Diagnosis and management of failed fibrinolysis or threatened reocclusion in acute ST-elevation myocardial infarction

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INTRODUCTION

Coronary reperfusion with fibrinolysis or primary percutaneous coronary intervention (PCI) substantially improves survival in patients with an acute ST-elevation myocardial infarction (STEMI) compared with no reperfusion therapy. PCI is preferred for most patients if it can be performed by an experienced operator with less than a 90-minute delay from presentation to the emergency department. However, fibrinolysis remains an important therapeutic modality, due in part to limited availability of primary PCI in some locations. (See "Acute ST-elevation myocardial infarction: Selecting a reperfusion strategy" and "Primary percutaneous coronary intervention in acute ST elevation myocardial infarction: Determinants of outcome" and "Acute ST-elevation myocardial infarction: The use of fibrinolytic therapy".)

The principle reasons for preference of PCI over fibrinolysis is the relatively high frequency of failure of fibrinolysis to establish reperfusion, early reocclusion after apparently successful fibrinolysis, and increased bleeding complications with fibrinolysis. (See 'Primary failure' below and 'Threatened reocclusion or reinfarction' below.)

This topic will review the roles of angiography followed by PCI (or coronary artery bypass graft surgery [CABG] if indicated) for failed fibrinolysis or threatened reocclusion and of retreatment

with fibrinolytic drugs for threatened reocclusion. The use of routine angiography after fibrinolysis is discussed separately. (See "Acute ST-elevation myocardial infarction: Selecting a reperfusion strategy".)

IMPORTANCE OF RESTORATION OF NORMAL FLOW

The mortality benefit after fibrinolytic therapy in patients with STEMI is related to the degree to which flow has been restored in the infarct-related artery. In the cardiac catheterization laboratory, patency of the infarct-related artery is usually graded according to the Thrombosis in Myocardial Infarction (TIMI) classification system. In clinical trials of fibrinolysis, patency is usually measured at 60 to 90 minutes after the administration of fibrinolytic therapy:

- TIMI 0 refers to the absence of any antegrade flow beyond a coronary occlusion.
- TIMI 1 flow is faint antegrade coronary flow beyond the occlusion, although filling of the distal coronary bed is incomplete.
- TIMI 2 flow is delayed or sluggish antegrade flow with complete filling of the distal territory.
- TIMI 3 flow is normal flow that fills the distal coronary bed completely.

Only TIMI 3 (normal) flow is associated with a mortality benefit after fibrinolysis (figure 1 and figure 2) [1-6]. The magnitude of this effect was illustrated in a meta-analysis of five trials of almost 4000 patients [2]. Short-term mortality (ranging from in-hospital to 30 days in the different trials) was 3.7, 7, and 8.8 percent among patients with TIMI grade 3, 2, and 0/1, respectively. (See 'Primary failure' below.)

Additionally, in patients who undergo diagnostic angiography after fibrinolysis, both TIMI 0/1 and 2 flow are associated with increased mortality compared with those with TIMI 3 (normal) flow [1]. (See 'Diagnosis' below.)

PRIMARY FAILURE

Primary failure of fibrinolysis is best treated with immediate percutaneous coronary intervention (PCI). Patients should be referred to a facility with PCI capability immediately after fibrinolysis in most cases, so that failed fibrinolysis can be managed expeditiously. This strategy will avoid the need to consider repeat fibrinolysis. (See "Percutaneous coronary intervention

after fibrinolysis for acute ST-elevation myocardial infarction", section on 'Patients treated at non-PCI hospitals or in an ambulance'.)

Primary failure based on clinical criteria is common. Using angiographic criteria of TIMI 3 flow within 90 minutes, failure is seen in 40 to 45 percent of patients [7].

Clinical manifestations — Primary failure of fibrinolysis is often clinically suspected by persistent or worsening chest pain (particularly if associated with other symptoms such as dyspnea and diaphoresis), persistent or worsening ST-segment elevation on the electrocardiogram (ECG), hemodynamic instability, and/or heart failure [8].

However, these parameters do not predict failed fibrinolysis in all patients [9-11]. Chest pain alone is subjective, especially if improved, and many patients do not have complete ST-segment elevation resolution [8,12]. In addition, ST-segment elevation resolution and patency of the infarct-related artery are not always correlated. As a result, in the absence of clear indications of reperfusion, the clinician must maintain a high index of suspicion for primary failure [13]. Persistent chest pain or the absence of at least 50 percent of the initial ST-segment elevation on a follow-up ECG 60 to 90 minutes after fibrinolytic therapy are suggestive of lack of adequate reperfusion and warrant early referral for coronary angiography [14-16]. (See 'Primary failure' above.)

