndromes (ACS) most often result from disruption of an atherosclerotic plaque and the subsequent cascade of pathologic processes that critically decrease coronary blood flow. The certainty of diagnosis, severity of symptoms, hemodynamic state, medical history, electrocardiogram, and biomarkers will determine the choice and timing of therapies used in individual patients. Patients with ST segment elevation acute myocardial infarction (STEMI) require rapid initiation of therapy aimed at achieving reperfusion and cardiovascular protective medications. Patients with unstable angina/non-ST segment elevation acute myocardial infarction (NSTEMI) require comprehensive medical therapy to prevent the evolution to myocardial infarction/death. Intermediate and high risk patients should undergo early invasive management and low risk patients stress testing to further risk stratify. These patients once stabilized require longer term risk stratification and secondary prevention measures. Patients with chest pain that is not due to cardiac disease need the etiology to be determined and inpatient or outpatient medical follow-up. This guideline describes principles of patient care derived from systematic analysis of scientific literature, expert opinion, the 2006 ACC/AHA UA/NSTEMI Clinical Practice Guideline and 2007 ACC/AHA STEMI guideline. The diagnostic and management strategies recommended are designed to be efficacious, efficient, reasonable, and as safe as possible given the current state of medical knowledge.

This management guideline assigns patients to three diagnostic and management categories:

Chest Pain

Unstable Angina/Non-ST Segment Elevation Acute Myocardial Infarction (NSTEMI)

ST Segment Elevation Acute Myocardial Infarction (STEMI)

II. Definitions

Chest Pain: Patients without evidence of acute myocardial infarction or active myocardial ischemia on electrocardiogram (ECG) with chest pain that is not definite angina. These patients are defined as not having features that give them an intermediate or high likelihood of significant coronary artery disease.

Unstable Angina: Patients without evidence of acute myocardial infarction who have chest pain (or other symptoms that may represent ischemia) and are felt to have an intermediate or high likelihood of significant coronary artery disease.

Non-ST Elevation AMI: Patients with chest pain or other symptoms suggestive of ischemia, usually with evidence of ischemia on ECG, with elevated cardiac enzymes in pattern consistent with infarction. Patients with ischemic ECG changes that persist for greater than 30 minutes (refractory unstable angina) are included in this category.

ST Segment Elevation AMI: Patients with symptoms suggestive of myocardial infarction and an ECG with ST segment elevation of 1 mm or more in two contiguous leads or left bundle branch block.

III. Diagnosis

Diagnosis of acute coronary syndrome depends on a directed clinical history, physical examination, and immediate reading of a resting 12 lead electrocardiogram. The ECG provides crucial information in the diagnosis of STEMI and NSTEMI. In patients with chest pain, assessment of the likelihood of coronary artery disease, the patient's hemodynamic stability, biomarkers, and the risk of adverse outcome will determine the choice and timing of patient management strategies.

The major factors in the initial history and physical exam that relate to the likelihood of coronary artery disease are the following:

- ❑ Chest pain assessment by physician (definite angina, probable angina, probably not angina, and not angina).
- ❑ Prior myocardial infarction or documented coronary artery disease
- ❑ Number of risk factors (diabetes, smoking, hypercholesterolemia, hypertension, post menopausal)
- ❑ Age

The nature, intensity, character, location, onset, and duration of chest pain should be determined from the history and documented in the medical record. Assessment of angina should conclude with a summary statement of the patient's symptoms to one of the following four categories: definite angina, probable angina, probably not angina, and not angina. Response to nitroglycerin should be noted. Associated symptoms should also be documented. Sharp, stabbing or pleuritic qualities of chest pain although making an ischemic etiology less likely do not completely exclude an ischemic etiology. In the Multicenter Chest Pain Study, acute ischemia was diagnosed in 22% of patients presenting with sharp or stabbing pain, 13% with some pleuritic qualities, and 7% of patients with pain fully reproduced with palpation. Patients with diabetes mellitus, women, and the elderly often present with atypical symptoms and these patients require a higher level of suspicion.

Electrocardiogram: The ECG is crucial in the diagnosis of UA/NSTEMI and STEMI. A recording should be made and reviewed by the physician within 5 minutes of the patient with chest pain or other symptoms suggestive of ischemia arriving in the emergency department. ST elevation ≥ 1 mm in two or more contiguous leads strongly suggests acute myocardial infarction. ST depression typically signifies ischemia or non-STEMI. A completely normal ECG in the emergency department does not exclude acute ischemic heart disease. Of patients with chest pain and an entirely normal ECG, 1 to 6% will eventually prove to have AMI and 4% or more will have unstable angina.

- ❑ Diagnostic criteria for STEMI:
 ≥ 1 mm ST elevation in 2 or more contiguous limb or precordial leads
 Left bundle branch block, not known to be old

- ❑ ECG findings useful for establishing the likelihood of coronary artery disease/ACS:
 ST segment depression ≥ 1 mm
 Inverted T-waves ≥ 1 mm in two or more contiguous leads

Patients who have sustained symptoms in the absence of a diagnostic ECG should have the ECG repeated within 20 to 30 minutes. Evidence of ischemia or infarction may develop within this period. Patients who present with chest pain and evidence of ischemia on ECG should have a repeat ECG when their chest pain is relieved to ensure that ECG evidence of ischemia has resolved. This allows identification of patients with resolution of symptoms but persistent silent ischemia.

Summary: Estimating the likelihood of CAD. Symptom characteristics, the presence of coronary artery

disease risk factors, and ECG findings should be combined to estimate a patient's likelihood of having coronary artery disease:

Likelihood of significant coronary artery disease in patients with symptoms suggesting ACS:

The estimated likelihood of significant coronary artery disease is used to classify patients into the chest pain and unstable angina/NSTEMI diagnostic and management categories. Biomarkers (cardiac troponin and B-type natriuretic peptide) can be used to further improve the diagnostic probabilities. Patients presenting with symptoms categorized as having a low likelihood of disease and negative initial biomarkers can be treated in the chest pain algorithm. Patients with intermediate or high likelihood of disease can be further stratified by their risk assessment.

Low Likelihood: (e.g., 1-14% likelihood)

- Chest pain, "probably not angina" in patients with one or no risk factors, but not diabetes.
- T wave flat or inverted < 1 mm.
- Normal ECG.

Intermediate Likelihood: (e.g., 15-84% likelihood)

- "Definite angina" in patients with no risk factors for CAD.
- "Probable angina" in patients with 1 or more risk factors.
- "Probably not angina" in patients with diabetes or with two or three other risk factors.
- Patients with extracardiac vascular disease.
- ST depression 0.5 to 1 mm.
- T wave inversion of ≥ 1 mm.

High Likelihood: (e.g., 85-99% likelihood)

- Known history of prior MI or CAD.
- "Definite angina" in male ≥ 60 or females ≥ 70 .
- Transient hemodynamic or ECG changes during pain.
- ST elevation or depression of ≥ 1 mm.
- Marked symmetrical T wave inversion in multiple leads.

IV. Risk Assessment

Acute chest pain carries a risk of morbidity and mortality that is largely determined by the clinical syndrome at the time of presentation.

Short term risk of death or nonfatal myocardial infarction in patients with symptoms suggesting ACS

Low risk:

- Nonresting angina with increased frequency, severity, or duration.
- Angina provoked at a lower threshold.
- Recent onset angina over last 2 weeks to 2 months.
- Normal or unchanged ECG.

Intermediate risk:

- Rest angina now resolved.
- Rest angina < 20 minutes in duration, angina with dynamic T wave changes.
- New onset angina < 2 weeks at minimal exertion.
- Age > 65 years.
- Q waves or ST depression on ECG.

High risk:

- Ongoing rest pain > 20 minutes.
- Angina with pulmonary edema, S3, or rales. Angina with new or worsening mitral regurgitation.
- Rest angina with dynamic ST changes ≥ 1 mm.
- Angina with hypotension.

Patients with intermediate or high likelihood of disease presenting in the low risk category and in the absence of elevated biomarkers may be treated in the chest pain algorithm. Patients with intermediate or high risk or with elevated biomarkers should be treated in the unstable angina/NSTEMI algorithm.

This risk of death or a recurrent cardiac event following an episode of acute coronary insufficiency is time dependent: the risk is highest at the time of presentation and falls rapidly over time. Patients with ACS have a risk of cardiac death of 5% at the time of presentation when untreated. This risk then declines markedly over time. By 6 months after presentation, patients with ACS have a risk that is indistinguishable from patients with chronic stable angina (0.2% risk of cardiac death per month).

TIMI Risk Score

A 7 point risk score for ACS patients was developed and validated to predict the risk of death, (re)infarction, or recurrent severe ischemia requiring revascularization. The score is defined as the simple sum of the following prognostic variables:

1. Age ≥ 65 years
2. More than 3 coronary risk factors
3. Prior angiographic coronary obstruction
4. ST-segment deviation
5. More than 2 angina events within 24 hours
6. Use of aspirin within 7 days
7. Elevated cardiac markers

Overall risk assessment in patients with acute coronary syndromes

The most important factors related to short term and long term survival in patients with ACS are the following:

1. Cardiac troponin I (TnI) and B-type natriuretic peptide (BNP)
2. Left ventricular function (LVEF)
3. Extent of coronary artery disease
4. Age
5. Co-morbid conditions
6. Unmodified coronary risk factors

Cardiac troponin and BNP are strong independent risk predictors for early and late events and mortality. Left ventricular function is also a strong predictor of subsequent cardiac death in patients with ACS. BNP adds independent prognostication to the LVEF. The extent of coronary artery disease defines both the likelihood of an acute event and the likelihood of ischemic myocardium at a distance and/or lack of collateral supply. Advanced age is an independent risk factor relating to lower functional reserve. Important co-morbid conditions include renal failure, chronic obstructive lung disease, cerebral vascular disease, and malignancy. Unmodified risk factors such as ongoing smoking or untreated hypercholesterolemia leave patients at a substantially higher risk of mortality.

