Acute ST-elevation myocardial infarction: Selecting a reperfusion strategy

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All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Jan 2024.**
This topic last updated: **Jun 29, 2022.**

INTRODUCTION

For most patients with acute ST-elevation myocardial infarction (STEMI), coronary artery reperfusion of the infarct-related artery with either primary percutaneous coronary intervention (PCI) or fibrinolytic therapy reduces mortality compared with no reperfusion. As the benefits of reperfusion decline rapidly with time, reperfusion should be implemented as soon as possible. (See "Primary percutaneous coronary intervention in acute ST elevation myocardial infarction: Determinants of outcome", section on 'Time from hospital arrival (door-to-balloon time)' and "Acute ST-elevation myocardial infarction: The use of fibrinolytic therapy", section on 'Timing' and 'Short duration of symptoms' below.)

This topic will discuss our approach to reperfusion therapy for patients with STEMI. Related topics include:

- (See "Percutaneous coronary intervention after fibrinolysis for acute ST-elevation myocardial infarction".)
- (See "Performance of prehospital fibrinolysis".)
- (See "Acute ST-elevation myocardial infarction: The use of fibrinolytic therapy", section on 'Initiation of therapy'.)
- (See "Acute ST-elevation myocardial infarction: Management of anticoagulation".)
- (See "Acute ST-elevation myocardial infarction: Antiplatelet therapy".)

- (See "Primary percutaneous coronary intervention in acute ST-elevation myocardial infarction: Periprocedural management".)

TERMINOLOGY

The following terms are used when evaluating time to treatment:

- **Door-to-needle time** refers to the time from presentation at a hospital (or ambulance) to the administration of fibrinolytic therapy.
- **Door-to-balloon time** refers to the time from presentation at a percutaneous coronary intervention (PCI) center to first balloon inflation. This term is used irrespective of whether stenting is performed. (See "Primary percutaneous coronary intervention in acute ST elevation myocardial infarction: Determinants of outcome", section on 'Time from hospital arrival (door-to-balloon time)'.)
- **PCI-related delay** is the difference between the door-to-balloon time and the anticipated door-to-needle time. The PCI-related delay overestimates the reperfusion delay for PCI somewhat, since PCI reperfusion is immediate while fibrinolytic therapy generally does not re-establish perfusion for about 30 minutes.
- **First medical contact to balloon** refers to the time between the first medical contact with the patient (which may be out of hospital) to first balloon inflation.
- **Door-in to door-out (DIDO) time** is the time from arrival at the first hospital to transfer from that hospital to the percutaneous coronary intervention hospital. This time should not exceed 30 minutes [1]. This is a performance measure in the United States.

INDICATIONS FOR REPERFUSION

Most patients with acute STEMI should receive immediate reperfusion therapy with either fibrinolytic therapy or primary percutaneous coronary intervention (PCI). Relative to no reperfusion, reperfusion lowers the risk of death. Direct supporting evidence comes from early randomized trials that compared fibrinolytic therapy with no reperfusion and indirect evidence from trials comparing fibrinolysis with balloon angioplasty or stenting. (See 'Evidence' below.)

With regard to fibrinolytic therapy, a 1994 meta-analysis found that the absolute mortality reduction from fibrinolytic therapy at five weeks was 3 percent for those presenting within six hours from symptom onset, 2 percent for those presenting within 7 to 12 hours, and a

nonsignificant 1 percent for those presenting within 13 to 18 hours [2]. The net effect in major fibrinolytic trials was an approximately 30 percent reduction in short-term mortality to a value of 7 to 10 percent.

REASONS TO NOT REPERFUSE

Patients for whom it is reasonable to not offer reperfusion include those who are moribund at the time of presentation and who are predicted to have a poor quality of life, those with another significant comorbidity, and those who present very late in the course of their illness.

PRIMARY PCI PREFERRED TO FIBRINOLYSIS

Primary percutaneous coronary intervention (PCI) is preferred to fibrinolytic therapy when it can be performed by skilled interventional cardiologists in a timely manner (algorithm 1). It should be performed within 120 minutes of first medical contact and ideally within 90 minutes.

Primary PCI may be preferred for some patients even when it cannot be performed in a timely manner. Examples of patients for whom even delayed PCI (>120 minutes from first medical contact) is preferred include those in whom the diagnosis is in doubt, those at high bleeding risk, and those at high risk of death such as those in cardiogenic shock. (See "Prognosis and treatment of cardiogenic shock complicating acute myocardial infarction", section on 'Prognosis'.)

