Overview of the acute management of non-ST-elevation acute coronary syndromes

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INTRODUCTION

Unstable angina (UA), acute non-ST-elevation myocardial infarction (NSTEMI), and acute ST-elevation myocardial infarction (STEMI) are the three presentations of acute coronary syndromes (ACS). The first step in the management of patients with ACS is prompt recognition, since the beneficial effects of therapy are greatest when performed soon after hospital presentation. For patients presenting to the emergency department with chest pain suspicious of an ACS, the diagnosis of MI can be confirmed by the electrocardiogram and serum cardiac biomarker elevation; the history is relied upon heavily to make the diagnosis of unstable angina. (See "Diagnosis of acute myocardial infarction" and "Initial evaluation and management of suspected acute coronary syndrome (myocardial infarction, unstable angina) in the emergency department".)

Once the diagnosis of either UA or an acute NSTEMI is made, the acute management of the patient involves the simultaneous achievement of several goals:

- Relief of ischemic pain. (See 'Initial medical therapy' below.)
- Assessment of the patient's hemodynamic status and correction of abnormalities. Hypertension and tachycardia, both of which will markedly increase myocardial oxygen

consumption requirements, may be managed with beta blockers and intravenous nitroglycerin.

- Estimation of risk. (See 'Early risk stratification' below.)
- Choice of a management strategy, ie, an early invasive strategy (with angiography and intent for revascularization with percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery as defined by the anatomy) versus a conservative strategy with medical therapy. (See 'Choosing a revascularization strategy' below.)
- Initiation of antithrombotic therapy (including antiplatelet and anticoagulant therapies) to prevent further thrombosis of or embolism from an ulcerated plaque.
- Beta blocker therapy to prevent recurrent ischemia and life-threatening ventricular arrhythmias.

The acute management goals should be followed by the administration of different drugs that may improve the long-term prognosis. Some of these therapies include:

- Long-term antiplatelet therapy to reduce the risk of recurrent coronary artery thrombosis or, with PCI, coronary artery stent thrombosis.
- Statins.
- Long-term oral anticoagulation in the presence of left ventricular thrombus or chronic atrial fibrillation to prevent embolization.
- Possible use of an angiotensin converting enzyme inhibitor in patients at increased risk.

This topic will summarize emergent/early management issues for patients with UA or acute NSTEMI and then direct the reader to a more detailed discussion in other topics. The management of the patient after a revascularization strategy has been chosen and carried out is discussed separately. (See "Overview of the nonacute management of unstable angina and non-ST-elevation myocardial infarction".)

The management of the patient with STEMI or with a complication of an acute MI (eg, cardiogenic shock, mitral regurgitation, ventricular septal defect) is discussed separately. (See "Overview of the acute management of ST-elevation myocardial infarction" and "Prognosis and treatment of cardiogenic shock complicating acute myocardial infarction" and "Acute myocardial infarction: Mechanical complications" and "Initial evaluation and management of

suspected acute coronary syndrome (myocardial infarction, unstable angina) in the emergency department".)

GENERAL PRINCIPLES

An increasing number of centers use structured algorithms, checklists, or critical pathways to screen patients with a suspected ACS (algorithm 1) [1-6]. Many of these strategies combine diagnostic evaluation, such as electrocardiography and serum biomarkers, with therapeutic interventions, such as aspirin, beta blockers, antithrombotic agents, and, in most patients, early coronary angiography and revascularization. (See "Initial evaluation and management of suspected acute coronary syndrome (myocardial infarction, unstable angina) in the emergency department".)

Definitions — Among patients considered to have angina, there are three presentations of angina that suggest an ACS:

- Rest angina, which is usually more than 20 minutes in duration
- New onset angina that markedly limits physical activity
- Increasing angina that is more frequent, longer in duration, or occurs with less exertion than previous angina

Unstable angina (UA) and acute NSTEMI differ primarily in whether the ischemia is severe enough to cause sufficient myocardial damage to release detectable quantities of a marker of myocardial injury (troponins):

- UA is considered to be present in patients with ischemic symptoms suggestive of an ACS and no elevation in troponins, with or without electrocardiogram changes indicative of ischemia (eg, ST-segment depression or transient elevation or new T-wave inversion).

- NSTEMI is considered to be present in patients having the same manifestations as those in UA, but in whom an elevation in troponins is present.

Since an elevation in troponins may not be detectable for hours after presentation, UA and NSTEMI are frequently indistinguishable at initial evaluation. As a consequence, initial management is the same for these two syndromes. For this reason, and because the pathogenic mechanisms of the two conditions are similar, they are often considered together. (See "Acute coronary syndrome: Terminology and classification".)

Older patients — Our approach to the management of older patients with non-ST-elevation ACS (NSTEACS) is broadly similar to that in younger individuals. Adjustments to treatment may

be made based on the patients' general health, weight, and renal function.

It is estimated that 60 to 65 percent of MIs occur in patients ≥65 years of age and 33 percent occur in patients ≥75 years of age [7,8]. In addition, as many as 80 percent of all deaths related to MI occur in persons ≥65 years of age.

Although patients age 75 and older have been underrepresented in clinical trials of ACS, the following observations concerning acute MI in older adults compared to younger patients are generally accepted [9]:

- Older patients are more likely to have an NSTEMI rather than a STEMI.
- Older patients more frequently have an atypical presentation, including silent or unrecognized MI due to presenting symptoms of syncope, weakness, or confusion (delirium) [9,10]. Delays in diagnosis have been well-documented and often lead to delays in therapy [9].
- Patients ≥75 years of age have a higher in-hospital mortality (19 versus 5 percent in one series) [11]. Both bleeding and recurrent MI are also more frequent [9]. (See 'Importance of dosing' below.)
- Older patients are more likely to have heart failure associated with the MI (40 versus 14 percent in one report), the risk for which increases progressively in each successive age group from 36 percent in those 65 to 69 years of age to 65 percent in those ≥85 years of age [12].

