Treatment of acute coronary syndrome: Part 1: Non-ST-segment acute coronary syndrome

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Objective: **Acute coronary syndrome is a common cause of morbidity and mortality, both in the United States and worldwide. The goal of this review is to familiarize clinicians with recent information regarding the diagnosis and treatment of acute coronary syndrome.**

Data Sources: **PubMed search and review of the relevant medical literature.**

Summary: **Acute coronary syndrome encompasses three clinical diagnoses: unstable angina, non-ST-segment elevation myocardial infarction), and ST-segment elevation myocardial infarction. The definition, pathophysiology, clinical presentation, diagnosis, and treatment of unstable angina/non-ST-segment elevation myocardial infarction are reviewed here. Diagnosing unstable angina/non-ST-segment elevation myocardial infarction is a significant challenge in critically ill patients not initially suspected of having acute coronary syndrome (i.e., noncardiac intensive care unit patients), and diagnostic and treatment strategies for these patients have not been clearly established.**

Conclusions: **Patients with acute coronary syndrome benefit from intensive medical therapy, including antianginal, antiplatelet, antithrombotic, and statin agents. Depending on their risk for future cardiovascular events as well as their risk of bleeding complications, patients may benefit from either an early invasive treatment strategy, in which routine coronary revascularization is performed, or a conservative strategy, in which revascularization is reserved for patients with recurrent or provocable cardiac ischemia. (Crit Care Med 2011; 39:000–000)**

Key Words: acute coronary syndrome; acute myocardial infarction; unstable angina; coronary artery disease

Acute coronary syndrome (ACS) encompasses three clinical conditions: unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction that results from an acute imbalance between myocardial oxygen supply and demand and leads to myocardial ischemia.

The patient with unstable angina has cardiac chest pain that is new or worsening (i.e., occurring at rest and/or increasing in intensity, duration, or frequency) without serologic evidence of myonecrosis (i.e., no elevation of serum troponin or creatine kinase MB isoenzyme concentration). Many, but not all, patients with unstable angina have dynamic electrocardiographic (ECG) changes (i.e., ST depression and/or T wave inversion). NSTEMI is diagnosed when the patient with cardiac chest pain has serologic evidence of myocardial necrosis in the absence of ST-segment elevation on the ECG. Unstable angina and NSTEMI are collectively referred to as NSTEMI-ACS. The patient with ST-segment elevation myocardial infarction has cardiac chest pain, serologic evidence of myonecrosis, and persistent (>20 mins) ST-segment elevation. Management of the patient with ST-segment elevation myocardial infarction will be discussed in an upcoming review article.

In the critically ill patient with ACS, it is important to determine whether ACS is primary or secondary. Most patients have primary ACS, which results from rupture of an atherosclerotic coronary plaque with subsequent platelet aggregation, thrombus formation, and subtotal coronary occlusion causing myocardial ischemia or infarction. Some patients have secondary ACS, which results from a transient or sustained marked imbalance between myocardial oxygen supply and demand. Substantial reductions in oxygen supply can be caused by anemia, hypoxemia, or systemic arterial hypotension; marked increases in oxygen demand can be caused by fever, tachycardia, severe systemic arterial hypertension, or thyrotoxicosis (1). In the patient with secondary ACS, therapy should be directed at correcting the underlying cause.

Epidemiology

Nearly 1.4 million people are hospitalized annually with ACS, of whom two-thirds have unstable angina or NSTEMI (2). ACS is more common in individuals with one or more risk factors for atherosclerosis, peripheral vascular disease, or a chronic inflammatory disorder such as rheumatoid arthritis, psoriasis, or infection.

