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The first part of this two-part series on myocardial reperfusion and revascularization outlined the pivotal pharmacological agents used to restore myocardial blood flow in the setting of acute coronary ischemia and/or thrombosis. The evolving role of low molecular weight heparin (LMWH), GP IIb/IIIa plate inhibitors, ADP receptor antagonists, and fibrinolytic agents was emphasized.

Despite excellent trials evaluating the safety and efficacy of specific agents, the lack of head-to-head comparisons among different reperfusion-directed regimens has made it difficult to endorse a "one regimen fits all" approach to patients with acute coronary ischemic syndrome. There are studies, however, that compare outcomes in patients treated medically vs. those managed with percutaneous coronary interventions (PCI), and risk-stratification schemes are available that can guide clinicians in selecting the most appropriate therapy for an individual patient.

With these practical issues in mind, the purpose of this review is to evaluate evidence-based trials that: 1) focus on drug-based regimens and combinations that produce the best outcomes in patients with ST-elevation MI, non-ST elevation MI, and unstable angina; and 2) evaluate risk-strafication trigger points and other criteria that will guide clinicians in selecting patients who are best managed medically as compared to those who ought to have PCI.

— The Editor

Acute Myocardial Infarction and Coronary Syndromes: Optimizing Selection of Reperfusion and Revascularization Therapies in the ED

Part II: Procedural Coronary Intervention (PCI), GP IIb/IIIa Inhibitors, Combination Therapies, Fibrinolysis-Mediated Myocardial Reperfusion, and the Paradigm Shift to Low Molecular Weight Heparin in Patients with Acute Coronary Syndrome

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Reperfusion Therapies—Options, Logistics, and Patient Outcomes

It is widely accepted that the early restoration of perfusion in the acute myocardial infarction (AMI) patient limits myocardial damage, preserves left ventricular function, and reduces mortality; such restoration may be accomplished by either administration of a fibrinolytic agent or procedural coronary intervention (PCI). The rapid application of

reperfusion therapy is mandatory in the patient with ST-elevation AMI. Naturally, a number of factors must be considered by clinicians regarding reperfusion treatment decisions when managing the AMI patient. Among the most important issues are time to application of the intervention and the level of experience of the invasive cardiologist.

Although primary angioplasty, in appropriately selected patients, may offer improved outcome over fibrinolysis, percutaneous transluminal coronary angioplasty (PTCA), or other forms of PCI (stenting) must be instituted as early as possible. In fact, a recent investigation demonstrated that the time to reperfusion in the patient with AMI who is treated with PTCA is related to outcome;[4] in this study, mortality in AMI patients was decreased in the patient subgroup treated within two hours as compared to those individuals managed with angioplasty after two hours of infarct onset. Consequently, if a delay in activation of the catheterization laboratory is anticipated or actually occurs, the physician must proceed with fibrinolysis if the patient is an appropriate candidate.

It should be stressed that restoration of perfusion does not occur immediately or soon after administration of the fibrinolytic agent. In fact, a "full fibrinolytic state" is not reached for at least 45-60 minutes after administration of the fibrinolytic agent. As a result, if one considers a timeline regarding various treatment options and the time to expected full benefit, actual reperfusion may not occur for at least 75-90 minutes in the fibrinolytic-managed patient, assuming a 30-minute door-to-drug interval.

In addition to the "time-to-therapy" parameter, technical expertise of the interventional cardiologist and hospital volume should be considered. In the GUSTO-IIb trial,[1] the majority of partcipating physicians performed at least 75 procedures per year; these results may not generalize to smaller-volume centers with less experienced operators (< 50 cases per year). Another study addressed these issues, i.e., hospital volume and physician experience relative to patient outcome in the PCI-managed individual.[2] Primary angioplasty was found to offer a greater chance of positive outcomes with physicians performing more procedures on a regular basis. Another investigation considered hospital volume in a comparison of fibrinolysis and primary angioplasty in patients with AMI.[3] The investigators found high-volume centers (i.e., those that perform frequent primary angioplasties) were associated with improved outcomes in the PCI group compared to the fibrinolytic group. Interestingly, lower-volume PCI centers demonstrated similar outcomes in the two treatment groups.

Another systems-related issue regarding time-to-arrival to the catheterization laboratory also must be considered. In certain centers, PCI may not be available, necessitating rapid transfer to another facility. Indications for transfer of a patient with AMI to a regional, tertiary care facility with PCI and cardiovascular surgery capabilities include patients with contraindications to fibrinolytic therapy who may benefit from PCI or coronary artery bypass graft (CABG), persistent hemodynamic instability, persistent ventricular dysrhythmias, or postinfarction or post-reperfusion ischemia. Hospital transfer for primary PCI is required for patients with fibrinolytic agent contraindications. The urgent transfer of a fibrinolytic-eligible AMI patient for primary PCI to another institution is not recommended until fibrinolytic therapy is initiated; delaying perfusion restoration in such a patient is not acceptable in most instances. If the patient is an acceptable candidate for fibrinolysis, the fibrinolytic agent should be started before or during transport to the receiving hospital.

Prior agreement between the emergency department (ED) and the inpatient physicians at institutions both with and without PCI capability must be obtained so that PCI consideration will not introduce further delays in fibrinolytic drug administration; such cooperation has been shown to limit additional delays in the administration of fibrinolytic agents to patients who are considered for PCI in AMI.[4] If performed without time delay in experienced hands, PCI appears to produce improved outcomes in the urgent management of AMI. It must be stressed that while PCI is felt to be superior in the treatment of AMI, it must be initiated within 90-120 minutes of arrival to the ED.[5-7]

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Table 1. A Comparison of the Pros and Cons of Thrombolysis and Primary Angioplasty in the Patient with AMI

THROMBOLYTIC	PTCA
• Immediately available	• Few exclusions
• No operator expertise	• Very reasonable outcome
• Proven track record	• Better initial flow
	• Fewer bleeding complications
• *Many exclusions*	• Definition of anatomy
• *More frequent bleeding complications*	• *Not immediately available*
	• *Operator expertise*

If the time required to mobilize staff and arrange for PCI is prolonged (i.e., > approximately 2 hours to balloon catheter inflation or stenting across the culprit coronary lesion), then fibrinolysis is preferred. Delays beyond this time period are unacceptable if the patient originally was a fibrinolytic candidate. These various time periods are suggestions; individual patient and system issues must be considered in the treatment decisions. Table 1 outlines advantages and disadvantages for the two major reperfusion methods available in patients with AMI.

Procedural Coronary Intervention: Unfractionated Heparin vs. Enoxaparin

Low Molecular Weight Heparin Combined with Fibrinolysis or PCI Plus a Glycoprotein (GP) IIb/IIIa Inhibitor in Acute Coronary Syndromes (ACS). Recent trials suggest that the low molecular weight heparin (LMWH) enoxaparin now can be considered a pivotal agent in reperfusion regimens. Heparin has been the standard antithrombin agent for management of AMI, particularly during the pre-PCI or fibrinolytic phase of therapy. However, much of the data in support of it are non-randomized and retrospective.[8] The role of LMWHs in this setting is now being intensively explored. Because of the prolonged half-life and the risk of possible hemorrhage during mechanical reperfusion, there has been concern about performing PCI in patients who received a LMWH for unstable angina or non ST-elevation myocardial infarction (MI).

Two recent trials evaluated the efficacy and safety of enoxaparin in patients with ST-segment elevation MI who were managed with fibrinolysis. The Hypertension Audit of Risk factor Therapy (HART)-II trial compared enoxaparin with heparin as adjunctive antithrombin therapy for 400 patients receiving front-loaded t-PA for ST-segment elevation AMI.[9] In this study, enoxaparin was administered intravenously (30 mg), followed by the standard subcutaneous regimen. The primary end points were infarct-related patency at 90 minutes after initiation of fibrinolytic therapy, reocclusion at 5-7 days, and safety. The TIMI grade 2 or 3 flow was comparable between groups: 80.1% with enoxaparin and 75.1% with heparin.