Some of the worse outcomes after acute MI probably result from comorbidities in older patients, but also can be attributed in part to a lower likelihood of receiving potentially beneficial therapies due to concerns about toxicity. Therapies such as beta blockers, percutaneous coronary intervention, or coronary artery bypass grafting are all utilized to a lesser degree in older patients [11-13].

A retrospective review of almost 57,000 patients with an NSTEACS found that after adjustment, patients (including those ≥75 years of age) who received more recommended therapies had lower in-hospital mortality rates than those who did not [14]. Thus, although concern about risks and side effects is appropriate and it is not clear that adjustment accounted for all risk factors, older age alone should not be an indication to withhold recommended therapy.

Women — The approach to women and men should be the same, despite the fact that women have more atypical symptoms, are older, have greater delays to presentation, and have higher prevalence of hypertension [15]. In addition, they are at higher risk of bleeding.

While most women who present with an ACS will have acute plaque rupture as the cause, other entities such as myocarditis, aortic dissection, or stress-induced cardiomyopathy should be considered (see "Clinical manifestations and diagnosis of stress (takotsubo) cardiomyopathy", section on 'Clinical manifestations'). In a one-year study of 323 women 45 years or older presenting to a community hospital who were diagnosed with an acute MI (including an elevated troponin), 5.9 percent met criteria for stress-induced cardiomyopathy [16].

Cocaine-associated myocardial infarction — MI is a well-described complication among patients presenting with cocaine-induced ischemic symptoms. Beta blockers should be avoided due to the possibility of exacerbation of coronary artery vasoconstriction in the setting of acute MI in patients whose MI might have been triggered by cocaine. (See "Clinical manifestations, diagnosis, and management of the cardiovascular complications of cocaine abuse", section on 'Reperfusion and revascularization'.)

INITIAL MEDICAL THERAPY

Patients with unstable angina (UA) or acute NSTEMI should be treated with an early medical regimen similar to that used in an acute STEMI with one exception: There is no evidence of benefit (and possible harm) from fibrinolysis. Initial therapy, which should be instituted within 20 minutes of presentation, is discussed in detail separately. (See "Initial evaluation and management of suspected acute coronary syndrome (myocardial infarction, unstable angina) in the emergency department", section on 'Immediate emergency department interventions'.)

Drug metabolism is more likely to be reduced in older patients, particularly with regard to drugs that are excreted by the kidney. Dose adjustment is necessary with glycoprotein IIb/IIIa inhibitors and unfractionated or low molecular weight heparin, but not with aspirin and clopidogrel [9]. (See 'Older patients' above.)

Antiischemic and analgesic therapy

Oxygen — In patients with STEMI who have an oxygen saturation ≥94 percent and no signs of respiratory distress, we suggest **not** routinely treating with supplemental oxygen. Patients with lower oxygen saturation or respiratory distress should be treated with oxygen as needed.

The best evidence regarding the possible benefits and harms of supplemental oxygen therapy comes from the DETO2X-AMI registry-based, open-label randomized trial published in 2017 [17]. In this study, 6629 patients with suspected MI and an oxygen saturation of 90 percent or higher were randomly assigned to receive either supplemental oxygen (6 liters per minute for 6 to 12 hours, delivered through an open face mask) or ambient air. There was no difference in

the rate of the primary end point of death from any cause within one year (5.0 versus 5.1 percent; hazard ratio [HR] 0.97, 95% CI 0.79-1.21). In addition, there was no difference in the rate of rehospitalization with MI within one year (3.8 versus 3.3 percent; HR 1.13, 95% CI 0.88-1.46). During a median follow-up of 2.1 years, there was no difference in the rate of the composite end point of all-cause death, rehospitalization for MI, or hospitalization for heart failure (11.2 versus 10.8 percent; HR 1.02, 95% CI 0.88-1.17) [18].

A 2018 meta-analysis of seven studies (n = 7702), in which most of the patients came from DETO2X-AMI, found that the routine use of oxygen did not decrease the individual risks of all-cause death, recurrent ischemia or MI, heart failure, or occurrence of arrhythmia events [19]. The findings in this meta-analysis were consistent with those in a 2016 Cochrane review [20].

A pathophysiologic basis for the potential of harm with supplemental oxygen in patients with normoxia has been articulated [21-23]. Hyperoxia, which might occur with the administration of oxygen to normoxic individuals, has been shown to have a direct vasoconstrictor effect on the coronary arteries [21].

The potential benefit from the use of hyperbaric oxygen therapy was evaluated in a 2015 meta-analysis of six small studies with 665 participants with MI or severe angina. While a reduction in the risk of death was found (relative risk 0.58, 95% CI 0.36-0.92), methodologic limitations of the studies prevent us from having confidence in the use of such therapy [24].

Nitroglycerin — Sublingual nitroglycerin is administered to patients presenting with ischemic type chest pain, followed by intravenous nitroglycerin in patients with persistent pain after three sublingual nitroglycerin tablets, hypertension, or heart failure. (See "Nitrates in the management of acute coronary syndrome".)