Pathophysiology

The most common cause of ACS is rupture of a "vulnerable" atherosclerotic coronary plaque. Less commonly, coronary embolism, coronary vasospasm resulting from focal endothelial dysfunction (e.g., Prinzmetal's angina), drug ingestion (e.g., cocaine), or spontaneous coronary artery dissection (i.e., seen in vasculitis and peripartum women) may acutely reduce coronary blood flow and cause myocardial ischemia. If the episode of myocardial ischemia is short-lived, cardiac symptoms are present transiently and serologic evidence of myonecrosis is absent, leading to a diagnosis of unstable angina. If myocardial ischemia is more

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Table 1. Likelihood that signs and symptoms represent a primary acute coronary syndrome

Feature	High Likelihood (Any of the Following)	Intermediate Likelihood (Absence of High Likelihood and Any of the Following)	Low Likelihood (Absence of High or Intermediate Features but may have)
History	Chest or left arm pain as the main symptom, similar in nature to previously noted angina Known coronary artery disease	Chest or left arm discomfort as main symptom Age >70 yrs Male gender Diabetes mellitus	Probable ischemic symptoms in the absence of any of the intermediate likelihood characteristics Recent cocaine use
Examination	Transient mitral regurgitation murmur, hypotension, diaphoresis, or pulmonary edema	Extracardiac vascular disease	Chest discomfort reproduced by palpation
Electrocardiogram	New or transient ST segment deviation (≥1 mm) or T wave inversion in multiple precordial leads	Q waves, ST-segment depression (0.5–1 mm), or T wave inversion (>1 mm) in leads with dominant R waves	T wave flattening or inversion <1 mm in leads with dominant R waves Normal electrocardiogram
Cardiac markers	Elevated serum troponin or creatine kinase MB concentration	Normal serum troponin or creatine kinase MB concentration	Normal serum troponin or creatine kinase MB concentration

Modified from Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. *Circulation* 2007; 116:e148–304.

prolonged, myonecrosis occurs and the patient is diagnosed with NSTEMI.

Clinical Presentation

Patient History and Physical Examination. The patient with ACS most commonly reports chest discomfort at rest. It is typically described as a "dull," "pressure," "heaviness," or "squeezing" sensation. The onset of pain can be sudden or gradual and can be either intermittent (i.e., "stuttering") or persistent with a duration of minutes to hours. A "prodrome" of exertional chest pain may or may not precede rest symptoms. Patients may report radiation of the discomfort to the neck, jaw, or either arm and associated symptoms include nausea, dyspnea, diaphoresis, abdominal pain, and/or syncope. An occasional patient presents with atypical symptoms such as sharp chest pain, indigestion or epigastric pain, fatigue, and/or dyspnea.

The physical examination in a patient with ACS is usually unremarkable. Patients with extensive myocardial ischemia may have examination findings consistent with left ventricular dysfunction such as a left ventricular gallop (usually an S3), tachycardia, hypotension, and signs of peripheral hypoperfusion.

Differential Diagnosis

It is important to exclude life-threatening causes of chest pain such as pneumothorax, pulmonary embolism, aortic dissection, and esophageal rupture. Non-life-threatening causes of chest pain such as pericarditis, costochondritis, and pneumonia should also be considered in the differential diagnosis. An acute intra-abdominal process such as a perforated peptic ulcer or acute cholecystitis can sometimes mimic ACS symptoms.

Diagnosis

Prompt diagnosis and treatment can minimize the complications of ACS. The diagnosis of ACS is based on four major components: the patient's history, physical examination, ECG, and cardiac biomarkers. Table 1 lists features of each of these components that indicate a high, intermediate, or low likelihood of primary ACS.

Electrocardiogram

Findings that suggest a high likelihood of NSTEMI-ACS include transient ST-segment depression (≥1 mm) or T wave inversion in two or more contiguous precordial leads that occurs with symptoms and resolves when the patient is asymptomatic. Conversely, an ECG that is normal during symptoms confers a low likelihood of ACS. The presence of ST-segment elevation in two contiguous leads, a new or indeterminate left bundle branch block, or isolated ST-segment depression in the right precordial leads (e.g., V1 and V2, indicative of an acute posterior infarct) suggests the presence of an ST-segment elevation myocardial infarction.