V. Initial Evaluation and Treatment

The intensity and urgency of care must be appropriately matched with the severity of the presenting symptoms. Rapidly identifying patients with a ST-segment elevation AMI is an urgent initial objective as time to reperfusion therapy is an important determinate of outcome. For all patients, anti-thrombotic and anti-ischemic therapy should be instituted promptly in the emergency department as soon as the working diagnosis of ACS is established.

The initial evaluation consists of the directed rapid history, a focused physical examination, an ECG, and laboratory testing for biomarkers (cardiac troponin and BNP). Patients can be stratified into the 3 diagnostic categories: STEMI, UA/NSTEMI, and chest pain.

A. ST Segment Elevation AMI

Patients with ongoing chest pain or symptoms having components typical of myocardial ischemia or infarction of 12 or less hours of duration in conjunction with a diagnostic ECG (≥ 1 mm ST elevation in two or more contiguous limb or precordial leads or left bundle branch block not known to be old) meet diagnostic criteria for STEMI and the STEMI team should be activated immediately for primary percutaneous coronary intervention (active STEMI team via page operator). Patients with resolution of chest pain but ST elevation on ECG and those with resolution of ST elevation should still be considered for direct catheterization. The fundamental goal in these patients is the rapid initiation of therapy aimed at complete reperfusion.

A 12-lead ECG should be performed and shown to an experienced emergency physician within 5 minutes of ED arrival for all patients with chest discomfort or any other symptom that may indicate STEMI.

Patients with cardiogenic shock, sustained ventricular arrhythmia, complete heart block, pulmonary edema or loss of consciousness should also be suspected of having an STEMI and 12 lead ECG promptly assessed for ST segment elevation on ECG.

The treatment of ST segment elevation AMI is detailed in the UCLA STEMI Guideline. Initial management is briefly summarized.

1. Activate the STEMI team by activating the group page via the page operator
2. All patients should receive regular ASA 162 mg or 325 mg as soon as possible unless a definite contraindication is present (evidence of ongoing life-threatening hemorrhage or a clear history of severe hypersensitivity to ASA). Have patient chew the aspirin. All patients should receive clopidogrel 600 mg dose in combination with aspirin, unless contraindicated, unless it is suspected that they have acute pericarditis, aortic dissection, or will need to undergo emergent CABG/other surgery. If aspirin allergic, use clopidogrel 600 mg loading dose alone.
3. Patients in which acute pericarditis or aortic dissection is not suspected, have no evidence of major or life-threatening hemorrhage, and no significant predisposition to hemorrhage should be given an intravenous bolus of heparin, low molecular weight heparin (enoxaparin) or fondaparinux.
4. Patients without contraindications should be treated with oral beta blockers (exclude cardiogenic shock, hypotension, symptomatic bradycardia, 2 or 3rd degree heart block, decompensated heart failure prior to treatment). IV beta blockers should be considered only if hypertension or tachycardia without any contraindication or precautions being present.
5. Patients with ongoing chest pain or heart failure despite sublingual (SL) nitroglycerin (NTG) and oral beta blockers, with SBP > 90 mmHg should be started on an intravenous nitroglycerin drip
6. The rapid initiation of therapy aimed at reperfusion (direct catheterization or thrombolytic therapy) should not be delayed. Direct catheterization is the preferred treatment strategy

Echocardiography can be very helpful in patients where the initial diagnosis is unclear and to distinguish between pericarditis, pulmonary embolization, or infarction. In patients suspected of having a thoracic aortic dissection, transthoracic echocardiography followed by transesophageal echocardiography or chest CT scanning are the preferred diagnostic strategies, as this represents a surgical emergency. In patients with clear evidence of ischemia or infarction and in whom alternative diagnoses are unlikely, initiation of therapy aimed at reperfusion should not be delayed to obtain echocardiography.

The goal is to perform primary PCI within 90 minutes of patient arrival in STEMI patients. This requires rapid diagnosis and emergent notification of the CCU fellow on call to activate the CLOT team.

B. Unstable Angina/Non-ST Segment Elevation AMI

Patients with intermediate or high likelihood of disease with intermediate or high risk features should be treated in the unstable angina/Non-STEMI algorithm. The severity of symptoms of ACS, ECG evidence of ischemia, and initial cardiac enzymes will dictate the initial intensity of therapy.

General care.

Monitoring: Patients should remain on continuous ECG monitoring for ischemia and arrhythmia detection.

Oxygen: Patients with obvious cyanosis, respiratory distress, or high risk features should receive supplemental oxygen. A finger pulse oximeter check should be used to confirm adequate oxygenation. If pulse oximeter saturation < 92% or abnormalities in ventilation (i.e. exchange of carbon dioxide) are suspected, full assessment including arterial blood gas determination should be considered prior to initiating oxygen. Routine use of oxygen in all patients is not indicated.

Activity: Patients should be placed at bed rest during the initial phase of medical management.

Diet: Patients should remain NPO except for meds until clinical stability demonstrated and necessity/timing of cardiac catheterization determined.

Patients with medically refractory chest pain associated with ischemic ECG changes that persist for greater than 30 minutes (refractory unstable angina/non-STEMI) should be included in this category and treated expeditiously using the direct catheterization strategy.

Laboratory Testing

- ECG initially, with ongoing or recurrent symptoms, with relief of chest pain, and 6 hours after admission.
- CBC with platelets
- PT (INR), PTT
- Serum lytes, creatinine, glucose
- Lipid panel on admission (nonfasting) unless patient has had a recent determination
- Hemoglobin A1c (screen for diabetes or assess control in diagnosed diabetics)
- Troponin I q6 x 2 and CK-MB should be measured q8 hours x 3 (omit 2nd/3rd CK-MB if 6 hour troponin is negative).
- BNP
- High sensitivity-C reactive protein (hs-CRP) (optional)

Cardiac Enzymes

Cardiac troponin I is specific for cardiac tissue and is detected in the serum only if myocardial injury has occurred. A radioimmunoassay for cardiac troponin I is now available and this test has improved sensitivity and specificity over CK-MB in the diagnosis and exclusion of myocardial injury. The troponin I assay allows

early identification and stratification of patients with chest pain suggestive of ischemia, allows identification of patients that present 48 hours to 6 days after infarction, and identifies patients with false positive elevations in CK-MB (such as in rhabdomyolysis).

Because troponin I increases to a first peak value 40 times the detection limit vs. CK-MB only 6-9 times there are not the borderline cases where although the CK-MB has started to rise early it has not yet exceeded the upper limit of normal (hence the need for the 3rd (16 hour) CK-MB measurement). By 6 hours after symptom onset using troponin I there is a 98% detection of patients who are ultimately shown to have a myocardial infarction. In addition, the troponin assay is a powerful, independent mortality risk marker in patients who present with acute myocardial infarction.

The prognostic value of troponin in ACS has also been shown with the troponin assay appearing to be a more sensitive indicator of myocardial cell injury than CK-MB. In the TIMI III study of 1404 patients with acute coronary syndromes, the mortality rate was significantly higher in the patients with troponins I > 0.5 ng/ml (3.7%) than in the patients with levels < 0.5 ng/ml (1.0%) $p < 0.001$. There were significant increases in mortality with increasing levels of cardiac troponin I (troponin < 0.5 ng/ml, mortality 1.0%; 0.5-1.0 ng/ml, 1.7%; 1.0-5.0 ng/ml, 3.6%; > 5.0 ng/ml, 6.8%). The troponin assay thus detects small amounts of myocardial injury (microinfarcts) missed by CK-MB and predicts which patients will otherwise have adverse outcomes despite ruling out for infarction by CK-MB (allowing the physician to identify which patients will benefit from intensified medical therapy and early invasive management).

There are other causes of myocardial injury besides coronary plaque rupture. Since the troponin assay is ultra-sensitive, troponin elevation may be seen in decompensated heart failure, myocarditis, hypoperfusion (syncope, prolonged tachycardias) and other types of myocardial injury. All troponin elevations are not myocardial infarctions. The patients clinical presentation, ECG, and other findings need to be carefully considered.

BNP and high sensitivity CRP have also been shown to provide independent prognostic information in ACS patients. A total of 450 patients in OPUS-TIMI 16 had assessment of troponin, BNP, and high sensitivity CRP biomarkers, obtained at the time of enrollment. In a multivariable model that included each biomarker, an elevated TnI (hazard ratio [HR] 1.8, $P=0.038$), CRP (HR 1.5, $P=0.045$), and BNP (HR 2.1, $P=0.001$) each was an independent predictor of the composite endpoint of death, MI, or CHF. This approach was validated in 1635 patients from TACTICS-TIMI 18. In a multivariable model containing all 3 biomarkers, an elevated TnI (odds ratio [OR] 2.1, $P=0.001$), CRP (OR 1.5, $P=0.025$), and BNP (OR 1.6, $P=0.019$) each was an independent predictor of the composite endpoint of death, MI, or CHF through 6 months. Categorizing patients on the basis of the number of elevated biomarkers at presentation, 31% had elevations in none of the biomarkers, 44% had an elevation in one, 20% had elevations in 2, and 5% had elevations in all 3. A statistically significant association was observed between the number of elevated biomarkers and mortality at 30 days ($P < 0.0001$), with a doubling in mortality risk for each additional biomarker that was elevated.