Nitrates must be used with caution or avoided in settings in which hypotension is likely or could result in serious hemodynamic decompensation, such as right ventricular infarction or severe aortic stenosis. In addition, nitrates are contraindicated in patients who have taken a phosphodiesterase inhibitor for erectile dysfunction within the previous 24 hours. (See "Sexual activity in patients with cardiovascular disease" and "Right ventricular myocardial infarction", section on 'Optimization of right ventricular preload'.)

Morphine — In the setting of acute MI, intravenous morphine should be avoided if possible and reserved for patients with an unacceptable level of pain since a large but retrospective study suggests its use is associated with an adverse effect on outcome. We give intravenous morphine sulfate at an initial dose of 2 to 4 mg, with increments of 2 to 8 mg repeated at 5- to 15-minute intervals.

In a study of 57,039 patients enrolled in the CRUSADE Initiative, a nonrandomized, retrospective observational registry of patients with NSTEACS, those treated with morphine (29.8 percent) had a higher adjusted risk of death than those not (odds ratio 1.48, 95% CI 1.33-1.64) [25]. It is possible those patients receiving morphine were at higher risk at baseline but the CRUSADE study suggests caution in its use.

While the mechanism(s) by which morphine might be associated with decreased survival is not known, at least two studies have raised the possibility that it acts by interfering with the antiplatelet effect of the $P2Y_{12}$ receptor blockers (see "Acute ST-elevation myocardial infarction: Antiplatelet therapy", section on 'Our approach to early DAPT'):

- In the IMPRESSION trial, 70 acute MI patients treated with ticagrelor were randomly assigned to receive intravenous morphine (5 mg) or placebo [26]. Morphine lowered (active) ticagrelor plasma concentration and impaired its antiplatelet effect.

- In a study of 24 healthy subjects who received a loading dose of 600 mg of clopidogrel and either 5 mg of intravenous morphine or placebo, morphine significantly delayed clopidogrel resorption and reduced the area under the curve levels of its active metabolite by 52 percent [27]. Platelet inhibition, as measured by multiple tests, was less pronounced in those given morphine.

- In a study of 50 patients with STEMI undergoing primary percutaneous coronary intervention who were randomly assigned to either prasugrel or ticagrelor, morphine was an independent predictor of high residual platelet reactivity at two hours (odds ratio 5.29, 95% CI 1.44-19.49) [28]. (See "Acute ST-elevation myocardial infarction: Antiplatelet therapy", section on 'Timing of initiation'.)

Beta blockers — Controlled trials have repeatedly documented the beneficial effects of beta blockers in patients with acute MI; however, there have been no randomized trials specifically addressing the efficacy of these drugs in NSTEACS.

Nevertheless, given the proven efficacy in unselected patients with an acute MI and the absence of harm in NSTEMI or UA, we start beta blocker therapy in all patients without contraindications within 24 hours [15]. In our view, treatment should include early use of intravenous beta blockade in patients without contraindications who have ongoing chest pain, hypertension, or tachycardia not caused by heart failure. A cardioselective agent (metoprolol or atenolol) is preferred.

However, based upon the results of the COMMIT/CCS2 trial, the largest placebo-controlled trial ever performed with beta blockers in acute MI, it seems reasonable to defer intravenous beta

blockers in patients who are hemodynamically compromised in whom mortality may actually be increased by such therapy. Once the patient is stable, an oral beta blocker can be started with gradual uptitration to the maintenance doses cited below. (See "Acute myocardial infarction: Role of beta blocker therapy".)

Statin therapy — For all patients with an acute coronary syndrome (ACS), we recommend high-intensity statin therapy (atorvastatin 80 mg daily or rosuvastatin 20 or 40 mg daily) regardless of baseline low density lipoprotein-cholesterol level. This issue is discussed in detail elsewhere. (See "Low-density lipoprotein-cholesterol (LDL-C) lowering after an acute coronary syndrome", section on 'Our approach to in-hospital therapy'.)

Antithrombotic therapy

Antiplatelet therapy — In the absence of an absolute contraindication, antiplatelet therapy with aspirin and a platelet $P2Y_{12}$ receptor blocker is indicated in **all** patients with an NSTEACS [15]. (See "Acute non-ST-elevation acute coronary syndromes: Early antiplatelet therapy".)

Anticoagulation — For all patients with NSTEACS, we recommend anticoagulant therapy as soon as possible after the diagnosis. (See "Anticoagulant therapy in non-ST elevation acute coronary syndromes".)

Importance of dosing — Excessive dosing of antithrombotic and antiplatelet agents is common and associated with an increase in bleeding risk. This issue is discussed separately. (See "Anticoagulant therapy in non-ST elevation acute coronary syndromes", section on 'Anticoagulant Use'.)

Transfusion thresholds — Red blood cell transfusion is generally reserved for severe or symptomatic anemia, such as hemoglobin <8 g/dL or hemoglobin 8 to 10 g/dL with hemodynamic instability or ongoing ischemia. Clinical judgment is required to determine if transfusion is likely to improve oxygen delivery or if there are other reasons to consider transfusion such as active bleeding or trauma.

The rationale for using a restrictive transfusion strategy (limiting transfusions, transfusing for a lower rather than a higher hemoglobin level) includes avoiding risks of transfusion reactions or transfusion-transmitted infection and limiting burdens and costs while using evidence-based thresholds for optimal outcomes. While anemia correlates with worse outcomes, this is likely to be an association rather than causation. (See "Indications and hemoglobin thresholds for RBC transfusion in adults", section on 'Overview of our approach'.)

Supporting data for the thresholds used in ACS are presented separately. (See "Indications and hemoglobin thresholds for RBC transfusion in adults", section on 'Acute MI'.)