Cardiac Biomarkers

The serologic detection of myonecrosis is necessary to distinguish between unstable angina and NSTEMI and helpful in distinguishing between cardiac and noncardiac diagnoses. Cardiac troponins (either I or T) are the preferred serum cardiac biomarkers for detecting myonecrosis (3). Troponins are contractile proteins found only in cardiac myocytes. When myonecrosis occurs, they are released into the blood, where they can be detected within 4–6 hrs of symptom onset. Serum troponin may be undetectable early after myocardial injury. Therefore, if clinical suspicion for ACS is high and the initial serum troponin concentration is normal, a second measurement should be obtained 4–8 hrs later. The troponins are more sensitive and specific than the total creatine kinase and creatine kinase MB, which are often included in laboratory "cardiac panels." Serum cardiac troponin levels remain elevated for 1–2 wks after an acute myocardial infarction, whereas the creatine kinase MB returns to normal within 24–48 hrs.

Diagnosing ACS in Critically Ill Patients

Although an increased serum troponin level is diagnostic of cardiomyocyte "injury," it is so sensitive that elevations are observed in numerous non ACS settings (Table 2). Accordingly two of three criteria must be met to diagnose myocardial infarction: prolonged ischemic symp-

Table 2. Conditions associated with elevated serum troponin levels

Cardiac	Noncardiac
Myocardial infarction/acute coronary syndrome	Shock
Percutaneous coronary intervention	Sepsis/systemic viral infections
Pericarditis	Vaccination
Myocarditis	Renal failure/hemodialysis
Congestive heart failure (acute or chronic)	Rhabdomyolysis
Takotsubo cardiomyopathy	Cerebrovascular accident/subarachnoid hemorrhage
Tachycardia	Chemotherapy
Defibrillation	Hypertension/hypotension
Myocardial contusion	Pulmonary embolism
Aortic dissection	Severe asthma/respiratory distress
Infiltrative disorders (amyloid, sarcoid, etc.)	Strenuous exercise

Table 3. Risk models used to identify high risk patients who would benefit from aggressive medical therapy and an early invasive strategy

Thrombolysis in Myocardial Infarction Risk Model Variables	Global Registry of Acute Coronary Events Risk Model Variables
Age >65 yrs	Age
Three or more risk factors for atherosclerosis	Killip class
Known coronary artery disease	Systolic arterial pressure
Two or more episodes of angina pain in the 24 hrs before hospitalization	ST-segment deviation of ≥0.05 mV
Aspirin use in the 7 days before hospitalization	Cardiac arrest during presentation
ST-segment deviation of ≥0.05 mV	Serum creatinine concentration
Elevated serum markers for myonecrosis (troponin or creatine kinase MB)	Elevated serum markers for myonecrosis (troponin or creatine kinase MB)
	Heart rate

toms, diagnostic ECG changes, and elevation of troponin or creatine kinase MB.

Elevated cardiac enzymes in the absence of chest pain or ECG changes should prompt the physician to consider conditions other than ACS and delay treatment with antiplatelet agents, anticoagulants, and an invasive strategy, unless otherwise indicated. With proper treatment of the non-ACS condition, serum cardiac enzyme levels typically normalize. In the patient with elevated serum troponin levels resulting from uncontrolled tachycardia or hypertension, administration of a β-adrenergic blocker or rate-limiting calcium channel blocker is appropriate. Conversely, these agents should be avoided if elevated serum troponin levels are the result of congestive heart failure, because diuresis and afterload reduction (i.e., an angiotensin-converting enzyme inhibitor) would be most appropriate in this situation. In the patient with renal failure, multiple medical conditions (volume overload, hypertension, anemia, acidosis, infection, etc.) may cause elevation of serum cardiac enzymes. Therapy directed at these conditions is more appropriate than approaching the patient as if he or she has an ACS. Accordingly, antiplatelet, anticoagulation therapy, and cardiac catheterization are not indicated in these patients.