Reocclusion within one week occurred in 9.1% of the patients who received heparin and in only 3.1% of those who received enoxaparin (P = 0.1). Bleeding complications were comparable between groups.[9] Menown and associates assessed the efficacy and safety of enoxaparin vs. heparin in 300 patients with AMI who received fibrinolytic therapy. The enoxaparin group received a 40 mg intravenous bolus followed by subcutaneous injections, while the heparin group received a 5000-unit bolus plus 30,000 units per 24 hours with adjustment to maintain an appropriate aPTT. The triple end point of death, AMI, or readmission with unstable angina at three months occurred in 36% of those who received heparin and in 26% of those who received enoxaparin (P = 0.04). Major bleeding was comparable between groups.[10]

In addition, other trials have assessed the safety of enoxaparin in the setting of PCI not associated with ST-segment elevation MI. The National Investigators Collaborating on Enoxaparin (NICE)-3 trial evaluated the incidence of bleeding while performing catheterization in 661 patients with ACS, all of whom received enoxaparin plus a GP IIb/IIIa inhibitor (either abciximab, eptifibatide, or tirofiban).[11] At the time of catheterization, enoxaparin (0.3 mg/kg IV) was administered if it had been more than eight hours since the last subcutaneous dose. The combination of enoxaparin with different GP IIb/IIIa inhibitors resulted in similar clinical outcomes and bleeding frequency in comparison with those seen in the large GP IIb/IIIa inhibitor trials.[11]

The NICE-4 trial combined enoxaparin with abciximab during PCI. Enoxaparin was given as a 0.75 mg/kg intravenous bolus dose while abciximab was administered in its usual fashion. Data from the first 310 patients who received enoxaparin and abciximab revealed that the incidence of major non-CABG bleeding and transfusion in this group was 0.6%, which compared favorably with an incidence of 2.7% occurring in patients receiving abciximab and low-dose heparin in the Evaluation of PTCA to Improve Long-term Outcome by GP IIb/IIIa receptor blockade (EPILOG) trial.[8] *(See Table 2 for a listing of trial acronyms and abbreviations.)* Another group assessed the safety and outcomes in patients with unstable angina or non ST-elevation MI. Of the 451 patients, a non-randomized 293 underwent catheterization within eight hours of the morning enoxaparin injection, which was followed by immediate PCI in 132 patients (28%). The procedures were done without additional heparin or enoxaparin. Major bleeding occurred in 0.8% of those who received catheterization, which was comparable to the 1.2% in those who were not studied.[12]

In 200 patients receiving elective PCI after three days of aspirin and tirofiban, another group performed a randomized comparison of periprocedural heparin vs. enoxaparin. Clinical outcomes and major bleeding were comparable between the groups at 30 days.[13] While not a study in the setting of PCI, the pharmacokinetics, pharmacodynamics, and safety of the combination tirofiban with enoxaparin vs. heparin in non-Q wave MI was addressed in a 55-patient series. As with most studies, more minor bleeding occurred with the enoxaparin combination while major bleeding was comparable. The combination of tirofiban and enoxaparin resulted in a more consistent inhibition of platelet aggregation and lower adjusted bleeding time than did the combination with heparin.[14]

The FRagmin during InStability in Coronary artery disease (FRISC-II) trial assessed the role of three months of dalteparin therapy after the use of PCI in patients with unstable angina or

Table 2. Abbreviations and Acronyms for Related Studies

ADMIRAL	=	Abciximab before Direct angioplasty and stenting in acute Myocardial Infarction Regarding Acute and Long-term follow-up
ASSENT-3	=	Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3
CADILLAC	=	Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
CAPTURE	=	C7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment
CURE	=	Clopidogrel in Unstable angina to prevent Recurrent Events
EPIC	=	Evaluation of c7E3 for Prevention of Ischemic Complications
EPILOG	=	Evaluation in PTCA to Improve Long-term Outcome by GP IIb/IIIa receptor blockade
EPISTENT	=	Evaluation of Platelet Inhibition in STENTing
ESSENCE	=	Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events
FRISC	=	FRagmin during InStability in Coronary artery disease
GUSTO	=	Global Utilization of Streptokinase and T-PA in Occluded arteries
HART	=	Hypertension Audit of Risk factor Therapy
IMPACT	=	Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis
NICE	=	National Investigators Collaborating on Enoxaparin
PACT	=	Plasminogen activator and Angioplasty Compatibility Trial
PARADIGM	=	Platelet Aggregation Receptor Antagonist Dose Investigation for reperfusion Gain in Myocardial infarction
PARAGON	=	Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in the Global Organization Network
PRISM	=	Platelet Receptor Inhibition in ischemic Syndrome Management
PRISM PLUS	=	PRISM in Patients Limited by Unstable Signs
PURSUIT	=	Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy
RAPPORT	=	Reopro And Primary PTCA Organization and Randomized Trial
RESTORE	=	Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis
TACTICS	=	Treat Angina with Aggrastat [tirofiban] and determine Cost of Therapy with Invasive or Conservative Strategy
TIMI	=	Thrombolysis In Myocardial Infarction

non ST-elevation MI or after the use of fibrinolysis in AMI. While the initial randomization compared three months of dalteparin vs. placebo, a second randomization, in a two-by-two design, compared the use of early PCI with its more conservative use. At six months, the composite end point of death or AMI was decreased by early PCI from 12.1% to 9.4% in those with less aggressive use (P = 0.031).[15] Dalteparin decreased adverse coronary events during the three-month administration, primarily in patients who received conservative use of PCI. It also was observed that there was no benefit from the three-month dalteparin administration in patients who were in the non-invasive segment of the study.

ENTIRE Study (ENoxparin and TNK-tPA with or without GP IIb/IIIa Inhibitor as REperfusion strategy in ST-elevation MI). The ENTIRE study was a phase II, stratified, randomized, open-label, angiographic trial to assess the safety and efficacy of enoxaparin as an adjunct to fibrinolytic therapy, with or without GP IIb/IIIa therapy, in patients with ST elevation MI.[16] Specifically, ENTIRE attempted to determine the dose of enoxaparin that 1) in combination with full-dose TNK-tPA (tenecteplase); and 2) in combination with a half dose of TNK-tPA (0.27 mg/kg) and full dose of abciximab (bolus 0.25 mg/kg, infusion 0.125 mg/kg/min x 12h) is associated with a TIMI grade 3 flow at 60 minutes in at least 60% of patients. The primary end point was TIMI 3 flow at 60 minutes, and TIMI major hemorrhage at 30 days. Secondary end points included ST segment restoration and ischemic events.

Preliminary results were reported for 461 patients (456 patients treated, with 30-day follow-up available for 424 patients) at the European Society for Cardiology (Sept. 2, 2001, Stockholm). Average age of the patients studied was 58 years; 80% were males; and 34% had an anterior MI. Study patients included those with ST-elevation MI, who had symptoms lasting 30 minutes or longer but fewer than six hours. After receiving aspirin, patients were randomized to receive standard reperfusion with full-dose TNK-tPA (0.53 mg/kg) or combination reperfusion consisting of abciximab plus one-half dose TNK-tPA (0.27 mg/kg). Patients in the standard reperfusion group were then randomly assigned to receive either unfractionated heparin (UFH) (60 U/kg bolus; infusion 1 U/kg/h) or enoxaparin for up to eight days of therapy. In the combination reperfusion group, patients were randomized to receive either UFH (40 U/kg bolus; infusion 7 U/kg/h) or enoxaparin for up to eight days of therapy. Subjects then underwent angiography and PCI, as indicated. Sheath removal following angiogram was performed four hours after PCI (or activated coagulation time [ACT] < 180 seconds) in the heparin group, eight hours after the last subcutaneous dose of enoxaparin in the standard reperfusion group, and eight hours after the last subcutaneous dose or four hours past the last IV dose of enoxaparin in the combination group.

Results of the study indicate that in angiographically evaluable patients, there were no significant differences in TIMI-2 and -3 blood flow at 60 minutes among the treatment arms, and in particular, no differences between UFH and enoxaparin. With respect to TIMI major hemorrhage at 30 days, there was a greater risk of hemorrhage in the combination (half-dose TNK-tPA plus

abciximab) group than in the full-dose TNK-tPA group, and no significant differences between the UFH and enoxaparin subsets within this treatment arm. Among all patients undergoing PCI (n = 181), TIMI major hemorrhage occured in 2.5% of enoxaparin-treated patients and in 6.7% of patients treated with UFH. At 30 days, the death/MI rate in the full-dose TNK-tPA group was 4.4% in the enoxaparin group and 14.9% in the UFH group (P = 0.005). The death/MI/major hemorrhage triple end point rate in the full-dose TNK-tPA group was 16.2% in patients treated with UFH and 6.3% in the enoxaparin group (P = 0.015).

Overall, the preliminary results of the ENTIRE trial suggest that regardless of whether full-dose fibrinolysis with TNK-tPA or combination therapy is employed for facilitated reperfusion in the setting of cardiac catheterization and/or PCI, the anticoagulant enoxaparin is at least as effective and safe as UFH in all patient subsets. Moreover, if preliminary results and trends are confirmed, patients treated with enoxaparin plus full-dose TNK-tPA may have better clinical outcomes than patients treated with full-dose fibrinolysis plus UFH. In addition, enoxaparin may be associated with a lower risk of hemorrhage than UFH in patients treated with half-dose TNK-tPA plus abciximab.[16]

In combination with the results reported in the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 and NICE-3 trials, enoxaparin's safety and efficacy in ACS patients treated with fibrinolysis either in the setting of medical (non-PCI) management, or in the setting of interventional (PCI/catheterization) approaches, has been confirmed in well-designed, randomized trials. Because of superior clinical outcomes as compared with UFH in specific patient subgroups, enoxaparin should be considered the anticoagulant of choice for a broad spectrum of patients with AMI, whether treated with fibrinolytic regimens and/or GP IIb/IIIa antagonists, and also in patients without ST-elevation treated with PCI.