Evidence — Initial evidence to support the preference for primary PCI comes from randomized trials of fibrinolysis compared with balloon angioplasty [3-6]. In the aggregate, these trials found about a 2 percent lower absolute risk of death with balloon angioplasty [7]. This evidence was followed by studies showing that PCI with stenting lowers the rate of death, nonfatal reinfarction, or stroke compared with balloon angioplasty [8]. Finally, primary PCI with stenting was directly compared with fibrinolysis in multiple randomized trials (DANAMI-2, PRAGUE-2, AIR PAMI, STAT, STOPAMI-1, and STOPAMI-2) [9-17]. In these studies there was a trend toward a lower risk of death with PCI versus fibrinolysis and a lower risk of recurrent myocardial infarction (MI).

A large 2009 meta-analysis of randomized controlled trials (RCT) and observational studies (OS), which compared primary PCI (with balloon angioplasty or stenting) to fibrinolysis, came to the following conclusions [18]:

- Primary PCI was associated with significant relative risk reductions in short-term (≤6 weeks) mortality of 34 percent in RCT and 23 percent in OS.
- Primary PCI was associated with significant reductions in long-term (>1 year) mortality of 24 percent and reinfarction of 51 percent in RCT.

The recommendation to perform primary PCI within 120 minutes of first medical contact is derived from outcomes seen in randomized trials and large observational studies. This issue is discussed in detail elsewhere. (See "Primary percutaneous coronary intervention in acute ST elevation myocardial infarction: Determinants of outcome", section on 'Time from hospital arrival (door-to-balloon time)'.)

Additional evidence to support a broad preference for primary PCI comes from studies which evaluated a pharmacoinvasive approach such as the STREAM trial. (See 'Pharmacoinvasive strategy' below.)

Diagnosis in doubt — In patients who present with signs and symptoms that are suggestive but not diagnostic of STEMI, primary PCI is preferred over fibrinolysis even when PCI will be associated with additional delays >30 minutes such as in patients who need be transferred from one facility to another. Examples include patients with nondiagnostic or borderline features on the electrocardiogram (ECG) or those with an ECG suggesting STEMI but an atypical history (eg, pericarditis). (See "Electrocardiogram in the diagnosis of myocardial ischemia and infarction".)

In some clinically stable patients where the diagnosis is in doubt and the physician believes that the time delay associated with performing echocardiography does not exceed the harm in delaying reperfusion, we consider performing immediate echocardiography. An echocardiogram with findings consistent with acute MI should lead to immediate angiography. A normal echocardiogram may warrant an expectant approach, particularly amongst those who are not exhibiting electrical or hemodynamic instability or those who have increased risk from anticoagulation or coronary intervention.

High bleeding risk — Fibrinolytic therapy carries a greater risk of major (and minor) bleeding compared with primary PCI. Intracranial hemorrhage is the most serious of these risks and occurs in approximately 0.7 percent of patients treated with fibrinolytics [19,20]. Although there are no randomized data specific to a high bleeding risk population, such patients appear to benefit more from primary PCI [21]. Given the excess risk of fibrinolysis in this population, it is likely PCI would have greater benefit than fibrinolysis even if treatment delays exceed 30 minutes.

Anticipated PCI delay — PCI should be performed within 120 minutes of first medical contact and ideally within 90 minutes. Among patients who have anticipated treatment delays for primary PCI, we consider fibrinolysis if it can be administered within 30 minutes of the anticipated PCI delay. Even among patients who might be considered for fibrinolysis based on timing, primary PCI is preferred in several settings, including the presence of contraindications to fibrinolysis (table 1), very high-risk patients, and those with late presentation.

A 2020 registry propensity-matched study comparing a pharmaco-invasive strategy with late primary PCI (>120 minutes from diagnosis) in over 4000 STEMI patients (see 'Pharmacoinvasive strategy' below) found better five-year survival with the former (89.8 versus 79.5 percent; adjusted hazard ratio 1.51, 95% CI 1.13-2.02) [22].

Very high-risk patients — The benefits of primary PCI over fibrinolysis are greater in very high-risk (of death) patients, including those patients with cardiogenic shock. This point was illustrated in an analysis of 16 randomized trials that compared primary PCI with or without stenting with fibrinolysis [23]. In this study, an increase in baseline mortality risk from 4.4 to 12.4 percent allowed for an increase in the acceptable PCI-related delay (equipoise) from 43 to 200 minutes.

As a result, transfer for PCI, even with a delay, is generally favored over fibrinolysis for patients with severe heart failure and/or pulmonary edema or those deemed to be at high risk on the basis of models such as the TIMI risk score (calculator 1) [10,24]. Very high-risk patients should receive primary PCI as soon as possible and within 120 minutes of first medical contact. The issue of whether fibrinolytic therapy might be reasonable for some of these patients with a very long delay to primary PCI is discussed elsewhere. (See "Prognosis and treatment of cardiogenic shock complicating acute myocardial infarction", section on 'Fibrinolysis'.)

