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Treatment of Patients with Unstable Angina and Non-ST Elevation Myocardial Infarction

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Determining how and when to treat patients who experience suspected unstable angina (UA) and non-ST elevation myocardial infarction (NSTEMI) is never simple. One of the greatest challenges comes from the distinction between patients who have developed a suspected disease and those who experience a proven disease and how this distinction affects treatment choices. In this article, the authors review the current literature and recommendations from the American College of Cardiology and American Heart Association for treatment of patients who present with UA/NSTEMI. A class 1 recommendation is given when there is evidence or general agreement that a given procedure or treatment is useful and effective. A Class 2a recommendation is given when conflicting evidence or a divergence of opinion exists, but the weight of evidence/opinion is in favor of usefulness/efficacy. This article puts treatment selection into perspective by reviewing benefits and risks of these therapies.

Understanding treatment benefit

Treatment selection for patients who have suspected acute coronary syndrome (ACS) must be based on risk assessment. Benefit from treatment should be considered as the number needed to treat (NNT) to prevent one adverse outcome, such as mortality or myocardial infarction (MI), derived from the *absolute* (not the relative) decrease in adverse outcomes. If a treatment decreases *relative* mortality/MI by 50%

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and baseline mortality/MI is 20%, the *absolute* decrease is 10% and the NNT is 10. If baseline mortality/MI is only 2%, however, mortality/MI is decreased to 1% and the NNT is 100. Generally, patients who have more severe disease have higher rates of adverse events and, therefore, treatment is more beneficial.

The accuracy of patient selection is another factor that is more subtle but has a major impact on the NNT to benefit from a given therapy. If the NNT is 100, but only half of the treated patients prove to have disease, the NNT is 200. In clinical practice, the accuracy of patient selection and the severity of disease are closely related. The presence of ischemic ECG changes or elevated cardiac markers is by far the most predictive for disease severity and presence of disease in patients who develop suspected UA and NSTEMI.

The number needed to harm (NNH) from a given therapy, however, is less impacted by accuracy of patient selection or disease severity. If the NNH (eg, to cause one intracranial hemorrhage) is 100, it may remain 100 whether or not the treated patient has the disease. Because a therapy is only indicated when treatment benefit outweighs harm, patients need to be selected more carefully for therapies that cause more severe untoward effects; thus, therapies which prove beneficial in patients who present with diagnostic findings of UA/NSTEMI (ischemic ECG changes or elevated cardiac markers) may not be beneficial when applied more broadly to patients who have suspected disease without these findings. Box 1 describes a treatment approach based on these concepts.

Therapies in unstable angina/non-ST elevation myocardial infarction

Aspirin

Aspirin (ASA) at a dose of 160 to 325 mg, should be administered immediately to all patients who have developed suspected UA/NSTEMI and who do not have a life-threatening allergy. The benefits of ASA far outweigh bleeding risks associated with its use. By preventing the formation of thromboxane A_2 through its irreversible inhibition of cyclooxygenase-1 within platelets, ASA decreases platelet aggregation and thrombus propagation. In the ISIS-2 trial, ASA was given at doses of 160 mg on presentation and continued for 1 month in patients who experience suspected MI [1]. The NNT was 40 to prevent one death. Pooled data from four trials involving 2448 patients who present with UA/NSTEMI reveals the NNT to prevent death or MI is 16 [2–6]. When used alone, ASA causes no increase in bleeding requiring transfusion or hemorrhagic stroke [1]. Contraindications to ASA include intolerance and allergy (primarily manifested as asthma), active bleeding, hemophilia, active retinal bleeding, severe untreated hypertension, an active peptic ulcer, or another serious

Box 1. Emergency department treatment approach based on risk assessment

Possible unstable angina/non-ST elevation myocardial infarction

This category represents most patients who may present with symptoms of chest pain, shortness of breath, weakness, upper abdominal pain, or other complaints consistent with ACS but lacking 1) elevation of cardiac markers, 2) ST-depression diagnostic of ischemia on ECG, or 3) shock or heart failure as a result of acute ischemia. Treat with:

