Clinical Policy: Indications for Reperfusion Therapy in Emergency Department Patients with Suspected Acute Myocardial Infarction

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This clinical policy focuses on indications for emergent fibrinolytic therapy in emergency department (ED) patients with suspected acute myocardial infarction (AMI). A writing subcommittee knowledgeable in AMI-related literature selected 2 areas of current interest and/or controversy to the practicing emergency physician:

1. What are the ECG indications for emergent fibrinolytic therapy?
2. What are the indications for fibrinolytic therapy in patients being treated at or transferred to a percutaneous coronary intervention center?

MEDLINE searches were performed to select literature for inclusion. Subcommittee members also supplied articles with

direct bearing on this policy. Articles included in this policy were graded on the basis of a predetermined formula taking into account design and quality of the study. Recommendations for patient management are provided for each of these topics based on strength of evidence (Level A, B, or C). Level A recommendations represent patient management principles that reflect a high degree of clinical certainty; Level B recommendations represent patient management principles that reflect moderate clinical certainty; and Level C recommendations represent other patient management strategies based on preliminary, inconclusive, or conflicting evidence, or based on panel consensus. This guideline is intended for physicians working in hospital-based EDs or chest pain evaluation units.

INTRODUCTION

Approximately 20% of hospitals in the United States have the capability to perform emergent percutaneous coronary intervention (PCI) in patients presenting to the emergency department (ED) with suspected acute myocardial infarction (AMI).[1] Patients presenting to institutions that do not perform emergent PCI are either treated onsite with fibrinolytic therapy or transferred for emergent PCI. Furthermore, it is not uncommon for patients to present to a PCI center during a time in which the catheterization laboratory is not immediately available. In patients being treated at or transferred to a PCI center, the emergency physician must take into account the treatment benefit of timely fibrinolytic therapy versus delayed PCI in determining which mode of reperfusion therapy is best for the patient. For emergency physicians practicing in remote regions of the United States, the decision has been effectively made by lack of timely access by ambulance or helicopter transport to a PCI institution. In other instances the decision has been made by written hospital policies and guidelines.

This clinical policy addresses indications for fibrinolytic therapy and is the second of a 2-part scheduled revision of the 2000 American College of Emergency Physicians (ACEP) clinical policy on AMI and unstable angina.[2] The first part focused on critical issues in the management of patients with non–ST-segment elevation acute coronary syndromes. This current clinical policy was created after careful review and critical analysis of the peer-reviewed literature. A writing subcommittee knowledgeable in AMI-related literature and clinical guidelines was selected to review the 2000 ACEP clinical policy in order to select key areas on which to focus this current policy.[2] Two critical questions in the management of patients with AMI of current interest and/or controversy were chosen by the subcommittee:

1. What are the ECG indications for emergent fibrinolytic therapy?
2. What are the indications for fibrinolytic therapy in patients being treated at or transferred to a PCI center?

METHODOLOGY

This clinical policy was created after careful review and critical analysis of the medical literature. Multiple MEDLINE searches were done. The medical literature was reviewed for articles that pertained to each critical question posed, and pertinent articles were selected. Subcommittee members also supplied articles from bibliographies of initially selected articles or from their own files.

The reasons for developing clinical policies in emergency medicine and the approaches used in their development have been enumerated.[3] This policy is a product of the ACEP clinical policy development process, including expert review, and is based on the existing literature; where literature was not available, consensus of emergency physicians was used. Expert review comments were received from individual emergency physicians and from individual members of the American College of Cardiology and the Society of Chest Pain Centers. Their responses were used to further refine and enhance this policy. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology or the practice environment changes significantly.

All articles used in the formulation of this clinical policy were graded by at least 2 subcommittee members for strength of evidence and classified by the subcommittee members into 3 classes of evidence on the basis of the design of the study, with design 1 representing the strongest evidence and design 3 representing the weakest evidence for therapeutic, diagnostic, and prognostic clinical reports, respectively (Appendix A). Articles were then graded on 6 dimensions thought to be most relevant to the development of a clinical guideline: blinded versus nonblinded outcome assessment, blinded or randomized allocation, direct or indirect outcome measures (reliability and validity), biases (eg, selection, detection, transfer), external validity (ie, generalizability), and sufficient sample size. Articles received a final grade (I, II, III) on the basis of a predetermined formula taking into account design and quality of study (Appendix B). Articles with fatal flaws were given an "X" grade and not used in the creation of this policy. Evidence grading was done with respect to the specific data being extracted, and the specific critical question being reviewed. Thus, the level of evidence for any 1 study may vary according to the question, and it is possible for a single article to receive different levels of grading as different critical questions are answered. Question-specific level of evidence grading may be found in the Evidentiary Table included at the end of this policy.

Clinical findings and strength of recommendations regarding patient management were then made according to the following criteria:

Level A recommendations. Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on strength of evidence Class I or overwhelming evidence from strength of evidence Class II studies that directly address all the issues).

Level B recommendations. Recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty (ie, based on strength of evidence Class II studies that directly address

the issue, decision analysis that directly addresses the issue, or strong consensus of strength of evidence Class III studies).

Level C recommendations. Other strategies for patient management that are based on preliminary, inconclusive, or conflicting evidence, or in the absence of any published literature, based on panel consensus.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as heterogeneity of results, uncertainty about effect magnitude and consequences, strength of prior beliefs, and publication bias, among others, might lead to such a downgrading of recommendations.

Recommendations offered in this policy are not intended to represent the only diagnostic and management options that the emergency physician should consider. ACEP clearly recognizes the importance of the individual physician's judgment. Rather, this guideline defines for the physician those strategies for which medical literature exists to provide support for answers to the crucial questions addressed in this policy.

Scope of Application. This guideline is intended for physicians working in hospital-based EDs or chest pain evaluation units.

Inclusion Criteria. This guideline is intended for adult patients presenting to the ED with suspected AMI.

Exclusion Criteria. This guideline is not intended for pediatric patients, patients with contraindications to fibrinolytic treatment, or patients in cardiogenic shock.

CRITICAL QUESTIONS

1. What are the ECG indications for emergent fibrinolytic therapy?

Patient Management Recommendations

Level A recommendations. Assess for fibrinolytic therapy in patients with symptoms suggestive of AMI and presenting within 12 hours of symptom onset if ECG reveals:

1. ST elevations greater than or equal to 0.1 mV (1 mm) in 2 or more contiguous *limb* leads or greater than or equal to 0.2 mV (2 mm) in 2 or more contiguous *precordial* leads lacking features of non-infarction causes of ST-segment elevation (eg, early repolarization, pericarditis, left ventricular hypertrophy [LVH], incomplete bundle branch block [BBB]).
2. Any type of BBB (right, left, and atypical – new or old) thought to be obscuring ST-segment analysis in patients with clinical presentation *strongly suggestive* of AMI.

Level B recommendations. Assess for fibrinolytic therapy in patients with symptoms suggestive of AMI and presenting within 12 hours of symptom onset if ECG reveals:

1. ST elevations greater than or equal to 0.1 mV (1 mm) in 2 or more contiguous *precordial* leads lacking features of non-infarction causes of ST-segment elevation (eg, early repolarization, pericarditis, LVH, incomplete BBB).
2. New or presumably new left bundle branch block (LBBB).
3. LBBB with concordant ST-segment deviations greater than or equal to 0.1 mV (1 mm) towards the major QRS deflection or discordant ST-segment deviations greater than or equal to 0.5 mV (5 mm) away from the major QRS deflection in 2 or more contiguous leads.
4. ST depressions greater than or equal to 0.2 mV (2 mm) with upright T-waves in 2 or more contiguous anterior precordial leads (V_1 to V_4) in patients with clinical presentation suggestive of AMI involving the posterior left ventricular wall.

Level C recommendations. Assess for fibrinolytic therapy in patients with symptoms suggestive of AMI and presenting within 12 hours of symptom onset if ECG reveals:

1. New or presumably new right bundle branch block (RBBB).
2. RBBB, atypical BBB, or ventricular paced and concordant ST-segment deviations greater than or equal to 0.1 mV (1 mm) towards the major QRS deflection or discordant ST-segment deviations greater than or equal to 0.5 mV (5 mm) away from the major QRS deflection in 2 or more contiguous leads.

While the patient's history and physical examination are important in the evaluation of potential AMI, the 12-lead ECG provides the vital information that is the major indication for fibrinolysis. Multiple randomized trials involving fibrinolytic therapy versus placebo have demonstrated that mortality is reduced in certain subgroups of patients with AMI.[4-13] The Fibrinolytic Therapy Trialists' (FTT) Collaborative Group analyzed all randomized fibrinolytic therapy trials of more than 1,000 patients and found that benefit of fibrinolytic therapy was observed only in patients with ST-segment elevation or BBB.[14] Benefit was demonstrated regardless of age, gender, systolic blood pressure, heart rate, history of prior myocardial infarction, or diabetes. Benefit was seen at all time intervals within the first 12 hours of symptom onset with greater benefit the earlier treatment was begun. Benefit was greatest in patients with BBB and anterior AMI and least in inferior AMI. Benefit from fibrinolytic therapy in patients with ST-segment elevation or BBB who present more than 12 hours after symptom onset has yet to be established.[11,13,14]

As ECG indications for emergency fibrinolytic therapy have significant ramifications for the ED management of patients with suspected AMI, the ACEP Clinical Policies Subcommittee performed a MEDLINE search of clinical trials using a combination of the key words "acute myocardial infarction," "ECG/electrocardiogram," and "thrombolytics/fibrinolytics." A review of potentially relevant abstracts was performed for possible inclusion in this policy. References from the 2000 ACEP clinical policy and the 2004 American College of Cardiology/American Heart Association (ACC/AHA) AMI guidelines were also reviewed for inclusion in this policy.[1,2] Finally, a detailed review of the FTT Collaborative Group and the 9 references included in this report was performed.[14] Since

publication of the follow-up report of the Late Assessment of Thrombolytic Efficacy (LATE) study, this subcommittee was unable to find any level I or II clinical trials of fibrinolytic therapy that investigated ECG criteria for fibrinolytic therapy or outcome in select subgroups of ECG findings.[13] As a result, only the FTT report, the 9 references included in the FTT report, and the follow-up report of the LATE study are included in the Evidentiary Table for this critical question.