Elevated serum troponin levels are present in up to 50% (4–6) of medical intensive care unit patients and associated with increased inhospital mortality, even in those without significant coronary artery disease (7–12). When the patient's clinical history is unavailable (i.e., patient is intubated and/or delirious) and the ECG is nondiagnostic, critical care providers often rely on cardiac biomarkers, particularly troponin, to establish a diagnosis of ACS. Unfortunately, because many conditions other than ACS may cause elevated serum troponin levels in the absence of significant obstructive coronary artery disease (Table 2), these diagnoses should be considered and excluded before a diagnosis of primary NSTEMI-ACS is made.

Several clinical clues may help in diagnosing primary NSTEMI-ACS in the critically ill patient. First, a history obtained from the patient's family or friends may reveal preceding symptoms of unstable or progressive angina. Second, comparison of recent and previous ECG tracings may reveal changes suggestive of ischemia and/or infarction. Third, imaging modalities such as echocardiography can identify new cardiac wall motion abnormalities suggestive of myocardial ischemia or infarction. Fourth, acute changes in the patient's condition such as hemodynamic instability, hypoxemia (from cardiogenic pulmonary edema), sustained ventricular arrhythmias, or a new mitral regurgitation murmur (from papillary muscle dysfunction) may represent clinical manifestations of ACS.

Importance of Risk Stratification

Early risk stratification is important to identify patients at high immediate and long-term risk of death and cardiovascular events, who should be evaluated by a cardiologist and in whom intensive medical therapy and an early invasive strategy may reduce that risk. It is equally important to identify patients at low risk in whom potentially hazardous and costly invasive and medical treatments provide little benefit or in fact may cause harm. Two risk-assessment algorithms—the Thrombolysis in Myocardial Infarction (TIMI) (13, 14) and Global Registry of Acute Coronary Events (GRACE) risk models (15) (Table 2)—have been developed for determining whether a patient is at high risk or at relatively low risk for having an ischemic event.

The TIMI risk score uses seven easily assessed variables to identify patients with ACS who are at risk for death, myocardial infarction, or recurrent ischemia within 14 days after hospitalization. Patients with three or more of the seven variables are considered to be at high risk, whereas those with no more than two of the variables are considered to be at low risk.

The GRACE risk model uses eight variables to predict whether a patient will die or have a myocardial infarction in the hospital or in the next 6 months. Each variable is assigned a numeric score on the basis of its specific value, and the eight scores are added to yield a total score, which is applied to a reference nomogram (available at www.outcomes-umassmed.org/grace) to determine the patient's risk.

A substantial benefit with an early invasive strategy has only been proved in patients at high risk (three or more TIMI risk factors or GRACE risk score >140) (Table 4). A comparison of the TIMI and

Table 4. Appropriate use and timing of invasive strategy in patients with acute coronary syndrome

Timing of Invasive Strategy	Indications
Emergent (<2 hrs)	Refractory angina with associated heart failure, arrhythmia or hemodynamic instability
Early invasive (<24 hrs)	Global Registry of Acute Coronary Events Risk Model score ≥140 and absence of very high risk features
Late invasive (within 72 hrs)	Recurrent symptoms or stress-inducible ischemia and Global Registry of Acute Coronary Events Risk Model score <140
Should not be performed	Low-risk patient and/or considered to be at increased risk for complication with invasive testing or percutaneous coronary intervention

GRACE risk algorithms showed that either can be used effectively to predict the rates of death or myocardial infarction for 1 yr after hospitalization for an ACS (16).

Because intensive medical therapy and invasive management are associated with bleeding complications, the patient's risk of such events should be assessed before these therapies are administered. The bleeding risk can be estimated with the tool available at www.crusadebleedingscore.org (17). Older age, female sex, low body weight, renal insufficiency, tachycardia, high or low systolic arterial pressure, low hematocrit, and a history of diabetes mellitus predict an increased risk of major bleeding (Table 5), often as a result of the administration of excessive doses of antiplatelet or anticoagulant agents.

Treatment

Treatment of the patient with primary ACS is summarized in Table 5 and aimed at: 1) relieving angina; 2) preventing thrombus propagation; 3) stabilizing the "vulnerable" plaque; and and 4) identifying those considered to be at high risk for developing recurrent ischemia or infarction that would benefit from coronary revascularization.