- Aspirin (ASA) (or clopidogrel if ASA-allergic)
- Oxygen, nitrates, and beta-blockers if there are no contraindications and the history is compelling

Likely or definite unstable angina/non-ST elevation myocardial infarction

These patients present with symptoms of ACS and 1) elevation of cardiac markers, 2) ST- depression diagnostic of ischemia on ECG, or 3) shock or heart failure as a result of acute ischemia. Treat with:

- ASA
- Oxygen (if hypoxic or in first 6 hours of symptoms)
- Nitrates
- Beta-blockers (if contraindications, then use Calcium Channel Blockers)
- Morphine
- UFH or LMWH
- Clopidogrel if PCI is not planned

If ischemia is ongoing with findings on ECG or cardiac markers, consider adding:

- GP 2b3a antagonist

If PCI is planned add:

- GP 2b3a antagonist (may be given in the cardiac catheterization lab)
- UFH or LMWH or bivalirudin
- Clopidogrel (may be given in the cardiac catheterization laboratory once indications for CABG are determined to be absent)

source of gastrointestinal or genitourinary bleeding. Administration and proper dosing should be confirmed in patients who have received ASA at home or in the prehospital setting. For ASA-allergic patients, give clopidogrel (see later discussion).

American College of Cardiology/American Heart Association Recommendations
Class 1:

- ASA should be administered as soon as possible after presentation and continued indefinitely.

Oxygen

It is common to administer to 2 L of oxygen by nasal cannula to all patients who develop suspected UA/NSTEMI, although little evidence of benefit exists other than in those with hypoxemia ($SaO_2 < 90\%$) or respiratory compromise. In patients who develop likely or definite UA/NSTEMI, oxygen should be delivered during the first 6 hours. Patients who experience severe respiratory distress or hypoxemia may need higher flow rates of oxygen administration or even intubation. Pulse oximetry is also recommended in patients who have developed likely or definite UA/NSTEMI to document oxygenation.

American College of Cardiology/American Heart Association Recommendations
Class 1:

- Supplemental oxygen for patients who experience cyanosis or respiratory distress: finger pulse oximetry or arterial blood gas determination to confirm adequate arterial oxygen saturation ($SaO_2 > 90\%$) and continued need for supplemental oygen in the presence of hypoxemia.

Beta-blockers

In addition to ASA, beta-blocking agents decrease mortality in patients who develop suspected MI. Though no trial has looked specifically at beta blockade in patients who experience UA/NSTEMI alone, data from trials including this patient population suggest a NNT of 140 to 160 to prevent one death at 7 to 14 days [7,8]. By selectively blocking β1 receptors located primarily in the myocardium, agents, such as metoprolol, atenolol, and esmolol, decrease myocardial oxygen demand by reducing heart rate, systemic arterial pressure, and myocardial contractility. As a consequence of reducing heart rate, diastole is prolonged, augmenting flow within the coronary vessels; therefore, beta-blocking agents may reduce mortality by decreasing infarct size and frequency of life-threatening arrhythmias.

Choices of commonly used selective beta-blockers and their dosing regimens are listed in Table 1. Contraindications to the use of beta-blockers include cardiogenic shock, active airway compromise caused by reactive airway disease—asthma or COPD—acute congestive heart failure (CHF), first-degree Atrioventricular (AV) block with a PR interval greater than 0.24

Table 1
Commonly used selective β1-receptor antagonists

Drug	Loading dose	Maintenance dose
Metoprolol	5 mg IV q 5 min × 3 doses	25–50 mg PO 15 min afterload and then q 6 h
Esmolol	0.5 mg/kg IV over 2–5 min	Titrate 0.05 mg/kg/min IV q 10–15 min until max drip of 0.3 mg/kg/min
Atenolol	5 mg IV q 5 min × 2 doses	50–100 mg PO 1–2 hours afterload and then q day