Late presentation — Late presentation refers to patients who present more than 12 hours after the onset of symptoms. Registry data suggest that late presentation occurs in 9 to 31 percent all STEMI patients [21,25]. In patients who present more than 12 hours after symptom onset, primary PCI may be of benefit if evidence of ongoing myocardial ischemia is present. Fibrinolytic therapy administered at this time is not likely to improve outcomes and carries with it the risk of serious bleeding, and we generally do not recommend it.

In asymptomatic, stable patients who present after 12 hours, there is no evidence that reperfusion with either fibrinolytic therapy or primary PCI is of benefit. Although there is little evidence, possible exceptions include patients who present after more than 12 hours (and up to 24 hours) and who have a larger area of myocardium at risk, hemodynamic instability, or

ongoing ischemic symptoms and for whom PCI is not available [26,27]. (See "Acute ST-elevation myocardial infarction: The use of fibrinolytic therapy", section on 'Timing'.)

FIBRINOLYSIS

We prefer primary percutaneous coronary intervention (PCI) to immediate fibrinolysis when both reperfusion strategies can be delivered in a timely manner (algorithm 1). We attempt to start fibrinolytic therapy within 10 minutes of the diagnosis of MI. Fibrinolytic therapy is used most commonly in locales where primary PCI is not available or when a significant delay to its delivery is anticipated. (See 'Primary PCI preferred to fibrinolysis' above.)

If the PCI-related delay (see 'Terminology' above) is greater than 90 minutes, fibrinolysis is preferred [28]. The recommendation to choose fibrinolysis rather than PCI if the latter cannot be performed within 120 minutes of first medical contact comes from randomized trials (figure 1) [29] and studies of community cohorts [28,30-32]. (See 'Evidence' above.)

When fibrinolytic therapy has been chosen as the primary reperfusion strategy (see 'Anticipated PCI delay' above), we suggest that most patients receive subsequent angiography and possible PCI of the infarcted artery. This is referred to as the pharmacoinvasive strategy. (See 'Pharmacoinvasive strategy' below.)

Pharmacoinvasive strategy — If fibrinolytic therapy has been chosen as the primary reperfusion strategy (see 'Anticipated PCI delay' above), we perform subsequent angiography and possible PCI of the infarcted artery in many cases (algorithm 1). This is referred to as the pharmacoinvasive strategy. With a pharmacoinvasive strategy, patients who receive fibrinolytic therapy, either in the prehospital setting or at a non-PCI-capable hospital, are transferred immediately to a PCI-capable hospital for early coronary angiography and PCI, generally within 2 to 24 hours depending upon time of day and other circumstances. It is reasonable to perform coronary arteriography after 24 hours (but before discharge) in lower-risk patients.

We recognize that some experts prefer to manage patients at very low risk (small infarct, inferior location, absence of heart failure or important arrhythmias, or relative contraindications to PCI) with a conservative strategy of “watchful waiting” with monitoring for spontaneous recurrent ischemia and, if not is seen, stress testing to evaluate for provocable ischemia. If ischemia is present, patients should undergo angiography and revascularization.

The rationale for performing PCI after fibrinolysis is that many patients have a persistent reduction in flow in the infarct-related artery and are at risk for reinfarction. Although fibrinolysis restores patency (TIMI grade 2 or 3) in 80 percent of infarct-related arteries,

normalization (TIMI grade 3) of blood flow is seen in only 50 to 60 percent of arteries. As mentioned above, the clinical benefits of fibrinolytic therapy are seen only with the restoration of normal flow (figure 2 and figure 3) [33,34]. (See "Diagnosis and management of failed fibrinolysis or threatened reocclusion in acute ST-elevation myocardial infarction", section on 'Primary failure'.)

The pharmaco-invasive approach has been compared with two reperfusion strategies:

- Fibrinolytic plus PCI only for a clinical indication (or late after fibrinolysis).

  Two meta-analyses of these trials comparing routine, early PCI after fibrinolysis (the pharmaco-invasive approach) with ischemia-guided (clinical indication) PCI concluded that patient outcomes are better with early routine PCI [35,36]. In a 2010 meta-analysis, the incidence of death or reinfarction at 30 days was lower with early PCI (odds ratio [OR] 0.65, 95% CI 0.49-0.88) without a significant increase in major bleeding (OR 0.93, 95% CI 0.67-1.34) [36].

- Primary PCI. This comparison differs from the studies which compared fibrinolysis alone with primary PCI. (See 'Evidence' above.)