Relieving Angina

Antianginal medications include nitroglycerin, morphine, β-adrenergic blockers, and calcium channel blockers. These medications favorably affect the balance between myocardial oxygen supply and demand.

Table 5. Variables associated with increased risk of bleeding complications

Age > 75 yrs
Female gender
Renal insufficiency (glomerular filtration rate <30 mL/min
Low body weight
Tachycardia
High or low systolic arterial pressure
Low hematocrit
Diabetes mellitus
Bleeding history
Use of femoral access
Intensive antiplatelet or anticoagulation therapy

Nitroglycerin increases myocardial oxygen supply by dilating coronary arteries and reduces myocardial oxygen demand by reducing left ventricular preload and afterload. Nitroglycerin can be given sublingually, by spray, or intravenously and is a first-line agent for treating chest pain resulting from cardiac ischemia. Intravenous morphine can be given for chest pain not immediately relieved with nitroglycerin; morphine reduces ventricular preload, which decreases myocardial oxygen demand.

Beta-adrenergic blockers decrease myocardial demand by reducing heart rate, blood pressure, and myocardial contractility. They also reduce the risk of recurrent myocardial infarction in patients with ACS. Intravenous administration should be considered in the patient with ACS with persistent chest pain, tachycardia, or hypertension. In the patient without these findings, treatment can be initiated orally. Beta-adrenergic blockers should be avoided in the patient with decompensated heart failure, advanced atrioventricular block, hypotension, or suspected cocaine use (as a result of the risk of unopposed α-adrenergic receptor stimulation).

Calcium channel blockers improve myocardial oxygen supply through coronary vasodilation and reduce oxygen demand by reducing afterload (i.e., systemic arterial pressure). Two calcium channel blockers—diltiazem and verapamil—also reduce heart rate and myocardial contractility, which further decreases myocardial oxygen demand. Calcium channel blockers are considered a second-line agent for angina relief in patients with ACS. A rate-limiting calcium channel blocker—diltiazem or verapamil—may be used in patients unable to take a β-adrenergic blocker and those with persistent ischemic symptoms despite treatment with nitroglycerin and a β-adrenergic blocker.

Reducing Thrombus Propagation

To reduce thrombus propagation, the patient with ACS should receive antiplatelet and antithrombotic therapy, unless contraindicated. Antiplatelet agents used in patients with ACS include aspirin, thienopyridines, and glycoprotein IIb/IIIa inhibitors. Antithrombotic agents used in patients with ACS include unfractionated heparin, low-molecular-weight heparin, fondaparinux, and bivalirudin. Although fibrinolytic therapy improves survival in patients with acute ST-segment elevation myocardial infarction, it is contraindicated in patients with unstable angina or NSTEMI in whom its administration has been shown to increase mortality.

Antiplatelet Therapy. Initiation of at least two antiplatelet agents—preferably aspirin and clopidogrel—is recommended in the patient with suspected or confirmed ACS. Aspirin blocks the synthesis of thromboxane A2, a potent vasoconstrictor and stimulator of platelet aggregation. Compared with placebo, aspirin (initial dose of 162–325 mg followed by 75–162 mg daily) reduces the risk of death or recurrent myocardial infarction by 50% in patients with ACS (18–21).

Thienopyridines (i.e., clopidogrel and prasugrel) block platelet adenosine diphosphate receptors, thereby reducing platelet activation and aggregation. Combined clopidogrel and aspirin therapy reduces short- (30-day) and long-term (1-yr) cardiovascular events in patients with ACS patints by 20% in comparison to treatment with aspirin alone (22–24). Prasugrel has a greater antiplatelet effect and more rapid onset of action than clopidogrel. In patients with ACS treated with aspirin and percutaneous coronary intervention, prasugrel therapy is associated with a lower risk of cardiovascular death, myocardial infarction, or stroke at 6 months than clopidogrel therapy (9.9% vs. 12.1%; $p < .001$) and an increased risk for major bleeding (2.4% vs. 1.8%; $p = .03$) (25). Currently, prasugrel is only approved for use in patients with ACS managed with percutaneous coronary intervention. It is not recommended in patients with weight <60 kg, age >75 yrs, or a history of transient ischemic attack, stroke, or intracranial bleeding resulting from excessive bleeding risk.