Patients without elevation of either the troponin I and BNP biomarker < 100 pg/ml on initial presentation and without an ECG diagnostic for infarction, may be considered lower risk and appropriate for the chest pain service. Patients with BNP results between 100-400 pg/ml may also be appropriate for this service in the absence of clinical symptoms of acutely decompensated heart failure or pulmonary embolization.

Initial Pharmacologic Treatment

1. **Antiplatelet Therapy:** The combination of antiplatelet therapy with **clopidogrel** and **aspirin** is recommended in all patients without contraindications (except patients receiving thrombolytics). All patients should receive regular **ASA** 325 mg as soon as possible unless a definite contraindication is present (evidence of ongoing life-threatening hemorrhage or a clear history of severe hypersensitivity to ASA). The initial ASA

should be chewed and given even if the patient reports daily use. ASA should be continued daily (81 to 162 mg) thereafter unless coronary artery disease is excluded and primary prevention is not indicated or a contraindication to ASA develops. All patients should receive **clopidogrel** 600 mg first dose, followed by 75 mg daily in combination with aspirin. Clopidogrel should be held in patients thought likely to require emergent CABG or other surgery. Patients unable to take ASA because of a history of true hypersensitivity or recent significant ASA induced GI bleeding may be started on **clopidogrel** 600 mg first dose, followed by 75 mg daily alone. It takes up to 3 days for the maximal antiplatelet effect if a loading dose is not used. *Meta-analysis of the four largest randomized placebo controlled studies suggests that ASA reduces the risk of MI by 48% and the risk of death by 51% in unstable angina. The CURE trial demonstrated that major cardiovascular events (CV death, nonfatal MI, and stroke) are reduced an addition 20% with clopidogrel plus aspirin compared to aspirin alone in acute coronary syndrome patients. More recent data supports a 600 mg loading dose for more rapid onset of antiplatelet effect.*

2. **Intravenous Heparin or Low Molecular Weight Heparin** should be started as soon as a diagnosis of intermediate or high risk unstable angina, non-STEMI or STEMI is made. In low risk patients the risk benefit ratio for heparin therapy should be considered. The initial dose of unfractionated heparin is 71 units/kg by IV bolus followed by a constant infusion of 14 units/kg/hr maintaining the activated partial thromboplastin time at 1.8 to 2.5 control (see Heparin Protocol). Alternately **Enoxaparin** in a dose of 1 mg/kg q12h SQ may be given. Heparin should be continued for 48-72 hours or until revascularization is performed. Heme positive stool, without overt gastrointestinal bleeding is not a contraindication to Heparin. Patients are at increased risk for recurrent ischemia in the first 24 hours that heparin is discontinued. *Five randomized studies demonstrate that heparin reduces the risk of developing myocardial infarction in patients with unstable angina. ASA, clopidogrel, and heparin's benefit in combination is suggested from the available studies and is strongly recommended as initial therapy. In the ESSENCE Trial, enoxaparin was more effective than unfractionated heparin in preventing coronary events in patients with unstable angina and non-Q wave MI. In A to Z and SYNERGY, there was no difference in outcome.*

3. **Beta Blockers** should be started in all patients, in the absence of contraindications. The intravenous form should be used to initiate therapy in high risk patients but the oral form can be used in intermediate and low risk patients. Assess patient to ensure no shock or decompensated heart failure before administration. In the presence of precautions such as existing pulmonary disease, LV dysfunction, bradycardia, initial selection should favor lower dose. A history of mild or moderate COPD or asthma should prompt a trial of a short-acting agent at a reduced dose rather than complete avoidance of beta-blocker therapy. Contraindications are cardiogenic shock, hypotension, symptomatic bradycardia, 2 or 3rd degree heart block without a pacemaker, until these conditions resolve. Diabetes and peripheral vascular disease are not contraindications. The target resting heart rate for beta blockade is 50 to 60 beats per minute. IV metoprolol is given in 5 mg increments by slow (over 1-2 minutes) IV administration repeated every 5 minutes for a total initial dose of 15 mg followed in 1 to 2 hours by 25 to 50 mg by mouth every 6 hours. For patients with preserved LV function use metoprolol or atenolol. For patients with left ventricular dysfunction with or without heart failure symptoms, carvedilol is preferred. Starting doses metoprolol 50 mg bid, carvedilol 6.25 mg bid. Titrate to target dose as tolerated (or dose below target that is best tolerated). Target doses metoprolol 100 mg bid, carvedilol 25 mg bid. *Beta blockers reduce the risk of progression to acute myocardial infarction, reduce heart failure, arrhythmias, and improve survival in patients with acute coronary syndromes.*

4. **Glycoprotein IIb/IIIa Receptor Antagonists** are indicated in patients undergoing percutaneous coronary intervention for acute coronary syndromes, in addition to therapy with aspirin, clopidogrel, and heparin. Abciximab has been shown to reduce the risk of myocardial infarction or death in patient undergoing coronary interventions and meta-analysis/individual clinical trials demonstrated a 20% risk reduction with the small molecule platelet receptor antagonists eptifibatid and tirofiban in patients undergoing coronary intervention.. Benefit is seen predominately in troponin positive patients undergoing PCI. In patients not undergoing PCI, these agents have failed to lower the risk of clinical events. Thus GP IIb/IIIa use is in general

not recommended. These agents are usually started in the catheterization laboratory, but may be started in troponin positive ACS patients where PCI is planned. See UCLA Glycoprotein IIb/IIIa Receptor Antagonist Guideline for further details.

5. ACE Inhibitors These agents are indicated in all patients with acute coronary syndromes, in the absence of contraindications. These agents have potent vascular and cardiac protective effects. Patients with acute myocardial infarction have improved early survival and less heart failure when treated with ACE inhibitors. Treatment should start within 12-24 hours and benefit is seen within 48 hours. ACEI treatment is not recommended in the first 12 hours of AMI, to avoid early hypotension. Contraindications include history of angioedema, cardiogenic shock, hypotension, hyperkalemia, and pregnancy. Renal insufficiency in the setting of AMI is a double indication for ACE inhibitors. The benefit of ACE inhibitors is independent of blood pressure or ventricular function status. Start at low dose and titrate up to clinical trial target doses. Angiotensin receptor antagonists should be used only in ACEI intolerant patients.

6. Statins These agents are indicated in all patients with acute coronary syndromes, irrespective of baseline LDL cholesterol. These agents have potent vascular and cardiac protective effects. Statins reduce vascular inflammation and stabilize the vulnerable atherosclerotic plaque, thereby markedly reducing the risk of vascular events. These benefits are seen in patients with cholesterol and LDL levels in the low, normal, and high range, so it is not necessary to await lipid levels results prior to initiation. Clinical trials have shown mortality reduction in patients with baseline LDL levels of 70 mg/dL and above. Initiation of statin therapy in patients with ACS results in a reduction in myocardial infarction, unstable angina, stroke, need for revascularization, hospitalization, and all cause mortality compared to patients treated with diet alone. This is true regardless of whether the patient has undergone CABG, PTCA, or is being treated medically. These benefits are seen early such that patients should be started on therapy in the first 24 hours of hospitalization. Early benefits (within 8 - 16 weeks) can be seen in patients presenting with acute coronary syndromes when started on immediate high dose statin treatment as shown in MIRACL. PROVE-IT demonstrated greater benefits of initiating high dose potent statin therapy as compared to moderate dose, less potent statin, irrespective of baseline LDL. Use potent statin agents at high dose (ie atorvastatin 80 mg daily). Adherence is markedly improved with in-hospital initiation.

7. Aldosterone Antagonists These agents are indicated in patients with AMI and left ventricular ejection fraction ≤ 0.40 and who have signs or symptoms of heart failure, in the absence of contraindications. These agents attenuate remodeling and have been demonstrated to benefit patients with acute myocardial infarction with left ventricular dysfunction with heart failure symptoms. Patients should be clinically stabilized prior to initiation of the aldosterone antagonist. This therapy is only indicated in patients with systolic dysfunction (LVEF ≤ 0.40), not all ACS patients. Start low dose and need to very closely monitor potassium levels and renal function (48 hours, 1 week, and 4 weeks). Hyperkalemia is an absolute contraindication. Use extreme caution if Cr > 2.5 mg/dL in men and > 2.0 mg/dL in women. Consider starting spironolactone at 6.25 mg PO daily with target dose of no more than 25 mg daily. Eplerone dosing is 25 mg daily starting dose with target dose of 50 mg daily. *The EPHEBUS trial demonstrated a 15% reduction in mortality with the selective aldosterone antagonist eplerenone in AMI patients with LVEF $< 40\%$ with heart failure signs or symptoms.*

8. Nitroglycerin should be administered sublingually to patients with chest pain promptly at the time of presentation pain every five minutes. Patients whose symptoms are not fully relieved with three sublingual nitroglycerin tablets and initiation of beta blocker therapy should be started on IV **nitroglycerin**. Patients with recurrent chest pain and high risk unstable angina should also be started if their blood pressure permits. With recurrent or ongoing chest pain, re-administer SL NTG and increase IV NTG drip. Hypotension with IV nitroglycerin may require fluid administration after assessment of the patients volume status. Patients without ongoing or refractory symptoms may receive topical or oral nitrates. Patients on IV NTG should be switched to oral or topical nitrate therapy once they have been symptom free for 24 hours. Nitrates do not routinely need to be continued beyond 48 to 72 hours in patients who do not have symptomatic angina. *There are no*

randomized studies of nitrates in unstable angina and the use of this agent is extrapolated. Nitrate use beyond 24 hours after myocardial infarction has not been shown to prolong survival or prevent recurrent coronary events.