Potassium and magnesium — There are no clinical trials documenting the benefits of electrolyte replacement in acute MI. We recommend maintaining the serum potassium concentration above 4.0 meq/L and a serum magnesium concentration above 2.0 meq/L (2.4 mg/dL or 1 mmol/L). Much of the evidence for this recommendation was derived from studies before the routine use of beta blocker and the use of reperfusion in many patients. (See "Ventricular arrhythmias during acute myocardial infarction: Incidence, mechanisms, and clinical features", section on 'Ventricular fibrillation'.)

A 2012 retrospective cohort study found that for patients with acute MI, the lowest mortality was observed in those with post-admission serum potassium values between 3.5 and <4.5 meq/L [29]. (See "Risk factors for adverse outcomes after ST-elevation myocardial infarction", section on 'Serum potassium'.)

We suggest that the serum potassium fall within the range of 3.5 to 4.5 meq/L. Some of our reviewers prefer a tighter range of 4.0 to 4.5 meq/L. It may be difficult to lower the potassium below 4.5 meq/L in some patients, such as those with chronic kidney disease.

Nonsteroidal antiinflammatory drugs — Nonsteroidal antiinflammatory drugs (except aspirin) should be discontinued immediately due to an increased risk of cardiovascular events associated with their use. (See "NSAIDs: Adverse cardiovascular effects".)

Intravenous glucose-insulin-potassium — We do not recommend the use of intravenous glucose-insulin-potassium (GIK) to improve outcomes in patients with suspected or diagnosed acute MI. Much of the available evidence comes from studies of patients with ST-elevation MI. The discussion of the potential use of GIK in these patients is found elsewhere. (See "Overview of the acute management of ST-elevation myocardial infarction", section on 'Therapies of unclear benefit'.)

The IMMEDIATE trial randomly assigned 871 patients with suspected ACS (approximately 60 percent without ST-elevation on the presenting electrocardiogram) to intravenous GIK or identical-appearing 5 percent glucose placebo, which was administered by paramedics in the out-of-hospital setting and continued for 12 hours [30]. There was no difference in the rate of progression to MI (as measured by biomarkers and electrocardiogram evidence) at 24 hours or the rate of death at 30 days among patients who received GIK compared to those who received placebo (48.7 versus 52.6 percent; odds ratio 0.88, 95% CI 0.66-1.13 and 4.4 versus 6.1 percent; odds ratio 0.72, 95% CI 0.40-1.29, respectively).

CHOOSING A REVASCULARIZATION STRATEGY

In patients with an NSTEMI or unstable angina, management is influenced by the choice of revascularization strategy, which include immediate revascularization (ie, angiography within two hours of presentation), invasive strategy (ie, angiography without prior imaging), and selective angiography (ie, stress or anatomic imaging followed by PCI as indicated). The selection of a revascularization strategy is discussed separately. (See "Non-ST-elevation acute coronary syndromes: Selecting an approach to revascularization".)

ARRHYTHMIA PREVENTION AND MANAGEMENT

Both atrial and ventricular arrhythmias can be seen during and after the acute phase of an acute NSTEMI. These include atrial fibrillation or flutter, which can cause symptomatic hypoperfusion due to a rapid rate, and life-threatening ventricular tachycardia (VT) or ventricular fibrillation (VF). (See "Supraventricular arrhythmias after myocardial infarction" and "Ventricular arrhythmias during acute myocardial infarction: Incidence, mechanisms, and clinical features".)

Prophylactic intravenous or intramuscular lidocaine to prevent VT/VF in the acute MI patient is **not** recommended [31]. Recommended prophylactic measures include early administration of a beta blocker and treatment of hypokalemia and hypomagnesemia. Treatment of ventricular tachyarrhythmias in the setting of acute MI is discussed separately. (See "Ventricular arrhythmias during acute myocardial infarction: Incidence, mechanisms, and clinical features".)

EARLY RISK STRATIFICATION

Early risk stratification in patients with acute coronary syndrome (ACS) is essential to identify those patients at highest risk for further cardiac events who may benefit from a more aggressive therapeutic approach [15,32]. Clinical trials have identified a number of factors predicting high risk and a benefit from an early invasive strategy [33-37]. These include the presence and extent of ST segment depression, elevated cardiac biomarkers, evidence of hemodynamic instability, and persistent chest pain despite appropriate medical therapy. These variables have been used to create risk scores such as TIMI, GRACE, and PURSUIT. Using an end point of death or MI at one year, and area under the survival curve (AUC), all three have good predictive ability, with GRACE being somewhat better than PURSUIT and TIMI [38]. Using an end point of death, MI, or urgent revascularization at 30 days and AUC analysis, all three predictors

were comparable with TIMI somewhat better than GRACE and PURSUIT [39]. (See "Risk stratification after non-ST elevation acute coronary syndrome".)

It should be noted, however, that individual factors in the seven-point TIMI risk score may carry more risk than others, or be more specific for ACS than others. As an example, serum troponin elevation and ST segment depression individually are markers of high risk, regardless of the other TIMI risk factors.

TIMI risk score — Analysis of data from the TIMI 11B and ESSENCE trials found that seven variables at presentation were independently predictive of outcome in patients with unstable angina or an acute NSTEMI; a value of one was assigned when a factor was present and 0 when it was absent (calculator 1) [40]:

- Age ≥65 years.
- Presence of at least three risk factors for coronary heart disease (hypertension, diabetes, dyslipidemia, smoking, or positive family history of early MI).
- Prior coronary stenosis of ≥50 percent.
- Presence of ST segment deviation on admission electrocardiogram.
- At least two anginal episodes in prior 24 hours.
- Elevated serum cardiac biomarkers.
- Use of aspirin in prior seven days (which is probably a marker for more severe coronary disease) [41].