ST-Segment Elevation

ST-segment elevation in the patient with presumed AMI presentation represents the major electrocardiographic indication for fibrinolysis. Current ACC/AHA guidelines recommend fibrinolytic therapy for AMI patients presenting within 12 hours of symptom onset and demonstrating ST-segment elevation in 2 contiguous limb leads or precordial leads (cited as level A evidence recommendation).[1] However, of the 9 studies analyzed by the FTT Collaborative Group, 6 studies defined injury as 1 mm ST-elevation in 2 or more contiguous limb leads (inferior: II, III aVF; lateral: I, aVL), and 2 mm ST-elevation in 2 or more precordial leads (V_1-V_6).[4-6,9,10,12] The Estudio Multicentrico Estreptoquinasa Republicas de America del Sur (EMERAS) study used identical criteria as above except for the lateral limb leads where 2 mm of ST-elevation was required in I and aVL.[11] The Second International Study of Infarct Survival (ISIS-2) focused on sum of ST-elevation in 4 regions of the heart for identification of injury: greater than or equal to 3 mm in the sum of elevation in II + III + aVF; greater than or equal to 6 mm in sum of $V_1+V_2+V_3$; greater than or equal to 6 mm in sum of $V_4+V_5+V_6$; and greater than or equal to 2 mm in sum of I + aVL.[7] Finally the Anglo-Scandinavian Study of Early Thrombolysis (ASSET) trial only classified ECGs as normal or abnormal and thus cannot be utilized to make any recommendations.[8] Based on analysis of the above data, the best level A evidence-based recommendations for ECG eligibility for fibrinolytic therapy are greater than or equal to 1 mm ST-segment elevation in 2 contiguous limb leads, and greater than or equal to 2 mm in 2 contiguous precordial leads. However, consensus opinion is that acute ST-segment elevation greater than or equal to 1 mm in 2 contiguous precordial leads is an indication for fibrinolytic therapy[1] though there are no studies that directly investigate this finding.[4-12] Addition of right ventricular leads (V_1R to V_6R) to patients with suspected inferior AMI (Figures 1A, B) or posterior lead (V_7 through V_9) in patients with suspected posterior AMI may increase the yield of identification of injury as well as identify patients at higher risk of adverse outcome.[15-25] Furthermore, the presence of reciprocal ST depressions in patients with borderline ST-segment elevations or atypical suspicion should heighten one's suspicion of STEMI.[26-28]

ST-segment elevation, however, is not an uncommon finding on the ECG in ED chest pain patients without acute coronary syndromes.[26,29,30] In 2 reviews of adult ED chest pain patients with ST-segment elevation on the ECG, the ST-segment abnormality resulted from AMI in only 15% to 31% of these populations. LVH was the most common cause of non-AMI ST-segment elevation (28% to 30%). Other findings responsible for this ST-segment elevation included benign early repolarization, acute myopericarditis, BBB, ventricular paced rhythm, and ventricular aneurysm.[29,30]

ST-Segment Depression

Current evidence strongly indicates that fibrinolytic therapy should not be used routinely in patients with ST-segment depression on the 12-lead ECG unless the evaluating physician suspects isolated posterior AMI.[14] Mortality rate may actually be increased by administration of fibrinolytics in this electrocardiographically diverse patient subgroup. In the FTT meta-analysis, mortality in patients with ST-segment depression was 15.2% in the fibrinolytic therapy group versus 13.8% in the control group.[1,14] Due to this finding, the ACC/AHA guidelines for AMI categorized ST-segment depression as a class III indication for fibrinolytic drugs (ie, no benefit with possible harm) except in patients in whom a true posterior AMI is suspected.[1] This subgroup of patients with ST-segment depression is very heterogeneous and includes patients with nonacute coronary syndrome conditions (eg, repolarization changes from LVH or incomplete BBB, electrolyte abnormalities, medication effects) and acute coronary syndrome conditions (unstable angina, non-ST-segment elevation AMI, and true posterior wall STEMI).

An important subset of electrocardiographic ST-segment depression presentation concerns the patient with acute posterior wall STEMI. Current ACC/AHA guidelines recommend as a class II recommendation the administration of fibrinolytic therapy to STEMI patients with ECG findings consistent with true posterior AMI and symptom onset less than 12 hours.[1] Posterior wall myocardial infarction refers to infarction of posterior wall of the left ventricle. Acute posterior wall myocardial infarction has been reported to represent 15% to 21% of AMIs, the vast majority occurring with infarction involving the inferior or lateral walls.[15,31] Isolated posterior wall AMI is associated with a significant amount of myocardium in jeopardy.[15,32] Theoretically, patients with large posterior acute infarcts should benefit from fibrinolytic agents if their infarct is due to acute occlusion of the circumflex artery or posterior descending artery. Retrospective analysis of the LATE Trial also casts some uncertainties about withholding fibrinolytic therapy from this heterogeneous group of patients.[13]

Boden et al[33] investigated the ECG criteria for diagnosing acute posterior injury. They reported retrospectively an analysis of patients with isolated precordial ST-segment depression of 1 mm or more in 2 or more leads V_1 through V_4 in the Diltiazem Reinfarction Study. All patients with posterior AMI had horizontal ST-segment depression and upright precordial T-waves (Figures 2A, B), whereas all patients with anterior non–STEMI had downsloping ST-segment depression with precordial T-wave inversion. The authors concluded that patients with anterior precordial ST-segment depression with upright T-waves in 2 or more contiguous leads should be considered eligible for fibrinolytic therapy.

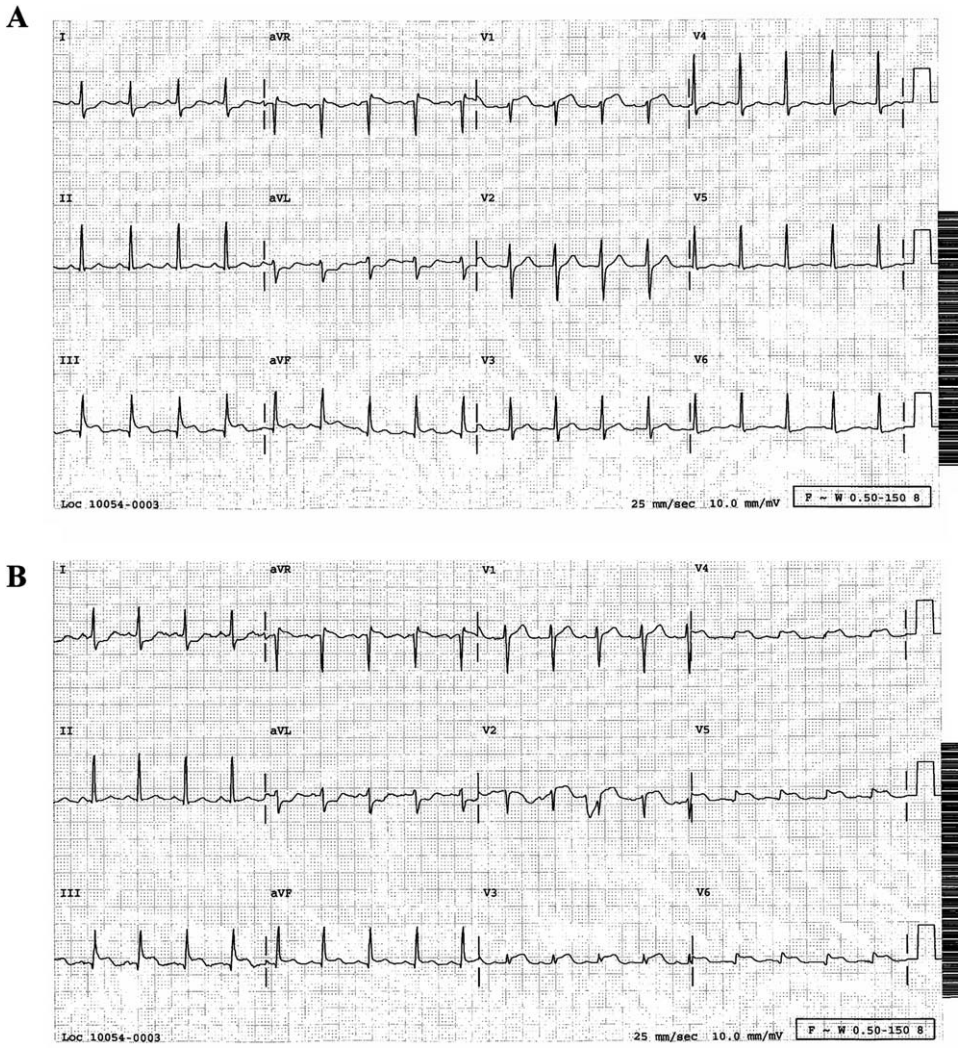

Figure 1. *A,* Isolated right ventricular AMI. Note the diagnostic ST-segment elevation in leads III and V_1, nondiagnostic ST-segment in lead II, and ST depression with terminal upright T waves in leads I and aVL (ie, reciprocal changes from right lateral injury). Since lead V_1 injury = V_2R injury, and right lateral injury = V_6R injury, theoretically this patient should have injury in leads V_2R to V_6R. *B,* Right ventricular leads in same patient confirming injury in leads V_2R through V_6R.