9. **Morphine Sulfate** can be considered for patients whose symptoms are not relieved with nitroglycerin and beta blockers unless contraindicated by hypotension, respiratory insufficiency, or intolerance. Morphine sulfate has potent analgesic and anxiolytic effects, as well as hemodynamic effects that are potentially beneficial in unstable angina. Morphine may mask ischemic symptoms and may not be appropriate in situations where recurrent symptoms will alter the choice and timing of therapy.

10. **Calcium Channel Blockers** should, in general, be avoided in patients with acute coronary syndromes. Patients with unstable angina which is accompanied by atrial fibrillation with rapid ventricular response who have not responded or have contraindications to beta blockers may benefit from the short term administration of a calcium channel blocker. *Randomized prospective studies have demonstrated an increased risk of myocardial infarction or death with calcium channel blockers in patients with unstable angina.*

11. **Thrombolytic Therapy** is not indicated in patients who do not have evidence of acute ST elevation or LBBB on their 12 lead ECG. *A meta-analysis of the 8 available trials show no improvement in outcome with thrombolytic therapy in patients with unstable angina/Non-STEMI.*

12. **Intra-aortic Balloon Counterpulsation** is indicated in ACS patients who have symptoms refractory to aggressive medical management or hemodynamic instability as a bridge to stabilize the patient while being evaluated for or undergoing revascularization. IABP is contraindicated in patients with moderate or severe aortic regurgitation.

Management Strategies

There are two alternative treatment strategies for patients with unstable angina/non-STEMI. They are termed early invasive and early conservative. In the early invasive strategy cardiac catheterization is performed routinely in all hospitalized patients that are without contraindications. In the early conservative strategy, cardiac catheterization is performed only for persistent or recurrent chest pain, congestive heart failure or depressed LV function, malignant ventricular arrhythmia, or physiologic stress testing indicating high risk.

Early invasive management

ACS patients with prior MI, PTCA, or CABG, history of congestive heart failure or LV dysfunction, persistent or recurrent chest pain/ischemia should undergo cardiac catheterization/early invasive management as the initial diagnostic and treatment strategy.

Early invasive management has been shown to be superior to conservative management in patients with intermediate or high risk features (TIMI risk score 3 or higher) who are potential candidates for revascularization. Early invasive management was particularly beneficial in patients with elevated troponin. In contrast patients without elevated troponins could be equally well managed with either an invasive or conservative strategy. High risk patients with elevated troponins should undergo cardiac catheterization in the first few hours of their hospital stay allowing for early risk stratification and early application of definitive revascularization. Low to intermediate risk patients, who are hemodynamically stable and chest pain free with borderline troponins, may have catheterization performed in the first 12 to 24 hours of hospitalization. Cardiac catheterization can be performed safely early in the setting of acute ischemia and infarction. There is no need to delay catheterization while waiting to see if the patient rules in or rules out for myocardial infarction. This strategy improves efficiency in management.

An early invasive strategy in patients with UA/NSTEMI who have any of the following high-risk indicators, in the absence of contraindications to revascularization, is highly recommended:

1. Recurrent angina/ischemia at rest with low-level activities despite intensive anti-ischemic therapy.
2. Elevated cardiac troponin I or troponin T
3. New or presumably new ST-segment depression
4. Recurrent angina/ischemi with CHF symptoms, and S3 gallop, pulmonary edema, worsening rales, or new or worsening mitral regurgitation
5. LVEF \leq 0.40
6. Hemodynamic instability
7. Sustained ventricular tachycardia
8. PCI with 6 months or Prior CABG

In the TIMI IIIB study, 1473 patients with unstable angina were randomized to the alternative strategies. At 45 days, 15.5% of the early invasive patients had cardiac events vs. 17.7% of the early conservative patients. The conservatively managed patients had a significantly increased incidence of recurrent ischemia and rehospitalization. In FRISC II and TACTIS-TIMI 18 the early invasive strategy was associated with a lower rate of myocardial infarction and death, with significant benefit in intermediate and high risk patients. In ISAR-COOL PCI in the first 2-3 hours of hospitalization was associated with better outcomes than a more delayed PCI strategy(3-5 days) was used.

An alternative strategy for low and selected intermediate risk patients is to perform physiologic stress testing and to catheterize only those patients with a high risk stress test result. Troponin positive patients derive the greatest benefit with the invasive strategy. However, there are other potential etiologies for troponin elevations such as heart failure, stroke, or pulmonary embolization. Thus elevated troponin in isolation does not determine the need for catheterization, but must be put in the proper clinical context.

Patients without elevation of either the troponin I and BNP biomarker $<$ 100 pg/mL on initial presentation and without an ECG diagnostic for infarction or ischemia, may be considered lower risk and appropriate for the chest pain service (see algorithm). Patients with BNP results between 100-400 pg/mL may also be appropriate for this service in the absence of clinical symptoms of acutely decompensated heart failure or pulmonary embolization.

Patients that present with symptoms without a diagnostic ECG and that are troponin I assay and BNP negative initially and troponin negative at 6 hours (and are chest pain free, without dynamic ischemia on ECG) may be considered good candidates for discharge with stress testing preformed on an outpatient basis. Alternatively early inpatient stress testing may be utilized. While patients with negative troponins/BNP/ECGs are at low risk for early events, they may still have significant coronary artery disease and long term risk or other significant conditions. Further evaluation with stress testing to risk stratify patients is indicated. Patients who are troponin I positive (in the appropriate clinical setting of ACS) may be better served to have early catheterization

Diagnostic Algorithms

- Patient with chest pain suspicious for unstable angina or acute myocardial infarction
- | | | |
|-----|------------------------|--|
| ECG | = diagnostic for STEMI | = direct cath |
| | = nondiagnostic | = troponin I / BNP (sent from ER STAT) |
-
- | | | |
|------------|------------|-----------------------------|
| Troponin I | = positive | = early invasive management |
| | = negative | = UA/NSTEMI management |

BNP	≡ positive (>400 pg/mL)	≡ ACS/HF/PE differential dx (high risk)
	≡ positive (100-400 pg/mL)	≡ ACS/HF/PE differential dx (interm risk)
	≡ negative (<100 pg/mL)	≡ UA/NSTEMI management

- Patient admitted for unstable angina/rule out infarction who remains clinically stable for 6 hours

ECG	≡ evolving infarction	≡ direct cath
	≡ nondiagnostic	≡ troponin I (sent 6 hours from admit)

Troponin I	≡ positive	≡ early invasive management
	≡ negative	≡ early inpatient stress testing or discharge for outpt stress within 72 hours

Echocardiography (2D) can be helpful in the stratification of patients with ongoing or recurrent symptoms in whom diagnostic ECG changes for ischemia or infarction are absent. Normal left ventricular function and the absence of wall motion abnormalities on echocardiography during chest pain, while not excluding an ischemic etiology for the symptoms, identifies patients at low short term risk for a major cardiac event.

Revascularization

The findings at cardiac catheterization can serve to guide the choice of therapy: revascularization vs. medical management. The extent of coronary artery disease angiographically along with the extent of LV dysfunction can identify patients who benefit from revascularization with coronary artery bypass grafting surgery. In patients with less extensive disease and an intermediate grade lesions of questionable physiologic significance, stress testing should be employed to help guide the choice of therapy.

Patients found at catheterization to have significant left main disease ($\geq 50\%$) or significant ($\geq 70\%$) three-vessel disease with depressed LV function ($EF < 0.50$) should be considered for early/ immediate CABG surgery. If the patient has received clopidogrel surgery should be delayed for 5 days, unless the benefits of early revascularization are believed to outweigh the increased bleeding risk.

Patients with two-vessel disease which includes a proximal severe stenosis ($>90\%$) of the LAD and depressed LV function should also be considered for early CABG surgery.

Patients with significant CAD should be considered for prompt revascularization (PCI or CABG) if they have any of the following: failure to stabilize with medical treatment; recurrent angina/ischemia at rest or with low-level activities; and/or ischemia accompanied by CHF symptoms, and S3 gallop, new or worsened MR, or marked ECG changes. Patients with elevated troponins in the ACS setting benefit from PCI.

Acute revascularization is indicated for patients with refractory pain (> 1 hour on aggressive medical therapy) who are found at catheterization to have an acutely occluded major coronary vessel or severe subtotal occlusion of a culprit vessel. Patients requiring emergent CABG should undergo surgery irrespective of having received clopidogrel. Patients requiring non-urgent CABG should have surgery delayed for 5 days off clopidogrel.