Unstable Angina and Non ST-Elevation MI, Current Management Options

The approach to patients with unstable angina (UA) and non ST-elevation MI continues to undergo refinement. New studies, however, increasingly support a paradigm shift toward giving enoxaparin a central role in patients with ACS, whether they are treated with medical or procedural interventions.[6,16-18]

In this regard, a combined analysis of Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events (ESSENCE) and Thrombolysis in Myocardial Infarction (TIMI)-11B was reported at the American College of Cardiology Scientific Assembly in March 2001. Conducted by investigators at the Royal Infirmary of Edinburgh, the study demonstrated that enoxaparin is superior to UFH in patients with unstable angina (UA)/non ST-segment elevation MI: 7.1% vs. 8.6% (P = 0.02) death/MI at 43 days. Decisions to proceed to revascularization were independent of trial randomization. The group analyzed a population comprising 6098 patients for death or MI at 43 days using chi-squared tests; 983 patients undergoing coronary artery bypass grafting were excluded. Clinicians were blinded to enoxaparin vs. UFH. PCI was not randomized but was performed at the discretion of the treating physician. The authors concluded that patients undergoing PCI (compared with those who were not) sustained more events, including events prior to PCI, consistent with a higher risk population. Enoxaparin treatment, when compared with UFH treatment, benefited both patients treated only medically, and those patients who underwent PCI following an initial period of medical stabilization.[17-20]

Another investigative cardiology group from Greece reported the results of a trial comparing enoxaparin vs. tinzaparin in the management of unstable coronary artery disease (EVET study). The researchers noted that LMWHs are rapidly emerging as an alternative form of antithrombotic therapy to the standard UFH. Despite similarities in origin, synthesis, and structure, the LMWHs have different pharmacokinetic and pharmacodynamic characteristics and possibly elicit different efficacy.

The aim of EVET was to compare head-to-head the efficacy of enoxaparin vs. tinzaparin for the management of ACSs. In a prospective study, 438 patients with unstable angina or non-Q wave MI were randomized to receive either subcutaneous injections of 100 UI/kg enoxaparin twice daily (n = 220) or 175 UI/Kg tinzaparin once daily (n = 218) for seven days. The primary end points were death, MI, refractory angina, and recurrence of unstable angina. Secondary end points were rehospitalization due to unstable angina or MI, death, and the need for revascularization at 30 days.

At seven days, recurrence of unstable angina occurred less frequently in the enoxaparin than in the tinzaparin group (24 of 220 vs 41 of 218, P = 0.029). No statistically significant differences were observed between these two groups with respect to death, MI, or refractory angina at seven days. At 30 days there were no differences between the two groups regarding rehospitalization and death. The need for revascularization at 30 days was significantly less frequent in the patients assigned to enoxaparin (36 of 220 vs 57 of 218, P = 0.019). Bleeding complication rates were similar in the two groups. These investigators concluded that antithrombotic treatment with enoxaparin for seven days was more effective than tinzaparin for reducing the incidence of recurrent angina in patients with unstable angina or non-Q wave MI in the early phase. Enoxaparin recipients also had significantly reduced need for revascularization at 30 days. This benefit was achieved without an increase in bleeding complications.

Non ST-Elevation MI: Procedural Vs. Medical Therapy. The syndrome of unstable angina and MI without ST-elevation accounts for about 1.4 million hospital admissions annually in the United States. As discussed in previous sections, until recently, therapy has focused primarily on medical management using a combination of antianginal agents, antithrombotic agents (including aspirin), and LMWHs. The most current studies have attempted to evaluate and compare early invasive and conservative strategies in patients with unstable coronary syndromes who are treated with GP IIb/IIIa inhibitors such as tirofiban.[21]

One group of investigators (the Treat Angina with Aggrastat [tirofiban] and Determine Cost of Therapy with Invasive or Conservative Strategy [TACTICS] study, 18 investigators) enrolled 2220 patients with unstable angina and MI without ST-segment

elevation who had electrocardiographic evidence of changes in the ST segment or T-wave, elevated levels of cardiac markers, a history of coronary artery disease, or all three findings.[22] All patients were treated with aspirin, heparin, and the glycoprotein IIb/IIIa inhibitor tirofiban. Patients were assigned randomly to an early invasive strategy, in which routine catherization was performed no later than 48 hours after presentation and revascularization was performed as appropriate, or to a more conservative (selectively invasive) strategy in which catheterization was performed only if the patient had objective evidence of recurrent ischemia or an abnormal stress test. The primary end point was a composite of death, nonfatal MI, and rehospitalization for an ACS at six months.

At six months, the rate of the primary end point was 15.9% with the use of the early invasive strategy, and 19.4% with the use of the conservative strategy (odds ratio 0.78; 95% confidence interval, 0.62-0.97; P = 0.025). The rate of death or non-fatal MI at six months was similarly reduced (7.3% vs 9.5%; odds ratio, 0.74; 95% confidence interval, 0.54-1.00; P < 0.05).

Based on these results, the investigators concluded that in patients with unstable angina and MI without ST-segment elevation who were treated with the glycoprotein IIb/IIIa inhibitor tirofiban, the use of an early invasive strategy significantly reduced the risk of major cardiac events.

The Role of Enoxaparin in PCI. The use of enoxaparin in interventional cardiology is supported by data from the ESSENCE and TIMI-11B clinical studies.[17,18] In the ESSENCE study, the need for revascularization procedures at 30 days was significantly less frequent with enoxaparin compared with UFH (27.0% vs 32.2%; P = 0.001).[17] In the TIMI-11B study, urgent revascularization was required in 10.7% of patients who received enoxaparin and 12.6% of patients who received UFH at 43 days (P = 0.05).[18] The incidence of cardiac and hemorrhagic events in patients undergoing PCI in the ESSENCE and TIMI-11B clinical studies was similar irrespective of the initial type of anticoagulation (enoxaparin or UFH), and the timing of the intervention.[17,18]

The results of the NICE-3 study initially were reported by investigators from the Texas Heart Institute at the American College of Cardiology Meeting. NICE-3 was a multicenter (46 sites in the United States and Canada), non-randomized, open-label, observational study that assessed the safety profile of enoxaparin, 1 mg/kg SC bid, plus a GP IIb/IIIa antagonist (tirofiban, n = 217; eptifibatide, n = 252; or abciximab, n = 147) in ACS patients.[23] Patients initially were treated with enoxaparin and a GP IIb/IIIa antagonist; the choice of GP IIb/IIIa antagonist was assigned by institution. If PCI was required, combination therapy was continued through the time of the procedure; if the last enoxaparin dose was greater than eight hours prior to PCI, an additional IV bolus of 0.3 mg/kg was used at the time of the procedure.

The primary end point of the study was the incidence of non-CABG major bleeding during the hospitalization, compared to a rate of 2% estimated from prior studies. Secondary end points included clinical outcomes. This group concluded that 1) the combination of enoxaparin and a GP IIb/IIIa antagonist does not result in an excess of non-CABG major bleeding; 2) patients on combination therapy can safely undergo PCI; 3) clinical outcomes in NICE-3 were comparable to those in prior studies; 4) it is not necessary to use UFH in ACS patients undergoing PCI who are treated with enoxaparin and a GP IIb/ IIIa antagonist.