Patients are considered to be at low risk with a score of 0 to 2, intermediate risk with a score of 3 to 4, and high risk with a score of 5 to 7 (figure 1).

GRACE risk score — The simplified GRACE calculation uses eight parameters to predict death and MI in hospital and at six months: age, heart rate, systolic blood pressure, creatinine, Killip Class congestive heart failure, cardiac arrest, ST segment deviation, and elevated cardiac enzyme markers [42,43].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Non-ST-elevation acute

coronary syndromes (non-ST-elevation myocardial infarction)" and "Society guideline links: Secondary prevention of cardiovascular disease".)

SUMMARY AND RECOMMENDATIONS

- **Initial medical therapy** – Unstable angina (UA) and acute non-ST-elevation myocardial infarction (NSTEMI) are medical emergencies that require the simultaneous application of multiple therapies (algorithm 1 and table 1). (See 'Initial medical therapy' above.)
  - **Antiischemic and antithrombotic therapies** – The initial therapy for patients with UA or NSTEMI includes antiischemic and antithrombotic therapies. (See 'Antiischemic and analgesic therapy' above and 'Antithrombotic therapy' above.)
  - **Choice of revascularization strategy** – In patients with UA or NSTEMI, the timing of coronary angiography and revascularization with percutaneous coronary intervention (PCI) are determined by the clinical features, risk factors, and signs of ongoing ischemia. (See "Non-ST-elevation acute coronary syndromes: Selecting an approach to revascularization".)

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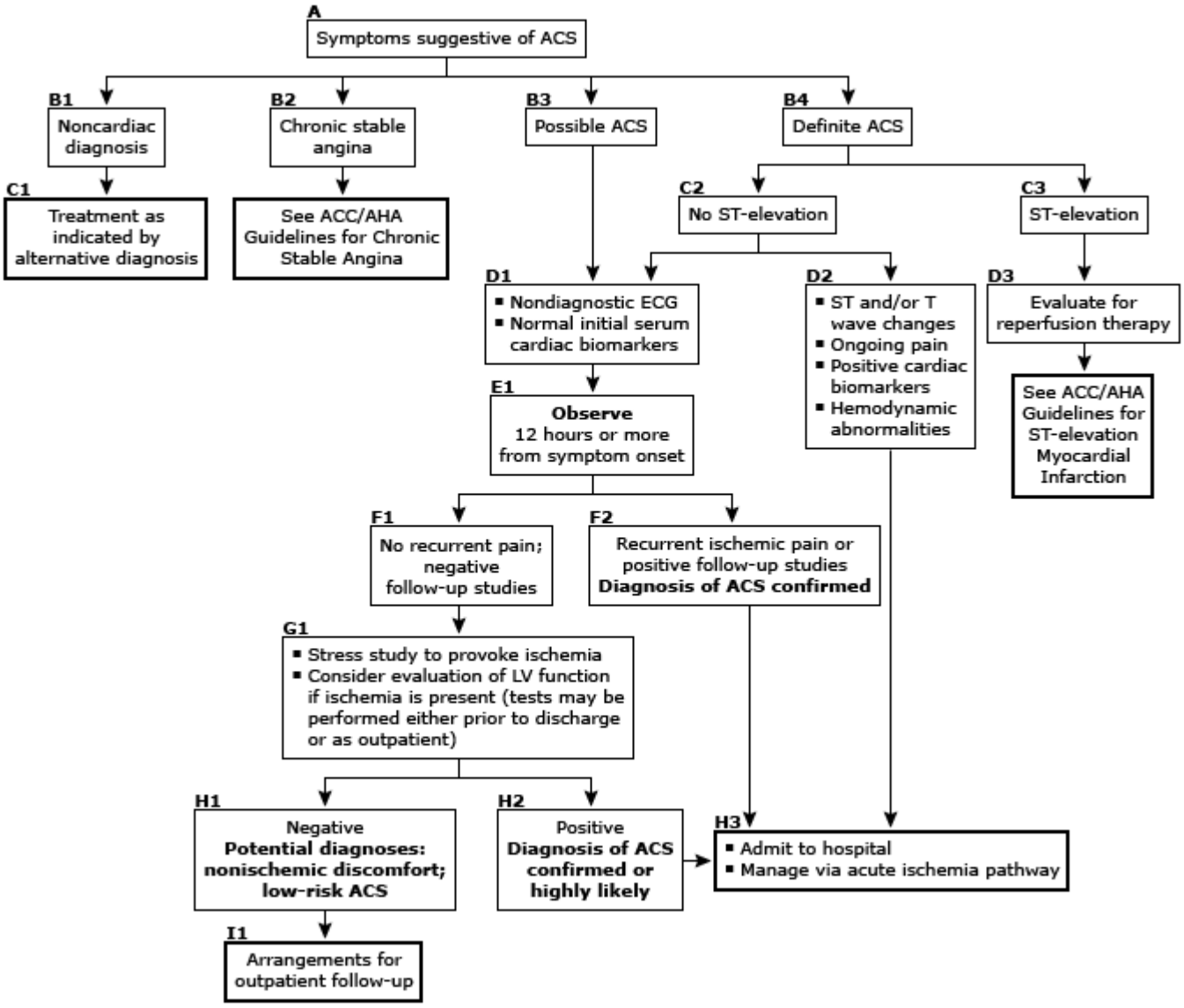
42. Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ 2006; 333:1091.
43. Tang EW, Wong CK, Herbison P. Global Registry of Acute Coronary Events (GRACE) hospital discharge risk score accurately predicts long-term mortality post acute coronary syndrome. Am Heart J 2007; 153:29.