Abbreviations: IV, intravenous; PO, per os (by mouth); q, every.

seconds, second- or third-degree AV block in the absence of a functioning pacemaker, bradycardia less than 50 beats per minute, and systolic blood pressure (BP) less than 90 mm Hg [2]. If potential side effects from beta blockade are a concern, esmolol, an ultra short-acting cardioselective β1 antagonist may be used. Alternatively, smaller doses of metoprolol, starting at 2.5 mg IV may also be administered in this setting. Beta-selective-blocking agents should not be administered to patients who have ACS precipitated by use of cocaine because of the risk for exacerbating coronary spasm by unopposed alpha effect.

American College of Cardiology/American Heart Association Recommendations

Class 1

- Administer a beta-blocker, with the first dose administered intravenously (IV) if there is ongoing chest pain, followed by oral administration, in the absence of contraindications.

Nitrates

Although not shown to affect mortality in patients who experience UA/NSTEMI [9,10], nitrates are recommended based on pathophysiologic principles and uncontrolled clinical observations. In a pooled analysis composed largely of patients from the Fourth International Study of Infarct Survival Collaborative Group (ISIS-4) trial, the NNT to prevent death (MI was not included) was 260 (not statistically significant), although the NNH was 120 to cause profound hypotension in the initial 24 hours [10]. Nitrates vasodilate coronary vessels and may decrease myocardial oxygen consumption through peripheral vasodilatation, leading to a decrease in preload and a more modest decrease in afterload [11]. This decrease in oxygen consumption may be offset by reflex tachycardia and contractility unless a beta-blocker is used concurrently. Nitroglycerin is administered routinely and immediately to patients who experience chest pain at doses of 0.4 mg sublingually every 5 minutes for a total of three doses.

Given the lack of clear benefit from the use of nitrates, caution should be used in patients at risk for hypotensive events, including those who develop

suspected right ventricular (RV) infarct or low systolic BPs. Significant bradycardia (<50 beats per minute) or tachycardia are also contraindications, although these recommendations are based on scant evidence [2,12]. IV access should be established before the use of nitrates in these patients to anticipate the need for volume resuscitation. Use of the agents for erectile dysfunction, sildenafil, or vardenafil within 24 hours, or tadalafil within 48 hours, is an absolute contraindication because of the risk for prolonged and exaggerated vasodilatation [13].

In patients who develop likely or definite ischemia, initial treatment consists of 0.4 mg of nitroglycerin sublingual tablet or spray repeated every 5 minutes for three doses. Treatment may be continued with 1 to 2 inches of 2% topical nitropaste applied to the chest wall. Indications for IV therapy include the first 24 to 48 hours for patients who develop likely or definite UA/NSTEMI and experience ongoing or recurrent ischemic discomfort, hypertension, or signs of CHF or for controlled titration of therapy. Recommended dosing starts at 10 to 20 μg/min and is titrated by 10 to 20 μg/min every few minutes. Aggressive titration is reasonable in a patient who has tolerated given an estimated dose of 80 μg/min for five minutes from sublingual dosing. Titration should continue until an effect is seen, or a decrease occurs in systolic pressure to 90 mm Hg, or a decrease in mean arterial pressure of greater than 30% in hypertensive patients or 10% in normotensive patients [2]. Tachyphylaxis develops with the use of nitrates, and recurrence of symptoms may mandate increasing dosages.

American College of Cardiology/American Heart Association Recommendations
Class 1:

- Administer nitroglycerin, sublingual tablet or spray, for the immediate relief of ischemia and associated symptoms.
- Adminster IV in patients who experience continuing or frequently occurring ischemia.