The potential lack of correlation between ST-segment elevation and TIMI flow grade was illustrated in the TIMI 14 trial of 444 patients with an interpretable ECG who underwent angiography at 90 minutes after fibrinolytic therapy [10,17]. TIMI 3 flow was present in only 79 percent of patients with complete (≥70 percent) ST-segment resolution and was also present in 44 to 50 percent of patients with partial or no ST-segment resolution. The latter patients were at increased risk for mortality, as the lack of complete ST-segment resolution was presumably due to extensive microvascular dysfunction [17].

Diagnosis — Primary failure can be suspected based on the patient's symptoms and ECG (see 'Clinical manifestations' above). The diagnosis is confirmed with coronary angiography.

Primary failure is defined as persistent occlusion of the infarct-related artery (TIMI grade 0/1 epicardial flow) at the time of coronary angiography. TIMI grade 0/1 occurred in 27 percent and was associated with a higher short-term mortality rate than TIMI 3 flow (8.8 versus 3.7 percent) [2]. Since mortality is also increased in patients with TIMI 2 flow, some have also considered TIMI 2 flow a sign of failed therapy (figure 1 and figure 2). (See 'TIMI grade 2 flow' below.)

In addition to patency of the epicardial coronary arteries, adequacy of microvascular flow, as determined by the myocardial perfusion grade, can also be assessed during angiography.

Myocardial perfusion grade may also be an important predictor of long-term benefit [18]. (See 'Primary failure' above.)

Management — Patients who are diagnosed with or strongly suspected of a primary failure of fibrinolysis should receive an additional attempt at reperfusion. We prefer rescue PCI over repeat fibrinolysis.

Rescue PCI — Rescue or salvage PCI is defined as PCI performed within 12 hours of failed fibrinolysis (primary failure) [19]. If rescue PCI (usually with stenting) is performed, it appears to be important that it be undertaken quickly. In general, we begin to mobilize patients with apparent failure to the cardiac catheterization laboratory at approximately 45 to 60 minutes following fibrinolysis such that, when necessary, rescue PCI may be performed as close to 90 minutes after fibrinolysis as possible. Accordingly, because 40 to 45 percent of patients who receive fibrinolytic therapy will experience primary failure, we generally recommend that all who present at non-PCI-capable hospitals are transferred to a PCI-capable hospital as soon as possible after administration of the fibrinolytic agent. We do not recommend that a decision to transfer be deferred until it is determined whether primary failure has occurred or not. PCI or, if appropriate, bypass surgery is recommended in patients with less than TIMI grade 3 flow.

Revascularization may be deferred in patients with TIMI 3 flow who are hemodynamically stable [8]. However, observational data suggest that even patients with TIMI 3 flow have reduced mortality if PCI of the infarct-related artery is performed. (See "Percutaneous coronary intervention after fibrinolysis for acute ST-elevation myocardial infarction".)

Early randomized trials comparing rescue PCI (most patients underwent balloon angioplasty rather than stenting) with conservative therapy in patients with failed fibrinolysis found a trend toward lower mortality and lower risks of heart failure and reinfarction with rescue PCI [20]. Subsequently, stenting was shown to be superior to balloon angioplasty [13].

The REACT trial randomly assigned 427 patients with STEMI and failed fibrinolysis to conservative medical therapy, repeat fibrinolysis with a fibrin-specific agent, or rescue PCI (69 percent with stenting). Failed fibrinolysis was defined as less than 50 percent ST-segment elevation resolution within 90 minutes after therapy [21,22]. PCI was performed within 12 hours of the onset of pain if angiography revealed less than TIMI grade 3 flow and more than 50 percent stenosis in the infarct-related artery. (See 'Procedural issues' below and 'TIMI grade 2 flow' below.)

The following significantly improved outcomes were noted with rescue PCI:

- A higher rate of event-free survival (primary endpoint of death, reinfarction, stroke, or severe heart failure) at six months (85 versus 69 and 70 percent compared with repeat fibrinolysis or conservative therapy, adjusted hazard ratio [HR] 0.43 [95% CI 0.26-0.72] and 0.47 [95% CI 0.28-0.79]) and at one year (82 versus 64 and 68 percent, adjusted HR 0.44 [95% CI 0.28-0.71] and 0.51 [95% CI 0.32-0.83], respectively).

- A lower rate of all-cause mortality at a median follow-up of 4.4 years (6.2 versus 12.7 and 12.8 percent compared with repeat fibrinolysis or conservative therapy).

- A higher rate of freedom from revascularization at one year (85 versus 67 percent compared with repeat fibrinolysis or conservative therapy).