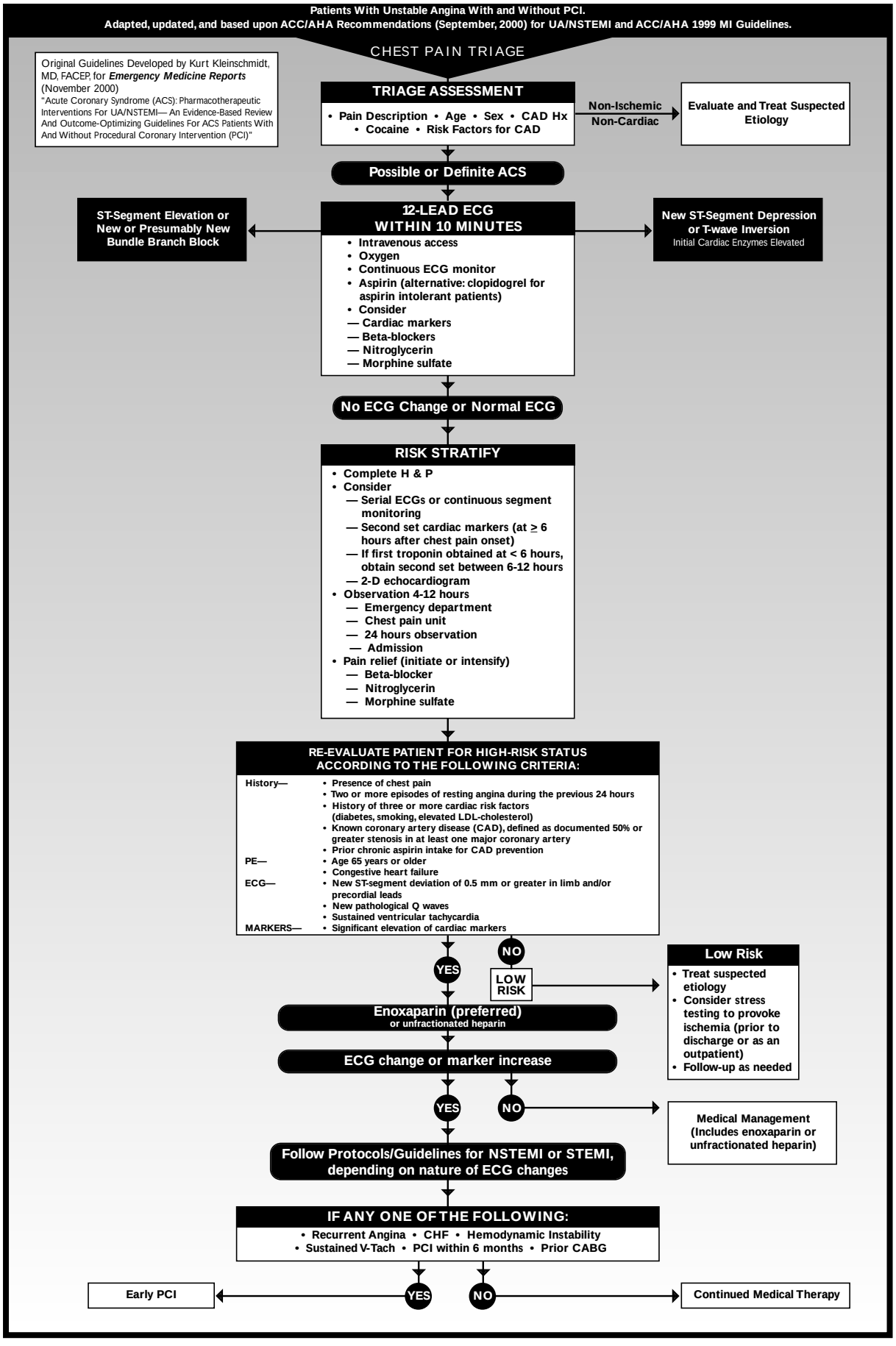
Publication of the NICE-3 study confirmed these initial conclusions. Safety end points included major hemorrhage compared with historical controls, minor bleeding, and platelet counts to seven days; efficacy end points included death, MI, and urgent revascularization. The combination of enoxaparin and a GP IIb/IIIa antagonist did not result in an excess of non-CABG major bleeding (0.7-3.2% of patients) and clinical outcomes were comparable with those in earlier studies. The NICE-3 study concluded that patients who received combination therapy that included enoxaparin and a GP IIb/IIIa antagonist can undergo PCI safely.[23] In the NICE-4 study, an intravenous bolus of enoxaparin 0.75 mg/kg plus abciximab 0.25 mg/kg bolus and 0.125 mg/kg/min infusion for 12 hours was administered during PCI in 826 patients. There was a low incidence of minor and major bleeding and transfusion, and infrequent major cardiac events to 30 days follow-up. Enoxaparin with concomitant abciximab was concluded to provide safe, well-tolerated, and effective anticoagulation in PCI.[20]

In summary, the most recent clinical trial data confirm enoxaparin as the LWMH of choice in patients with ACS and, in most cases, as the preferable substitute for UFH. Moreover, they also provide increasing evidence that patients with PCI can be safely and effectively managed using a combination of enoxaparin and GP IIb/IIIa antagonist. See Figures 1-3, in which protocols for managing the spectrum of ACS (unstable angina, non ST-elevation MI, and ST-elevation MI) are presented.

GP IIb/IIa Inhibitors. In patients receiving PCI, among the GP IIb/IIIa inhibitors, abciximab has demonstrated consistent benefit. In contrast, neither eptifibatide nor tirofiban significantly decreased ischemic events after PCI in the Randomized Efficacy Study of Tirofiban for Outcomes REstenosis (RESTORE) and Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT)-II trials, respectively. In the Evaluation of c7E3 for Prevention of Complications (EPIC), EPILOG, and Evaluation of Platelet Inhibition in STENTing (EPISTENT) trials, abciximab produced 4.5-6.4% absolute reductions in the 30-day composite end point, and these benefits persisted at six months in the EPIC and EPILOG trials (EPISTENT did not assess six-month outcomes).[24-28] The benefits also persisted at more extended follow-up. At one year, patients in the EPILOG trial had a significant reduction of the composite end point from 16.1% in the placebo group to 9.6% in the abciximab groups (P < 0.001).[27] At three years, patients in the EPIC trial also had a significant reduction of the composite end point from 47.2% in the placebo group to 41.1% in the abciximab bolus plus infusion group (P = 0.009).[26] In the EPISTENT trial, the composite end point of mortality or AMI at one year was significantly reduced in the stent plus abciximab group (5.3%), compared to the stent plus placebo group (11.0%; p < 0.001).[29]

The C7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment (CAPTURE) trial, which evaluated abciximab and mandatory PCI, found significant benefit at 30

Figure 1. Guidelines for Effective Management of Unstable Angina



days, but not at six months.[30] Various factors may be responsible for the lack of enduring benefits. Patients received abciximab for only one hour after PCI in the CAPTURE trial vs. for 12 hours after PCI in both the EPIC and EPILOG trials. The 12-hour administration period post-procedure may be very important for establishing the long-term (6 months to 3 years) benefit of abciximab. This difference supports the concept of arterial passivation, in which the agent affects the vessel wall surface so as to inhibit further platelet-thrombin deposition. The significance of the pharmacologic differences between abciximab and the small molecule agents is unclear; however, they might contribute to the potential passivation associated with abciximab.

The GP IIb/IIIa inhibitors work comparably during the 12-36 hour intravenous infusions. The prolonged platelet-bound biologic half-life of abciximab might account for its prolonged effect on platelet function. The longer duration of action may have been the reason for abciximab's success with a 12-hour infusion vs. the 20-72 hour infusions used with eptifibatide or tirofiban. The highest risk for thrombotic events after PCI is within 48 hours. The prolonged and tapered effect of abciximab neutralizes platelets while the vessel heals itself, providing "artificial" passivation when the patient's thrombosis risk profile gradually progresses from high-risk to low-risk.[27]

The role of GP IIb/IIIa inhibitors in patients who are not necessarily having a PCI is controversial. All of the trials (Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy [PURSUIT], Platelet Receptor Inhibition in ischemic Syndrome Management [PRISM], PRISM in Patients Limited by Unstable Signs [PRISM-Plus], and Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in the Globe Organization Network [PARAGON]) included patients who did and did not receive PCI and, importantly, the use of PCI was not randomized.[31-34] Differentiating the outcomes of patients who received only medical therapy vs. those having a PCI is not easy. These groups were not differentiated in the PARAGON trial and no differences were found between the groups in the PURSUIT trial. As noted above, the PURSUIT trial also was interesting because the benefit among geographic locations varied directly with the frequency of catheterizations performed in the locations, supporting the concept that GP IIb/IIIa inhibitors might be optimal in the PCI population.[31-33]

The PRISM trial noted a significant reduction in the combination of death and AMI at 30 days in those treated only medically with tirofiban.[33] However, the data presented on the population receiving only medical therapy were limited and were not either a primary or secondary end point. Patients treated with tirofiban and heparin, without PCI, had an improved 30-day composite outcome compared to those treated with only heparin in PRISM-PLUS. Once again, the data pertaining to those treated only medically was very limited. The CAPTURE trial, despite having mandated PCI, did start with an 18-24 hour infusion of abciximab before PCI.[30] During this "medical-only treatment" phase of the study, the AMI rate was reduced from 2.1% to 0.6% in the abciximab arm.

Oral Platelet Antagonists—The Role of Clopidogrel Pretreatment

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial was designed to compare the efficacy and safety of the early and long-term use of clopidogrel plus aspirin with those of aspirin alone in patients with ACSs and no ST-segment elevation.[35] In the CURE, trial 12,562 patients who had presented within 24 hours after the onset of symptoms were randomly assigned to receive either clopidogrel (300 mg immediately, followed by 75 mg once daily) or placebo, in addition to aspirin, for 3-12 months.