Table 6. Therapy of acute coronary syndrome based on risk stratification of the patient

Therapy	Initiation	Duration	Dose, Route, and Duration	Dosing With Reduced Glomerular Filtration Rate
Low-risk patient				
Antianginal				
Beta-blocker[a]	Immediately	Hospitalization ± indefinitely	Metoprolol, 5 mg IV boluses (three given 2–5 mins apart), then 50 mg orally twice daily titrated up to 100 mg twice daily or atenolol, 5–10 mg IV bolus then 100 mg orally daily	No change
Nitroglycerin	Immediately	Hospitalization ± indefinitely	0.3–0.6 mg sublingually or 5–10 μg/min IV initially and increased by 10 μg/min every 5 min	No change
Diltiazem or verapamil[a]	Immediately	Hospitalization ± indefinitely	30–90 mg orally four times daily or up to 360 mg of long-acting preparation orally daily	No change
Lipid-lowering				
Statin	Before hospital discharge	Indefinitely	Atorvastatin, 80 mg orally daily	No change
Antiplatelet				
Aspirin	Immediately	Indefinitely	162–325 mg orally initial dose, then 81 mg orally daily	No change
Clopidogrel	Immediately	1–12 months	300 mg orally initial dose, then 75 mg orally daily	No change
Anticoagulant				
Unfractionated heparin	Immediately	2–5 days	60 U/kg IV bolus, then 12 U/kg IV adjusted to achieve an activated partial thrombin time of 50–70 secs	No change
High-risk patient				
Antianginal				
Beta-blocker[a]	Immediately	Hospitalization ± indefinitely	Metoprolol, 5 mg IV boluses (three given 2–5 mins apart) then 50 mg orally twice daily titrated up to 100 mg twice daily or atenolol, 5–10 mg IV bolus then 100 mg orally daily	No change
Nitroglycerin	Immediately	Hospitalization ± indefinitely	0.3–0.6 mg sublingually or 5–10 μg/min IV initially and increased by 10 μg/min every 5 mins	No change
Diltiazem or verapamil[a]	Immediately	Hospitalization ± indefinitely	30–90 mg orally four times daily or up to 360 mg of long-acting preparation orally daily	No change
Lipid-lowering				
Statin	Before hospital discharge	Indefinitely	Atorvastatin, 80 mg orally daily	No change
Antiplatelet				
Aspirin	Immediately	Indefinitely	162–325 mg orally initial dose then 81 mg orally daily	No change
Clopidogrel	Immediately	1–12 months	300 mg orally initial dose then 75 mg orally daily	No change
Glycoprotein IIb/IIIa inhibitor (eptifibatide, tirofiban, or abciximab)	At time of PCI	12–24 hrs post-PCI	Abciximab, 0.25 mg/kg IV bolus then 0.125 μg/kg/min IV for 12 hr or eptifibatide, 180 μg/kg IV bolus then 2.0 μg/kg/min IV for 18–24 hrs or tirofiban, 0.4 μg/kg/min IV for 30 mins then 0.1 μg/kg/min IV for 12–24 hrs	Avoid abciximab; with eptifibatide and tirofiban, reduce rate of maintenance infusion by 50% with creatine clearance <50 mL/min or <30 mL/min, respectively
Anticoagulant				
Unfractionated heparin or	Immediately	2–5 days	60 U/kg IV bolus then 12 U/kg IV adjusted to achieve an activated partial thrombin time of 50–70 secs	No change
Enoxaparin or	Immediately	Duration of hospitalization (up to 8 days); discharge after successful PCI	1 mg/kg subcutaneously twice daily	Extend dosing interval to 1 mg/kg every 24 hrs if creatine clearance <30 mL/min
Bivalirudin	Immediately	4 hrs post-PCI	0.75 mg/kg intravenous bolus followed by an infusion of 1.75 mg/kg/hr	No change
Invasive management				
Coronary angiography followed by revascularization (if appropriate)	Up to 36–80 hrs after hospitalization; within 24 hrs in "very-high-risk" patients			Weigh increased risk of bleeding vs. benefit of invasive strategy

PCI, percutaneous coronary intervention; IV, intravenous.
[a]Avoid in the patient with decompensated heart failure, hypotension, or hemodynamic instability.