TIMI grade 2 flow — The above studies largely evaluated the efficacy of rescue PCI in patients, most of whom had failed fibrinolysis (TIMI grade 0/1 flow), although some patients with TIMI grade 2 flow were enrolled. Thus, the optimum treatment in patients with TIMI grade 2 flow is less well studied [18,23,24]. As noted above, patients with TIMI grade 2 flow have higher mortality rates than those with TIMI grade 3 (normal) flow: 7 versus 3.7 percent in a meta-analysis (figure 1 and figure 2) [2]. (See 'Importance of restoration of normal flow' above.)

Additional evidence to support rescue PCI for patients with TIMI grade 2 flow comes from an analysis of 668 patients (105 of whom were treated with rescue PCI) with TIMI grade 2 or 3 flow at angiography in the TIMI 10B trial [18]. Rescue PCI was associated with a trend toward reduction in mortality at two years (4 versus 11 percent).

Although the evidence to support rescue PCI for patients with TIMI grade 2 flow is less robust than that for TIMI grade 0/1, we suggest this approach. This is based on the inclusion of such patients in REACT and the increasing data suggesting benefit from routine angiography and PCI after fibrinolysis when appropriately timed. (See 'Rescue PCI' above and "Percutaneous coronary intervention after fibrinolysis for acute ST-elevation myocardial infarction".)

Procedural issues — Depending on the fibrinolytic agent chosen, the half-life of fibrinolytic activity may range from 50 to 90 minutes. Consequently, there is likely to be at least some fibrinolytic still on board when proceeding with rescue PCI. This may have an impact on decisions made at the time of PCI regarding the use of adjunctive antiplatelet and antithrombin therapy. Although large randomized clinical trials have not been performed to guide decisions, some reasonable options for adjunctive therapy are as follows:

- **Use of adjunctive IIb/IIIa glycoprotein inhibitors** – Because of the potential increased risk of intracranial hemorrhage associated with the combined use of IIb/IIIa inhibitors and

fibrinolytic agents, it is wise to use caution when using it during rescue PCI. Factors to consider include the thrombus burden identified during coronary angiography, the age of the patient, the type of fibrinolytic used, and the time passed since the fibrinolytic agent was administered. (See "Acute ST-elevation myocardial infarction: Antiplatelet therapy", section on 'Intravenous agents'.)

- **Choice of oral P2Y12 inhibitor** – Because most guidelines recommend that clopidogrel 300 mg be administered at the time of administration of a fibrinolytic agent, in most circumstances, clopidogrel will already be on board. It is our practice at the time of rescue PCI to complete a standard 600 mg load of clopidogrel by administering another 300 mg. If no clopidogrel has yet been given, it would be the interventionalist's choice regarding which $P2Y_{12}$ agent to administer. (See "Acute ST-elevation myocardial infarction: Antiplatelet therapy", section on 'Our approach to early DAPT'.)

- **Choice of antithrombin agent** – Because heparin is often started at the time of fibrinolytic agent administration, it seems reasonable to continue with heparin as the antithrombin agent during rescue PCI. Adjusting the dose according to the measured activated clotting time (ACT) may be accomplished in a similar manner as during standard PCI. Although not much data exist regarding the use of bivalirudin, in some circumstances, such as the presence of heparin-induced thrombocytopenia, its use may be considered. (See "Acute ST-elevation myocardial infarction: Management of anticoagulation", section on 'Primary percutaneous coronary intervention'.)

- **Radial or femoral access** – In most patients, we prefer radial rather than femoral artery access in order to decrease the likelihood of significant bleeding after fibrinolysis. (See "Periprocedural complications of percutaneous coronary intervention", section on 'Radial artery access'.)

- **Direct stenting and predilation** – Direct stenting (stenting without predilation of the coronary lesion) may improve myocardial perfusion and the incidence of death, MI, or heart failure compared with conventional stenting in patients who undergo PCI after fibrinolysis. This was illustrated in an observational study in which the choice of procedure was at the discretion of the treating physician [25]. Among patients with occluded infarct-related arteries, the likelihood of achieving TIMI myocardial perfusion grade 3 was significantly greater with direct stenting (54 versus 25 percent with conventional stenting).

Repeat fibrinolysis — Repeat fibrinolysis for failed primary fibrinolysis is usually considered when access to PCI is not available. However, it is not well studied. A 2007 meta-analysis included three trials that randomly assigned 410 patients to repeat fibrinolysis (all with

alteplase) or conservative therapy with follow-up between in-hospital discharge and six months [20]. There was no significant difference in all-cause mortality, reinfarction, or stroke between the two groups, and both treatments were inferior to rescue PCI. (See 'Rescue PCI' above.)