The first primary outcome—a composite of death from cardiovascular causes, nonfatal MI, or stroke—occurred in 9.3% of the patients in the clopidogrel group and 11.4% of the patient in the placebo group (relative risk with clopidogrel as compared with placebo, 0.80; 95% confidence interval, 0.72-0.90; $P < 0.001$). The second primary outcome (the first primary outcome or refractory ischemia) occurred in 16.5% of the patients treated with clopidogrel and 18.8% of the patients in the placebo group (relative risk, 0.86 $P < 0.001$). The percentage of patients with major bleeding was greater in the clopidogrel group (relative risk, 1.38), although the percentage of patients with life-threatening bleeding was not greater.[35] Among 2568 patients receiving PCI in the CURE study, pretreatment with clopidogrel also was beneficial in those patients undergoing mechanical revascularization.[36]

Combination Therapies in the Reperfusion-Treated Patient

Recent research has evaluated the use of therapeutic combinations, including GP IIb/IIIa inhibition with both PCI and fibrinolysis, low-dose fibrinolysis followed by primary angioplasty, and stent placement during PCI. As emphasized, reperfusion with primary PCI may be improved with the use of GP IIb/IIIa inhibitors, although there are conflicting results regarding their use in non-PCI patients. Abciximab with stenting in AMI has been studied in the Reopro And Primary PTCA Organization and Randomized Trial (RAPPORT),[37] the Abciximab before Direct angioplasty and stenting in acute Myocardial Infarction Regarding Acute and Long-term follow-up (ADMIRAL),[30] and the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trials.[38] In the RAPPORT trial, a significant reduction in the combined end point of death, MI, and urgent need for revascularization was noted at 30 days;[37] no significant differences, however, were seen at six months. An increase in major bleeding episodes and the need for transfusions was encountered in the abciximab group, which was likely due to high-dose heparin therapy.

The ADMIRAL trial reported a significantly lower rate of occurrence of the combined end point of death, recurrent MI, and target vessel revascularization at 30 days in the treatment group.[29] In addition, lower doses of heparin were given to patients in the abciximab group, and no increase in major bleeding was observed. The CADILLAC trial randomized primary PCI patients with AMI to stenting and abciximab vs. placebo.[38] Preliminary results suggest that the abciximab-treated patients

Figure 2. Guidelines for Effective Management of Non ST-Elevation MI

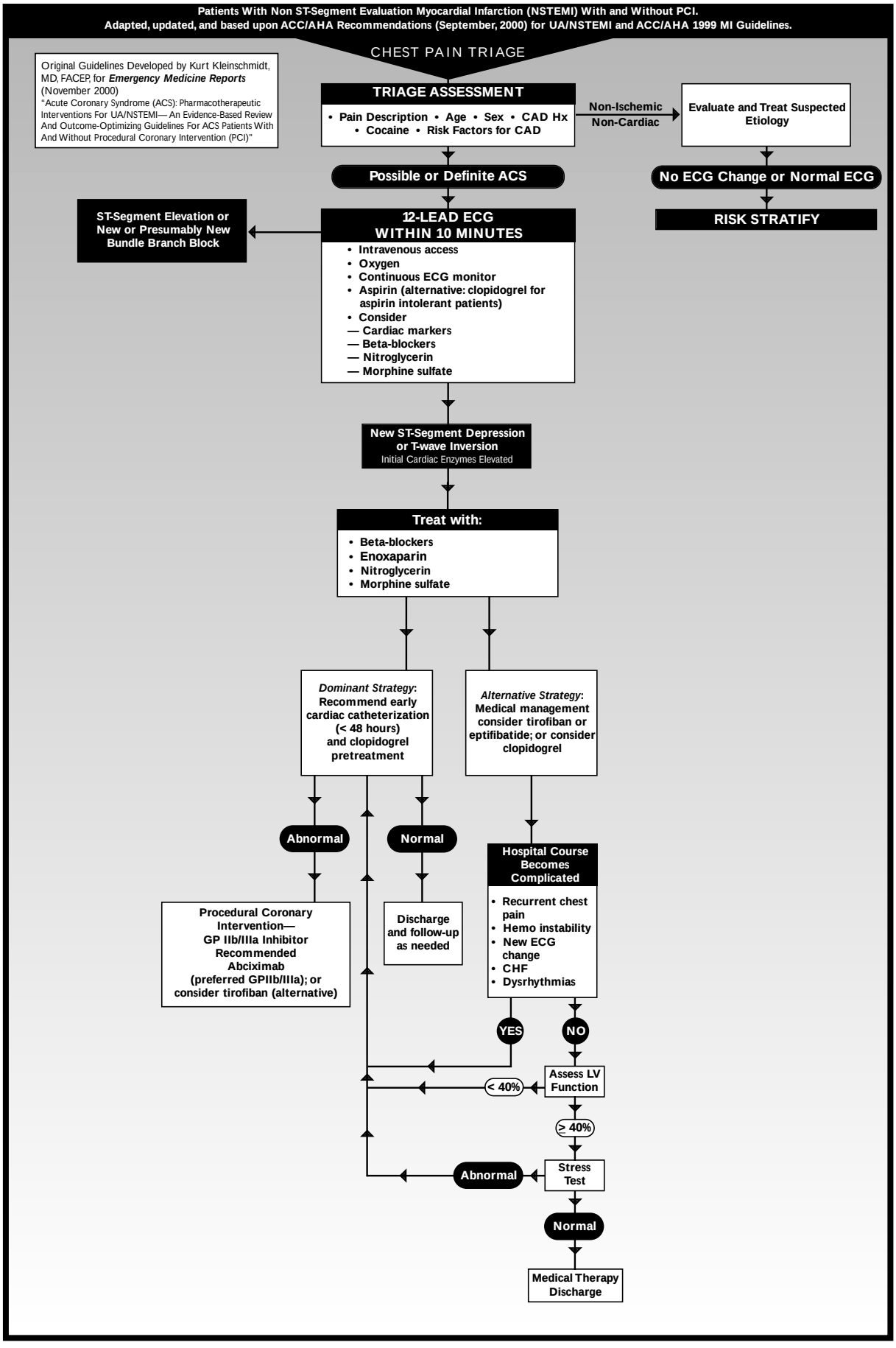
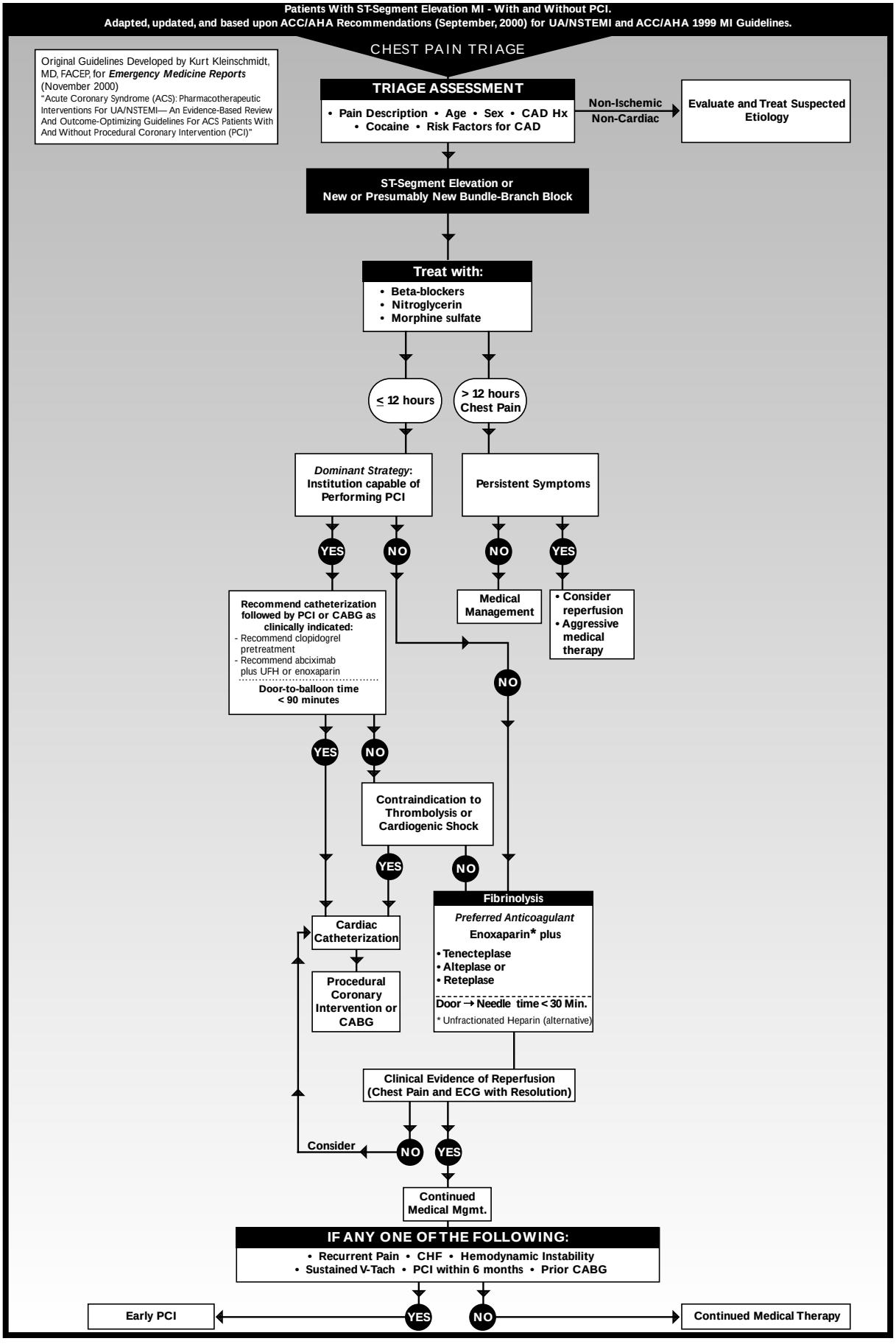


