

Update in Nonpulmonary Critical Care

Management of Acute Coronary Syndromes

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INTRODUCTION

The medical intensivist is often confronted with patients suffering myocardial ischemia or infarction. Patients may overflow from a full coronary care unit (CCU); they may develop coronary ischemia after admission to intensive care units for unrelated reasons or during weaning from mechanical ventilation, or patients with coronary ischemia in combination with severe illness in other organ systems may be admitted preferentially to a noncardiac unit. The need for rapid decisions about potentially risky therapy and to prioritize cardiologic intervention in a patient with multisystemic illness demands that the intensivist understand the contemporary approach to this group of disorders.

The traditional approach includes the use of β -adrenergic blockade and nitroglycerin to reduce myocardial oxygen demand and adequate hemoglobin and oxygen to support myocardial oxygen supply. New medical options to restore blood flow have become available in the past few years, including thrombolytics, antithrombotics, and glycoprotein receptor, GPIIb/IIIa, inhibitors. The best approach to specific syndromes has been clarified in recent large clinical trials. The purpose of this review is to summarize the evidence supporting the use of new thrombolytic and antithrombotic therapy for acute, life-threatening syndromes of coronary insufficiency.

Acute coronary syndromes (ACS) are divided into unstable angina (UA), non-ST segment elevation myocardial infarction (non-STEMI—associated with myocardial necrosis), and ST segment elevation myocardial infarction (STEMI). This classification is useful for therapeutic purposes, but the syndromes share common pathophysiologic origins. ACS begins with coronary artery plaque rupture, activation of the clotting cascade and platelets, thrombus formation, and abruptly decreased coronary blood flow (1). Importantly, it is often the nonobstructive, lipid-rich coronary plaque with a thin fibrous cap (“vulnerable plaque”) which is prone to rupture. An inflammatory process involving activated macrophages and T lymphocytes and their proteinases and cytokines contributes to the plaque rupture and thrombosis (2).

Whether the plaque rupture causes no symptoms, UA, non-STEMI, STEMI, or sudden death depends on factors such as the depth of rupture, the thrombotic milieu, and collateral circulation. Autopsy and catheterization studies suggest that UA and non-STEMI result from transient total occlusion of the coronary vessel with spontaneous reperfusion,

whereas a STEMI results from sustained thrombotic occlusion (3–5). The best clinical data implicating thrombosis in the pathophysiology of ACS are that antithrombotic and antiplatelet therapies reduce mortality. These data for each ACS are reviewed in the following sections.

STEMI

Goals of medical therapy are to achieve rapid and complete reperfusion of the infarct vessel and to reduce the risk of recurrent myocardial infarction (MI).

Antiplatelet and Antithrombotic Agents

Aspirin (160 to 325 mg) should be given as soon as possible to all patients with acute MI. To accelerate absorption, a non-enteric-coated tablet should be chewed and swallowed. The Second International Study of Infarct Survival (ISIS-2) of 17,187 patients with suspected acute MI demonstrated a 23% reduction in 35-d mortality and large reductions in recurrent infarction and stroke in aspirin-treated patients (6).

Unfractionated heparin should be administered to all patients receiving reperfusion therapy with fibrin-specific thrombolytic agents with the dose adjusted to maintain activated partial thromboplastin time (aPTT) at 1.5 to 2.0 times control (7). The duration of therapy should be 48 h unless the patient is at high risk for systemic emboli, such as patients with a large or anterior MI, previous embolus, atrial fibrillation, or known left ventricular thrombus by echocardiography. In these clinical situations, unfractionated heparin should be continued until anticoagulation with warfarin is achieved. In patients with STEMI who do not require full anticoagulation, venous thromboembolism prophylaxis with subcutaneous heparin should be administered until patients are ambulatory.

Thrombolytic Therapy

Large, randomized, placebo-controlled trials demonstrated that thrombolytic therapy for STEMI or new left bundle branch block reduces short-term mortality by approximately 18% (8). There is no benefit of thrombolysis in patients with UA or non-STEMI. Speed is essential. Survival is improved only if thrombolytic therapy is given less than 12 h after symptom onset, and short-term mortality increases with the time from symptom onset to therapy.