Topic 68 Version 57.0

GRAPHICS

Algorithm for evaluation and management of patients suspected of having AC



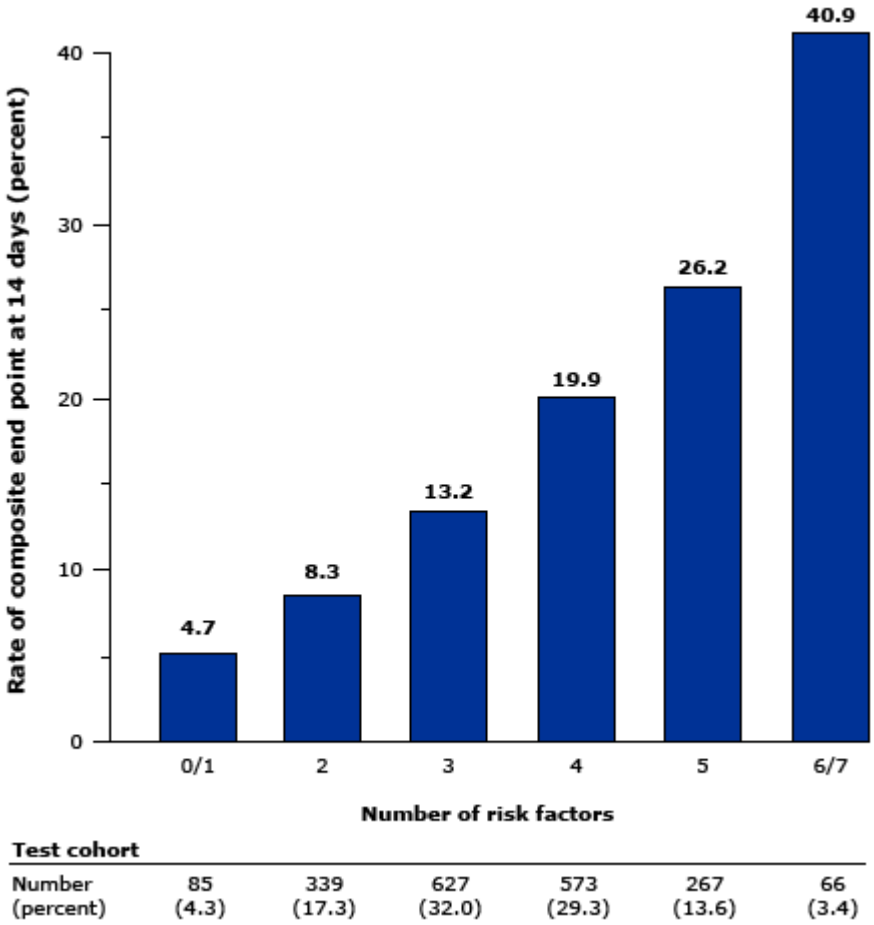
To facilitate interpretation of this algorithm and a more detailed discussion in the text, each box is assigned a letter code that reflects its level in the algorithm and a number that is allocated from left to right across the diagram on a given level.

ACC/AHA: American College of Cardiology/American Heart Associations; ACS: acute coronary syndrome; ECG: electrocardiogram; LV: left ventricular.

Reproduced with permission from: Anderson J, Adams C, Antman E, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 2002 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction): developed in collaboration with the American College of

Emergency Physicians, American College or Physicians, Society for Academic Emergency Medicine, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2007; 50:e1.

Thrombolysis in Myocardial Infarction (TIMI) risk score for non-ST elevation acute coronary syndrome



Rates of all-cause mortality, myocardial infarction, and severe recurrent ischemia prompting urgent revascularization at 14 days after randomization according to the number of risk factors among patients with a non-ST elevation acute coronary syndrome in TIMI 11B and ESSENCE. The risk factors were age ≥65 years; presence of at least three risk factors for coronary disease; prior coronary stenosis of ≥50 percent; presence of ST segment deviation on admission electrocardiogram; at least two anginal episodes in prior 24 hours; use of aspirin in prior seven days; and elevated serum cardiac biomarkers. Event rates increased significantly as the TIMI risk score rose. Patients are considered to be at low risk with a score of 0 to 2, intermediate risk with a score of 3 to 4, and high risk with a score of 5 to 7.

Adapted from: Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA 2000; 284:835.

Graphic 67473 Version 5.0

ST-elevation myocardial infarction (STEMI) or non-ST-elevation acute coronary syndrome (NSTEACS): Rapid overview of emergency management

Initial assessment:

- Consider the diagnosis in patients with chest discomfort, shortness of breath, or other suggestive symptoms. Women, older adults, and patients with diabetes may have "atypical" presentations.
- Obtain 12-lead ECG within 10 minutes of arrival; repeat every 10 to 15 minutes if initial ECG is nondiagnostic but clinical suspicion remains high (initial ECG often **not** diagnostic).
    1. STEMI: ST-segment elevations ≥1 mm (0.1 mV) in 2 anatomically contiguous leads or ≥2 mm (0.2 mV) in leads V2 and V3 **or** new left bundle branch block and presentation consistent with ACS. If ECG suspicious but not diagnostic, consult cardiologist early.
    2. Non-STEMI or unstable angina: ST-segment depressions or deep T-wave inversions without Q waves or possibly no ECG changes.
- Obtain emergency cardiology consultation for ACS patients with cardiogenic shock, left heart failure or sustained ventricular tachyarrhythmia.