In patients with significant CAD not included in the above recommendations, performing PCI and/or stenting on the culprit lesion at the time of initial presentation ACS has been shown to be superior. Alternately, aggressive medical therapy without revascularization can be utilized as the initial strategy if a culprit lesion is not clear.

C. Chest Pain

Patients with chest pain or symptoms that possibly represent ischemia who are judged in the initial evaluation phase to have a low likelihood of disease or to be at low risk for adverse outcomes and without elevation in initial troponin I and BNP can be safely evaluated further on the Chest Pain Service. These patients may be admitted for an initial observation period and in the absence of recurrent symptoms undergo early physiologic stress testing or be discharged for outpatient stress testing. Alternately, in select cases these patients may be discharged directly for outpatient stress testing.

Chest Pain Inpatient or Observational Care

Patients who are judged at initial evaluation to have a low risk for adverse outcomes who are admitted to the hospital for observation or in whom after an initial observation period are reassessed to be at low risk should undergo expeditious diagnostic assessment. These patients should receive ASA as part of their initial therapy. Use of clopidogrel and heparin should be determined based on a individual basis.

Patients who remain chest pain free, have no ischemic changes on their ECG, have two negative troponins 6 hours apart, and demonstrate no hemodynamic or arrhythmic instability are candidates for outpatient stress testing. The patients may be discharged home on ASA with prn SL NTG and scheduled for outpatient stress testing within 72 hours. Treatments to reduce the patients long-term cardiovascular risk should also be provided, as indicated.

Initial Therapy:

ASA: all patients without contraindications should be started on ASA (consider clopidogrel)

NTG SL: prescription and instructions on the prn use should be given

Appointment for stress testing within 72 hours

These patient should have a follow-up appointment within 72 hours. Exercise or pharmacologic stress testing should be an integral part of the outpatient evaluation of low-risk patients with chest pain. Testing should be done within 72 hours of presentation. Patients should have explicit written instructions as to the importance of the follow-up evaluation and to re-present immediately if chest pain recurs. Care should be taken to help to ensure that stress testing takes place **within 72 hours** and that patients are not lost to follow-up.

Patients with established coronary artery disease who are already on medical therapy and are felt to be appropriate candidates for outpatient management should have their medical regimen reviewed and dosages increased as appropriate and as tolerated.

As an alternative, early inpatient stress testing may performed. The safety of performing stress testing 6 to 12 hours after admission has been demonstrated in a number of clinical studies. The chances of a clinically significant event being precipitated with stress testing has been shown to be very low in this setting. Early stress testing may also allow for earlier identification of the patient who is having an electrocardiographically silent ischemia at a time when they may still benefit from acute revascularization.

To expedite the patient's work-up and improve efficiency, the patient's management should be planned for in advance, communicated to the nurse, and discussed in detail with the patient and family members, and any potential delays anticipated. Stress testing can be tentatively scheduled for on an inpatient basis to occur 7 hours after the patient is admitted or alternately on a outpatient basis to occur within 72 hours. The cardiac catheterization laboratory should be informed that a potential diagnostic catheterization may be required when the results of stress testing are available. Patients should be kept NPO expect for medications 4-6 hours prior to stress testing so that diagnostic catheterization can be performed the same day as the stress test is obtained, if an invasive evaluation is indicated. Discharge needs and follow-up should be addressed early so that patients with negative or low risk results can be discharged home expeditiously.

Patients with **high-risk results** on physiologic stress testing should be referred for cardiac catheterization. Patients with coronary artery disease but low or intermediate risk results on physiologic stress testing may be started on anti-anginal medical therapy, being referred for catheterization only if their symptoms are refractory to maximal medical therapy or medical therapy is not well tolerated.

VI. Noninvasive Testing

Physiologic stress testing has prognostic value in chest pain and unstable angina to predict death and myocardial infarction. Exercise or pharmacologic stress testing should generally be an integral part of the inpatient or outpatient evaluation of low risk patients with chest pain or unstable angina. Choice of initial stress testing modality should be based on an evaluation of the patient's resting ECG, his or her physical ability to perform exercise, and the imaging modality that is the most readily available. Choice among the different imaging modalities that can be used with exercise or pharmacologic stress testing can be based on cost and accessibility of results since expertise in echocardiography and nuclear imaging is available at UCLA.

The approach to stress testing for evaluation of ischemia in patients presenting to the EMC with chest pain at UCLA has been to combine an imaging modality with stress testing in all patients. Patients with resting ST depression, Q waves, LV hypertrophy, LBBB or IVCD, pre-excitation or who are receiving digoxin should be tested using an imaging modality. Exercise treadmill testing alone maybe considered in patients who are males, with a entirely normal ECG, who are not taking digoxin, and who have a low pre-test probability of ischemia. In these patients it is unclear if an imaging modality adds importantly to a standard treadmill test for initial testing. Repeat testing combined with an imaging modality should be performed in patients with a nonischemic ETT but at a low workload (<6 METs) since these patients have an intermediate risk that can be further stratified.

Patients unable to exercise due to physical limitations (e.g. arthritis, amputation, severe peripheral vascular disease, severe COPD, general debility) should undergo pharmacologic stress testing in combination with an imaging modality.

Provocation of ischemia at a low workload (e.g. < 5 to 6 METs) signifies a high-risk patients who would generally merit referral to cardiac catheterization. Patients without ischemia with an adequate degree of stress (> 6 METs) have a good prognosis and can be managed medically. Patients with only a low workload but no evident ischemia or those who develop ischemia at a high workload, represent an intermediate risk group for whom several alternative strategies can be proposed.

<u>Exercise Test Result</u>	<u>Annual Cardiac Mortality</u>	<u>Management</u>
low risk	< 1%	medical
intermediate risk	2-3%	either
high risk	> 4%	medical + catheterization

A stress test result of intermediate risk combined with evidence of LV dysfunction should prompt referral to cardiac catheterization. An attempt to estimate a patient's risk based on the clinical presentation, risk factors, and stress testing results provides more clinically useful information than a simple normal/abnormal reading of the stress test.

VII. Hospital and Post-Discharge Care

Patients with Coronary Atherosclerosis

Patients with established coronary artery, cerebral vascular, and peripheral atherosclerosis are at high risk for vascular events and cardiac death regardless of identifiable risk factors and regardless of whether they have undergone revascularization. Combination cardiovascular protective therapy targeting the underlying atherosclerotic disease process can markedly improve clinical outcome in patients with atherosclerosis, whereas failure to employ these therapies increases patient mortality. Compliance and treatment utilization can be enhanced by employing secondary prevention measures prior to hospital discharge. Patients should not be discharged from the hospital (including chest pain, unstable angina, acute myocardial infarction, cardiac catheterization, angioplasty, coronary bypass, ischemic heart failure hospitalizations, and diabetes hospitalization for any reason) without initiation of definitive atherosclerosis treatment, unless contraindications exist and are documented.

In patients with coronary, cerebral, or peripheral atherosclerosis and/or diabetes:

Prior to hospital discharge	Send admission (nonfasting) cardiovascular lipid panel and baseline LFTs Prescribe antiplatelet Rx, statin, ACEI, beta blocker, exercise, O3FA, and dietary Rx Document smoking status and advice to stop smoking
Six week follow-up visit	Obtain fasting cardiovascular lipid panel and LFTs in 6 weeks Adjust statin dose or add combination therapy to achieve LDL cholesterol < 70 mg/dL Recheck in 6 months, review medications on each subsequent visit Reinforce adherence to the atherosclerosis treatment regimen

A nonfasting lipid panel obtained in the first 6-12 hours after the onset of acute myocardial infarction has been shown to be relatively accurate. Subsequently, the acute phase reaction, which can begin at 12-24 hours and can take up to 6 weeks to reverse, can lower LDL levels by 25-50%. Lipid panels obtained 12 hours or more after an acute event or after CABG should be interpreted with caution, recognizing the true baseline LDL is likely to be much higher requiring a higher statin dose to achieve LDL < 70 mg/dL. If a lipid panel has not been obtained on admission or in the first few hours of hospitalization, empiric statin initiation and dosing is recommended.

Comprehensive Risk Reduction for Outpatients with Atherosclerosis or Diabetes

There are four classes of medications that have been proven to reduce cardiovascular events and mortality in patients with coronary, other vascular disease, and diabetes. It is recommended that patients with coronary, other vascular disease, and/or diabetes be treated with all four medications, unless contraindications exist or treatment is not tolerated. Individualization of therapy depending on other medical issues and risk of side effects, may be appropriate in certain circumstances. If a patient is not treated with one or more of these medications, it is recommended that the reason be documented in the medical record. The benefits of combination medical therapy with regards to the reduction in the risk of MI, stroke, rehospitalization, need for revascularization, and death continue long term. Since patients with clinically evident atherosclerosis remain at life long risk, life long treatment with each agent is recommended, so long as it well tolerated.

Evidence-based, Mortality Reducing Therapy for Patients with Atherosclerosis or Diabetes:

<u>Aspirin and/or clopidogrel</u>	All patients with atherosclerosis or diabetes, life long therapy*
<u>Beta blocker</u>	All patients with atherosclerosis or diabetes, life long therapy*
<u>ACE inhibitor</u>	All patients with atherosclerosis or diabetes, life long therapy*
<u>Statin</u>	All patients with atherosclerosis or diabetes, life long therapy*
<u>Omega-3 fatty acid</u>	All patients with atherosclerosis or diabetes, life long therapy*

* unless contraindicated, not tolerated, or reason for not using documented in the medical record

Aldosterone antagonists: Patients who are post MI and LVEF ≤ 0.40 , with signs or symptoms of heart failure or diabetes, have reduced mortality risk with aldosterone antagonists (unless contraindicated).