  In the STREAM trial, 1892 patients who presented within three hours were randomly assigned to undergo either fibrinolytic therapy with bolus tenecteplase or primary PCI [37]. Patients who could undergo PCI within one hour were excluded. In the lytic group, coronary angiography was performed urgently for evidence of reperfusion failure or routinely at 6 to 24 hours. There was no difference in the primary composite end point (death, shock, congestive heart failure, or reinfarction up to 30 days) between the two groups (12.4 versus 14.3 percent, respectively; relative risk 0.86, 95% CI 0.68-1.09). The rates of intracranial hemorrhage were 1.0 and 0.2 percent before a protocol amendment allowed for a lower dose of lytic for patients ≥75 years. At one year, there was no difference in the rates of all-cause mortality: 6.7 versus 5.9 percent, respectively (risk ratio 1.13, 95% CI 0.79-1.62) [38].

  In STREAM, the time to reperfusion with fibrinolysis (tenecteplase) was shortened and patients were referred to a percutaneous coronary intervention (PCI) center for elective or rescue PCI. With this strategy, patients treated with early fibrinolysis or primary PCI had a similar incidence of adverse outcomes at 30 days. Moreover, only 36 percent of patients underwent rescue PCI and 64 percent had an elective coronary angiogram and PCI within 24 to 48 hours. Persistence of symptoms or lack of ST-segment resolution should prompt rescue PCI. Limitations of STREAM include protocol change and an older approach to the use of antithrombotic therapies.

While fibrinolysis leads to efficacy outcomes comparable to primary PCI in patients who present early (such as in STREAM), we prefer the latter due to concerns about the safety (eg, intracranial hemorrhage) of lytic therapy.

Failed fibrinolysis or threatened reocclusion — For patients with evidence of failed fibrinolysis or threatened reocclusion, as manifested by findings such as persistent or recurrent chest pain, ST-segment elevation, or hemodynamic or electrical instability, including those with cardiogenic shock, we recommend immediate PCI, also known as "rescue PCI." (See "Diagnosis and management of failed fibrinolysis or threatened reocclusion in acute ST-elevation myocardial infarction" and "Percutaneous coronary intervention after fibrinolysis for acute ST-elevation myocardial infarction".)

PCI may need to be performed urgently in about 30 percent of patients who receive fibrinolytic therapy.

Facilitated PCI — We do not recommend facilitated (with fibrinolytic therapy) PCI, which refers to treatment with fibrinolytic therapy just prior to (within three hours of) planned primary PCI due to significant increases in mortality, nonfatal reinfarction, urgent target lesion revascularization and stroke, and a trend toward a higher rate of major bleeding. (See "Percutaneous coronary intervention after fibrinolysis for acute ST-elevation myocardial infarction", section on 'Facilitated PCI (with fibrinolytic therapy)'.)

PATIENT CHARACTERISTICS INFLUENCING CHOICE

We prefer primary percutaneous coronary intervention (PCI) to fibrinolysis for most patients with STEMI if it can be performed by skilled practitioners within 120 minutes of first medical contact. Clinical situations which might alter the 120-minute rule (see 'Primary PCI preferred to fibrinolysis' above) have not adequately been studied. Until well-performed studies present evidence that 120 minutes is not the optimal cut point for patients with any of these characteristics, we recommend 120 minutes as the cut point between primary PCI and fibrinolysis for most patients, though it is likely that various risk characteristics alter how fast time-dependent benefit of PCI erodes.

A few patient characteristics may influence the time at which outcomes are similar with either reperfusion strategy [28]. Non-patient-related factors that may increase the PCI delay are long door-to-door transfer times and off-hour presentation [39]. In certain patients, the delay to PCI may be more tolerable. In others, it should be avoided. (See "Primary percutaneous coronary

intervention in acute ST elevation myocardial infarction: Determinants of outcome", section on 'Hospital performance'.)

Short duration of symptoms — The time from symptom onset plays a role in determining the relative benefit of primary PCI compared with fibrinolysis. As the length of time from the onset of symptoms to intervention increases, outcomes are worse irrespective of reperfusion strategy. However, the benefits from reperfusion are lost more quickly with fibrinolytic therapy as the time from symptom onset increases [40-42]. (See "Primary percutaneous coronary intervention in acute ST elevation myocardial infarction: Determinants of outcome", section on 'Time from symptom onset' and "Acute ST-elevation myocardial infarction: The use of fibrinolytic therapy", section on 'Timing'.)