THREATENED REOCCLUSION OR REINFARCTION

Threatened reocclusion is best treated with immediate percutaneous coronary intervention (PCI) with stenting (rather than repeat fibrinolysis). Patients should be referred to a facility with PCI capability soon after fibrinolysis in most cases. This strategy will avoid the need to consider repeat lysis, except in rare cases.

After apparently successful fibrinolysis by clinical criteria, early recurrence of ischemia or ST segment shifts on the ECG has been observed in 20 to 30 percent of patients [26,27] and thrombotic coronary reocclusion at the time of angiography in 5 to 15 percent [4,28-31]. Reinfarction occurs in 3 to 5 percent and is clinically silent in over 50 percent of cases [31-34].

Demographic and clinical variables have not proven very helpful in predicting which patients will develop reocclusion [28,29,31,32]. One early fibrinolytic trial attempted to identify angiographic predictors of reocclusion [35]. The following angiographic variables, identified at 90 minutes after thrombolytic therapy, were associated with a significantly higher rate of infarct-related artery reocclusion (in the absence of PCI): TIMI grade 2 flow, lesion ulceration, the presence of collaterals, high-grade residual stenosis, and lesions that were eccentric or thrombotic. Other studies did not find angiographic features at a 90-minute baseline study to be helpful for predicting reocclusion [36,37]. Differences among these trials could explain the different findings [35].

Outcomes — Reocclusion of an infarct-related artery after reperfusion therapy is associated with a significant increase in mortality [28,31-34]. Patients with coronary reocclusion have a worse 30-day and one-year mortality compared with those without [27,28,31-33]. The data are conflicting as to whether 30-day survivors of reinfarction do [32] or do not [31] have a modest increase in risk from 30 days to one year.

Diagnosis — The following are accepted criteria to diagnose, or at a minimum strongly suspect, threatened reocclusion [15,16]:

- Within the first 18 hours after initial fibrinolysis, a recurrent elevation in cardiac biomarkers accompanied by recurrent ST-segment elevation on ECG and at least one other supporting criterion (such as recurrent chest pain or hemodynamic decompensation).

- After 18 hours, a biomarker rise of at least 50 percent and at least one additional criterion are sufficient for the diagnosis.

Threatened reocclusion is characterized by the development of early recurrent ischemia after apparently successful fibrinolysis.

Objective evidence of thrombotic reocclusion includes persistent or recurrent chest pain associated with new or worsening ST-segment elevation, the development of new ischemic ECG changes after initial resolution, or a second elevation in cardiac biomarkers (usually troponin).

Management — Patients with evidence of recurrent ischemia or infarction should be rapidly managed with angiography followed by PCI (or coronary artery bypass graft surgery [CABG] if appropriate), if possible. If urgent angiography is not available, repeat fibrinolysis is a reasonable alternative if ST-segment elevation on an ECG is present.

We prefer angiography and PCI in these patients, assuming that catheterization can be performed within two hours. If catheterization will be delayed, repeat fibrinolysis with tenecteplase, alteplase, or reteplase may be preferred in patients with ST elevation. Patients receiving repeat fibrinolytic therapy should be observed for stability as other medical therapies are continued or augmented.

PCI — PCI is the treatment of choice for patients with threatened reocclusion or recurrent MI. The magnitude of the benefit was illustrated in a retrospective review of 20,100 patients from trials of fibrinolytic therapy [31]. Among the 4.2 percent with a recurrent MI, the in-hospital mortality was 23.6 percent in those who were treated medically and did not undergo revascularization compared with 5.2 percent with PCI; an equivalent benefit was seen with the smaller number of patients who underwent CABG.

A similar dramatic reduction in mortality with revascularization was noted in a review from two fibrinolytic trials [33]. Among the 4 percent of patients with reinfarction, 30-day mortality was significantly lower in patients treated with revascularization compared with medical therapy (11 versus 28 percent). The revascularization procedure was PCI or surgery (performed in 35 percent in United States centers and 15 percent in centers in other countries) or repeat thrombolysis (performed in 28 percent in United States centers and 47 percent in centers in other countries). Thirty-day mortality (11 percent) was not affected by the type of revascularization.

Repeat fibrinolytic therapy — The efficacy of retreatment with a fibrinolytic agent has been evaluated primarily in patients with threatened reocclusion and ST-segment elevation on an ECG. Most retreatment studies have involved alteplase and, to a lesser degree, other

nonantigenic agents such as tenecteplase; streptokinase should be **avoided** because of antigenicity and relative resistance. After repeat fibrinolysis, patients should be referred to a facility with PCI capability.