In addition to treatment with the above medications, the following treatment goals should be achieved and maintained, with careful documentation in the medical record:

LDL < 70 mg/dL	Once achieved, document with biannual or annual lipid panel (Secondary goal HDL > 40 mg/dL, Triglycerides < 150 mg/dL)
BP < 140/90 mmHg	Document on each follow-up visit, with additional monitoring as indicated
BP < 130/80 mmHg	If diabetes or renal failure (if diabetes and renal insufficiency BP < 125/75)
No smoking	Current status with regards to smoking should be documented in all current/former smokers. Recommendation for smoking cessation and nicotine replacement/Zyban®/behavior modification attempts should be documented
HbA1C <7.0%	Diabetes management, tight control in diabetics
30-60 min, daily	Physical activity
BMI 21-25 kg/m ²	Achieve weight goal via Mediterranean or therapeutic lifestyle change (TLC) diet.

Medical Regimen for Patients with Atherosclerosis

Aspirin and/or Clopidogrel: Antiplatelet therapy reduces the risk of vascular events in patients with atherosclerosis. Patients should continue on ASA, 81 mg to 162 mg per day indefinitely after discharge. Contraindications include true aspirin allergy with nasal polyposis and active bleeding. Patients with acute coronary syndromes should be treated with combined aspirin and clopidogrel (75 mg daily) for 12 months or indefinitely. Patients that have contraindications or intolerance to ASA should be treated with **clopidogrel** 75 mg daily. Patients with a recurrent event despite ASA should be considered for aspirin plus clopidogrel treatment.

In patients with coronary artery disease, ASA lowers the risk of myocardial infarction, unstable angina, need for revascularization, and death. Pooling data from the four largest trials suggests a 48% reduction in the risk of myocardial infarction and a 51% reduction in the risk of death. This benefit continues beyond ten years. CURE demonstrated the additional benefit of 3 to 12 months of clopidogrel in combination with aspirin in acute coronary syndrome patients.

Statins and other lipid lowering agents: Statins have potent vascular and cardiac protective effects. Statins are indicated in all patients with atherosclerosis or diabetes. Statins reduce vascular inflammation and stabilize the vulnerable atherosclerotic plaque, thereby markedly reducing the risk of vascular events. These benefits are seen in patients with cholesterol and LDL levels in the low, normal, and high range. Clinical trials have shown mortality reduction in patients with baseline LDL levels of 70 mg/dL and above. Initiation of statin therapy in patients with documented atherosclerosis results in a reduction in myocardial infarction, unstable angina, stroke, need for revascularization, hospitalization, and all cause mortality compared to patients treated with diet alone. This is true regardless of whether the patient has undergone CABG, PTCA, or is being treated medically.

These benefits are seen early such that patients should be started on therapy prior to hospital discharge. Early benefits (within 8 - 16 weeks) can be seen in patients presenting with ACS when started on immediate, high dose potent statin treatment (e.g. atorvastatin 80 mg/d) as shown in MIRACL and PROVE-IT.

The starting dose of statin should be a dose estimated to achieve at least a LDL < 70 mg/dL based on the baseline lipid panel or empiric dosing based on clinical trials. In patients where the baseline LDL is known, the use of the UCLA LDL Treatment to Goal Guide is recommended (Table 1). In ACS patients, high dose potent statin treatment, regardless of baseline LDL is recommended. In non-ACS patients where the baseline LDL is pending or not known, empiric doses may be used. Patients who fail to achieve target lipid levels (**LDL < 70 mg/dL**) at 6 weeks after initiation of therapy should have their dose increased or an additional

agent (ezetimibe, niacin, or cholesterol binding resin) added. The combination of a statin and ezetimibe may also be used as first line therapy to achieve LDL goal, with the exception of patients with ACS in whom high dose, potent statin therapy is preferred.

The target lipid levels in patients with AVD or diabetes are LDL cholesterol < 70 mg/dL HDL cholesterol > 40 mg/dL, and triglycerides (TG) < 150 mg/dL. The ideal LDL in all patients is likely LDL < 70 mg/dL (ongoing trials are evaluating this further). The benefits of statins are seen in men and women, older and younger patients, diabetics and nondiabetics. Contraindications include pregnancy or serious underlying liver disease. Obtain baseline LFTs. LDL must be treated to goal first, but if HDL remains below 40 mg/dL or TG remain above 150 mg/dL, specific HDL raising and/or triglyceride lowering interventions such as Niacin, fibrates, or high dose fish oil capsules should be considered (weighing potential benefits with the potential risk of additional side effects and drug interactions). Table 2

Patients with atherosclerosis and/or diabetes will live longer when treated with a HMG CoA Reductase Inhibitor. In the 4S trial there was a 34% risk reduction in major cardiac events, a 42% risk reduction in cardiovascular mortality and a 30% reduction in all cause mortality associated with statin treatment. The LIPID trial demonstrated that even patients with "low or normal" levels of total cholesterol and LDL cholesterol (LDL 70-170 mg/dl) have mortality reduction with statin treatment. The HPS trial demonstrated that patients with LDL < 100 at baseline, derive similar risk reduction to those with higher LDLs. Patients should be educated that these medications are for the treatment of atherosclerosis, not because the patient has "failed" dietary treatment and that use of these medications lowers the risk of recurrent events, need for revascularization, hospitalizations, strokes, and mortality.

ACE Inhibitors: These agents have potent vascular and cardiac protective effects. These agents are indicated in all patients with atherosclerosis. Patients with coronary, peripheral, cerebral vascular disease, and diabetes have reduced risk of MI, stroke, heart failure, and death when treated with an ACE inhibitor. This is true even if the blood pressure and ejection fraction are normal. All post CABG, post PTCA, post unstable angina, post MI, stable CAD, PVD, CVD, and diabetic patients should receive an ACE inhibitor, unless a specific contraindication is documented. Patients with acute myocardial infarction have improved early survival and less heart failure when treated with ACE inhibitors. All MI patients without contraindications should be started on ACE inhibitors within 12-24 hours and treated long term. Patients with left ventricular dysfunction should be started and maintained on an ACE inhibitor indefinitely. Renal insufficiency in the setting of CAD or diabetes is not a contraindication but rather a double indication for ACE inhibitors. The benefit of ACE inhibitors is independent of blood pressure status. Use target doses. Contraindications include history of angioedema, cardiogenic shock, hyperkalemia, and pregnancy. Angiotensin receptor antagonists should be used in ACEI intolerant patients.

The HOPE and EUROPA trials demonstrated that in patients with CAD, CVD, PVD or diabetes the use of an ACE inhibitor was associated with a reduction in cardiovascular events, cardiovascular mortality, and all cause mortality. The PEACE trial was underpowered. This benefit was seen in patients without hypertension and with normal left ventricular ejection fractions. Long term treatment with ACEI is thus indicated in any patient with atherosclerosis.

Beta Blockers: These agents should be considered in all patients with atherosclerosis, since they reduce the risk of myocardial infarction and make it more likely that a patient will survive an infarction. These agents should be considered first line agents for the symptomatic control of angina. In addition these agents prolong survival in patients with previous myocardial infarction as well as reduce the risk of unstable angina in patients with coronary artery disease. These agents also attenuate the remodeling process post myocardial infarction and reduce the risk of developing heart failure. In a patient with coronary artery disease and hypertension, beta blockers are an excellent first line agent. The duration of benefit with therapy extend indefinitely. Use target doses as clinically tolerated. In patients with LVEF < 0.40 with or without heart failure symptoms, carvedilol is preferred. Contraindications include symptomatic bradycardia, 2nd/3rd degree AV block without pacemaker, cardiogenic shock, acutely decompensated heart failure, severe asthma or COPD, diabetic with recurrent life threatening hypoglycemic episodes. Please note that diabetes, peripheral

vascular disease, mild/moderate asthma or COPD, asymptomatic bradycardia, and heart failure are not contraindications and should not preclude the use of beta blockers.

Omega-3 Fatty Acids: Omega-3 fatty acids have been demonstrated to have a variety of cardiovascular protective effects. Fish oil supplementation has been demonstrated in clinical trial to reduce the risk of cardiovascular events by 10 to 20%. This benefit was additive to cardiovascular protective medications. It is recommended that all patients with atherosclerosis or diabetes be treated with omega 3 fatty acid supplementation, with therapy beginning in the hospital. Patients may be treated with fish oil capsules containing 800 to 1000 mg of omega-3 fatty acids (eicosapentaenoic acid, [EPA] and docosahexaenoic acid, [DHA]) PO daily. Alternative supplements include flax seed oil or canola oil.