Most individuals who present ≤3 hours from symptom onset are on the steep portion of the survival versus time-to-reperfusion curve (figure 4) [40,41,43]. In this early stage, there is an opportunity for substantial myocardial salvage and mortality reduction. It is in this time window that fibrinolytic therapy is most likely to be effective. Thus, for those patients who cannot receive expert primary PCI within approximately 120 minutes of first medical contact, fibrinolytic therapy has an advantage. (See "Acute ST-elevation myocardial infarction: The use of fibrinolytic therapy", section on 'Timing'.)

Approximately half of patients with STEMI present more than three to four hours after symptom onset [44]. Such patients are on a flatter portion of the survival versus time-to-reperfusion curve for fibrinolytic therapy (figure 4). They are usually better served by the greater efficacy and reduced stroke risk of primary PCI, despite the time required for transfer. However, a delay to implementation of PCI related to transfer eventually erodes the benefit of primary PCI over fibrinolysis.

Age and infarct location — The issue of whether age or infarct location affect the PCI-related delay at which the mortality rates with PCI and fibrinolysis are equal (equipoise) was evaluated in a study from National Registry of Myocardial Infarction [28]:

- **Age** – Equipoise occurred at 71 minutes of PCI-related delay in patients <65 years and at 155 minutes in patients ≥65 years. This means that at any PCI-related delay greater than these values, the odds of survival with PCI was no longer higher than that with fibrinolysis. One explanation of the age-related difference is that fibrinolysis has a greater major bleeding rate in older adult patients, so there is more time to implement PCI to avoid a devastating bleeding complication.

- **Infarct location** – Patients with anterior infarction lost the advantage of PCI at shorter PCI-related delays than did patients with non-anterior infarcts (table 2).

RECOMMENDATIONS OF OTHERS

Our recommendations are in broad agreement with guidelines from the American College of Cardiology Foundation/American Heart Association and the European Society of Cardiology on ST-elevation myocardial infarction and percutaneous coronary intervention [26,27,45,46].

SOCIETY GUIDELINE LINKS

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

SUMMARY AND RECOMMENDATIONS

- **Indications for reperfusion** – Coronary artery reperfusion with either primary percutaneous coronary intervention (PCI) or fibrinolytic therapy improves clinical outcomes in nearly all groups of patients with an acute ST-elevation myocardial infarction (STEMI) who present within 12 hours of symptom onset. For these patients, we recommend reperfusion therapy compared with no reperfusion (**Grade 1A**). (See 'Indications for reperfusion' above.)

- **Primary PCI preferred to fibrinolysis** – For most STEMI patients who present within 12 hours of symptom onset, we recommend primary PCI rather than immediate fibrinolysis if PCI can be delivered within 120 minutes of first medical contact by skilled practitioners (algorithm 1) (**Grade 1A**). (See 'Primary PCI preferred to fibrinolysis' above.)

  We prefer to have patients undergo PCI within 90 minutes if possible.

- **Fibrinolysis** – For patients who cannot receive timely primary PCI, fibrinolytic therapy should be given (algorithm 1). Fibrinolytic therapy should be administered within 30 minutes of arrival at the hospital, and as soon as 10 minutes if possible. (See 'Fibrinolysis' above.)

  - **Angiography after fibrinolysis** – Most patients who are primarily treated with fibrinolysis should undergo diagnostic coronary angiography and PCI within 3 to 24 hours after fibrinolysis (algorithm 1). (See 'Pharmacoinvasive strategy' above.)

- **Late presentation** – For patients who present after 12 hours (and up to 24 hours) of symptom onset and have evidence of ongoing ischemia, we suggest PCI as opposed to no reperfusion therapy (algorithm 1) (**Grade 2C**). (See 'Late presentation' above.)

ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges Duane Pinto, MD, MPH, who contributed to earlier versions of this topic review.