Interestingly, the LATE study, which investigated outcomes in patients with a discharge diagnosis of non-STEMI AMI who were treated with fibrinolytic drugs 6 hours to 24 hours after symptom onset, found that only patients with ST-segment depression of 2 mm or more had a significant reduction in mortality (31.9% versus 20.1% control).[13] It has been hypothesized that the subgroup of patients with ST-segment depression actually represented patients with large posterior transmural infarctions that would thus account for the results.[34]

Bundle Branch Block

Current ACC/AHA guidelines recommend fibrinolytic therapy in AMI patients with "new or presumably new LBBB" as a Class I indication (cited as level A evidence).[1] The FTT trial is cited as evidence for this recommendation. However, only 6 of the 9 trials included in the FTT analysis included BBB as an entry criteria and none of these studies made a distinction from right, left, or atypical, and from new or old.[14] There were only 2,146 (4%) patients with BBB out of a total of 58,600 patients. In this undifferentiated group of BBB, mortality was 18.7% in the fibrinolytic treated patients versus 23.6% in controls (observed minus expected = −24.5; variance = 83.3). Due to the relatively small number of these patients included in the FTT report, it suggests that these patients with undifferentiated BBB most likely had symptoms strongly suggestive of AMI in order to be enrolled in these clinical trials. Studies since the FTT report have failed to clarify this issue, and it has become commonplace for clinical trials in AMI to either exclude all BBB patients or to include only patients with new or presumably new LBBB as one of the entry criteria.

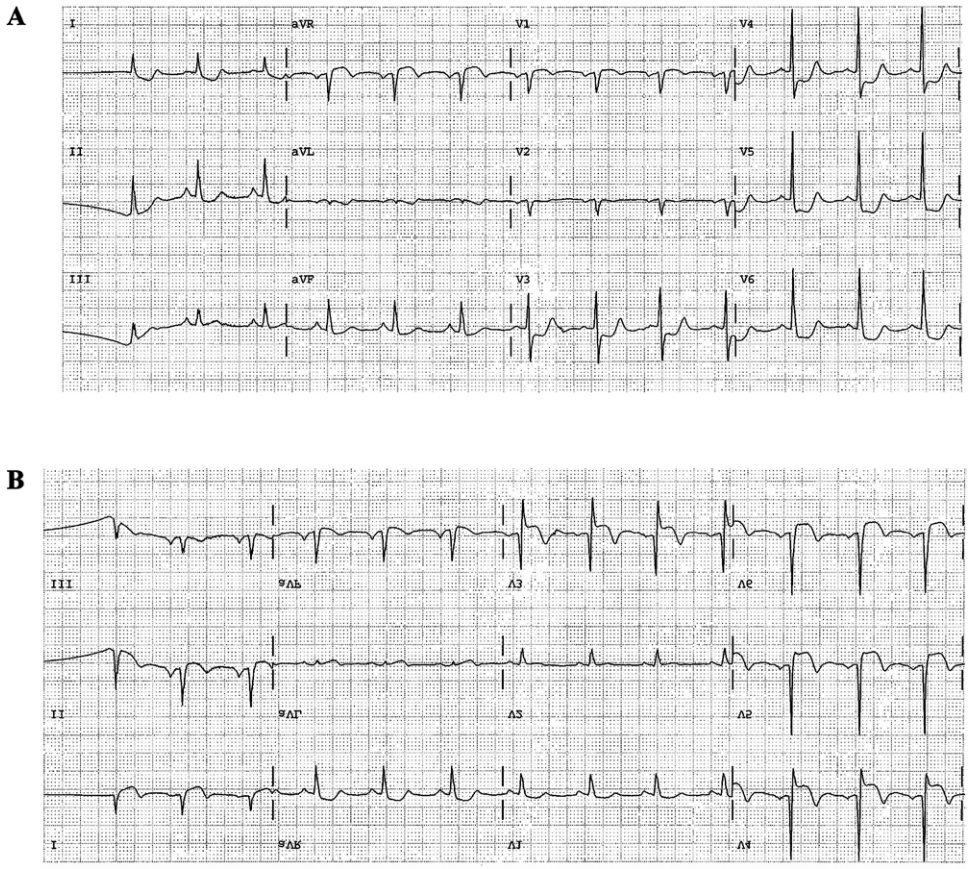

Figure 2. *A,* 12-lead ECG demonstrating an isolated acute posterior AMI. Note the prominent R wave, horizontal ST-segment depression, and upright T wave in leads V_3 through V_6. *B,* Upside down mirror image of Figure 2A representing classical ST-segment elevation in leads V_3 through V_6.

Multiple studies have demonstrated that fibrinolytic therapy and other evidence-based therapy is underutilized in patients with BBB and that patients with RBBB have similar outcomes (if not worse) to patients with LBBB.[35-44] Studies have also demonstrated that new or presumably new RBBB is not an uncommon presentation of transmural AMI, occurring in approximately 5% to 10% of AMI patients.[35,37,39,40,43,44] Go et al[44] analyzed outcome in AMI patients with right or left BBB pattern in the Second National Registry of Myocardial Infarction (NRMI-2). Out of a total of 297,832 AMI patients, 19,967 (6.7%) patients demonstrated LBBB on initial ECG and 18,354 (6.2%) patients demonstrated RBBB. In the subgroup of patients less than 75 years of age with symptom onset less than 12 hours of presentation (and ST-segment elevation for non-BBB patients), the distribution of AMI patients receiving emergent fibrinolytic therapy was 65.5% in patients without BBB, 32% with RBBB, and 16.7% with LBBB. Patients with RBBB or LBBB also had lower rates of treatment with aspirin, heparin, nitrates, and beta-blockers during the first 24 hours of ED presentation. After adjusting for patient characteristics, patients with RBBB had a 64% increased odds ratio of inhospital death (95% CI 1.57 to 1.71), and patients with LBBB had a 34% increased odds ratio of death as compared to patients without BBB. The above data provides support that both right and left BBB can obscure ST-segment analysis and is consistent with previous (1999) ACC/AHA guidelines recommending "BBB (obscuring ST-segment analysis) and history suggesting AMI" as one of the Class I eligibility criteria for fibrinolytic therapy (replaced on current guidelines with "new or presumably new LBBB").[1,45]

Since AMI frequently presents with atypical symptoms, reliance on history alone to guide reperfusion management is problematic in patients with "new or presumably new LBBB."[46-48] Furthermore, the incidence of AMI in chest pain patients with LBBB is low with one study demonstrating that approximately 10% of these individuals actually experienced AMI.[49] Thus the clinician is faced with a significant dilemma either to treat all patients with new or presumably new LBBB and any type of chest pain with the result that many non-AMI patients are subjected to the risks of fibrinolytic therapy (ie, low specificity, high sensitivity), or to treat only the patients with classic presentation of AMI with the result that many AMI patients with LBBB are not treated (ie, high specificity, low sensitivity).

It is a commonly taught medical dictum that the ECG diagnosis of AMI in the presence of LBBB is extremely difficult, if not outright impossible. A multitude of studies, however, has cast some degree of doubt on this maxim.[50-54] In order to understand the manifestations of acute coronary syndromes in the presence of LBBB, one must learn the expected ECG patterns in these patients with altered intraventricular conduction. In the patient with LBBB, the anticipated ST-segment T-wave configurations are discordant, directed opposite from the major, terminal portion of the QRS complex. This property is called QRS complex-T-wave axes discordance. As such, leads with predominantly negative QRS complexes (either QS or rS complexes) likely have elevated ST-segments and prominent, upright T-waves. Leads with large monophasic R-waves demonstrate ST-segment depression and inverted T-waves. Loss of this normal QRS complex T-wave axes discordance in patients with LBBB may imply injury or ischemia. The loss of this discordance, if present, usually takes the form of concordance with the ST-segment/ T-wave complex occurring on the same side of the isoelectric baseline as the major terminal portion of the QRS complex (Figure 3).

Wackers[51] reported on findings of 96 patients with LBBB and suspected AMI. Fifty-five patients were diagnosed with AMI. ST-segment changes were considered significant if they demonstrated a concordance of 2 mm or more or a discordance of 7 mm or more with the direction of QRS deflection. The sensitivity, specificity, and positive predictive value of these findings for AMI were 54%, 97%, and 96%, respectively. Hands et al[52] described 35 patients with suspected AMI in the presence of LBBB; AMI was diagnosed in 20 patients. ST-segment concordance had a sensitivity for AMI of 16.7% with a specificity and positive predictive value of 90.9% and 80%, respectively. Hands et al[52] did not study discordance of ST-segments.

Sgarbossa et al[50] reported on the ECG findings in 131 patients with LBBB enrolled in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) trial. Three ECG findings were found to be independently predictive of AMI: ST-segment elevation of 1 mm or more and concordant with the QRS complex (sensitivity 73%, specificity 92%), ST-segment depression of 1 mm or more and concordant with the QRS in one or more precordial leads V_1 through V_3 (sensitivity 25%, specificity 96%), and ST-segment elevation of 5 mm or more and discordant with the QRS complex (sensitivity 31%, specificity 92%).

Shlipak et al[55] retrospectively reported on Sgarbossa et al's criteria for predicting AMI in the presence of LBBB and concluded that these criteria are a poor indicator of AMI and that all patients with LBBB should be considered for fibrinolytic treatment. Although this study has serious design flaws, it found high specificities for the Sgarbossa et al criteria. ST-segment elevation concordant with QRS complex had a sensitivity of 7% and specificity of 100%. ST-segment depression concordant with the QRS complex in leads V_1, V_2, or V_3 had a sensitivity of 3% and specificity of 100%, and ST-elevation of 5 mm or more in discordant leads had a sensitivity of 19% with specificity of 82%.

Li et al[56] also performed a retrospective cohort trial investigating the use of the Sgarbossa et al criteria in ED patients with AMI and electrocardiographic LBBB pattern. All 3 of the Sgarbossa et al criteria demonstrated low sensitivity and high specificity for AMI. Only 2 criteria, concordant ST-segment elevation or a combination of all 3 criteria, had positive likelihood ratios greater than 1; concordant ST-segment elevation had a positive likelihood ratio of 16 and a combination of all 3 criteria demonstrated a positive likelihood ratio of 3. Of the LBBB patterns encountered, 11 patients (6%) had new LBBB – of which 6 (55%) had AMI.

Edhouse et al[57] retrospectively reviewed the Sgarbossa et al clinical decision rule in patients with LBBB and suspected AMI. Sensitivity of the Sgarbossa et al criteria for AMI was 80% (95% CI 63% to 95%) with specificity of 100%. Twenty-three percent of the patients with AMI did not receive fibrinolytics, and of these patients, the decision not to administer fibrinolytics was based on the interpretation of a single ECG. Only 48% of the patients receiving fibrinolytics had a final diagnosis of AMI. The authors concluded that patients with any of the Sgarbossa et al predictive criteria should receive fibrinolytics, and patients not meeting these criteria should undergo serial ECGs in order to demonstrate evolving ischemia.