The benefits of thrombolytic therapy also decrease with age (8). Data from the Medicare database suggest that elderly patients who meet thrombolytic criteria have a survival advantage with thrombolysis between the ages of 65 and 75 yr but thereafter have increased mortality if they receive lytics (9). Therefore, in patients with STEMI older than 75 yr of age, emergent percutaneous coronary intervention (PCI) should be considered.

Although front-loaded tissue plasminogen activator (t-PA), combined with aspirin and full-dose unfractionated heparin is superior to streptokinase therapy, only 54% of patients

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achieve normal flow in the infarct vessel at 90 min with this therapy (10, 11). Newer thrombolytics have been developed with the hopes of improving coronary artery patency and survival. These agents, such as reteplase (r-PA) and tenecteplase (TNK-t-PA), have greater fibrin specificity and a longer half-life than t-PA, allowing bolus dosing. Two large trials compared front-loaded t-PA with r-PA and TNK-t-PA, respectively (12, 13). Despite theoretical benefits of the newer agents, 30-d mortality (7.47% for r-PA versus 7.24% for t-PA; and 6.18% for TNK-t-PA versus 6.15% for t-PA) and major bleeding risk were similar.

Why Thrombolytics Fail

As thrombolytics lyse fibrin in the clot, thrombin is exposed. Thrombin activates platelets, causing a conformational change in the most abundant platelet GPIIb/IIIa receptor. The activated GPIIb/IIIa receptor avidly binds fibrinogen and initiates new platelet aggregation.

The additive benefit of platelet inhibition to thrombolysis was first shown in the ISIS-2 (6), where the combination of streptokinase plus aspirin reduced short-term mortality significantly more than either therapy alone. However, aspirin is a weak platelet antagonist, and platelet-rich thrombus is often visible in the infarct vessel despite thrombolytics, aspirin, and unfractionated heparin (14). Intravenous GPIIb/IIIa inhibitors have been developed with greater *in vitro* platelet inhibitory activity than aspirin. Two recent Phase II trials reported improved 90-min infarct vessel patency and flow when GPIIb/IIIa inhibition was added to half-dose t-PA or r-PA compared with full-dose thrombolytics alone (15, 16). These patients also received aspirin and unfractionated heparin, and bleeding rates were similar. Phase III trials are ongoing to determine if half-dose thrombolytic therapy with aggressive platelet inhibition will lower STEMI mortality compared with current thrombolytic strategies.

PCI

An alternative to thrombolytic therapy for STEMI is emergent PCI. A meta-analysis of randomized trials comparing PCI with thrombolytics for STEMI at high-volume hospitals suggests that PCI improves 30-d survival free of reinfarction (11.9% versus 7.2%). Stroke risk is also reduced with PCI compared with thrombolytic therapy (17). As with medical reperfusion therapy, speed is critical in reducing short-term mortality (18). Recent data also suggest that 5-yr survival free of reinfarction remains significantly greater for patients treated with PCI compared with thrombolytic therapy (19). Furthermore, use of PCI with stenting and GPIIb/IIIa inhibition results in greater scintigraphic myocardial salvage than thrombolytic therapy (20).

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS AND β -BLOCKERS

Several large trials evaluated the addition of an ACE inhibitor to high-risk postinfarction patients, including those with left ventricular dysfunction or congestive heart failure during the CCU course (21–23). Therapy was initiated 3 to 16 d after admission. These trials demonstrated approximately 20% reduction in mortality and 20 to 25% reductions in cardiovascular mortality and congestive heart failure. In four large randomized, placebo-controlled trials evaluating ACE inhibitor therapy initiated on the first CCU day in all patients with acute myocardial infarction (24), 30-d mortality was reduced 7% as was the development of congestive heart failure. ACE inhibitors should not be administered until the systolic pressure is at least 100 mm Hg. The recent Heart Outcomes Prevention Eval-

uation (HOPE) study suggests that certain ACE inhibitors may also reduce atherosclerosis progression, with large reductions in death, MI, and stroke (25). In the acute setting, intravenous β -blockade reduces short-term mortality by 15%, in addition to reducing ventricular fibrillation, and recurrent ischemia (26). Large placebo-controlled trials demonstrated that chronic β -blockade post-MI reduces mortality, sudden death, and recurrent MI each by 25% (27, 28). Even in patients already undergoing ACE inhibitor therapy post-MI for left ventricular dysfunction, addition of a β -blocker is beneficial (29).