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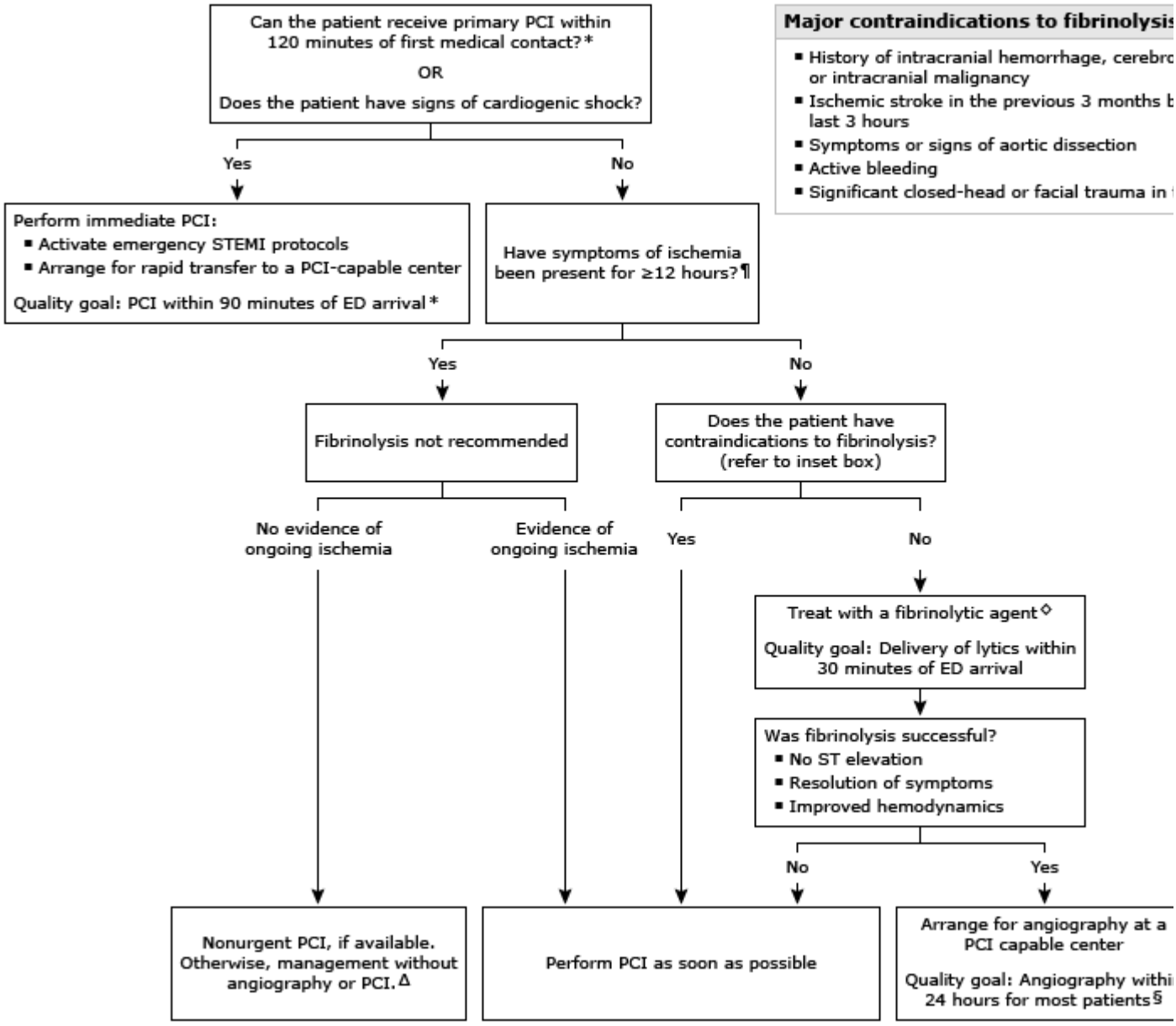
GRAPHICS

Selecting a reperfusion strategy in patients with acute STEMI



STEMI: ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; ED: emergency department; AMI: acute myocardial infarction.

* This time includes all time required for transfer and other aspects of care until balloon dilation, thrombectomy, or other definitive percutaneous intervention is performed.

¶ Refer to UpToDate content on selecting a reperfusion strategy in STEMI for more information on patients with late presentation.

Δ For patients who do not undergo either PCI or fibrinolysis, refer to UpToDate content for a discussion of optimal medical management.

◇ The selection and use of a specific fibrinolytic agent and the associated anticoagulant and antiplatelet therapies are discussed in UpToDate content on fibrinolysis in AMI.

§ Patients at high risk of reocclusion should undergo PCI sooner, while low-risk patients can undergo PCI later. More information on the use of angiography and PCI after fibrionlysis for the treatment of STEMI can be found in UpToDate.

¥ Refer to UpToDate content for the details on the absolute and relative contraindications to fibrinolysis in patients with acute STEMI.