Theoretically, these rules of concordance and discordance developed in the LBBB patient presentation can be applied to patients with RBBB (Figure 4), atypical BBB, and ventricular paced patterns. However, only the ventricular paced pattern has been investigated. Sgarbossa et al[58] reported on findings in 32 patients with AMI and paced rhythm in the GUSTO-I trial. Just as was found in patients

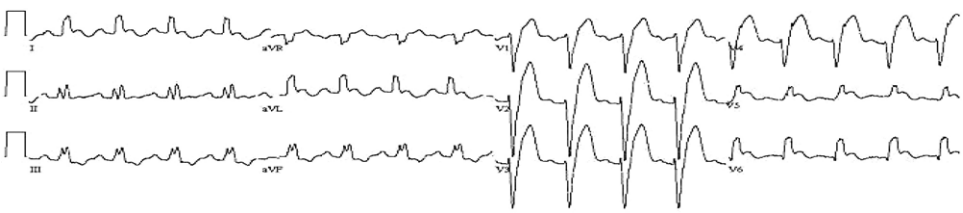

Figure 3. 12-lead ECG demonstrating electrocardiographic AMI in the setting of LBBB. Note the concordant ST-segment elevation in leads I, aVL, V_5 and V_6. Also note the excessive discordant ST-segment elevation in leads V_1 through V_4.

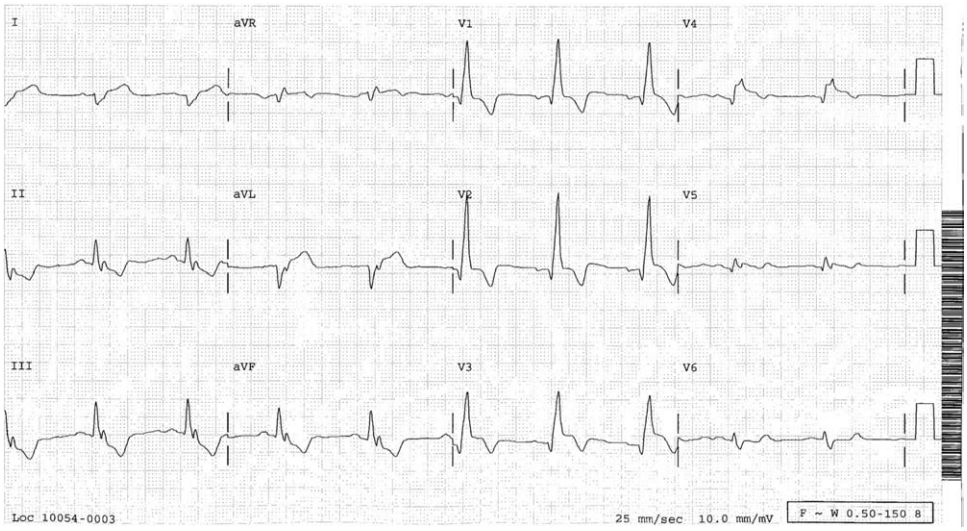

Figure 4. AMI in the presence of RBBB. Note the pseudonormalization of ST segments in lead V_1 with concordant ST segment elevation ≥1 mm in leads V_2 through V_4. Also note early Q wave formation in leads V_1 through V_5. Unlike LBBB, anterior Q waves are not obscured by the presence of RBBB.

with LBBB, 3 electrocardiographic findings were found to be independently predictive of AMI in paced rhythm: ST-segment elevation greater than or equal to 5 mm and discordant with the QRS complex (sensitivity 53%, specificity 88%), ST-segment elevation greater than or equal to 1 mm and concordant with the QRS complex (sensitivity 18%, specificity 94%), and ST-segment depression greater than or equal to 1 mm in one or more precordial leads V_1 through V_3 (sensitivity 29%, specificity 82%).

2. What are the indications for fibrinolytic therapy in patients being treated at or transferred to a PCI center?

Exclusion Criteria: Patients undergoing facilitated PCI with glycoprotein IIb/IIIa platelet inhibitors alone or in combination with half dose fibrinolytics.

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Administer fibrinolytic therapy to patients whose STEMI is identified less than 3 hours after symptom onset and expected delay time from initial STEMI identification in the ED until PCI (ie, balloon time) is greater than 90 minutes.*

Level C recommendations. Administer fibrinolytic therapy to high-risk patients whose STEMI is identified less than 6 hours after symptom onset and expected delay time from initial STEMI identification in the ED until PCI time (ie, balloon time) is greater than 90 minutes.*

*There is insufficient evidence to make any recommendations in non-high-risk STEMI patients presenting greater than 3 hours after symptom onset, and high-risk patients presenting greater than 6 hours after symptom onset. Time of symptom onset, extent and location of injury, patient risk, and availability of timely PCI need to be taken into consideration.

Only a minority of hospitals in the United States have the capability to perform PCI on patients presenting to the ED with indications for emergent reperfusion therapy.[1] As a result, emergency physicians practicing at non-PCI institutions are faced with the delays inherent in ambulance or helicopter transport if they decide to transfer STEMI patients to a PCI center. Even emergency physicians practicing at PCI centers are frequently faced with instances in which the cardiac catheterization lab is not immediately available. In both situations, the question becomes, "how long is too long" to wait for PCI instead of administering immediate fibrinolytic therapy.

While PCI and fibrinolysis are both effective reperfusion modalities, when compared in a meta-analysis of randomized controlled trials, PCI had significant advantages, including reduced short-term mortality (9% versus 7%; $P=0.0002$), markedly reduced early reinfarction (7% versus 3%; $P<0.0001$), reduced rate of stroke (2% versus 1%; $P=0.0004$), and reduced long-term adverse outcomes.[59] However, in analysis of registry data (with longer delays to PCIs) these benefits were less evident.[60-62] Therefore, for patients presenting to centers without PCI capability or to PCI centers in which PCI is not immediately available, the optimal reperfusion strategy is not clear.

ACC/AHA guidelines for STEMI state as a Class I recommendation (cited as level of evidence A) that if PCI cannot be provided within 90 minutes of presentation, patients should undergo fibrinolysis unless contraindicated. Further Class I recommendations (level of evidence B) maintain that primary PCI is "generally preferred" for patients presenting within 3 hours of symptoms onset if the "expected door-to-balloon time minus the expected door-to-needle time" is within 1 hour, while fibrinolysis is "generally preferred" if this PCI-

related delay is greater than 1 hour.[1] For patients presenting greater than 3 hours after symptom onset, the ACC/AHA guidelines state that PCI is "generally preferred" if it can be provided within 90 minutes of presentation.[1]

To determine the indications for fibrinolytic therapy in patients experiencing a delay in PCI due to transport time or delay in catheterization lab availability, the ACEP Clinical Policies Subcommittee performed a MEDLINE search utilizing the following key words/phrases in combination with myocardial infarction: "facilitated angioplasty," "facilitated coronary intervention," "transfer," "transport," "rescue PCI," "rescue angioplasty," "prehospital fibrinolytics," and "prehospital thrombolytics." The subcommittee also reviewed all meta-analyses on the use of fibrinolytics and PCI in the treatment of AMI as well as current guidelines from the ACC/AHA for the treatment of STEMI. A review of potentially relevant abstracts was performed for possible inclusion in this policy. Chosen papers were subsequently graded by ACEP criteria according to the weight of evidence as it applies to our critical question. Only clinical trials that directly or indirectly investigated treatment delay effects of fibrinolytics versus PCI are listed for this critical question in the Evidentiary Table. In the following sections we discuss trials investigating time-to-treatment benefit for fibrinolytic therapy, trials investigating time-to-treatment benefit for PCI, trials directly comparing treatment delay effects of fibrinolytics versus PCI, trials investigating onsite fibrinolytics, and trials investigating prehospital fibrinolysis versus transfer to a PCI center in order to determine indications for fibrinolytic therapy in patients being treated at or transferred to a PCI center.

Trials Investigating Symptom Onset to Treatment Time for Fibrinolysis and PCI

In patients treated with fibrinolytics, the old adage "time is muscle" is supported by convincing evidence.[14,63,64] Mortality benefit is 30 per 1,000 patients presenting within 6 hours of symptom onset, 20 per 1,000 for those presenting 7 to 12 hours after symptom onset, and a statistically nonsignificant trend of 10 per 1,000 for those presenting 13 to 18 hours after symptom onset.[14] The relationship between the absolute benefit of fibrinolytic therapy and treatment delay is best described as a nonlinear curve (Boersma Curve) with greatest benefit in patients presenting during the first hour of symptom onset with subsequent rapid decline.[65] However, recent observations from data on prehospital fibrinolytic therapy suggest the original Boersma Curve actually underestimates the benefits of early fibrinolysis, and should be shifted approximately 45-60 minutes to the right (Figure 5).[66]

Though intuitively, the same principle should apply to patients undergoing PCI, the evidence for a time-dependent decrease in treatment efficacy is less consistent. Analysis of NRMI-2 registry data failed to find any relationship between mortality and symptom onset-to-balloon time, although an increase in mortality was demonstrated for door-to-balloon times of greater than 120 minutes.[67] A smaller, retrospective study analyzing data from the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO IIb) trial similarly failed to demonstrate a relationship between mortality and symptom-to-balloon time, although again an increase in mortality with longer enrollment-to-balloon times was revealed.[68] These multicenter, real world findings should be interpreted with some caution as door-to-balloon times correlate with other quality indicators of excellent care at participating hospitals. In a single center study, Juliard et al[69] also failed to find a significant relationship between symptom-onset-to-Thrombolysis in Myocardial Infarction (TIMI) 3 flow time and mortality in 499 STEMI patients (mortality 3.2%) treated with PCI presenting within 6 hours of symptom onset based on univariate or multivariate analysis. However, looking at door-to-TIMI 3 flow using multivariate linear regression analysis of variables linked on mortality, they found a mortality odds ratio of 1.27 for each 15-minute treatment delay [95% CI 1.06-1.52]. Illustrating the complexity of the question, in another single center investigation, De Luca et al[70] had results which contrasted with the above studies, finding that mortality increases with increasing symptom onset-to-balloon, but not door-to-balloon, times.