Choice of agent — In patients who will be retreated with fibrinolytic therapy, we use alteplase, tenecteplase, or reteplase. Alteplase is the best studied of the three. Retreatment with streptokinase or anistreplase should be avoided due to the potential for neutralizing antibodies, which might render such therapy ineffective [38,39].

There are two major concerns with repeat fibrinolysis:

- Excess bleeding risk, particularly with early reuse
- Decreased efficacy, in view of initial treatment failure

A number of reports have demonstrated the feasibility and efficacy of repeat fibrinolytic therapy with alteplase [40-43]. As an example, a retrospective study assessed the outcome of repeat infusions of alteplase in 52 patients with an acute MI who developed early recurrent myocardial ischemia with threatened reinfarction after initial therapy with either alteplase (46 patients) or streptokinase (six patients) [42]. Retreatment was given within one hour of the first infusion in 67 percent and within 72 hours in 92 percent. The following findings were noted:

- Complete resolution of acute ischemia within one hour of the second infusion was achieved in 85 percent; one-half of these patients had a sustained response and avoided further coronary intervention.
- Bleeding complications occurred in 19 percent, but only 4 percent required transfusion.
- Fibrinogen levels fell by 25 percent and plasminogen levels by 63 percent; these changes were only slightly greater than those in patients who had received only one alteplase infusion and were not additive to those observed after the first infusion.

A later study evaluated the effects of retreatment with alteplase given for early signs of reocclusion after fibrinolysis, as manifested by recurrent chest pain lasting for more than 30 minutes with re-elevation of the ST segment [43]. This complication occurred in 26 of 652 patients (4 percent) treated with alteplase, usually within 24 hours of the first infusion, particularly if intravenous heparin was not used. The second dose of alteplase was 50 mg when threatened reocclusion occurred within 24 hours of initial therapy and 100 mg after 24 hours. The following results were noted:

- All patients had a good clinical response to retreatment; the new ST-segment changes disappeared and pain resolved within 100 minutes (median 50 minutes).

- Angiographic findings, determined at one hour, were less favorable. Coronary artery patency was observed in 73 percent of patients who had received intravenous heparin and only 40 percent of those not receiving heparin.

- Bleeding rates were similar to those after a single dose of alteplase.

Randomized trials have not been performed to assess the comparative efficacy of repeat fibrinolysis and PCI in patients with recurrent ischemia or threatened reinfarction. This issue was assessed in a retrospective review of the 4 percent of patients (n = 2301) who developed early reinfarction after initial fibrinolysis in the GUSTO-I (alteplase) and ASSENT 2 (tenecteplase) trials [33]. Repeat fibrinolysis (performed in 28 percent in United States centers and 47 percent in centers in other countries) and revascularization with PCI or surgery (performed in 35 percent in United States centers and 15 percent in centers in other countries) were equally effective and were associated with a significantly lower 30-day mortality than conservative therapy (11 and 11 versus 28 percent) without any increase in the rate of stroke.

Thus, repeat fibrinolytic infusions are feasible, can stabilize a substantial number of patients with threatened early infarction, and, even when relief of ischemia is temporary, can reduce myocardial damage in those proceeding to mechanical or surgical revascularization. However, there is limited information regarding the safety of PCI or surgery in the early hours after a second course of therapy with fibrinolytic drugs.

Reinfarction in a new territory — Studies in patients with an acute coronary syndrome have demonstrated multiple unstable plaques within the coronary circulation. Thus, reinfarction might occur in a new territory rather than reflecting failed fibrinolysis in the index territory.

This issue was addressed in a report from the HERO-2 trial of bivalirudin versus unfractionated heparin prior to streptokinase administration [44]. Confirmed reinfarction occurred in 552 patients (3.2 percent). Among these patients, 67 percent had ST elevation in the index territory, 18 percent had no new ECG changes, 2 percent had new bundle branch block, and 4 percent (0.15 percent of all patients) had ST elevation in a new territory at a mean of 46 hours.

For patients with reinfarction in a new territory, which is usually diagnosed at the time of coronary angiography, we usually perform PCI of the artery supplying this new territory unless the coronary anatomy requires CABG.

PATIENTS REQUIRING CABG

Urgent coronary artery bypass graft surgery (CABG) is needed infrequently after fibrinolysis. Percutaneous coronary intervention (PCI) is preferred in this setting because of increased risks of perioperative mortality and major hemorrhage with CABG, especially if the interval between administration of the fibrinolytic agent and surgery is short. In an analysis from the TIMI II study, 390 patients underwent CABG after fibrinolytic treatment [45]. Patients undergoing surgery within 24 hours of study, compared with those undergoing later surgery, had higher rates of perioperative mortality (17 versus 4 percent) and major hemorrhage (74 versus 51 percent).