Graphic 138821 Version 1.0

Absolute and relative contraindications to the use of thrombolytic therapy in patients with acute ST-elevation myocardial infarction*

Absolute contraindications
History of any intracranial hemorrhage
History of ischemic stroke within the preceding three months, with the important exception of acute ischemic stroke seen within three hours, which may be treated with thrombolytic therapy
Presence of a cerebral vascular malformation or a primary or metastatic intracranial malignancy
Symptoms or signs suggestive of an aortic dissection
A bleeding diathesis or active bleeding, with the exception of menses; thrombolytic therapy may increase the risk of moderate bleeding, which is offset by the benefits of thrombolysis
Significant closed-head or facial trauma within the preceding three months
Relative contraindications
History of chronic, severe, poorly controlled hypertension or uncontrolled hypertension at presentation (eg, blood pressure >180 mmHg systolic and/or >110 mmHg diastolic; severe hypertension at presentation can be an absolute contraindication in patients at low risk)
History of ischemic stroke more than three months previously
Dementia
Any known intracranial disease that is not an absolute contraindication
Traumatic or prolonged (>10 min) cardiopulmonary resuscitation
Major surgery within the preceding three weeks
Internal bleeding within the preceding two to four weeks or an active peptic ulcer
Noncompressible vascular punctures
Pregnancy
Current warfarin therapy; the risk of bleeding increases as the INR increases
For streptokinase or anistreplase, a prior exposure (more than five days previously) or allergic reaction to these drugs

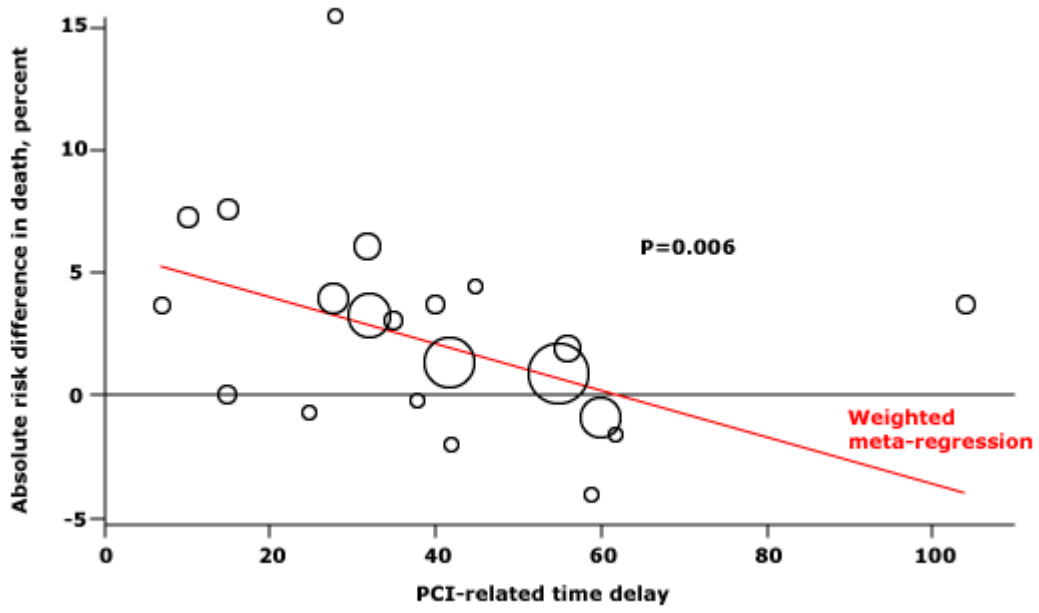
INR: international normalized ratio.

* May not be all-inclusive or definitive.

Data from: Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation 2004; 110:588.

Graphic 68784 Version 11.0

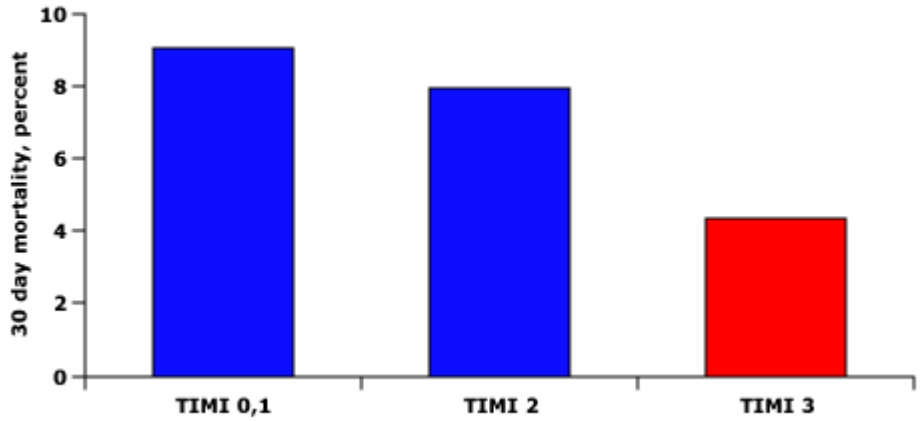
Absolute risk reduction in 4- to 6-week mortality rates with primary PCI as function of PCI-related time delay



Circles reflect the sample size of the individual study. Values >0 represent benefit and values <0 represent harm.