Figure 3. Guidelines for Effective Management of ST-Elevation MI



appeared to have had a modest reduction in acute events. The use of glycoprotein inhibitors in the setting of AMI treated with PCI appears to benefit the appropriately selected patients.

Perhaps the most interesting and controversial arena involves a "combination therapy" approach to the AMI patient, using a fibrinolytic agent and glycoprotein inhibitor. The IMPACT-AMI study examined patients with AMI and randomly assigned them to receive either eptifibatide or placebo.[39] In addition, patients received aspirin, heparin, and tissue plasminogen activator. Thus, this study looked at the role of a GP IIb/IIIa inhibitor (eptifibatide) in conjunction with a fibrinolytic agent in AMI—a departure from studies of unstable angina with or without catheter-mediated revascularization. The highest dose of eptifibatide studied achieved higher 90-minute patency rates than placebo, but similar rates of in-hospital death, stroke, reinfarction, vascular procedures, and new heart failure.[39]

The Platelet Aggregation Receptor Antagonist Dose Investigation for reperfusion Gain in Myocardial infarction (PARADIGM) trial was designed to assess the safety and efficacy of combination therapy involving the platelet glycoprotein GP IIb/IIIa inhibitor lamifiban when given with fibrinolytic agents (tPA or streptokinase) to patients with ST-segment elevation AMI.[40] A composite of angiographic, continuous electrocardiographic, and clinical markers of reperfusion was the primary efficacy end point; bleeding was the primary safety end point. Lamifiban induced more rapid reperfusion though a higher rate of bleeding was noted as well (transfusions in 16.1% lamifiban-treated vs 10.3% placebo-treated patients). This trial, while small, suggests that such combination therapy may hasten clinical improvement and favorably alter outcome; additional, large trials are required to further explore this issue.

The use of reduced-dose fibrinolytic agent in the AMI patient who is a candidate for primary PCI also has been explored. The Plasminogen activator and Angioplasty Compatibility Trial (PACT) trial randomized patients in the ED to either reduced-dose tPA (50 mg) or placebo in preparation for primary angioplasty.[41] Fibrinolytic-managed patients demonstrated higher rates of infarct vessel patency and TIMI grade 3 flow with similar rates of adverse effect, suggesting that reperfusion can be enhanced prior to immediate PCI. This approach, called "facilitated percutaneous coronary intervention," suggests that early reperfusion therapy prior to catheterization not only is safe but also effective.

A significant development in the use of PCI in the treatment of AMI involves coronary stents. In the recent past, early use of stenting in the AMI patient was considered problematic due to the real possibility of stent thrombosis. With the introduction of aggressive antiplatelet therapy using aspirin, ticlopidine, or clopidogrel, the rates of stent thrombosis have significantly decreased. Exploring early stent placement in the AMI patient, the PAMI-stent trial compared urgent treatment with PTCA with or without stenting in 900 patients.[42] Stenting significantly reduced both stenosis and re-occlusion at six months. No differences in death, reinfarction, or stroke at six months, however, were noted. Thus, it appears that in selected patients with AMI, primary stenting can be applied safely and effectively, resulting in a lower incidence of recurrent infarction and a significant reduction in the need for subsequent target-vessel revascularization compared with balloon angioplasty.

Summary

It is widely accepted that the early restoration of perfusion in the AMI patient limits myocardial damage, preserves left ventricular function, and reduces mortality; such restoration may be accomplished by either administration of a fibrinolytic agent or performance of PTCA; in the rare case, emergent coronary artery bypass grafting is a third revascularization method.

The rapid application of reperfusion therapy is mandatory in the patient with ST-elevation AMI. Many factors must be considered by both emergency and cardiovascular physicians regarding early reperfusion treatment decisions when managing the AMI patient. While primary angioplasty may offer improved outcome over fibrinolysis, PTCA must be applied early without prolonged delay. Should catheterization laboratory activation delay either be anticipated or occur, the treating physician must proceed with fibrinolysis if the patient is an appropriate candidate. Prior agreement between the ED and the cardiovascular physicians at institutions with angioplasty capability must be obtained so that consideration of PCI will not introduce further delays in fibrinolytic drug administration; such cooperation has been shown to limit additional delays in the administration of fibrinolytic agents in patients who are considered for PTCA in AMI.

The data suggest that PTCA, if applied without time delay and in experienced hands, can produce improved outcomes in AMI. It must be stressed, however, that although PTCA is felt to be superior in the treatment of AMI, this procedure must be initiated within 90 minutes of patient arrival to the hospital ED.[4] If the time required to mobilize staff and arrange for PTCA is prolonged (i.e., > 90 minutes to balloon catheter inflation across the culprit coronary lesion), then fibrinolysis is the preferred mode of therapy.[4] Delays beyond this time period are unacceptable if the patient originally was considered to be fibrinolytic a candidate.

When fibrinolysis is employed, the most recent evidence suggests a therapeutic paradigm shift toward a regimen that combines enoxaparin with full-dose TNK-tPA. Compared to a more traditional UFH/TNK-tPA combination, the substitution of UFH with enoxaparin produces a relative reduction of 26% in the frequency of ischemic complications of acute MI. In light of its ease of administration, predictable anti-thrombin activity, and improved outcomes, a TNK-tPA plus enoxaparin reperfusion regimen must be considered the pharmacological cocktail of choice.

Several issues must be considered by the physician when evaluating the relative desirability of various therapeutic options. First, the literature base for answering questions related to therapeutic options is somewhat heterogeneous in construction (e.g., differing therapies, study sites, outcome measures, etc.). Therefore, making absolute, all-encompassing recommendations is impossible.

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Physician CME Questions

65. The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial showed that:
    A. fiibrinolysis was better tolerated than PCI.
    B. enoxparin produced better outcomes than UFH.
    C. that the combination of clopidogrel plus aspirin produced better outcomes in patient with unstable angina than aspirin alone.
    D. All of the above

66. In patients receving PCI for myocardial revascularization, which of the following agents has demonstrated consistent benefit?
    A. Abciximab
    B. Fibrinolysis
    C. Digoxin
    D. Calcium blockers

67. The NICE-4 and NICE-3 studies confirm:
    A. the safety and efficacy of enoxaparin plus fibrinolytics.
    B. the safety and efficiacy of enoxaparin plus UFH in AMI.
    C. the safety and efficacy of enoxaparin plus GP IIb/IIIa inhibitors in in ACS patients undergoing PCI.
    D. All of the above

68. The ESSENCE study confirmed the superiority of enoxaparin over UFH in:
    A. ST-elevation MI.
    B. stable angina.
    C. unstable angina.
    D. All of the above

69. The PCI-CURE study demonstrates that pretreatment with clopidogrel:
    A. is not beneficial in patients undergoing mechanical revascularization.
    B. is beneficial in patients undergoing mechanical revascularization.
    C. is associated with an increase in angina.
    D. All of the above

70. Investigators have found that institutions that perform a high volume of PCI/angioplasties:
    A. have better outcomes than insitutions that are low-volume centers.
    B. have inferior outcomes than institutions that are low-volume centers.
    C. have the same outcomes as institutions that are low-volume centers.
    D. All of the above

71. A full fibrinolytic state is achieved within how many minutes of giving a fibrinolytic agents?
    A. 5 minutes
    B. 10-15 minutes
    C. 15-20 minutes
    D. 20-30 minutes
    E. at least 45-60 minutes after administration