Looking at the prehospital component of the delay to treatment, Zijlstra et al,[71] in a meta-analysis of 10 randomized trials comparing PCI to fibrinolysis, found that the combined 30-day endpoint of death, reinfarction, and stroke for patients presenting less than 2 hours, 2 to 4 hours, and greater than 4 hours from symptom onset was 5.8%, 8.6%, and 7.7% respectively, in the PCI group as compared to 12.5%, 14.2%,

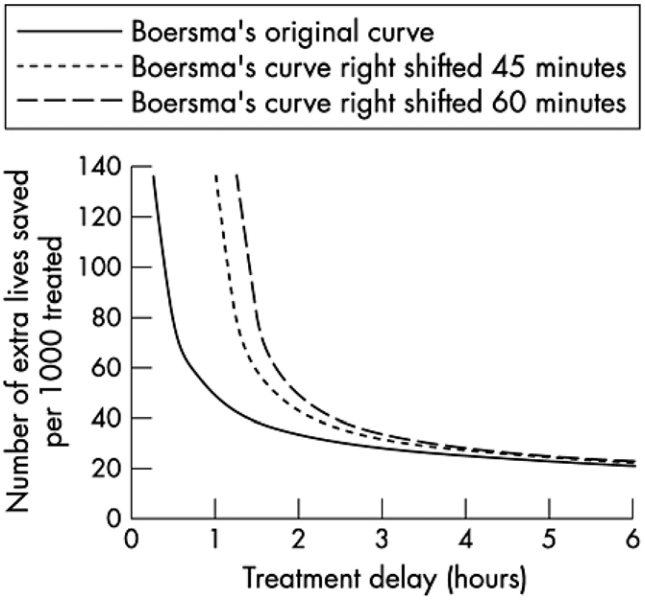

Figure 5. Number of extra lives saved per 1,000 patients treated with fibrinolytics at different time treatment delays from symptom onset.

From Terkelsen CJ, Lassen JF, Norgaard BL, et al. Are we underestimating the full potential of early thrombolytic treatment in patients with acute myocardial infarction? *Heart*. 2003;89:483-484. Reproduced with permission from the BMJ Publishing Group.

and 19.4% respectively, in the fibrinolysis group. Increase in presentation delay was associated with older age, female gender, diabetes, and higher heart rate. Importantly, after adjusting for these clinical characteristics in multivariate analysis, time from symptom onset was no longer significant and suggests that individual patient risk factors must be taken into consideration.

Several studies have investigated time dependent treatment benefits of PCI in higher-risk (TIMI risk score greater than or equal to 1) versus lower-risk (TIMI risk score less than 1) patients.[70,72,73] In the aforementioned study, De Luca et al[70] demonstrated that symptom onset-to-balloon time was significantly associated with 1-year mortality in higher-risk patients in an incremental fashion for less than or equal to 2 hours (5.7%), 2 to 4 hours (6.3%), 4 to 6 hours (11.9%), and greater than 6 hours (13%). In the lower-risk patients, there was no relationship between mortality and symptom onset-to-balloon time. In a secondary analysis of the data, De Luca et al[72] reported a 1.075 increase in relative risk of death for every 30-minute delay after adjusting for age, gender, diabetes, and previous revascularization (95% CI 1.008 to 1.15). Likewise, Antoniucci et al[73] demonstrated a similar relationship between mortality and symptom onset-to-balloon time for less than 2 hours (4.8%), 2 to 4 hours (7.9%), 4 to 6 hours (12.9%), and greater than 6 hours (11.5%) in higher-risk patients, but no relationship in lower-risk patients. Brodie et al[74] demonstrated a correlation between outcome and delay only in patients with cardiogenic shock.

Though the evidence for time-to-treatment benefit for primary PCI in STEMI patients is less convincing than for fibrinolysis, it seems that the adage "time is muscle" has greater significance in higher-risk patients presenting within 6 hours of symptom onset, and lower-risk patients presenting within 2 to 4 hours of symptom onset. Much larger studies are needed to confirm these findings as well as to better determine the relationship of symptom onset-to-balloon time and outcomes in lower-risk patients.

Trials Investigating the Effect of PCI-Related Treatment Delay on Outcome

Kent et al[75]investigated the effect of PCI-related treatment delay, defined as the time-to-treatment with PCI minus the time-to-treatment with fibrinolysis, in 10 trials comparing fibrinolysis to PCI. They found that PCI had a mortality advantage over fibrinolytic therapy until the PCI-related delay reached 50 minutes, at which point they became equivalent. Nallamothu and Bates[76] used variance-weighted linear regression to analyze data from 21 of 23 trials included in the Keeley et al[59] meta-analysis and found that if the PCI-related time delay was less than 62 minutes, PCI had a 4- to 6-week mortality benefit over fibrinolytics. For the combined outcome of death, reinfarction, and stroke, PCI was superior to fibrinolysis if the PCI-related delay time was less than 93 minutes. These data were analyzed by Betriu and Masotti as well, who found that mortality benefit became equivalent after a PCI-related delay of 110 minutes.[77] These different results may have been due to a correction for an estimation of door-to-reperfusion time used in 2 of the 21 trials in the Nallamothu and Bates[76] analysis. The Percutaneous Transluminal Coronary Angioplasty (PCAT) Collaborators performed a meta-analysis of 11 randomized trials from 1989 to 1996 that compared the outcome of PCI versus fibrinolytics at 6-month follow-up.[78] The average PCI-related time delays between first balloon inflation and fibrinolysis were divided into less than 35 min, 35 to 55 minutes, and greater than 55 minutes. The absolute risk reduction of 30-day death or nonfatal myocardial infarction with PCI declined from 11% to 4.6% to 3.8% ($P=0.06$) with increasing relative treatment delay. These results also suggest that PCI has improved long-term outcome over fibrinolytics even with a PCI-related treatment delay of approximately 1 hour.[78] External validity of the conclusions of the above studies are limited by the short door-to-balloon times, relatively small number of patients with treatment delays greater than 1 hour, and the fact that the studies incorporated in the data analysis span greater than a decade during which there has been a rapid evolution in treatment of STEMI patients with PCI (eg, IIb/IIIa glycoprotein inhibitors, stents). Conclusions also are limited as no analysis is made regarding time delay effects of infarct location or extent, patient risk factors, and symptom onset time on outcome.

Trials Investigating Onsite Fibrinolysis Versus Transfer to a PCI Center

A number of randomized, controlled trials, attempting to address the lack of widespread availability of PCI, compared the outcomes of patients treated at noninterventional centers with those transferred for PCI.[79-86]

Only the Air Primary Angioplasty in Myocardial Infarction (Air PAMI) study attempted to analyze PCI-related time delays in high-risk patients.[81] In this study, 138 STEMI patients with TIMI risk score greater than or equal to 1 were randomized to onsite fibrinolysis versus transfer for primary PCI. At 30 days a nonsignificant trend for reduction of major cardiac adverse events was observed for the transfer group (38% reduction; $P=0.33$; 95% CI for risk difference −1.53 to 5.46). Obviously, conclusions of the study are limited by small sample size and failure of non-transfer group to be managed with early PCI. Dalby et al[82] performed a meta-analysis of 6 trials comprising 3,750 patients comparing fibrinolysis at a community hospital (1 study included investigated prehospital fibrinolysis) versus transfer for PCI. Transfer time was always less than 3 hours and mean additional time-to-treatment for PCI as compared to fibrinolysis ranged from 70 minutes to 103 minutes. Patients transferred for primary PCI had a 68% reduction in reinfarction (95% CI 34% to 84%; $P<0.001$), 56% reduction in stroke (95% CI 15% to 77%; $P=0.015$), and a trend for reduction in all-cause mortality (95% CI −3% to 36%; $P=0.08$). Dalby et al[82] conclude that transfer for primary PCI remains superior to immediate fibrinolysis.

Two studies in Dalby's analysis included a "drip and ship" arm with patients receiving fibrinolytics during transfer, with equivocal results.[83,84] The first, a pilot feasibility study in the Netherlands, compared accelerated tissue plasminogen activator (tPA) given at community hospitals, tPA given during transfer to a PCI center (with rescue PCI if indicated), and transfer for primary PCI.[83] Seven centers participated in this study with distances from referral

center to PCI center ranging from 25 kilometers to 50 kilometers and a mean transport time of 20 minutes (did not exceed 30 minutes). With only 224 patients, the study was not powered to detect a difference in the combined outcome of death, reinfarction, and stroke at 42 days, and no significant differences were seen. Of note, 60% (n=45) of the patients receiving tPA during transport had TIMI 2 or 3 flow on initial coronary arteriogram and did not undergo immediate PCI. No severe complications occurred in the transfer group and the authors concluded that acute transfer for rescue or primary PCI is feasible and safe. In the PRAGUE Study, involving 17 community hospitals and 4 PCI hospitals in Prague (Czech Republic), 300 patients within 6 hours of onset of STEMI were divided between treatment with streptokinase (group A), administration of streptokinase prior to transfer for PCI (group B), or transfer to an interventional center for primary PCI (group C).[84] Transport distance ranged from 5 km to 74 km, with a mean transport time of 38 minutes for group B and 35 minutes for group C. Patients treated with primary PCI were found to have a significantly lower rate of reinfarction at 30 days than those in the other 2 treatment arms (10% in group A versus 7% in group B versus 1% in group C; $P<0.03$). Conclusions from this study are limited by the nontraditional definition of reinfarction (doubling of CK levels or new ECG changes) and lack of blinded outcome assessment.