Aldosterone Antagonists: These agents are indicated in patients with AMI and left ventricular ejection fraction ≤ 0.40 and who have signs or symptoms of heart failure or diabetes, in the absence of contraindications. These agents attenuate remodeling and have been demonstrated to benefit patients with acute myocardial infarction with left ventricular dysfunction with heart failure symptoms. Patients should be clinically stabilized prior to initiation of the aldosterone antagonist. This therapy is only indicated in patients with systolic dysfunction (LVEF ≤ 0.40), not all ACS patients. Start low dose and need to closely monitor potassium levels and renal function. Hyperkalemia is an absolute contraindication. Use extreme caution if Cr > 2.5 mg/dL in men or > 2.0 mg/dL in women. Starting either spironolactone at 6.25 mg PO daily with target dose of no more than 25 mg daily or Eplerenone 25 mg daily starting dose with target dose of 50 mg daily. *The EPHESUS trial demonstrated a 15% reduction in mortality with the selective aldosterone antagonist eplerenone in AMI patients with LVEF $< 40\%$ with heart failure signs or symptoms.*

Nitrates: These agents should be considered second line agents after beta blockers for the symptomatic control of angina. There is no long term data that nitrates improve prognosis in patients with coronary artery disease so that their use is dictated solely for symptom relief. Patients who are not having symptomatic angina do not need to be routinely discharged on long acting nitrates. When long acting nitrates are indicated, a daily nitrate free interval is necessary to decrease tolerance. Patient should be discharged with prn SL nitroglycerine as well as instructions as to its use.

Calcium channel blockers: These agents decrease chest pain but do not decrease the risk of a cardiac event or improve outcome, independent of blood pressure control. In patients with angina there is an increased risk of coronary events with calcium blockers as compared to angina control with beta blockers. In patients with coronary artery disease and hypertension these agents should be reserved for patients who are intolerant of or fail to have their blood pressure controlled with beta blockers, ACE inhibitors, angiotensin receptor blockers, diuretics, and their combination.

Antiarrhythmic agents: Type I antiarrhythmic agents markedly increase the risk of sudden death in patients with coronary artery disease. This is because all type I antiarrhythmic agents markedly lower the fibrillation threshold of ischemic myocardium. Even when used to maintain sinus rhythm for atrial fibrillation or when guided by EPS or Holter monitoring, these agents increase the risk of overall mortality for CAD patients. These agents should be avoided in all patients with CAD except those with ICDs or in whom the risk benefit ratio has been carefully considered. Amiodarone should be considered the only safe antiarrhythmic agent in patients with CAD. *Compared to placebo amiodarone was neutral with respect to sudden death and mortality in post MI trials.*

Exercise: Patients should receive specific instructions for a minimum of 5 x week aerobic exercise program. Exercise increases HDL, reduces the risk of myocardial infarction, and improves survival in patients with coronary artery disease. Either a home based program or supervised cardiac rehabilitation can be recommended. After AMI or CABG a supervised cardiac rehabilitation program is recommended. Exercise is an essential component of the management of patients with coronary artery disease and is highly effective in preventing subsequent cardiac events. Patients should be offered referral to a cardiac rehabilitation program in their area. In addition to a specific exercise prescription patients require instructions on activities that are permissible and those that should be avoided (e.g. heavy lifting).

Smoking Cessation: Particular attention should be paid to smoking cessation counseling. Patients who continue to smoke after presenting with unstable angina have 5.4 times the risk of death from all causes compared to patients who stop smoking. Patients should be offered intensive smoking cessation intervention during hospitalization. This should include both physician and nurse counseling focusing on relapse prevention. Patients should receive a relapse prevention manual and be given written information about the outpatient behavioral modification programs available and the option of nicotine replacement therapy and/or bupropion (Zyban). The recommendation for smoking cessation should be clearly documented in the medical record.

Diet: Although standard dietary intervention alone has not been shown to be beneficial, other dietary interventions such as the Mediterranean diet may provide benefit. Patients and family members, if available, should receive counseling on the National Cholesterol Education Program TLC diet or Mediterranean diet and recommended body weight (body mass index) during the hospitalization. Information on the outpatient dietary modification programs available should be provided. Supplementation with Omega 3 fatty acids has lowered the risk of recurrent myocardial infarction. Discourage use of very low fat diets.

Patient Education: The patient and his or her family member or advocate should be instructed regarding the use of medications and monitoring of symptoms. The purpose, dose, and major side effects of each medication prescribed should be explained. Written medication sheets and a medication schedule should be provided to each patient. The warning signs of a heart attack should be discussed with each patient and their immediate plan of action reviewed, including call 911. A patient education sheet should be provided. Patients should be instructed to contact their primary care physician or cardiologist if they have a non-acute change in symptom pattern and discuss whether changes in the management plan are warranted. *Patient delays in seeking medical attention are a major contributor to diminished benefit with reperfusion therapy. Detailed patient education has been demonstrated to reduce the time to treatment in acute myocardial infarction.*

Follow-up: Continuation of the therapies targeting the underlying atherosclerotic disease process markedly improve clinical outcome in patients with atherosclerosis. The continued use of the beneficial therapies prescribed should be strongly reinforced during patient follow-up. The medications the patient is taking should be reviewed on each visit. If one or more of the survival enhancing medications is not prescribed, the specific contraindication or intolerance should be clearly documented in the medical record.

After initial statin treatment, a fasting lipid panel should be obtained at 6 weeks to evaluate whether target lipid levels have been achieved and guide cholesterol lowering medication dosing adjustments. Obtain LFTs at 6 weeks and with any dose escalation. CPK need only be checked if muscular symptoms arise. Document LDL < 70 mg/dL on biannual or annual basis. Document BP and Diabetes control. The need for daily aerobic exercise should be reinforced and the patient's progress monitored. Stress testing does not appear to be indicated in the routine follow-up of patients with coronary artery disease and should, in general, be performed for specific reasons such as a change in symptoms or in following patients with silent ischemia.

Document:

Current medications (if ASA, beta blocker, ACE inhibitor, or statin not currently prescribed, document contraindication, intolerance, or alternative medication utilized)

LDL, HDL, and TG (from within last 1 year)

Current blood pressure

Weight and height (body mass index)

If history of heart failure, LVEF

If diabetes, HbA1c from within last 1 year, annual ophthalmology retinal exam, foot exam and care

If history of smoking, current status and advice to quit smoking

Use of pneumococcal vaccination if heart failure, CAD, diabetes, pneumonia, age > 65.

Annual influenza vaccination

Patients without Coronary Artery Disease

Patients with peripheral vascular disease, cerebral vascular disease, and diabetes should be treated with the secondary prevention measures as above. Patients who on the basis of their complete evaluation and physiologic stress testing are felt not to have clinically evident coronary artery disease, other vascular disease, or diabetes should be advised regarding effective primary prevention measures. Therapy that has been appears to prolong survival in individuals without overt coronary artery disease includes aspirin, smoking cessation, and exercise. Male patients over the age of 40 and females over the age of 50 with one or more additional cardiovascular risk factors without contraindications should be started on ASA at a dose of 81 mg to 162 mg daily. Cardiovascular events can be reduced with control of blood pressure using beta blockers, ACE inhibitors, or diuretics in patients with hypertension. Cholesterol lowering medications can reduce the risk of myocardial infarction but no reduction in overall mortality has been demonstrated in individuals without overt CAD, PVD, CVD, or diabetes. Therapy should be reserved for patients with hypercholesterolemia in the setting of additional risk factors. Patients and their families and advocates should understand the most likely diagnosis at the conclusion of their evaluation. All patients should be counseled on risk factor modification. Patients should be advised as to the warning signs of a heart attack and to seek medical attention if suggestive symptoms occur.

Medical Record

The patient's medical record at the time of hospital discharge should summarize cardiac events, results of diagnostic testing, current symptoms, and the discharge medical regimen. The major instructions, postdischarge follow-up plan, follow-up physician, and the patient's understanding and plan for adherence to the recommendations should be documented in the medical record. The comprehensive care plan for secondary prevention should be summarized. The primary care physician that will be providing follow-up care should be contacted and the treatment plan discussed.

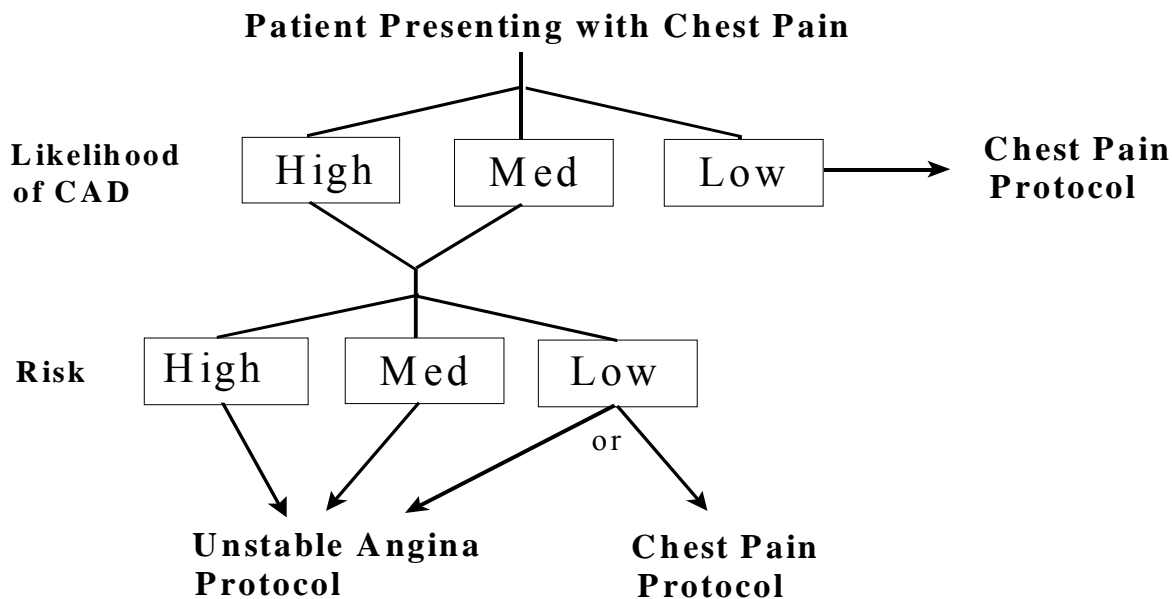
Clinical Guidelines Committee, UCLA Division of Cardiology