Initial interventions:

- Assess and stabilize airway, breathing, and circulation.
- Attach cardiac and oxygen saturation monitors; provide supplemental oxygen as needed to maintain O_2 saturation >90%. Establish IV access.
- Treat sustained ventricular arrhythmia rapidly according to ACLS protocols.
- Give aspirin 325 mg (nonenteric coated) to be chewed and swallowed (unless aortic dissection is being considered). If oral administration is not feasible, give as rectal suppository.
- Perform focused history and examination: Look for signs of hemodynamic compromise and left heart failure; determine baseline neurologic function, particularly if fibrinolytic therapy is to be given.
- Obtain blood for cardiac biomarkers (troponin preferred), electrolytes, hematocrit/hemoglobin. Perform coagulation studies for patients taking anticoagulants or as otherwise indicated (eg, known coagulopathy).
- Give 3 sublingual nitroglycerin tablets (0.4 mg) 1 at a time, spaced 5 minutes apart, or 1 aerosol spray under tongue every 5 minutes for 3 doses **if** patient has persistent chest discomfort, hypertension, or signs of heart failure **and** there is no sign of hemodynamic compromise (eg, right ventricular infarction) and no use of phosphodiesterase inhibitors (eg, for erectile dysfunction); add IV nitroglycerin for persistent symptoms.
- Treat left heart failure if present: Give afterload-reducing agent (eg, nitroglycerin sublingual tablet and/or IV drip at 40 mcg/minute provided no hypotension and no phosphodiesterase inhibitors [eg,

for erectile dysfunction]; titrate drip up quickly based on response); give loop diuretic (eg, intravenous furosemide); administer noninvasive positive pressure ventilation (eg, BLPAP) to appropriate patients.

- Give beta blocker (eg, metoprolol tartrate 25 mg orally) **if** no signs of heart failure and not at high risk for heart failure and no signs of hemodynamic compromise, bradycardia, or severe reactive airway disease. If hypertensive, may initiate beta blocker IV instead (eg, metoprolol tartrate 5 mg intravenous every 5 minutes for 3 doses as tolerated).

- Morphine sulfate is indicated for chest discomfort refractory to nitrates and other antiischemic therapies. Give 2 to 4 mg slow IV push every 5 to 15 minutes.

- Start 80 mg of atorvastatin as early as possible and preferably before PCI in patients not on statin. If patient is taking a low- to moderate-intensity statin, switch to atorvastatin 80 mg.

Acute management STEMI:

- Select reperfusion strategy: Primary PCI strongly preferred, especially for patients with cardiogenic shock, heart failure, late presentation, or contraindications to fibrinolysis. Activate cardiac catheterization team as indicated. For patients with symptoms of >12 hours, fibrinolytic therapy is not indicated, but emergent PCI may be considered, particularly for patients with evidence of ongoing ischemia or those at high risk of death.

- Treat with fibrinolysis if PCI unavailable within **120 minutes of first medical contact,** symptoms <12 hours, and no contraindications.*

- **Give oral antiplatelet therapy (in addition to aspirin) to all patients:**

1. **Patients treated with fibrinolytic therapy:** Give clopidogrel loading dose 300 mg if age 75 years or less; if age over 75 years, give loading dose of 75 mg.

2. **Patients treated with no reperfusion therapy:** Give ticagrelor loading dose 180 mg.

3. **Patients treated with primary PCI:** Give ticagrelor loading dose of 180 mg or prasugrel loading dose of 60 mg (if no contraindications: prior stroke or TIA, or relative contraindications for prasugrel such as those age 75 years or older, weight less than 60 kg). For patients at high risk of bleeding or those for whom prasugrel or ticagrelor cannot be used, we give clopidogrel 600 mg.

- **Give anticoagulant therapy to all patients:**

1. **For patients treated with primary PCI,** we prefer UFH to bivalirudin. This recommendation assumes that patients will receive a potent oral antiplatelet agent (ticagrelor or prasugrel), which we prefer to clopidogrel. For those patients who receive clopidogrel, we prefer bivalirudin.

    - **Dosing of UFH:** An initial IV bolus of 50 to 70 units/kg up to a maximum of 5000 units. Additional heparin may be given in the catheterization laboratory based on the results of ACT monitoring.
    - **Dosing of bivalirudin:** Initial bolus of 0.75 mg/kg IV followed by IV infusion of 1.75 mg/kg per hour; can be discontinued after PCI.

2. **For patients treated with fibrinolysis,** we prefer enoxaparin for patients not at high bleeding risk or fondaparinux for those at high bleeding risk. For those patients in whom PCI is possible or likely after fibrinolytic therapy, UFH is reasonable.

- **Dosing of enoxaparin**
  - Patients <75 years: Loading dose of 30 mg IV bolus followed by 1 mg/kg subcutaneously every 12 hours; maximum of 100 mg for the first 2 subcutaneous doses. The first subcutaneous dose should be administered with the IV bolus.
    - Dose adjustment for renal impairment (CrCl <30 mL/minute)*: Loading dose of 30 mg IV followed by 1 mg/kg subcutaneously every 24 hours. The first subcutaneous dose should be administered with the IV bolus.
  - Patients ≥75 years: No IV loading dose. Administer 0.75 mg/kg subcutaneously every 12 hours; maximum of 75 mg for the first 2 doses.
    - Dose adjustment for renal impairment (CrCl <30 mL/minute)*: No IV loading dose. Administer 1 mg/kg subcutaneously every 24 hours.
  - Supplemental IV bolus dose for patients who will receive PCI after >1 dose of therapeuti enoxaparin: 0.3 mg/kg if last enoxaparin dose was given 8 to 12 hours earlier; no supplemental IV dose if last enoxaparin dose was within 8 hours; use UFH if last enoxaparin dose was more than 12 hours ago.
- **Dosing of UFH:** IV bolus of 60 to 100 units/kg to a maximum of 4000 units, followed by an I infusion of 12 units/kg per hour (maximum 1000 units per hour) adjusted to achieve a goal aPTT of approximately 50 to 70 seconds (1.5 to 2 times control).
- **Dosing of fondaparinux:** 2.5 mg intravenously, followed by 2.5 mg subcutaneously every 24 hours. This drug should be avoided in CrCl <30 mL/minute.