Graphic 67756 Version 3.0

Thrombolysis in myocardial infarction (TIMI) grade 3 coronary flow is associated with improved survival after thrombolysis

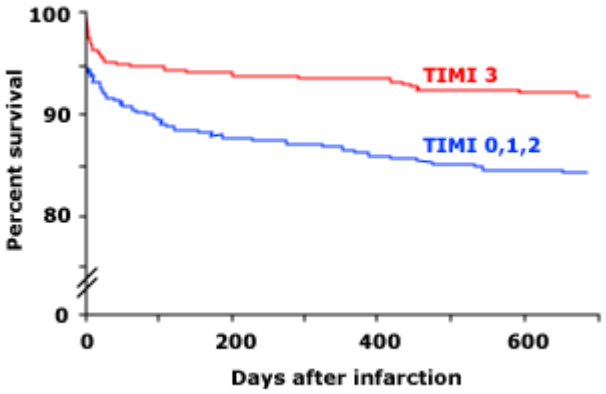


In the Global Utilization of t-PA and Streptokinase for Occluded Coronary Arteries (GUSTO-I) trial, the 30-day mortality rate after thrombolysis for acute ST-elevation myocardial infarction varied with the degree of vessel patency achieved. The mortality was lowest (4.3 percent) in patients with TIMI grade 3 (normal) flow in the infarct-related artery at 90 minutes. Partial restoration of flow (TIMI grade 2) did not improve outcomes compared with no or faint flow (TIMI grade 0 or 1).

Data from The GUSTO Investigators. N Engl J Med 1993; 329:673.

Graphic 75629 Version 7.0

Survival after thrombolytic therapy is better with Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow

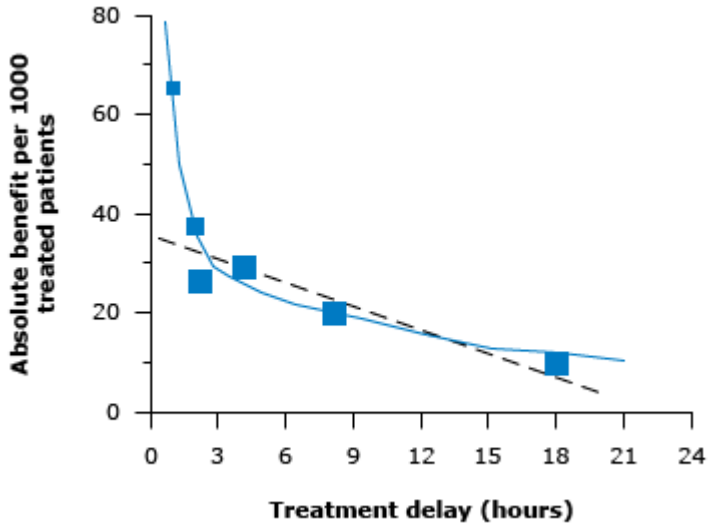


Among all patients with acute ST-elevation myocardial infarction entered into the GUSTO-I trial, those with TIMI grade 3 (normal) flow in the infarct-related artery at 90 minutes after thrombolytic therapy had a significantly higher rate of two-year survival than patients with TIMI grades 0, 1, or 2. Partial restoration of flow (TIMI grade 2) did not improve outcomes compared with no or faint flow (TIMI grade 0 or 1). A similar relationship was seen when the analysis was limited to patients who were alive at 30 days after the infarction (not shown).

Data from Ross AM, Coyne KS, Moreyra E, et al, for the GUSTO-I Angiography Investigators. Circulation 1998; 97:1549.

Graphic 70952 Version 6.0

Time to thrombolysis and 35-day mortality



The importance of time to thrombolysis in acute myocardial infarction and the absolute reduction in 35-day mortality in a meta-analysis of over 50,000 patients. The benefit from thrombolytic therapy is greatest when it is administered within 2 hours of symptom onset. The survival benefit is progressively reduced as the delay in therapy increases; after 2 hours, the benefit from thrombolytic therapy fits a linear function (black dashed line) in which the benefit falls by approximately 1.6 lives per 1000 patients per hour of treatment delay.

Data from Boersma E, Maas ACP, Simoon ML. Lancet 1996; 348:771.

Graphic 53374 Version 6.0

Time at which PCI loses superiority in survival over fibrinolysis varies depending upon patient risk

Pre-hospital delay (minutes)	Age <65 years		Age ≥65 years	
	Anterior infarction	Non-anterior infarction	Anterior infarction	Non-anterior infarction
0-120	40 minutes	58 minutes	107 minutes	168 minutes
121+	43 minutes	103 minutes	148 minutes	179 minutes

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