Table 7. Randomized clinical trials comparing timing of invasive treatment strategies in patients with acute coronary syndrome[a]

Early vs. Late Invasive Therapy in Non-ST Segment Elevation Myocardial Infarction Acute Coronary Syndrome					
Trials	ELISA	ISAR-COOL	OPTIMA	TIMACS	ABOARD
Patients	220	410	142	3031	352
Enrollment period	2000–2001	2000–2002	2004–2007	2003–2008	2006–2008
Time to angio, hrs[b]	6 vs. 50	2.4 vs. 86	0.5 vs. 25	14 vs. 50	1.2 vs. 21
Invasive, %[b]	74/77	78/72	100/99	74/69	91/81
Primary outcome	Infarct size lactate dehydrogenase	D/MI 1 month	D/MI/unplanned revascularization 30 days	D/MI/S 6 months	Troponin release
End point met	Yes	Yes	No	No	No

D, death; MI, myocardial infarction.

[a]Studies: ABOARD, Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate of Delayed Intervention; ELISA, Early or Late Intervention in Unstable Angina; ISAR-COOL, Intracoronary Stenting With Antithrombotic Regimen Cooling-Off; TIMACS, Timing of Intervention in Acute Coronary Syndromes trial; [b]at the time the primary end point was reported.

The glycoprotein IIb/IIIa inhibitors—abciximab, eptifibatide, and tirofiban—block the platelet IIb/IIIa receptor, which is essential for platelet aggregation. These agents reduce recurrent ischemia and myocardial infarction in patients with ACS who undergo percutaneous coronary intervention (26–29). In the patient with NSTEMI-ACS in whom an invasive (e.g., cardiac catheterization) strategy is planned, either clopidogrel or a glycoprotein IIb/IIIa inhibitor should be used in conjunction with aspirin (i.e., dual antiplatelet therapy) (1).

Antithrombotic Therapy. Antithrombotic therapy should be initiated promptly in the patient with suspected or proven ACS, unless contraindicated. The choice of agent is based on two factors: 1) the planned treatment strategy of either a "conservative," ischemia-guided approach or an "early invasive" coronary angiography-guided approach; and 2) the patient's risk of having a bleeding complication.

Unfractionated heparin (UFH) accelerates the inactivation of thrombin and clotting factors IXa and Xa. Its advantages include ease of administration (intravenous) and rapid reversibility with protamine in the patient with bleeding complications. Its disadvantages include a variable anticoagulant effect, the need for frequent monitoring, and associated thrombocytopenia in 1% to 2% of patients. Like with all antithrombotic agents, the most common complication associated with UFH therapy is bleeding, particularly when used in combination with a glycoprotein IIb/IIIa inhibitor.

The low-molecular weight heparins are fragments of UFH. In comparison with UFH, low-molecular weight heparin has a more predictable anticoagulant effect, lower incidence of thrombocytopenia, and does not require serum monitoring. In patients with ACS treated with a conservative, ischemia-guided strategy, low-molecular weight heparin is superior to UFH in preventing inhospital death or myocardial infarction with similar rates of bleeding complications (30, 31). In patients with ACS treated invasively, low-molecular weight heparin (e.g., enoxaparin) therapy is associated with a higher rate of bleeding than UFH, with a similar rate of death or myocardial infarction (32).