The PRAGUE-2 trial, a follow-up investigation of the PRAGUE study, randomized 850 STEMI patients presenting to a community non-PCI hospital to streptokinase treatment versus immediate transfer to a PCI center.[85] Participating centers included 7 PCI centers and 41 community non-PCI centers. The distance from community hospitals and PCI centers ranged from 5 km to 120 km, with a mean transport time of 48 minutes (total delay 68 minutes due to an additional 20 minutes required for randomization). On interim analysis, the study was stopped prematurely by the ethics committee due to a 2.5-fold excess mortality in the streptokinase group in patients treated greater than 3 hours after symptom onset. Overall, 30-day mortality was 6.8% in the PCI group versus 10% in streptokinase group ($P=0.12$; intention to treat analysis). Among the 299 patients randomized greater than 3 hours after symptom onset, the mortality was 6% in the PCI group versus 15.3% in the streptokinase group ($P<0.02$). The authors conclude that long distance transport for PCI is safe and should be the preferred strategy in patients presenting greater than 3 hours after symptom onset. For patients presenting less than 3 hours after symptom onset, either strategy was equally effective.

The Danish trial in AMI-2 (DANAMI-2) randomized patients presenting to 24 referral hospitals to treatment with accelerated tPA or transfer to 5 PCI centers.[86] Enrollment was stopped after the third interim analysis had demonstrated that PCI was superior to fibrinolysis in the referral hospitals. The median time-to-symptom onset ranged from 104 to 107 minutes (interquartile (IQ) range 54 to 205 minutes) in the 4 treatment groups. The median interval from arrival to transport was 50 minutes (IQ range 39-65) and median time of transport 32 minutes (IQ range 20-45). In the referral group, total time from symptom onset until start of treatment was 169 minutes (IQ range 110 to 270 minutes in the fibrinolytic group, and 224 (IQ range 171-317 minutes) in the transfer group. Among the transfer group, the primary endpoint of 30-day death, reinfarction, or disabling stroke was reached in 14.2% of fibrinolytic patients as compared to 8.5% in PCI patients ($P=0.002$). This better outcome observed was driven by a reduction in 30-day reinfarction (6.2% versus 1.9%; $P<0.001$). There were no significant differences in death (8.5% versus 6.5%; $P=0.20$) or the rate of stroke (2.0% versus 1.6%; $P=0.64$). Ninety-six percent of the patients in the referral group were transferred to the invasive-treatment center within 2 hours of presentation. Even ignoring the rate of reinfarction (driven by the fact that the fibrinolytic patients were primarily medically managed during the follow-up time period), this data suggests that there was no harm in awaiting PCI providing patients can be transferred within 2 hours of initial presentation.

Trial Investigating Prehospital Fibrinolysis versus Transfer to a PCI Center

Several studies have addressed the utilization of prehospital fibrinolysis in patients being transferred to a PCI center in mobile emergency care units. The Comparison of Angioplasty and Prehospital Thrombolysis in AMI (CAPTIM) study group randomized 840 patients to prehospital fibrinolysis versus primary PCI on arrival to a PCI center in an intention to treat fashion.[79] The median time delay from symptom onset until treatment was 130 minutes in the prehospital fibrinolysis group and 190 minutes in the PCI group. Thirty-three percent of fibrinolytic treated patients underwent rescue or urgent PCI and 70% of these patients underwent PCI within 30 days of initial presentation. No statistically significant differences were seen in the 421 patients assigned primary PCI versus 419 patients assigned prehospital fibrinolysis in death (4.8% versus 3.8%; $P=0.61$), reinfarction (1.7% versus 3.7%); $P=0.13$), disabling stroke (0% versus 1.0%; $P=0.22$), or the composite endpoint (6.2% versus 8.2%; 95% CI for risk difference −1.53 to 5.46; $P=0.29$). The authors conclude that transfer for primary angioplasty was not better than prehospital fibrinolysis provided patients in the fibrinolytic treated group are transferred to a PCI center for rescue PCI and provided the median PCI-related time delay is 60 minutes. In a subsequent substudy of the CAPTIM report, Steg et al[80] investigated outcome in patients randomized less than 2 hours of symptom onset (n=460) versus greater than 2 hours after symptom onset (n=374 patients). There was no statistically significant difference in the combined primary outcome measure between prehospital fibrinolysis versus primary PCI for the composite endpoint. However, for patients randomized within 2 hours of symptom onset, there was a strong trend towards lower 30-day mortality (2.2% versus 5.7%; $P=0.058$) and a lower rate of cardiogenic shock (1.3% versus 5.3%; $P=0.032$) with prehospital fibrinolysis versus primary PCI, suggesting that patients presenting early after symptom onset may benefit from prehospital fibrinolysis if PCI-related time delay is greater than 60 minutes. Limitations of the CAPTIM data include small sample size that prevented analysis of effects of patient risk factors, infarct location/size on outcome, and more detailed analysis of effects on PCI-

related time delay at specific time intervals. Furthermore, the substudy is a retrospective study performed after the initial CAPTIM study with no pre-specified time intervals for investigating outcome.

Based on the studies reviewed above, it seems safe to withhold fibrinolytic therapy in STEMI patients presenting less than 3 hours after symptom onset being transferred to a PCI center in a timely fashion. In patients presenting greater than 3 hours after symptom onset, PCI is the preferred therapy. Theoretically these findings should translate to the treatment delays that may occur at PCI centers to patients that are awaiting PCI. There is insufficient evidence to make any recommendations regarding potential benefits or risks of administering fibrinolytic therapy ("drip and ship") when patients are transferred in a timely manner. Additionally, these studies do not address effects of patient risk and infarct size on these findings.

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Evidentiary Table.

Study	Year	Design	Intervention(s)/ Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
GISSI[4]	1986	Randomized, open label	1.5 MU streptokinase vs standard treatment in patients admitted within 12 h of symptom onset; ECG eligibility criteria: ≥1 mm elevation or depression in any limb lead, or ≥2 mm elevation or depression in any precordial leads or "site undefined" defined as BBB with repolarization changes masking pathological Q waves and ST changes	Inhospital mortality analyzed in an intention to treat fashion	N=11,712 patients; mortality 10.7% in streptokinase group vs 13% in control group (18% reduction in mortality; P=0.0002; RR 0.81); benefit was function from time to symptom onset to treatment; inhospital stay ranged from 14 to 21 days in >90% of patients; subgroup analysis revealed benefit only in anterior and multi-infarct location; no benefit with inferior, lateral, or undifferentiated BBB infarcts; trend for worsened outcome in patients with undifferentiated ST depression	No routine antiplatelet therapy; no routine heparin; patients not randomized until after they were admitted to CCU	Precordial lead elevation, (2 mm), I (benefit ≤9 h); Limb lead elevation (1 mm), III (benefit ≤9 h); Undifferentiated BBB, III (benefit ≤9 h); New LBBB, X; ST depression III (no benefit); Precordial ST depression, X
ISAM Study Group[5]	1986	Randomized, placebo-controlled	1.5 MU streptokinase vs placebo in patients ≤75 y who could be treated with study medication within 6 h of symptom onset; ECG eligibility criteria: ≥1 mm elevation in limb leads or ≥2 mm elevation in precordial leads	Primary end point was 21-day mortality; secondary endpoint was infarct size as assessed by area under CK-MB curve and ejection fraction as assessed 3-4 weeks post enrollment	N=1,741; trends in decreased mortality for streptokinase group vs placebo (6.3% vs 7.1%; P=NS); streptokinase group had smaller infarct size (P<.02) and greater ejection fraction (P<.005) vs placebo	Study not powered to show mortality benefit; subgroup analysis for infarct site not performed; only patients ≤75 y eligible	Precordial lead elevation, (2 mm), III (benefit ≤ 6 h); Limb lead elevation (1 mm), III (benefit ≤6 h); Undifferentiated BBB, X; New LBBB, X; ST depression, X; Precordial ST depression, X

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
AIMS Trial Study Group[6]	1988	Randomized, placebo-controlled	30 units APSAC vs placebo in patients ≤70 y who could be treated with study medication within 6 h of symptom onset; ECG eligibility criteria: ≥1 mm elevation in limb leads or ≥2 mm elevation in precordial leads	30-day mortality	N=1,004; mortality reduction of 47% (6.4% in APSAC group vs 12.2% in placebo group; *P*=0.002; 95% CI 21% to 65%); benefit similar in patients treated <4 h and 4-6 h after symptom onset	No routine aspirin therapy; only patients ≤70 y eligible; no subset analysis by infarct location	Precordial lead elevation, (2 mm), II (benefit ≤6 h); Limb lead elevation (1 mm), II (benefit ≤ 6 h); Undifferentiated BBB, X; New LBBB, X; ST depression X; Precordial ST depression, X
ISIS-2 Collaborative Group[7]	1988	Randomized, placebo-controlled	1.5 MU streptokinase, aspirin, both, or neither in 2 x 2 factorial design in patients within 24 h of symptom onset of suspected AMI; no predefined ECG eligibility criteria; for subset analysis, following definitions utilized: inferior AMI: inferior ST elevation ≥3 mm in sum of II, III, aVF; anterior AMI: ≥6 mm in sum of $V_1+V_2+V_3$ and/or ≥6 mm in sum of $V_4+V_5+V_6$ and/or ≥2 mm in I + aVL; ST–depression AMI: ST depression as extreme as elevations discussed above; BBB AMI: any type of BBB	Primary endpoint: 5 week cardiovascular mortality; secondary endpoints: strokes, reinfarction, bleeding events	N=17,187; streptokinase alone and aspirin alone each produced a significant reduction in mortality; the combination of streptokinase and aspirin was significantly better than either agent alone (42% odds reduction in patients treated with both versus neither); improved outcome at all time intervals in first 24 h of symptom onset; benefit seen in patients with anterior, inferior, and BBB AMI; no benefit in ST-depression AMI	No routine heparin; non-standard definition of injury; subset analysis not performed to determine characteristics of patients >12 h from symptom onset that benefited from treatment (eg, did these patients all have marked injury pattern with stuttering symptoms)	Precordial lead elevation, (2 mm), I (benefit ≤24 h); Limb lead elevation (1 mm), I (benefit ≤24 h); Undifferentiated BBB, II (benefit ≤24 h); New LBBB, X; ST depression III (no benefit); Precordial ST depression, X