Non-STEMI AND UA

Goals of evaluation and therapy include relief of ischemic chest pain, prevention of recurrent ischemia and MI, and risk stratification. The cornerstones of medical therapy include β -blockers and nitroglycerin to relieve angina, and anticoagulation and antiplatelet agents to prevent coronary occlusion. Despite aspirin and unfractionated heparin, however, the short-term risk of death or MI in UA/non-STEMI patients in several recent large trials remains 8 to 15%.

Low-molecular-weight Heparin

Low-molecular-weight heparins (LMWH), like unfractionated heparin, activate antithrombin and inhibit factor Xa and thrombin. Unlike unfractionated heparin, LMWH inhibit Xa to a much greater extent than thrombin, thus patients are anticoagulated, but the aPTT is not prolonged. Compared with unfractionated heparin, LMWH have a longer half-life, better bioavailability with less protein binding and less interaction with platelet factor 4. Therefore, there is a predictable response to a weight-based standard dose. The longer half-life allows for subcutaneous dosing. Risk of heparin-induced thrombocytopenia is lower owing to reduced interaction with platelet factor 4.

Two randomized trials compared the LMWH enoxaparin with unfractionated heparin in patients with UA or non-STEMI (30, 31). All patients received aspirin. In both studies, there were reductions in short-term outcomes of death, MI, and recurrent angina in patients randomized to LMWH. A combined analysis of these two trials showed significant 20% reductions in the short-term risk of death and nonfatal MI in patients randomized to LMWH (32).

Antiplatelet Therapy

Platelet activation and aggregation is a hallmark pathophysiologic finding in patients with UA/non-STEMI. Despite permanent inhibition of cyclooxygenase activity, aspirin is a weak platelet antagonist. In contrast, intravenous GPIIb/IIIa inhibitors result in 80% inhibition of platelet aggregation to a wide variety of agonists, and reduce 30-d cardiac events in high-risk patients undergoing PCI (33). Several studies evaluated whether the addition of a GPIIb/IIIa inhibitor to aspirin and unfractionated heparin reduces death, MI, and refractory angina in patients with UA/non-STEMI. A combined analysis (34) of three randomized, placebo-controlled trials (35–37) found the following: First, there was homogeneity between all three studies, strengthening the findings. Second, early treatment with a GPIIb/IIIa inhibitor reduced early death and myocardial infarction by 34%. Third, patients proceeding to PCI had the greatest benefit receiving a GPIIb/IIIa inhibitor, with a 41% reduction in death and MI. These data suggest that early treatment with a GPIIb/IIIa inhibitor in the high-risk UA/non-STEMI patient, particularly those patients in whom PCI is planned, reduces short-term death and MI. Although minor bleeding was increased with the GPIIb/IIIa inhibitors, major bleeding rate was not.

For patients who are unable to take either GPIIb/IIIa inhibitors or aspirin, a thienopyridine (clopidogrel or ticlopidine) should be considered. These agents inhibit adenosine diphosphate–induced platelet aggregation, and compared with placebo, prevent recurrent ischemic events and MI in UA patients. These agents, together with aspirin, are currently also indicated in patients who receive PCI with a stent.

REVASCULARIZATION

Several randomized trials have evaluated whether routine cardiac catheterization with PCI or coronary artery bypass grafting should be considered for patients with UA/non-STEMI. In two of the earlier trials (38, 39), there was no difference in the primary endpoint of death or nonfatal MI in patients randomized to conservative versus invasive strategies. In contrast, a recent trial using modern stents and GPIIb/IIIa inhibitors when indicated randomized 2,347 patients who had stabilized with UA/non-STEMI to a conservative or invasive strategy (40). Relative risk of 6-mo death or nonfatal MI was reduced 21% in patients randomized to the invasive arm. Quality of life, including readmission for unstable angina, was also better in patients treated invasively. The benefit of an invasive or conservative approach depends on comorbidities and stratification for risk of death and MI, which is described subsequently.