3. **For patients not receiving reperfusion therapy,** we use enoxaparin or UFH.

- **Dosing of enoxaparin:** Dose same as for patients treated with fibrinolysis (refer to section above).
- **Dosing of UFH:** IV bolus of 50 to 70 units/kg to a maximum of 5000 units, followed by an IV infusion of 12 units/kg per hour adjusted to achieve a goal aPTT of approximately 50 to 70 seconds (1.5 to 2 times control).

Acute management of unstable angina or non-STEMI:

- **Give antiplatelet therapy (in addition to aspirin) to all patients:**

1. **Patients not treated with an invasive approach:** Give ticagrelor loading dose 180 mg. For these patients who are at very high risk (eg, recurrent ischemic discomfort, dynamic ECG changes, or hemodynamic instability), consider adding a GP IIb/IIIa inhibitor (either eptifibatide or tirofiban).

2. **For patients managed with an invasive approach:** Give ticagrelor loading dose of 180 mg at presentation. Prasugrel loading dose of 60 mg may be used as an alternative if given after diagnostic coronary angiography.

For patients age 75 years or older, who weigh less than 60 kg, or with past stroke or TIA, ticagrelor or clopidogrel are preferred to prasugrel. Clopidogrel may be given in a dose of 300 to 600 mg, but we prefer 600 mg. For patients otherwise at high risk for bleeding due to prior hemorrhagic stroke, ongoing bleeding, bleeding diathesis, or clinically relevant anemia or thrombocytopenia, clopidogrel 300 to 600 mg is an option.

For patients treated with an invasive approach and who receive bivalirudin, we do not recommend routinely giving a GP IIb/IIIa inhibitor; for those patients treated with heparin and who are troponin-positive, we suggest adding a GP IIb/IIIa inhibitor (either abciximab or eptifibatide) given after diagnostic angiography. For those undergoing an invasive approach who are at very high risk (eg, recurrent ischemic discomfort, dynamic ECG changes, or hemodynamic instability), we consider adding a GP IIb/IIIa inhibitor prior to diagnostic angiography (either eptifibatide or tirofiban) or after diagnostic angiography (abciximab or eptifibatide). Refer to text for dosing.

- **Give anticoagulant therapy in all patients:**

1. **For patients undergoing urgent catheterization (within 4 hours) or those managed with an early invasive strategy (angiography within 4 to 48 hours),** we use either heparin or bivalirudin. We prefer initiation of heparin in the emergency department and a switch to bivalirudin in the catheterization laboratory.

    - **Dosing of UFH:** IV bolus of 60 to 70 units/kg to a maximum of 5000 units, followed by an IV infusion of 12 units/kg per hour adjusted to achieve a goal aPTT of approximately 50 to 70 seconds (1.5 to 2 times control).
    - **Dose of bivalirudin:** If bivalirudin is given in the emergency department, IV bolus of 0.1 mg/kg and an infusion of 0.25 mg/kg per hour before angiography. If PCI is performed, an additional 0.5 mg/kg bolus is given and the infusion rate is increased to 1.75 mg/kg per hour.

2. **For patients receiving a noninvasive approach,** we recommend either fondaparinux or enoxaparin.

    - **Enoxaparin** is an alternative to UFH for patients not undergoing an early invasive approach. No loading dose is necessary. Dosing is 1 mg/kg subcutaneously every 12 hours. Dose adjustment for renal impairment (CrCl <30 mL/minute)*: 1 mg/kg subcutaneously every 24 hours.
    - **Fondaparinux:** 2.5 mg subcutaneously every 24 hours. This drug should be avoided in patients with a CrCl <30 mL/minute.

Other important considerations:

- Cocaine-related ACS: Give benzodiazepines (eg, lorazepam 2 to 4 mg IV every 15 minutes or so) as needed to alleviate symptoms; Give standard therapies (eg, aspirin, nitroglycerin) but do **not** give beta blockers.

- Stop NSAID therapy if possible.

- Correct any electrolyte abnormalities, especially hypokalemia and hypomagnesemia, which often occur together.

ACLS: advanced cardiac life support; ACS: acute coronary syndrome; ACT: activated clotting time; aPTT: activated partial thromboplastin time; BLPAP: bilevel positive airway pressure; CrCl: creatinine clearance estimated using Cockcroft-Gault equation (a calculator is available in UpToDate); ECG: electrocardiogram; GP: glycoprotein; IV: intravenous; NSAID: nonsteroidal antiinflammatory drug; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; TIA: transient ischemic attack; UFH: unfractionated heparin.

* Repeated doses of low molecular weight heparin in patients with renal insufficiency may lead to accumulation and increased risk of bleeding to varying degrees. By contrast, UFH is not dependent primarily upon renal function for clearance and may be a preferred option for patients with CrCl <20 mL/minute, kidney failure, or receiving dialysis.

Graphic 75032 Version 37.0