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Wilcox et al for the ASSET Study Group[8]	1988	Randomized, placebo-controlled	100 mg tPA + heparin vs heparin in patients ≤75 y with symptoms suggestive of AMI in whom treatment could be started within 5 h of symptom onset	30-day mortality	N=5,011; 26% reduction in mortality in tPA treated patients (7.2% vs 9.8%; 95% CI 11-39%)	No routine aspirin therapy; ECG subset analysis performed only for "normal" ECG versus "abnormal" ECG; no definitions of ECG abnormalities (ie, impossible to make any recommendations regarding ECG criteria for fibrinolytics); only patients in whom study drug could be administered within 5 h of symptom onset were included in trial	Precordial lead elevation, (2 mm), X; Limb lead elevation (1 mm), X; Undifferentiated BBB, X; New LBBB, X; ST depression, X; Precordial ST depression, X
Rossi and Bolognese for the USIM Collaborative Group[9]	1991	Randomized, placebo-controlled	1 MU urokinase (2 boluses 60 min apart) plus heparin vs heparin alone in patients admitted to the CCU within 4 h of symptom onset; ECG eligibility criteria: ≥1 mm "shifts" in limb leads or ≥2 mm "shifts" in precordial leads	Inhospital mortality (9-16 days in >90% of patients); secondary endpoints were nonfatal cardiac events and bleeding complications	N=2,201; no difference in outcome seen between urokinase and placebo (8% vs 8.3%); reduced mortality in "non-Q wave" AMI in patients treated with urokinase (8% vs 12.5%; *P*=0.0008); based on comments in the conclusion and on study entry criteria, this subgroup of "non-Q wave" AMI refers to patients with ST-segment depression on initial ECG (see ECG eligibility criteria; at time of this study, it was a common mistake to refer to ST-segment depression AMI as "non-Q wave" AMI); trend for a 27% reduction in mortality in anterior AMI; increased mortality in patients with inferior AMI in urokinase group (5.8% vs 3.2%; *P*=0.04)	No routine aspirin therapy; only patients who were admitted within 4 h of symptom onset were included in trial; urokinase used as fibrinolytic agent	Precordial lead elevation, (2 mm), III (benefit ≤4 h); Limb lead elevation (1 mm), II (no benefit with urokinase); Undifferentiated BBB, X; New LBBB, X; ST-depression, III (Benefit ≤4 h); Precordial ST depression, X

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
ISIS-3 Collaborative Group[10]	1992	Randomized, open label	1.5 MU SK or 0.6 MU/kg tPa or 30 U APSAC in combination with aspirin in a 3 x 2 factorial design in patients with suspected AMI	35-day mortality; secondary endpoints consisted of bleeding complications, stroke, and cardiac-related adverse outcomes	N=41,299; no difference in 35-day mortality between SK (10.6%), tPA (10.3%), or APSAC (10.5%)	No definitions of ECG abnormalities; no subgroup analysis for infarct site; no IV heparin (50% of patients received subcutaneous heparin); all patients with "clear" indication for fibrinolytic therapy received 1 of the 3 fibrinolytic agents; only patients with "uncertain" indication for fibrinolytic therapy were randomized to fibrinolytic vs control (this is the group that was reported in the FTT analysis); note: "uncertain" defined in vague terminology consisting of "perhaps because the patient presented more than 6 h after pain onset or because there was no definite ST-segment elevation on the initial electrocardiogram;" data was not reported for the small subset of "uncertain" AMI who did not receive a fibrinolytic agent; patients with "clear" indications presented within 6 h of symptom onset	Precordial lead elevation, (2 mm), X; Limb lead elevation (1 mm), X; Undifferentiated BBB, X; New LBBB, X; Precordial ST depression, X

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
EMERAS Collaborative Group[11]	1993	Randomized, placebo-controlled	1.5 MU SK vs control in patients with suspected AMI presenting within 24 h of symptom onset and have "no clear indication for, or contraindication to," SK; study amended after onset of randomization to 6-24 h after results of ISIS-2 were known (15% of total patients presented in 0-6 h window and these patients were included in final analysis); no predefined ECG eligibility criteria; for subset reporting, the following definitions were used: inferior AMI: ST elevation ≥1 mm in at least 2 of leads II, III, aVF; anterior AMI: ST elevation ≥2 mm in at least 2 of leads V_1-V_6, I, AVL; BBB AMI: any type of BBB; ST depression AMI: ST depression ≥1 mm in 2 limb leads or ≥2 mm in 2 precordial leads	Inhospital mortality; secondary endpoints included adverse events, 35-day mortality, and 1-y mortality	N=4,534; trend for 14% reduction in inhospital mortality in patients presenting 7-12 h from symptom onset (11.7% vs 13.2%; 95% CI from 33% reduction to 12% increase)	No routine heparin; unclear why patients presenting <6 h from symptom onset included in final study population as study is a "trial of late thrombolysis"; no subset analysis of outcome for various ECG subgroups; unclear why study population consisted of patients with "no clear indications" for fibrinolytic therapy (ie, what were the characteristics of the excluded patients in the 7-14 h timeframe that were considered to have "clear" indications for fibrinolytic therapy)	Precordial lead elevation (2 mm), X; Limb lead elevation (1 mm), X; Undifferentiated BBB, X; New LBBB, X; Precordial ST depression, X

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
LATE Study Group[12]	1993	Randomized, placebo-controlled trial	100 mg tPA vs placebo in patients presenting 6-24 h after symptom onset; ECG eligibility criteria: ≥1 mm elevation in limb leads or ≥2 mm elevation in precordial leads; ST depression ≥2 mm in at least 2 leads; BBB with elevated markers	35-day mortality	N=5,711; trend toward decreased mortality in tPA group when analyzed by intention-to-treat analysis (8.9% vs 10.3%; relative reduction 14%; 95% CI 0 to 28%); significant decrease in mortality in 6-12 h subgroup when analyzed by survival analysis (8.9% vs 12%; relative reduction 26%; 95% CI 6.3% vs 45%); subgroup analysis reveals benefit only seen if delay time from presentation until treatment is <3 h	45% of patients had delay time of >3 h from admission to randomization; only 64% of patients received heparin; unclear how many patients with stuttering pre-infarctional angina had time of symptom onset referenced as time of onset of stuttering symptoms as opposed to time of continual symptoms that prompted patient presentation; no subgroup analysis performed for infarct site	Precordial lead elevation, (2 mm), II (benefit 6-12 h if treatment delay time <3 h); Limb lead elevation (1 mm), II (benefit 6-12 h if treatment delay time <3 h); Undifferentiated BBB, X; New LBBB, X; ST depression, X; Precordial ST depression, X
LATE Study Investi-gators[13]	1996	Secondary retrospective analysis of the LATE study (above) which was a randomized, placebo-controlled study	100 mg tPA vs placebo in patients presenting 6-24 h after symptom onset; ECG eligibility criteria: ≥1 mm elevation in limb leads or ≥2 mm elevation in precordial leads; ST-depression ≥2 mm in at least 2 leads; BBB with elevated markers	1-y mortality	N=5,711 (2,973 with ST elevation or BBB, 528 with ST-depression, and 1,258 with other ECG findings); no benefit from tPA treatment in patients with ST-segment elevation or BBB (21.2% vs 22.4%); benefit in ST-segment elevation AMI patients treated within 3 h of admission as compared to >3 h (15.8% vs 13.0%; *P*=0.028); patients presenting with ST-depression >2 mm had significant benefit from treatment with tPA (20.1% vs 31.9%; *P*=0.006)	See above limitations of original LATE report; retrospective analysis; no analysis of location or morphology of ST depression	Precordial lead elevation, (2 mm), II (benefit 6-12 h if treatment delay <3 h); Limb lead elevation (1 mm), II (benefit 6-12 h if treatment delay time <3 h); Undifferentiated BBB, III (benefit 6-12 h if treatment delay time <3 h); New LBBB, X; ST depression, (2 mm), II (benefit >6-12 h if treatment delay time <3 h); Precordial ST depression, III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
FTT Collaborative Group[14]	1994	Meta-analyses of all randomized trials with >1,000 patients of fibrinolytics vs controls	Various fibrinolytic regiments versus controls (see below for details of each of 9 studies included in the FTT analyses)	35-day mortality; secondary endpoints included major inhospital events	N=58,600; benefit of fibrinolytic treatment was seen in patients with ST-elevation or BBB; benefit a function of time from symptom onset to treatment (greater benefit with earlier treatment); significant benefit ≤12 h and trend for 12-24 h	Individual studies had varying definitions for ECG criteria for injury (see individual studies); no individual study addressed precordial ST elevation of 1 mm even though ACC/AHA guidelines list this as a class IA recommendation for fibrinolytic therapy; the 9,158 patients from ISIS-3 patients should not have been included; ISIS-3 was designed to compare SK vs tPA vs APSAC (ie, not placebo controlled except in small subset of patients with "uncertain" AMI); the definition of eligibility criteria for this "uncertain" category is not clear (see grading of ISIS-3 below); ISIS-3 reports 9,475 patients in "uncertain" subgroup whereas FTT reports 9,158; furthermore, outcome in the subgroup of patients who did not receive fibrinolytics is not even provided in ISIS-3 report; very limited data in regards to patients treated within 6-24 h; subgroup analysis not performed for subtypes of BBB (ie, left, right, atypical and new vs old); the FTT Collaborative Group does not report any patients in USIM with ST-depression, however, as USIM required ST-segment shifts (elevation or depression of 1 mm in limb leads and 2 mm in precordial leads), the 10% of USIM patients categorized as "other" in the FTT report undoubtedly represent ST-depression AMI; mortality in this subgroup of patients was significantly decreased and exclusion of these patients from the FTT subgroup analysis cast doubt on their findings on ST-depression AMI; individual studies did not collect necessary data to analyze the subgroup of patients with posterior AMI presenting with anterior ST-depressions that theoretically should benefit	Precordial lead elevation (2 mm), I (benefit ≤12 h); Limb lead elevation (1 mm), I (benefit ≤12 h); Undifferentiated BBB, I (benefit ≤12 h); New LBBB, X ST depression, III (no benefit) Precordial ST depression, X