72. Although PCI is felt to be superior in appropriate centers in patients with AMI, the procedure must be initiated within 90-120 minutes after arrival to ED.
    A. True
    B. False

Emergency Medicine Reports CME Objectives

To help physicians:

- quickly recognize or increase index of suspicion for specific conditions;
- understand the epidemiology, etiology, pathophysiology, and clinical features of the entity discussed;
- be educated about how to correctly perform necessary diagnostic tests;
- take a meaningful patient history that will reveal the most important details about the particular medical problem discussed;
- apply state-of-the-art therapeutic techniques (including the implications of pharmaceutical therapy discussed) to patients with the particular medical problems discussed;
- understand the differential diagnosis of the entity discussed; understand both likely and rare complications that may occur;
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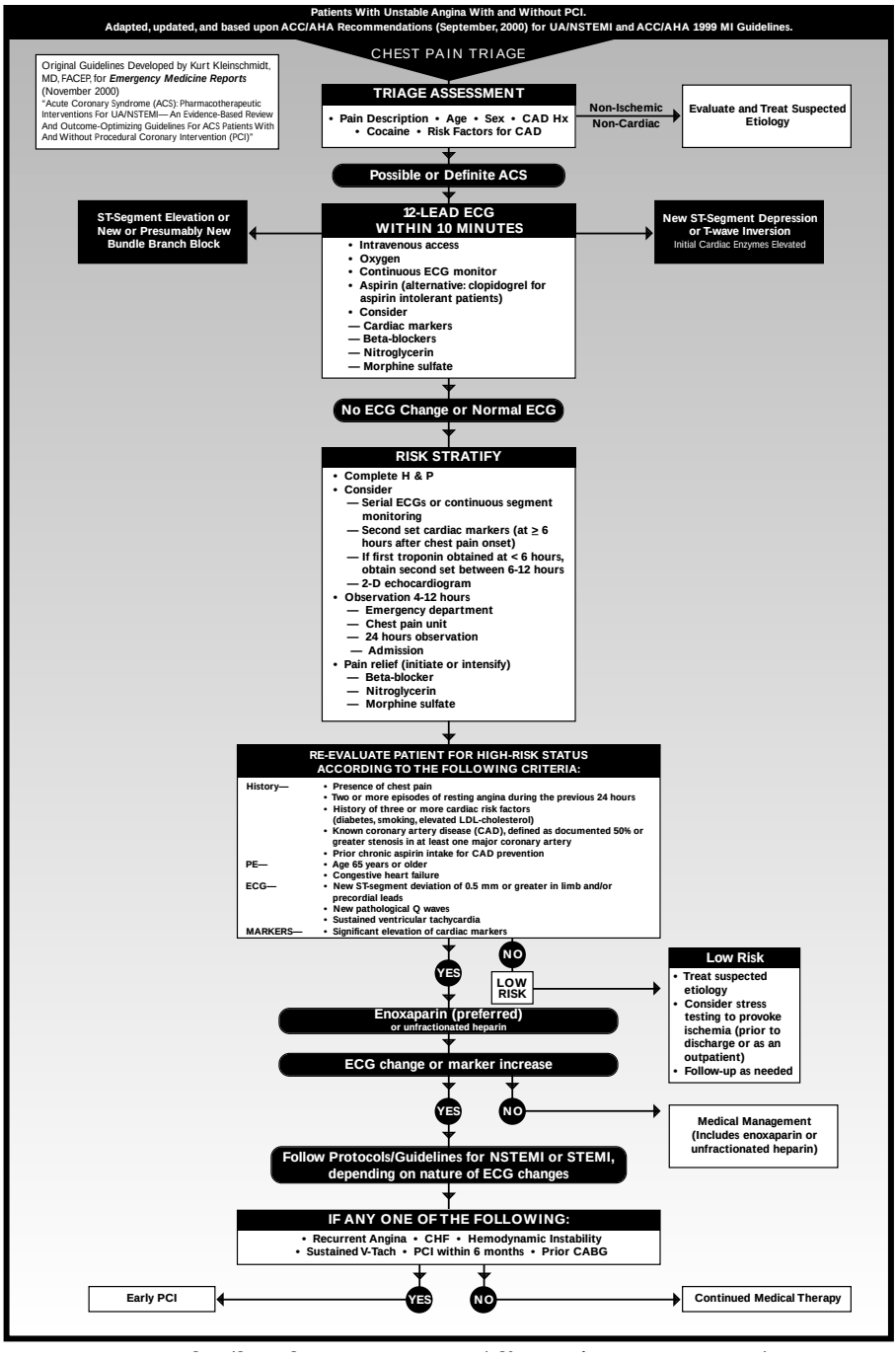
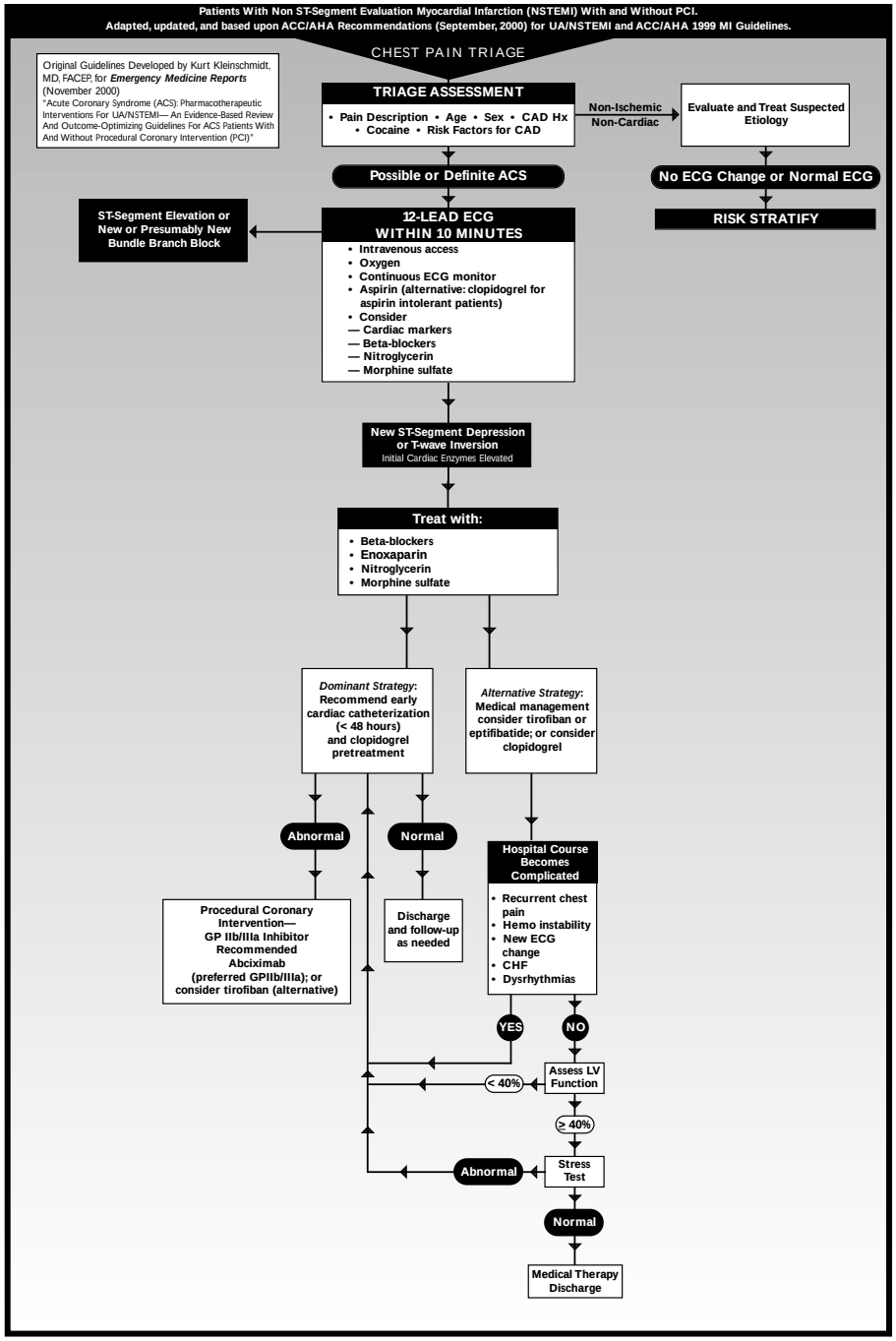
AMI and Acute Coronary Syndromes: Part II