The risk of bleeding for patients undergoing CABG after fibrinolysis may vary with the specific fibrinolytic agent. Tenecteplase is associated with significantly less fibrinogen depletion than either alteplase or reteplase [46]. As a result, patients treated with tenecteplase may be able to undergo CABG within 24 hours of fibrinolysis more safely than patients treated with the other agents, although this has not been specifically demonstrated in clinical studies.

While early morbidity and mortality are of concern in this setting, long-term outcome is much better and suggests that surgery may be appropriate for carefully selected patients [31,45].

RECOMMENDATIONS OF OTHERS

Our recommendations are generally in agreement with those of other major societal organizations [15,16,47].

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

- **Definitions** – Among patients treated with fibrinolytic drugs for ST-elevation myocardial infarction (STEMI), there are two types of failed therapy: primary failure and threatened reocclusion.
    - **Primary failure** – Primary failure of fibrinolysis occurs when there is evidence of continuing or worsening myocardial ischemia after fibrinolysis. (See 'Primary failure'

above.)

- **Threatened occlusion** – Threatened reocclusion is characterized by the development of early recurrent ischemia after apparently successful fibrinolysis. (See 'Threatened reocclusion or reinfarction' above.)

- **Management**

  - **Primary failure of fibrinolysis** – For patients with evidence of primary failure of fibrinolysis, we recommend urgent rescue percutaneous coronary intervention (PCI) as opposed to either repeat fibrinolysis or conservative care (**Grade 1B**). PCI should be carried out as soon as the diagnosis of primary failure of fibrinolysis is confirmed. If rescue PCI cannot be performed within 12 hours, we suggest conservative care as opposed to repeat fibrinolysis (**Grade 2B**). (See 'Rescue PCI' above.)

  - **Threatened occlusion** – For patients with evidence of threatened reocclusion after fibrinolysis, we recommend urgent PCI as opposed to either repeat fibrinolysis or conservative care (**Grade 1B**). If PCI cannot be performed within two hours, we suggest repeat fibrinolysis with a nonantigenic agent as opposed to conservative care (**Grade 2B**). (See 'Threatened reocclusion or reinfarction' above.)

REFERENCES

1. GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993; 329:673.
2. Anderson JL, Karagounis LA, Califf RM. Metaanalysis of five reported studies on the relation of early coronary patency grades with mortality and outcomes after acute myocardial infarction. Am J Cardiol 1996; 78:1.
3. Vogt A, von Essen R, Tebbe U, et al. Impact of early perfusion status of the infarct-related artery on short-term mortality after thrombolysis for acute myocardial infarction: retrospective analysis of four German multicenter studies. J Am Coll Cardiol 1993; 21:1391.
4. GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993; 329:1615.
5. Simes RJ, Topol EJ, Holmes DR Jr, et al. Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion. Importance of

early and complete infarct artery reperfusion. GUSTO-I Investigators. Circulation 1995; 91:1923.

6. Ross AM, Coyne KS, Moreyra E, et al. Extended mortality benefit of early postinfarction reperfusion. GUSTO-I Angiographic Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial. Circulation 1998; 97:1549.
7. Cannon CP, Gibson CM, McCabe CH, et al. TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI 10B trial. Thrombolysis in Myocardial Infarction (TIMI) 10B Investigators. Circulation 1998; 98:2805.
8. Goldman LE, Eisenberg MJ. Identification and management of patients with failed thrombolysis after acute myocardial infarction. Ann Intern Med 2000; 132:556.
9. Holmes DR Jr, Gersh BJ, Ellis SG. Rescue percutaneous coronary intervention after failed fibrinolytic therapy: have expectations been met? Am Heart J 2006; 151:779.
10. de Lemos JA, Antman EM, Giugliano RP, et al. ST-segment resolution and infarct-related artery patency and flow after thrombolytic therapy. Thrombolysis in Myocardial Infarction (TIMI) 14 investigators. Am J Cardiol 2000; 85:299.
11. de Lemos JA, Morrow DA, Gibson CM, et al. Early noninvasive detection of failed epicardial reperfusion after fibrinolytic therapy. Am J Cardiol 2001; 88:353.
12. Califf RM, O'Neil W, Stack RS, et al. Failure of simple clinical measurements to predict perfusion status after intravenous thrombolysis. Ann Intern Med 1988; 108:658.
13. Schömig A, Ndrepepa G, Mehilli J, et al. A randomized trial of coronary stenting versus balloon angioplasty as a rescue intervention after failed thrombolysis in patients with acute myocardial infarction. J Am Coll Cardiol 2004; 44:2073.
14. Van de Werf F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 2008; 29:2909.
15. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013; 127:e362.
16. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College

of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013; 127:529.