Fondaparinux is a factor Xa inhibitor that does not cause thrombocytopenia. In a study comparing fondaparinux to enoxaparin in patients with ACS, short-term (9-day) risk of death, myocardial infarction, or recurrent ischemia was similar for both, but there was a significantly lower rate of major bleeding with fondaparinux therapy (33). In conservatively treated patients at high risk for bleeding, fondaparinux is the preferred antithrombotic agent (1).

Bivalirudin is a direct thrombin inhibitor and does not cause thrombocytopenia. In a study of patients with ACS managed with an invasive strategy, bivalirudin alone was compared with either UFH or low-molecular weight heparin in combination with a glycoprotein IIb/IIIa inhibitor (34). The incidence of death, myocardial infarction or recurrent ischemia was similar among the different therapies, but bivalirudin had a significantly lower rate of bleeding. Bivalirudin is an acceptable antithrombotic option for patients treated with an invasive strategy, particularly those considered at high risk for having a bleeding complication.

Stabilizing the 'Vulnerable' Plaque

Statin therapy promotes plaque stabilization and restores endothelial function. In patients with ACS, intensive lipid-lowering with atorvastatin (80 mg) reduces the incidence of death, myocardial infarction, and recurrent ischemia, even in those with "normal" (<100 mg/dL) low-density lipoprotein levels (35, 36).

Early Invasive versus Conservative Treatment Strategy

In the patient considered to be at risk for developing recurrent ischemia or infarction despite intensive medical therapy, an early invasive strategy is usually recommended; cardiac catheterization is performed (within 24–48 hrs of admission) and coronary revascularization is accomplished percutaneously or surgically, if indicated. In the low-risk patient, revascularization may offer no clinical benefit and may, in fact, result in harm. In such a patient, a conservative "ischemia-guided" strategy should be pursued, in which cardiac catheterization is recommended only if recurrent or provocable ischemia occurs (i.e., during a noninvasive stress test) (Table 2).

The patient's risk can be assessed on the basis of a validated scoring system or on certain clinical characteristics. The most commonly used risk scores are the TIMI and GRACE risk scores (13–15). Clinical factors that favor an invasive approach include: recurrent angina/ischemia at rest despite maximal medical therapy, elevated cardiac biomarkers, new ST-segment depression, signs/symptoms of heart failure, hemodynamic instability, sustained ventricular tachycardia, recent percutaneous coronary intervention, history of coronary bypass surgery, and depressed left ventricular systolic function. Clinical factors that favor a conservative approach include a low TIMI or GRACE risk score, patient preference, and significant comor-

bidities (i.e., advanced dementia, neurologic illness, malignancy, etc.) in which the patient's quality of life is not expected to be significantly improved with coronary revascularization.

Timing of Angiography and Intervention

Data support a primary invasive strategy over a conservative strategy in patients with ACS who are not considered to be at low risk for ischemic complications. A very early invasive strategy, as opposed to a delayed invasive strategy, has been tested in five prospective randomized controlled trials (Table 6) (37–41). Coronary angiography should be performed emergently (within 2 hrs) in individuals at very high risk of having death or myocardial infarction, within 24 hrs in those at high risk of having complication inhospital, and within 72 hrs in patients with an indication who are at low risk of having an ischemic complication (Table 3).

There is no evidence that delaying intervention to provide extended "upstream" pharmacologic treatment—including intensive antithrombotic and antiplatelet therapy—is superior to a strategy of optimal medical treatment and angiography as early as possible. Ischemic events, bleeding complications, and hospitalization duration is lower with an early as opposed to a later invasive strategy.

CONCLUSION

ACS is a common clinical syndrome usually caused by subtotal coronary occlusion resulting from acute plaque rupture and thrombus formation. The patient's history, ECG, and serologic cardiac biomarkers are used to make the diagnosis. In critically ill patients, diagnosing ACS can be difficult. Treatment goals include relieving ischemia, preventing thrombus propagation, stabilizing the vulnerable plaque (with antianginal, antiplatelet, antithrombotic, and statin medications), and identifying the patient at high risk for recurrent ischemia or infarction who would benefit from an invasive strategy.

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