Morphine

Morphine is recommended to relieve pain and discomfort believed to be caused by acute myocardial infarction (AMI). Although no randomized trials have defined its role or dosing regimen, morphine is recommended for pain relief in patients who experience ongoing ischemic discomfort despite treatment with ASA, beta-blockers, and nitroglycerin. Relief of pain and anxiety is believed to decrease adrenergic outflow thereby decreasing myocardial oxygen demand. In the absence of hypotension, morphine may be started at doses of 1 to 5 mg IV [2]. Morphine's major side effects include hypotension, respiratory depression, and nausea, sometimes requiring the use of antiemetics.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are recommended during initial hospitalization for all patients who develop AMI, especially those who experience anterior wall MI or CHF with BP greater than 100 mm Hg [14]. The NNT is 200 to prevent one death. Evidence to support treatment with these agents in the emergency department (ED) is lacking, and therapy should be initiated after the patient has demonstrated hemodynamic stability, usually within the first 36 hours. Generally, a short-acting ACE inhibitor, such as captopril, is started first, allowing titration according to BP.

American College of Cardiology/American Heart Association recommendations for angiotensin-converting enzyme inhibitors
Class 1:

- In patients who experience left ventricular systolic dysfunction, CHF, or diabetes when hypertension persists despite treatment with nitroglycerin and a beta-blocker.

Class 2:

- All patients post UA/NSTEMI.

Calcium channel blockers

Calcium channel blockers reduce cellular membrane influx of calcium, but have variable effects on peripheral arterial vasodilatation, inotropy, chronotropy and atrioventricular conduction. Their role in UA/NSTEMI seems primarily limited to symptom control when contraindications to beta-blockers are present, such as patients who experience cocaine-induced chest pain and coronary vasospasm.

Rapid-release short-acting dihydropyridines, such as nifedipine, nisoldipine, and nicardipine, cause greater peripheral arterial vasodilatation than conduction-slowing effects and have been shown to be detrimental in the setting of UA [15,16]—their use is to be avoided [2]. The nondihydropyridines, such as verapamil and diltiazem, have more effect on slowing atrioventricular and sinus node conduction, thereby decreasing oxygen demand by decreasing contractility, heart rate, and afterload, which may impart benefit [17,18].

American College of Cardiology/American Heart Association recommendations for calcium channel blockers
Class 1:

- In patients who experience frequent or continuing ischemia when beta-blockers are contraindicated in the absence of severe systolic dysfunction or other contraindications.

Class 2a:

- In addition to beta-blockers and nitrates when ischemia persists.

Heparin

The significant benefit shown from heparin use in patients who develop UA/NSTEMI was largely from the pre-ASA era. A meta-analysis of all six randomized controlled trials in UA patients receiving heparin plus ASA versus ASA alone revealed a trend to benefit, with a NNT of 20 to prevent death or MI and a NNH of 90 to cause major bleeding, although neither of these reached statistical significance [19].

Heparin exerts its anticoagulant effect by accelerating the action of circulating antithrombin, which prevents thrombus propagation but does not lyse existing thrombi. Low molecular weight heparins (LMWH) are degradation products of unfractionated heparin (UFH). The pharmacodynamic and pharmacokinetic profiles of the different commercial preparations vary. LMWHs can be delivered subcutaneously. Unlike UFHs, they usually do not require laboratory monitoring of activity. Contraindications to any heparin include a history of heparin-induced thrombotic thrombocytopenia. Contraindications to treatment with LMWH include known sensitivity to pork, and caution should be used in extremes of weight or severe renal dysfunction.

Low molecular weight heparins versus unfractionated heparin

Although the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend that LMWH is preferable to UFH in patients who develop UA/NSTEMI, both agents exhibit comparable efficacy and safety. A recent meta-analysis compared enoxaparin with UFH in six trials involving 21,946 patients who develop UA/NSTEMI [20]. Although enoxaparin reportedly showed a NNT of 110 to reduce death or MI with no increase in NNH, one of the six trials accounted for most of the positive effect. In this trial, thrombolysis in myocardial infarction (TIMI)-11b, patients were randomized to UFH for an average of 3 days and compared with enoxaparin treatment for 6 weeks [21]. Given the difference in duration of these treatments, which was structured into the study design, direct comparison of outcomes for these regimens is questionable. If this study is removed from the analysis, no statistically significant difference exists in outcomes in the remaining 18,775 patients. Analysis of UFH compared with two other LMWHs, dalteparin [22] and nadroparin [23], showed no statistically significant benefit over UFH.