LIPID-LOWERING THERAPY

Aggressive management of coronary artery risk factors is critical in preventing recurrent nonfatal MI and mortality. In patients 3 to 20 mo post-MI with average cholesterol levels below 240 mg/dl, randomization to a statin compared with placebo over 5 yr resulted in a 24% reduction in nonfatal MI or cardiovascular mortality (41). A recent study randomized non-STEMI and UA patients to high-dose statin therapy or placebo for 16 wk. Therapy was initiated within 24 to 96 h of admission. The primary endpoint of death, nonfatal MI, resuscitated cardiac arrest, and recurrent symptomatic ischemia was significantly reduced by 16% in the aggressive lipid-lowering group

(42). These data suggest that early initiation of risk factor modification is beneficial in patients with ACS.

RISK STRATIFICATION FOR UA/NON-STEMI

Clinical, electrocardiographic, and laboratory values allow rapid identification of the higher risk patient in whom more aggressive medical treatment and cardiac catheterization with revascularization may be reasonable. A crescendo pattern of angina before admission, and hemodynamic instability during an ischemic episode, including hypotension, pulmonary edema, or new mitral regurgitation murmur, indicate a higher risk patient (43). An admission electrocardiogram demonstrating any of the following predicts increased risk of mortality, compared with more minor ST segment or T-wave changes (44, 45): (1) transient 0.05 mV flat ST segment depression in ≥ 2 leads (1-yr death or MI +16.3%), (2) deep precordial T-wave inversions in ≥ 5 leads (30-d death or MI +14%), or (3) left bundle branch block (1-yr death or MI +22.9%). A troponin T level > 0.1 ng/ml at baseline or 6 to 12 h after admission also identifies a high-risk patient (46). Recurrent ischemia occurs in approximately 34% of patients with UA/non-STEMI during their index hospitalization, and, in one in five, is refractory to medical therapy (47). Patients with refractory ischemia with associated ST changes are at very high risk for MI or death.

A recent analysis of over 7,000 UA/non-STEMI patients (48) identified seven risk predictors: age > 65 yr, ≥ 3 risk factors for coronary artery disease, known prior coronary artery disease, ST segment depression on the admission electrocardiogram, ≥ 2 episodes of rest angina within 24 h of admission, aspirin use in the last 7 d before admission, and elevated troponin. The interaction between these risk factors and short-term morbidity and mortality is shown in Figure 1, which demonstrates that as the number of risk factors increases, so does risk of death, nonfatal MI, and requirement for urgent revascularization. Patients with multiple risk factors should be considered early for more aggressive medical therapy, cardiac catheterization, intra-aortic balloon counterpulsation, and revascularization.

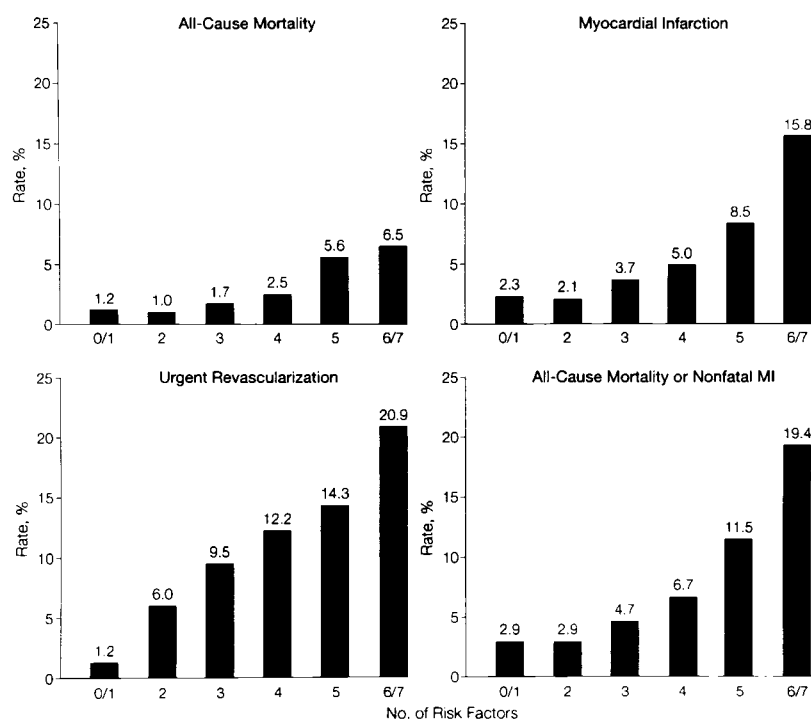


Figure 1. Event rates according to the number of multivariate predictors of short-term outcomes in patients with UA/non-STEMI. Rates are for the first 14 d after randomization, as calculated from the 3,910 participants in the Thrombolysis in Myocardial Infarction (TIMI) IIB trial (Reference 31). Figure from Reference 48, reprinted by permission.