Guidelines for Effective Management of Unstable Angina



Guidelines for Effective Management of Non ST-Elevation MI



Supplement to *Emergency Medicine Reports*, October 22, 2001: "Acute Myocardial Infarction and Coronary Syndromes: Optimizing Selection of Reperfusion and Revascularization Therapies in the ED. Part II: Procedural Coronary Intervention (PCI), GP IIb/IIIa Inhibitors, Combination Therapies, Fibrinolysis-Mediated Myocardial Reperfusion, and the Paradigm Shift to Enoxaparin in Patients with Acute Coronary Syndromes."
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Emergency Medicine Reports
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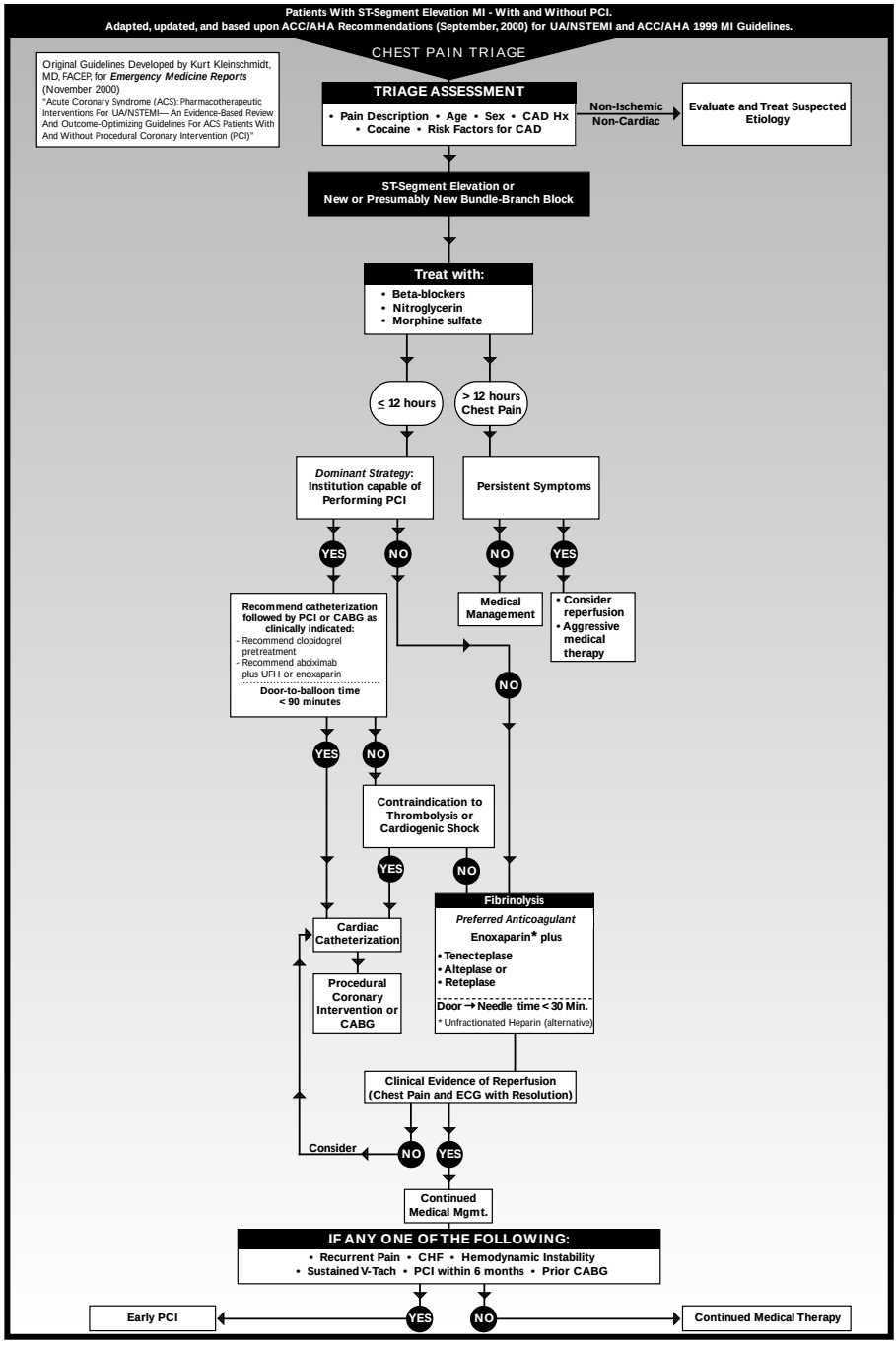
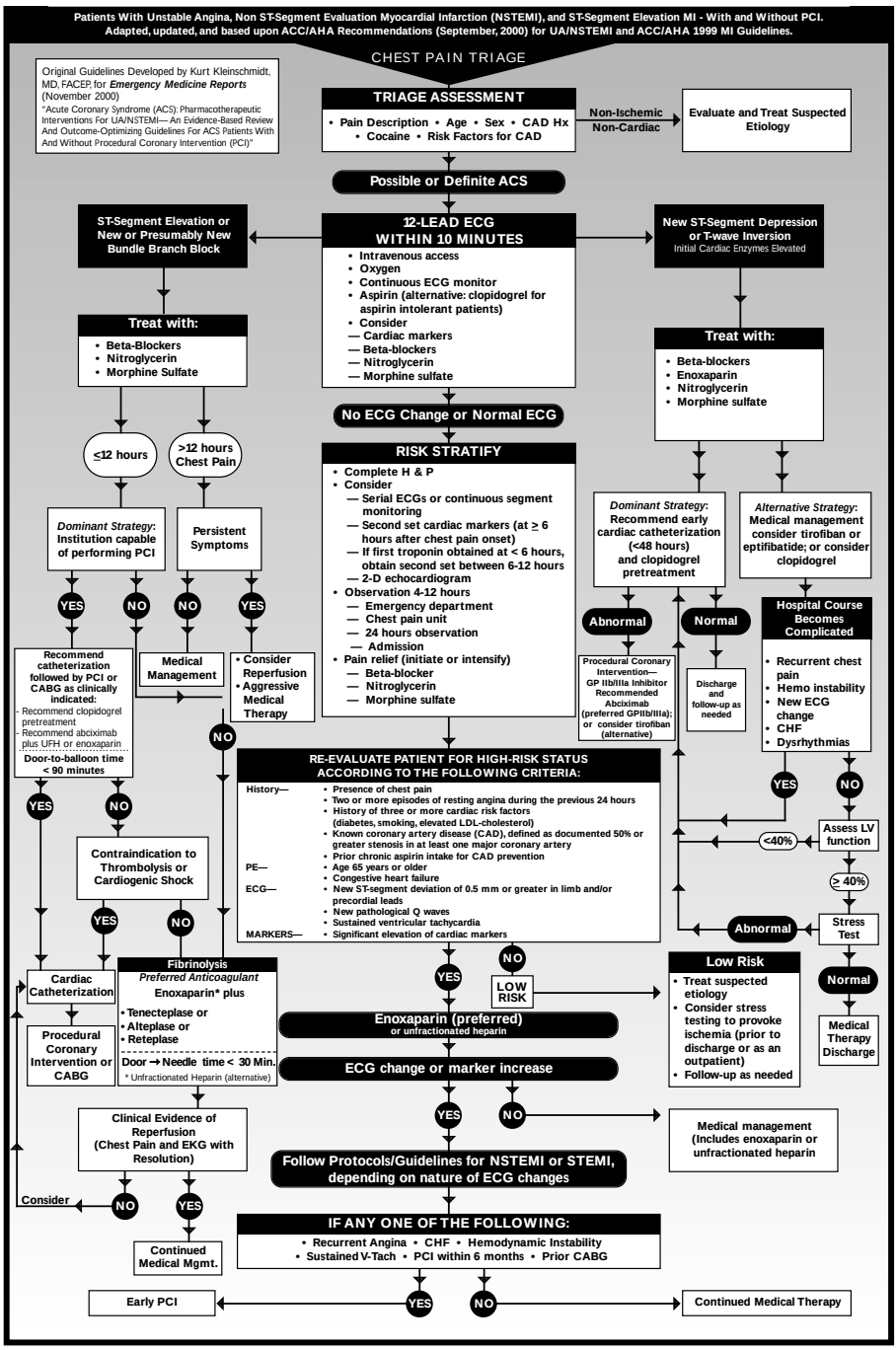
AMI and Acute Coronary Syndromes: Part II

Guidelines for Effective Management of ST-Elevation MI



Acute Coronary Syndrome Management



Supplement to *Emergency Medicine Reports*, October 22, 2001: "Acute Myocardial Infarction and Coronary Syndromes: Optimizing Selection of Reperfusion and Revascularization Therapies in the ED. Part II: Procedural Coronary Intervention (PCI), GP IIb/IIIa Inhibitors, Combination Therapies, Fibrinolysis-Mediated Myocardial Reperfusion, and the Paradigm Shift to Enoxaparin in Patients with Acute Coronary Syndromes."
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