American College of Cardiology/American Heart Association recommendations

Class 1:

- Anticoagulation with subcutaneous LMWH or IV UFH should be added to antiplatelet therapy with ASA or clopidogrel.

Class 2a:

- Enoxaparin is preferable to UFH as an anticoagulant in patients who develop UA/STEMI in the absence of renal failure and unless CABG is planned within 24 hours.

Heparin dosing in acute coronary syndrome

Intravenous unfractionated heparins

- 60-70 U/kg IV bolus (max 5000 U) and 12–15 U/kg/h infusion (max 1000 U/h)
- Maintain partial thromboplastin time (PTT) 60–80 seconds based on nomogram

Low molecular weight heparins approved for use in unstable angina/non-ST elevation myocardial infarction

- Enoxaparin 1 mg/kg subcutaneously twice a day
- Dalteparin 120 IU/kg subcutaneously twice a day

Adenosine diphosphate receptor antagonists

Ticlopidine and clopidogrel are thienopyridines, which are noncompetitive antagonists of platelet adenosine diphosphate receptor. They irreversibly inhibit platelet activation but require several days to take complete effect. For secondary prevention, both have been shown to reduce adverse events in patients who develop atherosclerotic vascular disease. Clopidogrel is the preferred agent, demonstrating fewer adverse effects than ticlopidine (thrombotic thrombocytopenia purpura and neutropenia) [24].

In the acute setting, clopidogrel has been studied in UA/NSTEMI and seems to have some benefit in combination with ASA. In the CURE trial, patients who presented with UA/NSTEMI received usual care and were randomized to clopidogrel versus placebo [25]. The NNT was 50 to prevent cardiovascular death, stroke, or MI. The NNH with major bleeding was 100. Of note, the Clopidogrel in Unstable angina to prevent Recurrent Events trial only found benefit in patients who exhibited ST depression or positive cardiac markers (the definite UA/NSTEMI group). The initial study protocol, which included high-risk patients without these findings, was modified after the first 3000 patients because of lack of benefit.

In patients who underwent coronary artery bypass graft surgery (CABG) after angiography, patients treated with clopidogrel showed a significantly increased rate of major perioperative bleeding—9% versus 6% [25]. For this reason, it is recommended that, clopidogrel should be withheld for 5 to 7 days before CABG. In the acute setting, any patient going to angiography may prove to be a CABG candidate; therefore, patients who have suspected ACS and are selected for angiography should be treated only with clopidogrel after the need for CABG has been precluded.

American College of Cardiology/American Heart Association recommendations

Class 1:

- Give clopidogrel to all patients who have ACS that are ASA allergic.
- Give clopidogrel to patients who have ischemic ST depression or elevated cardiac markers.
- Initiate treatment as early as possible.
- Withhold clopidogrel treatment in patients undergoing angiography until the need for emergent CABG has been excluded.

Dosing in ACS:

- Clopidogrel: 300–600 mg by mouth initially, then 75 mg by mouth each day
- Ticlopidine: 500 mg loading dose, then 250 mg by mouth twice a day

Glycoprotein IIb/IIa receptor antagonists

Thrombus formation occurs when activated platelets form clot by initial adhesion to the endothelium and then aggregation with each other. Platelets aggregate when activated fibrin links platelets together by binding to the glycoprotein (GP) 2b3a receptor on each. By blocking this receptor, GP 2b3a antagonists block thrombus formation. Of the three agents approved for use in the United States (Box 2), two of these, tirofiban and eptifibatide, are approved for use in medical management of ACS. The efficacy of GP 2b3a antagonists in decreasing adverse outcomes in ACS patients receiving percutaneous coronary intervention (PCI) have been documented in numerous trials. In pooled data of trials from 4952 patients who experience UA/NSTEMI and received PCI treated with GP 2b3a antagonists compared with placebo, the NNT was 17 to prevent death or MI [2].