TABLE 1. MAJOR THERAPEUTIC DRUGS USED IN PATIENTS WITH ACS

Thrombolytics	Indications	Contraindications
	STEMI or new LBBB within 12 h of symptom onset, especially in those younger than 75 yr of age	Stroke within 1 yr, cerebral hemorrhage or intracranial pathology, pericarditis, active internal organ bleeding such as gastrointestinal, suspected aortic dissection, uncontrolled hypertension (> 180/110 mm Hg), cardiopulmonary resuscitation > 10 min, pregnancy, major trauma, including surgery, within 2–4 wk, puncture of a noncompressible vessel, use of therapeutic anticoagulants
Examples	Initial Dose	Additional Dose
Tissue plasminogen activator	15-mg bolus	0.75 mg/kg infusion over 30 min (maximum 50 mg), then 0.5 mg/kg infusion over 60 min (maximum 35 mg)
Reteplase	10-U bolus	10-U bolus 30 min later
Tenecteplase	Weight (kg)	Dose (mg)
	< 60	30
	60–69	35
	70–79	40
	80–89	45
	≥ 90	50
GPIIb/IIIa Inhibitors	Indications	Contraindications
	High risk UA/non-STEMI, (especially in those for whom PCI is planned)	Active bleeding, major surgery within 3 mo stroke within 6 mo, thrombocytopenia, recent trauma within 2 to 4 wk, uncontrolled hypertension, creatinine clearance < 30 ml/min*
Examples	Initial Dose	Additional Dose
Abciximab	0.25 mg/kg bolus	0.125 µg/kg infusion (maximum 10 µg/min) for up to 24 h if PCI planned
Eptifibatid	180 µg/kg bolus	2 µg/kg infusion for 24 to 48 h
Tirofiban	0.4 µg/kg bolus over 30 min	0.1 µg/kg infusion for 24 to 48 h.
LMWH	Indications	Contraindications
	Alternative to unfractionated heparin in UA/non-STEMI	Creatinine clearance < 30 ml/min, active bleeding heparin-induced thrombocytopenia, morbid obesity, need for immediate major surgery, need to monitor activated clotting time (such as with PCI)
Examples	Initial Dose	Additional Dose
Enoxaparin	1 mg/kg	Subcutaneously twice daily
Dalteparin	120 IU/kg	Subcutaneously twice daily
Thienopyridines	Indications	Contraindications
	Aspirin allergy in UA/non-STEMI patients, all patients following PCI with stent	Known prior reaction including neutropenia to ticlopidine, thrombotic thrombocytopenia purpura to either agent
Examples	Initial Dose	Additional Dose/Comments
Clopidogrel	75 mg daily	To be used for 30 d if patient received stent
Ticlopidine	250 mg twice daily	A substitute for clopidogrel if former not tolerated

Definition of abbreviation: LBBB = left bundle branch block.

* Tirofiban can be used with creatinine clearance < 30 ml/min at half dose. Tirofiban is dialyzable.

CONTRAINDICATIONS AND DRUG INTERACTIONS

Unfortunately, many patients in the medical intensive care unit have contraindications to aggressive antithrombotic and antiplatelet therapy because of active bleeding or intercurrent illness. The indications and contraindications for a variety of new therapies in patients with ACS are listed in Table 1.

SUMMARY

The treatment of acute coronary syndromes took a new direction a decade or more ago, when the emphasis shifted from relieving ischemic pain to relieving ischemia. Routine, formulaic use of nitroglycerine, morphine, and lidocaine is now archaic. Currently, a widening array of thrombolytic, antithrombotic,

and antiplatelet agents is available. Extensive clinical trials continue to refine their use. The near future will likely witness further refinement, as well as new agents promising greater efficacy. The availability of effective treatment has created the need to quickly categorize and stratify patients in order to match specific treatment to specific syndromes.

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