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Kent et al[75]	2001	Meta-regression analysis of 10 randomized, controlled trials	Assessed the relationship between outcome and PCI-related delay, defined as door-to-balloon time minus door-to-needle time, by using data from trials comparing PCI with fibrinolysis for AMI	The primary outcome was 30-day mortality	2,628 patients; for each additional 10 min of PCI-related delay, the benefit of PCI over fibrinolysis decreased by 1.7% ($P<$ 0.001); the 2 treatments became equivalent after a 50-min delay	PCI-related time delay is not necessarily an independent variable, it may be a marker of the quality of care at the treating hospital; there is little data for longer PCI-related time delays longer than 50-min	II
Nallamothu and Bates[76]	2003	Meta-regression analysis of 21 randomized, controlled trials	Assessed the relationship between outcome and PCI-related delay, defined as door-to-balloon time minus door-to-needle time, by using data from trials comparing PCI with fibrinolysis for AMI	The primary outcome was 4- to 6-week mortality (included 21 studies); the secondary outcome was 4- to 6-week combined death, reinfarction and stroke (included 13 studies)	7,419 patients; the mortality benefit of PCI over fibrinolysis declined by 0.94% for every additional 10 min of PCI-related delay (P=0.006); the 2 treatments became equivalent after a 62 min delay; for the combined endpoint, the 2 treatments became equivalent at 93 min	PCI-related time delay is not necessarily an independent variable, it may be a marker of the quality of care at the treating hospital; there is little data for a PCI-related time delay greater than 60 min; conclusions about the impact of longer delays are largely extrapolated	I
Grines et al (PCAT Collaborators)[78]	2003	Meta-analysis of 11 randomized, controlled trials	Compared outcomes after treatment with fibrinolytics versus primary PCI for AMI	The primary outcome was the relative risk of death, reinfarction, stroke, bleeding and CABG at 30 days and 6 mo (if available); subgroup analyses included patient age, sex, comorbidities, and time from symptom onset	2,725 patients; 30-day mortality risk was 4.3% for patients treated with primary PTCA and 6.9% for patients receiving fibrinolysis (RR 0.62, 95% CI 0.44-0.86 P=0.004); at 6 months, the RR of death for patients treated with PCI was 0.73 (P=0.040); the benefit of PCI in reducing reinfarction and stroke was greater	6 mo follow-up data was missing for 2 trials, which differed from others in direction of treatment effect; when deaths were imputed for the missing data, the mortality difference at 6 mo was no longer significant; with 1 exception, all included studies were performed at highly experienced centers, potentially limiting external validity; a significant minority of studies used streptokinase rather than tPA; no studies used stents or GP IIb/IIIa inhibitors	I

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Bonnefoy et al[79]	2002	Randomized, multicenter, controlled trial, open-label with blinded outcome assessment	Compared outcomes with primary PCI vs prehospital fibrinolysis with transfer to an invasive center for rescue angioplasty, if necessary	The primary outcome was the composite of death, nonfatal reinfarction, and nonfatal disabling stroke at 30 days	840 patients; the composite event rate was 8.2% in the prehospital fibrinolysis group and 6.2% in the primary angioplasty group (P=0.29); individually, none of the components of the composite endpoint achieved statistical significance either	Trial terminated due to lack of funding after enrollment of 70% of planned recruitment; limited generalizability to the U.S. as fibrinolytics were administered by a physician in the prehospital setting; only 27% patients undergoing angioplasty received GP IIb/IIIa inhibitors, which may have attenuated the benefits associated with PCI	II
Steg et al[80]	2003	Subgroup analysis of prospective, randomized, controlled trial	Using patient data from the Bonnefoy et al[79] study, compared patients who were randomized within 2 h of symptom onset to those who were randomized after 2 h	The primary outcome was the composite of death, nonfatal reinfarction, and nonfatal disabling stroke at 30 days	840 patients; 460 were enrolled within 2 h of symptom onset and 374 within 2 to 6 h; whether the patients presented "early" or "late," there was no difference in the primary outcome between the fibrinolysis and PCI groups; there was a trend toward reduction of mortality with fibrinolysis vs PCI in the group presenting within 2 h (2.2% vs 5.7%, P=0.058)	Subgroup analysis of an underpowered study	III
Grines et al[81]	2002	Randomized, controlled, multicenter trial with blinded outcome assessment	High-risk patients with STEMI or LBBB were randomized to either emergent transfer to an interventional center or fibrinolysis at a noninterventional center	The primary end point was the combined occurrence of death, nonfatal reinfarction or disabling stroke at 30 days	138 patients; there was no difference between the 2 treatment groups in the primary endpoint; there was a trend towards an improved outcome with transfer for PCI	The trial was terminated after enrollment of only 32% of the anticipated sample size due to poor recruitment; the study was therefore underpowered; of note, revascularization with PTCA or CABG occurred in 52% of patients randomized to onsite fibrinolysis within the first 30 days	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Dalby et al[82]	2003	Meta-analysis of 6 randomized, controlled trials	Included trials that compared transfer of patients for PCI vs immediate local fibrinolysis for AMI	The primary end point was the 30-day composite of death, reinfarction, or stroke	3,750 patients; significant reduction in RR favoring transfer for primary PCI (RR 0.58; 95% CI, 0.47 to 0.71; $P<0.001$); results were driven by reduction in reinfarction and stroke	Inclusion of CAPTIM trial, which compared prehospital fibrinolysis with transfer for PCI, negated the mortality benefit seen in the other trials, which all compared inhospital fibrinolysis with transfer for PCI; transfer times in most trials still shorter than those normally seen in registries; angioplasty performed in high volume centers by experienced operators; GP IIb/IIIa inhibitors not consistently used with PCI	I
Vermeer et al[83]	1999	Multicenter, randomized, controlled trial	Compared transfer for primary PCI vs local fibrinolytic therapy with tPA versus transfer for "facilitated" PCI after tPA in patients presenting with STEMI	The primary endpoint was "safety and feasibility of transfer during AMI"; the secondary endpoint was death and reinfarction at 42 days	224 patients; transport complications were 2 episodes each VF, bradycardia, and hypotension; the combined endpoint of death and reinfarction were seen in 16% of the tPA group, 14% of the "facilitated" group, and 8% of the primary PCI group (nonsignificant difference)	Small "feasibility" study, not powered for efficacy; stents were used only for dissection or stenosis >50%; no GP IIb/IIIa inhibitors were used; short transport times due to well-organized interhospital transport system limits external validity; non-blinded outcome assessment	II
Widimsky et al[84]	2000	Prospective, multicenter, randomized controlled trial	Compared streptokinase at community hospitals vs streptokinase during transport for PCI vs immediate transport for primary PCI in patients presenting with STEMI	Primary combined clinical endpoint of death, reinfarction, and stroke at 30 days	300 patients; the combined endpoint occurred in 23% of the streptokinase group, in 15% of the streptokinase plus PCI group, and 8% of the primary PCI group ($P<0.02$); of combined endpoints, only reinfarction was significantly different among the groups	Small sample size; non-blinded outcome assessment; nontraditional definition of reinfarction (a more than double increase in CK MB and/or new ECG changes); excluded 252 patients with AMI for unspecified reasons; short transport times limit external validity; streptokinase, rather than a fibrin-specific thrombolytic was used; no GP IIb/IIIa inhibitors were used	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Widimsky et al[85]	2003	Randomized, multicenter, controlled trial	Patients presenting to community hospital with STEMI were randomized either to fibrinolysis or transfer for primary PCI	The primary endpoint was mortality at 30 days; secondary endpoints included 30-day mortality among subgroups of patients treated within 0-3 h and 3-12 h after symptom onset	850 patients; the 30-day mortality was 10.0% in the fibrinolysis group vs 6.8% in the PCI group (P=0.12); there was no difference in mortality among patients randomized within 3 h of symptom onset, but among those presenting later, mortality was 15.3% in the fibrinolysis group vs 6.0% in the PCI group (P <0.02)	The study was terminated prematurely by the Ethics Committee due to the excess mortality in patients treated with fibrinolysis after 3 h from symptom onset; some treating physicians at community hospitals elected not to randomize patients to fibrinolysis, and instead transferred them for PCI; streptokinase, rather than a fibrin-specific fibrinolytic, was used; although stents were used in 63% of interventions, no GP IIb/IIIa inhibitors were given in PCI arm; door-to-balloon times were shorter than those seen in observational registries; non-blinded outcome assessment	II
Andersen et al[86]	2003	Randomized, multicenter, controlled trial, with blinded outcome assessment	Compared fibrinolysis with PCI for STEMI; those who presented to noninvasive centers and were assigned to PCI were transferred to an invasive center	The primary endpoint was a composite of death, clinical evidence of reinfarction, or disabling stroke at 30 days	1,129 patients who were enrolled at referral hospitals and transferred to an invasive center; of patients randomized at referral hospitals, the primary endpoint was reached in 8.5% of the patients in the angioplasty group, compared with 14.2% of those in the fibrinolysis group (P=.002); the only component of the combined endpoint that was independently significant was reinfarction, with 6.2% vs 1.9% (P<0.001)	An efficient transfer process, and the fact that a physician accompanied the patient in the ambulance, limits external validity; it was recommended that suspected failed reperfusion be treated with repeat fibrinolysis rather than PCI, which occurred in 26 and 15 patients respectively; patients judged to be at high-risk during transfer were excluded	I

ACC/AHA, American College of Cardiology/American Heart Association; *AMI*, acute myocardial infarction; *APSAC*, anisoylated purified streptokinase activator complex; *BBB*, bundle branch block; *CABG*, coronary artery bypass graft; *CCU*, critical care unit; *LBBB*, left bundle branch block; *MU*, million units; *PCI*, percutaneous coronary intervention; *PTCA*, percutaneous transluminal coronary angioplasty.

Appendix A. Literature classification schema.*

Design/Class	Therapy†	Diagnosis‡	Prognosis§
1	Randomized, controlled trial or meta-analyses of randomized trials	Prospective cohort using a criterion standard	Population prospective cohort
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing ≥2 interventions.
‡Objective is to determine the sensitivity and specificity of diagnostic tests.
§Objective is to predict outcome including mortality and morbidity.

Appendix B. Approach to downgrading strength of evidence.

	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X