Although the ACC/AHA guidelines recommend use of these agents in certain UA/NSTEMI patients who are managed medically, definitive evidence of benefit in this setting is lacking [26]. Only one trial has been designed specifically to study this question. Seven thousand eight hundred patients who present with ST-segment depression or elevated cardiac markers who were not undergoing early revascularization were randomized to usual care in addition to placebo compared with two dosage regimens for abciximab [27]. No difference existed in the individual or combined endpoints of death or MI. Boersma and colleagues [28] performed a meta-analysis reviewing all large, randomized placebo-controlled trials of patients who experience UA/NSTEMI receiving GP 2b3a antagonists. The NNT to prevent death or MI was 100 in 31,402 treated patients; however, analysis of the 19,416 medically managed patients who did not undergo coronary revascularization revealed no reduction in death or MI [28]. NNH with major bleeding was 100.

Box 2. GP 2b3a receptor antagonists approved in the United States

Abciximab
- Murine Fab fragment
- Approved only for PCI
- 0.25 mg/kg bolus, then 0.125 μg/kg/min infusion (max-10 μg/min) for 12–24 hours

Tirofiban
- Synthetic non peptide
- Approved for PCI or medical management of ACS
- 0.4 μg/kg/min for 30 minutes (equals 0.2 μg/kg bolus), then 0.1 μg/kg/min infusion for 48–96 hours

Eptifibatide
- Synthetic cyclic heptapeptide
- Approved for PCI or medical management of ACS
- 180 μg/kg bolus then 2.0 μg/kg/min infusion for 72–96 hours

Why, then, is there controversy about whether GP 2b3a antagonists are of benefit in medically managed patients who experience UA/NSTEMI? Possibly, in patients who are randomized to treatment, those that undergo PCI account for all the benefit demonstrated in the treatment group. Based on this evidence, the strength of recommendation for the use of GP2b3a antagonists in medically managed patients who develop UA/NSTEMI patients was downgraded from class 1 to class 2a in the 2002 ACC/AHA guidelines. Although treatment with GP 2b3a antagonists is still deemed acceptable in patients who experience continuing ischemia, an elevated troponin, or "other high-risk features," these should be given only to patients who are believed to have UA/NSTEMI (ie, elevated cardiac markers or clearly ischemic ECG changes). It is controversial whether the evidence at this time supports the use of these agents in any patient with UA/NSTEMI not undergoing PCI.

American College of Cardiology/American Heart Association recommendations
Class 1:
- Administer a platelet GP 2b3a antagonist to patients in whom catheterization and PCI are planned. They may be administered just before PCI. From an ED standpoint, deferring administration of GP 2b3a antagonists until the catheterization determines the coronary anatomy is acceptable.

Class 2a:

- Eptifibatide or tirofiban should be administered to patients who experience continuing ischemia, an elevated troponin, or high-risk features when PCI is not planned.
- Treatment with ASA, heparin, and clopidogrel should proceed as recommended whether or not GP 2b3a antagonist treatment is indicated.

Direct thrombin inhibitors

Direct thrombin inhibitors (DTI) are anticoagulants that specifically bind to thrombin, theoretically providing more predictable effects than anticoagulants, such as heparin, which require a cofactor, such as antithrombin, for thrombin inactivation. The first agent in this class, hirudin, was extracted from the medicinal leech. The agents approved in the United States are lepirudin and desirudin (recombinant forms of hirudin), bivalirudin (a synthetitic hirudin analog previously known as hirulog), and argatroban (a synthetic molecule unrelated to hirudin) [29]. Of these, only bivalirudin is approved for patients who have ACS and only for patients who experience UA undergoing PCI.