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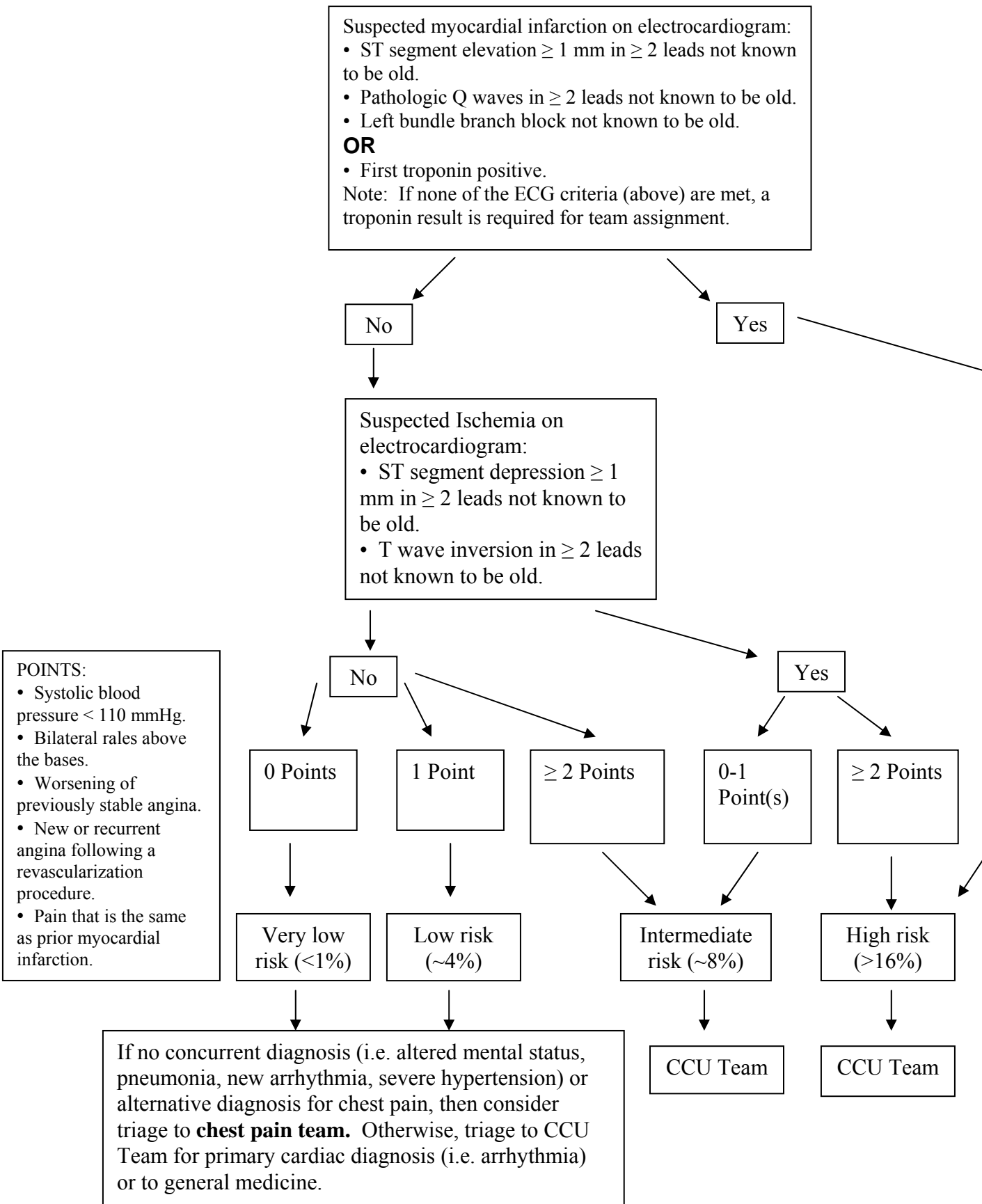
Patient Stratification



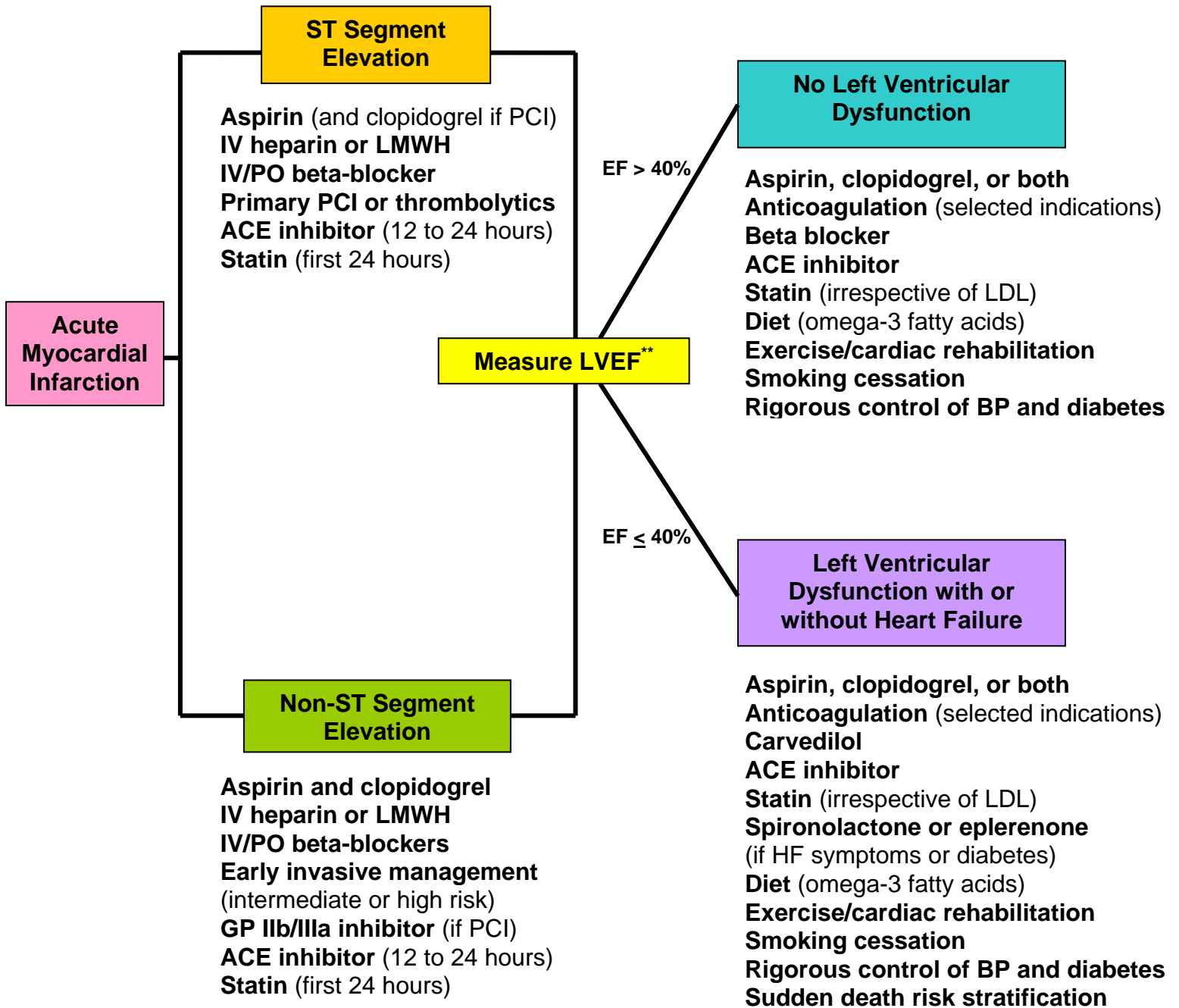
Treatment Stratification

	<i>Low Likelihood</i>	<i>Medium Likelihood</i>	<i>High Likelihood</i>
<i>Low Risk</i>	ASA Outpt/(Inpt) Stress Test	ASA/Clopid/(Heparin) Outpt/Inpt Stress Test/Cath	ASA/Clopid/(Heparin) Outpt/Inpt Cath/(Stress Test)
<i>Medium Risk</i>	ASA/Clopidogrel Outpt/(Inpt) Stress Test/Cath	ASA/Clopid/Heparin Inpt Cath	ASA/Clop/Heparin Inpt Cath
<i>High Risk</i>	ASA/Clopid/(Heparin) Outpt/(Inpt) Stress Test/Cath	ASA/Clop/Heparin Inpt Cath	ASA/Clop/Heparin/(gpRA) Inpt Cath

Chest Pain Service Triage Algorithm



Treatment Algorithm for Acute Myocardial Infarction with or without Left Ventricular Dysfunction*



*All patients without contraindications or intolerance.

**Include ischemic risk stratification, if not previously catheterized (i.e. stress testing).