17. de Lemos JA, Braunwald E. ST segment resolution as a tool for assessing the efficacy of reperfusion therapy. J Am Coll Cardiol 2001; 38:1283.
18. Gibson CM, Cannon CP, Murphy SA, et al. Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary intervention to long-term outcomes after thrombolytic administration in acute myocardial infarction. Circulation 2002; 105:1909.
19. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of pat ients with ST-elevation myocardial infarction. www.acc.org/qualityandscience/clinical/state ments.htm (Accessed on August 24, 2006).
20. Wijeysundera HC, Vijayaraghavan R, Nallamothu BK, et al. Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction: a meta-analysis of randomized trials. J Am Coll Cardiol 2007; 49:422.
21. Gershlick AH, Stephens-Lloyd A, Hughes S, et al. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. N Engl J Med 2005; 353:2758.
22. Carver A, Rafelt S, Gershlick AH, et al. Longer-term follow-up of patients recruited to the REACT (Rescue Angioplasty Versus Conservative Treatment or Repeat Thrombolysis) trial. J Am Coll Cardiol 2009; 54:118.
23. Gibson, M, Schweiger, et al. Outcomes of adjunctive PTCA/stenting for TIMI grade 2 flow following thrombolysis (abstract). J Am Coll Cardiol 1998; 31:231A.
24. Ellis SG, Lincoff AM, George BS, et al. Randomized evaluation of coronary angioplasty for early TIMI 2 flow after thrombolytic therapy for the treatment of acute myocardial infarction: a new look at an old study. The Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Study Group. Coron Artery Dis 1994; 5:611.
25. Ly HQ, Kirtane AJ, Buros J, et al. Angiographic and clinical outcomes associated with direct versus conventional stenting among patients treated with fibrinolytic therapy for ST-elevation acute myocardial infarction. Am J Cardiol 2005; 95:383.
26. Armstrong PW, Fu Y, Chang WC, et al. Acute coronary syndromes in the GUSTO-IIb trial: prognostic insights and impact of recurrent ischemia. The GUSTO-IIb Investigators. Circulation 1998; 98:1860.
27. Langer A, Krucoff MW, Klootwijk P, et al. Prognostic significance of ST segment shift early after resolution of ST elevation in patients with myocardial infarction treated with

thrombolytic therapy: the GUSTO-I ST Segment Monitoring Substudy. J Am Coll Cardiol 1998; 31:783.

28. Ohman EM, Califf RM, Topol EJ, et al. Consequences of reocclusion after successful reperfusion therapy in acute myocardial infarction. TAMI Study Group. Circulation 1990; 82:781.
29. Ellis SG, Topol EJ, George BS, et al. Recurrent ischemia without warning. Analysis of risk factors for in-hospital ischemic events following successful thrombolysis with intravenous tissue plasminogen activator. Circulation 1989; 80:1159.
30. Meijer A, Verheugt FW, Werter CJ, et al. Aspirin versus coumadin in the prevention of reocclusion and recurrent ischemia after successful thrombolysis: a prospective placebo-controlled angiographic study. Results of the APRICOT Study. Circulation 1993; 87:1524.
31. Gibson CM, Karha J, Murphy SA, et al. Early and long-term clinical outcomes associated with reinfarction following fibrinolytic administration in the Thrombolysis in Myocardial Infarction trials. J Am Coll Cardiol 2003; 42:7.
32. Hudson MP, Granger CB, Topol EJ, et al. Early reinfarction after fibrinolysis: experience from the global utilization of streptokinase and tissue plasminogen activator (alteplase) for occluded coronary arteries (GUSTO I) and global use of strategies to open occluded coronary arteries (GUSTO III) trials. Circulation 2001; 104:1229.
33. Barbash GI, Birnbaum Y, Bogaerts K, et al. Treatment of reinfarction after thrombolytic therapy for acute myocardial infarction: an analysis of outcome and treatment choices in the global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries (gusto I) and assessment of the safety of a new thrombolytic (assent 2) studies. Circulation 2001; 103:954.
34. Dönges K, Schiele R, Gitt A, et al. Incidence, determinants, and clinical course of reinfarction in-hospital after index acute myocardial infarction (results from the pooled data of the maximal individual therapy in acute myocardial infarction [MITRA], and the myocardial infarction registry [MIR]). Am J Cardiol 2001; 87:1039.
35. Gibson CM, Cannon CP, Piana RN, et al. Angiographic predictors of reocclusion after thrombolysis: results from the Thrombolysis in Myocardial Infarction (TIMI) 4 trial. J Am Coll Cardiol 1995; 25:582.
36. Wall TC, Mark DB, Califf RM, et al. Prediction of early recurrent myocardial ischemia and coronary reocclusion after successful thrombolysis: a qualitative and quantitative angiographic study. Am J Cardiol 1989; 63:423.
37. Reiner JS, Lundergan CF, van den Brand M, et al. Early angiography cannot predict postthrombolytic coronary reocclusion: observations from the GUSTO angiographic study.

Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries. J Am Coll Cardiol 1994; 24:1439.

38. Buchalter MB, Suntharalingam G, Jennings I, et al. Streptokinase resistance: when might streptokinase administration be ineffective? Br Heart J 1992; 68:449.
39. Squire IB, Lawley W, Fletcher S, et al. Humoral and cellular immune responses up to 7.5 years after administration of streptokinase for acute myocardial infarction. Eur Heart J 1999; 20:1245.
40. White HD, Cross DB, Williams BF, Norris RM. Safety and efficacy of repeat thrombolytic treatment after acute myocardial infarction. Br Heart J 1990; 64:177.
41. White H. Thrombolytic treatment for recurrent myocardial infarction. BMJ 1991; 302:429.
42. Barbash GI, Hod H, Roth A, et al. Repeat infusion of recombinant tissue-type plasminogen activator in patients with acute myocardial infarction and early recurrent myocardial ischemia. J Am Coll Cardiol 1990; 16:779.
43. Simoons ML, Arnout J, van den Brand M, et al. Retreatment with alteplase for early signs of reocclusion after thrombolysis. The European Cooperative Study Group. Am J Cardiol 1993; 71:524.
44. Edmond JJ, French JK, Stewart RA, et al. Frequency of recurrent ST-elevation myocardial infarction after fibrinolytic therapy in a different territory as a manifestation of multiple unstable coronary arterial plaques. Am J Cardiol 2006; 97:947.
45. Gersh BJ, Chesebro JH, Braunwald E, et al. Coronary artery bypass graft surgery after thrombolytic therapy in the Thrombolysis in Myocardial Infarction Trial, Phase II (TIMI II). J Am Coll Cardiol 1995; 25:395.
46. Armstrong PW, Collen D. Fibrinolysis for acute myocardial infarction: current status and new horizons for pharmacological reperfusion, part 1. Circulation 2001; 103:2862.
47. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012; 33:2569.

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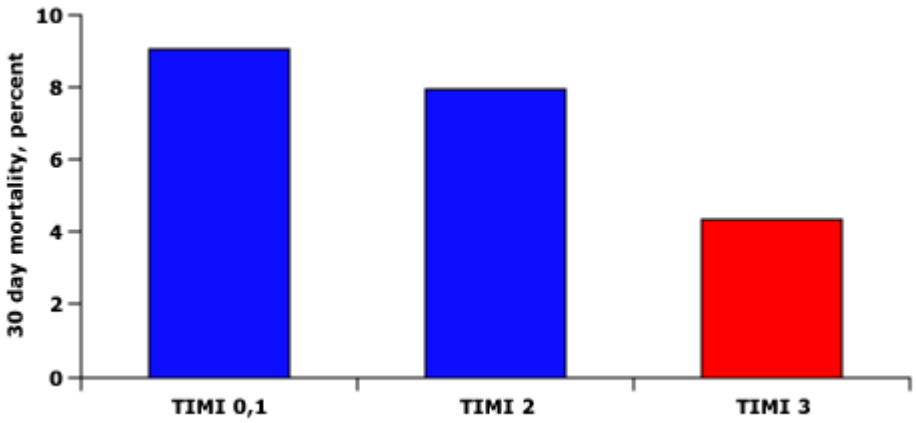
GRAPHICS

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.

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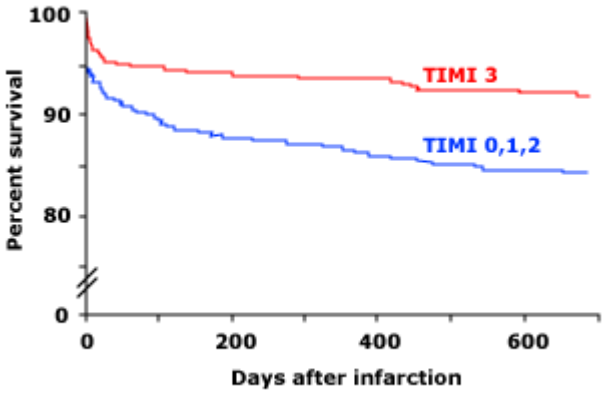
Survival after thrombolytic therapy is better with Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow



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