Some benefit may exist from the use of DTIs in patients who experience UA/NSTEMI, although the only currently approved uses in these patients are for PCI or for anticoagulation of patients who have a history of heparin-induced thrombocytopenic purpura. The GUSTO-IIb trial randomized patients who presented with suspected MI to 72 hours of IV recombinant hirudin versus UFH [30]. In the 8011 patients who presented without ST elevation, no statistically significant benefit existed in death or MI at 30 days. OASIS 2 [31] compared higher doses of recombinant hirudin (0.4 mg/kg bolus and 0.15 mg/kg/h infusion compared with 0.1 mg/kg bolus and 0.1 mg/kg/h infusion) to UFH in 10,141 patients who presented with UA/NSTEMI. Again, no statistically significant difference existed in death or MI at 7 days, although the NNT was 110 to prevent the combined endpoint of death, MI, or refractory ischemia. Number needed to harm was 200 to cause major bleeding. When these two trials were combined with nine smaller trials in a recent meta-analysis, DTI treatment compared with heparin resulted in a NNT of 110 to prevent death or MI in 20,570 patients who presented with UA/NSTEMI [32]. No difference existed in intracranial bleeding, and major bleeding was decreased by 0.4% overall. DTIs were shown to be of equivalent efficacy to GP 2b3a antagonists in patients undergoing PCI [33].

Percutaneous coronary intervention—conservative versus early invasive strategies

Emergent PCI was shown to have significant benefit in patients experiencing STEMI. The results are less clear in patients who present

with UA/NSTEMI. In an early conservative strategy, patients who present with UA/NSTEMI are selected for cardiac catheterization using echocardiography, stress testing, and recurrent symptoms to identify persistent ischemia or decreased left ventricular function. In an early invasive approach, routine cardiac catheterization is performed either emergently or, more commonly, within 48 hours after admission. Use of the conservative strategy typically results in cardiac catheterization of one third to one half of the patients. Initial studies suggested that a conservative strategy was equivalent to or better than routine catheterization for all patients presenting with UA/NSTEMI [34–36].

More recent studies, however, have shown benefit from an early invasive strategy for patients who develop definite UA/NSTEMI (elevated cardiac markers or ST depression). This benefit may be caused by improved outcomes in PCI with the use of GP 2b3a antagonists and coronary stents. In TACTICS-TIMI-18, 2220 patients who presented with UA/NSTEMI were randomized to an early invasive versus conservative strategy [37]. The NNT was 45 to prevent death or MI at 6 months with the early invasive approach. In FRISC-2, the two approaches were compared in 2457 patients who presented with UA/NSTEMI [38]. Criteria for catheterization in the conservative arm were more stringent than other studies, and only 10% of patients received cardiac catheterization. The NNT was 37 to prevent one death or MI at 6 months using the early invasive approach. Currently, either strategy is considered acceptable.

American College of Cardiology/American Heart Association recommendations for early cardiac catheterization
Class 1

- Recurrent angina/ischemia with low-level activities despite intensive anti-ischemic therapy
- Troponin elevation
- Ischemic ST depression
- Ischemia with shock, heart failure, or depressed systolic function
- High risk findings on noninvasive stress testing
- Sustained ventricular tachycardia
- PCI within 6 months or prior CABG
- In the absence of above-mentioned findings, either an early conservative or early invasive strategy may be offered if no contraindications for revascularization.

Summary

ED management of patients who present with UA/NSTEMI is unique because these patients often present with suspected rather than proven disease. Because the impact of treatment varies depending on severity of illness and certainty of diagnosis, treatment selection in patients who present

with UA/NSTEMI should be tailored to these factors. In general, patients with ECG changes, such as ischemic ST depression or elevation of cardiac markers, can be classified as definite UA/NSTEMI. Although all patients who have suspected or definite disease should be given ASA, and most patients should receive beta-blockers, medications such as heparin and clopidogrel have been shown to be of clearest benefit in patients who have definite disease. GP 2b3a antagonists have been shown to be of clearest benefit in patients receiving PCI. Other treatments are of benefit in select situations.

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